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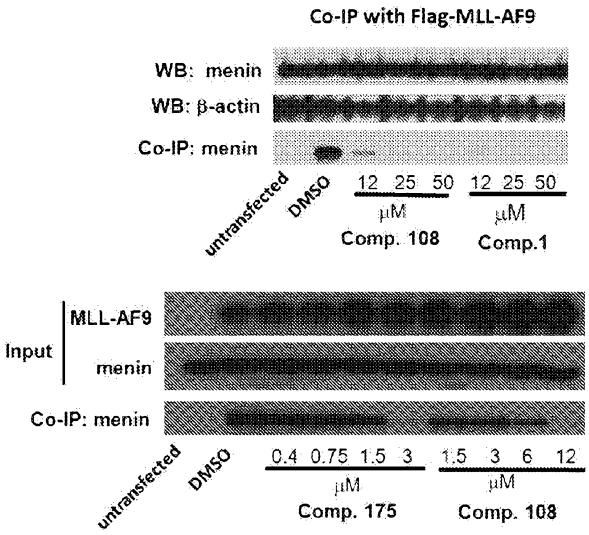

(57) Abstract: The present invention relates generally to thienopyrimidine and thienopyridine class compounds and methods of use thereof. In particular embodiments, the present invention provides compositions comprising thienopyrimidine and thienopyridine class compounds and methods of use to inhibit the interaction of menin with MLL1, MLL2 and MLL-fusion oncoproteins (e.g., for the treatment of leukemia, solid cancers and other diseases dependent on activity of MLL1, MLL2, MLL fusion proteins, and/or menin).

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COMPOSITIONS COMPRISING THIENOPYRIMIDINE AND THIENOPYRIDINE COMPOUNDS AND METHODS OF USE THEREOF

The present application claims priority to United States Provisional Patent Application Serial Number 61/780,099, filed March 13, 2013, the entire disclosure of which is herein incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under R01 CA160467-01 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention relates generally to thienopyrimidine and thienopyridine class compounds and methods of use thereof. In particular embodiments, the present invention provides compositions comprising thienopyrimidine and thienopyridine class compounds and methods of use to inhibit the interaction of menin with MLL1, MLL2 and MLL-fusion oncoproteins (e.g., for the treatment of leukemia, solid cancers and other diseases dependent on activity of MLL1, MLL2, MLL fusion proteins, and/or menin).

BACKGROUND OF THE INVENTION

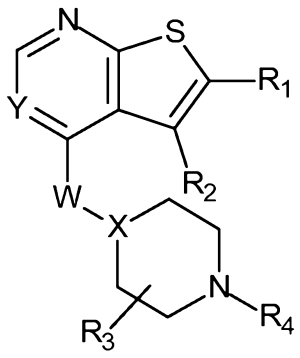
Chromosomal translocations that affect the proto-oncogene Mixed Lineage Leukemia (MLL) occur in aggressive human acute leukemias, both in children and adults (Sorensen et al., J Clin Invest., 1994.93(1): p. 429-37., Cox, et al., Am J Clin Pathol., 2004. 122(2): p. 298-306., herein incorporated by reference in their entireties). They are particularly common in infants with acute myeloblastic leukemia (AML) and acute lymphoblastic leukemia (ALL) and constitute up to 80% of all infant acute leukemia cases. Fusion of MLL with one of 60 partner genes forms a chimeric oncogene which upregulates HOX genes resulting in a blockage of blood cell differentiation that ultimately leads to acute leukemia (Eguchi et al. Int J Hematol., 2003.

78(5): p. 390-401., herein incorporated by reference in its entirety). Patients with leukemias harboring MLL translocations have a very poor prognosis (35 % five year survival) and it is clear that novel therapeutic strategies are urgently needed to treat these leukemias (Slany. Hematol Oncol., 2005. 23(1): p. 1-9., herein incorporated by reference in its entirety). Menin is a critical cofactor in MLL-associated leukemias. Menin is a tumor-suppressor protein encoded by the Multiple Endocrine Neoplasia (MEN) gene. Menin is a ubiquitously expressed nuclear protein that is engaged in interactions with a cohort of transcription factors, chromatin modifying proteins, and DNA processing and repair proteins (Agarwal et al. Horm Metab Res., 2005. 37(6): p. 369-74., herein incorporated by reference in its entirety). The biological function of menin remains unclear and is context dependent. It functions as a tumor suppressor in endocrine organs (Marx. Nat Rev Cancer., 2005. 5(5): p. 367-75., herein incorporated by reference in its entirety) but has an oncogenic role in myeloid cells (Yokoyama et al., Cell., 2005.123(2): p. 207-18., herein incorporated by reference in its entirety). Association of menin with oncogenic MLL fusion proteins constitutively up-regulates expression of HOX genes and impairs proliferation and differentiation of hematopoietic cells leading to leukemia development. Myeloid cells transformed with oncogenic MLL-AF9 fusion protein require menin for efficient proliferation (Chen et al., Proc Natl Acad Sci USA., 2006.103(4): p. 1018-23., herein incorporated by reference in its entirety). Menin is also required to maintain oncogenic transformation induced by other MLL translocations, including MLL-ENL, MLL-GAS7 and MLL-AF6 (Yokoyama et al., Cell., 2005.123(2): p. 207-18., herein incorporated by reference in its entirety), demonstrating that menin functions as a general oncogenic cofactor in MLL-related leukemias and implies the interaction of menin with MLL fusions and MLL is a valuable target for molecular therapy. The leukemogenic activity of MLL fusion oncoproteins is dependent on association with menin. Therefore, selective targeting of this interaction could provide an attractive therapeutic approach to develop novel drugs for leukemias with translocations of *MLL* gene and other leukemias with upregulation of *HOX* genes.

SUMMARY OF THE INVENTION

In some embodiments, the present invention provides compositions for the treatment of leukemia which inhibit binding of one or more MLL fusion proteins to menin and/or MLL wild type to menin. In some embodiments, the composition comprises a thienopyrimidine and thienopyridine class compounds.

In some embodiments, the thienopyrimidine and thienopyridine class compound is of the general formula:

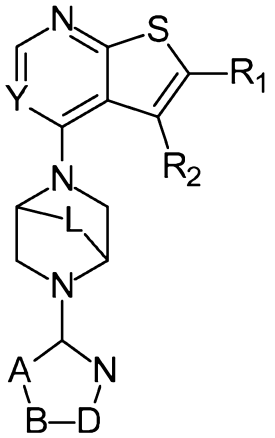


wherein X, Y, W, R1, R2, R3, and R4 are independently selected from any of the respective substituents described herein or depicted in any of Tables 1-8 or described elsewhere herein, in any combination. For example, in some embodiments, R_1-R_4 each independently consist of or comprise: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., mono-, di-, tetra-,penta- and trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkycyano (e.g., cyano, methylcyano, ethylcyano, etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, alkyl-substituted cycloalkyl group, cycloalkoxy group, cyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring (e.g., heteroaryl), a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl,

aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring (e.g., heteroaryl), a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents (e.g., substituted heteroaryl), or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof.

In some embodiments, the thienopyrimidine and thienopyridine class compound is of a general formula of:

Subscaffold 1



wherein R1 and R2 both independently comprise or consists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., mono-, di-, tetra-,penta- and trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), 1-trihalo, 2-halo-ethane, trihalobutane, etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-

substituted cycloalkyl group, alkyl-substituted cycloalkyl group, cycloalkoxy group, cyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring (e.g., heteroaryl), a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring (e.g., heteroaryl), a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents (e.g., substituted heteroaryl), or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof; and wherein A, B, and D each independently comprise or consist of: C, N, O, or S; wherein when one or more of A, B, and/or D comprise O or S, there is no further substitution at that respective position; wherein when one or more of A, B, and/or D comprise N or C that respective position is optionally substituted, wherein the substituent at that respective position comprises or consists of: alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more

nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor, a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring (e.g., heteroaryl) comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings (e.g., heteroaryl), cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof; and wherein Y is N or C, and wherein when Y is C the Y position may be substituted with R^a, with R^a consisting of or comprising an H, alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)), 1-trifluoro,2-ethanol, alcohol (e.g., $(CH_2)_nOH$, wherein n=0-10), alkoxy (e.g., $(CH_2)_n$-OR, wherein n=0-10, wherein R is alkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-aromatic, $(CH_2)_n$-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle with one or more N, S, O, etc.), amino (e.g., alkyl amine, amino alkyl, etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.; and wherein L is present or absent and comprises alkylene (e.g. methylene, -CH_2-, ethylene, -CH_2-CH_2-, etc) or oxalkylene (e.g. –O-, -CH_2-O-CH_2) groups.

In some embodiments, R1 of subscaffold 1 is selected from an alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group, See, e.g., compound 1), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)), trihaloisopropyl (e.g.,trifluoroisopropyl (See, e.g., compound 38)), 1-fluoro,2-trifluoro,ethane (See, e.g., compound 21), 1-trifluoro,2-ethanol (See, e.g., compound 23)), alcohol, amino (e.g., alkyl

amine, amino alkyl, etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.

In some embodiments, R2 of subscaffold 1 is selected from a halogen (e.g., Cl, F, Br, I), alkyl (e.g., branched, straight chain (e.g., methyl), cycloalkyl, heteroalkyl, alkyl-substituted aryl, substituted alkyl (e.g., halo-substituted alkyl, alcohol, amino, etc.), OH, SH, NH_2, etc.

In some embodiments, A of subscaffold 1 is selected from C, N, O, or S; wherein when A is O or S, there is no further substitution at that respective position; wherein, when A is N, it is optionally substituted with one substituent that comprises or consists of: alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., methyl, propyl), cycloalkyl (e.g., cyclopropane, cyclopentante, cyclohexane)), heteroalkyl (e.g., methyl propyl ether ($CH_2O(CH2)_2CH_3$), methylamine (CH_2NH_2), aminomethyl (CH_2NH), etc.), alkyl-substituted aryl (e.g., methylbenzene, ethylbenzene, propylbenzene, butylbenzene, etc.), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl), trihalobutyl group (e.g., trifluorobutyl group), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane, trifluoroethanol), alcohol-substituted alkyl, amino-substituted alkyl, substituted cycloalkyl, substituted aromatic ring (e.g., propylbenzene, 1-ethyl-4methoxybenzene, 1-propyl-4-methoxy-benzene, etc.)), alcohol, amino, and/or combinations thereof.; wherein when A is C, it is optionally substituted with one or two substituents that comprises or consists of: alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., methyl, propyl), cycloalkyl (e.g., cyclopropane, cyclopentante, cyclohexane)), heteroalkyl (e.g., methyl propyl ether, methylamino, etc.), alkyl-substituted aryl (e.g., methylbenzene, ethylbenzene, propylbenzene, butylbenzene, etc.), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl), trihalobutyl group (e.g., trifluorobutyl group), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane, trifluoroethanol), alcohol-substituted alkyl, amino-substituted alkyl, substituted cycloalkyl, substituted aromatic ring (e.g., propylbenzene, 1-ethyl-4methoxybenzene, 1-propyl-4-methoxy-benzene, etc.)), alcohol, amino, and/or combinations thereof.

In some embodiments, B of subscaffold 1 is selected from C, N, O, or S; wherein when B is O or S, there is no further substitution at that respective position; wherein, when B is N, it is optionally substituted with one substituent that comprises or consists of: alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., methyl, propyl), cycloalkyl (e.g., cyclopropane,

cyclopentante, cyclohexane)), heteroalkyl (e.g., methyl propyl ether, methylamino, etc.), alkyl-substituted aryl (e.g., methylbenzene, ethylbenzene, propylbenzene, butylbenzene, etc.), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl), trihalobutyl group (e.g., trifluorobutyl group), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane, trifluoroethanol), alcohol-substituted alkyl, amino-substituted alkyl, substituted cycloalkyl, substituted aromatic ring (e.g., propylbenzene, 1-ethyl-4-methoxybenzene, 1-propyl-4-methoxy-benzene, alcohol, amino, and/or combinations thereof.; wherein when B is C, it is optionally substituted with one or two substituents that comprises or consists of: alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., methyl, propyl), cycloalkyl (e.g., cyclopropane, cyclopentante, cyclohexane)), alkyl-substituted cycloalkyl (e.g. methylcyclohexyl), heteroalkyl (e.g., methyl propyl ether, methylamino, etc.), alkyl-substituted aryl (e.g., methylbenzene, ethylbenzene, propylbenzene, butylbenzene, etc.), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), dihalomethyl group (e.g. difluoromethyl group), monohalomethyl group (3.g. monofluoromethyl group)), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl), trihalobutyl group (e.g., trifluorobutyl group), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane (See, e.g., compound 21), trifluoroethanol), alcohol-substituted alkyl, amino-substituted alkyl, substituted cycloalkyl, substituted aromatic ring (e.g., propylbenzene, 1-ethyl-4methoxybenzene, 1-propyl-4-methoxy-benzene, etc.)), alcohol, amino, and/or combinations thereof (See, e.g., Table 1).

In some embodiments, D of subscaffold I is selected from C, N, O, or S; wherein when D is O or S, there is no further substitution at that respective position; wherein, when D is N, it is optionally substituted with one substituent that comprises or consists of: alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., methyl, propyl), cycloalkyl (e.g., cyclopropane, cyclopentante, cyclohexane)), heteroalkyl (e.g., methyl propyl ether, methylamino, etc.), alkyl-substituted aryl (e.g., methylbenzene, ethylbenzene, propylbenzene, butylbenzene, etc.), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl), trihalobutyl group (e.g., trifluorobutyl group), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane, trifluoroethanol), alcohol-substituted alkyl, amino-substituted alkyl, substituted cycloalkyl, substituted aromatic ring (e.g., propylbenzene, 1-ethyl-4methoxybenzene,

1-propyl-4-methoxy-benzene, etc.)), alcohol, amino, and/or combinations thereof.; wherein when D is C, it is optionally substituted with one or two substituents that comprises or consists of: alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., methyl, propyl), cycloalkyl (e.g., cyclopropane, cyclopentante, cyclohexane)), heteroalkyl (e.g., methyl propyl ether, methylamino, etc.), alkyl-substituted aryl (e.g., methylbenzene, ethylbenzene, propylbenzene, butylbenzene, etc.), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl), trihalobutyl group (e.g., trifluorobutyl group), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane, trifluoroethanol), alcohol-substituted alkyl, amino-substituted alkyl, substituted cycloalkyl, substituted aromatic ring (e.g., propylbenzene, 1-ethyl-4methoxybenzene, 1-propyl-4-methoxy-benzene, etc.)), alcohol, amino, and/or combinations thereof (See, e.g., Table 1).

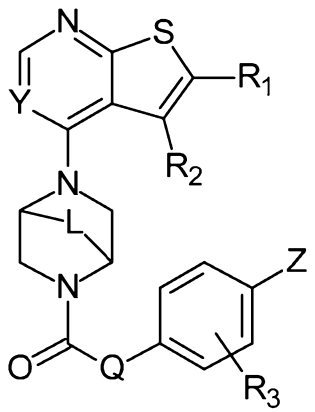
In some embodiments, Y of subscaffold 1 is selected from N or C.

In some embodiments, L of subscaffold 1 is alkylene (e.g. methylene, -CH_2-, ethylene, -CH_2-CH_2-, etc) or oxalkylene (e.g. –O-, -CH_2-O-CH_2) groups.

In some embodiments, compositions comprising one or more of compound 1-42 of Table 1 are provided.

In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 2



;

wherein R1 and R2 both independently comprise or consist of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl

(e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., mono-, di-, tetra-,penta- and trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, cycloalkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof; wherein R3 comprises or consists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thioalkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-

substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, a hydrogen bond donor or a hydrogen bond acceptor, a sulfur-containing group (e.g., thiol, sulfide, disulfide, sulfoxide, sulfone (e.g., dimethyl sulfone, sulfonyl-amino (SO_2NH_2), sulfonyl-methane (SO_2CH_3), amino-sulfonyl-methane ($NHSO_2CH_3$), amino-sulfonyl-amino ($NHSO_2NH_2$), methy-sulfonyl-amino ($CH_2SO_2NH_2$; See, e.g. compound 96), methyl-sulfonyl-methane ($CH_2SO_2CH_3$), methyl-sulfonyl-halomethane ($CH_2SO_2CH_3$)) and/or combinations thereof; wherein R3 is present at 1-4 positions on the phenyl ring;

wherein L is present or absent and comprises alkylene (e.g. methylene, -CH_2-, ethylene, -CH_2-CH_2-, etc) or oxalkylene (e.g. –O-, -CH_2-O-CH_2) groups;

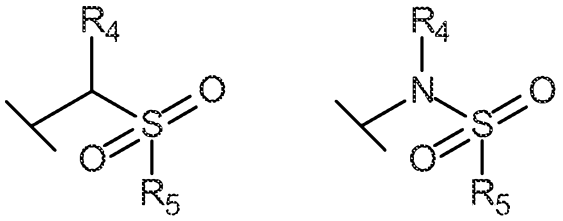
wherein Q comprises alkyl (C_{1-5}) or heteroalkyl with one or more N, O atoms;

wherein Y is N or C, and wherein when Y is C the Y position may be substituted with R^a, with R^a consisting of or comprising an alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)), trihaloisopropyl (e.g.,trifluoroisopropyl , 1-fluoro,2-trifluoro,ethane , 1-trifluoro,2-ethanol, alcohol (e.g., $(CH_2)_nOH$, wherein n=0-10), alkoxy (e.g., $(CH_2)_n$-OR, wherein n=0-10, wherein R is alkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-aromatic, $(CH_2)_n$-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle with one or more N, S, O, etc.), amino (e.g., alkyl amine,

amino alkyl, etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.;

wherein Z comprises or consists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thioalkyl, a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, a hydrogen bond donor or a hydrogen bond acceptor, a sulfur-containing group (e.g., thiol, sulfide, disulfide, sulfoxide, sulfone), a group selected from $CHR^4SO_2R^5$ or $NR^4SO_2R^5$, in which R^4 comprises or cosists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), alkylnitrile group (e.g.

ethanenitryle group, CH_2CN), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), a carbocyclic ring, a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, alkyl-substituted cycloalkyl group, cycloalkoxy group, cyclolkylamine, etc.) and R^5 comprises or consists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thioalkyl, a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof, R^5 might also be a part of the 3-8 member aromatic or non-aromatic ring comparising C,N,O,S (e.g. compounds 52,53,55). In some embodiments, Z comprises:



or .

In some embodiments, Z is selected from: dimethyl sulfone, amino-sulfonyl-methane ($NHSO_2CH_3$), amino-sulfonyl-amine ($NHSO_2NH_2$), methyl-sulfonyl-amino ($CH_3SO_2NH_2$, methylamino-sulfonyl-methane ($NCH_3SO_2CH_3$; See e.g., compound 46), amino-sulfonyl-amino-methane ($NHSO_2NHCH3$), amino-sulfonyl-ethane-2-amine ($NHSO_2CH_2CH_2NH_2$), amino-sulfonyl-ethane ($NHSO_2CH_2CH_3$), amino-sulfonyl-dimethylamine ($NHSO_2N(CH3)_2$; See, e.g., compound 51), amino-sulfonyl-isopropane ($NHSO_2{}^iPr$), amino-sulfonyl-heterocycloalkane (e.g., amino-sulfonyl-1-pyridine, amino-sulfonyl-1-oxazine, amino-sulfonyl-1-pyrazine, etc.), amino-sulfonyl-alkyl (e.g., amino-sulfonyl-methane ($NHSO_2CH_3$), amino-sulfonyl-ethane ($NHSO_2CH_2CH_3$), amino-sulfonyl-propane ($NHSO_2(CH_2)_2CH_3$), amino-sulfonyl-butane ($NHSO2(CH_2)_3CH_3$), etc.), sulfinic acid, thiocyante, etc.), and/or combinations thereof.

In some embodiments, R1 of subscaffold 2 is selected from an alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl), trihalobutyl group (e.g., trifluorobutyl group), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane, trifluoroethanol), alcohol, amino, etc. (See, e.g., Table 2).

In some embodiments, R2 of subscaffold 2 is selected from a halogen (e.g., Cl, F, Br, I), alkyl (e.g., branched, straight chain (e.g., methyl), cycloalkyl, heteroalkyl, etc.), alkyl-substituted aryl, substituted alkyl (e.g., halo-substituted alkyl, alcohol, amino, etc.), alcohol (e.g. OH, methanol, ethanol, etc), SH, NH_2, etc.

In some embodiments, R3 of subscaffold 2 is selected from hydrogen, alkyl (C_1-C_5), haloalkyl (e.g. CF_3), alcohol (e.g., OH, methanol, ethanol, isopropanol, etc.), alkoxy (e.g. methoxy, ethoxy, etc), amine (e.g. –NH2), halogen (Cl, Br, F, I), methyl-sulfonyl-amine ($CH_2SO_2NH_2$), etc. (See, e.g., Table 2). In some embodiments, R3 can be present at more than 1 position of the phenyl ring.

In some embodiments, R3 of subscaffold 2 is present at the ortho or meta positions of the benzene ring. In some embodiments, R3 groups are present at two or more positions on the benzene.

In some embodiments, Z of subscaffold 2 comprises an H, alkyl group, amino group (e.g., primary, secondary, alkylamine, aminoalkyl, etc.), halogen, heterocycle, sulfone-cotaining group (see e.g., Table 2), $CHR^4SO_2R^5$ or $NR^4SO_2R^5$ in which R4 and R5 are independently selected from an alkyl (e.g., branched, straight chain (e.g., methyl), cycloalkyl, heteroalkyl, etc.), substituted or non-substituted heterocycle comprising one or more N, C, O or S, thrihaloalkane, amino, alcohol, alkyl-substituted aryl, substituted or non-substituted heterocyclic ring, substituted alkyl (e.g., halo-substituted alkyl, alcohol, amino, cyano, aryl, heterocyclic ring, etc.), cyano, etc.

In some embodiments, R3 and Z groups (e.g., $(CH)_2NH$ in compound 81) bridge two positions of the benzene ring of subscaffold 2.

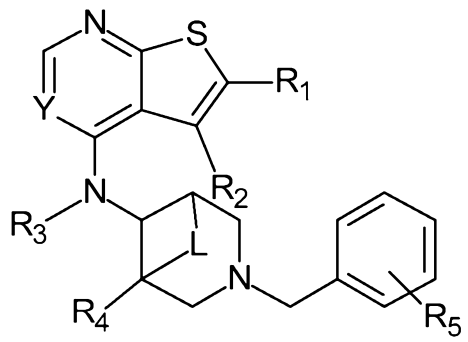
In some embodiments, L of subscaffold 2 is alkylene (e.g. ethylene, $-CH_2-CH_2-$, etc) or oxalkylene (e.g. –O-, $-CH_2-O-CH_2$) groups.

In some embodiments, Q of subscaffold 2 is alkylene (e.g. C1-C5) or oxyalkylene (e.g. $-CH_2-O-CH_2-$).

In some embodiments, compositions comprising one or more of compound 43-104 and 284-287 of Table 2 are provided.

In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 3



wherein R1,R2, R3, and R4 independently comprise or consist of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., mono-, di-, tetra-,penta- and trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g., ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof; wherein R5 comprises or consists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propanol, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy

group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), amide, alkylamide, a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acycloikylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof. In some embodiments, R5 is present at the ortho, meta, or para position of the benzene ring of subscaffold 3. In some embodiments, the benzene ring of subscaffold 3 comprises R5 groups at two or more (e.g., 2, 3, 4, or 5) positions. In some embodiments, an R5 group bridges two positions of the benzene ring of subscaffold 3 (See e.g., 3-keto,4-amino-propane of compound 136 of Table 3); and wherein Y is N or C, and wherein when Y is C the Y position may be substituted with R^6, with R^6 consisting of or comprising an alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)), trihaloisopropyl (e.g.,trifluoroisopropyl , 1-fluoro,2-trifluoro,ethane , 1-trifluoro,2-ethanol , alcohol (e.g., $(CH_2)_nOH$, wherein n=0-10), alkoxy (e.g., $(CH_2)_n$-OR, wherein n=0-10, wherein R is alkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-aromatic, $(CH_2)_n$-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle with one or more N, S, O, etc.), amino (e.g., alkyl amine, amino alkyl,

etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.; and wherein L is present or absent and comprises alkylene (e.g. methylene, -CH_2-, ethylene, -CH_2-CH_2-, propylene, -CH_2-CH_2-CH_2-, etc) or oxalkylene (e.g. –O-, -CH_2-O-CH_2) groups.

In some embodiments, R1 of subscaffold 3 comprises or consists of trifluoroethane. In some embodiments, R1 of subscaffold 3 comprises or consists of trihaloethane (e.g., trifluoroethane), 2-dihalo-4-butanol (e.g., 2-difluoro-4-butanol, etc.), an alkyl chain (e.g., straight chain alkyl (e.g., methane, ethane, propane, butane, etc.), branched alkyl, cycloalkyl, or combinations thereof), 2-dihalo-propane (e.g., 2-difluoro-propane, etc.), etc. (See Table 3).

In some embodiments, R2 of subscaffold 3 is selected from a halogen (e.g., Cl, F, Br, I), alkyl (e.g., branched, straight chain (e.g., methyl), cycloalkyl, heteroalkyl, etc.), alkyl-substituted aryl, substituted alkyl (e.g., halo-substituted alkyl, alcohol, amino, etc.), alcohol (-OH, -CH_2OH, etc) SH, NH_2, etc.

In some embodiments, R3 of subscaffold 3 consists of H. In some embodiments, R3 of subscaffold 3 comprises or consists of an alkyl (e.g., methane, ethane, propane, butane, etc.), amine (e.g., NH_2, NH-alkyl (e.g., NH-methyl, NH-ethyl, NH-CH_2-Ph, etc.), NH-alcohol (e.g., NH-CH_2-CH_2-OH), etc.), alcohol (e.g., methanol, ethanol, butanol, propanol, -CH_2-$CHOHCH_2OH$, etc.), halo-substituted alkyl, combinations thereof, etc. (See Table 3). In some embodiments, R3 is fused in a ring with R2 (See, e.g. compound 158).

In some emobodiments, R4 of subscaffold 3 comprises or consists of an amine (e.g., NH_2, alkylamine (e.g., methylamine, ethylamine, propylamine, etc.), aminoalkyl (e.g., straight chain alkyl, cycloalkyl, or combinations thereof (See, e.g., compound 171)), amino-alkyl-phenyl (e.g., amino-methyl-phenyl, amino-ethyl-phenyl, etc.), etc.), alcohol (e.g., OH, methanol, ethanol, propanol, isopropanol, etc.), substituted amine (-NHR^3) or substituted alcohol (–OR^3), in which R^3 is alkyl, alkyl-aryl (substituted and non-substituted), alkyl-cycloalkyl (substituted and non-substituted), alkyl-aromatic ring substituted or non-substituted, akyl-non aromatic ring (C,N,O,S) substituted or non-substituted, or any of the R4 groups depicted in Tables 4, 5, or 7. In some embodiments, R4 comprises or cosists of aminomethyl phenyl (See, e.g. compound 167), aminoethyl phenyl (See, e.g., compound 168), amino-methyl-cyclopentane (See, e.g., compound 169), aminomethyl, n-methanal pyrrolidine, aminoethyl cyclopentane, aminomethyl ($NHCH_3$), methylamine (CH_2NH_2), n-sulfonyl-methyl pyrrolidine (See, e.g., compound 173), O-methyl phenyl (See, e.g. compound 174), etc., see Table 4.

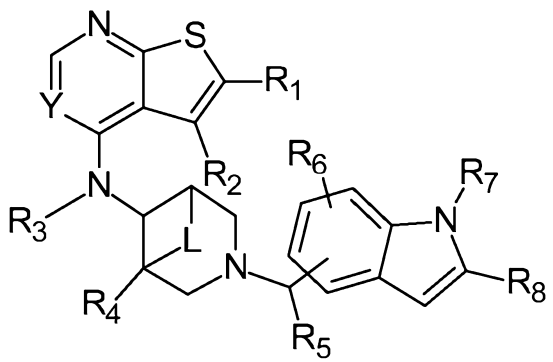
In some embodiments, R5 of subscaffold 3 comprises or consists of: H, an alcohol (e.g., OH, methanol, ethanol, etc.), alkane, cycloalkane (e.g., substituted cycloalkane (e.g., cyanocyclopropane)), amine, halogen (e.g., chlorine, fluorine, bromine, iodine, etc.), heterocyclic ring (e.g., attached at any position on the heterocyclic ring: morpholine, piperidine, methylpiperidine, pyrrole, thiophene, piperazine, etc.), alkylamine (e.g., methylamine, ethylamine, propylamine, 1,4-dimethyl-piperazine, etc.), alkylalkohol (e.g. $-CH_2OH$), alkoxy, carboxamido, O-dihalomethane, sulfonyl-amine, trihalomethane (e.g., trifluoromethane), etc. In some embodiments, the benzene ring of subscaffold 3 comprises R5 groups at two or more (e.g., 2, 3, 4, or 5) positions.

In some embodiments, L of subscaffold 3 is alkylene (e.g. ethylene, $-CH_2-CH_2-$, compound 135) or oxalkylene (e.g. –O-, $-CH_2-O-CH_2$) groups.

In some embodiments, compositions comprising one or more of compound 105-159 of Table 3, 165-174 of Table 4 and 280 and 282 of Table 7 are provided.

In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 4



;

wherein R1, R2, R3, R4, R5, R6, R7, R8 each independently comprise or consist of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propyl, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), amine,

alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, an amide, an alkylamide, a cyano group, methyl carbonitrile (e.g. CH_2CN), $-SO_2CH_3$ group, sulfonyl group, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a substituted or non-substituted heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof; and

wherein any of the H atoms, R6, R7 and R8 on the indole of subscaffold 4 may be replaced with one of: halogen (e.g., F, Cl, Br, I, etc.), alcohol (e.g., OH, methanol, ethanol, etc.), alkyl (C1-C5), alkoxy (e.g. methoxy, ethoxy, etc), amine (e.g. NH_2, methylamine, ethylamine, etc), cyano group (e.g., CN, methyl carbonitrile, ethyl carbonitrile, etc.), an amide (e.g. $CONH_2$, acetamide, etc), $-SO_2CH_3$ group; wherein R6 can be present on either the benzyl and/or pyrole portion of the indole ring , and wherein R6 can be present at one or more of the positions of the benzyl and/or pyrole portion of the indole ring that are not otherwise occupied by a substituent; and wherein Y is N or C, and wherein when Y is C the Y position may be substituted with R^a, with R^a consisting of or comprising an alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)),

trihaloisopropyl (e.g.,trifluoroisopropyl , 1-fluoro,2-trifluoro,ethane , 1-trifluoro,2-ethanol), alcohol (e.g., $(CH_2)_nOH$, wherein n=0-10), alkoxy (e.g., $(CH_2)_n$-OR, wherein n=0-10, wherein R is alkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-aromatic, $(CH_2)_n$-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle with one or more N, S, O, etc.), amino (e.g., alkyl amine, amino alkyl, etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.;

wherein L is present or absent, and if present it comprises alkylene (e.g. methylene, $-CH_2-$, ethylene, $-CH_2-CH_2-$, propylene, $-CH_2-CH_2-CH_2-$, etc) or oxalkylene (e.g. –O-, $-CH_2-O-CH_2$) groups.

In some embodiments, R1 of subscaffold 4 comprises or consists of monohaloethane, dihaloethane or trihaloethane (e.g., monofluorothane, difluoroethane and trifluoroethane) group, (see Table 5).

In some emobodiments R2 is H or another R2 substituent described herein.

In some embodiments R3 of subscaffold 4 comprises or consists of an alkyl (e.g., methane, ethane, propane, butane, etc.), amine (e.g., NH_2, NH-alkyl (e.g., NH-methyl, NH-ethyl, $NH-CH_2-Ph$, etc.), NH-alcohol (e.g., $NH-CH_2-CH_2-OH$), etc.), an alcohol (e.g., methanol, ethanol, butanol, propanol, $CH_2CHOHCH_2OH$, etc.), a heterocyclic ring, an alkyl-heterocyclic ring (e.g., ethyl-morpholine (see compound 238), propyl-indole, etc.), etc.. In some embodiments, R3 is fused in a ring with R2 (See, e.g. compound 158).

In some emobodiments R4 comprises or consists of amine (e.g. $-NH_2$), $NH-(CH_2)_{1-6}$-phenyl (see compound 288), $NH-(CH_2)_{1-6}$-(substituted aromatic ring) (see compound 289), aminomethyl, aminoakyl N-formylpyrrolidine (see compound 161 in Table 5), aminoakyl N-sulfonylpyrrolidine (see compound 173 in Table 5), $-CH_2-OH$ (see compounds 163-164 in Table 5).

In some emobodiments, R5 is $-CH_2-OH$ (see compound 211, Table 5).

In some embodiments, R6 is an alkyl (e.g., methane, ethane, propane, butane, etc.), cycloalkane (e.g., cyclopropane (See, e.g., compound 293) , cyclobutane, cyclopentane, cyclohexane, etc.), halogen (e.g., Br, F, Cl, I, etc.), haloalkane (e.g., monohaloalkane, dihaloalkane (e.g., difluoromethane (See, e.g., compound 305)), trihaloalkane (e.g., trichloroethane)), amine (e.g., NH_2, NH-alkyl (e.g., NH-methyl, NH-ethyl, $NH-CH_2-Ph$, etc.) alkyl-amine (e.g., $(CH_2)_{1-6}-NH_2$)), O-alkyl (e.g., OCH_3, OCH_2CH_3, etc.), NH-alcohol (e.g., $NH-CH_2-CH_2-OH$), etc.), an alcohol (e.g., methanol, ethanol, butanol, propanol, $CH_2CHOHCH_2OH$,

etc.), or any R6 group of Tables 4, 5, or 7. In some embodiments, R6 is present on either the benzyl and/or pyrrole portions of the indole ring. In some embodiments R6 on indole ring is present at more than one position on the benzyl and/or pyrrole portions of the indole ring.

In some embodiments, R7 is H, alkyl (e.g., methyl, ethyl, propyl, butyl, etc.), haloalkane, cycloalkyl (e.g., cyclopropane (e.g., methyl cyclopropane), cyclobutane, cyclopentane, cyclohexane, etc.), an alcohol (e.g., OH, methanol, ethanol, propanol, butanol, etc.), a substituted or non-substituted heterocycle (See, e.g., compound s 427 and 430), a substituted or non-substituted heteroaromatic ring (e.g., pyrazole, triazole (e.g., 1,2,4 triazole), isoxazole (e.g., dimethyl isoxazole), $(CH_2)_n$-OR (wherein n=1-10 and R is an aromatic ring, heteroaromatic ring, cycloalkyl, heterocycle, substituted ring, etc.), alkyl-heterocycle (e.g., $(CH_2)_{1-6}$-piperidine (See, e.g., compound 328), $(CH_2)_{1-6}$-piperazine (See, e.g., compound 336), $(CH_2)_{1-6}$-pyrazole (See, e.g., compounds 309, 324, 388)), $(CH_2)_n$-R (wherein n=1-10 and R is an aromatic ring, heteroaromatic ring, cycloalkyl, heterocycle, substituted ring, etc.), $(CH_2)_n$-O-$(CH_2)_m$-R (wherein n=1-10, m=1-10, and R is an aromatic ring, heteroaromatic ring, cycloalkyl, heterocycle, substituted ring, etc.), substituted or non-substituted alkyl-heteroaromatic ring (e.g. CH_2-thiadiazole (See, e.g., compound 322), CH_2-thiadiazole –CH_3, CH_2-thiazolidine (See, e.g., compound 323), CH_2-pyridine (See, e.g., compound 329), CH_2-pyrazole (See, e.g., compound 309), CH_2-triazole (See, e.g., compound 311), CH_2-oxazole (See, e.g., compounds 353, 361), CH_2-CH_2-triazole, ethyl-thiomorpholine (See, e.g., compound 360), etc), amide (e.g. acetamide, see, e,g, compound 189), alkyl-SO_2-alkyl (See, e.g., compounds 354, 395), amine (e.g., NH_2, NH-alkyl (e.g., NH-methyl, NH-ethyl, NH-CH_2-Ph, etc., NH-alcohol (e.g., NH-CH_2-CH_2-OH), etc.), $(CH_2)_{1-6}CONH_2$ (See, e.g., compound 310), substituted or non-substituted alcohol (e.g., methanol, ethanol, butanol, propanol, $CH_2CHOHCH_2OH$, etc.), $(CH_2)_{1-6}$-CO-halogen (See, e.g., compound 306), $(CH_2)_{1-6}$-CO-NH_2 (See, e.g., compound 307), alkyl-diol (See, e.g., compounds 308, 338, 346, 348), diol-substituted alkyl or heteroalkyl chain with a terminal substitution (wherein the terminal substitution is selected from amide, cycloalkyl, heterocycle, aromatic ring, heteroaromatic ring, any of which may be further substituted (See, e.g., compounds 333, 338, 346, 348, 413 and 427-430)), or any R7 substituents in the compounds of Tables 4, 5, or 7 (See, e.g., compounds 312-320, 330, 331, 333, 334, 337, 339-345, 350-351, 355-359, 362-365, 367-379, 394, 396-406).

In some embodiments, R8 of subscaffold 4 comprises or consists of: H, alkyl (e.g., methyl, ethyl, propyl, butyl, etc.), cycloalkyl (e.g., cyclopropane (e.g., methyl cyclopropane),

cyclobutane, cyclopentane, cyclohexane, etc.), a primary alcohol (e.g., OH, methanol, ethanol, propanol, butanol, etc.), a secondary alcohol, a substituted or non-substituted heteroaromatic ring (e.g., pyrazole, triazole (e.g., 1,2,4 triazole, 1,2,3 triazole (e.g., alkyl-substituted triazole (See, e.g., compound 303))), isoxazole, isopropylisopropanolamine ($CH_2CHOHCH_2NHCH(CH_3)_2$); sulfonamide, a cyano group (e.g., CN, methyl carbonitrile, ethyl carbonitrile, propyl carbonitrile, etc.), amide (e.g., $CONH_2$, methylcarboxamido (e.g., CH_2CONH_2, $CH_2CONH\text{-}C_{1\text{-}6}$ (See compound 291)), ethyl carboxamido ($CH_2CH_2CONH_2$), carboxyamido-methane (e.g., $CONHCH_3$ or $NHCOCH_3$), etc.), $CH_2CHOHCH_2OH$ (See, e.g., compound 300), methylsulfonyl, sulfonamide, ketone (e.g., =O), or any R8 substituents in the compounds of Tables 4, 5, or 7 (See e.g., compounds 292, 297, etc.).

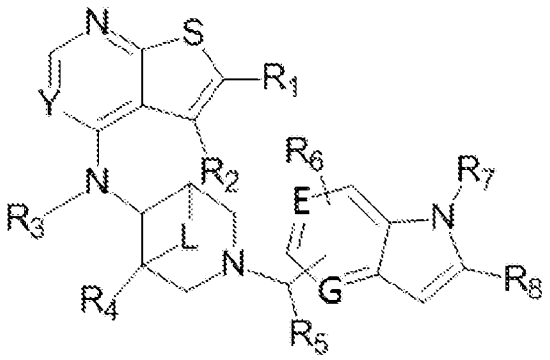
In some embodiments, the substituted indole ring of subscaffold 4 is: cyano substituted (e.g., 1- carbonitrile, 2- carbonitrile, etc.), methyl-carbonitrile substituted (e.g., 5-methyl-carbonitrile, etc.), methylcyclopropane substituted (e.g., 1- methylcyclopropane), halo-substituted (e.g., 3-halo (e.g., 3-fluoro, 4-fluoro, 6-fluoro, etc.)), alkyl substituted (e.g., 1-alkyl (e.g., 1-methyl, 1-ethyl, 1-propyl, etc.)), alcohol-substituted (e.g., OH substituted (e.g., 6-OH), methanol substituted (e.g., 1-methanol), ethanol substituted (e.g., 1-ethanol), etc.), O-methyl substituted (e.g., 4-O-methyl, 6-O-methyl, etc.), alkoxy substituted (e.g. 1-O-methoxy, 1-O-ethoxy, etc), heterocyclic aromatic ring (or ring system) substituted (e.g., imidazole), amine substituted (e.g., NH_2, methylamine, ethylamine (e.g., 1-ethylamine, etc.), aminomethyl, etc.), dihydroxy substituted (e.g., 1,2-propanediol, etc.), amide substituted (e.g., 1-propanamide), acetamide, 1-methyl 1,2,3-triazole substituted, 1-ethyl imidazole substituted, heterocycle substituted, carboxamido substituted (e.g., 1-carboxamido), sulfonyl substituted (e.g., 1-sulfonyl methyl (SO_2CH_3), ether substituted (e.g., isopropanol methyl ether ($CH_2CHOHCH_2CH_3$), keto-substituted (e.g., 1-keto), isopropanol-amine-isopropyl substituted ($CH_2CHOHCH_2NHCH(CH_3)_2$, combinations thereof depicted in Table 4, or combinations thereof not depicted in Table 4).

In some embodiments, L is H.

In some embodiments, compositions comprising one or more of compound 160-164, 290-417, 423-430 (Table 4) and 175-252 of Table 5 and compounds 278, 279, 281 of Table 7 are provided.

In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 4b



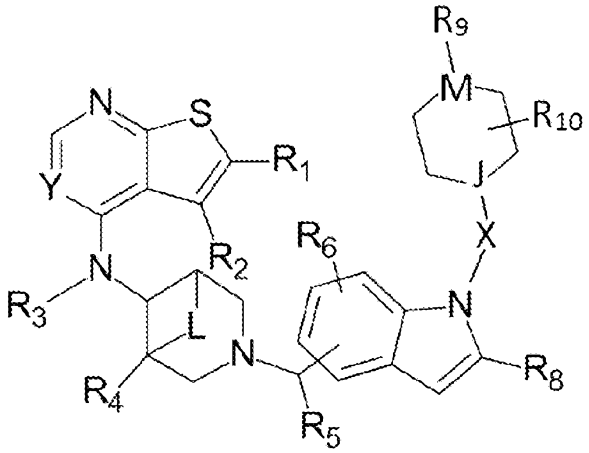
;

wherein R1, R2, R3, R4, R5, R6, R7, R8, L, Y, and any substituents thereof each independently comprise or consist of any of the groups and substituents provided above for subscaffold 4; and wherein E and G are independently N or C, wherein E and G are independently and optionally substituted with a R6.

In some embodiments, compositions comprising one or more of compound 380 and/or 422, are provided. In some embodiments, subscaffold 4b is modified with any of the substituents described or depicted for subscaffold 4.

In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 4c



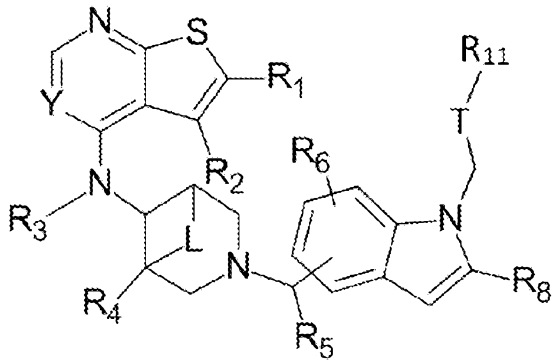
wherein R1, R2, R3, R4, R5, R6, R7, R8, L, Y, and any substituents thereof each independently comprise or consist of any of the groups and substituents provided above for subscaffold 4; wherein X is $(CH_2)_{0-6}$; and wherein J and M are independently N, O, S, or C; wherein R9

comprises or consists of: H, alkyl (e.g., methyl, ethyl, propyl, isopropyl, etc.), CO-alkyl (formyl, acetyl, propanoyl, etc.), CO-alkenyl (e.g., CO-ethenyl, CO-propenyl), CO-alkynyl (e.g., CO-ethynyl, CO-propynyl), CO-$(CH_2)_{1-6}$-aryl, CO-$(CH_2)_{1-6}$-heteroaryl, CO-$(CH_2)_{1-3}$-trifluoromethane, CO-$(CH_2)_{1-6}$-cycloalkane, alcohol (e.g., OH, methanol, ethanol, propanol, etc.), $CONH_2$, $CO(CH_2)_{1-6}$, O_2 (See, e.g., compound 368), SO_2NH_2, SO_2-amino-dialkyl (See, e.g., compound 375), SO_2-NH-alkyl (See, e.g., compound 405),CO-amino-dialkyl (See, e.g., compound 376), SO_2-$(CH_2)_{1-6}$ (See, e.g., compound 377), SO_2- alkenyl (e.g., SO_2-ethenyl, SO_2-propenyl), SO_2-alkynyl (e.g., SO_2-ethynyl, SO_2-propynyl), CO-$(CH_2)_{1-6}$, or other sutiable substituents described herein; and wherein R10 comprises or consists of: H, alkyl (e.g., methyl, ethyl, propyl, etc.), =O, trifluoromethane, alcohol (e.g., OH, methanol, ethanol, propanol, etc.), or other sutiable substituents described herein.

In some embodiments, compositions comprising one or more of compounds: 336, 337, 339-344, 355-358, 360, 364, 366-370, 372, 375-378, 393, 394, 396-406, 426 and/or 428-429 are provided. In some embodiments, subscaffold 4c is modified with any of the substituents described or depicted for subscaffold 4.

In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 4d



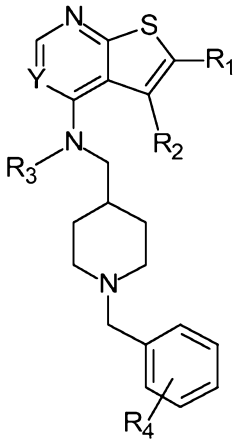
wherein R1, R2, R3, R4, R5, R6, R7, R8, L, Y, and any substituents thereof each independently comprise or consist of any of the groups and substituents provided above for subscaffold 4; wherein T is a heteroaromatic ring or cycloalkane; and wherein R11 comprises or consists of: H, alkyl (e.g., methyl, ethyl, propyl, isopropyl, etc.), alcohol (e.g., OH, methanol, ethanol, propanol, etc.), O-alkyl, O-$(CH_2)_{1-3}$-cycloalkane (See, e.g., compound 312), $(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-O-alkyl (See, e.g., compound 313), $(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-cycloalkane (See, e.g., compound 318), (CH2)1-

3-heteroaromatic (See, e.g., compounds 345 or 347), or any other suitable substituents described herein.

In some embodiments, T is a: 5-membered ring comprising carbon atoms and one or more of N, S, and/or O (e.g., pyrrole, furan, thiophene imidazole, pyrazole, oxazole, isoxazole, thizole, isothiazole, triazoles, furazan, oxadiazole, thiadiazole, dithiazole, tetrazole, etc.); 6-membered ring comprising carbon atoms and one or more of N, S, and/or O (e.g., pyridine, pyran, thiopyran, diazines, oxazine, thiazine, dioxine, dithiine, triazine, tetrazine, etc.); or a cyclopropane, cyclobutane, cyclopentane, or cyclohexane; and wherein R11 extends from any suitable position on the T ring.

In some embodiments, compositions comprising one or more of compounds: 303, 304, 312, 313, 318, 322, 323, 327, 331, 332, 334, 335, 345, 347, 349-353, 361, 365, 379, 381, 382, and 388-392 are provided. In some embodiments, subscaffold 4d is modified with any of the substituents described or depicted for subscaffold 4. In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 5



wherein R1, R2, R3 and R4 independently comprise or consist of: H,

alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane),

trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thioIkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acycloIkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof; and

wherein any of the H atoms on the benzene ring of subscaffold 5 may be replaced with one of: halogen (e.g., F, Cl, Br, I, etc.), alcohol (e.g., OH, methanol, ethanol, etc.), cyano group (e.g., CN, methyl carbonitrile, ethyl carbonitrile, etc.), amine (e.g. NH_2, methylamine, ethylamine, etc.), trifluoromethane, alkyl (e.g., methane, ethane, propane, etc.), alkoxy (e.g. methoxy, ethoxy, etc), halogen substitited alkoxy (e.g. trifluoromethoxy), ketone, sulfonyl group (e.g. slufonamide), substituted or non-substituted heterocyclic ring (e.g. comprising carbon and one or more nitrogen oxygen and/or sulfur members), etc. ; and wherein Y is N or C, and wherein when Y is C the Y position may be substituted with R^9, with R^9 consisting of or comprising an alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)), trihaloisopropyl (e.g.,trifluoroisopropyl , 1-fluoro,2-trifluoro,ethane , 1-trifluoro,2-ethanol),

alcohol (e.g., $(CH_2)_nOH$, wherein n=0-10), alkoxy (e.g., $(CH_2)_n$-OR, wherein n=0-10, wherein R is alkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-aromatic, $(CH_2)_n$-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle with one or more N, S, O, etc.), amino (e.g., alkyl amine, amino alkyl, etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.;

In some embodiments, R1 of subscaffold 5 comprises or consists of: H, trifluoroethane, or another R1 group provided herein.

In some embodiments, R2 of subscaffold 5 comprises or consists of H.

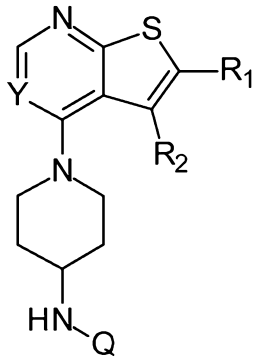
In some embodiments, R3 of subscaffold 5 comprises or consists of alkyl group (e.g. n-buthyl, compound 264).

In some embodiments, R4 of subscaffold 5 comprises or consists of: H, aminosulfonyl, halogen (e.g., Cl, Br, F, I, etc.), a substituted or non-substituted heterocycle (e.g., piperidine, 1,4-oxazinane, piperazine, morpholine), cyano group (e.g., CN, cyanomethane, cyanoethane, etc.), alkoxy (e.g. O-methyl), amine (e.g. NH_2, methylamine, ethylamine, etc.), alcohol (e.g., OH, methanol, ethanol, etc.), trifluoromethane, ketone (e.g. acetyl), halogen substitited alkoxy (e.g. O-trifluoromethane, OCF_3, alkyl (e.g., methane, ethane, propane, etc.), etc.

In some embodiments, compositions comprising one or more of compound 253-277 of Table 6 are provided.

In some embodiments, the thienopyrimidine class compound is of a general formula of:

Subscaffold 6



wherein Q, R1 and R2 comprises or consists of: H, an alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane,

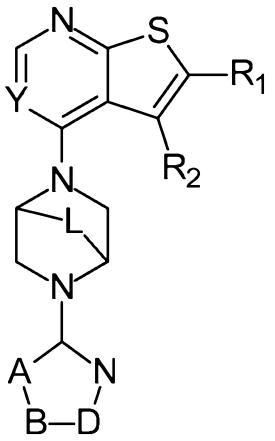
cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof; and wherein Y is N or C, and wherein when Y is C the Y position may be substituted with R^a, with R^a consisting of or comprising an H, alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)), trihaloisopropyl (e.g.,trifluoroisopropyl), 1-fluoro,2-trifluoro,ethane , 1-trifluoro,2-ethanol), alcohol (e.g., $(CH_2)_nOH$, wherein n=0-10), alkoxy (e.g., $(CH_2)_n$-OR, wherein n=0-10, wherein R is alkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-aromatic, $(CH_2)_n$-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle with one or more N, S, O, etc.), amino (e.g., alkyl amine, amino alkyl,

etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.; and wherein L is present or absent and comprises alkylene (e.g. methylene, -CH_2-, ethylene, -CH_2-CH_2-, etc) or oxalkylene (e.g. –O-, -CH_2-O-CH_2) groups.

In some embodiments, the present invention provides a composition comprising a compound having the structure of one or subscaffolds 1-6; wherein any of R1-R5, A, B, D, Q, L,W, X, Y, and Z each independently comprise organic substituents comprising fewer than 40 atoms selected from C, H, N, O, P, S, Cl, Br, F, and I. In some embodiments, the compound is selected from compounds 1-430. In some embodiments, R1 is CH_2CF_3.

In some embodiments, a compound of the present invention has a general structure of one of:

Subscaffold 1



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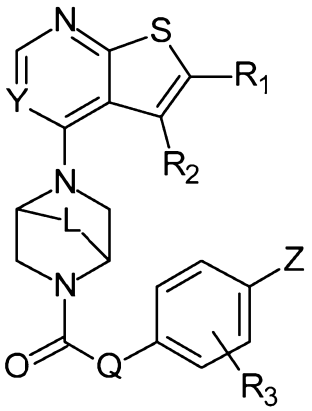
Subscaffold 2



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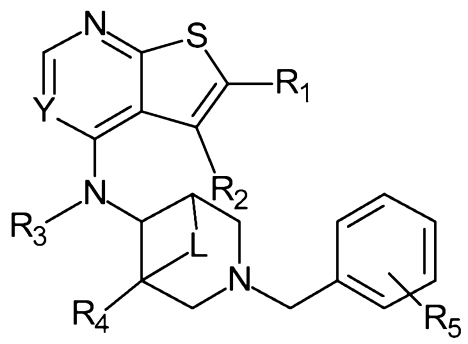
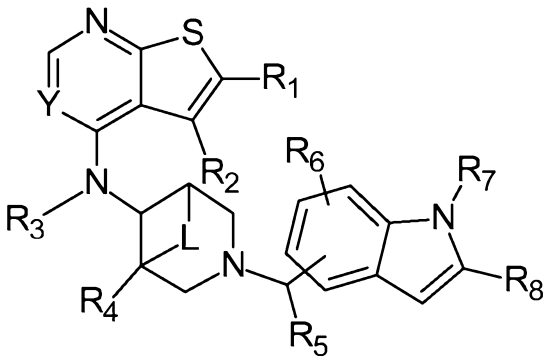
Subscaffold 3



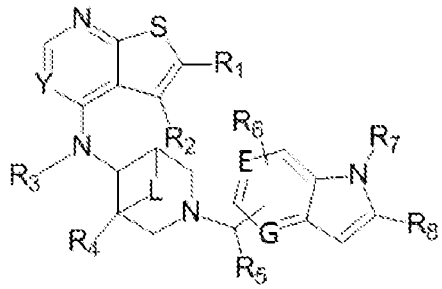
;

Subscaffold 4



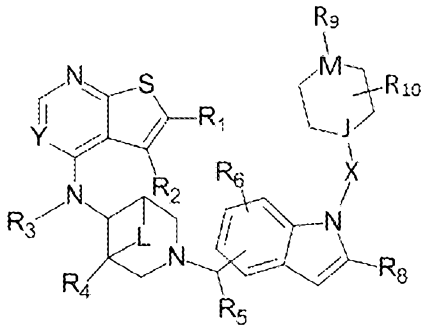
;

Subscaffold 4b



;

Subscaffold 4c



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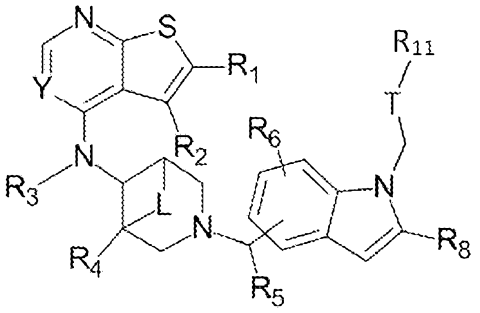
Subscaffold 4d



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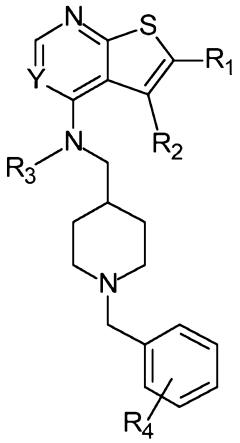
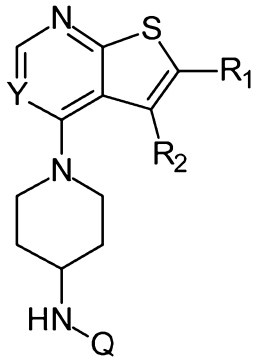
Subscaffold 5



; and

Subscaffold 6



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In some embodiments, all substituents (e.g., R1-R11, A, B, D, E, G, J, L, M, Q, T, X, Y, and Z) independently consist of or comprise any of the functional groups set forth herein, and in any suitable combination.

In some embodiments, R1-R11, when present on a subscaffold, each independently comprise or consist of any sutiable combination of, for example: C_1-C_{10} alkanes (e.g.,straight, branched, or cyclic), halogens (e.g., Cl, Br, F, or I), OH groups (e.g., alkyl-OH), O-alkyl groups, NH_2 groups, N-dialkyl , NH-alkyl groups, CN groups, heteroalkyl groups, aromatic groups, heteroaromatic groups, a sulfone-containing group, (e.g., $CH_2SO_2CH_3$, $CH_2SO_2NH_2$, $NHSO_2CH_3$, $NCH_3SO_2CH_3$, $NHSO_2NHCH_3$, $NHSO_2CH_2CH_3$, $NHSO_2(CH_2)_2NH_2$, $NHSO_2N(CH_3)_2$, $NHSO_2(CH_2)_{1\text{-}5}CH_3$, and $NHSO_2(CH_2)_2NHCOCH_3$), S, O, or N atoms, and combinations thereof.

In some embodiments, R1-R11 are independently selected from any of the respective substituents described herein or depicted in any of Tables 1-8, in any combination. For example, in some embodiments, R1-R11, when present on a subscaffold, each independently comprise or consist of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., mono-, di-, tetra-,penta- and trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, alkyl-substituted cycloalkyl group, cycloalkoxy group, cyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring (e.g., heteroaryl), a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring (e.g., heteroaryl), a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents (e.g., substituted heteroaryl), or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof.

In some embodiments, A comprises or consists of: C, N, O, or S; wherein when A comprises O or S, there is no further substitution at that respective position; wherein when A comprises N or C that respective position is optionally substituted, wherein the substituent at that respective position comprises or consists of: alkyl group (e.g., straight-chain alkyl (e.g., methane,

ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor, a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring (e.g., heteroaryl) comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings (e.g., heteroaryl), cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof

In some embodiments, B comprises or consists of: C, N, O, or S; wherein when B comprises O or S, there is no further substitution at that respective position; wherein when B comprises N or C that respective position is optionally substituted, wherein the substituent at that respective position comprises or consists of: alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted

alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor, a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring (e.g., heteroaryl) comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings (e.g., heteroaryl), cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof

In some embodiments, D comprises or consists of: C, N, O, or S; wherein when D comprises O or S, there is no further substitution at that respective position; wherein D comprises N or C that respective position is optionally substituted, wherein the substituent at that respective position comprises or consists of: alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine,

dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thiolkyl, combinations thereof, etc.), a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor, a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring (e.g., heteroaryl) comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings (e.g., heteroaryl), cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof.

In some embodiments, E comprises or consists of: C or N, and is optionally substituted with any sutable R6 substituent described herein.

In some embodiments, G comprises or consists of: C or N, and is optionally substituted with any sutable R6 substituent described herein.

In some embodiments, J comprises or consists of: C, N, S, or O.

In some embodiments, L is present or absent, and when present comprises or consists of: wherein L is present or absent and comprises alkylene (e.g. methylene, -CH_2-, ethylene, -CH_2-CH_2-, etc) or oxalkylene (e.g. –O-, -CH_2-O-CH_2) groups.

In some embodiments, M comprises or consists of: C, N, S, or O.

In some embodiments, Q comprises or consists of: alkyl (C_{1-5}) or heteroalkyl with one or more N, O, or S atoms.

In some embodiments, T is a: 5-membered ring comprising carbon atoms and one or more of N, S, and/or O (e.g., pyrrole, furan, thiophene imidazole, pyrazole, oxazole, isoxazole, thizole, isothiazole, triazoles, furazan, oxadiazole, thiadiazole, dithiazole, tetrazole, etc.); 6-membered ring comprising carbon atoms and one or more of N, S, and/or O (e.g., pyridine, pyran, thiopyran, diazines, oxazine, thiazine, dioxine, dithiine, triazine, tetrazine, etc.); or a

cyclopropane, cyclobutane, cyclopentane, or cyclohexane. In some embodiments, any suitable R1 substitutent extends from any suitable position on the T ring.

In some embodiments, X is any suitable connector, for example an alkyl chain (e.g., $(CH_2)_{1-3}$), but may comprise other linear connectors, for example also comprising S, O, or N.

In some embodiments, Y comprises or consists of: O, S, N or C, and wherein when Y is N or C the Y position may be substituted with R^a, with R^a consisting of or comprising an alkyl (e.g., branched (e.g., isopropyl), straight chain (e.g., propyl), cycloalkyl (e.g., cyclopropyl)), heteroalkyl (e.g., methyl propyl ether), alkyl-substituted aryl (e.g., ethylbenzene), substituted alkyl (e.g., halo-substituted alkyl (e.g., trihalomethyl group (e.g., trifluoromethyl group), monohaloalkyl group (e.g. monofluoroethyl group), dihaloalkyl group (e.g. difluoroethyl group), trihaloethyl group (e.g., trifluoroethyl group), trihalopropyl (e.g., trifluoropropyl ($(CH_2)_2CF_3$), trihalobutyl group (e.g., trifluorobutyl group ($(CH_2)_3CF_3$)), trihaloisopropyl (e.g.,trifluoroisopropyl (See, e.g., compound 38)), 1-fluoro,2-trifluoro,ethane (See, e.g., compound 21), 1-trifluoro,2-ethanol (See, e.g., compound 23)), alcohol (e.g., $(CH_2)_nOH$, wherein n=0-10), alkoxy (e.g., $(CH_2)_n$-OR, wherein n=0-10, wherein R is alkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-aromatic, $(CH_2)_n$-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle with one or more N, S, O, etc.), amino (e.g., alkyl amine, amino alkyl, etc.), cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, combinations thereof, etc.; and wherein L is present or absent and comprises alkylene (e.g. methylene, -CH_2-, ethylene, -CH_2-CH_2-, propylene, -CH_2-CH_2-CH_2-, etc) or oxalkylene (e.g. –O-, -CH_2-O-CH_2) groups.

In some embodiments, Z comprises or consists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thioalkyl, a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group,

cycloalkoxy group, acyclolkylamine, etc.), a halogen (e.g., F, Cl, Br, I, and At), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, a hydrogen bond donor or a hydrogen bond acceptor, a sulfur-containing group (e.g., thiol, sulfide, disulfide, sulfoxide, sulfone), a group selected from $CHR^4SO_2R^5$ or $NR^4SO_2R^5$, in which R^4 comprises or cosists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), alkylnitrile group (e.g. ethanenitryle group, CH_2CN), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), a carbocyclic ring, a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, alkyl-substituted cycloalkyl group, cycloalkoxy group, cyclolkylamine, etc.) and R^5 comprises or consists of: H, alkyl group (e.g., straight-chain alkyl (e.g., methane, ethane, propane, butane, pentane, hexane, etc.), branched alkyl group (e.g., iso-propane, 2-methyl-hexane, 3-methyl,2-propyl-octane, etc.), cycloalkyl (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, etc.), branched cyclic alkyl (e.g., methylcyclohexane, ethylcyclobutane, propylcyclohexane, etc.)), a substituted alkyl group (e.g., halogen-substituted alkyl group (e.g., trihaloethane (e.g., trifluoroethane), halomethane (e.g., fluoromethane), dihalomethane (e.g., difluoromethane), trihalomethane (e.g., trifluoromethane), etc.), alkoxy group (e.g., ether, alcohol, etc.), alkylamine (e.g., primary amine (e.g., ethylamine,

iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, etc.), secondary amines (e.g., dimethylamine, methylethanolamine, diphenylamine, etc.), tertiary amine (e.g., trimethylamine, triphenylamine, etc.), thioalkyl, a substituted cycloalkyl group (e.g., halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, etc.), a ketone, a carbocyclic ring, an aromatic ring, a substituted aromatic ring (e.g., branched aromatic ring (e.g.,ethylbenzene, methyl benzene, etc.), halobenzene (e.g., chlorobenzene, fluorobenzene, etc.)), a heterocyclic aromatic ring (e.g., comprising one or more nitrogen, oxygen and/or sulfur members which may be non-substituted or substituted with alkyl, aryl, halogen, hydrogen bond donor or acceptor), a heterocyclic non-aromatic ring (e.g., comprising carbon and one or more nitrogen, oxygen and/or sulfur members), carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof, R^5 might also be a part of the 3-8 member aromatic or non-aromatic ring comparising C,N,O, or S.

In some embodiments, the present invention provides methods for the treatment of a disease or condition comprising: administering a thienopyrimidine or thienopyridine class compound to a subject suffering from said disease or condition. In some embodiments, the thienopyrimidine or thienopyridine class compounds comprise one of subscaffolds 1-6. In some embodiments, the thienopyrimidine or thienopyridine class compounds comprise one or compound 1-430. In some embodiments, the disease or condition comprises leukemia or a solid tumor cancer (e.g., breast cancer, prostate cancer, lung cancer, liver cancer, pancreatic cancer, glioblastoma and melanoma, etc.). In some embodiments, the leukemia comprises acute leukemias, chronic leukemias, lymphoblastic leukemias, lymphocytic leukemias, myeloid leukemias, myelogenous leukemias, Acute lymphoblastic leukemia (ALL), Chronic lymphocytic leukemia (CLL), Acute myelogenous leukemia (AML), Chronic myelogenous leukemia (CML), Hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), Large granular lymphocytic leukemia, MLL-positive leukemias, MLL-induced leukemias, MLL-rearranged leukemias, etc.

In some embodiments, the present invention provides methods of inhibiting the interaction of MLL (MLL1 and MLL2) or MLL fusion protein and menin comprising: (a)

providing: (i) a sample comprising MLL (or MLL fusion proteins) and menin; and (ii) a thienopyrimidine and thienopyridine class compounds; (b) administering said composition to said sample; and (c) inhibiting the interaction between said MLL and said menin, or said MLL fusion proteins and said menin. In some embodiments, the thienopyrimidine or thienopyridine class compound comprises one of subscaffolds 1-6. In some embodiments, the thienopyrimidine or thienopyridine class compound comprises one of compound 1-430.

The compositions may comprise combinations of any of the above compounds with one another or with other compounds of interest. Stereoisomers, salts, and derivates of the compounds are further contemplated.

In some embodiments, the present invention provides a method comprising administering a composition for the treatment of leukemia (e.g., which inhibits binding of one or more MLL fusion proteins to menin or MLL wild type to menin) to a subject suffering from leukemia. In some embodiments, the leukemia comprises AML or ALL. In some embodiments, the composition comprises a thienopyrimidine or thienopyridine class compound. In some embodiments, the composition comprises a compound of the general structure of one or subscaffolds 1, 2, 3, 4, 4b, 4c, 4d, 5, or 6. In some embodiments, the composition comprises one of compounds 1-430 and/or a derivative thereof.

In some embodiments, the present invention provides a method of screening compounds effective in treating leukemia comprising assaying one or more compounds for inhibition of the interaction between MLL (or MLL fusion protein) and menin. In some embodiments, the screening is performed in vitro. In some embodiments, the screening is performed in vivo. In some embodiments, the assaying comprises a fluorescence polarization assay. In some embodiments, the assaying comprises a time-resolved fluorescence resonance energy transfer assay. In some embodiments, the assaying comprises a nuclear magnetic resonance (NMR) methods. In some embodiments, the assaying comprises cellular assays and/or animal (e.g., mice) studies.

In some embodiments, the present invention provides a method of inhibiting the interaction of MLL and menin comprising: (a) providing: (i) a sample comprising MLL and menin and (ii) a composition configured to inhibit the interaction of MLL and menin, (b) administering the composition to the sample, (c) contacting MLL and/or menin with the composition, and (d) inhibiting the interaction between MLL and menin, and between MLL fusion proteins and menin. In some embodiments, the sample comprises cells from a subject

suffering from leukemia. In some embodiments, the subject is a human subject or a human patient. In some embodiments, the cells are within a subject suffering from leukemia. In some embodiments, the composition comprises a thienopyrimidine and thienopyridine class compound. In some embodiments, the present invention comprises any structural derivatives of Compounds 1-430.

In some embodiments, the present invention provides methods comprising the use of a composition and/or compound described herein (e.g., a derivative of one of Subscaffolds 1-6, one of compounds 1-430, etc.). In some embodiments, the present invention provides methods comprising the use of a composition and/or compound described herein (e.g., a derivative of one of Subscaffolds 1-6, one of compounds 1-430, etc.) for the treatment of leukemia.

In some embodiments, the present invention provides methods for the treatment of a disease or condition comprising: administering a composition described herein to a subject suffering from said disease or condition. In some embodiments, thedisease or condition comprises a leukemia, hematologic malignancies, solid tumor cancer, or diabetes. In some embodiments, the leukemia comprises AML, ALL, or Mixed Lineage Leukemia.

In some embodiments, the present invention provides methods for inhibiting the interaction of menin and one or more of MLL1, MLL2, a MLL fusion protein, and a MLL Patrial Tandem Duplication, comprising administering a composition described herein to the sample comprising MLL and menin.

In some embodiments, the present invention provides methods for treating disorder mediated by chromosomal rearrangement on chromosome 11q23, comprising administering to a subject in need thereof a therapeutically effective amount of a composition described herein.

In some embodiments, the present invention provides methods for treating a disorder mediated by menin interaction with another protein, comparsing administering to a subject in need thereof a therapeutically effective amount of a composition described herein.

BREIF DESCRIPTION OF THE DRAWINGS

Figure 1. Validation of direct binding of thienopyrimidine compounds to menin: a) X-ray structure of menin in complex with compound 1; b) Isothermal Titration Calorimetry (ITC) for binding of compound 1 to menin.

Figure 2. Co-Immunoprecipitation (co-IP) experiment performed in HEK293 cells transfected with MLL-AF9 demonstrating inhibition of the menin-MLL-AF9 interaction in human cells by thienopyrimidine compounds: 1, 108, 175.

Figure 3. Thienopyrimidine compounds selectively inhibit proliferation of MLL leukemia cells as shown in MTT cell viability assay performed for compounds 1 and 108 (72h incubation time) in MLL-AF9 transformed mouse bone marrow cells (BMC) and in E2H-HLF transformed BMC, which were used as a negative control cell line.

Figure 4. Thienopyrimidine compounds inhibit growth of MLL-AF9 transformed BMC as demonstrated in the growth curves experiments.

Figure 5. Growth curves experiments performed for compound 175 in MLL-AF9 transformed BMC and Hoxa9/Meis1 transformed BMC (negative control cell line), showing great selectivity of the compound towards MLL fusion protein transformed cells.

Figure 6. Growth curves experiments performed for compound 175 in MLL-AF6 and MLL-GAS7 transformed BMC.

Figure 7. Compound 108 reduces colony number (left) and changes morphology of colonies (right) as assessed in colony formation assay performed in MLL-AF9 BMC. Each round takes 7 days.

Figure 8. Menin-MLL inhibitors induce differentiation in MLL-AF9 BMC as assessed by change in expression level of CD11b differentiation marker (left) and change in cell morphology (right).

Figure 9. Differentiation induced in MLL-AF9 BMC upon treatment with Compound 175: A. Change in expression level of CD11b, B. Change in cell morphology.

Figure 10. Menin-MLL inhibitors downregulate expression of downstream targets of MLL fusion proteins: *Hoxa9* and *Meis1*. A. qRT-PCR performed in MLL-AF9 BMC for Compounds 1 and 108. B. qRT-PCR performed in MLL-AF9 BMC for Compound 175.

Figure 11. Menin-MLL inhibitors selectively inhibit growth of human MLL leukemia cell lines as shown by MTT cell viability assay performed for Compound 108 after 3 days of incubation in different human leukemia cell lines.

Figure 12. Thienopyrimidine compounds induce apoptosis (A) and cell cycle arrest (B) in human MLL leukemia cell lines (e.g. MV4;11 with MLL-AF4 translocation).

Figure 13. Thienopyrimidine compound 175 selectively inhibits growth of human MLL leukemia cell lines (A) and has a limited effect in non-MLL leukemia cell lines (B).

Figure 14. Thienopyrimidine compounds downregulate expression of downstream targets of MLL fusion proteins (*Hoxa9* and *Meis1*) in human MLL leukemia cell lines.

Figure 15. Thienopyrimidine compounds induce differentiation in human MLL leukemia cell lines: MV4;11 (A) and THP-1 (B).

Figure 16. Pharmacokinetic (PK) profile of compound 108 after oral (p.o.) and intravenous (i.v.) injections of the compound to mice.

Figure 17. MTD (Maximum Tolerated Dose) studies with compound 108 in mice after i.p. (intraperitoneal) injections of the compound.

Figure 18. *In vivo* efficacy studies with compound 108 in mice model of MLL-AF9 leukemia. Increase in survival of leukemic mice was observed after once daily i.p. injections of 75mg/kg dose.

Figure 19. PK profile in mice for compound 175 after i.p. and oral administration of the compound.

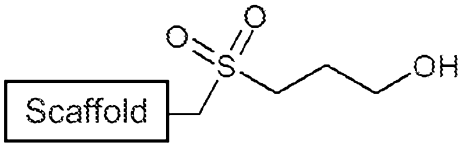
Figure 20. PK profile for Compound 219 after i.v. (15mg/kg) and oral (30mg/kg) administration of the compound.

Figure 21. *In vivo* efficacy experiment with Compound 219 in BALB/c mice injected subcutaneously with MV4;11 MLL leukemia cells. Compound administered once daily via i.p. at 25 mg/kg and 35 mg/kg doses.

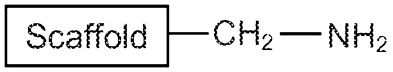
DEFINITIONS

The nomenclature used herein for referring to substituents is either IUPAC format or a modified format in which functional groups within a substituent are read in the order in which

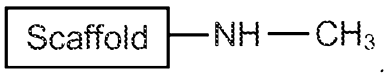
they branch from the scaffold or main structure. For example, in the modified nomenclature, methyl-sulfonyl-propanol refers to $CH_2SO_2CH_2CH_2CH_2OH$ or:



As another example, according to the modified nomenclature, a methyl-amine substituent is:



while an amino-methyl substituent is:



All chemical names of substituents should be interpreted in light of IUPAC and/or the modified nomenclature and with reference to the chemical structures depicted and/or described herein.

The term "system" refers a group of objects, compounds, methods, and/or devices that form a network for performing a desired objective.

As used herein a "sample" refers to anything capable of being subjected to the compositions and methods provided herein. The sample may be in vitro or in vivo. In some embodiments, samples are "mixture" samples, which samples from more than one subject or individual. In some embodiments, the methods provided herein comprise purifying or isolating the sample. In some embodiments, the sample is purified or unpurified protein. In some embodiments, a sample may be from a clinical or research setting. In some embodiments, a sample may comprise cells, fluids (e.g. blood, urine, cytoplasm, etc.), tissues, organs, lysed cells, whole organisms, etc. In some embodiments, a sample may be derived from a subject. In some embodiments, a sample may comprise one or more partial or whole subjects.

As used herein, the term "subject" refers to any animal including, but not limited to, humans, non-human primates, bovines, equines, felines, canines, pigs, rodents (e.g., mice), and the like. The terms "subject" and "patient" may be used interchangeably, wherein the term "patient" generally refers to a human subject seeking or receiving treatment or preventative measures from a clinician or health care provider.

As used herein, the terms "subject at risk for cancer" or "subject at risk for leukemia" refer to a subject with one or more risk factors for developing cancer and/or leukemia. Risk

factors include, but are not limited to, gender, age, genetic predisposition, environmental exposure, and previous incidents of cancer, preexisting non-cancer diseases, and lifestyle.

As used herein, the terms "characterizing cancer in subject" "characterizing leukemia in subject" refers to the identification of one or more properties of a cancer and/or leukemia sample in a subject, including but not limited to, the presence of benign, pre-cancerous or cancerous tissue or cells and the stage of the cancer (e.g., leukemia). Cancers (e.g., leukemia) may be characterized by identifying cancer cells with the compositions and methods of the present invention.

The terms "test compound" and "candidate compound" refer to any chemical entity, pharmaceutical, drug, and the like that is a candidate for use to treat or prevent a disease, illness, sickness, or disorder of bodily function (*e.g.*, cancer). Test compounds comprise both known and potential therapeutic compounds. A test compound can be determined to be therapeutic by screening using the screening methods of the present invention.

As used herein, the term "effective amount" refers to the amount of a compound (*e.g.*, a compound having a structure presented above or elsewhere described herein) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not limited to or intended to be limited to a particular formulation or administration route.

As used herein, the term "co-administration" refers to the administration of at least two agent(s) (*e.g.*, a compound having a structure presented above or elsewhere described herein) or therapies to a subject. In some embodiments, the co-administration of two or more agents/therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents/therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents/therapies are co-administered, the respective agents/therapies are administered at lower dosages than appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents/therapies lowers the requisite dosage of a known potentially harmful (*e.g.*, toxic) agent(s).

As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo*, *in vivo* or *ex vivo*.

As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants. (See *e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975]).

As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (*e.g.*, acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Examples of bases include, but are not limited to, alkali metals (*e.g.*, sodium) hydroxides, alkaline earth metals (*e.g.*, magnesium), hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like.

For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

As used herein, the term "instructions for administering said compound to a subject," and grammatical equivalents thereof, includes instructions for using the compositions contained in a kit for the treatment of conditions characterized by viral infection (*e.g.*, providing dosing, route of administration, decision trees for treating physicians for correlating patient-specific characteristics with therapeutic courses of action). The compounds of the present invention (e.g. as shown in structures above and elsewhere presented herein) can be packaged into a kit, which may include instructions for administering the compounds to a subject.

As used herein, the term "alkyl" refers to a moiety consisting of carbon and hydrogen containing no double or triple bonds. An alkyl may be linear, branched, cyclic, or a combination thereof, and may contain from one to fifty carbon atoms. Examples of alkyl groups include but are not limited to methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl isomers (e.g. n-butyl, iso-butyl, tert-butyl, etc.) cyclobutyl isomers (e.g. cyclobutyl, methylcyclopropyl, etc.), pentyl isomers, cyclopentane isomers, hexyl isomers, cyclohexane isomers, and the like. Unless specified otherwise (e.g., substituted alkyl group, heteroalkyl, alkoxy group, haloalkyl, alkylamine, thioalkyl, etc.), an alkyl group contains carbon and hydrogen atoms only.

As used herein, the term "linear alkyl" refers to a chain of carbon and hydrogen atoms (e.g., ethane, propane, butane, pentane, hexane, etc.). A linear alkyl group may be referred to by the designation $-(CH_2)_qCH_3$, where q is 0-49. The designation "C_{1-12} alkyl" or a similar designation, refers to alkyl having from 1 to 12 carbon atoms such as methyl, ethyl, propyl isomers (e.g. n-propyl, isopropyl, etc.), butyl isomers, cyclobutyl isomers (e.g. cyclobutyl, methylcyclopropyl, etc.), pentyl isomers, cyclopentyl isomers, hexyl isomers, cyclohexyl isomer, heptyl isomers, cycloheptyl isomers, octyl isomers, cyclooctyl isomers, nonyl isomers, cyclononyl isomers, decyl isomer, cyclodecyl isomers, etc. Similar designations refer to alkyl with a number of carbon atoms in a different range.

As used herein, the term "branched alkyl" refers to a chain of carbon and hydrogen atoms, without double or triple bonds, that contains a fork, branch, and/or split in the chain (e.g., 3,5-dimethyl-2-ethylhexane, 2-methyl-pentane, 1-methyl-cyclobutane, ortho-diethyl-cyclohexane, etc.). "Branching" refers to the divergence of a carbon chain, whereas

"substitution" refers to the presence of non-carbon/non-hydrogen atoms in a moiety. Unless specified otherwise (e.g., substituted branched alkyl group, branched heteroalkyl, branched alkoxy group, branched haloalkyl, branched alkylamine, branched thioalkyl, etc.), a branched alkyl group contains carbon and hydrogen atoms only.

As used herein, the term "cycloalkyl" refers to a completely saturated mono- or multi-cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. Cycloalkyl groups of the present application may range from three to ten carbons (C_3 to C_{10}). A cycloalkyl group may be unsubstituted, substituted, branched, and/or unbranched. Typical cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. If substituted, the substituent(s) may be an alkyl or selected from those indicated above with regard to substitution of an alkyl group unless otherwise indicated. Unless specified otherwise (e.g., substituted cycloalkyl group, heterocyclyl, cycloalkoxy group, halocycloalkyl, cycloalkylamine, thiocycloalkyl, etc.), an alkyl group contains carbon and hydrogen atoms only.

As used herein, the term "heteroalkyl" refers to an alkyl group, as defined herein, wherein one or more carbon atoms are independently replaced by one or more heteroatoms (e.g., oxygen, sulfur, nitrogen, phosphorus, silicon, or combinations thereof). The alkyl group containing the non-carbon substitution(s) may be a linear alkyl, branched alkyl, cycloalkyl (e.g., cycloheteroalkyl), or combinations thereof. Non-carbons may be at terminal locations (e.g., 2-hexanol) or integral to an alkyl group (e.g., diethyl ether).

As used herein, the term "substituted" (e.g., substituted alyklene) means that the referenced group (e.g., alkyl, aryl, etc.) comprises a substituent group (e.g., carbon/hydrogen-only substituent, heterosubstituent, halosubstituent, etc.). The term "optionally substituted", as used herein, means that the referenced group (e.g., alkyl, cycloalkyl, etc.) may or may not be substituted with one or more additional group(s). Substituent groups may be selected from, but are not limited to: alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, hydroxyl, alkoxy, mercaptyl, cyano, halo, carbonyl, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, perhaloalkyl, perfluoroalkyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Non-limiting examples of substituents include, halo, --CN, --OR, --C(O)R, -OC(O)R, --C(O)OR, OC(O)NHR, --$C(O)N(R)_2$, --SR--, --S(=O)R, --$S(=O)_2R$, --NHR, --$N(R)_2$, --NHC(O)--, NHC(O)O--, --C(O)NH--, $S(=O)_2NHR$, --$S(O)_2N(R)_2$, --$NHS(=O)_2$, --$NHS(O)_2R$, C^1-C^6alkyl, C^1-C^6alkoxy,

aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted C^1-C^6alkyl, halo-substituted C^1-C^6alkoxy, where each R is independently selected from H, halo, C^1-C^6alkyl, C^1-C^6alkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted C^1-C^6alkyl, halo-substituted C^1-C^6alkoxy.

As used herein, the term "substituted alkyl" refers to an alkyl group, as defined herein, displaying one or more non-carbon-atom-containing moieties (e.g., a group containing non-carbon atoms, possibly in addition to carbon atoms). The non-carbon-atom-containing moieties atoms may comprise: oxygen, sulfur, nitrogen, phosphorus, silicon, halogens (e.g. chlorine, bromine, flourine, iodine, etc.), or combinations thereof). The non-carbon-atom-containing moieties may also comprise carbon and hydrogen. The alkyl group containing the non-carbon substitution(s) may be a linear alkyl, branched alkyl, cycloalkyl (e.g., cycloheteroalkyl), or combinations thereof. Examples of substituted alky groups include: 2-hexanol, diethyl ether (also a heteroalkyl), 1-chloro-propane, etc.

As used herein, the terms "heteroaryl" or "heteroaromatic" refer to monocyclic, bicyclic, tricyclic, and other multicyclic ring systems (e.g., having four or greater ring members), wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms selected from nitrogen, oxygen and sulfur, and wherein each ring in the system contains 3 to 7 ring members. Unless otherwise defined herein, suitable substituents on the unsaturated carbon atom of a heteroaryl group are generally selected from halogen; --R, --OR, --SR, --NO_2, --CN, --$N(R)_2$, --NRC(O)R, --NRC(S)R, --$NRC(O)N(R)_2$, --$NRC(S)N(R)_2$, --$NRCO_2R$, --NRNRC(O)R, --NRNRC(O)$N(R)_2$, --$NRNRCO_2R$, --C(O)C(O)R, --$C(O)CH_2C(O)R$, --CO_2R, --C(S)R, --$C(O)N(R)_2$, --$C(S)N(R)_2$, --$OC(O)N(R)_2$, --OC(O)R, --C(O)N(OR)R, --C(NOR)R, --$S(O)_2R$, --$S(O)_3R$, --$SO_2N(R)_2$, --S(O)R, --$NRSO_2N(R)_2$, --$NRSO_2R$, --N(OR)R, --$C(=NH)$--$N(R)_2$, --$P(O)_2R$, --$PO(R)_2$, --$OPO(R)_2$, --$(CH_2)O_2NHC(O)R$, phenyl (Ph) optionally substituted with R, --O(Ph) optionally substituted with R, --$(CH_2)1$-2(Ph), optionally substituted with R, or --CH=CH(Ph), optionally substituted with R, wherein each independent occurrence of R is selected from hydrogen, optionally substituted C^1-C^6alkyl, optionally substituted C^1-C^6alkoxy, an unsubstituted 5-6 membered heteroaryl, phenyl, --O(Ph), or --CH_2(Ph), or two independent occurrences of R, on the same substituent or different substituents, taken together with the atom(s) to which each R is bound, to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Non-limiting examples of

heteroaryl groups, as used herein, include benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl, triazolyl and tetrazolyl. Any substituents depicted in structures or examples herein, should be viewed as suitable substituents for use in embodiments of the present invention.

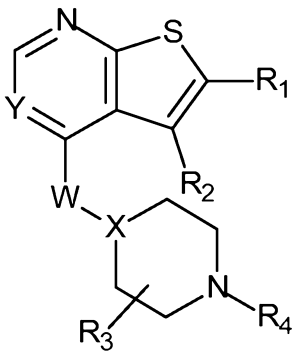
As used herein, the terms "heterocycloalkyl" of "heterocycle" refer to a cycloalkyl, as defined herein, wherein one or more of the ring carbons are replaced by a moiety selected from --O--, --N=, --NR--, --C(O)--, --S--, --S(O)-- or --$S(O)_2$--, wherein R is hydrogen, C^1-C^8alkyl or a nitrogen protecting group, with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-limiting examples of heterocycloalkyl groups, as used herein, include morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,4-dioxanyl, 1,4-dithianyl, thiomorpholinyl, azepanyl, hexahydro-1,4-diazepinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, thioxanyl, azetidinyl, oxetanyl, thietanyl, oxepanyl, thiepanyl, 1,2,3,6-tetrahydropyridinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[4.1.0]heptanyl.

DETAILED DESCRIPTION

The present invention provides thienopyrimidine and thienopyridine class compounds. In certain embodiments, thienopyrimidine compounds are provided for the treatment or prevention of one or more diseases or conditions (e.g., leukemia). Embodiments of the present invention directed towad the treatment and/or prevention of leukemia or recurrence thereof are described herein; however, it should be understood that the compositions and methods described herein are not limited to the leukemia application. Rather, in some embodiments, the compositions and methods described herein should be understood to also be useful for the treatment and/or

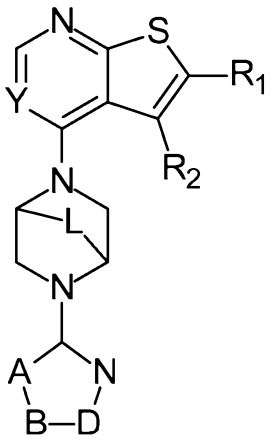
prevention of other cancers, including but not limited to breast, pancreastic, prostate, liver and colon cancers, glioblastoma, diabetes etc. The compounds provided herein are not limited to therapeutic uses; any additional uses for this class of compounds are also contemplated.

In some embodiments, thienopyrimidine and thienopyridine class compounds of the present invention comprise a general formula of:



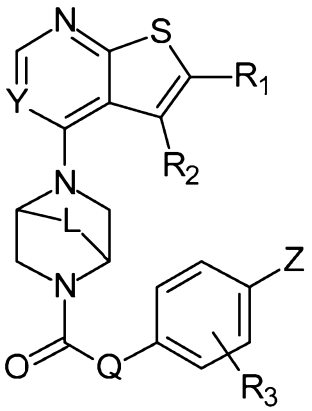
; wherein W, X, Y,and R1-R4 independently comprise any suitable substituents described herein, or otherwise understood to one of skill in the art. In some embodiments, a thienopyrimidine class compound of the present invention comprises a general formula of one of:

Subscaffold 1



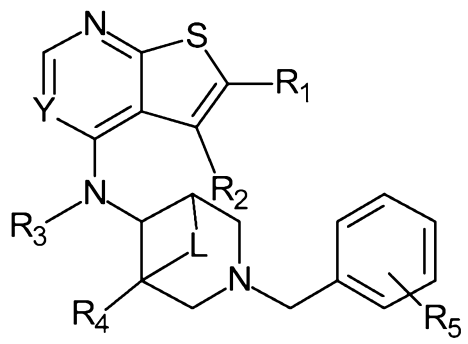
;

Subscaffold 2



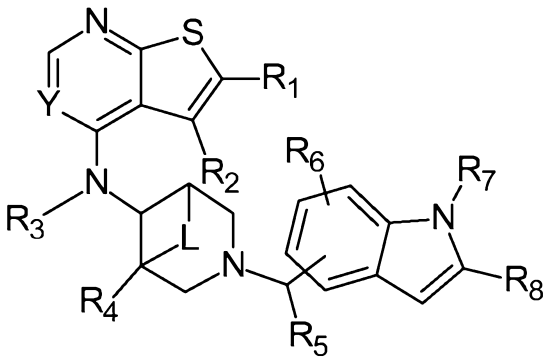
;

Subscaffold 3



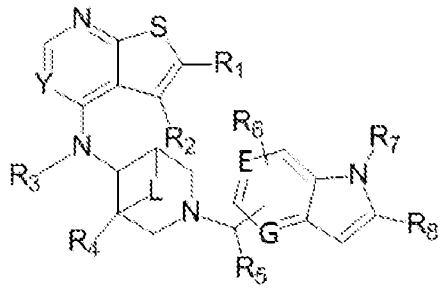
;

Subscaffold 4



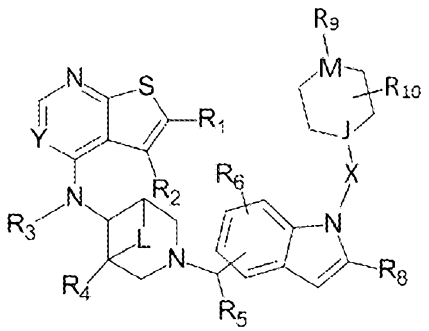
;

Subscaffold 4b



;

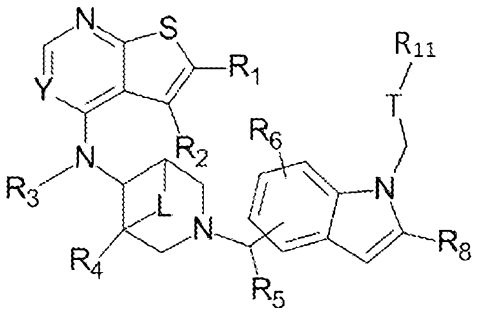
Subscaffold 4c

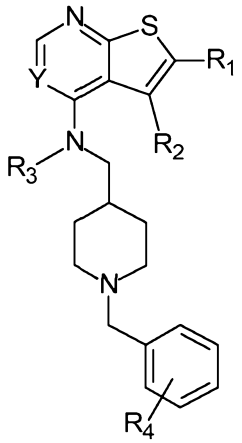


;

Subscaffold 4d

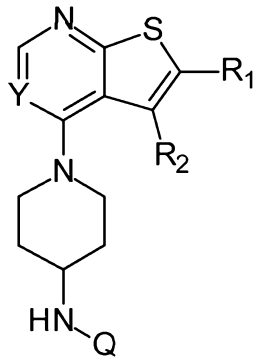
Subscaffold 5



; 

; and

Subscaffold 6



In some embodiments, the R1-R11, A, B, D, E, G, J, L, M, Q, T, X, Y, and Z of the above structures each independently comprise or consist of one or any combination of the following moieties:

Single atoms: H, Cl, Br, F, or I;

Alkanes (alkyl groups): methane (methyl), ethane (ethyl), propane (propyl), butane (butyl), pentane (pentyl), hexane (hexyl), or any suitable straight chain or branched C^1-C^{20} alkane;

Alkenes: methene, ethene, propene, butene, pentene, hexene, or any suitable C^7-C^{20} alkene;

Alkynes: methyne, ethyne, propyne, butyne, pentyne, hexyne, or any suitable C^7-C^{20} alkyne;

Cycloalkanes: cyclopropane, cyclobutane, cyclopentane, cyclohexane, or any suitable C^7-C^{20} cycloalkane;

Aromatic rings (e.g., carbon-only or heteroaromatics (e.g., heteroaryl)): furan, benzofuran, isobenzofuran, pyrrole, indole, isoindole, thiophene, benzothiophene, benzo[c]thiophene, imidazole, benzimidazole, purine, pyrazole, indazole, oxazole, benzooxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, benzene, napthalene, pyridine, quinolone, isoquinoline, pyrazine, quinoxaline, pyrimidine, quinazoline, pyridazine, cinnoline, phthalazine, triazine (e.g., 1,2,3-triazine; 1,2,4-triazine; 1,3,5 triazine), thiadiazole, etc.;

Haloalkanes: halomethane (e.g., chloromethane, bromomethane, fluoromethane, iodomethane), di-and trihalomethane (e.g., trichloromethane, tribromomethane, trifluoromethane, triiodomethane), 1-haloethane, 2-haloethane, 1,2-dihaloethane, 1-halopropane, 2-halopropane, 3-halopropane, 1,2-dihalopropane, 1,3-dihalopropane, 2,3-dihalopropane, 1,2,3-trihalopropane, and any other sutable combinations of alkanes (or substituted alkanes) an halogens (e.g., Cl, Br, F, I, etc.);

Alcohols: OH, methanol, ethanol, propanol, butanol, pentanol, hexanol, cyclic alcohols (e.g., cyclohexanol), aromatic alcohols (e.g., phenol), or any other suitable combination of an OH moiety with a second moiety;

Ketones: methyl methyl ketone (acetone), methyl ethyl ketone (butanone), propyl ethyl ketone (pentanone),), or any other suitable combination of alkyl chains with =O;

Aldehydes: methanal, ethanal, propanal, butanal, pentanal, hexanal, or any other suitable combination of alkyl chain with =O;

Carboxylates: methanoate, ethanoate, propanote, butanoate, pentanoate, hexanoate, or any other suitable combination of alkyl chain with OO^-;

Carboxylic acids: methanoic acid, ethanoic acid, propanoic acid, butanoic acid, pentanoic acid, hexanoic acid, or any other suitable combination of alkyl chain with OOH;

Ethers: methoxy, ethoxy, methylmethoxy, ethylmethoxy, or any other suitable combination of alkyl chains surrounding an O;

Amides: methanamide ($CONH_2$), ethanamide (CH_2CONH_2), propanamide ($(CH_2)_2CONH_2$), alkan^{n}amide ($(CH_2)_nCONH_2$), n-methyl alkan^{n}amide ($(CH_2)_nCONHCH_3$), c-methyl alkan^{n}amide ($(CH_2)_nNHCOCH_3$), n-alkyl alkan^{n}amide ($(CH_2)_nCONH(CH_2)_mCH_3$), c-methyl alkan^{n}amide ($(CH_2)_nNHCO(CH_2)_mCH_3$), etc.;

Primary amines: NH_2, methylamine, ethylamine, cyclopropylamine, etc.;

Secondary amines: aminomethyl ($NHCH_3$), aminoethyl ($NHCH_2CH_3$), methyl-aminomethyl (CH_2NHCH_3; aka methylamine-methane), alkyl^n-aminomethane ($(CH_2)_nNHCH_3$), etc.;

Tertiary amines: dimethylamine ($N(CH_3)_2$), dimethylamine ($N(CH_3)_2$), methyl-ethyl-amine ($NCH_3CH_2CH_3$), methane-diethylamine ($CH_2N(CH_2CH_3)_2$; aka methylamine-diethane), etc.;

Azides: methyl azide (CH_2NNN), ethyl azide ($(CH_2)_2NNN$), alkyl^n azide ($(CH_2)_nNNN$), etc.

Cyanates: methyl cyanate (CH_2OCN), ethyl cyanate ($(CH_2)_2OCN$), alkyl^n cyanate ($(CH_2)_nOCN$), etc.

Cyanos: cyano (-CN), methyl carbonitrile (CH_2CN), ethyl carbonitrile ($(CH_2)_2CN$), alkyl^n carbonitrile ($(CH_2)_nCN$), etc.

Thiols: methanethiol (CH_2SH), ethanethiol ($(CH_2)_2SH$), alkan^{n}ethiol ($(CH_2)_nSH$), etc.

Sulfides: dimethyl sulfide (CH_2SCH_3), methyl-ethyl sulfide ($CH_2SCH_2CH_3$), alkyl^n-alkyl^m sulfide ($(CH_2)_nS(CH_2)_{m-1}CH_3$), etc.;

Sulfoxides: dimethyl sulfoxide (CH_2SOCH_3), methyl-ethyl sulfoxide ($CH_2SOCH_2CH_3$), alkyl^n-alkyl^m sulfoxide ($(CH_2)_nSO(CH_2)_{m-1}CH_3$), etc.;

Sulfone: dimethyl sulfone ($CH_2SO_2CH_3$; aka methyl-sulfone-methyl), methyl-ethyl sulfone ($CH_2SO_2CH_2CH_3$; aka methyl-sulfone-ethyl), alkyl^n-alkyl^m sulfone ($(CH_2)_nSO_2$ $(CH_2)_{m-1}CH_3$; aka alkyl^n -sulfone- alkyl^m), $R^xSO_2R^y$ (wherein Rx and Ry are independently selected from any of the moieties provided in this list or combinations thereof), etc.;

Sulfinic acids: SO_2H, methyl sulfinic acid (CH_2SO_2H), ethyl sulfinic acid ($(CH_2)_2SO_2H$), alkyl^n sulfinic acid ($(CH_2)_nSO_2H$), etc.;

Thiocyanate: SCN, methyl thiocyanate (CH_2SCN), ethyl thiocyanate ($(CH_2)_2SCN$), alkyl^n thiocyanate ((CH_2)nSCN), etc.;

Phosphates: $OP(=O)(OH)_2$, methyl phosphate ($CH_2OP(=O)(OH)_2$), ethyl phosphate ($(CH_2)_2OP(=O)(OH)_2$), alkyl^n phosphate ($(CH_2)_nOP(=O)(OH)_2$), etc.

In various embodiments, the above listed moieties are attached at the X, Y, Z, A, B, D, and/or R positions in any suitable conformation. In some embodiments, the above listed functional groups are combined to produce the substituents depicted in compounds 1-430 of Tables 1-8.

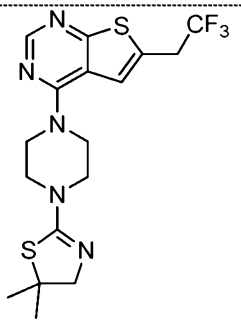
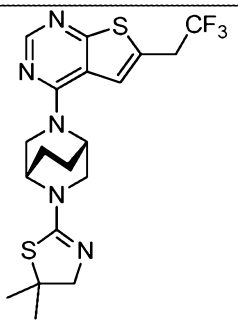
Table 1: Examples of subscaffold 1 of inhibitors of menin-MLL.

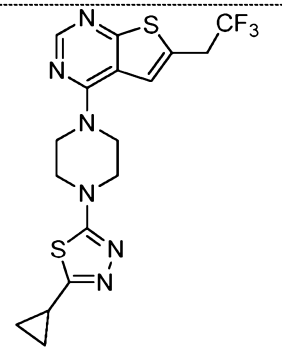
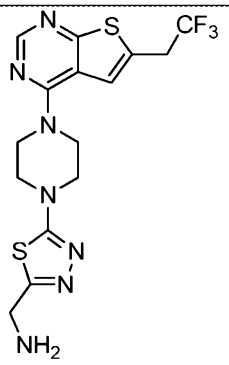
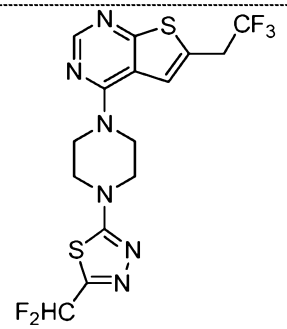
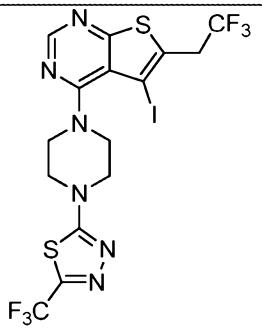
LC-MS conditions:

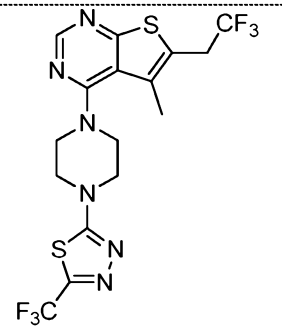
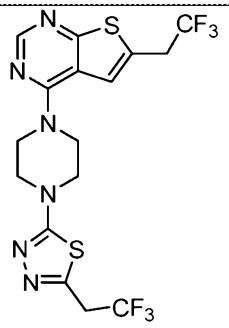
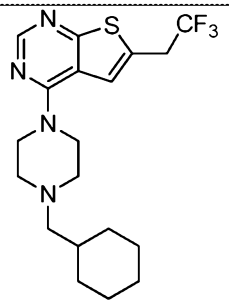
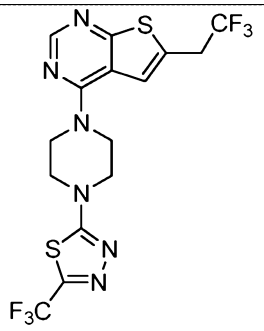
Column type: Phenomenex Kinetex 2.6u C18
Column dimensions: 3.0 mm×50 mm
Temperature: 60°C
Solvent A: 0.1% TFA in water
Solvent B: 0.1% TFA in MeCN
Gradient program: 5% to 100% B / 6min
UV wavelength: 254 nm

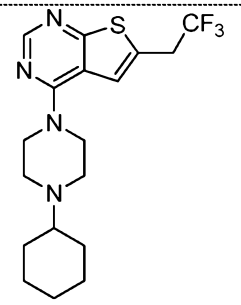
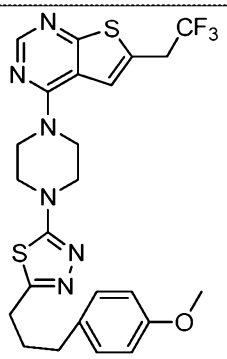
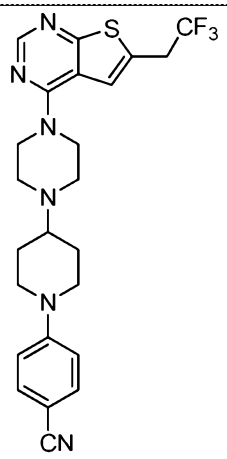
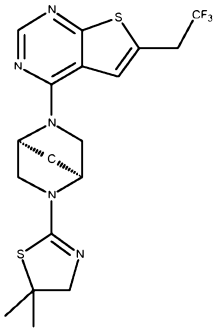
TLC conditions:

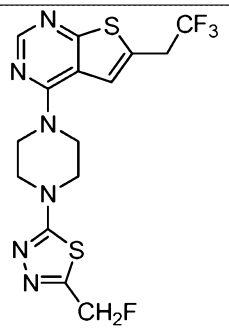
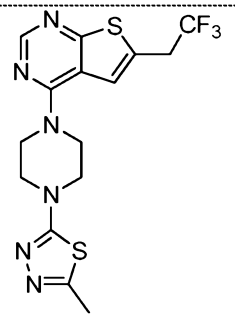
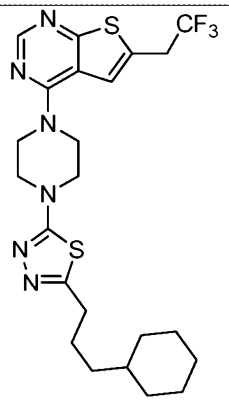
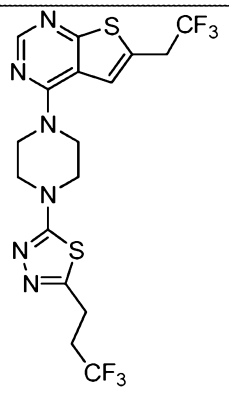
Plates: Pre-coated Silica Gel 60 F_{254}
Developing solvent:DCM:MeOH:$NH_3{\cdot}H_2O$, 20:1:0.1

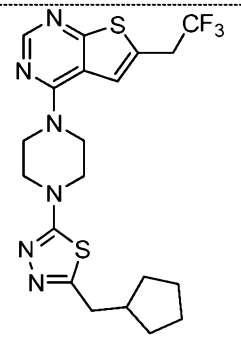
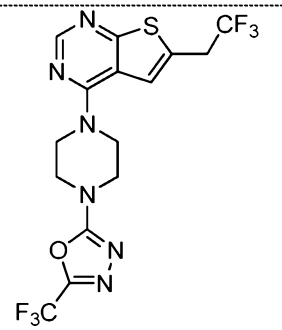
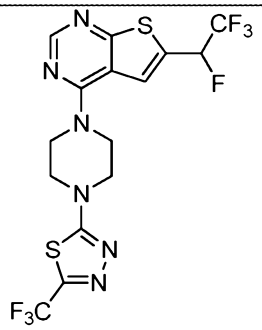
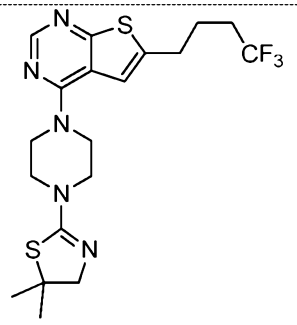
compound#	Structure	$[MH]^+$	LC-MS RT, min. or TLC R_f
Inhibitors with IC50 <0.1μM			
1		416.1	0.5
2		442.1	0.6
Inhibitors with IC50 0.1μM-0.5μM			

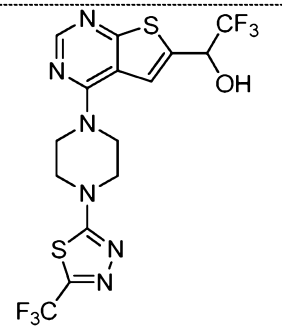
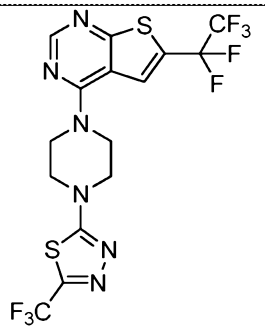
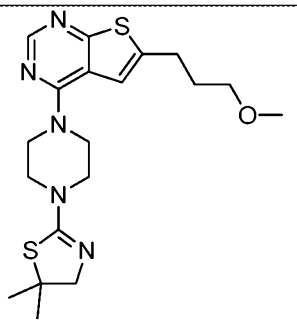
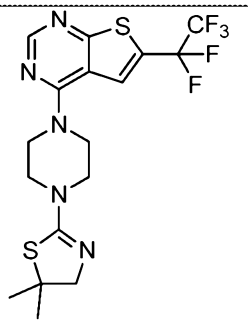
3		427.3	1.71 min
4		399.1	1.13 min
5		437.2	2.03 min
6		581.2	2.51 min

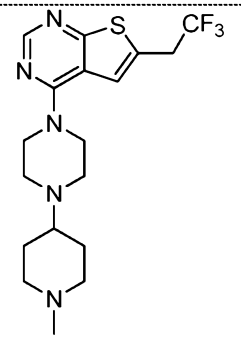
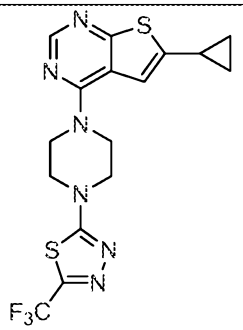
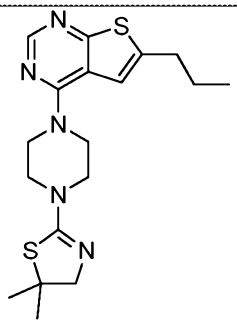
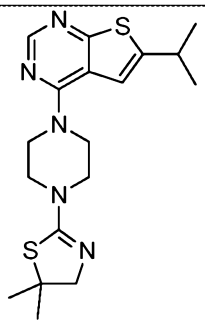
7		469.3	2.78 min
8		469.3	2.22 min
9		399.0	1.64 min
10		455.1	0.5

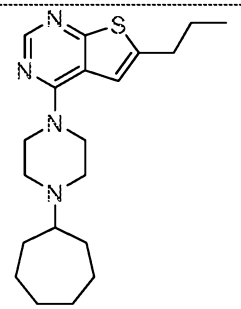
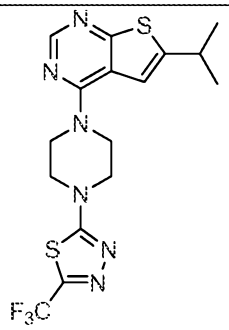
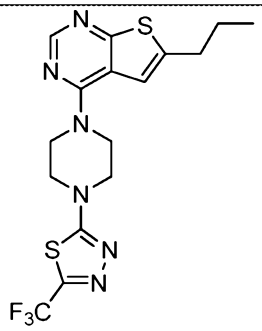
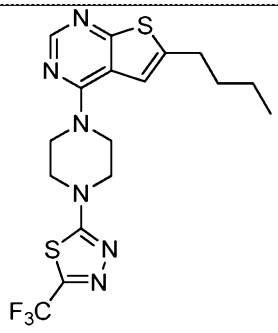
11		385.5	1.42 min
12		535.2	0.6
13		487.2	0.3
14	AND Enantiomer 	427.1	0.5

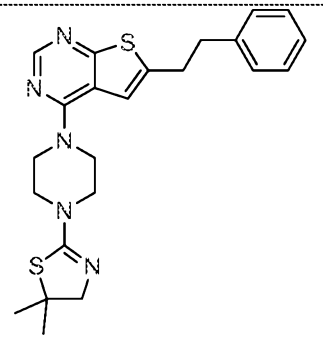
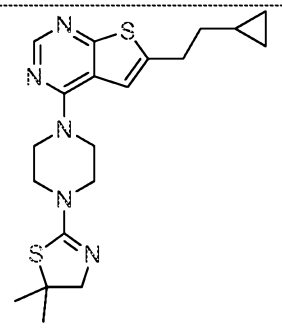
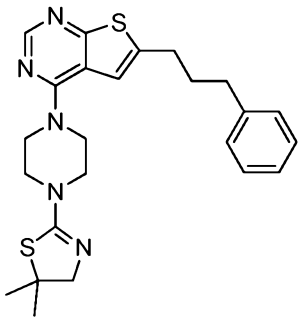
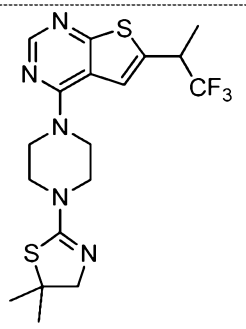
Inhibitors with IC50 0.5μM-2μM			
15		419.2	1.89 min
16		401.2	1.51 min
17		511.3	2.56 min
18		483.4	1.89 min

19		469.3	2.50 min
20		439.0	2.30 min
21		473.2	2.48 min
22			

23		471.5	1.93 min
24		491.0	2.73 min
25		406.5	1.25 min
26		452.0	1.87 min

27			
28		413.0	2.01 min
29		327.5	1.42 min
30		376.5	1.42 min

31		359.5	1.61 min
32		415.6	2.07 min
33		415.6	2.09 min
34		429.4	2.26 min

35		438.2	0.6
36		402.2	0.6
37		452.2	0.6
38		430.1	0.7

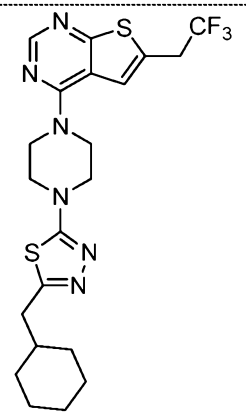
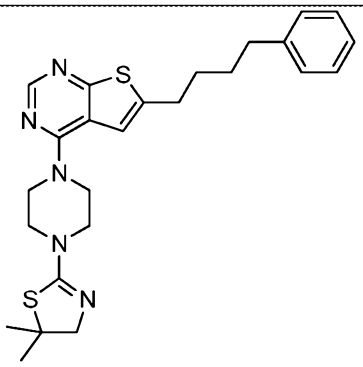
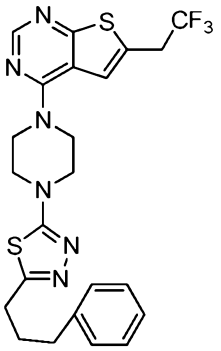
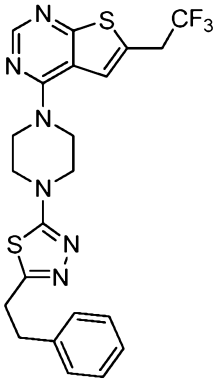
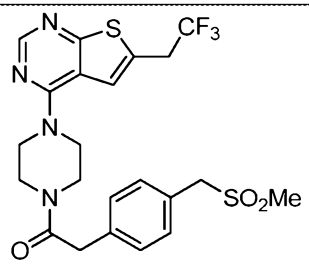
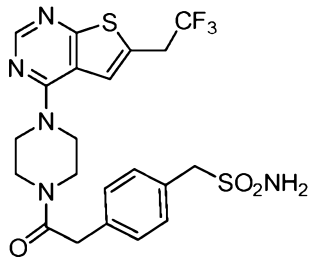
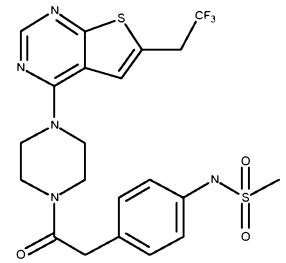
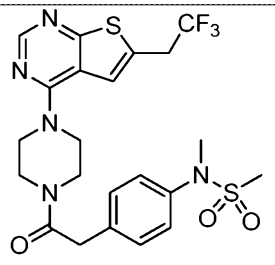
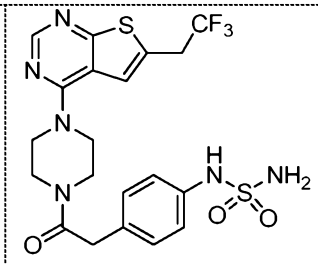
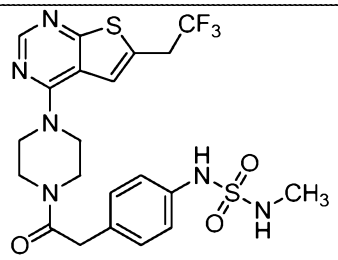
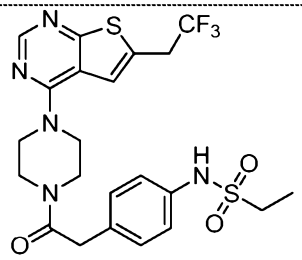
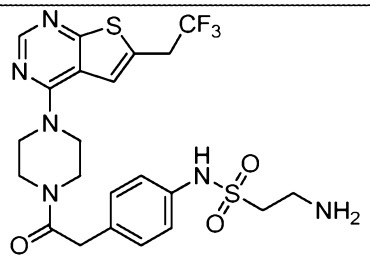
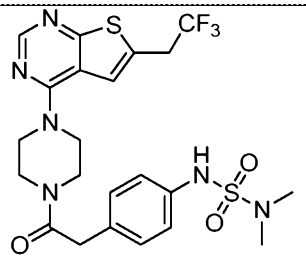
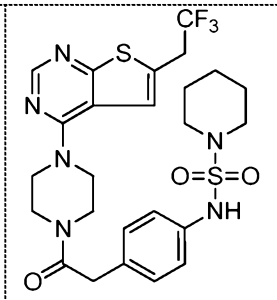
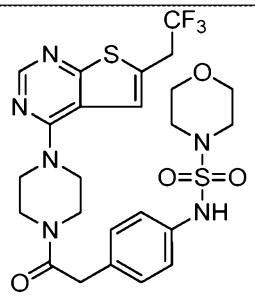
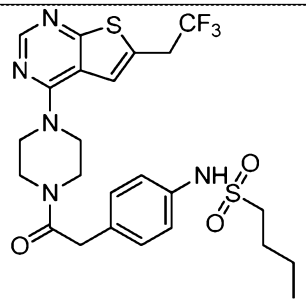
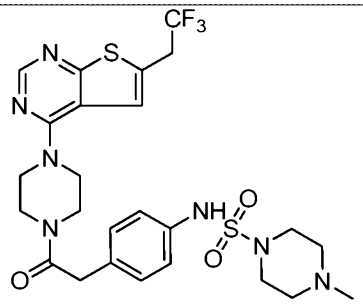
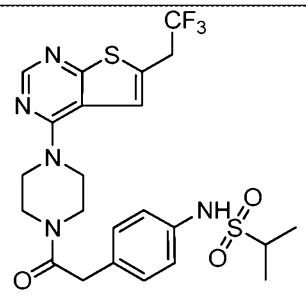
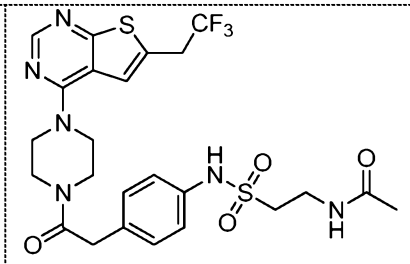
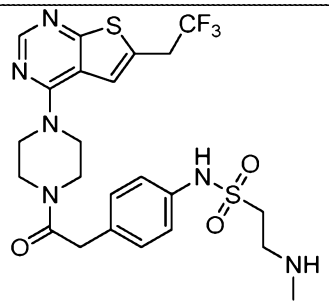
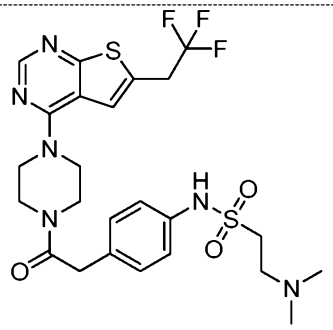
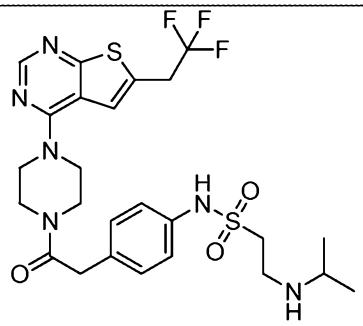
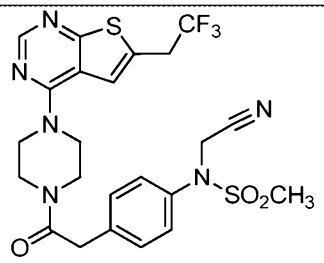
39		483.2	0.6
40		466.2	0.6
41		505.2	0.6
42		491.1	0.6

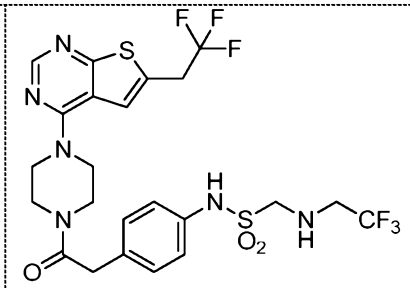
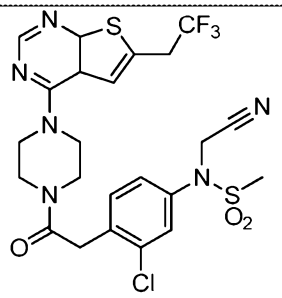
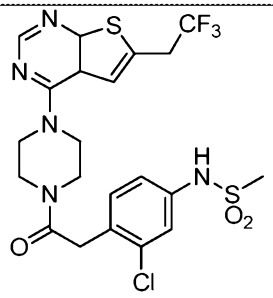
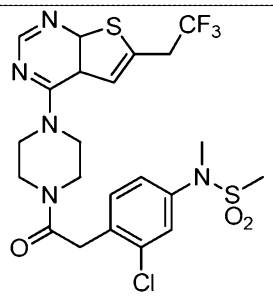
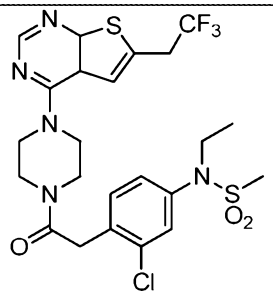
Table 2: Examples of subscaffold 2 of inhibitors of menin-MLL.

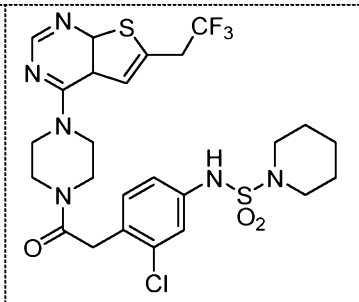
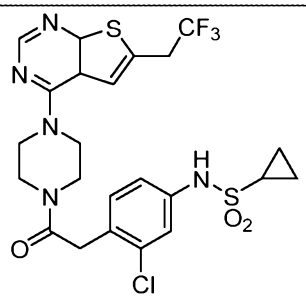
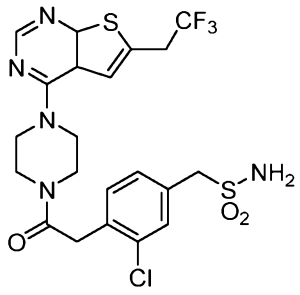
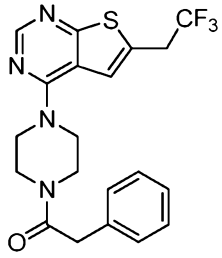
Compound#	Structure	$[MH]^+$	LC-MS RT, min. or TLC R_f
Inhibitors with IC50 <0.1μM			
43		513.1	0.4
44		514.1	0.2
45		514.3	1.76 min
46		528.1	1.70 min

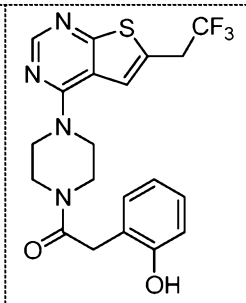
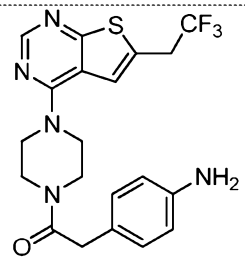
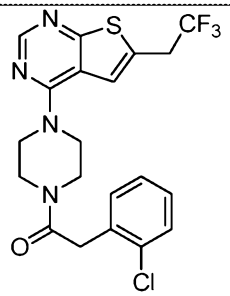
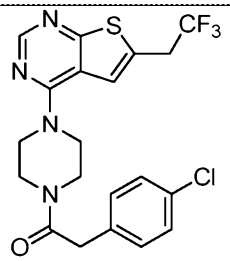
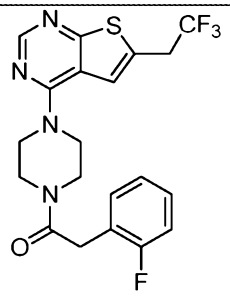
47		515.2	1.44 min
48		529.0	1.69 min
49		528.1	1.85 min
50		543.4	1.57 min
51		543.4	1.90 min

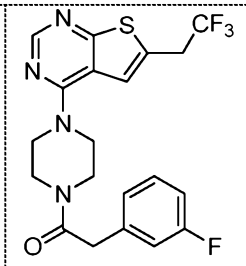
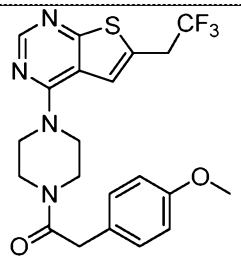
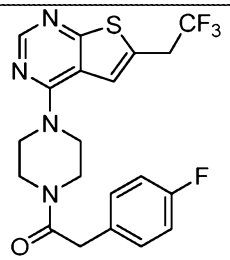
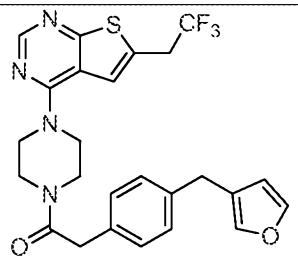
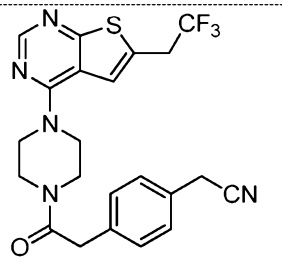
52		583.0	2.04 min
53		585.1	1.73 min
54		556.3	1.99 min
55		598.0	1.52 min
56		542.2	1.82 min

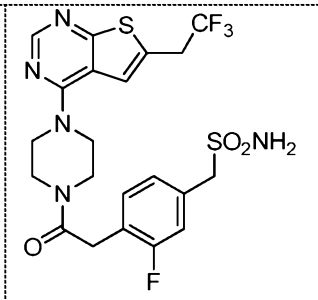
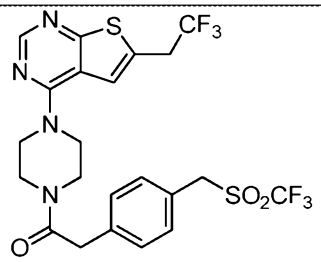
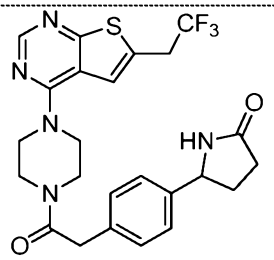
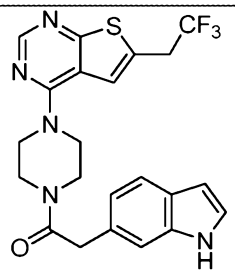
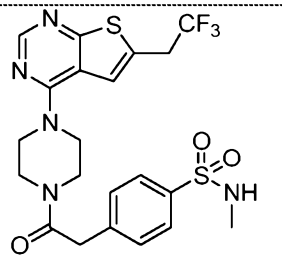
57		585.1	1.57 min
58		556.9	1.43 min
59		571.3	1.45 min
60		585.1	1.51 min
61		553.0	1.77 min

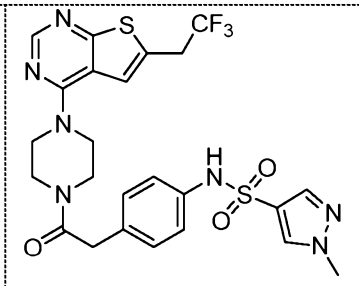
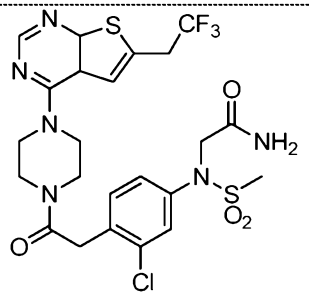
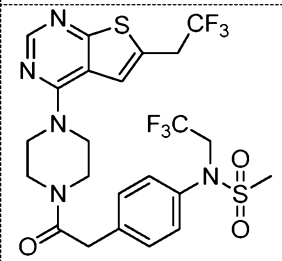
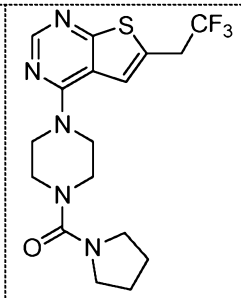
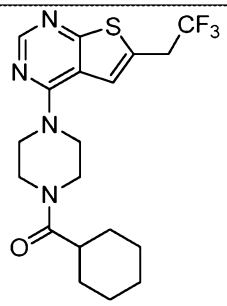
62		625.4	1.74 min
63		587.0	2.15 min
64		547.9	2.02 min
65		562.0	2.07 min
66		576.1	2.13 min

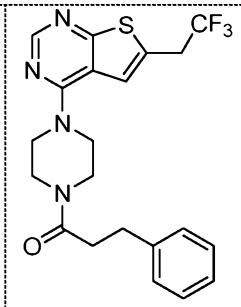
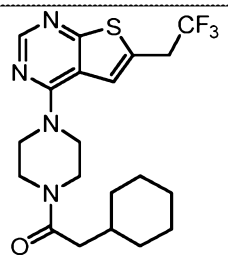
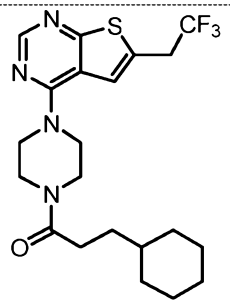
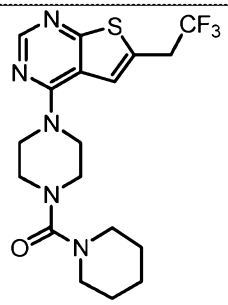
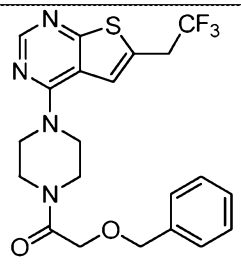
284		617.3	2.37 min
285		574.3	2.14 min
286		548.2	1.78 min
Inhibitors with IC50 0.1μM-0.5μM			
67		421.1	0.6

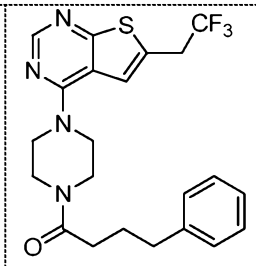
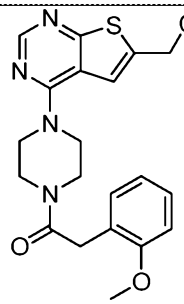
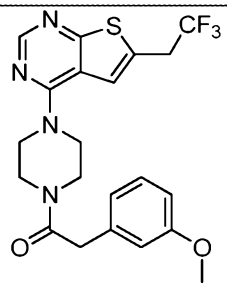
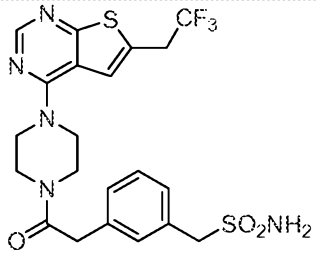
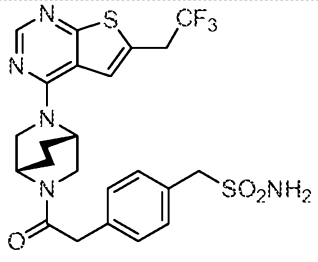
68		437.1	0.5
69		436.1	0.5
70		455.1	0.6
71		455.1	0.6
72		439.1	0.6

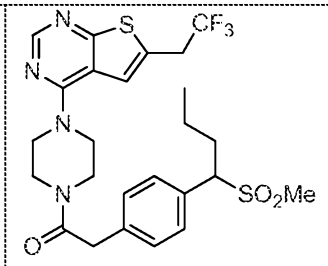
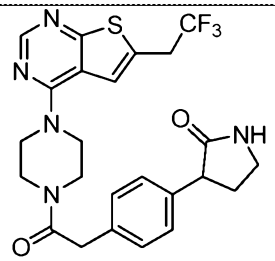
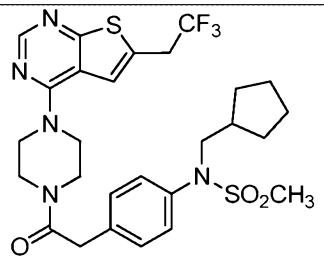
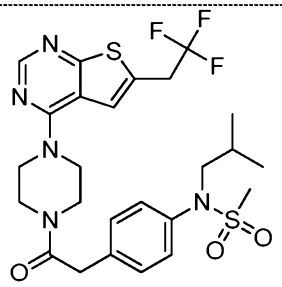
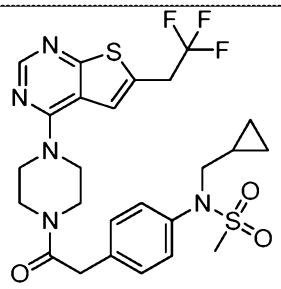
73		439.1	0.6
74		451.1	0.5
75		439.1	0.6
76		501.2	0.6
77		460.1	0.5

78		532.1	0.2
79		567.1	0.4
80		504.1	1.50 min
81		460.0	1.76 min
82		514.3	1.60 min

83		580.0	1.71 min
84		605.3	1.90 min
85		596.3	2.23 min
Inhibitors with IC50 0.5μM-2μM			
86		400.1	0.4
87		413.2	0.5

88		435.1	0.6
89		427.2	0.6
90		441.2	0.6
91		414.2	0.4
92		451.1	0.5

93		449.2	0.6
94		451.1	0.5
95		451.1	0.5
96		514.1	0.2
97		540.1	0.2

98		555.2	0.4
99		504.4	1.60 min
100		596.3	2.26 min
101		570.1	2.11 min
102		568.3	2.10 min

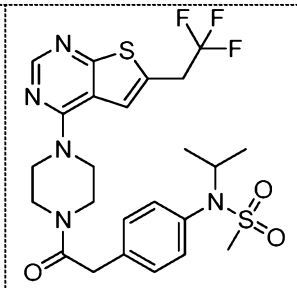
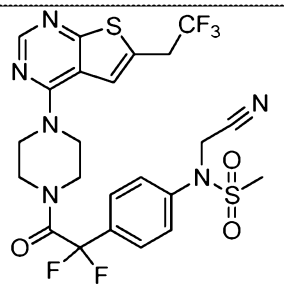
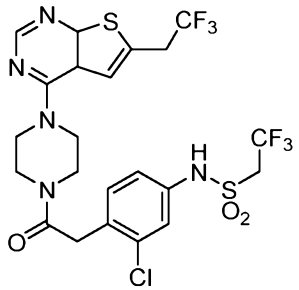
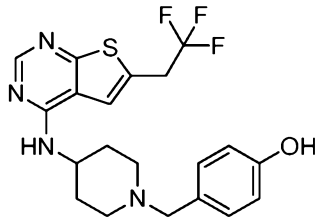
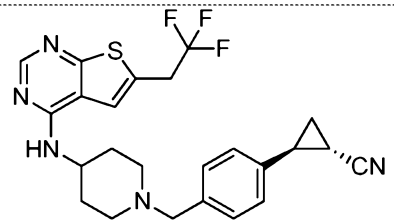
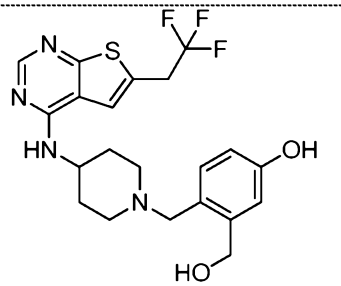
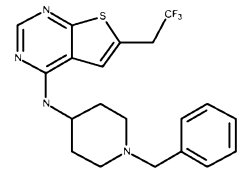
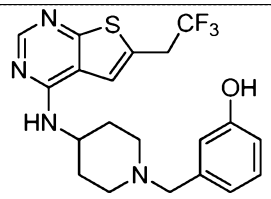
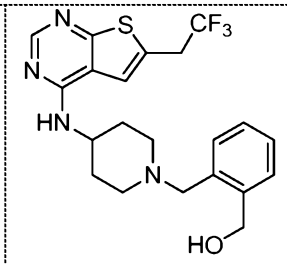
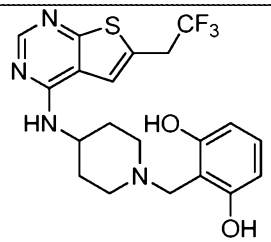
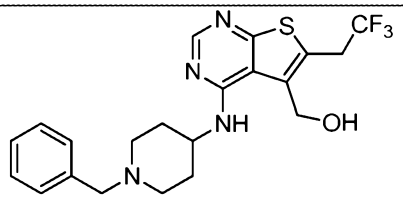
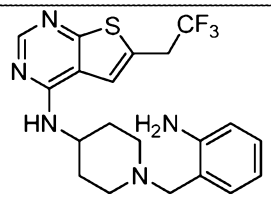
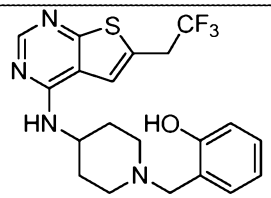
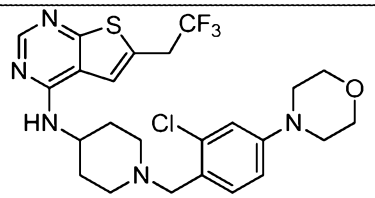
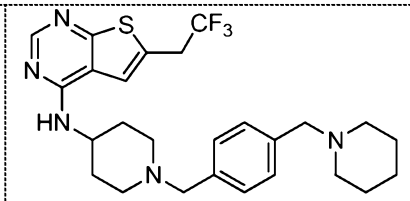
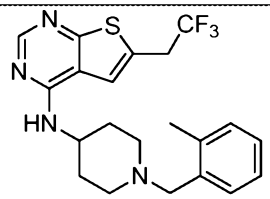
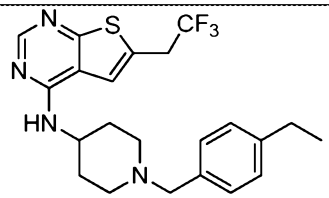
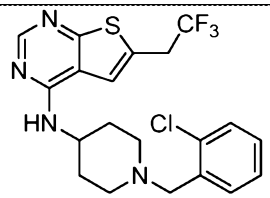
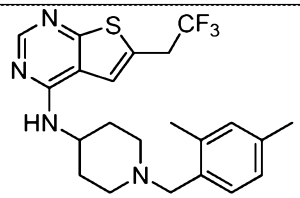
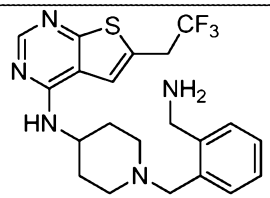
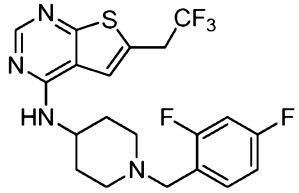
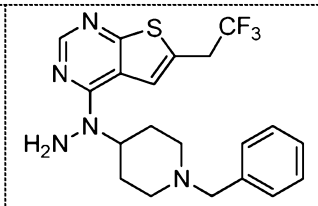
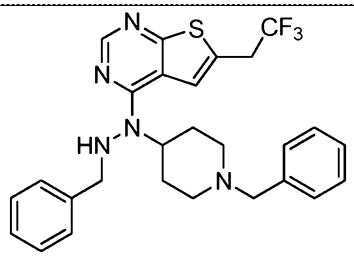
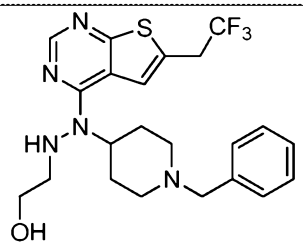
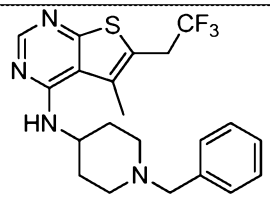
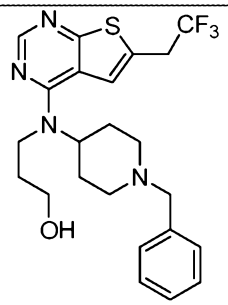
103		556.0	1.99 min
104		589.1	2.30 min
287		616.1	2.31 min

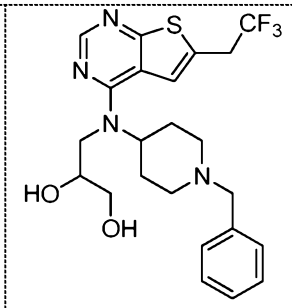
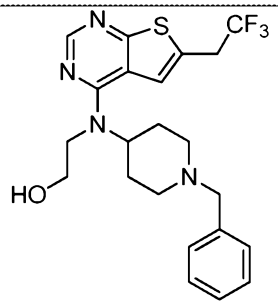
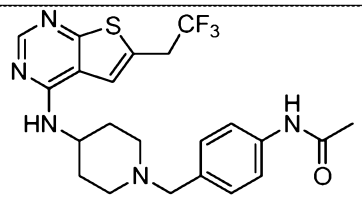
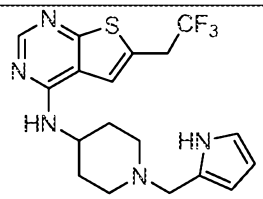
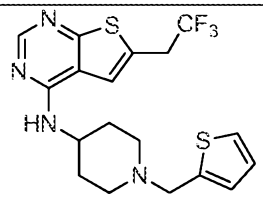
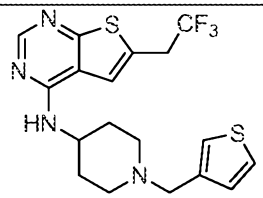
Table 3: Examples of subscaffold 3 of inhibitors of menin-MLL.

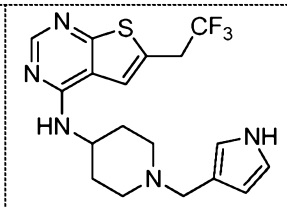
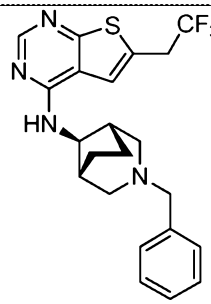
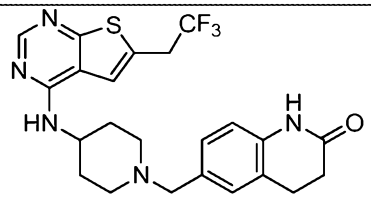
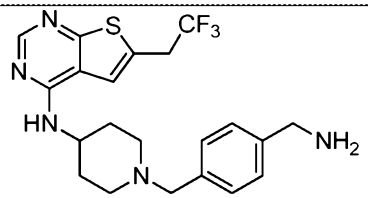
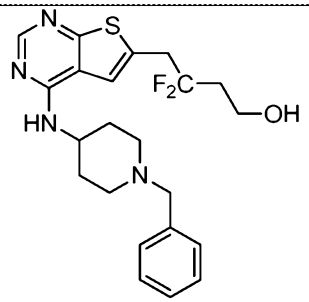
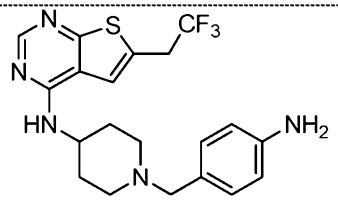
Compound#	Structure	$[MH]^+$	LC-MS RT, min. or TLC R_f
Inhibitors with IC50 <0.1μM			
105		423.1458	0.3
106		472.31	1.46 min
Inhibitors with IC50 0.1μM-0.5μM			
107		453.1	1.25 min
108		407.5	1.72 min
109		423.1	1.31 min

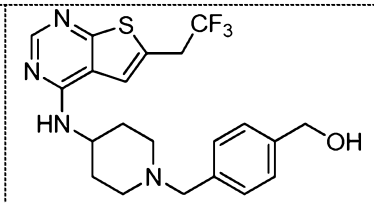
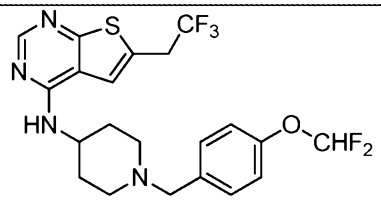
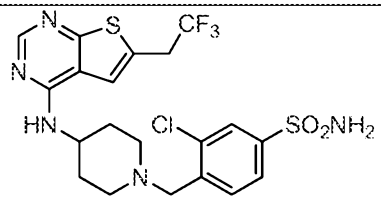
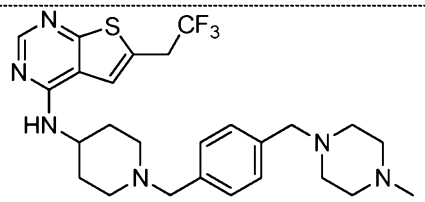
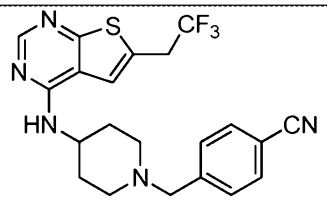
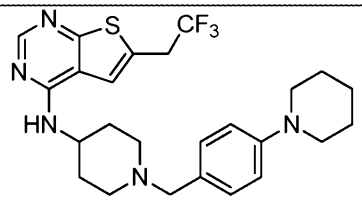
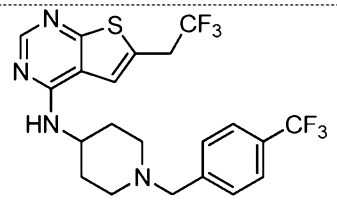
110		437.2	1.32 min
111		439.3	1.28 min
112		437.2	1.31 min
113		422.2	1.61 min
114		423.2	1.30 min
115		526.3	1.59 min

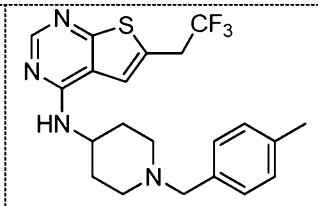
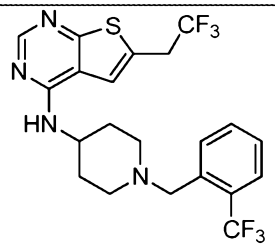
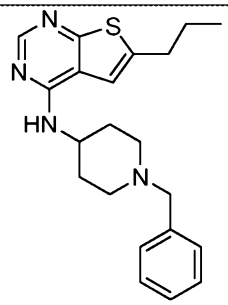
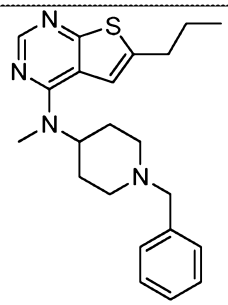
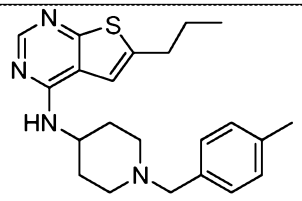
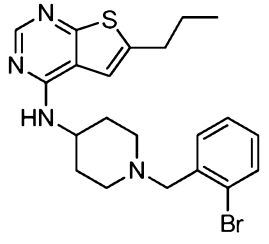
116		504.1	1.47 min
117		421.0	1.55 min
118		435.4	2.06 min
119		441.1	1.76 min
120		435.5	1.59 min
121		436.3	1.12 min
122		457.3	1.65 min

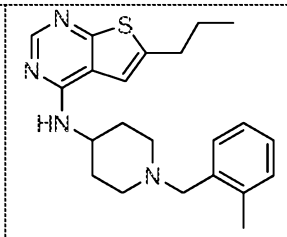
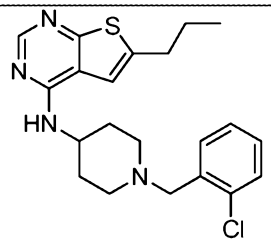
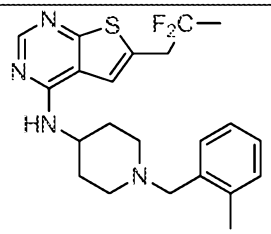
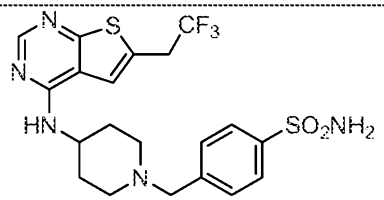
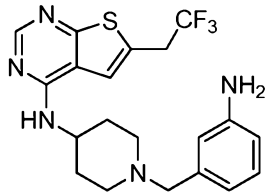
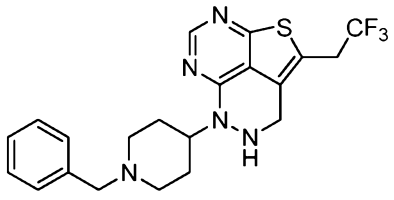
123		422.1618	0.2
124		512.2093	0.4
125		466.1885	0.1
126		420.7	1.47 min
127		465.2	0.1

128		481.1	0.1
129		451.1	0.3
130		464.2	1.32 min
131		396.1	1.25 min
132		413.5	1.37 min
133		413.5	1.37 min

134		396.1459	0.3
135		433.3	1.62 min
Inhibitors with IC50 0.5μM-2μM			
136		476.2	1.35 min
137		436.3	1.05 min
138		433.3	1.15 min
139		422.2	1.01 min

140		437.2	1.16 min
141		473.2	1.57 min
142		520.3	1.41 min
143		519.4	1.28
144			
145			
146		475.0	1.72 min

147		421.3	1.95 min
148		475.0	1.54 min
149		367.0	1.29 min
150		381.5	1.42 min
151		381.5	1.46 min
152		447.0	1.44 min

153		381.5	1.42 min
154			
155		403.6	1.35 min
156		486.4	1.49 min
157		422.1629	0.3
158		434.1630	0.2

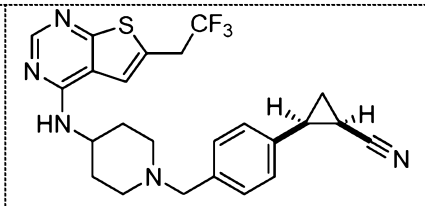
159		472.3	1.51 min

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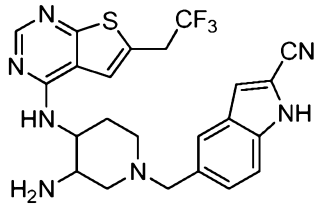
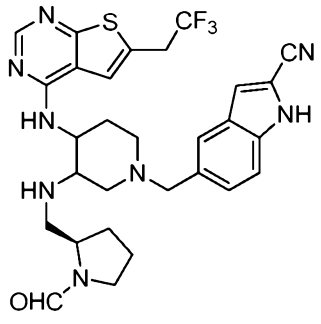
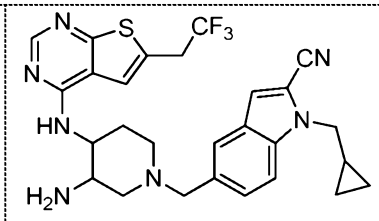
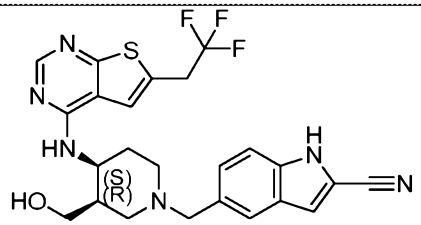
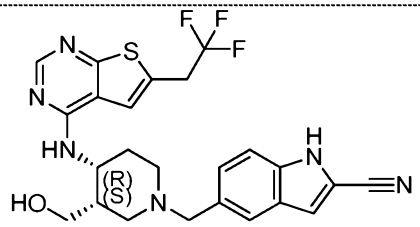
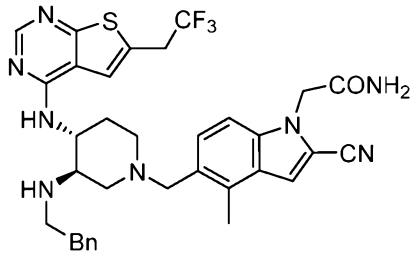
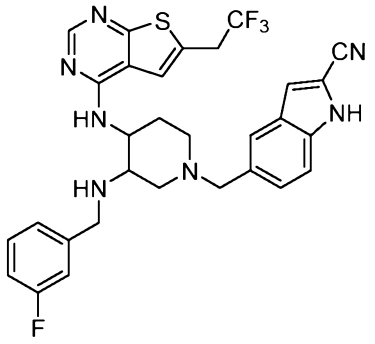
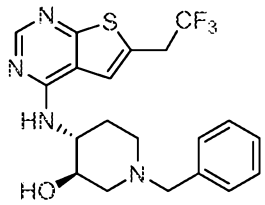
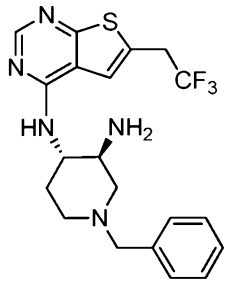
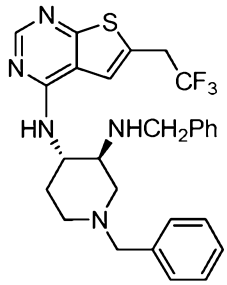
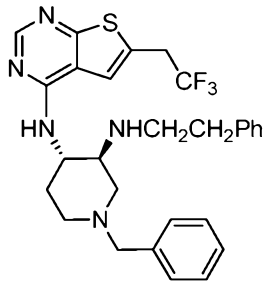
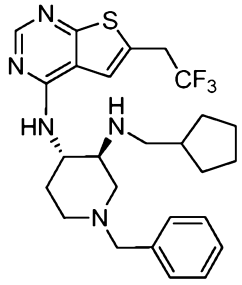
Table 4: Examples of subscaffold 3 and 4 of inhibitors of menin-MLL.

Compound#	Structure	$[MH]^+$	LC-MS RT, min. or TLC R_f
Inhibitors with IC50 <0.1μM			
160		486.1676	0.2
161		597.2367	0.2

162		540.2159	0.3
163		501.1	1.91 min
164		501.1	1.94 min
288		661.2677	0.1
289		594.2057	0.1
Inhibitors with IC50 0.1μM-0.5μM			

165		423.1458	0.2
166		422.1625	0.2
167		512.2095	0.3
168		526.2243	0.3
169		504.2400	0.3

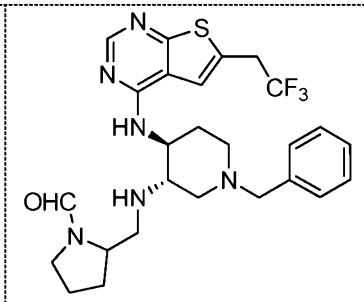
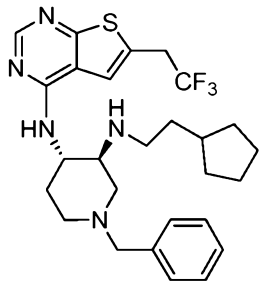
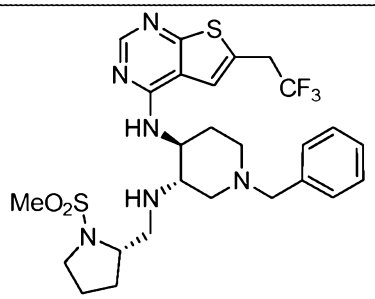
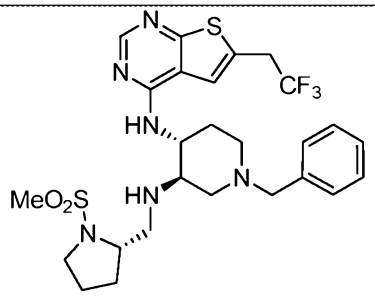
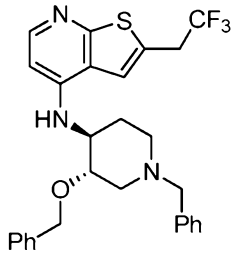
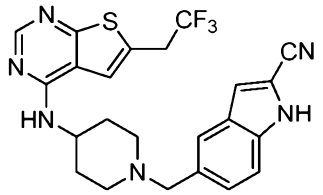
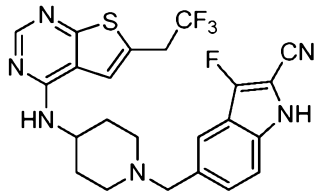
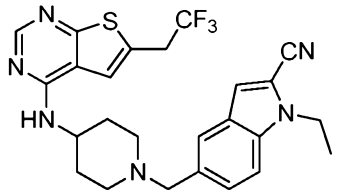
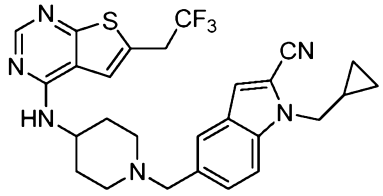
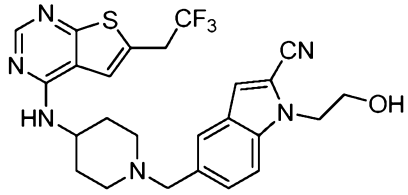
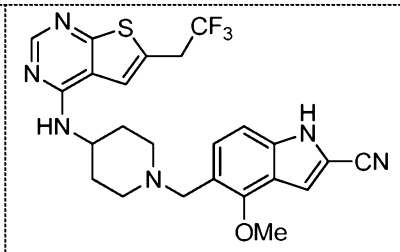
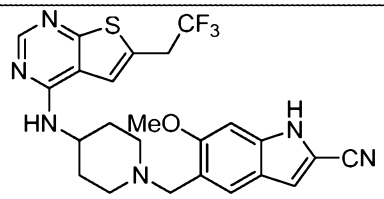
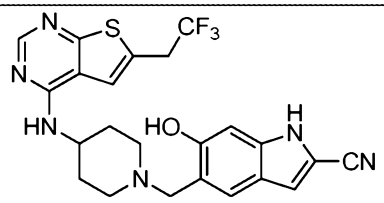
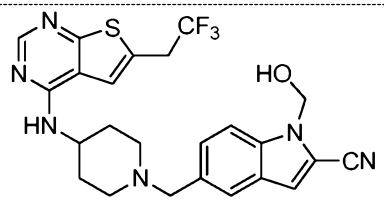
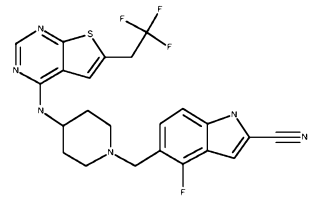
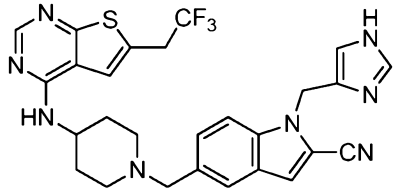
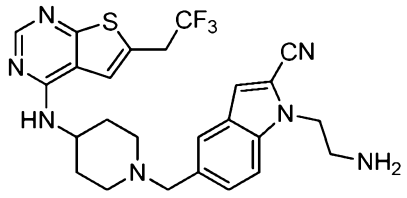
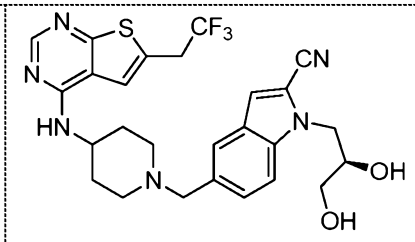
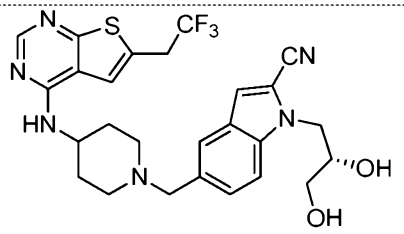
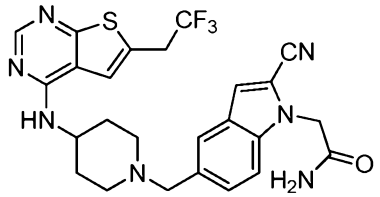
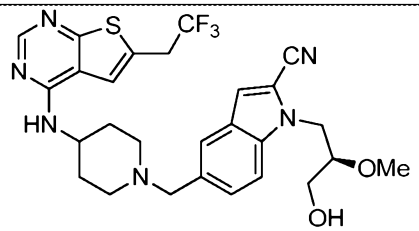
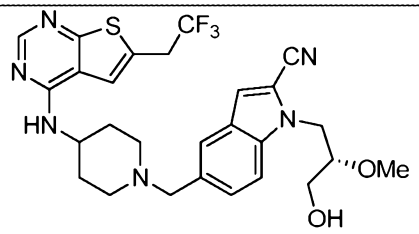
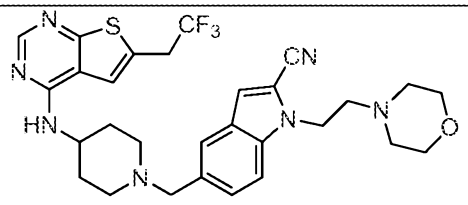
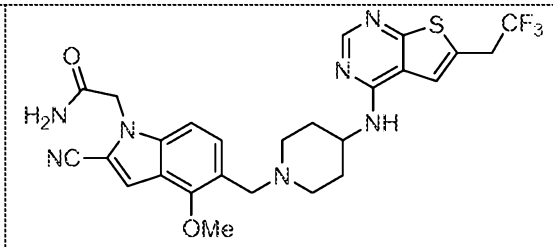
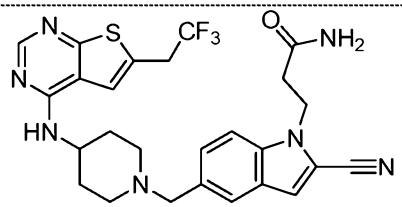
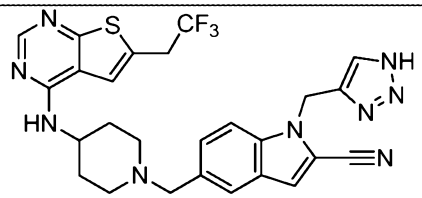
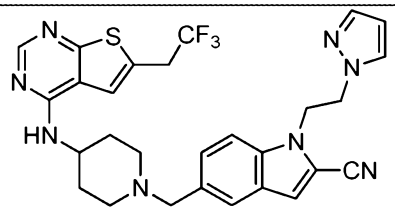
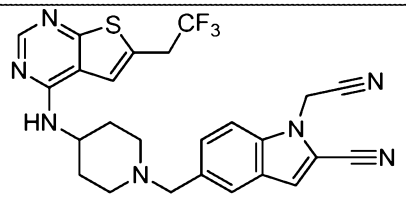
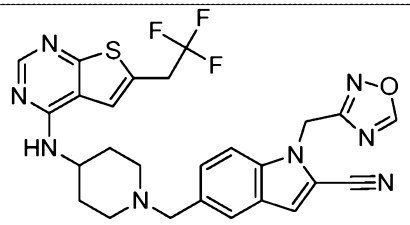
170		533.2310	0.3
171		518.2557	0.3
172		583.2127	0.3
173		583.2133	0.3
174		512.1974	0.3

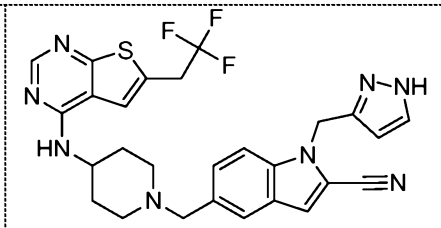
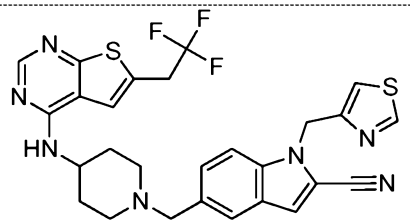
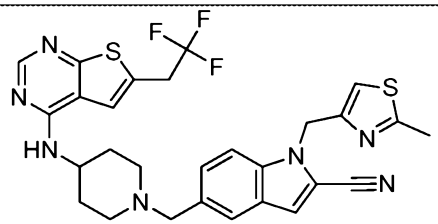
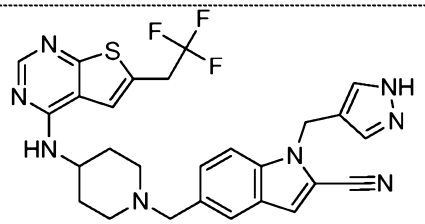
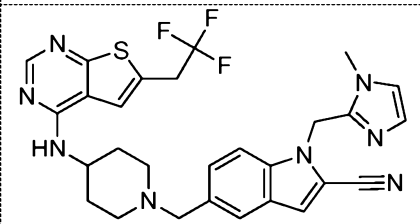
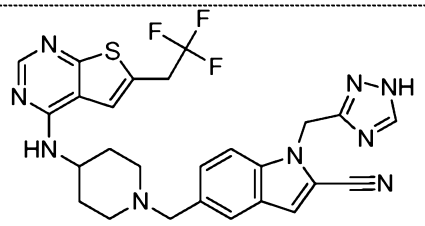
Table 5: Examples of subscaffold 4 of inhibitors of menin-MLL.

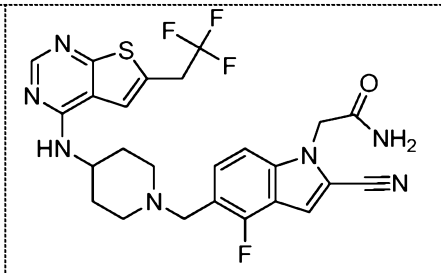
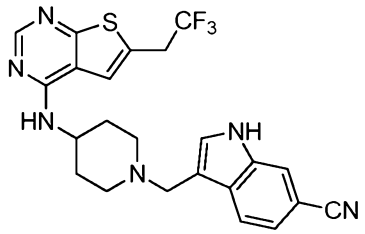
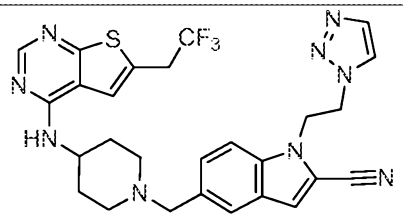
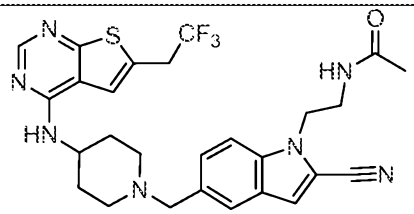
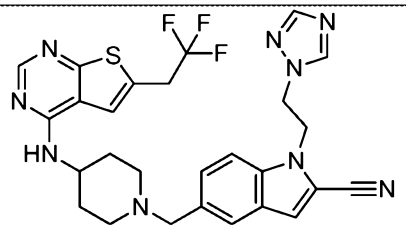
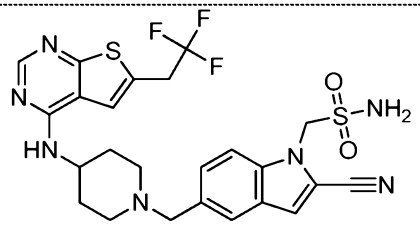
Compound#	Structure	[MH]+	LC-MS RT, min. or TLC R_f
Inhibitors with IC50 <0.1μM			
175		471.1579	0.3
176		489.1485	0.3
177		499.1891	0.4
178		525.2052	0.4
179		515.1828	0.2

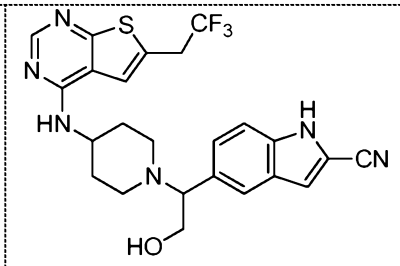
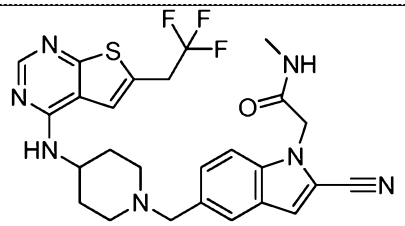
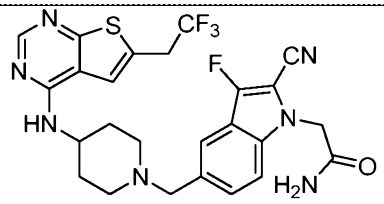
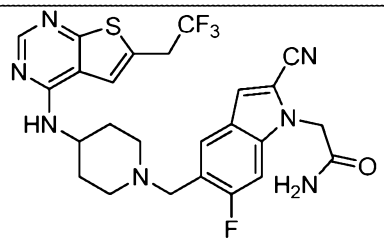
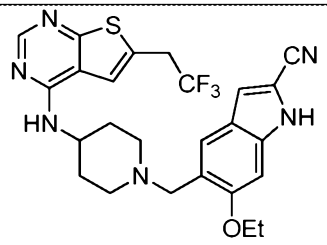
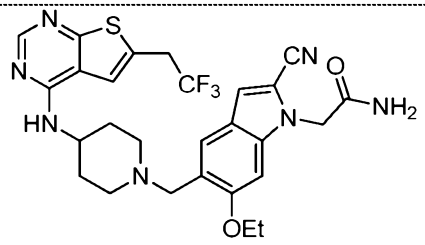
180		501.1684	0.3
181		501.1675	0.3
182		487.1519	0.3
183		501.1678	0.2
184		489.4	1.60 min
185		551.2	1.23 min
186		514.1998	0.1

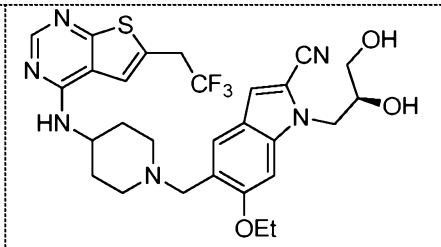
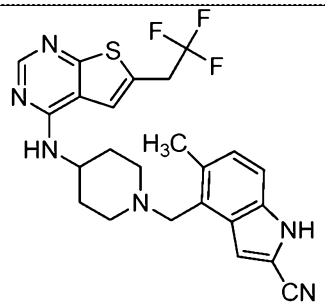
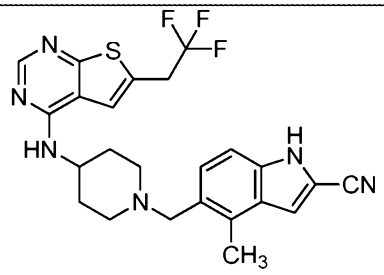
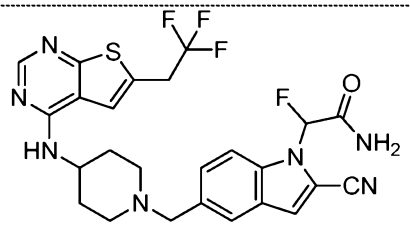
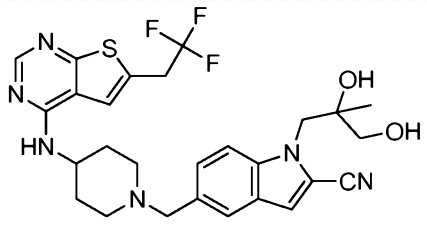
187		545.1951	0.2
188		545.1941	0.2
189		528.1783	0.2
190		559.2098	0.2
191		559.2096	0.2
192		584.2415	0.15

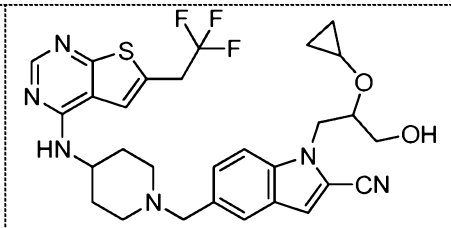
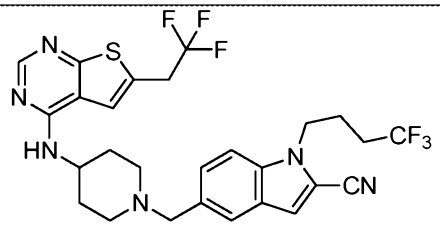
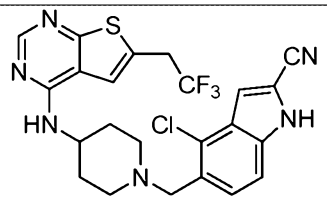
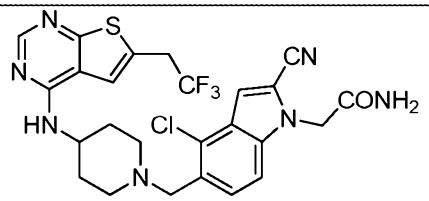
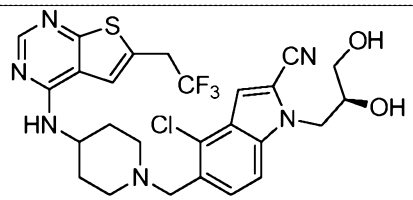
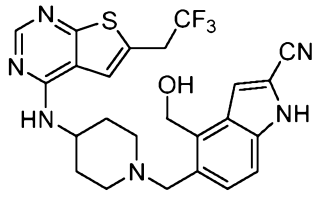
193		558.123	0.1
194		542.5	1.33 min
195		552.4	1.55 min
196		565.3	1.63 min
197		510.4	1.65 min
198		553.6	1.63 min

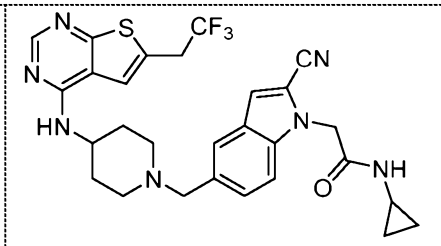
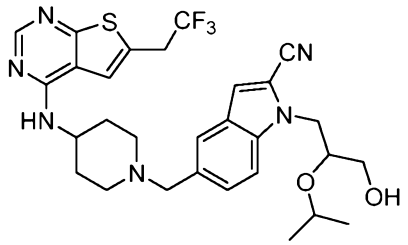
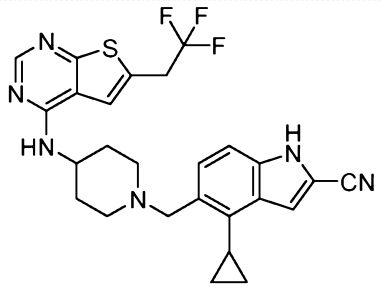
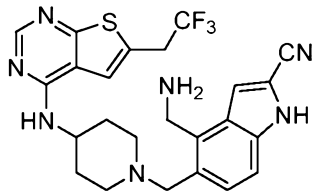
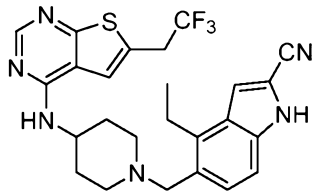
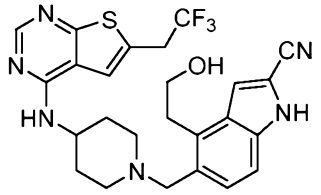
199		551.8	1.65 min
200		568.3	1.73 min
201		582.1	1.80 min
202		551.2	1.55 min
203		565.3	1.31 min
204		552.4	1.52 min

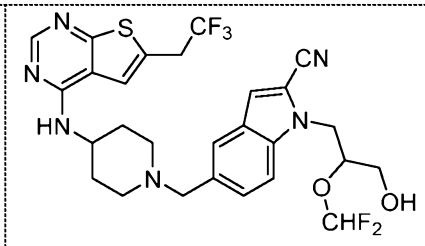
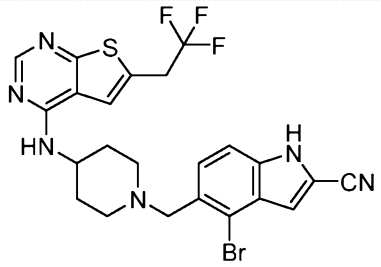
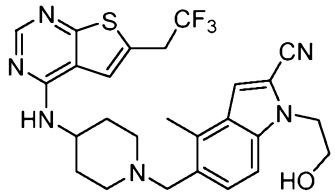
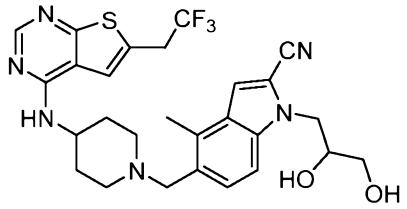
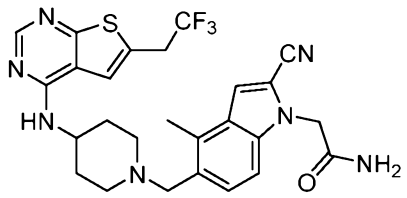
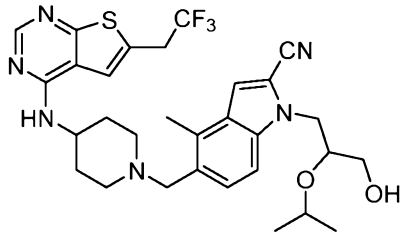
205		546.1	1.48 min
206		471.1576	0.4
207		566.5	1.53 min
208		556.0	1.46 min
209		566.2	1.52 min
210		564.4	1.43 min

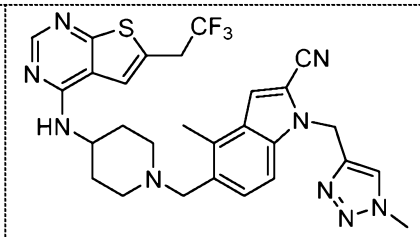
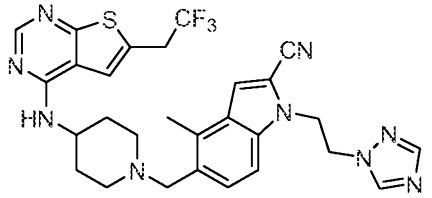
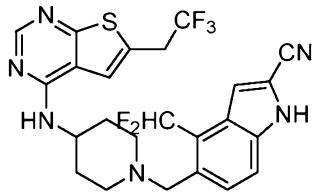
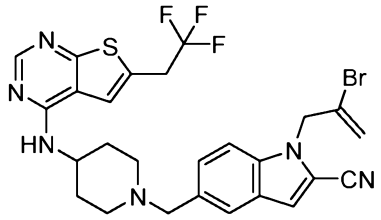
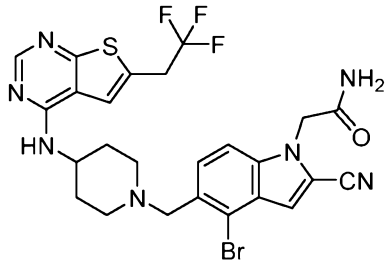
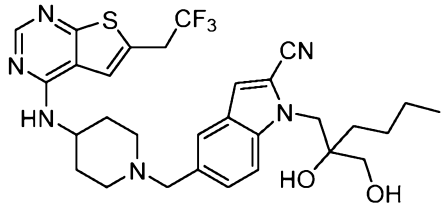
211		501.1	1.77 min
212		541.9	1.82 min
213		546.1690	0.1
214		546.1693	0.1
215		515.1835	0.2
216		572.2050	0.1

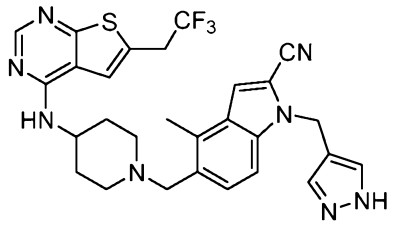
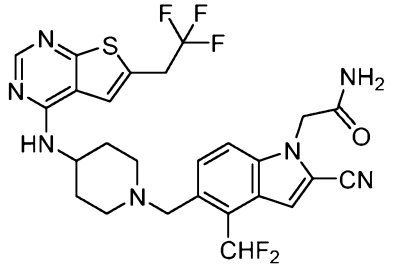
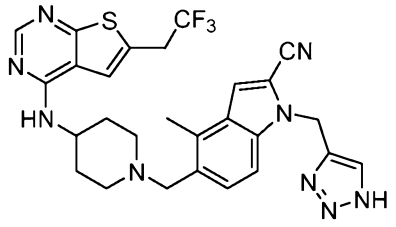
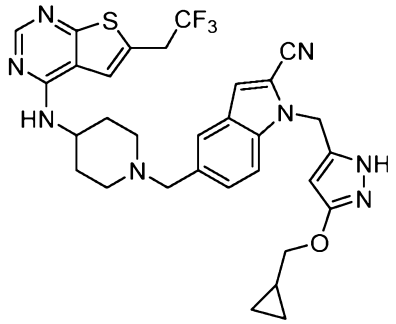
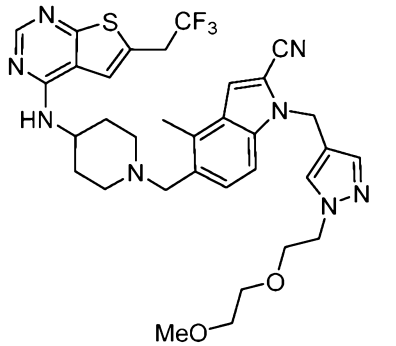
217		589.2204	0.1
218		485.2	2.10 min
219		485.2	2.02 min
220		546.4	1.86 min
221		559.0	1.82 min

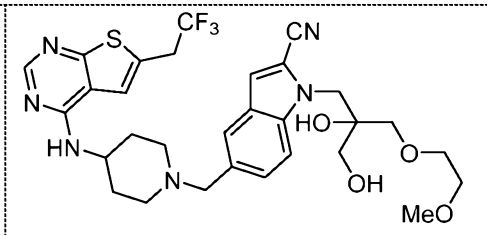
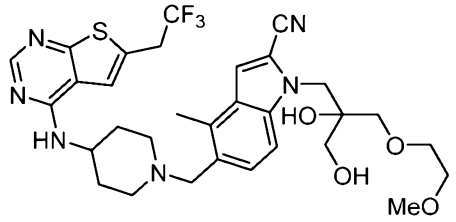
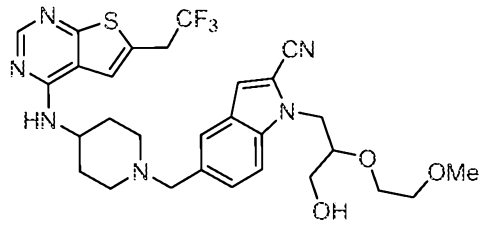
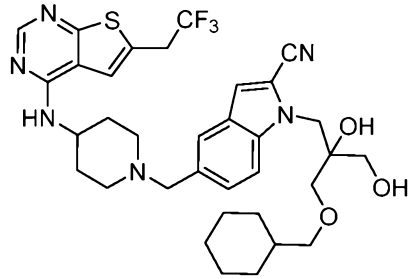
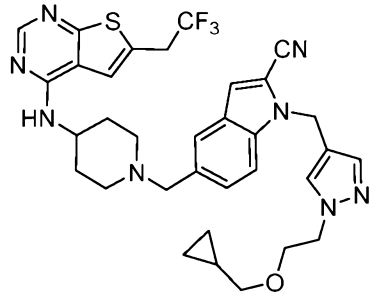
222		585.1	1.72 min
223		581.2	2.12 min
224		505.1181	0.3
225		562.1400	0.1
226		579.1552	0.1
290		501.1	1.60 min

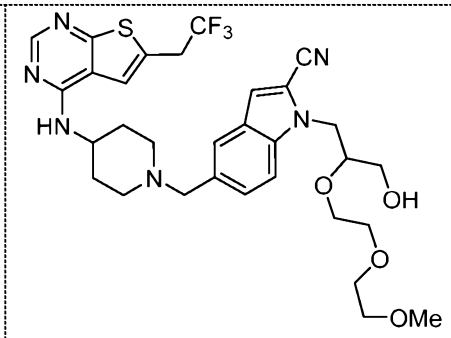
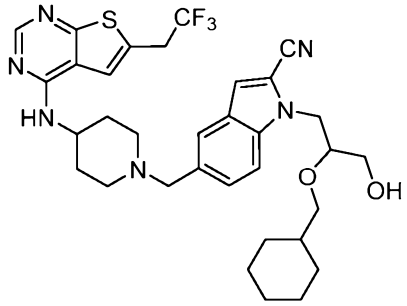
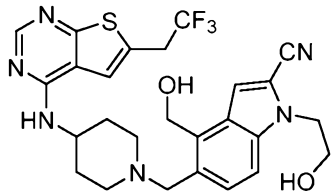
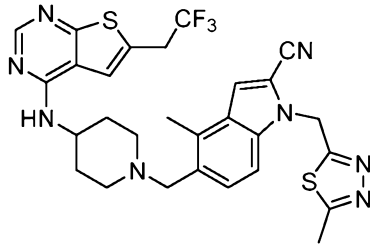
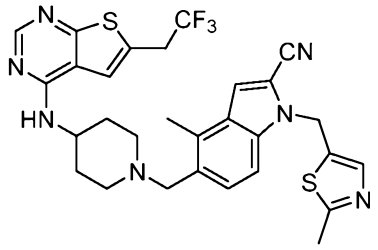
291		568.3	1.65 min
292		587.3	1.86 min
293		511.6	1.92 min
294		500.2	1.37 min
295		499.3	2.00 min
296		515.2	1.82 min

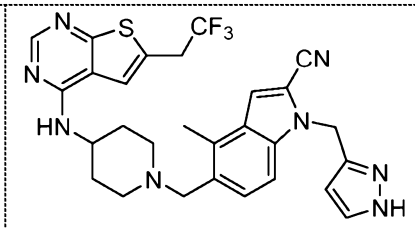
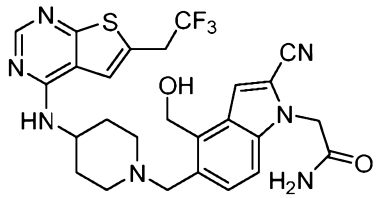
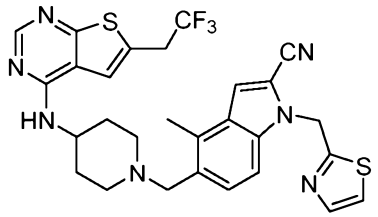
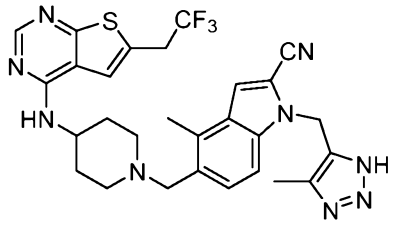
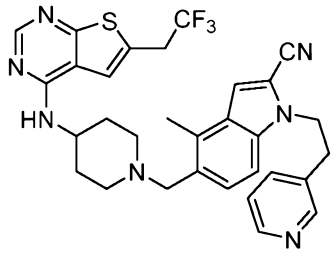
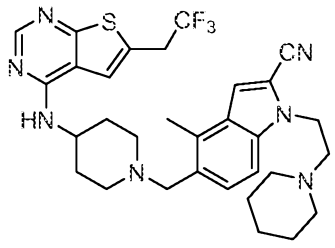
297		595.4	1.94 min
298		551.2	2.01 min
299		529.0	1.64 min
300		559.0	1.57 min
301		542.2	1.56 min
302		601.4	1.94 min

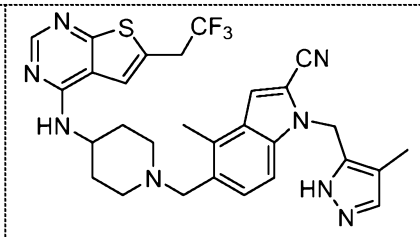
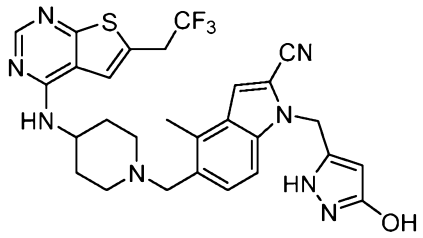
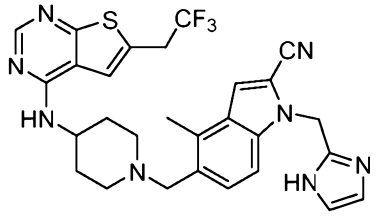
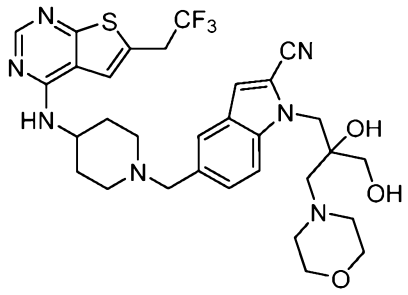
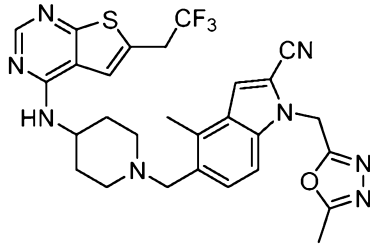
303		580.3	1.73 min
304		580.3	1.65 min
305		521.2	1.75 min
306		591.5	1.96 min
307		606.5	1.78 min
308		601.4	1.92 min

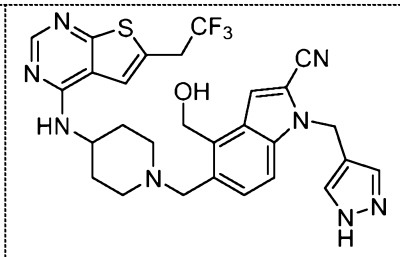
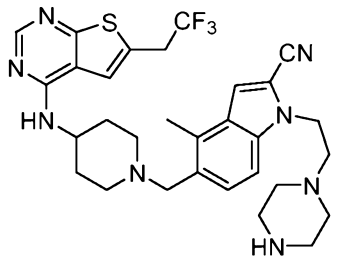
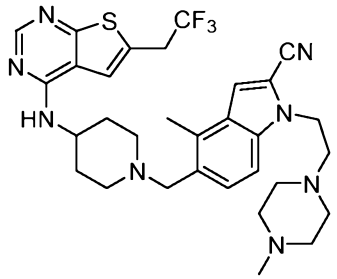
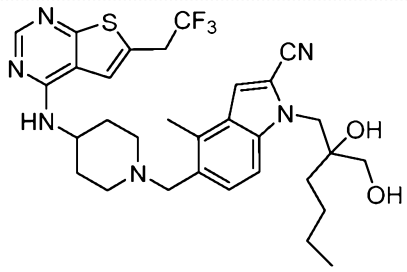
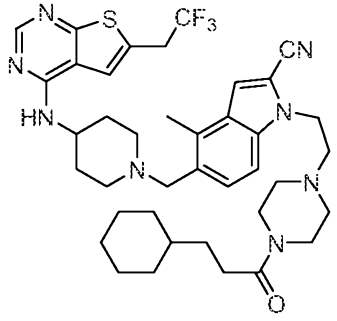
309		565.3	1.74 min
310		578.5	1.64 min
311		566.5	1.69 min
312		621.5	2.12 min
313		667.4	2.14 min

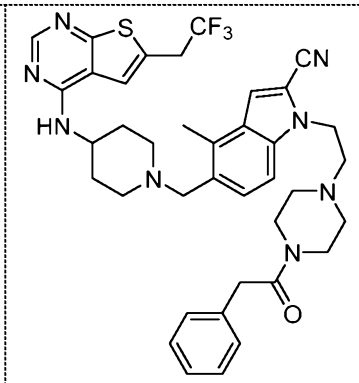
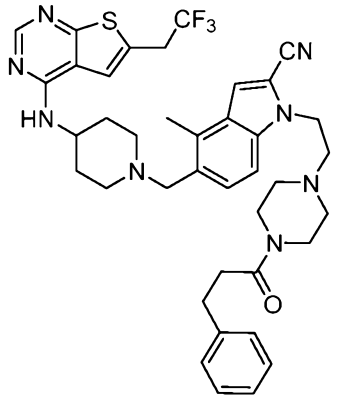
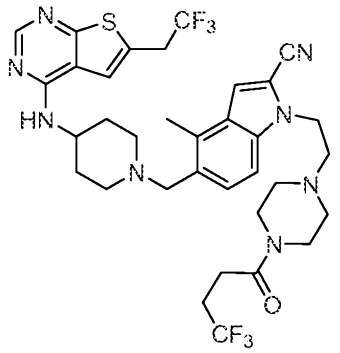
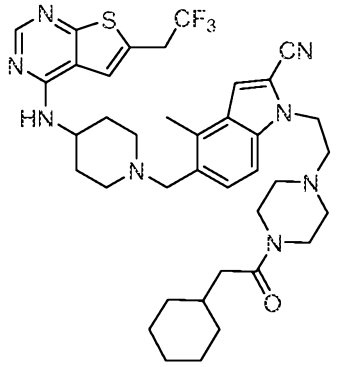
314		633.5	1.96 min
315		647.6	2.00 min
316		603.5	1.95 min
317		671.6	2.45 min
318		649.4	2.38 min

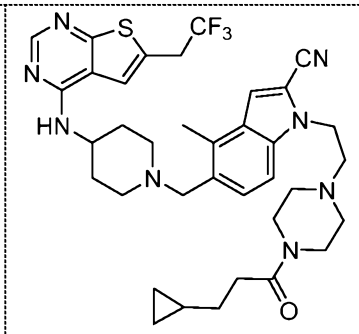
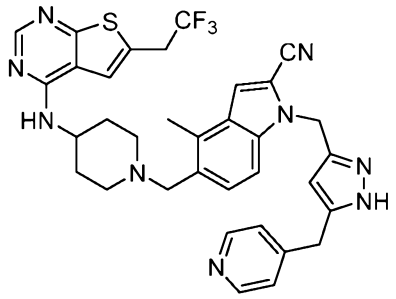
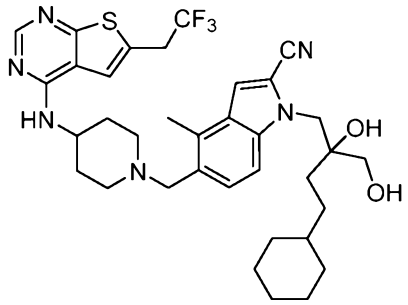
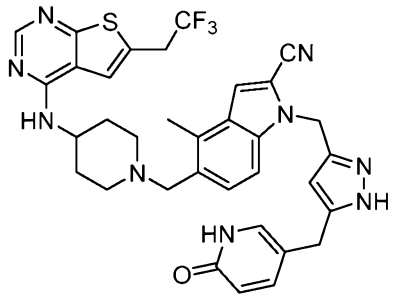
319		647.6	2.12 min
320		641.3	2.48 min
321		544.9	1.51 min
322		597.2	1.75 min
323		596.3	1.83 min

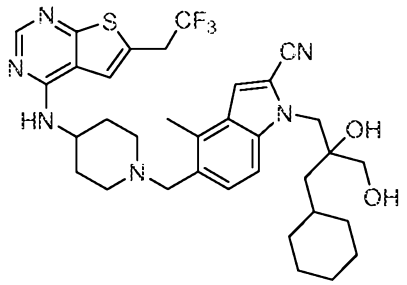
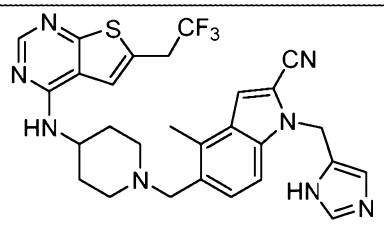
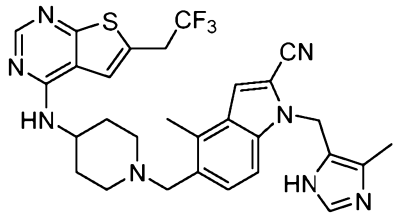
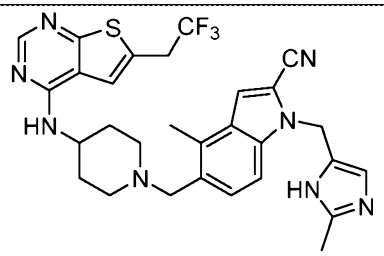
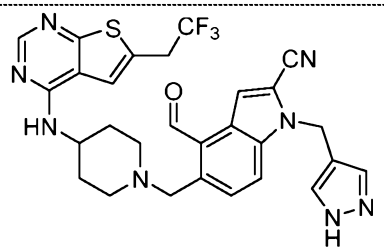
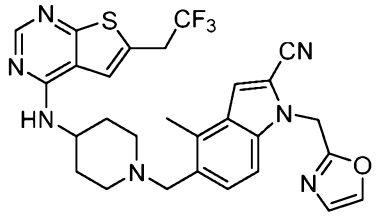
324		565.3	1.74 min
325		558.1	1.38 min
326		582.4	1.83 min
327		580.3	1.69 min
328		590.6	1.46 min
329		596.6	1.49 min

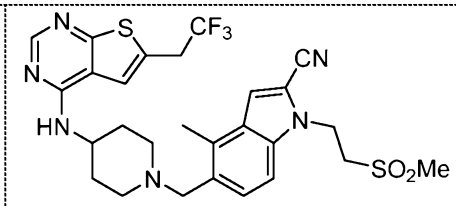
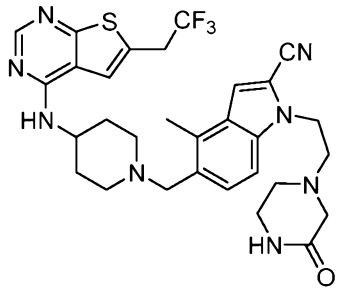
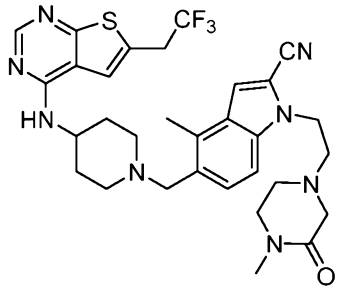
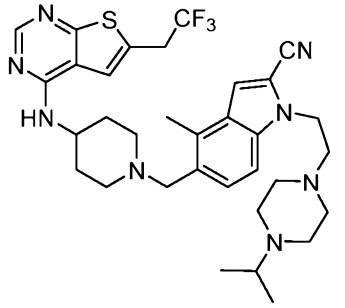
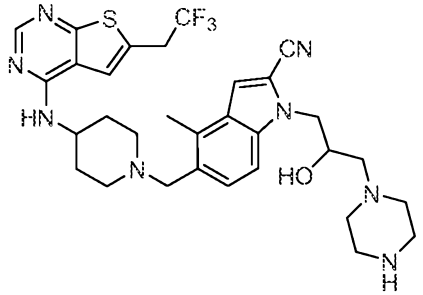
330		579.4	1.47 min
331		567.4	1.58 min
332		565.6	1.35 min
333		644.6	1.46 min
334		581.2	1.71 min

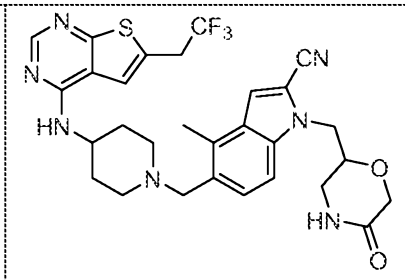
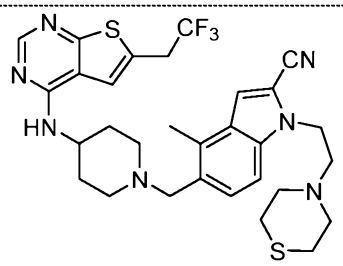
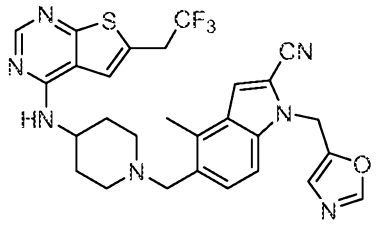
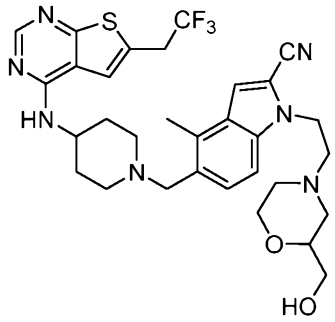
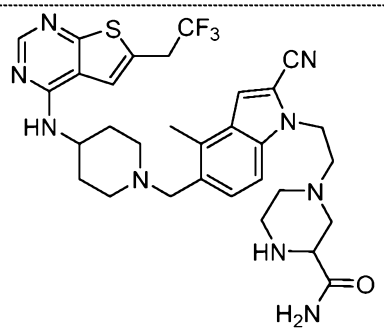
335		581.2	1.60 min
336		597.5	1.44 min
337		611.6	1.53 min
338		615.5	1.93 min
339		735.5	2.24 min

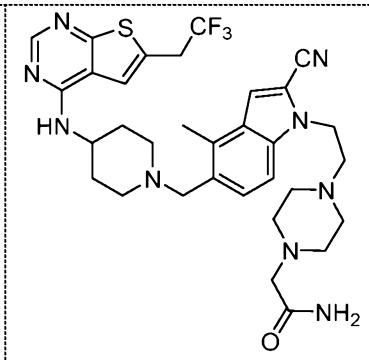
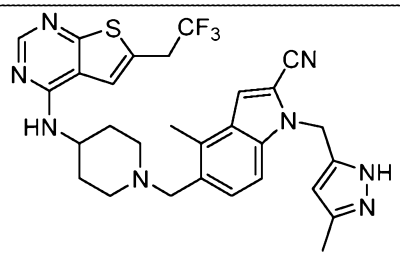
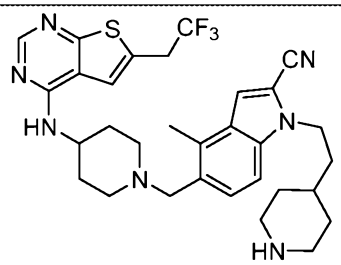
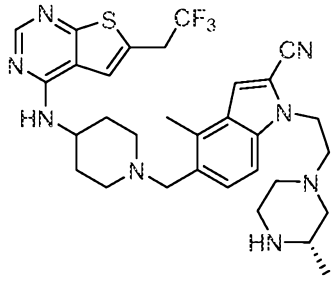
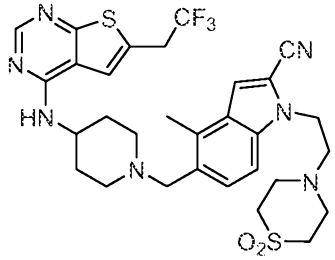
340		715.4	1.91 min
341		729.5	2.01 min
342		721.4	1.97 min
343		721.4	2.06 min

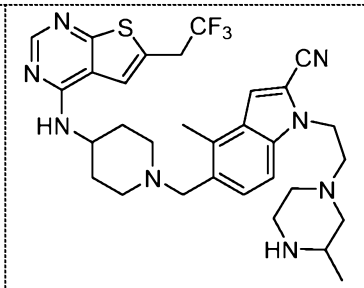
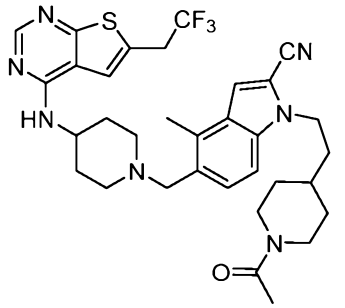
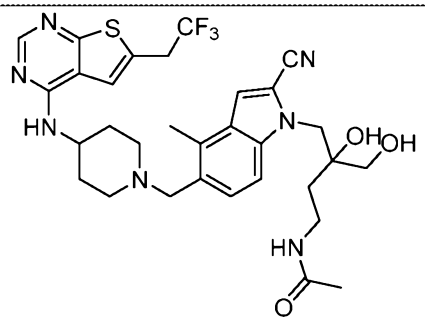
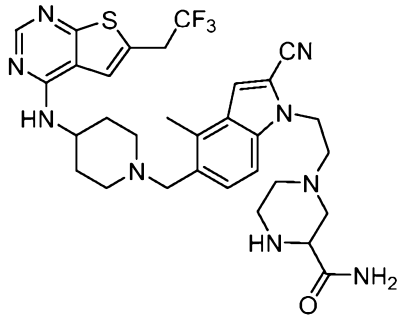
344		693.5	1.91 min
345		656.3	1.54 min
346		669.5	2.29 min
347		672.5	1.73 min

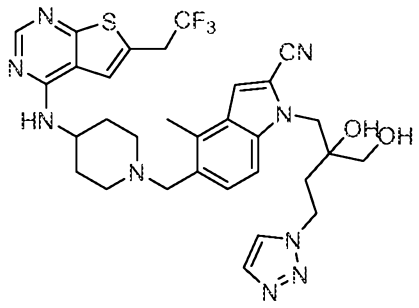
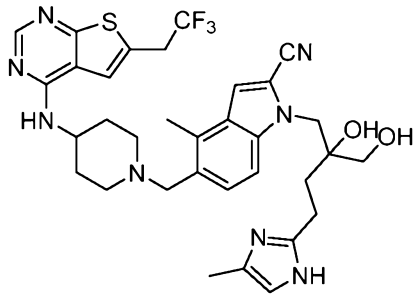
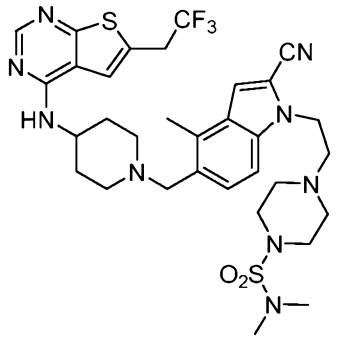
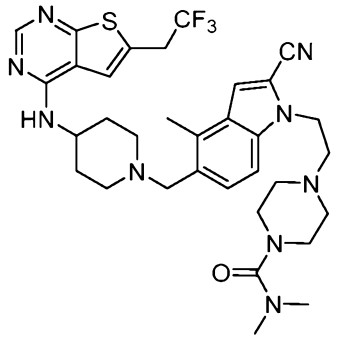
348		655.4	2.19 min
349		565.3	1.43 min
350		579.4	1.48 min
351		579.4	1.47 min
352		579.4	1.63 min
353		566.5	1.83 min

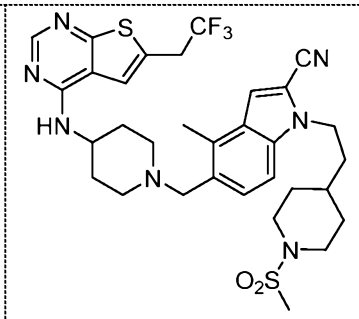
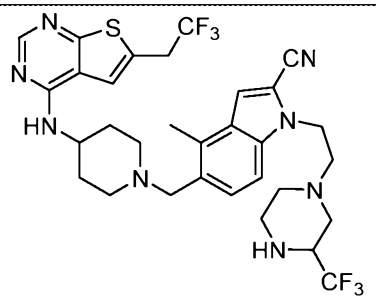
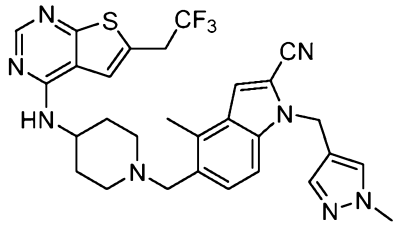
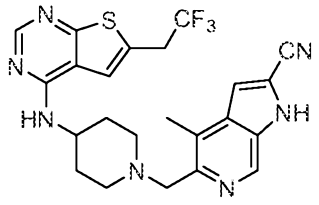
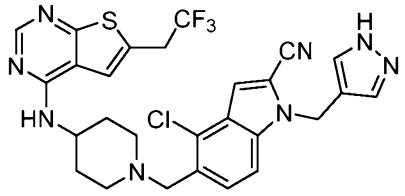
354		591.5	1.70 min
355		611.3	1.57 min
356		625.4	1.55 min
357		639.5	1.57 min
358		627.5	1.46 min

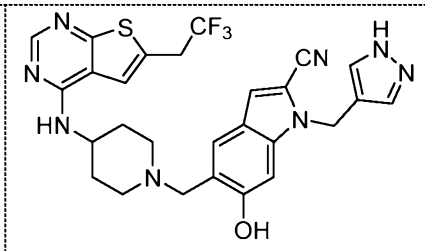
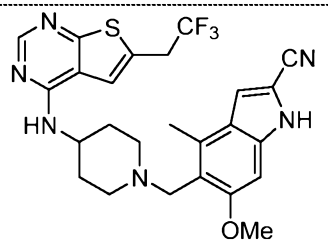
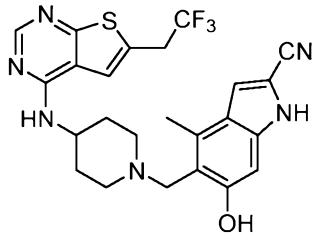
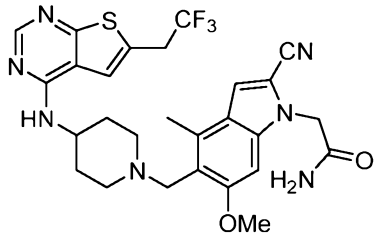
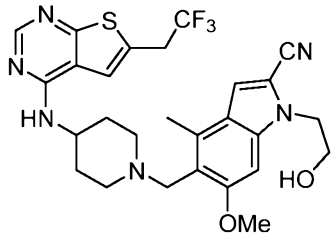
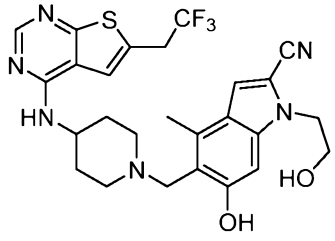
359		598.4	1.60 min
360		614.3	1.53 min
361		566.2	1.74 min
362		628.4	1.43 min
363		640.4	1.45 min

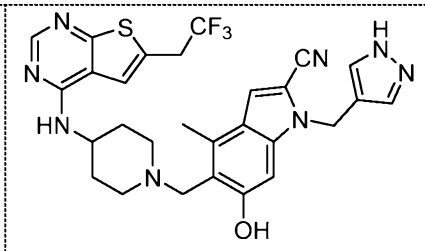
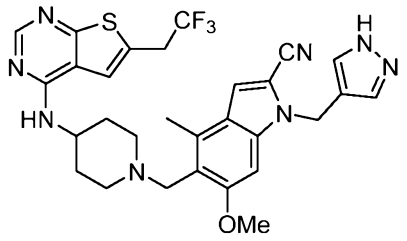
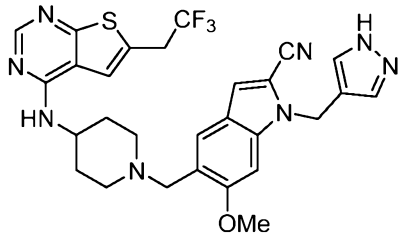
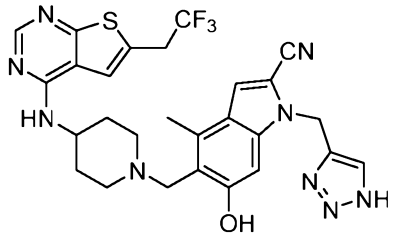
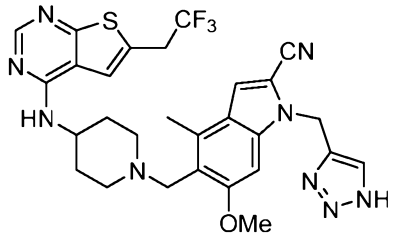
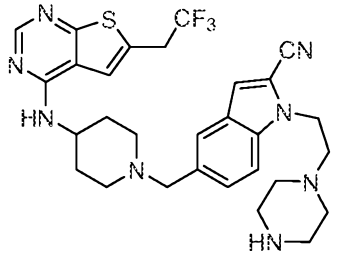
364		654.5	1.46 min
365		579.4	1.85 min
366		596.3	1.55 min
367		611.3	1.49 min
368		646.4	1.80 min

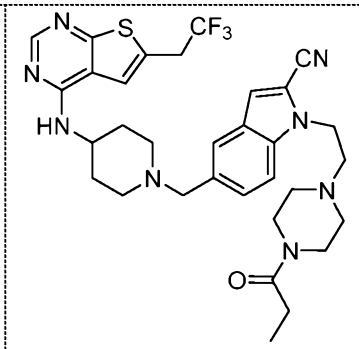
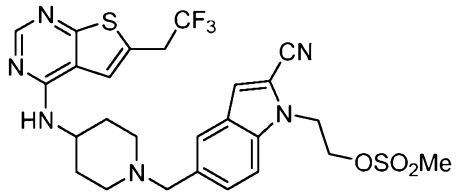
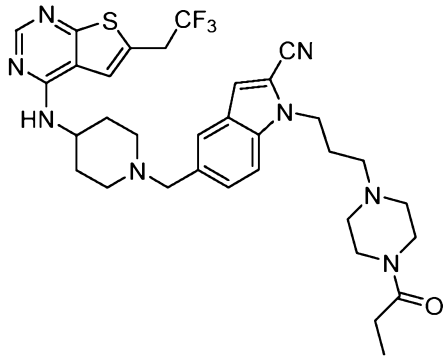
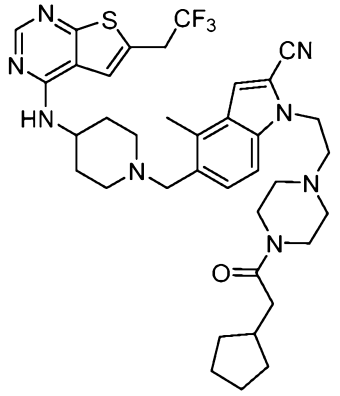
369		611.6	1.52 min
370		638.3	1.89 min
371		644.6	1.70 min
372		641.3	1.60 min

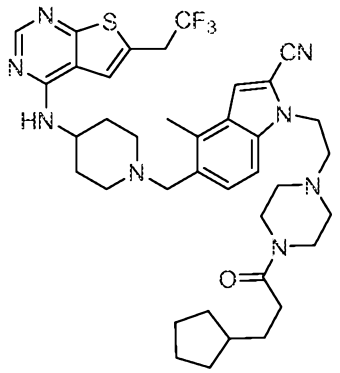
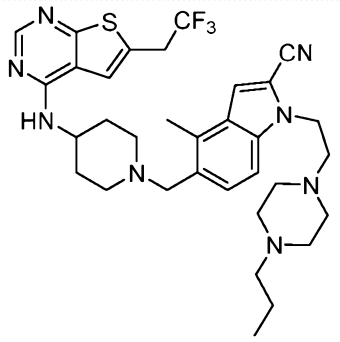
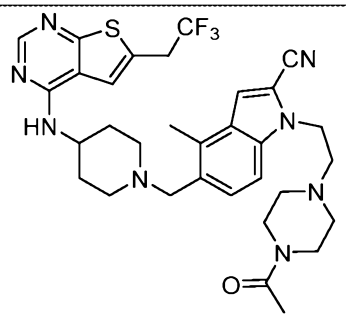
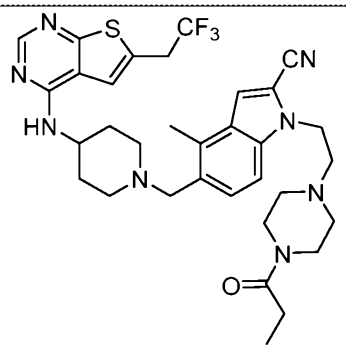
373		654.5	1.72 min
374		579.1	1.64 min
375		704.3	1.75 min
376		668.6	1.63 min

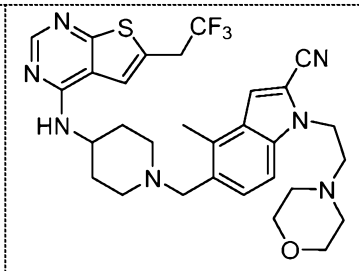
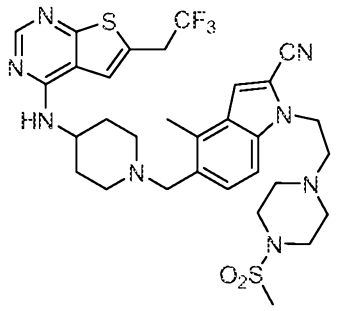
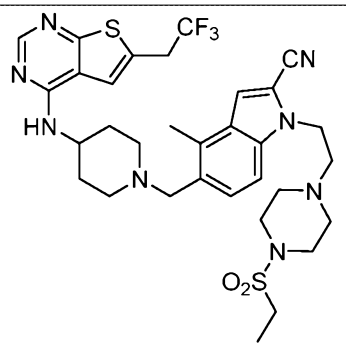
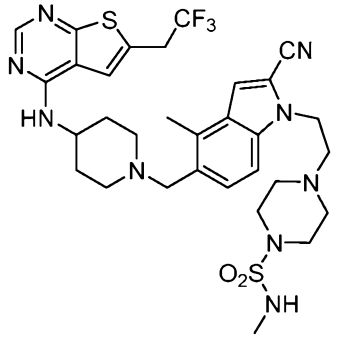
377		674.3	2.11 min
378		665.3	1.73 min
379		579.4	1.95 min
380		472.3	1.55 min
381		585.1554	0.2

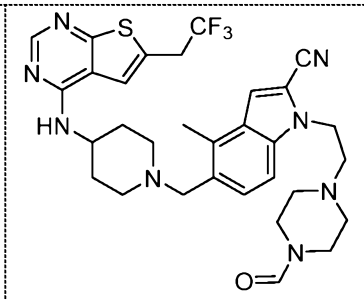
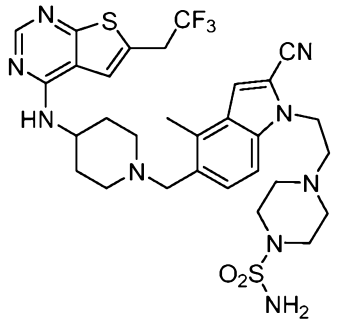
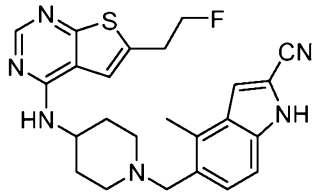
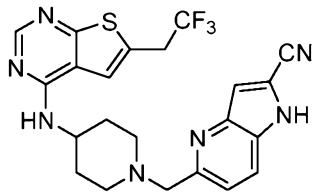
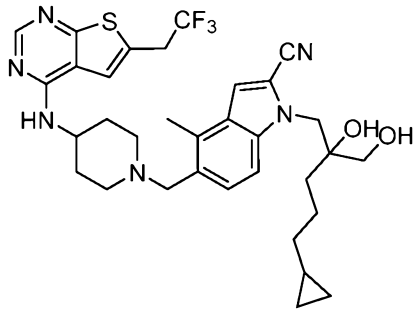
382		567.1893	0.2
383		515.1837	0.3
384		501.1674	0.2
385		572.2047	0.1
386		559.3001	0.1
387		545.1943	0.1

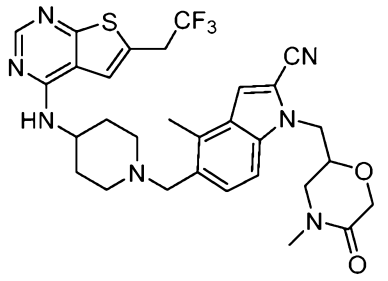
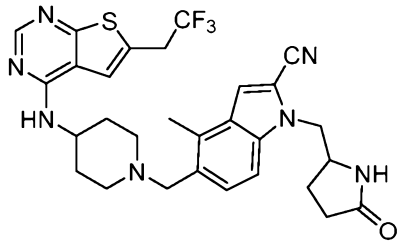
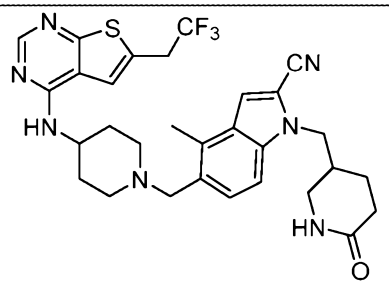
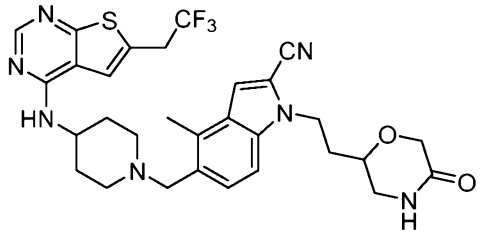
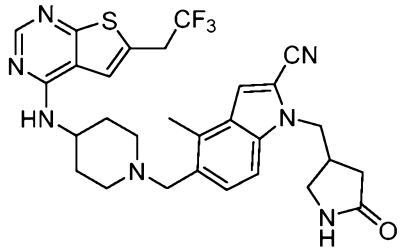
388		581.2050	0.1
389		595.2214	0.1
390		581.2056	0.1
391		582.2001	0.1
392		596.2159	0.1
393		583.2570	0.1

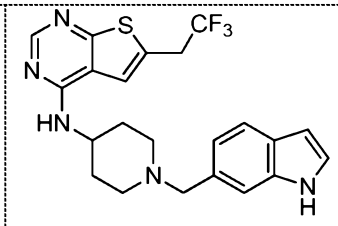
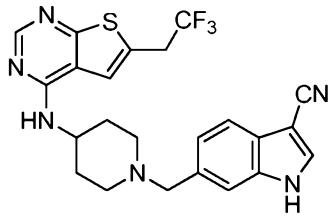
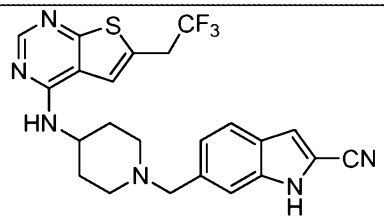
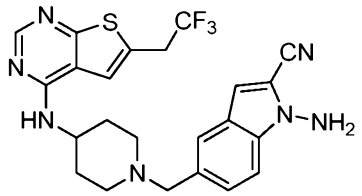
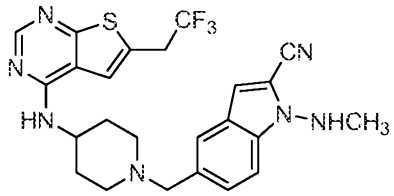
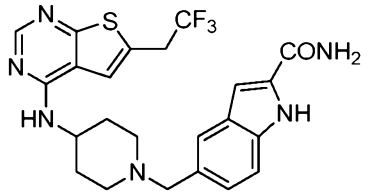
394		639.2833	0.2
395		593.1615	0.2
396		653.2995	0.2
397		707.3461	0.2

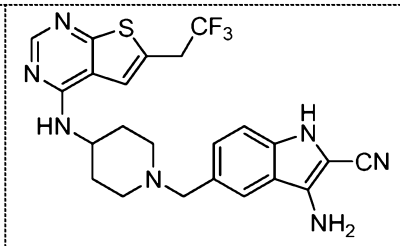
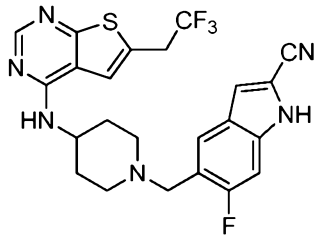
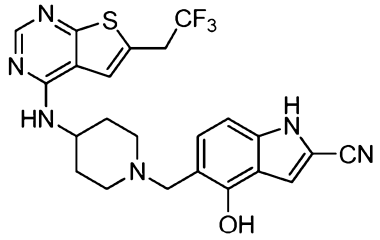
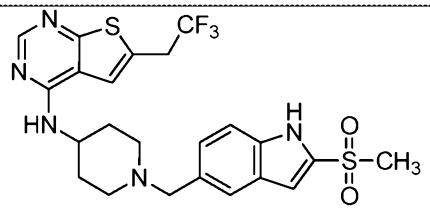
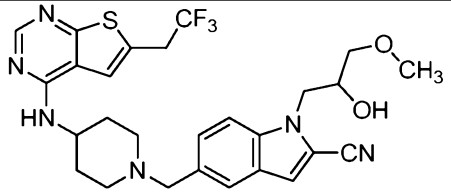
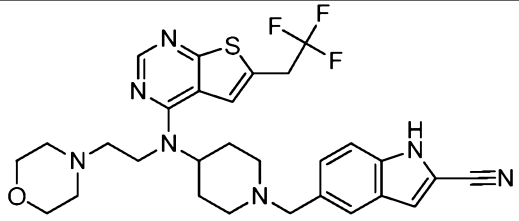
398		721.3622	0.2
399		639.3203	0.2
400		639.2837	0.2
401		653.2989	0.2

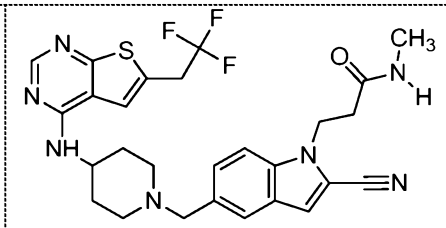
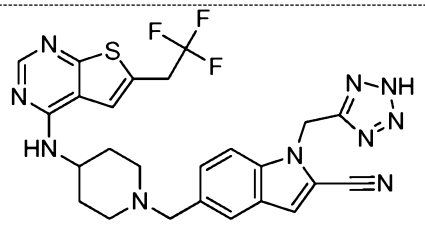
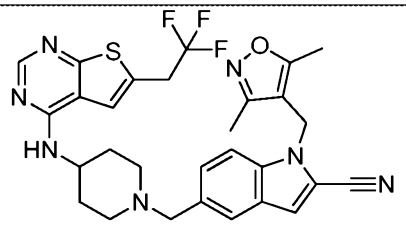
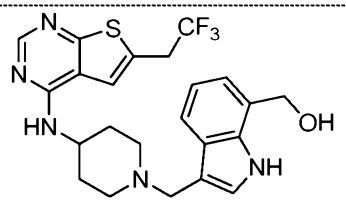
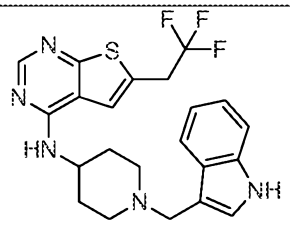
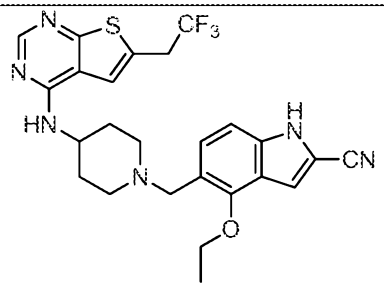
402		598.2566	0.3
403		675.2503	0.2
404		689.2663	0.2
405		690.2613	0.2

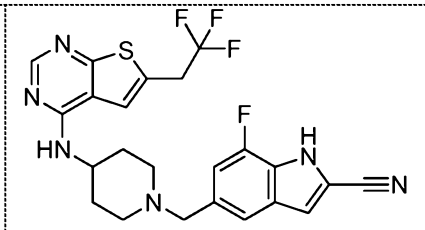
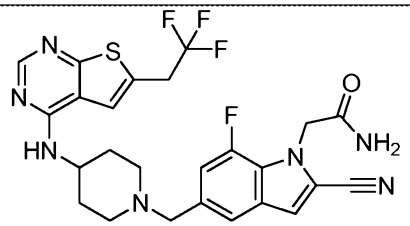
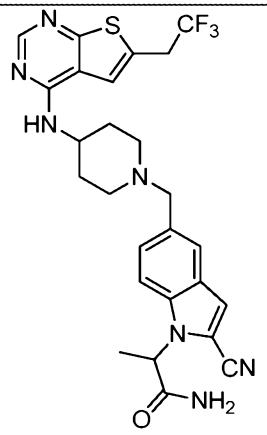
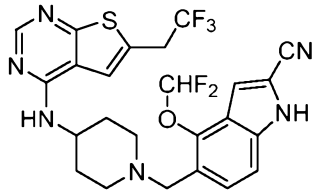
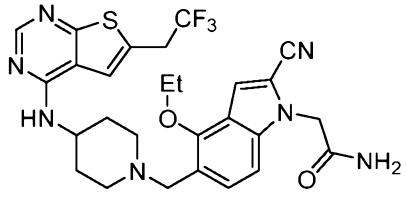
406		625.2682	0.2
407		676.2457	0.1
423		449.1915	0.2
424		472.3	1.65 min
425		641.3	2.29 min

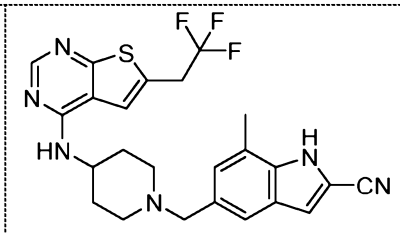
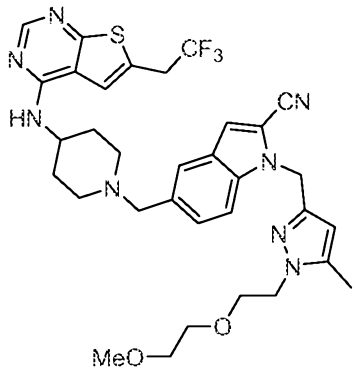
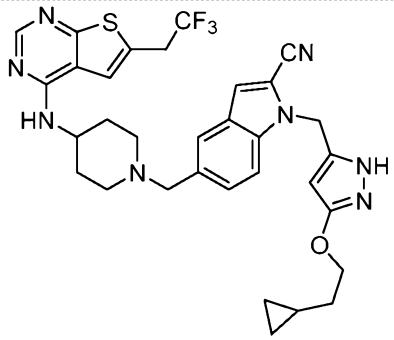
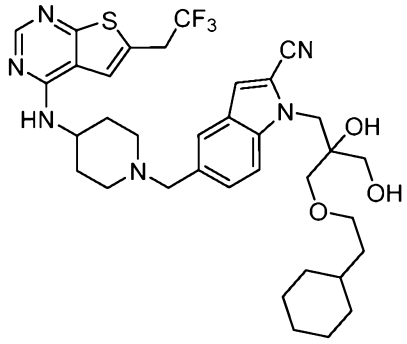
426		612.5	1.63 min
427		582.4	1.64 min
428		596.3	1.60 min
429		612.5	1.67 min
430		582.4	1.60 min
Inhibitors with IC50 0.1μM-0.5μM			

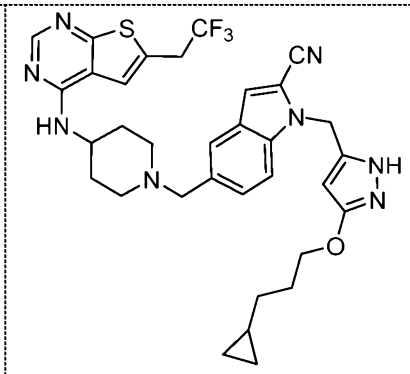
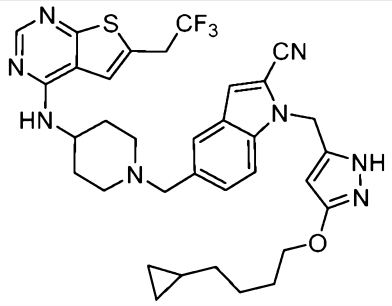
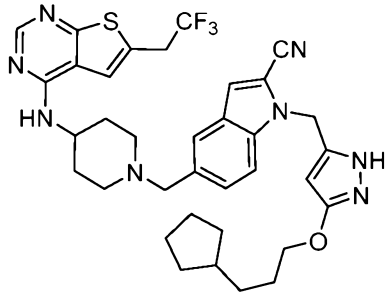
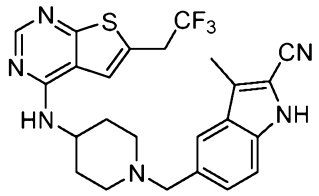
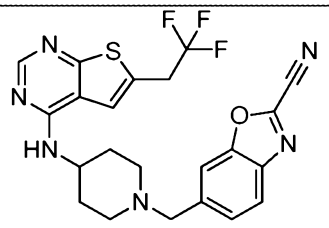
227		446.2	1.53 min
228		471.1584	0.3
229		471.1579	0.3
230		486.1675	0.2
231		500.1844	0.3
232		489.1685	0.2

233		486.1679	0.3
234		489.1483	0.3
235		487.1517	0.3
236		524.8	1.45 min
237		559.3	1.57 min
238		584.2	1.52 min

239		556.3	1.52 min
240		553.3	1.52 min
241		580.3	1.81 min
242		476.1729	0.2
243		446.2	1.52 min
244		515.2	1.98 min

245		489.1	1.96 min
246		546.1	1.77 min
247		542.1945	0.1
408		537.1	1.87 min
409		571.9	1.78 min

410		485.5	1.66 min
411		667.4	2.23 min
412		635.3	2.32 min
413		685.7	2.55 min

414		649.4	2.46 min
415		663.5	2.53 min
416		678.5	2.68 min
417		485.1732	0.3
Inhibitors with IC50 0.5μM-2μM			
248		473.2	1.47 min

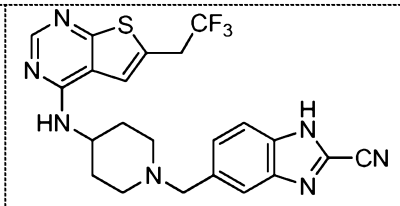
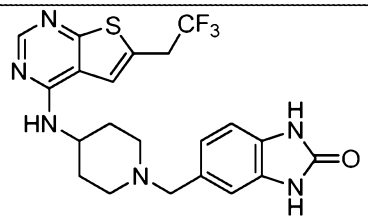
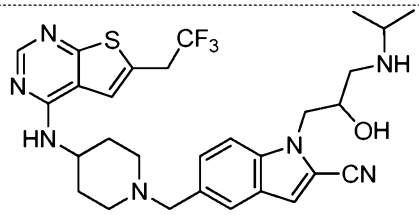
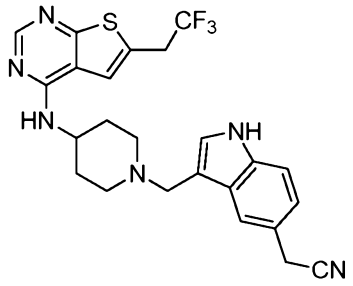
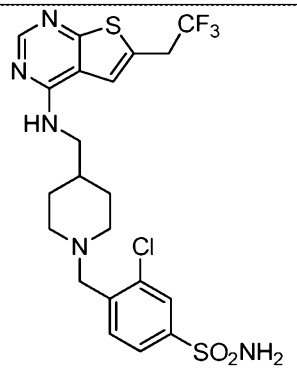
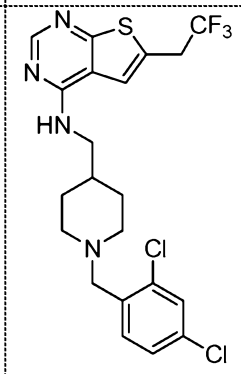
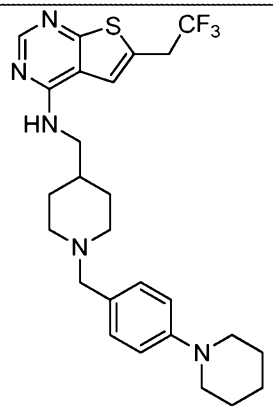
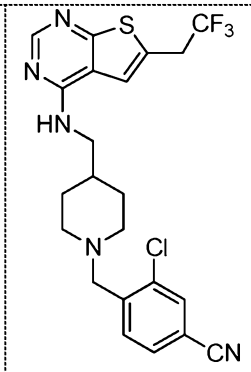
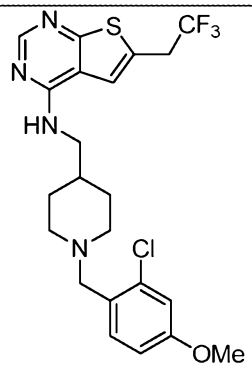
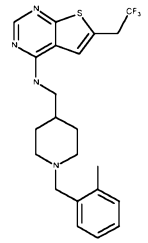
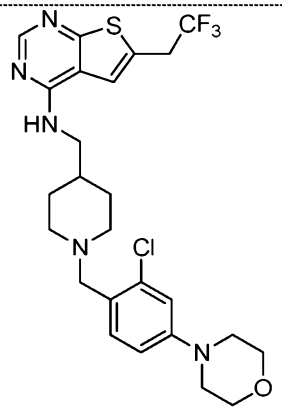
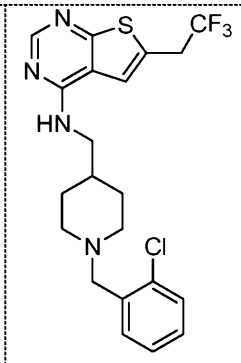
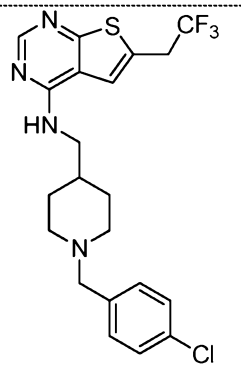
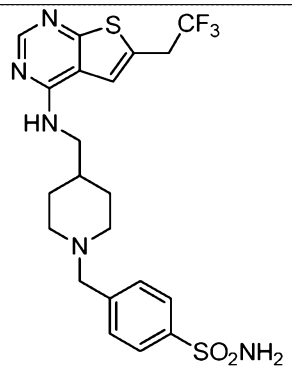
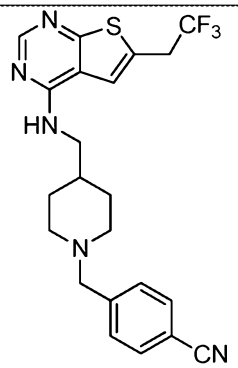
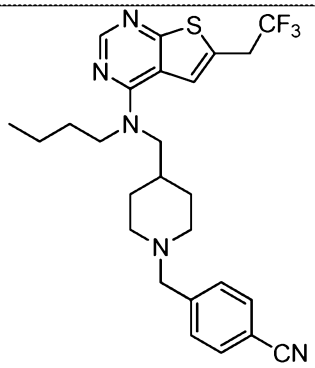
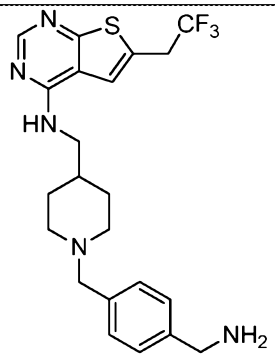
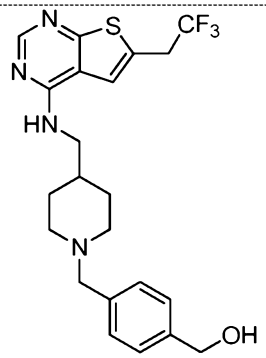
249		472.3	1.39 min
250		463.3	1.14
251		586.4	1.27 min
252		485.1735	0.3

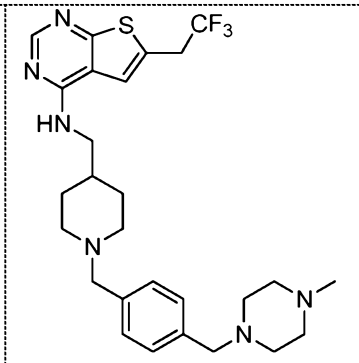
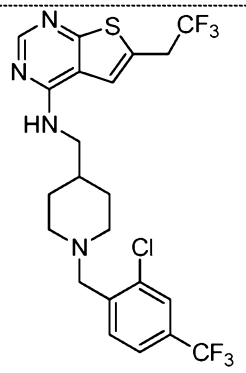
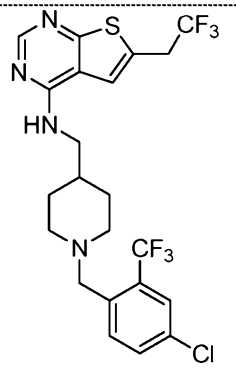
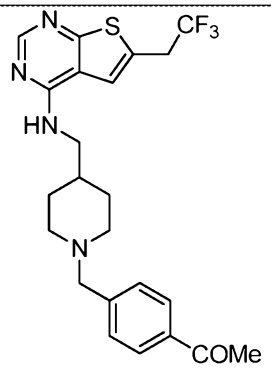
Table 6: Examples of subscaffold 5 of inhibitors of menin-MLL.

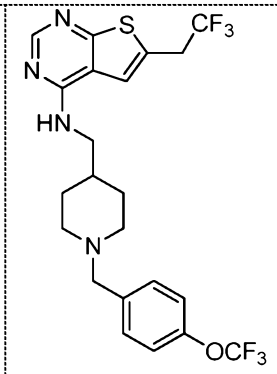
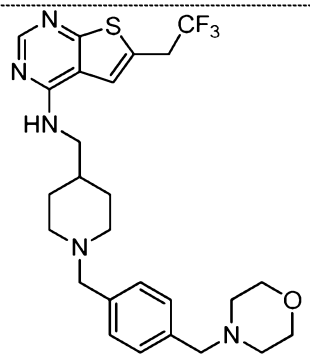
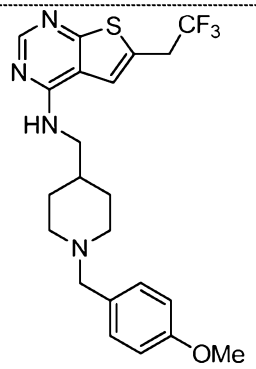
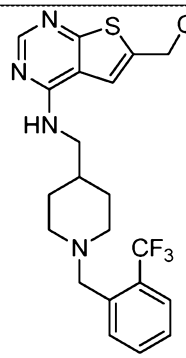
Compound#	Structure	$[MH]^+$	LC-MS RT, min. or R_f
Inhibitors with IC50 0.1μM-0.5μM			
253		534.1	1.20 min
254		489.1	1.63 min
255		504.4	1.52 min

256		480.1	1.65 min
257		485.2	1.67 min
258		435.4	1.49 min
259		540.4	1.57 min

260		455.2	1.54 min
261		455.2	1.59 min
262		500.2	1.45 min
263		446.2	1.62 min

Inhibitors with IC50 0.5μM-2μM			
264		502.3	1.77 min
265		450.4	1.09 min
266		451.3	1.15 min

267		533.5	1.26 min
268		523.6	1.68 min
269		523.3	2.00 min
270		463.0	1.76 min

271		505.3	1.70 min
272		520.3	1.19 min
273		451.3	1.50 min
274		489.5	1.49 min

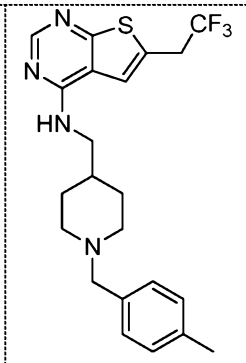
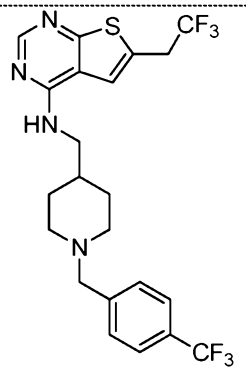
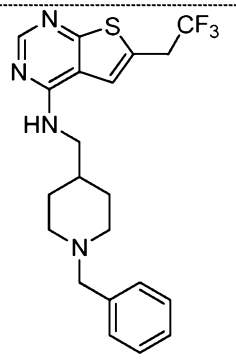
275		435.4	1.79 min
276		489.5	1.58 min
277		421.0	1.27 min

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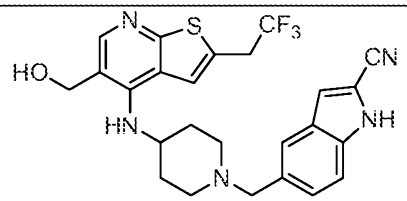
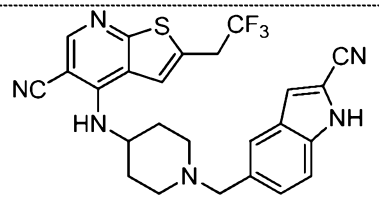
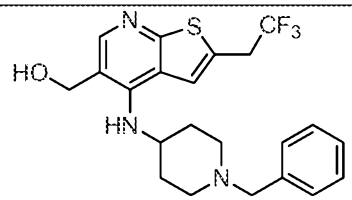
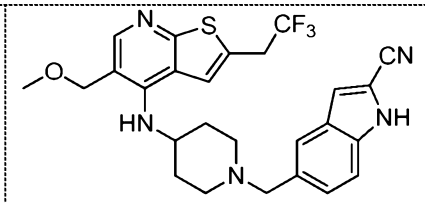
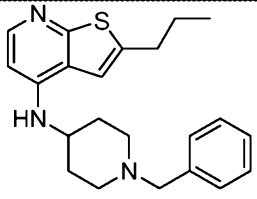
Table 7: Examples of subscaffold 3 and 4 of inhibitors of menin-MLL.

Compound#	Structure	$[MH]^+$	LC-MS RT, min. or TLC R_f
Inhibitors with IC50 <0.1μM			
278		500.2	1.45 min
279		431.2	1.78 min
280		436.0	1.19 min
Inhibitors with IC50 0.1μM-0.5μM			
281		450.1	1.30 min
Inhibitors with IC50 0.5μM-2μM			
282		366.3	1.35 min

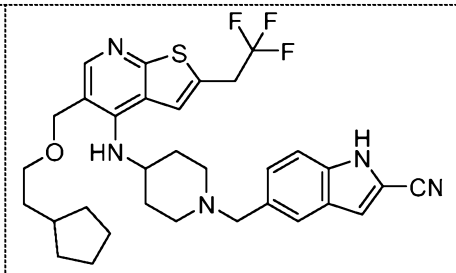
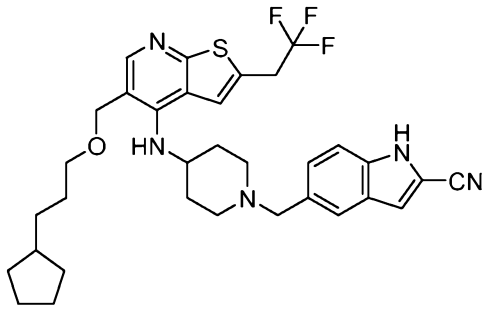
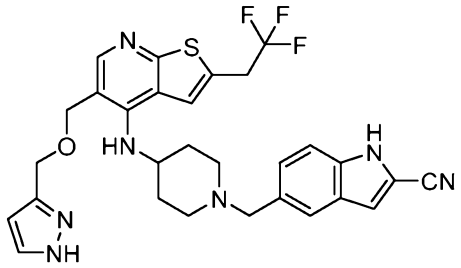
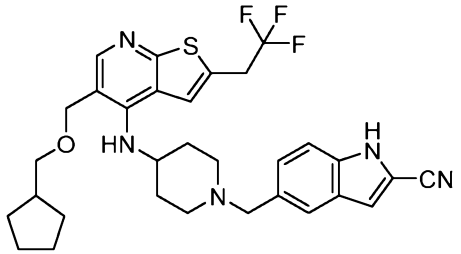
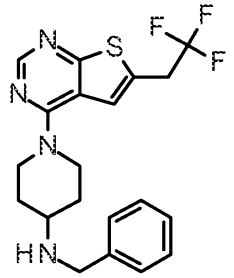
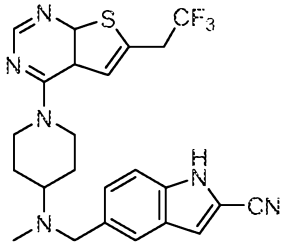
418		596.6	2.03 min
419		610.4	2.15 min
420		580.0	1.49 min
421		582.4	1.94 min

Table 8. Examples of subscaffold 6 of inhibitors of menin-MLL.

Compound#	Structure	$[MH]^+$	LC-MS RT, min. or TLC R_f

283			
422		487.1883	0.3

In other embodiments, additional substituents, not depicted in Tables 1-8 or described herein by name or formula, are formed by combination of the above functional groups; such substituents are within the scope of the present invention, and may be appended to one or more of subscaffolds 1-6 to yield compositions within the scope of the present invention.

Subscaffolds 1-6 are provided herein as exemplary subscaffolds of the general thienopyrimidine and thienopyridine class of compounds. While these subscaffolds, with any combination of the substituents depicted or described herein (e.g., explicitly or through combination of functional groups), are within the scope of embodiments of the invention, the present invention is not limited to such subscaffolds. Thienopyrimidine and thienopyridine derivatives of subscaffolds 1-6 are also within the scope of embodiments of the present invention. Substitutions and/or addition/deletion of substituents of subscaffolds 1-6 that produce functional equivalents and/or improved functionality (e.g., enhanced therapeutic effect, enhanced bioavailability, improved human tolerance, reduced side effects, etc.) are also within the scope of embodiments of the present invention.

In some embodiments, the present invention provides compositions and methods for prevention and/or treatment of leukemia (e.g. MLL-related leukemia and other acute leukemias). In some embodiments, the present invention provides compositions and method for the inhibition

of the protein-protein interaction between menin and MLL fusion proteins and/or menin and MLL wild type proteins (both MLL1 and MLL2). In some embodiments, compositions and methods inhibit the interaction that is important for the oncogenic (e.g. leukemogenic) potential of MLL fusions. In some embodiments, the present invention provides small molecule inhibitors of interactions between menin and MLL fusion proteins and/or menin and MLL wild type proteins (both MLL1 and MLL2). In some embodiments, compositions and methods reverse (e.g. inhibit, decrease, abolish, etc.) the oncogenic (e.g. leukemogenic) potential of MLL fusion proteins. In some embodiments, compositions find utility in targeted therapies (e.g. anti-leukemia agents). In some embodiments, compounds block menin-MLL interactions.

In some embodiments, the present invention provides compositions which inhibit the interaction between MLL (e.g. MLL fusion proteins and MLL wild type proteins, both MLL1 and MLL2) and menin. In some embodiments, any compounds, small molecules (e.g. pharmaceuticals, drugs, drug-like molecules, etc.), macromolecules (e.g. peptides, nucleic acids, etc.) and/or macromolecular complexes which inhibit the MLL-menin interaction find utility in the present invention. In some embodiments, the present invention provides small molecule compounds which inhibit MLL-menin interactions. In some embodiments, compositions of the present invention decrease the affinity of menin for MLL (e.g. MLL fusion proteins) and/or MLL (e.g. MLL wild type proteins, both MLL1 and MLL2) for menin. In some embodiments, compositions of the present invention disrupt bonding (e.g. hydrogen bonding, ionic bonding, covalent bonding, etc.), molecular interactions (e.g. hydrophobic interactions, electrostatic interactions, van der Waals interactions, etc.), shape recognition, and/or molecular recognition between MLL (e.g. MLL fusion proteins or MLL wild type protein) and menin. However, an understanding of the mechanisms of action is not required to practice the invention and the invention is not limited to any particular mechanism of action.

The present invention provides any small molecules or classes of small molecules which disrupt, target, or inhibit MLL/menin interactions; and/or treat/prevent leukemia. In some embodiments, small molecules are effective in inhibiting the interaction of MLL-fusion proteins with menin or MLL wild type protein with menin. In particular embodiments, the present invention provides thienopyrimidine and thienopyridine classes of small molecules. In some embodiments, thienopyrimidine small molecules of the present invention inhibit the interaction of MLL (e.g. MLL-fusion proteins or MLL wild type, both MLL1 and MLL2) with menin. In some embodiments, thienopyrimidine and thienopyridine small molecules of the present

invention inhibit the oncogenic (e.g. leukemogenic) effects of MLL-fusion proteins, and/or MLL-menin and MLL fusion protein-menin interactions. In some embodiments, thienopyrimidine and thienopyridine small molecules of the present invention treat and/or prevent leukemia (e.g. MLL-dependant leukemias, MLL-related leukemias, or other leukemias with and without high level of *HOX* genes expression etc.).

In some embodiments, the present invention provides administration of compositions of the present invention to subjects (e.g. leukemia patients) to treat or prevent disease (e.g. cancer, leukemia, MLL-related leukemia, etc.). In some embodiments, the present invention provides administration of compositions for the treatment or prevention of leukemia (e.g. acute leukemias, chronic leukemias, lymphoblastic leukemias, lymphocytic leukemias, myeloid leukemias, myelogenous leukemias, Acute lymphoblastic leukemia (ALL), Chronic lymphocytic leukemia (CLL), Acute myelogenous leukemia (AML), Chronic myelogenous leukemia (CML), Hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), Large granular lymphocytic leukemia, MLL-positive leukemias, MLL-induced lukemias, etc.).

In some embodiments, any of the above compounds is co-administered or used in combination with a known therapeutic agent (e.g., methotrexate, 6-mercaptopurine, antibody therapies, etc.). In some embodiments, a compound of the present invention is co-administered with another therapeutic agent effective in treating one or more leukemias.

In some embodiments, a compound of the present invention is co-administered with one or more therapeutic agents approved for the treatment of Acute Lymphoblastic Leukemia (ALL), for example: ABITREXATE (Methotrexate), ADRIAMYCIN PFS (Doxorubicin Hydrochloride), ADRIAMYCIN RDF (Doxorubicin Hydrochloride), ARRANON (Nelarabine), Asparaginase Erwinia chrysanthemi, CERUBIDINE (Daunorubicin Hydrochloride), CLAFEN (Cyclophosphamide), CLOFARABINE, CLOFAREX (Clofarabine), CLOLAR (Clofarabine), Cyclophosphamide, Cytarabine, CYTOSAR-U (Cytarabine), CYTOXAN (Cyclophosphamide), Dasatinib, Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Erwinaze (Asparaginase Erwinia Chrysanthemi), FOLEX (Methotrexate), FOLEX PFS (Methotrexate), GLEEVEC (Imatinib Mesylate), ICLUSIG (Ponatinib Hydrochloride), Imatinib Mesylate, MARQIBO (Vincristine Sulfate Liposome), Methotrexate, METHOTREXATE LPF (Methorexate), MEXATE (Methotrexate), MEXATE-AQ (Methotrexate), Nelarabine, NEOSAR (Cyclophosphamide), ONCASPAR (Pegaspargase), Pegaspargase, Ponatinib Hydrochloride,

RUBIDOMYCIN (Daunorubicin Hydrochloride), SPRYCEL (Dasatinib), TARABINE PFS (Cytarabine), VINCASAR PFS (Vincristine Sulfate), Vincristine Sulfate, etc.

In some embodiments, a compound of the present invention is co-administered with one or more therapeutic agents approved for the treatment of Acute Myeloid Leukemia (AML), for example: ADRIAMYCIN PFS (Doxorubicin Hydrochloride), ADRIAMYCIN RDF (Doxorubicin Hydrochloride), Arsenic Trioxide, CERUBIDINE (Daunorubicin Hydrochloride), CLAFEN (Cyclophosphamide), Cyclophosphamide, Cytarabine, CYTOSAR-U (Cytarabine), CYTOXAN (Cyclophosphamide), Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, NEOSAR (Cyclophosphamide), RUBIDOMYCIN (Daunorubicin Hydrochloride), TARABINE PFS (Cytarabine), TRISENOX (Arsenic Trioxide), VINCASAR PFS (Vincristine Sulfate), Vincristine Sulfate, etc.

In some embodiments, a compound of the present invention is co-administered with one or more therapeutic agents approved for the treatment of Chronic Lymphocytic Leukemia (CLL), for example: Alemtuzumab, AMBOCHLORIN (Chlorambucil), AMBOCLORIN (Chlorambucil), ARZERRA (Ofatumumab), Bendamustine Hydrochloride, CAMPATH (Alemtuzumab), CHLORAMBUCILCLAFEN (Cyclophosphamide), Cyclophosphamide, CYTOXAN (Cyclophosphamide), FLUDARA (Fludarabine Phosphate), Fludarabine Phosphate, LEUKERAN (Chlorambucil), LINFOLIZIN (Chlorambucil), NEOSAR (Cyclophosphamide), Ofatumumab, TREANDA (Bendamustine Hydrochloride), etc.

In some embodiments, a compound of the present invention is co-administered with one or more therapeutic agents approved for the treatment of Chronic Myelogenous Leukemia (CML), for example: BOSULIF (Bosutinib), Bosutinib, CLAFEN (Cyclophosphamide), Cyclophosphamide, Cytarabine, CYTOSAR-U (Cytarabine), CYTOXAN (Cyclophosphamide), Dasatinib, GLEEVEC (Imatinib Mesylate), ICLUSIG (Ponatinib Hydrochloride), Imatinib Mesylate, NEOSAR (Cyclophosphamide), Nilotinib, Omacetaxine Mepesuccinate, Ponatinib Hydrochloride, SPRYCEL (Dasatinib), SYNRIBO (Omacetaxine Mepesuccinate), TARABINE PFS (Cytarabine), TASIGNA (Nilotinib), etc.

In some embodiments, a compound of the present invention is co-administered with one or more therapeutic agents approved for the treatment of Meningeal Leukemia, for example: CYTARABINE, CYTOSAR-U (Cytarabine), TARABINE PFS (Cytarabine), etc.

In some embodiments, the compositions of the present invention are provided as pharmaceutical and/or therapeutic compositions. The pharmaceutical and/or therapeutic

compositions of the present invention can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional carriers; aqueous, powder, or oily bases; thickeners; and the like can be necessary or desirable. Compositions and formulations for oral administration include powders or granules, suspensions or solutions in water or non aqueous media, capsules, sachets or tablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders can be desirable. Compositions and formulations for parenteral, intrathecal or intraventricular administration can include sterile aqueous solutions that can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients. Pharmaceutical and/or therapeutic compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome containing formulations. These compositions can be generated from a variety of components that include, but are not limited to, preformed liquids, self emulsifying solids and self emulsifying semisolids.

The pharmaceutical and/or therapeutic formulations of the present invention, which can conveniently be presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical/nutriceutical industries. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. The compositions of the present invention can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention can also be formulated as suspensions in aqueous, non aqueous, oil-based, or mixed media. Suspensions can further contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension

can also contain stabilizers. In one embodiment of the present invention the pharmaceutical compositions can be formulated and used as foams. Pharmaceutical foams include formulations such as, but not limited to, emulsions, microemulsions, creams, jellies and liposomes. While basically similar in nature these formulations vary in the components and the consistency of the final product.

Dosing and administration regimes are tailored by the clinician, or others skilled in the pharmacological arts, based upon well known pharmacological and therapeutic considerations including, but not limited to, the desired level of therapeutic effect, and the practical level of therapeutic effect obtainable. Generally, it is advisable to follow well-known pharmacological principles for administrating chemotherapeutic agents (e.g., it is generally advisable to not change dosages by more than 50% at time and no more than every 3-4 agent half-lives). For compositions that have relatively little or no dose-related toxicity considerations, and where maximum efficacy is desired, doses in excess of the average required dose are not uncommon. This approach to dosing is commonly referred to as the "maximal dose" strategy. In certain embodiments, the compounds are administered to a subject at a dose of about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the compounds described herein are co-administered with another agent (e.g., as sensitizing agents), the effective amount may be less than when the agent is used alone. Dosing may be once per day or multiple times per day for one or more consecutive days.

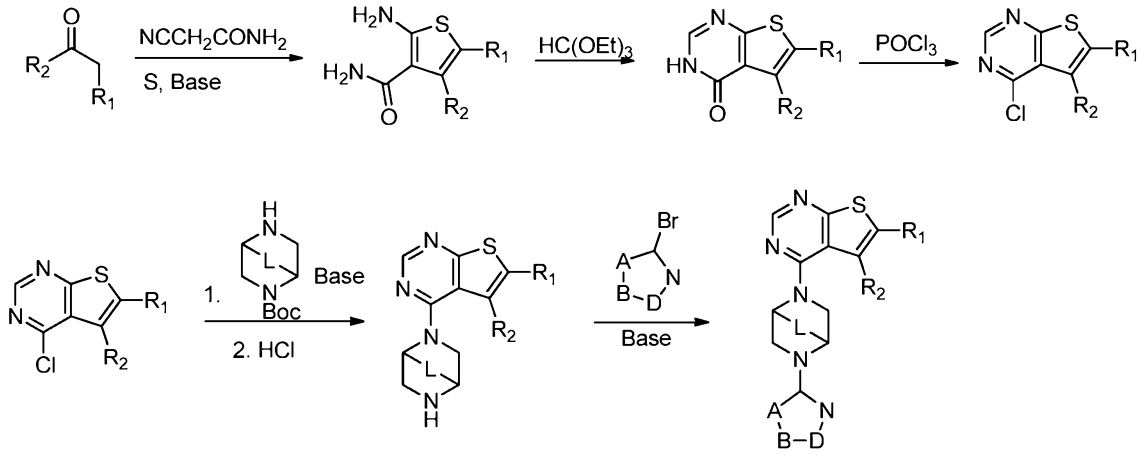
EXPERIMENTAL

Example 1

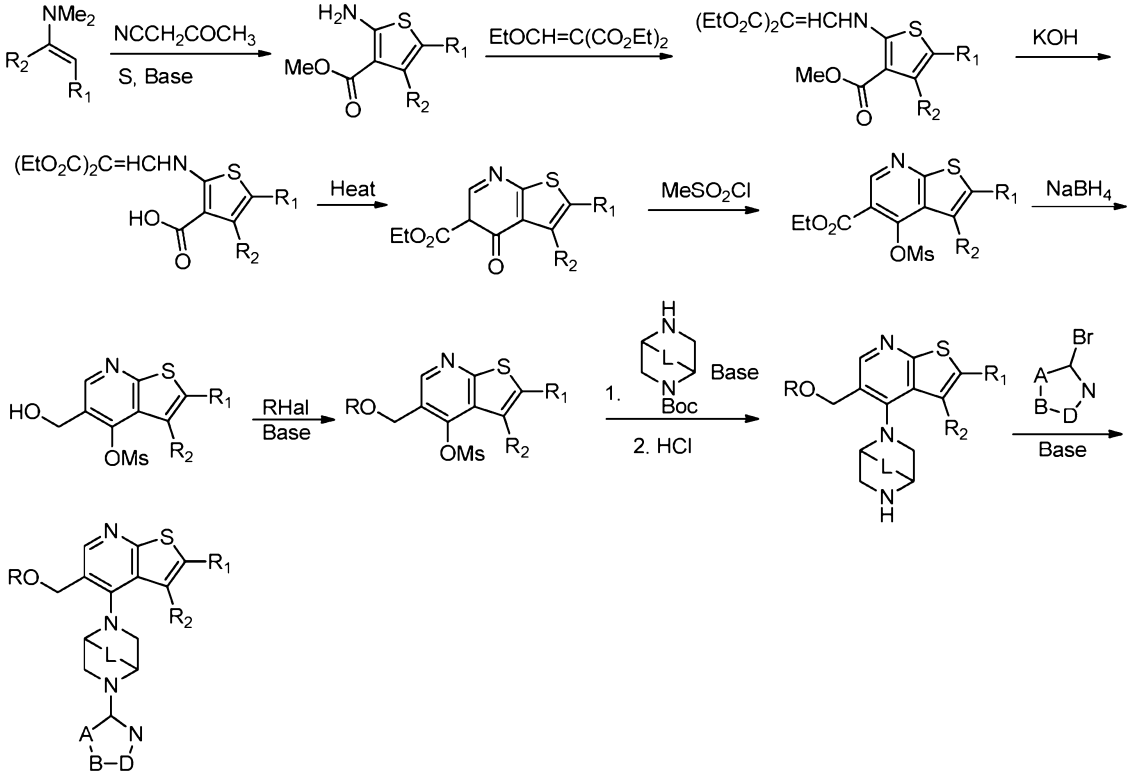
General methods of compounds synthesis

Compounds of subscaffold 1 can be prepared according to the following general method (Scheme 1 and 2).

Scheme 1.

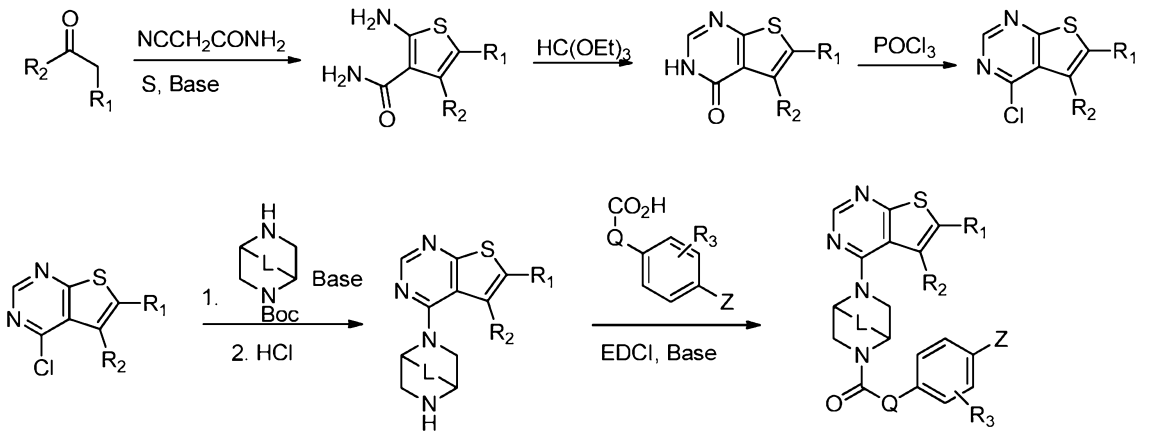

NCCH2CONH2
S, Base
HC(OEt)3
POCl3
1.
Base
Boc
2. HCl
Base

Scheme 2.

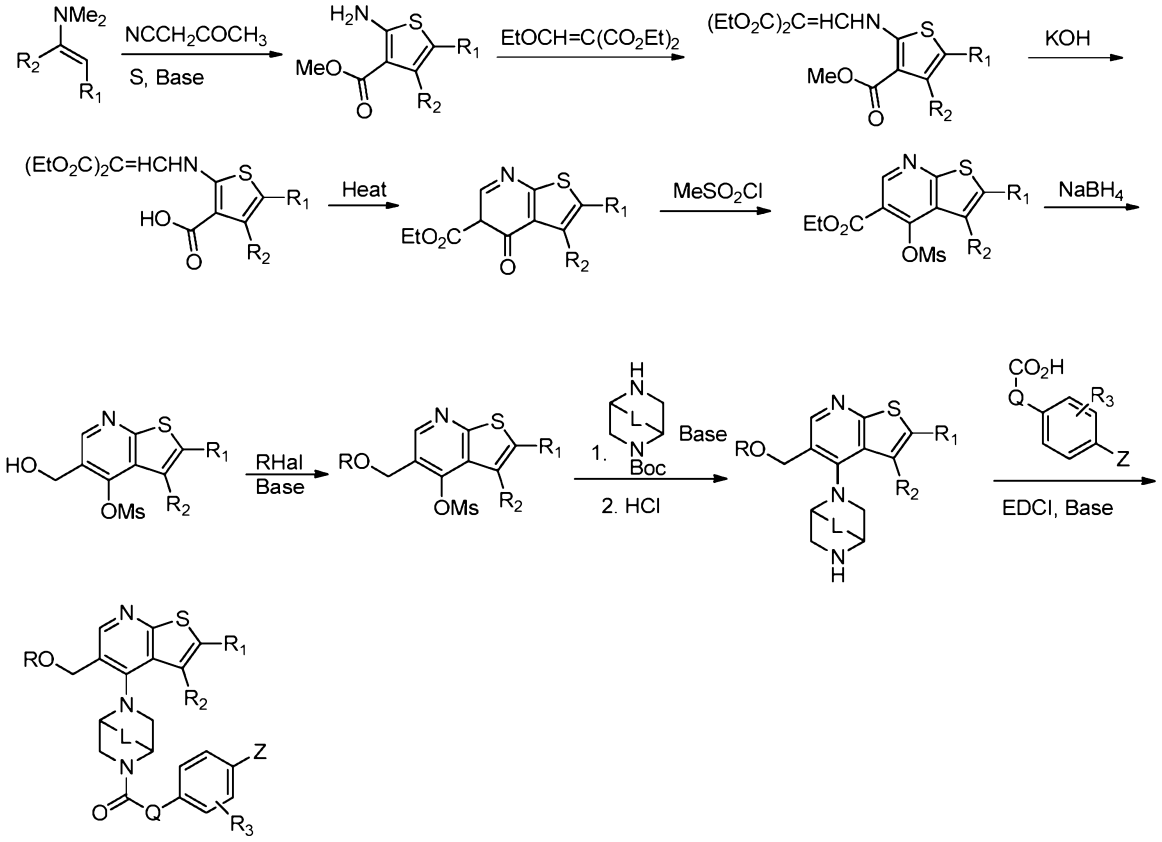

NMe2
R2
R1
NCCH2COCH3
S, Base
H2N
S
MeO
O
R1
R2
EtOCH=C(CO2Et)2
(EtO2C)2C=HCHN
KOH
HO
Heat
N
EtO2C
MeSO2Cl
OMs
NaBH4
RHal
Base
RO
1.
2. HCl
Boc
Br
A
B
D

Compounds of subscaffold 2 can be prepared according to the following general method (Scheme 3 and 4).

Scheme 3.

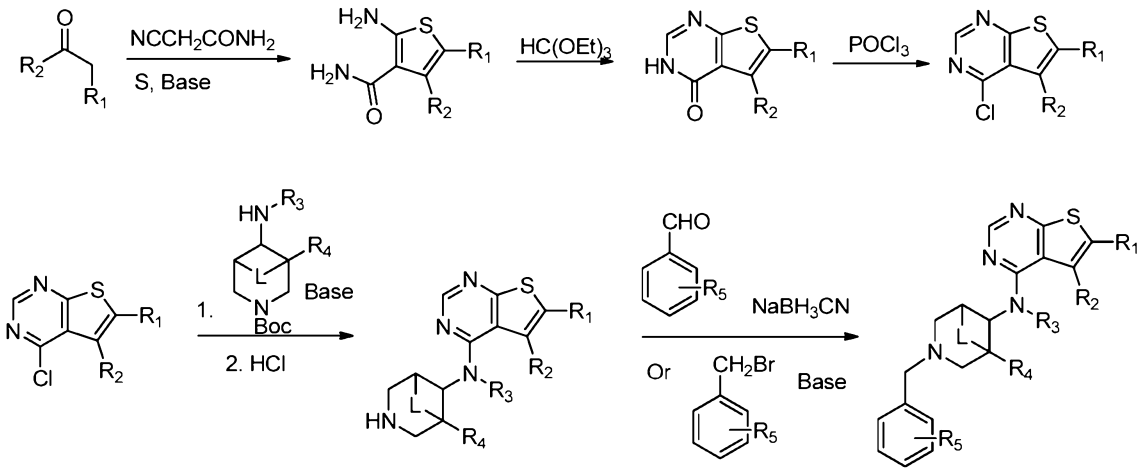


Scheme 4.

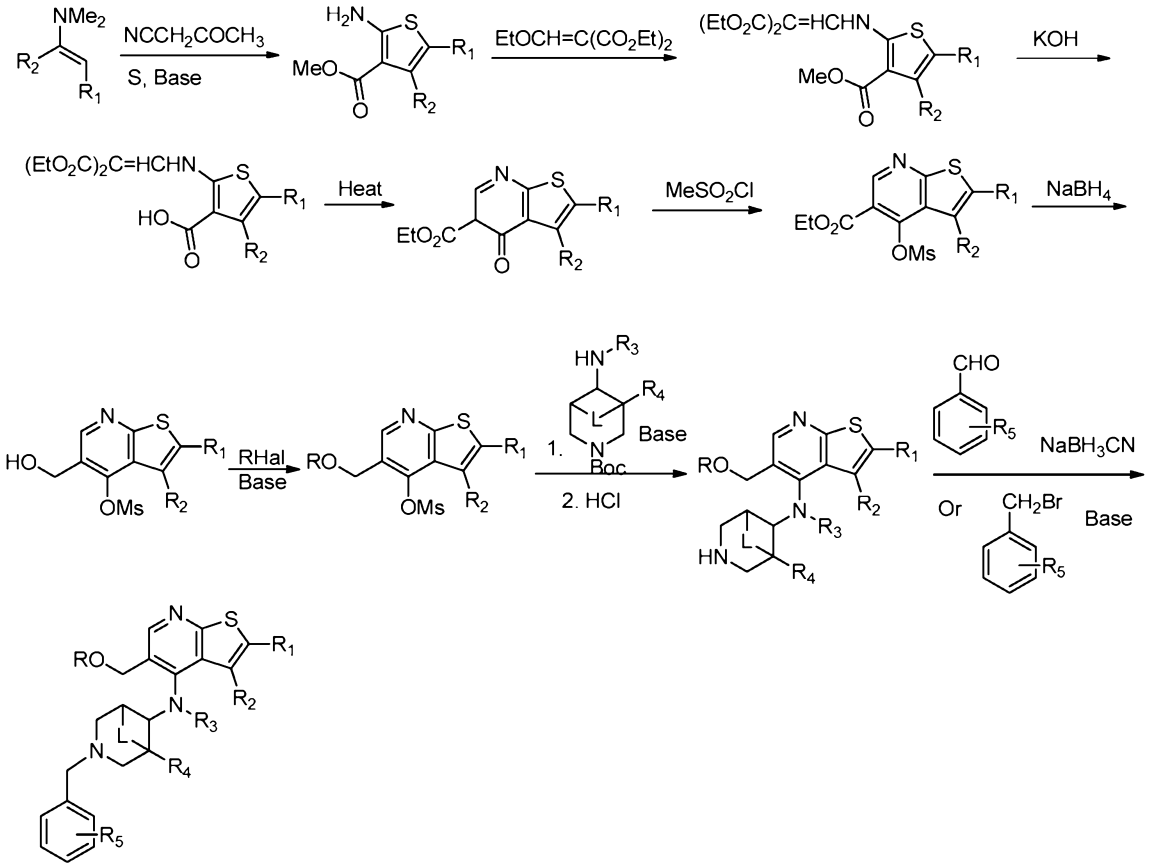


Compounds of subscaffold 3 can be prepared according to the following general method (Scheme 5 and 6).

Scheme 5.



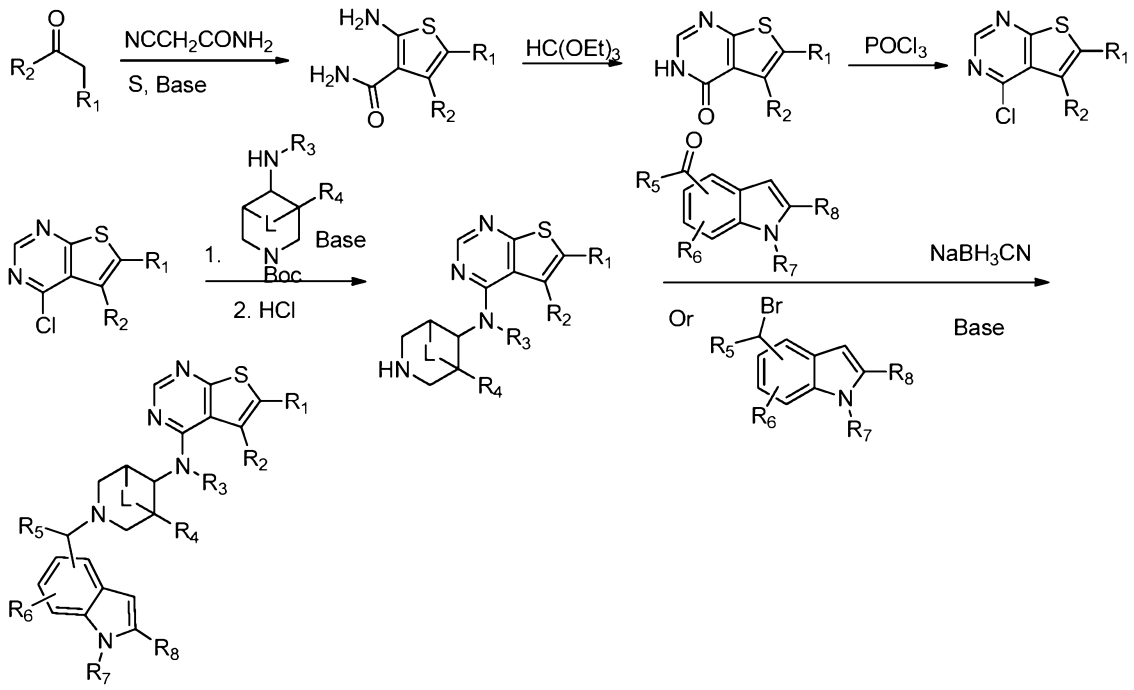
Scheme 6.



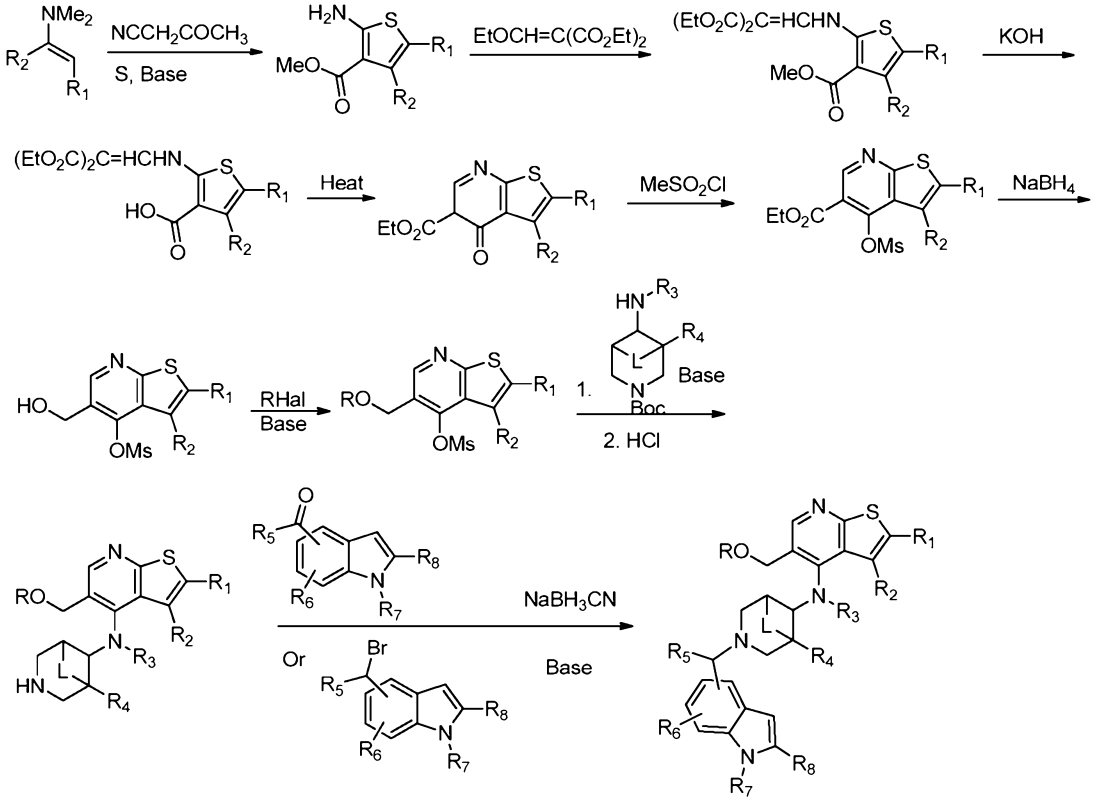
5

Compounds of subscaffold 4 can be prepared according to the following general method (Scheme 7, 8 and 9).

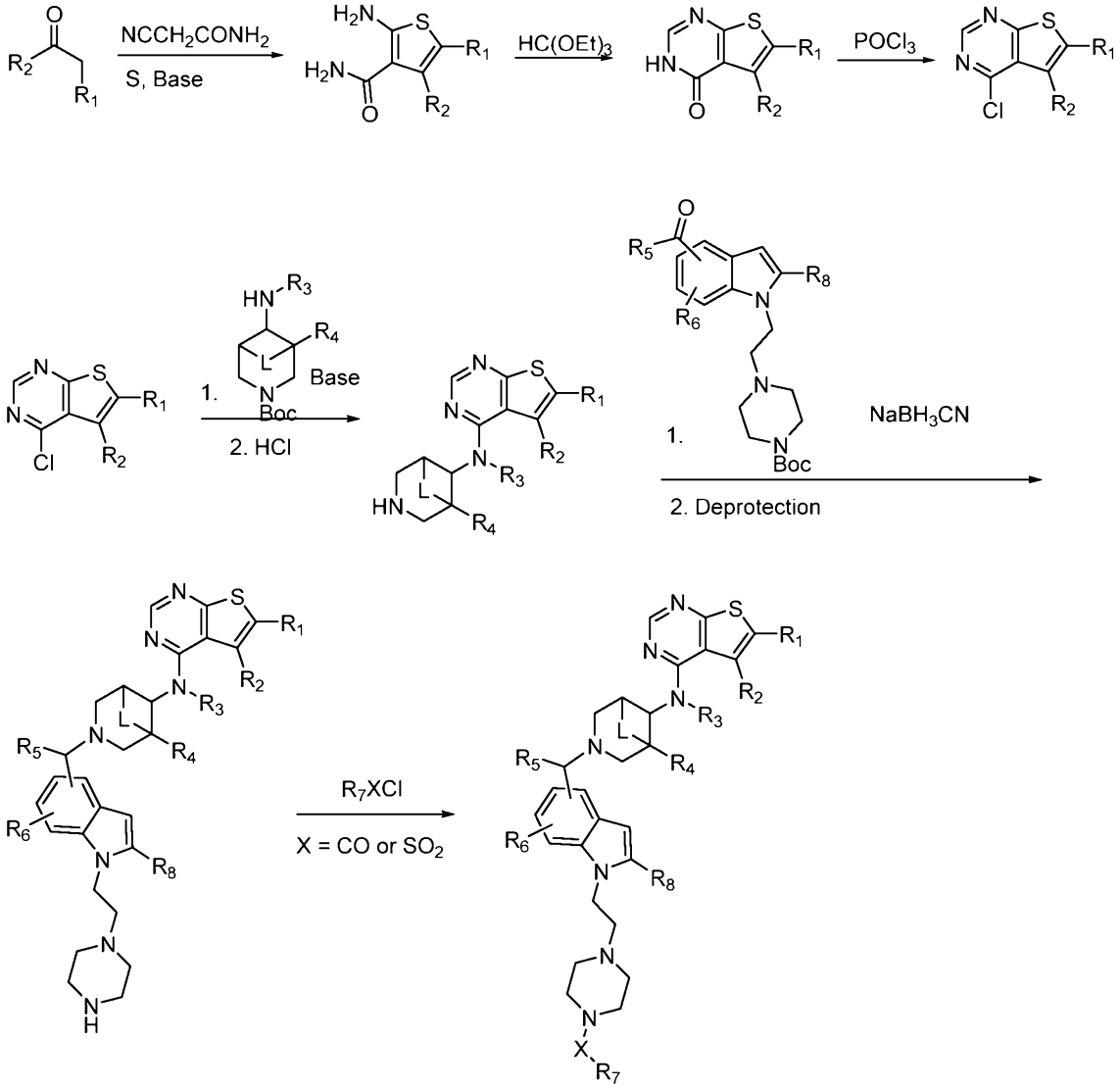
Scheme 7.



Scheme 8.



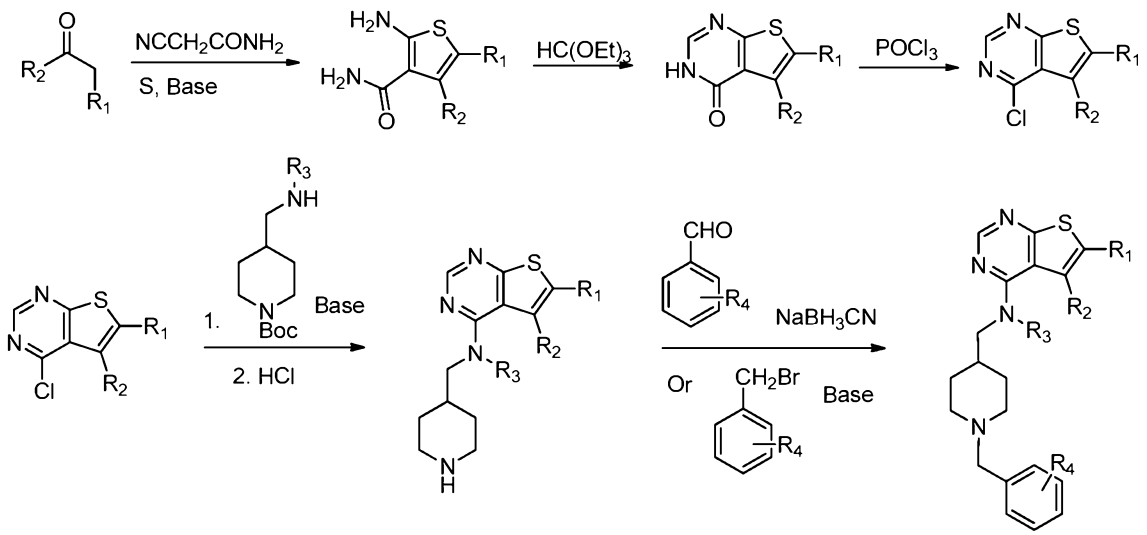
Scheme 9.



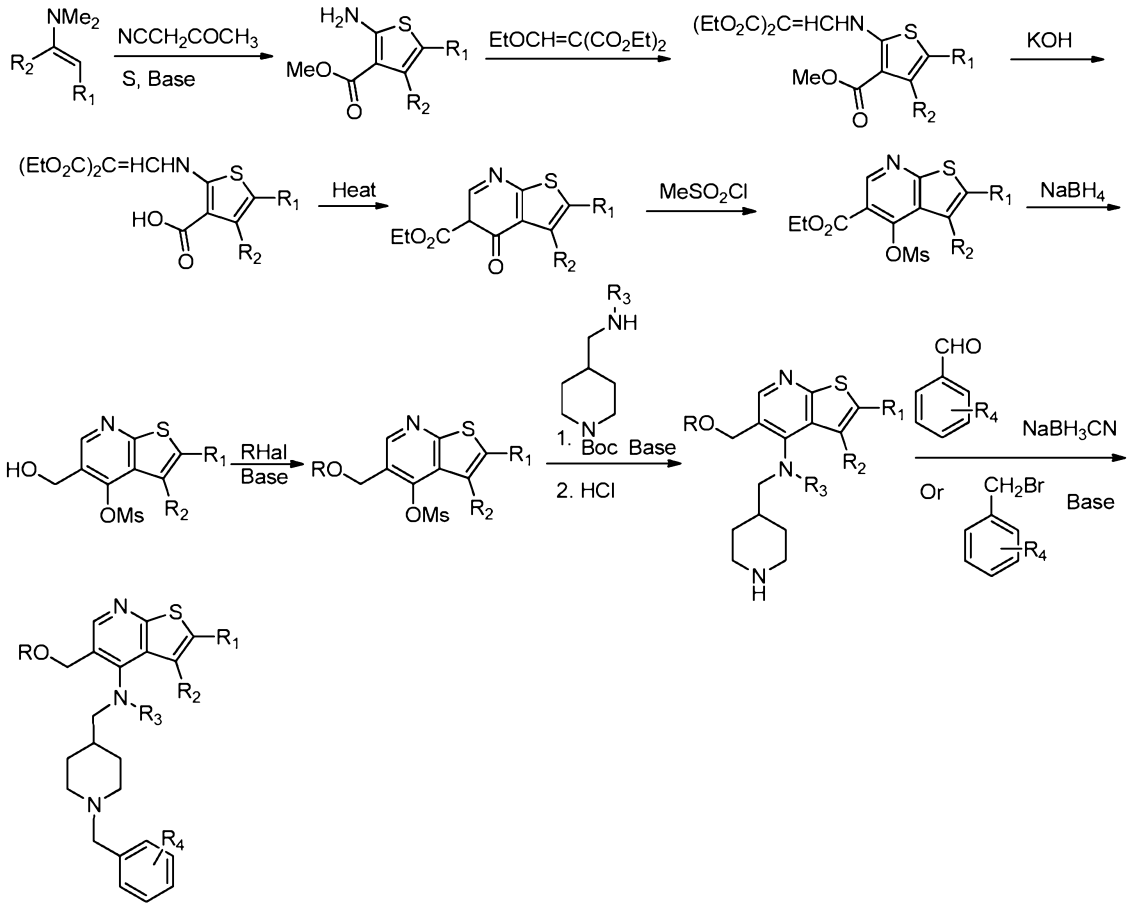
5

Compounds of subscaffold 5 can be prepared according to the following general method (Scheme 10 and 11).

Scheme 10.

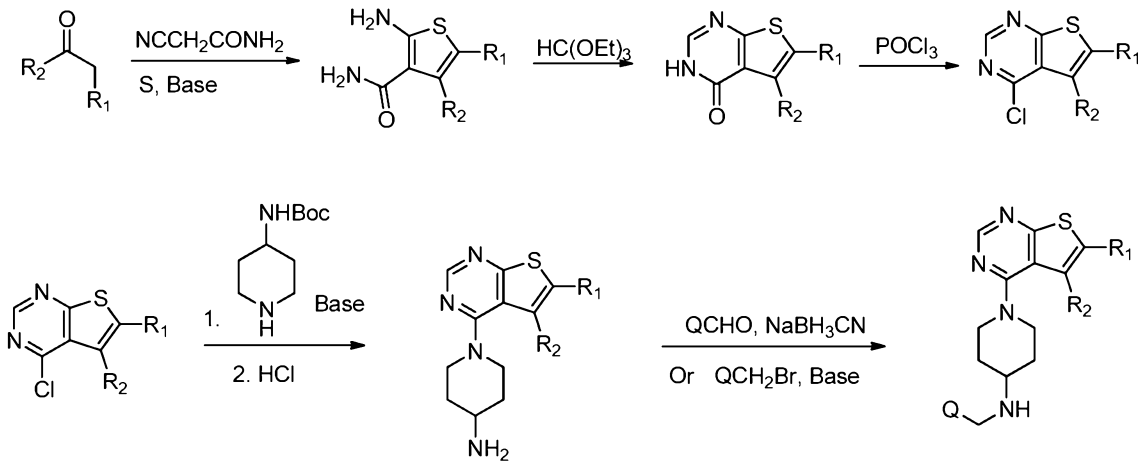

NCCH2CONH2
S, Base
HC(OEt)3
POCl3
1.
Base
Boc
2. HCl
CHO
NaBH3CN
Or
CH2Br
Base

Scheme 11.

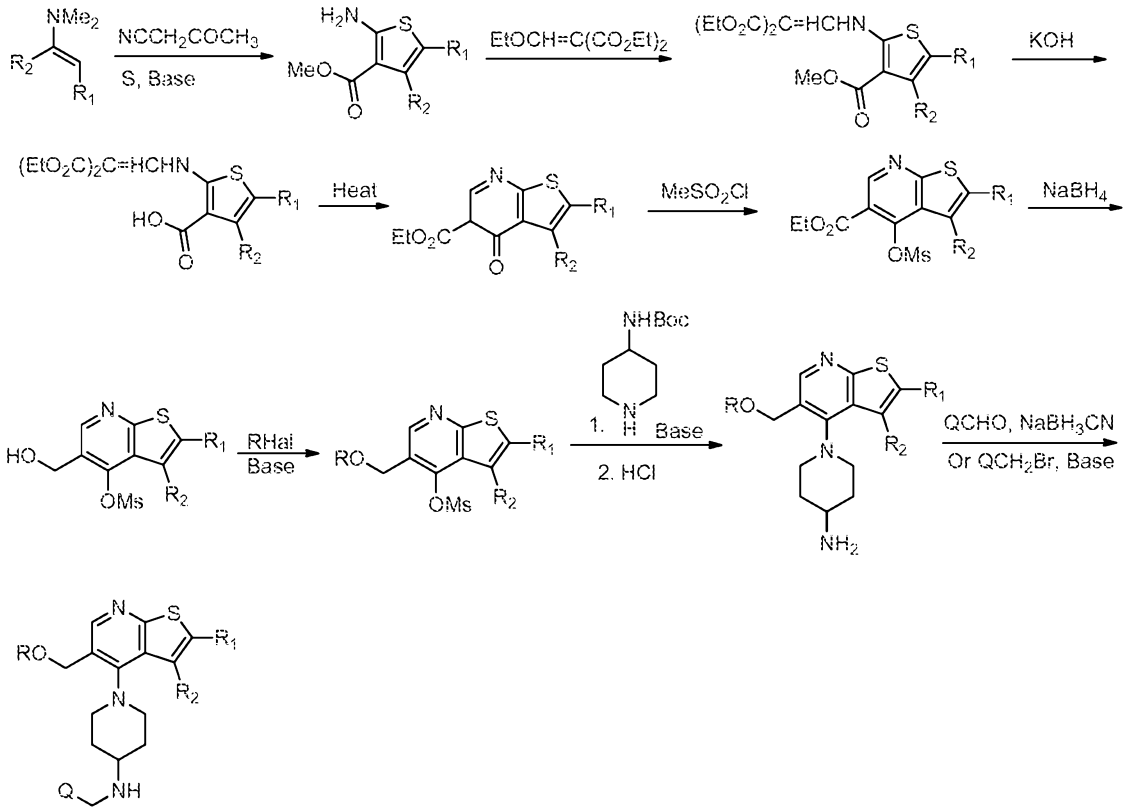


Compounds of subscaffold 6 can be prepared according to the following general method (Scheme 12 and 13).

Scheme 12.

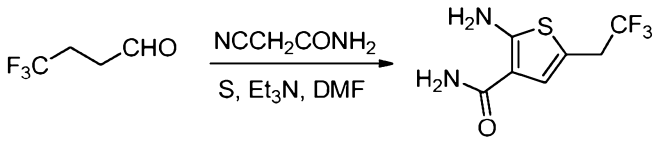

NCCH2CONH2
S, Base
HC(OEt)3
POCl3
NHBoc
1.
Base
2. HCl
QCHO, NaBH3CN
Or QCH2Br, Base

Scheme 13.



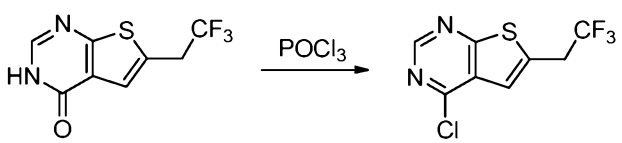
Example 1

Representative procedure for the synthesis of compounds from subscaffold 1



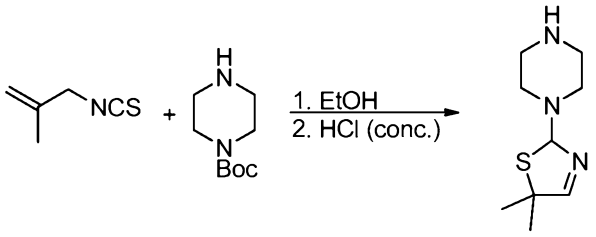
4,4,4-trifluorobuteraldehyde 5g (39.6 mmol), cyanoacetamide 3.36g (39.6 mmol) and sulfur 1.28g (39.6 mmol) was stirred in 40mL of DMF in the presence of 6.7 mL of triethylamine for 24 hs. Solvent was evaporated under reduced pressure and the residue was loaded on silica gel column and eluted with pure ethyl acetate to afford 8.4g of 2-amino-5-(2,2,2-trifluoroethyl)thiophene-3-carboxamide. ^{1}H NMR $CDCl_3$ (300MHz): 7.97 (s, 1H), 6.76 (s, 1H), 3.59 (br, 2H), 3.35 (q, 2H, *J* 10.3 Hz), 2.98 (s, 1H), 2.88 (s, 1H). ^{13}C NMR $CDCl_3$ (75MHz): 168.6, 125.6, 124.3, 111.7, 107.3, 36.8, 34.7 (q, *J* 31.4 Hz).

8.4g of 2-amino-5-(2,2,2-trifluoroethyl)thiophene-3-carboxamide was refluxed in a mixture of 28mL of triethylorthoformate and 20mL of acetic acid for 4 hs. Solvents were removed under reduced pressure and the residue was triturated hexane-ethyl acetate mixture (1:1). The solid was filtered off to afford 5.7g of 6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4(3H)-one. ^{1}H NMR MeOH-d4 (300MHz): 12.6 (br, 1H), 8.14 (s, 1H), 7.42 (s, 1H), 4.07 (q, 2H, *J* 11.0 Hz). ^{13}C NMR MeOH-d4 (75MHz): 164.5, 157.01, 146.1, 128.4, 124.6, 123.5, 33.6 (q, *J* 31.5 Hz).

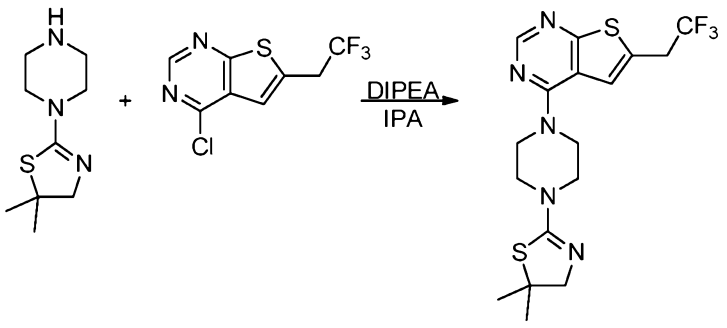


5.7g of 6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4(3H)-one was added to 16mL of $POCl_3$ with one drop of DMF. The heterogeneous mixture was refluxed for 3hs and then evaporated.

The residue was quenched with ice and saturated ammonia solution and extracted with chloroform. Combined extracts were evaporated with silica gel and loaded on a short silica gel column. The column was eluted with hexane-ethyl acetate (5:1) to afford 5.9g of 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine. ^{1}H NMR $CDCl_3$ (300MHz): 8.86 (s, 1H), 7.39 (s, 1H), 3.76 (q, 2H, *J* 9.9 Hz). ^{13}C NMR $CDCl_3$ (75MHz): 169.0, 154.7, 153.2, 129.9, 125.3, 123.5, 121.3, 35.9 (q, *J* 33.0 Hz).



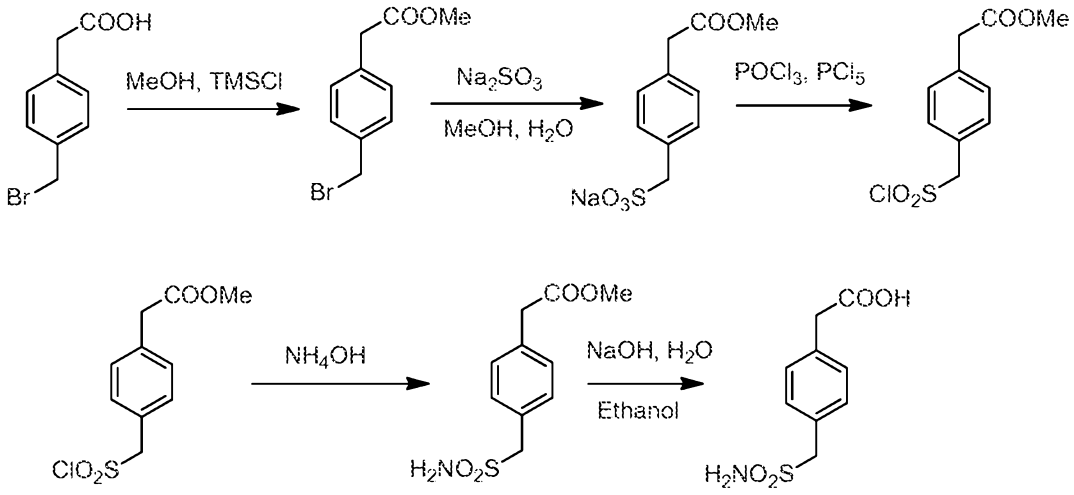
0.5g of 3-isothiocyanato-2-methylprop-1-ene was added to dropwise via syringe to a solution of 1-Bocpiperazine in 5mL of ethanol. The mixture was stirred for 1.5hs at RT and then evaporated. The residue was washed several times with diethyl ether to produce 1.1g of white solid intermediate, which was dissolved in 3mL of conc. HCl and heated in the pressure tube at 100 degrees for 1.5 hours. Cooled solution was quenched with ammonia solution and extracted with ethyl acetate. Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to afford pure 382mg of 5,5-dimethyl-2-(piperazin-1-yl)-2,5-dihydrothiazole, which was use as is in the next step. ^{1}H NMR (400 MHz, CDCl3): δ 1.53 (6H, s), 2.96 (4H, t, J=5 Hz), 3.49 (4H, t, J=5 Hz), 3.73 (2H, s). ^{13}C NMR (100 MHz, CDCl3): δC 28.83 (2C), 45.76 (2C), 49.34 (2C), 59.52, 73.30, 164.16; mp 67°C -70°C; Mass spec (ES+): m/z 199.2 (M^{+}+1).



A solution of 0.5 g of 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine (2.4 mmol), 0.56g of 5,5-dimethyl-2-(piperazin-1-yl)-2,5-dihydrothiazole (2.8 mmol), and 0.91g of *N,N*-diisopropylethylamine (7.1 mmol) in 20mL of THF was refluxed for 6 h. After cooling, the mixture was partitioned between ethyl acetate and H_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to a pale yellow solid. Purification by silica gel column chromatography using dichloromethane/methanol (97:3) as eluent gave 0.82g of 4-(4-(5,5-dimethyl-4,5-dihydrothiazol-2-yl)piperazin-1-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine (**compound 1**) as a pale yellow solid. Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol. ^1H NMR (400 MHz DMSO-d6): δ 8.46 (s, 1H), 7.70 (s, 1H), 4.37 (s, 1H), 4.09 (m, 4H), 3.81, (m, 4H), 3.45 (q, 2H, J=10.1Hz), 1.61 (s, 6H). ESI MS [MH^+]: 416.1.

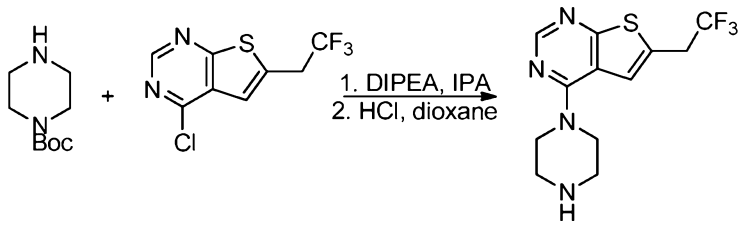
Example 2

Representative procedure for the synthesis of compounds from subscaffold 2

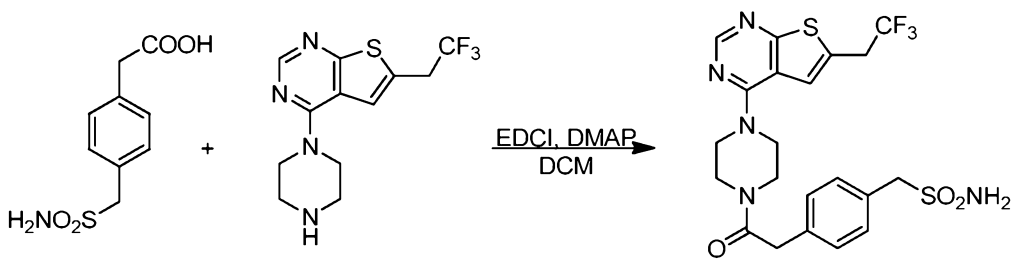


To a solution of 2g of 4-(bromomethyl)phenyl acetic acid in 20mL of methanol was added 0.2 mL of TMSCl and mixture was stirred for 2hrs. The solvent was removed in vacuo and residue was twice redissolved in MeOH and reconcentrated to give desired product, which was used in the xet step without purification. Bromoester was refluxed in 50 mL of water in the presence of 2.5g of sodium bisulfilte for 3hs. After cooling down the precipitate was filtered off and dried on

the funnel overnight. The solid was suspended in 15mL of $POCl_3$ and 1g of PCl_5 was slowly added to a suspension. The mixture stirred for 3hs at RT. A mixture was concentrated and 10mL of conc. ammonia in water was slowly added to 0 °C, redissolved compound in 30mL of acetonitrile. After stirring for 12hs at RT, a mixture was concentrated, partitioned between ethyl acetate and saturated sodium carbonate solution. Organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The intermediate ester was dissolved in 5mL of EtOH and 10ml of 10M NaOH was added. The mixture was stirred for 24hs and then concentrated. Acidification with 12M HCl resulted in precipitate. 2-(4-(sulfamoylmethyl)phenyl)acetic acid was filtered off and dried overnight. Used without purification in the next step.



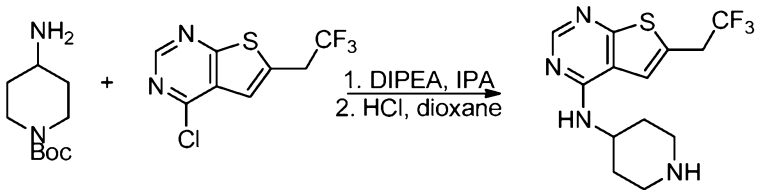
190mg of 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine (0.75 mmol) was added to a stirred solution of 290mg of N,N-diisopropylethylamine (2.25 mmol) and 168mg of 1-Boc-piperazine (0.9 mmol) in 20mL and was heated at reflux overnight. Solvent was removed under reduced pressure and the residue was loaded on silica gel column. Elution with DCM:MeOH produced 215mg of Boc-intermediate as a pale yellow solid. Later it was dissolved in20mL of 4M HCl in dioxane and stirred for 2 hs. Solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and saturated sodium carbonate solution. Organic layer was washed with brine, dried over $MgSO_4$ and evaporated to afford 150mg of 4-(piperazin-1-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine, which was used in the next step without purification.



23mg of 2-(4-(sulfamoylmethyl)phenyl)acetic acid (0.1 mmol), 20mg of 4-(piperazin-1-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine (0.067 mmol), 20mg of EDCI (0.1 mmol) and 4mg of DMAP (0.033 mmol) was stirred in 2mL of DCM. After 2hs reaction mixture was concentrated and residue was loaded on silica gel column. Elution with DCM-MeOH 9:1 and evaporation of fraction produced 38mg of (4-(2-oxo-2-(4-(6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)ethyl)phenyl)methanesulfonamide (**compound 44**). ^{1}H NMR (400 MHz, CDCl3): δ 8.44 (s, 1H), 7.36 (d, 2H, J=8 Hz), 7.25 (d, 2H, J=8 Hz), 7.20 (s, 1H), 4.88 (s, 2H), 4.26 (s, 1H), 3.5-4.0 (m, 10H). ESI MS [MH^+]: 514.1. Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol.

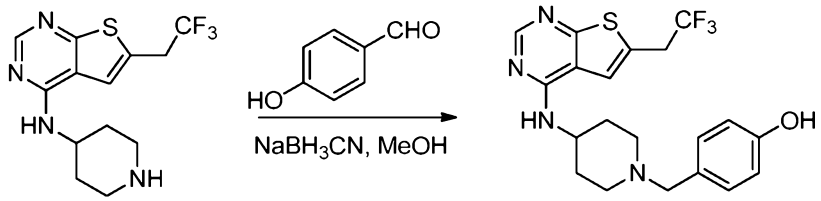
Example 3

Representative procedure for the synthesis of compounds from subscaffold 3



4.8g of 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine (19mmol) was added to a stirred solution of 7.4g of N,N-diisopropylethylamine (57 mmol) and 4.56g of 4-amino-N-Boc-piperidine (22.8 mmol) in 95mL and was heated at reflux overnight. On the morning reaction mixture was evaporated with silica gel and loaded on the column. The product was eluted with hexane-ethyl acetate from 1:1 to 1:5 yielding 7.42 g of boc-derivative. Boc-intermediate was dissolved in 40mL of 4M HCl in dioxane and stirred for 2hs. Solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and saturated sodium

carbonate solution. Organic layer was washed with brine, dried over $MgSO_4$ and evaporated to afford 5.3 g of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine, which was used in later steps without purification. ^{1}H NMR (600 MHz, CDCl3): δ 8.47 (s, 1H), 7.13 (s, 1H), 5.32 (d, 1H, J=7.7Hz), 4.32 (m, 1H), 3.64 (q, 2H, 10Hz), 3.19 (m, 2H), 2.83 (m, 2H), 2.57 (br, 1H), 2.14 (m, 2H), 1.55 (m, 2H). ^{13}C NMR (150 MHz, CDCl3): δC 166.85, 155.96, 154.33, 128.12, 126.62, 118.66, 116.48, 47.98, 45.32, 35.56 (q, J=31.5Hz), 33.10. ESI MS [MH^+]: 317.2.



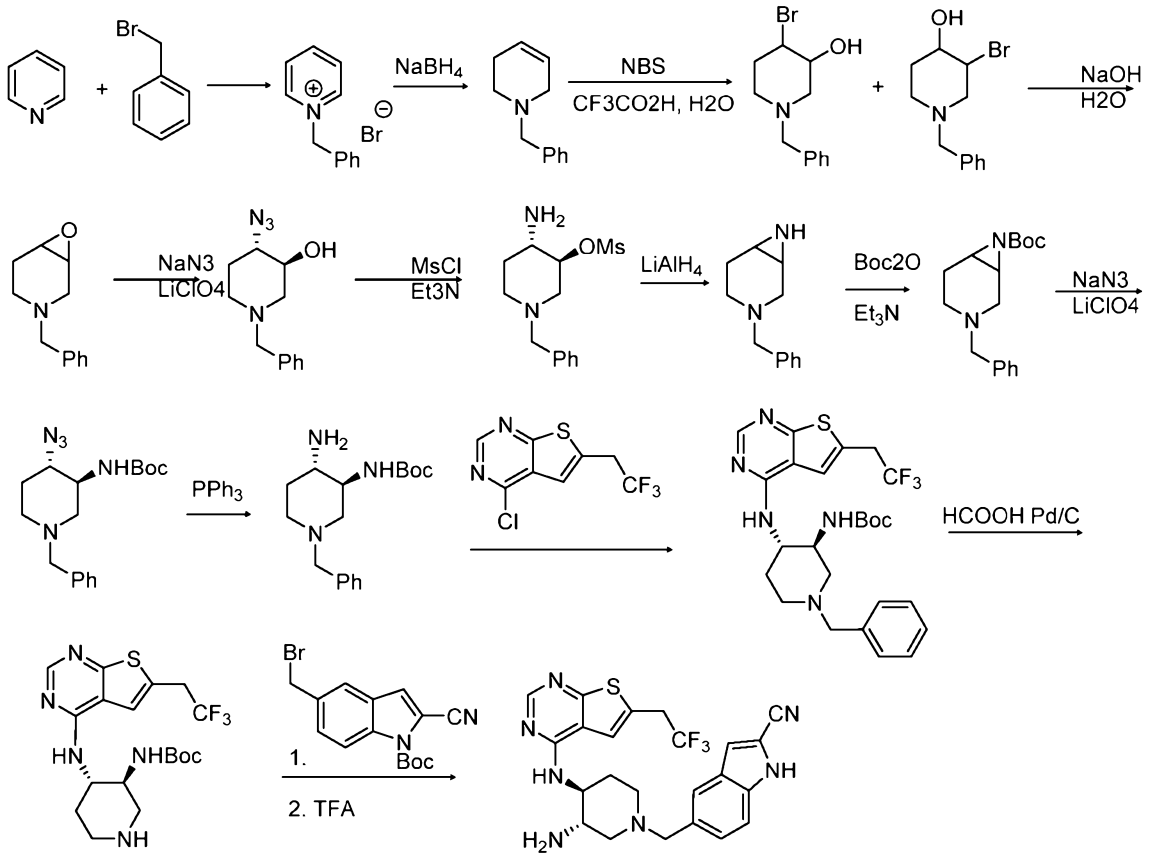
59mg of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (0.19 mmol) and 21mg of p-hydroxybenzaldehyde (0.19 mmol) were dissolved in 0.5mL of MeOH in the presence of 10ukL of acetic acid. 19mg of $NaBH_3CN$ (0.3 mmol) was slowly added to that mixture and solution was stirred for 24hs. All volatiles were removed under reduced pressure and residue was partitioned between water and ethyl acetate. Organic layer was washed with brine, dried over magnesium sulfate and evaporated. The residue was purified on silica gel column with DCM:MeOH:Et3N as eluent resulting in 62mg of 4-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenol (**compound 105**). ^{1}H NMR (600 MHz, CDCl3): δ 8.46 (s, 1H), 7.09 (d, 2H, J=8.4Hz), 7.07 (s, 1H), 6.68 (d, 2H, J=8.4Hz), 5.28 (d, 1H, J=7.7Hz), 4.21 (m, 1H), 3.59 (q, 2H, 9.9Hz), 3.46 (s, 2H), 2.96 (m, 2H), 2.21 (m, 2H), 2.09 (m, 2H), 1.62 (m, 2H). ^{13}C NMR (150 MHz, CDCl3): δC 166.45, 156.08, 155.98, 154.14, 131.01, 128.23, 125.57, 118.65, 116.52, 115.62, 62.48, 52.10, 47.96, 35.50 (q, J=31.5Hz), 31.89. ESI MS [MH^+]: 423.1458. Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol.

Example 4

Analytical data for selected compounds from subscaffold 3 and 4 and representative procedures for their synthesis

Compound 160

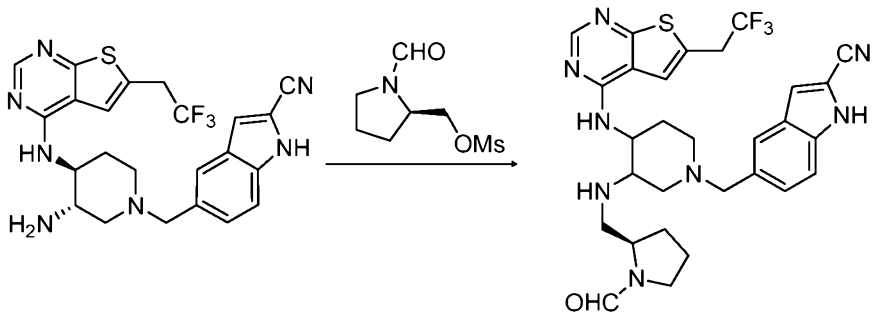
Synthesized according to this synthetic route:



Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, CD_3OD): δ 8.41 (s, 1H), 7.76 (s, 1H), 7.62 (m, 2H), 7.57 (d, 1H, J=8.3Hz), 7.33 (s, 1H), 4.57 (m, 1H), 4.05 (m, 1H), 3.96 (m, 1H), 3.91 (q, 2H, J=10.3Hz), 3.53 (m, 1H), 3.42 (m, 1H), 3.22 (m, 1H), 2.60 (m, 2H), 2.16 (m, 1H), 2.04 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD): δC 167.34, 158.35, 154.49, 138.61, 130.12, 128.67, 127.53, 127.29, 125.19, 121.45, 118.12, 114.51, 113.72, 112.03, 111.14, 53.12, 52.61, 51.47, 51.22, 50.34, 49.41, 35.46 (q, J=33Hz), 30.32. ESI MS [MH^+]: 486.1676.

Compound 161

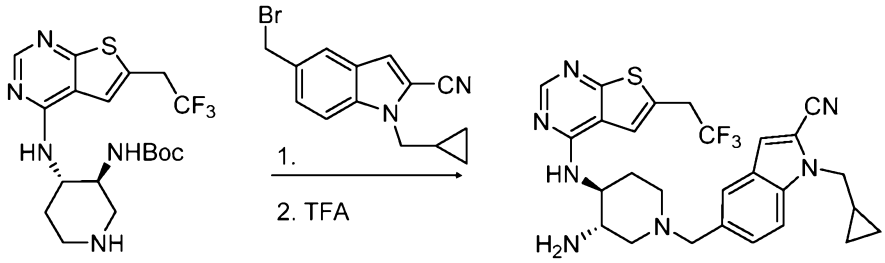
Synthesized according to this synthetic route:



Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, CD_3OD): δ 9.34 (s, 1H), 8.39 (s, 1H), 7.72 (s, 1H), 7.59 (m, 2H), 7.53 (d, 1H, J=8.3Hz), 7.29 (s, 1H), 4.51 (m, 1H), 4.02 (m, 1H), 3.91 (m, 1H), 3.88 (q, 2H, J=10.3Hz), 3.54 (m, 2H), 3.51 (m, 1H), 3.41 (m, 2H), 3.19 (m, 1H), 2.98 (m, 2H), 2.59 (m, 2H), 2.12 (m, 1H), 2.03 (m, 1H), 1.97 (m, 2H), 1.85 (m, 1H), 1.83 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD): δC 168.29, 164.2, 157.42, 154.41, 139.41, 131.32, 128.62, 127.41, 127.05, 124.49, 121.42, 117.12, 113.94, 113.45, 111.97, 111.21, 63.11, 53.31, 52.59, 51.42, 51.13, 50.48, 48.31, 48.21, 47.97, 35.48 (q, J=33Hz), 30.21, 28.71, 26.33. ESI MS [MH^+]: 597.2367.

Compound 162

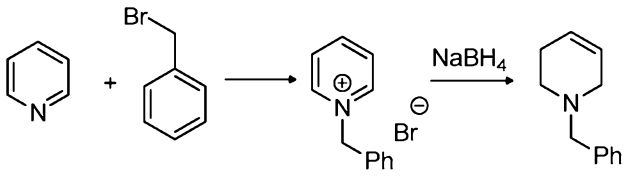
Synthesized according to this synthetic route:



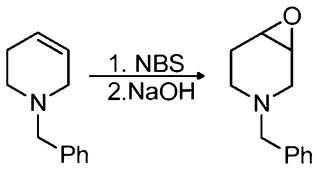
Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, CD_3OD): δ 8.39 (s, 1H), 7.74 (s, 1H), 7.61 (m, 2H), 7.52 (d, 1H, J=8.3Hz), 7.27 (s, 1H), 4.54 (m, 1H), 4.24 (m, 2H), 4.03 (m, 1H), 3.94 (m, 1H), 3.88 (q, 2H, J=10.3Hz), 3.51 (m, 1H), 3.37 (m, 1H), 3.21 (m, 1H), 2.58 (m, 2H),

2.16 (m, 1H), 2.03 (m, 1H), 1.28 (m, 1H), 0.59 (m, 2H), 0.48 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): δC 167.24, 158.39, 154.62, 138.67, 130.19, 128.64, 127.62, 127.38, 125.55, 121.75, 118.37, 114.53, 113.85, 112.07, 111.07, 62.75, 53.33, 52.73, 51.39, 51.25, 50.52, 49.43, 35.52 (q, J=33Hz), 31.23, 12.50, 4.18. ESI MS [MH^+]: 540.2159.

Compound 165

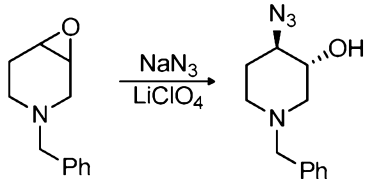


2.4mL of benzyl bromide (20 mmol) was added dropwise over an hour to a solution of 1.6mL of pyridine in 5mL of acetonitrile. Then reaction mixture was heated at 70 to 72° C for 3 hours. Solvent was removed under reduced pressure and the residue was dissolved in 16mL of ethanol. 1.1g of sodium borohydride (30 mmol) was added in small portions over 30 minutes. After stirring for 24hs reaction mixture was carefully quenched with 50mL of water and solvents were removed in vacuo. The residue was portioned between ethyl acetate and 2M NaOH solution. Organic extracts were washed with brine, dried over $MgSO_4$ and evaporated to afford crude 3.36g of crude 1-benzyl-1,2,3,6-tetrahydropyridine which was used in the next step without purification.

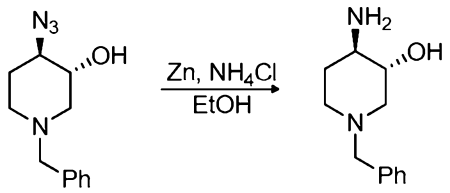


3.36g of 1-benzyl-1,2,3,6-tetrahydropyridine (0.19 mmol) was dissolved in 35mL of water containing 1.5mL of trifluoroacetic acid (0.2 mmol). To that solution 5.87g of NBS was added in small portions. After 4hs reaction mixture was transferred to 50mL of 20% NaOH solution and stirred overnight. On the morning reaction mixture was extracted with dichloromethane and combined organic fractions were dried over sodium sulfate and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate 3:1 as

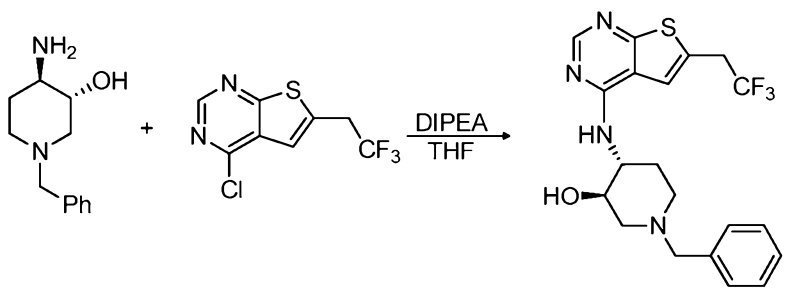
eluent. Evaporation of solvent produced 1.2g of 3-benzyl-7-oxa-3-azabicyclo[4.1.0]heptane as colorless oil.



A solution of 1.2g of 3-benzyl-7-oxa-3-azabicyclo[4.1.0]heptane (6.3 mmol) was refluxed in the presence of 0.62g of sodium azide (9.5 mmol) and 3g of lithium perchlorate (19 mmol) for 4hs. After completion reaction mixture was evaporated and the residue was extracted with dichloromethane, washed with water and combined organic fractions were dried over sodium sulfate and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate 4:1 as eluent affording 980mg of trans-4-azido-1-benzylpiperidin-3-ol.

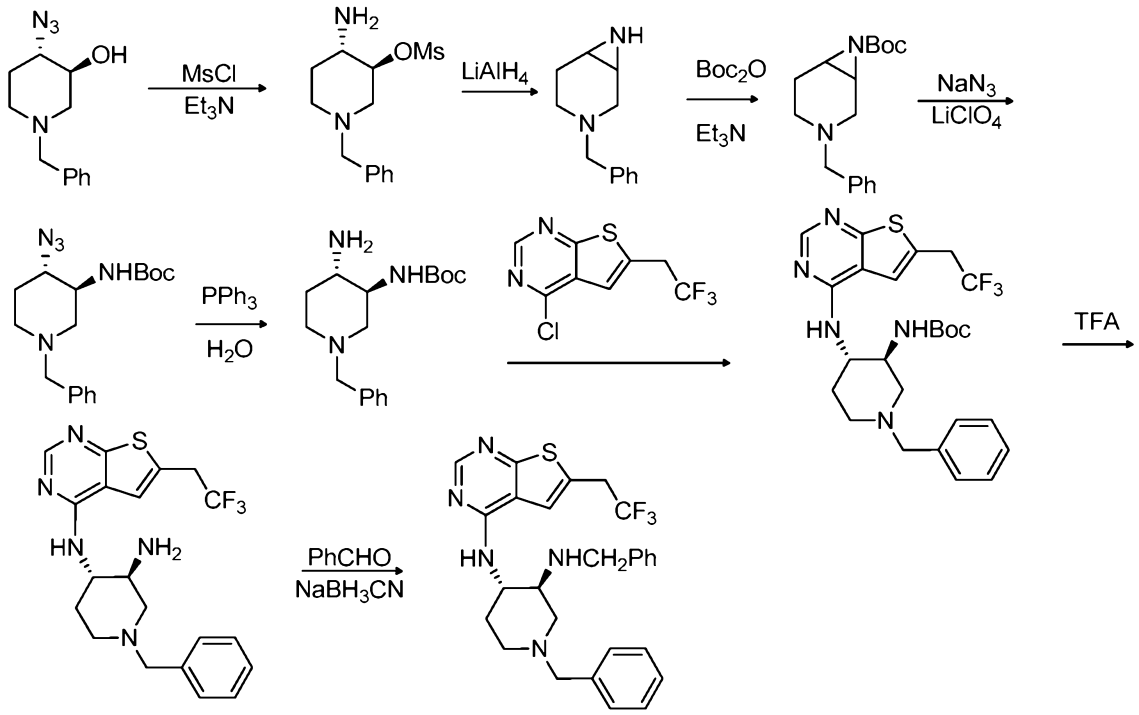


201mg of trans-4-azido-1-benzylpiperidin-3-ol (0.87 mmol) was dissolved in 3ml of EtOH-water 3:1. To that solution 77mg of zinc (12 mmol), 112mg of ammonium chloride (2.1 mmol) were added and heterogeneous mixture was refluxed for 10 minutes. After cooling down reaction mixture was diluted with 8mL of ethyl acetate and 0.5mL of conc. ammonia in water, filtered off. Organic layer washed with brine, dried over sodium sulfate and evaporated. The residue was purified on silica gel column using DCM:MeOH 10:1 as eluent affording 120mg of trans-4-amino-1-benzylpiperidin-3-ol.



The mixture of 36.7mg of trans-4-amino-1-benzylpiperidin-3-ol (0.18 mmol), 30mg of 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine (0.12 mmol) and 46mg of N,N-diisopropylethylamine (0.36 mmol) was refluxed in 0.75mL of isopropanol for 18hs. Then reaction mixture was concentrated and purified on silica gel column eluting with DCM:MeOH 20:1 to afford 45mf of trans-1-benzyl-4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-3-ol (**Compound 163**). Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol. ^{1}H NMR (600 MHz, CD_3OD) of HCl salt, signals are all broadened because of intramolecular H-bond: δ 8.37 (1H), 7.51-7.60 (6H), 4.43 (4H), 4.12 (1H), 3.85 (2H), 3.55 (2H), 3.21 (1H), 2.99 (1H), 2.06 (1H). ^{13}C NMR (150 MHz, CD_3OD): δC 165.78, 158.45, 153.97, 132.59, 131.46, 130.51, 130.18, 127.45, 125.62, 122.09, 118.50, 68.02, 61.86, 56.88, 54.15, 52.38, 35.81 (q, J=31.5Hz), 28.14. ESI MS [MH^+]: 423.1458.

Compound 167

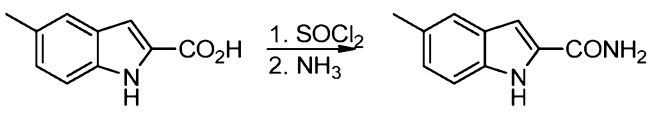


Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, CD_3OD): δ 8.69 (s, 1H), 7.87 (s, 1H), 7.66 (m, 2H), 7.55 (m, 3H), 7.44 (m, 2H)m 7.34 (m, 2H), 5.13 (m, 1H), 4.53 (m, 3H), 4.35 (m, 2H), 4.07 (m, 1H), 3.99 (q, 2H, J=10.3Hz), 3.75 (m, 1H), 3.63 (m, 1H), 3.42 (m, 1H), 2.41 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): δC 159.23, 158.93, 151.86, 132.75, 132.67, 132.65, 131.70, 130.59, 129.75, 129.20, 127.37, 125.54, 122.78, 119.37, 4095, 38.63, 35.33 (q, J=33Hz), 33.39, 33.25, 33.15, 25.98, 25.97. ESI MS [MH^+]: 512.2095.

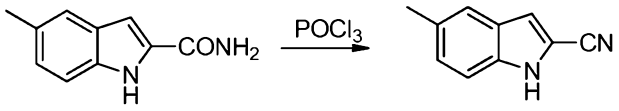
Example 5

Analytical data for selected compounds from subscaffold 4 and representative procedures for their synthesis

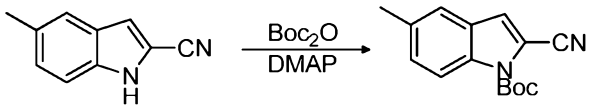
Compound 175



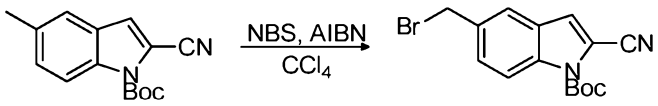
A mixture of 0.5g of 5-methylindole-2-carboxylic acid, 0.25mL of thionyl chloride, 5mL of chloroform and small drop of DMF was refluxed for 2hs. The reaction mixture was cooled to RT, poured into a mixture of 5g of ice and 5mL of 25% ammonia solution, and then stirred for 2hs. The precipitated product was filtered off, washed with water and dried to yield 350mg of 5-methylindole-2-carboxamide. ^{1}H NMR (600 MHz, DMSO-d6): δ 11.37 (s, 1H), 7.89 (br, 1H), 7.36 (s, 1H), 7.30 (d, 1H, J=8.4Hz), 7.28 (br, 1H), 7.02 (s, 1H), 6.99, (d, 1H, J=8.4Hz), 2.36 (s, 3H). ^{13}C NMR (150 MHz, CDCl3): δC 160.95, 132.95, 129.77, 126.15, 125.44, 123.10, 118.77, 110.02, 100.65, 19.20.



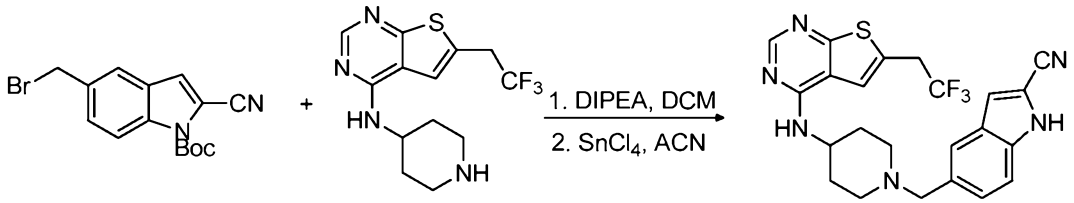
A mixture of 340mg of 5-methylindole-2-carboxamide (1.95 mmol), 1.5g of phosphorus oxychloride (9.75) and 8mL of chloroform was refluxed for 2hs. Then cooled solution was poured into 20mL of water and stirred for 1hr. After separation the organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate 5:1 to afford 245mg of 5-methyl-1H-indole-2-carbonitrile. ^{1}H NMR (600 MHz, CDCl3): δ 8.61 (br, 1H), 7.44 (s, 1H), 7.30 (d, 1H, J=8.4Hz), 7.21 (d, 1H, J=8.4Hz), 7.11 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, CDCl3): δC 135.34, 131.25, 128.28, 126.53, 121.33, 114.41, 113.95, 111.39, 106.11, 21.36.



To a solution of 245mg of 5-methyl-1H-indole-2-carbonitrile (1.6 mmol) in 5mL of acetonitrile 0.434mL of di-tert-butyl dicarbonate (1.9 mmol) and 29mg of DMAP (0.24 mmol) were added and stirred at room temperature for 30 min. The solvent was removed in vacuo, and the resultant crude product was purified by column chromatography (silica gel) using pure hexane-ethyl acetate 10:1 as an eluant to afford 334mg of tert-butyl 2-cyano-5-methyl-1H-indole-1-carboxylate. ^{1}H NMR (600 MHz, CDCl3): δ 8.10 (d, 1H, J=8.8Hz), 7.39 (s, 1H), 7.31 (d, 1H, J=8.8Hz), 7.26 (s, 1H), 2.45 (s, 3H), 1.72, (s, 9H). ^{13}C NMR (150 MHz, CDCl3): δC 148.22, 134.94, 133.78, 129.85, 121.61, 121.24, 115.53, 113.46, 108.76, 85.54, 28.05, 21.21.



To a stirred solution of 334mg of tert-butyl 2-cyano-5-methyl-1H-indole-1-carboxylate (1.3 mmol) in carbon tetrachloride (5 mL) was added 232mg of *N*-bromosuccinimide (1.3 mmol) and 11mg of AIBN (0.065 mmol). The mixture was refluxed for 1 h, then cooled and concentrated, and the residues were purified by chromatography on silica gel using hexane-ethyl acetate 20:1 to give 340mg of tert-butyl 2-cyano-5-bromomethyl-1H-indole-1-carboxylate. ^{1}H NMR (600 MHz, CDCl3): δ 8.22 (d, 1H, J=8.8Hz), 7.64 (s, 1H), 7.53 (d, 1H, J=8.8Hz), 7.31 (s, 1H), 4.60 (s, 2H), 1.73, (s, 9H). ^{13}C NMR (150 MHz, CDCl3): δC 147.64, 136.27, 133.92, 129.34, 127.45, 122.33, 121.15, 116.46, 113.02, 109.75, 87.14, 33.23, 28.01.

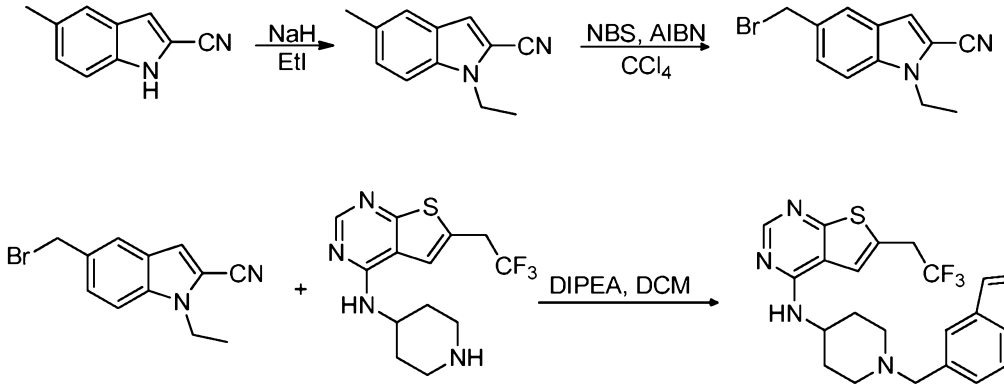


16.7mg of tert-butyl 2-cyano-5-bromomethyl-1H-indole-1-carboxylate (0.05 mmol) and 15.8mg of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (0.05 mmol) were dissolved in 0.6mL of DCM. 12.9mg of DIPEA (0.1 mmol) was added to that solution and reaction mixture was stirred for 18hs. Then reaction mixture was directly loaded on silica gel column and the product was eluted with DCM-MeOH 30:1. After evaporation of solvent boc-protected intermediate was dissolved in 0.5mL of ACN and 0.06mL of $SnCl_4$ (0.5 mmol) was added. The homogenous reaction mixture was stirred for 1h and then all volatiles were removed in vacuo. The residue was quenched ammonia and extracted with ethyl acetate. Combined organic fractions were dried over $MgSO_4$ and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate-MeOH 1:1:0.1 to produce 16mg of 5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (**Compound 175**). Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol. The hydrochloride salt was recrystallized from methanol. ^{1}H NMR (600 MHz, DMSO-d6): δ 12.62 (s, 1H), 10.74 (br, 1H), 8.33 (s, 1H), 8.07 (d, 1H, J=7Hz), 7.93, s, 1H), 7.70 (s, 1H), 7.62 (d, 1H, J=12Hz), 7.56 (d,

1H, J=12Hz), 7.45 (s, 1H), 4.36 (s, 1H), 4.30 (m, 1H), 4.03 (q, 2H, J=11Hz), 3.41 (m, 2H), 3.11 (m, 2H), 2.12 (m, 2H), 1.98 (m, 2H).

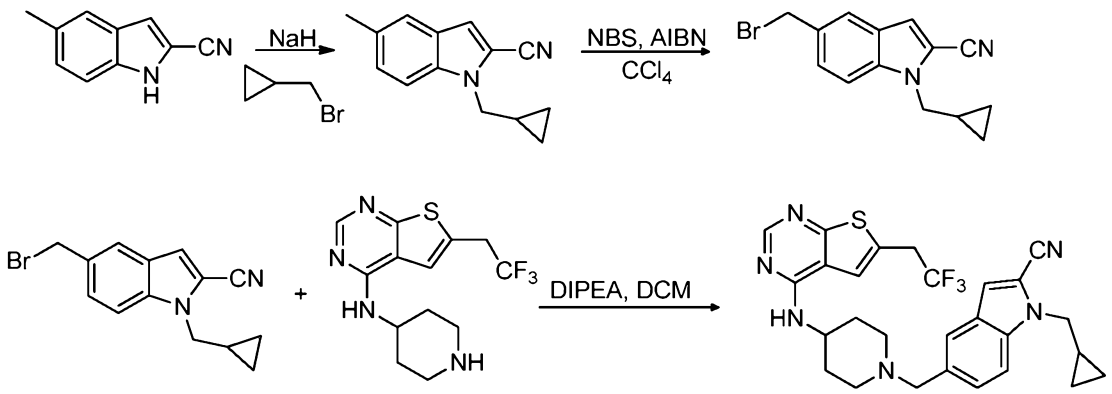
^{13}C NMR (150 MHz, DMSO-d6): δC 165.88, 155.72, 153.78, 137.18, 128.42, 126.97, 125.78, 125.37, 124.52, 122.22, 121.31, 116.12, 114.22, 113.36, 112.54, 106.84, 59.27, 50.36, 45.46, 33.73 (q, J=33Hz), 28.23. ESI MS [MH$^+$]: 471.1579.

Compound 177



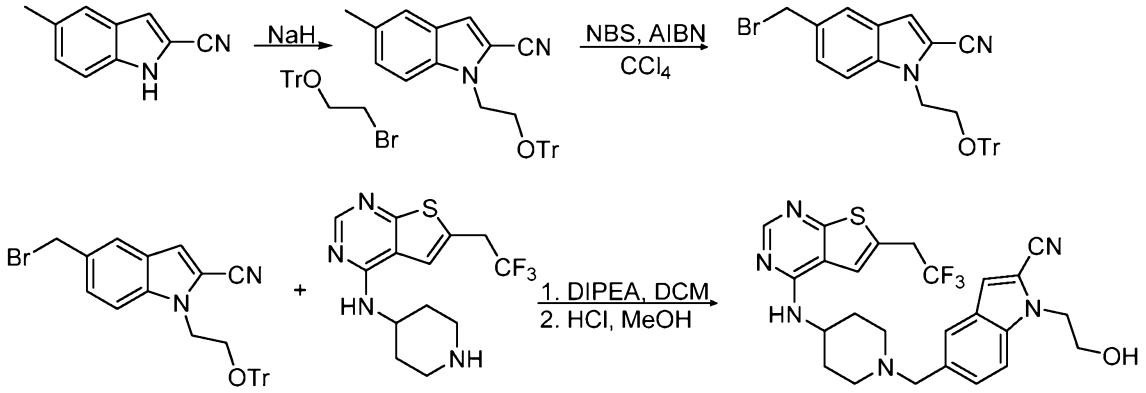
Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.68 (s, 1H), 7.94 (s, 1H), 7.82 (s, 1H), 7.69 (d, 1H, J=8.4Hz), 7.62 (d, 1H, J=8.4Hz), 7.35 (s, 1H), 4.63 (m, 1H), 4.48 (s, 2H), 4.45 (q, 2H, J=7.2Hz), 3.99 (q, 2H, J=10.3Hz), 3.63 (m, 2H), 3.26 (m, 2H), 2.34 (m, 2H), 2.14 (m, 2H), 1.45 (t, 3H, 7.2Hz). ^{13}C NMR (150 MHz, MeOD-d4): δC 149.93, 138.83, 132.93, 129.40, 127.94, 127.30, 127.26, 125.43, 123.06, 122.70, 118.69, 114.30, 113.86, 112.75, 112.60, 111.75, 62.02, 52.39, 48.39, 41.53, 35.22 (q, J=33Hz), 29.53, 15.76. ESI MS [MH$^+$]: 499.1891.

Compound 178



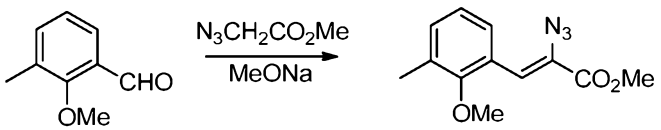
Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.40 (s, 1H), 7.94 (s, 1H), 7.72 (d, 1H, J=8.8Hz), 7.61 (d, 1H, J=8.8Hz), 7.59 (s, 1H), 7.35 (s, 1H), 4.48 (m, 3H), 4.27 (m, 2H), 4.88 (q, 2H, J=10.6Hz), 3.61 (m, 2H), 3.25 (m, 2H), 2.34 (m, 2H), 2.02 (m, 2H), 1.30 (m, 1H), 0.58 (m, 2H), 0.50 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 164.91, 157.63, 153.86, 139.38, 130.60, 129.39, 127.91, 127.49, 127.17, 125.66, 123.22, 121.97, 118.29, 114.36, 112.89, 112.18, 61.96, 52.69, 50.85, 47.34, 35.54 (q, J=33Hz), 29.95, 12.65, 4.38. ESI MS [MH^{+}]: 525.2052.

Compound 179



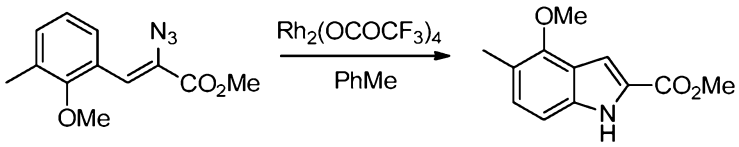
Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.75 (s, 1H), 7.96 (s, 1H), 7.88 (d, 1H, J=8.8Hz), 7.74 (d, 1H, J=8.8Hz), 7.64 (s, 1H), 7.37 (s, 1H), 4.67 (m, 1H), 4.51 (m, 3H), 4.03 (q, 2H, J=10.6Hz), 3.93 (m, 2H), 3.65 (m, 2H), 3.30 (m, 2H), 2.36 (m, 2H), 2.18 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 164.91, 139.70, 133.26, 129.21, 127.95, 127.11, 127.10, 125.48, 123.11, 122.84, 122.79, 118.74, 114.21, 113.09, 112.99, 61.95, 61.79, 52.29, 49.60, 48.54, 35.12 (q, J=33Hz),29.45. ESI MS [MH^{+}]: 515.1828.

Compound 180

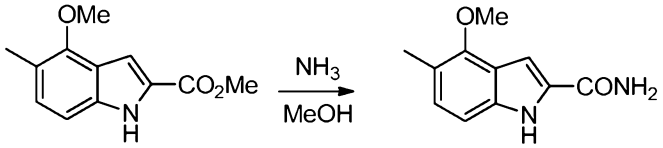


To the mixture of 2.46g of 2-methoxy-3-methylanisaldehyde (16 mmol) and 4.72g of methyl azidoacetate (41 mmol) in 20 mL of MeOH is added 7.6mL of 5.4M MeONa over 30 minute at -10 degrees. After addition the mixture was stirred for additional hour at the same temperature and then transferred in cold room (4 degrees) and stirred overnight. On the morning reaction

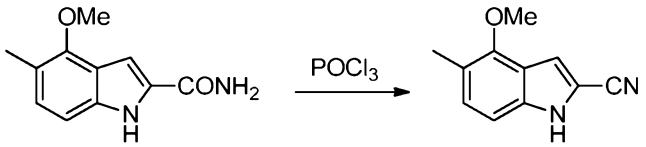
mixture was poured in 0.5L mixture of ice and conc. ammonium chloride solution, stirred for 10 minutes and filtered off. The solid was washed with plenty of ice cold water and then moved at ambient temperature. After air drying for 1hr the solid was dissolved in 50mL of DCM, dried over magnesium sulfate and passed through short silica gel plug. Evaporation of solvent produced 3.5g of methyl 2-azido-3-(2-methoxy-3-methylphenyl)acrylate, that was used in the next step without further purification.



4.16g of methyl 2-azido-3-(2-methoxy-3-methylphenyl)acrylate (16.8 mmol) was dissolved in 20mL of toluene. 560mg of rhodium (II) trifluoroacetate dimer (0.84 mmol) was added and the reaction mixture was heated at 50 degrees for 24hs. Then solvent was evaporated and residue was loaded on silica gel column and eluted with hexane-ethyl acetate 10:1 to produce after evaporation 1.3g of methyl 4-methoxy-5-methyl-1H-indole-2-carboxylate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.05 (br, 1H), 7.32 (s, 1H), 7.11 (d, 1H, J=8Hz), 7.04 (d, 1H, J=8Hz), 4.03 (s, 3H), 3.94 (s, 1H), 2.33 (s, 1H).

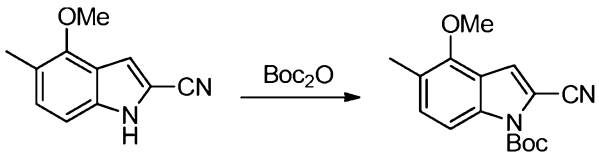


80mg of methyl 4-methoxy-5-methyl-1H-indole-2-carboxylate (0.39 mmol) was heated at 80 degrees in a sealed tube with 1mL of 7M ammonia in methanol. After one week reaction the solvent evaporated to produce 79 mg of 4-methoxy-5-methyl-1H-indole-2-carboxamide that was used without purification in the next step.

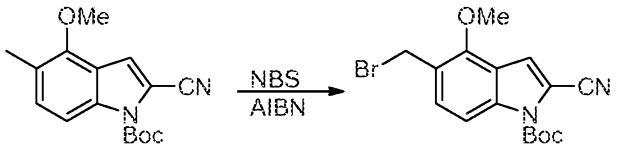


A mixture of 79mg of 4-methoxy-5-methyl-1H-indole-2-carboxamide (0.39 mmol), 0.19mL of phosphorus oxychloride (2 mmol) and 1.5mL of chloroform was refluxed for 2hs. Then cooled

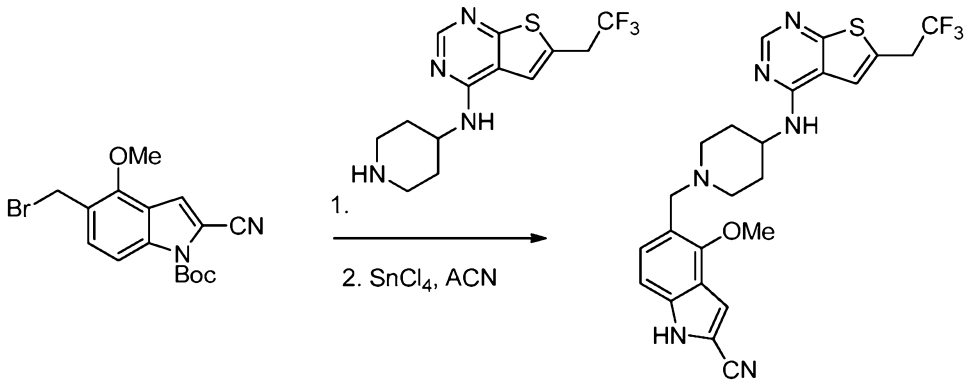
solution was poured into 10mL of water and stirred for 1hr. After separation the organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate 5:1 to afford 51mg of 4-methoxy-5-methyl-1H-indole-2-carbonitrile.



To a solution of 390mg of 4-methoxy-5-methyl-1H-indole-2-carbonitrile (2.1 mmol) in 7mL of acetonitrile 0.574mL of di-tert-butyl dicarbonate (0.74 mmol) and 25mg of DMAP (0.21 mmol) were added and stirred at room temperature for 30 min. The solvent was removed in vacuo, and the resultant crude product was purified by column chromatography (silica gel) using hexane-ethyl acetate 10:1 as an eluent to afford 561mg of tert-butyl 2-cyano-4-methoxy-5-methyl-1H-indole-1-carboxylate.

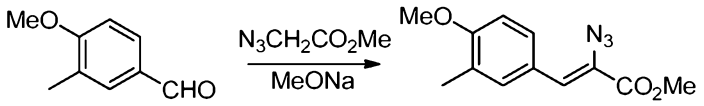


To a stirred solution of 561mg of tert-butyl 2-cyano-4-methoxy-5-methyl-1H-indole-1-carboxylate (1.96 mmol) in carbon tetrachloride (9 mL) was added 349 mg of *N*-bromosuccinimide (1.96 mmol) and 64mg of AIBN (0.39 mmol). The mixture was refluxed for 1 h, then cooled and concentrated and filtered through short silica gel plug using hexane-ethyl acetate 10:1 to give 852mg of crude tert-butyl 5-(bromomethyl)-2-cyano-4-methoxy-1H-indole-1-carboxylate that was used in the next step without further purification.

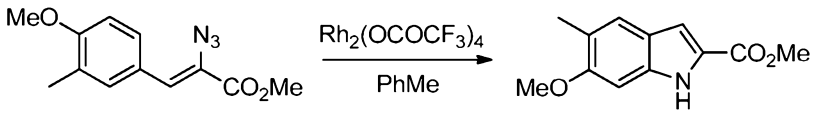


852mg of crude tert-butyl 2-cyano-5-bromomethyl-1H-indole-1-carboxylate (1.96 mmol) and 829mg of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (2.62 mmol) were dissolved in 5mL of DCM. 1.3mL of DIPEA (7.5 mmol) was added to that solution and reaction mixture was stirred for 18hs. Then reaction mixture was directly loaded on silica gel column and the product was eluted with Hexane-Ethyl acetate-MeOH 2:1:0.1. After evaporation of solvent boc-protected intermediate was dissolved in 14mL of ACN and 1.7mL of $SnCl_4$ (0.5 mmol) was added. The homogenous reaction mixture was stirred for 1h and then all volatiles were removed in vacuo. The residue was quenched ammonia and extracted with ethyl acetate. Combined organic fractions were dried over $MgSO_4$ and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate-MeOH 1:1:0.2 to produce 494mg of 4-methoxy-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (**Compound 180**). Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol. Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): δ 8.71 (s, 1H), 7.85 (s, 1H), 7.60 (s, 1H), 7.45 (d, 1H, J=8Hz), 7.23 (d, 1H, J=8Hz), 4.63 (m, 1H), 4.46 (s, 2H), 4.29 (s, 3H), 4.01 (q, 2H, J=10.5Hz), 3.64 (m, 2H), 3.29 (m, 2H), 2.33 (m, 2H), 2.13 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 155.08, 149.56, 142.48, 133.14, 130.79, 130.44, 127.31, 123.36, 122.79, 118.72, 118.60, 114.63, 113.09, 110.78, 107.95, 108.25, 61.21, 56.92, 52.45, 35.11 (q, J=33Hz), 29.50. ESI MS [MH^+]: 501.1684.

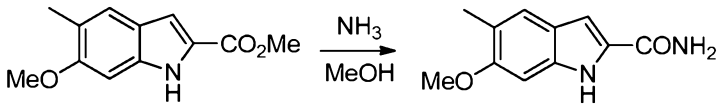
Compound 181 and 182



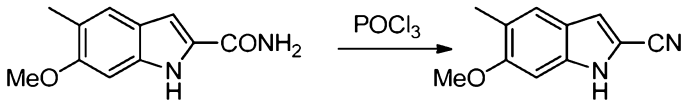
To the mixture of 6.59g of 3-methylanisaldehyde (44 mmol) and 12.65 g of methyl azidoacetate (110 mmol) in 60 mL of MeOH is added 20mL of 5.4M MeONa over 30 minute at -10 degrees. After addition the mixture was stirred for additional hour at the same temperature and then transferred in cold room (4 degrees) and stirred overnight. On the morning reaction mixture was poured in 1L mixture of ice and conc. ammonium chloride solution, stirred for 10 minutes and filtered off. The solid was washed with plenty of ice cold water and then moved at ambient temperature. After air drying for 1hr the solid was dissolved in 50mL of DCM, dried over magnesium sulfate and passed through short silica gel plug. Evaporation of solvent produced 9.8g of methyl 2-azido-3-(4-methoxy-3-methylphenyl)acrylate, that was used in the next step without further purification.



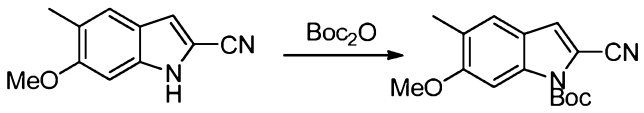
250mg of 2-azido-3-(4-methoxy-3-methylphenyl)acrylate (1mmol) was dissolved in 1mL of toluene. 30mg of rhodium (II) trifluoroacetate dimer (0.045 mmol) was added and the reaction mixture was heated at 50 degrees for 24hs. Then solvent was evaporated and residue was loaded on silica gel column and eluted with hexane-ethyl acetate 10:1 to produce after evaporation 125mg of methyl 6-methoxy-5-methyl-1H-indole-2-carboxylate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.73 (br, 1H), 7.39 (s, 1H), 7.10 (s, 1H), 6.77 (s, 1H), 3.92 (s, 3H), 3.88 (s, 1H), 2.28 (s, 1H).



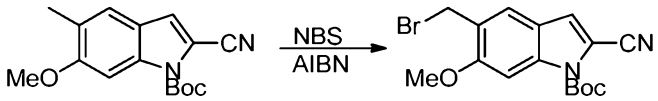
200mg of methyl 6-methoxy-5-methyl-1H-indole-2-carboxylate (1 mmol) was heated at 80 degrees in a sealed tube with 2mL of 7M ammonia in methanol. After one week reaction the solvent evaporated to produce 202 mg of 6-methoxy-5-methyl-1H-indole-2-carboxamide that was used without purification in the next step.



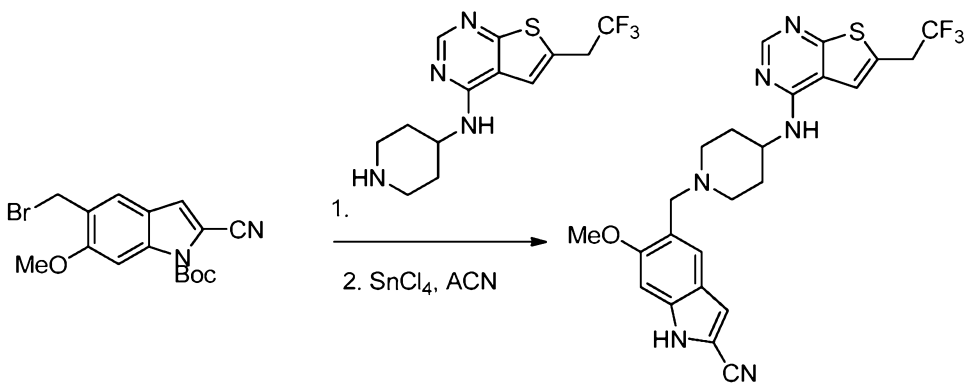
A mixture of 202mg of 6-methoxy-5-methyl-1H-indole-2-carboxamide (1 mmol), 0.47mL of phosphorus oxychloride (5 mmol) and 3mL of chloroform was refluxed for 2hs. Then cooled solution was poured into 10mL of water and stirred for 1hr. After separation the organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate 5:1 to afford 116mg of 6-methoxy-5-methyl-1H-indole-2-carbonitrile. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26 (br, 1H), 7.37 (s, 1H), 7.06 (s, 1H), 6.76 (s, 1H), 3.88 (s, 1H), 2.28 (s, 3H).



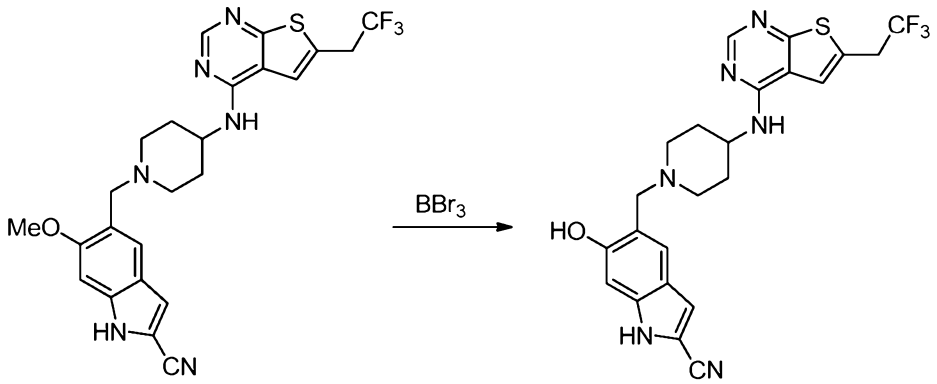
To a solution of 116mg of 6-methoxy-5-methyl-1H-indole-2-carbonitrile (0.62 mmol) in 2mL of acetonitrile 0.171mL of di-tert-butyl dicarbonate (0.74 mmol) and 20mg of DMAP (0.24 mmol) were added and stirred at room temperature for 30 min. The solvent was removed in vacuo, and the resultant crude product was purified by column chromatography (silica gel) using hexane-ethyl acetate 10:1 as an eluent to afford 174mg of tert-butyl 2-cyano-6-methoxy-5-methyl-1H-indole-1-carboxylate.



To a stirred solution of 174mg of tert-butyl 2-cyano-6-methoxy-5-methyl-1H-indole-1-carboxylate (0.61 mmol) in carbon tetrachloride (2.5 mL) was added 108 mg of *N*-bromosuccinimide (0.61 mmol) and 11mg of AIBN (0.065 mmol). The mixture was refluxed for 1 h, then cooled and concentrated and filtered through short silica gel plug using hexane-ethyl acetate 10:1 to give 223mg of crude tert-butyl 5-(bromomethyl)-2-cyano-6-methoxy-1H-indole-1-carboxylate that was used in the next step without further purification.

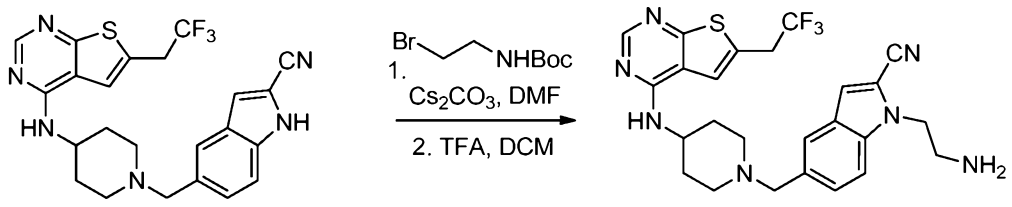


223mg of tert-butyl 2-cyano-5-bromomethyl-1H-indole-1-carboxylate (0.61 mmol) and 193mg of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (0.61 mmol) were dissolved in 2mL of DCM. 0.22mL of DIPEA (0.2 mmol) was added to that solution and reaction mixture was stirred for 18hs. Then reaction mixture was directly loaded on silica gel column and the product was eluted with DCM-MeOH 30:1. After evaporation of solvent boc-protected intermediate was dissolved in 0.5mL of ACN and 0.06mL of $SnCl_4$ (0.5 mmol) was added. The homogenous reaction mixture was stirred for 1h and then all volatiles were removed in vacuo. The residue was quenched ammonia and extracted with ethyl acetate. Combined organic fractions were dried over $MgSO_4$ and concentrated. The residue was purified on silica gel column using hexane-ethyl acetate-MeOH 1:1:0.1 to produce 210mg of 6-methoxy-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (**Compound 181**). Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol. Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): δ 8.71 (s, 1H), 7.87 (s, 1H), 7.86 (s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 4.66 (m, 1H), 4.49 (s, 2H), 4.03 (m, 5H), 3.69 (m, 2H), 3.34 (m, 2H), 2.36 (m, 2H), 2.18 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 158.72, 149.70, 140.86, 133.08, 128.17, 127.75, 127.31, 12,3.36, 122.81, 121.69, 118.72, 115.07, 114.82, 114.60, 107.47, 94.60, 57.67, 56.62, 52.72, 35.22 (q, J=33Hz), 29.53. ESI MS [MH^+]: 501.1675.



500mg of 6-methoxy-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (1 mmol) was slowly added to 5mL of 1M BBr_3 in DCM at 0 degrees and reaction mixture was brought to RT. After 4days ice was added to reaction mixture in the presence of sodium bicarbonate. Volatile organic was evaporated and the residue was partitioned between water and ethyl acetate-methanol 10:1. Organic layer was evaporated with silica gel and loaded on the column. The product was eluted with hexane-ethyl acetate-methanol 1:1:0.1, evaporation of fractions produced 300mg of 6-hydroxy-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (**Compound 182**). Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol. Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.70 (s, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.21 (s, 1H), 6.98 (s, 1H), 4.64 (m, 1H), 4.48 (s, 1H), 4.01 (q, 2H, J=10.3Hz), 3.66 (m, 2H), 3.35 (m, 2H), 2.37 (m, 2H), 2.12 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 157.64, 156.62, 153.92, 141.09, 130.54, 127.75, 127.48, 125.65, 121.96, 121.59, 118.27, 115.23, 114.85, 113.98, 107.11, 97.45, 57.78, 52.88, 47.29, 35.54 (q, J=33Hz), 29.95. ESI MS [MH^+]: 487.1519.

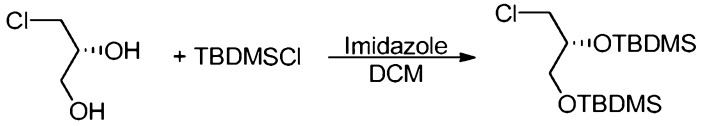
Compound 186



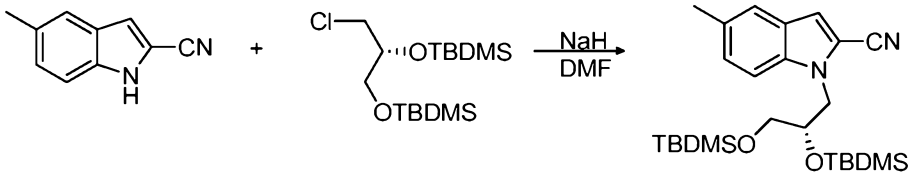
Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.37 (s, 1H), 8.08 (s, 1H), 7.74 (d,

1H, J=8.8Hz), 7.69 (s, 1H), 7.64 (d, 1H, J=8.8Hz), 7.54 (s, 1H), 4.74 (m, 1H), 4.48 (m, 3H), 3.88 (q, 2H, J=10.6Hz), 3.60 (m, 2H), 3.21 (m, 2H), 2.34 (m, 2H), 2.05 (m, 2H). ESI MS [MH^+]: 514.1998.

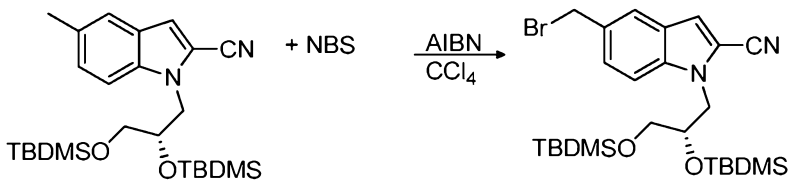
Compound 188



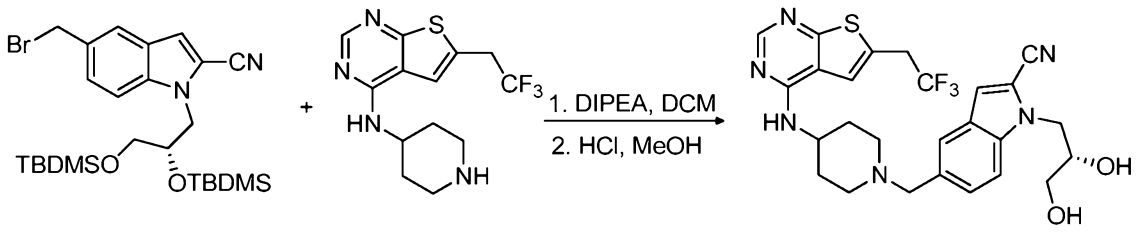
331 mg of (R)-3-chloropropane-1,2-diol (3 mmol) and 530 mg of imidazole (7.8 mmol) were dissolved in 5mL of dry dichloromethane. Then 7.2mL of 1M TBDMSCl in dichloromethane was added. Reaction mixture was stirred overnight and then diluted with 20mL of water. After separation the organic layer was dried over sodium sulfate and concentrated to produce 850mg of (R)-5-(chloromethyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane. The material was used as is in the next step.



To a solution of 39mg of 5-methyl-1H-indole-2-carbonitrile (0.25 mmol) in 0.5 mL of DMF 15mg of NaH (60% in oil, 0.375 mmol) was added and mixture was stirred for 30min. Then 170mg of (R)-5-(chloromethyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (0.5 mmol) was added and stirring continued for 24hs. The reaction mixture was diluted with 10mL of water and extracted with DCM. Combined organic extracts dried over sodium sulfate, concentrated and purified using silica gel column eluting with hexane-ethyl acetate 50:1 to afford 56 mg of (S)-1-(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-5-methyl-1H-indole-2-carbonitrile. ^{1}H NMR (600 MHz, CDCl3): δ 8.09 (d, 1H, J=8.8Hz), 7.35 (s, 1H), 7.24 (d, 1H, J=8.8Hz), 7.18 (s, 1H), 4.04 (m, 1H), 3.82 (m, 1H), 3.77 (m, 2H), 3.68 (m, 1H), 2.43 (s, 3H), 1.08 (m, 18H), 0.26 (m, 12H).



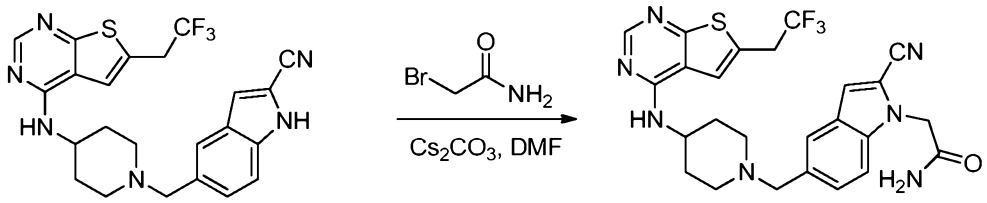
To a stirred solution of 55mg of (S)-1-(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-5-methyl-1H-indole-2-carbonitrile (0.12 mmol) in carbon tetrachloride (0.5 mL) was added 21.3 mg of *N*-bromosuccinimide (0.12 mmol) and 1.1mg of AIBN (0.0065 mmol). The mixture was refluxed for 1 h, then cooled, concentrated and filtered through short silica gel plug using hexane-ethyl acetate 10:1 to give 58mg of crude (S)-1-(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-5-(bromomethyl)-1H-indole-2-carbonitrile that was used in the next step without further purification.



58mg of (S)-1-(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-5-(bromomethyl)-1H-indole-2-carbonitrile (0.1 mmol) and 31mg of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (0.12 mmol) were dissolved in 0.2mL of DCM. 26mg of DIPEA (0.2 mmol) was added to that solution and reaction mixture was stirred for 18hs. Then reaction mixture was directly loaded on silica gel column and the product was eluted with DCM-MeOH 30:1. After evaporation of solvent TBDMS-protected intermediate was dissolved in 0.2mL of MeOH and 0.02mL of 12M HCl was added. The homogenous reaction mixture was stirred overnight and then all volatiles were removed in vacuo. The residue was quenched ammonia and extracted with ethyl acetate. Combined organic fractions were dried over $MgSO_4$ and concentrated. The residue was purified on silica gel column using DCM-MeOH 20:1 to afford 15.9mg of 5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (**Compound 188**). Its monohydrochloride salt was obtained by adding 1 equivalent of 1N HCl solution in diethyl ether to a solution of compound in ethanol. Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.63 (s, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.77 (d, 1H, J=8.6Hz), 7.63 (d, 1H, J=8.6Hz), 7.37 (s, 1H), 4.57 (m, 1H), 4.56 (m, 1H), 4.50

(s, 2H) 4.37 (m, 1H), 4.04 (m, 1H), 3.99 (q, 2H, J=10.3Hz), 3.65 (m, 2H), 3.60 (d, 2H, J=5.5Hz), 3.29 (m, 2H), 2.37 (m, 2H), 2.12 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 157.45, 150.99, 139.90, 132.27, 129.16127.89, 127.37, 127.00, 125.54, 123.11, 122.50, 118.58, 114.32, 114.25, 113.35, 113.31, 72.35, 64.85, 61.99, 52.44, 49.82, 48.12, 35.32 (q, J=33Hz), 29.64. ESI MS [MH$^+$]: 545.1941.

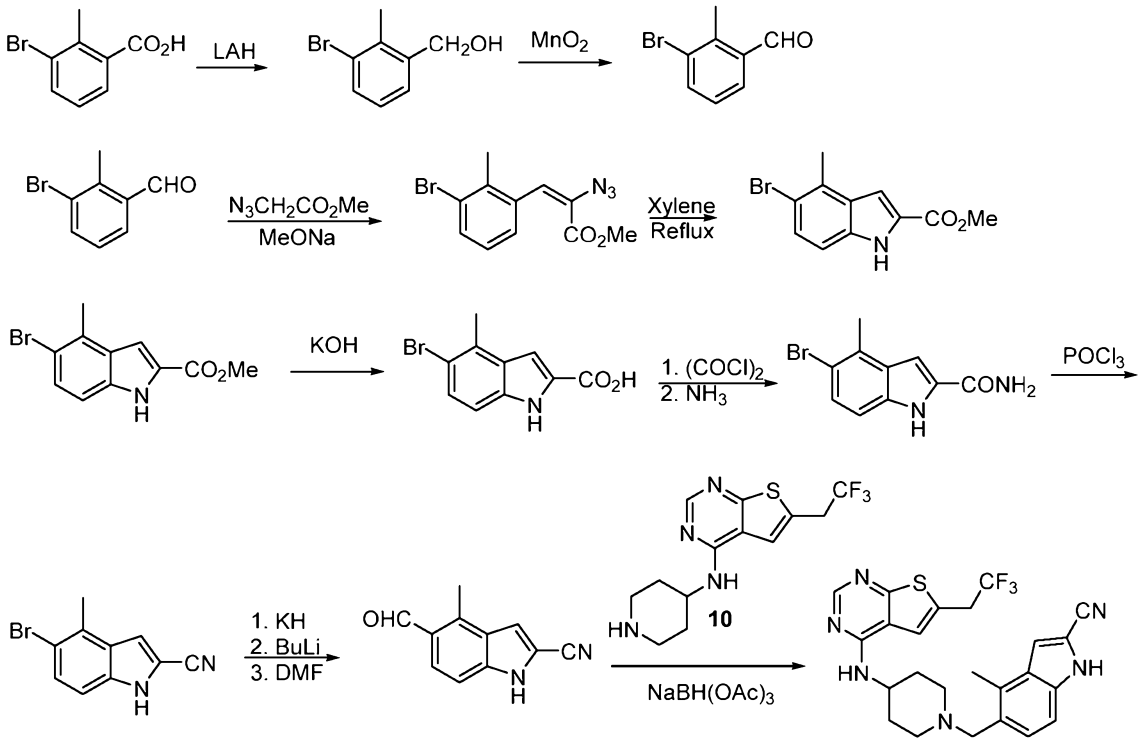
Compound 189



760 mg of 5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile hydrochloride (1.5 mmol) and 207mg of bromoacetamide (1.5 mmol) were dissolved in 3.6mL of dry DMF. 1.96g of cesium carbonate (6 mmol) was added and reaction mixture was stirred for 4hs. Then it was quenched with 50mL of water and extracted with DCM-MeOH 10:1. Combined organic extracts were evaporated with silica gel and loaded on column. The product was eluted with DCM-MeOH 10:1 mixture. After evaporation of product containing fractions it was recrystallized from MeOH to produce 319mg of 2-(2-cyano-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indol-1-yl)acetamide, which was converted to hydrochloride salt by dissolving in 5mL of MeOH, adding of 1eq of 1M HCl in water. Hydrochloride salt can be recrystallized further from MeOH. Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.44 (s, 1H), 7.91 (s, 1H), 7.57 (m, 2H), 7.41 (s, 1H), 5.10 (s, 2H), 4.53 (m, 1H), 4.47 (s, 1H), 3.89 (q, 2H, J=10.3Hz), 3.62 (m, 2H), 3.24 (m, 2H), 2.35 (m, 2H), 1.93 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 171.07, 157.66, 153.62, 140.17, 130.77, 129.55, 127.95, 127.10, 125.64, 123.46, 121.90, 118.31, 114.76, 113.69, 113.52, 112.60, 61.96, 52.67, 49.60, 47.98, 47.40, 35.52 (q, J=33Hz), 29.96. ESI MS [MH$^+$]: 528.1783.

Compound 219

Compound 219 was synthesized according following route:



Step 1: 30 g of 3-bromo-2-methylbenzoic acid (139 mmol) was dissolved in 180mL of THF, cooled to 0 degrees and 9.5g of lithium aluminium hydride (250 mmol) was added in small portions. After stirring for 3hs no starting material was observed by TLC. Reaction mixture was carefully quenched with 20mL of ethyl acetate and 20mL of water. Silica gel was added and mixture was evaporated to dryness, loaded on small silica gel column. The product was eluted with hexane:ethyl acetate (1:1) resulting in 24g of pure alcohol after evaporation. ^{1}H NMR (600 MHz, $CDCl_3$): 7.50 (d, 1H, J=8.1Hz), 7.29 (d, 1H, J=8.1Hz), 7.04 (t, 1H, J=8.1Hz), 4.68 (s, 2H), 2.40 (s, 3H), 1.90 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): 140.60, 135.84, 132.03, 127.12, 126.70, 126.05.

Step 2: 24g of (3-bromo-2-methylphenyl)methanol (119 mmol) was dissolved in 240mL of dichloromethane and 103g of manganese (IV) oxide (1.2 mol) was added. After stirring overnight TLC showed no starting material. Reaction mixture was evaporated with silica gel and loaded on small silica gel column. The product was eluted with hexane:ethyl acetate (10:1) to afford 18.6g of pure aldehyde after evaporation. ^{1}H NMR (600 MHz, $CDCl_3$): 10.25 (s, 1H), 7.78

(m, 2H), 7.23 (t, 1H, J=7.7Hz), 2.75 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 191.84, 137.72, 130.93, 130.20, 127.61, 127.37, 126.82, 18.13.

Step 3:

To the mixture of 18.6g of 3-bromo-2-methylbenzaldehyde (93 mmol) and 26.8g of methyl azidoacetate (233 mmol) in 130 mL of MeOH was added 43mL of 5.4M MeONa over 30 minute at -10 degrees. After addition the mixture was stirred for additional hour at the same temperature and then transferred in cold room (4 degrees) and stirred overnight. On the morning reaction mixture was poured in 1L mixture of ice and conc. ammonium chloride solution, stirred for 10 minutes and filtered off. The solid was washed with plenty of ice cold water and then moved at ambient temperature. After air drying for 1hr the solid was dissolved in 100mL of DCM, dried over magnesium sulfate and passed through short silica gel plug. Evaporation of solvent produced 21.1g of methyl (E)-2-azido-3-(3-bromo-2-methylphenyl)acrylate, that was used in the next step without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): 7.72 (d, 1H, J=7.7Hz), 7.53 (d, 1H, J=7.7Hz), 7.10 (s, 1H), 7.07 (t, 1H, J=7.7Hz), 3.93 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 163.61, 136.65, 133.94, 133.09, 129.25, 128.76, 126.78, 125.81, 123.64, 53.10, 20.04.

Step 4:

21.1g of methyl (E)-2-azido-3-(3-bromo-2-methylphenyl)acrylate (71mmol) was dissolved in 700mL of xylene. The mixture was refluxed for 10 minutes. Reaction mixture was cooled to RT and kept in -20 freezer overnight. The precipitated product was filtered off and dried on funnel to produce 10.0g of methyl 5-bromo-4-methyl-1H-indole-2-carboxylate. ^{1}H NMR (600 MHz, $CDCl_3$): 8.98 (br s, 1H), 7.44 (d, 1H, J=8.4Hz), 7.24 (s, 1H), 7.14 (d, 1H, J=8.4Hz), 3.96 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 162.12, 135.38, 131.56, 129.52, 128.98, 127.36, 115.92, 110.82, 107.70, 52.15, 18.97.

Steps 5-7: 10.0g of methyl 5-bromo-4-methyl-1H-indole-2-carboxylate (38 mmol) was refluxed in solution of 10.6 g KOH (190 mmol) in 130mL of methanol for 1hr. Reaction mixture was then concentrated and acidified with 12M HCl in water. Precipitated product was filtered off. After drying the 5-bromo-4-methyl-1H-indole-2-carboxylic acid was added to solution of 6.5 mL of oxalyl chloride (76 mmol) in 200mL of dichloromethane with 0.6mL of DMF. After stirring for

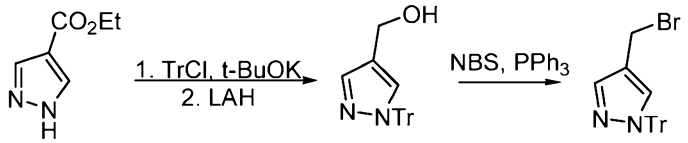
1hr reaction mixture was cooled in ice-water bath and 40mL of conc. ammonia in water was added dropwise. The heterogeneous mixture was stirred for another 3hs and filtered off to obtain amide. A mixture of 5-bromo-4-methyl-1H-indole-2-carboxamide from previous step, 36mL of phosphorus oxychloride (380 mmol) and 120mL of chloroform was refluxed for 5hs. Then reaction mixture was evaporated to dryness and quenched with ice and conc. ammonia (about 40mL). The formed precipitate was filtered off, washed with plenty of water and dissolved in 100mL of THF. The solution was evaporated with silica gel, loaded on medium silica gel column. The product was eluted hexane: ethyl acetate (2:1) affording 7.4g of pure nitrile after evaporation. . ^{1}H NMR (600 MHz, Me_2CO-d_6): 11.42 (br s, 1H), 7.49 (d, 1H, J=8.8Hz), 7.42 (s, 1H), 7.32 (d, 1H, J=8.4Hz), 2.59 (s, 3H). ^{13}C NMR (150 MHz, Me_2CO-d_6): 137.48, 131.99, 130.95, 129.33, 117.21, 114.93, 113.71, 112.95, 108.51, 19.59.

Step 8: 2.35g of 5-bromo-4-methyl-1H-indole-2-carbonitrile (10 mmol) was dissolved in 100mL of THF, the flask was flushed with argon and 3.2g of potassium hydride was added (30% suspension in oil, 24 mmol), after stirring for 5 minutes reaction mixture was cooled to -90 degrees (internal temperature, ethanol/N_2(liq.)) and 11.8mL of tert-butyl lithium (20 mmol) was slowly added to maintain the temperature in the range -95 – -90. After stirring for 1hr 3.8ml of DMF (50 mmol) was added dropwise and reaction mixture was allowed to warm to -70 degrees and kept 30 minutes at that temperature. The reaction mixture was quenched with 2.9mL of acetic acid (50 mmol) and warmed to RT. After addition of 100mL of brine organic phase was separated, evaporated with silica gel and loaded on medium silica gel column. Elution started with pure hexane and then product was washed out with hexane:THF (1:1). After evaporation of product containing fractions 1.11g of pure aldehyde was obtained. ^{1}H NMR (600 MHz, CD_3CN): 10.39 (s, 1H), 7.82 (d, 1H, J=8.4Hz), 7.51 (s, 1H), 7.43 (d, 1H, J=8.4Hz), 2.86 (s, 3H). ^{13}C NMR (150 MHz, CD_3CN): 191.15, 138.90, 137.17, 127.26, 126.94, 126.55, 113.70, 113.11, 109.97, 107.19, 13.39

Step 9: 800mg of 5-formyl-4-methyl-1H-indole-2-carbonitrile (4.35 mmol), 1.83g of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (5.22 mmol) and 1.2mL of triethylamine (8.7 mmol) were mixed in 43mL of dry dichloromethane. 1.84g of sodium triacetoxyborohydride (8.7 mmol) was added to it in one portion. After stirring overnight TLC showed absence of starting aldehyde in reaction mixture was transferred in

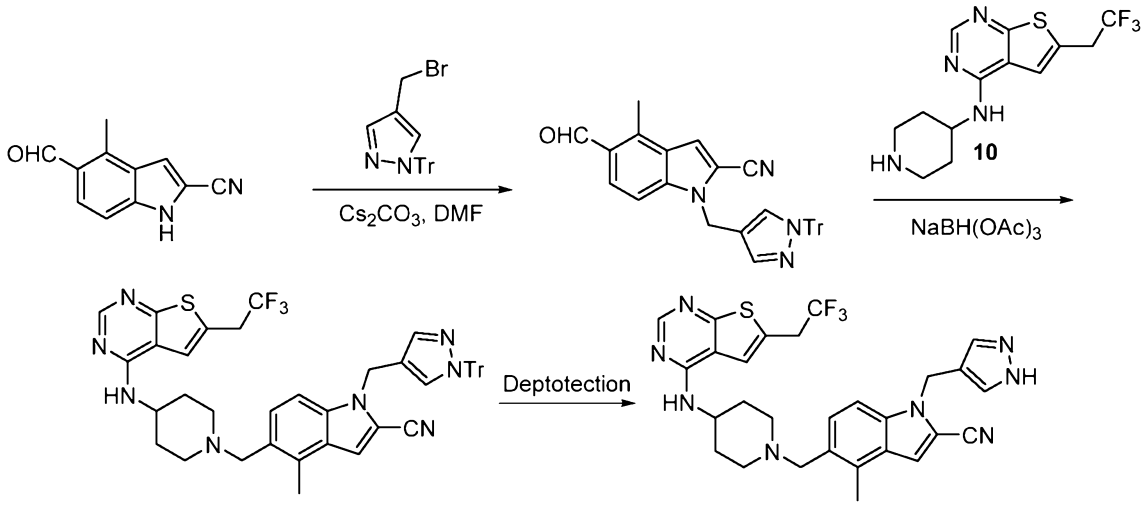
separatory funnel and washed with 50mL of 1M NaOH. Organic phase was evaporated with silica gel and loaded on silica gel column. The product was eluted starting from DCM:MeOH:NH_3*H_2O 40:1:0.1 to 15:1:0.1. Evaporation of solvent gave 2.08g of oily product, which was dissolved in 5mL of diethyl ether and crystallized upon standing. The product was filtered off, washed with additional 10mL of ether and thoroughly dried to afford 1.95g of white crystalline product (**Compound 219**, >99% purity HPLC). ^{1}H NMR (600 MHz, $CDCl_3$): 10.02 (br s, 1H), 8.46 (s, 1H), 7.31 (d, 1H, J=8.4Hz), 7.24 (d, 1H, J=8.4Hz), 7.22 (s, 1H), 7.16 (s, 1H), 5.53 (d, 1H, J=7.7Hz), 4.22 (m, 1H), 3.64 (q, 2H, J=10.5Hz), 3.60 (s, 2H), 2.90 (d, 2H, J=11.7Hz), 2.56 (s, 3H), 2.25 (t, 2H, J=10.8Hz), 2.07 (d, 2H, J=10.6Hz), 1.57 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): 166.75, 156.20, 154.39, 136.31, 130.67, 129.22, 127.71, 127.42, 123.86, 118.98, 116.57, 114.55, 112.79, 108.89, 105.94, 100.00, 60.35, 52.42, 48.16, 35.51 (q, J=32Hz), 32.39, 15.12. HR MS (ESI): $C_{24}H_{23}F_3N_6S$ + H^+ calculated 485.1730; found 485.1732.
The compound was converted to hydrochloride salt by dissolving in 5mL of MeOH, adding 4.4mL of 1M HCl in water (4.4 mmol) and drying.

Compound 309



Step 1: 5g of ethyl 1H-pyrazole-4-carboxylate (35.7 mmole) was dissolved in 70mL of DMF, and 4.8g of potassium tert-butoxide (42.8 mmol) was added. After stirring for 30 minutes 13.9g of trityl chloride (50 mmol) was added in small portions. TLC indicated no starting material after 1hr of stirring and reaction mixture was diluted with 300ml of water and extracted with 3x50ml of DCM. Organic extracts were evaporated and then dissolved in 300mL of THF. 2.03 g of lithium aluminohydride (53.6 mmol) was added in small portions. After 1 hr reaction mixture was quenched with 10mL of ethyl acetate following by 5mL of water. 15g of silica gel was added, mixture was evaporated and loaded on small silica gel column. The product was eluted with hexane-ethyl acetate 1:1 mixture. Evaporation of product containing fractions resulted in 11.75g of (1-trityl-1H-pyrazol-4-yl)methanol.

Step 2: To a solution of 11.75g of (1-trityl-1H-pyrazol-4-yl)methanol (34.5 mmol), 9.04g triphenylphopshine (34.5 mmol) in 90mL of DCM was added 6.14g of N-Bromosuccinimide (34.5 mmol) at 0 degrees. Then mixture was stirred for 30 minutes and transferred in separatory funnel, washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate. After evaporation the residue was purified on conditioned silica gel column using hexane-ethyl acetate 10:1. Column conditioning (50g of silica gel): washed with 500mL of 0.05% of ammonia (conc. in water) in ethyl acetate, 500mL of pure ethyl acetate and 500mL of hexane. After evaporation of product containing fractions 11.09g of 4-(bromomethyl)-1-trityl-1H-pyrazole was obtained, that was used in subsequent step immediately (decomposes on standing).



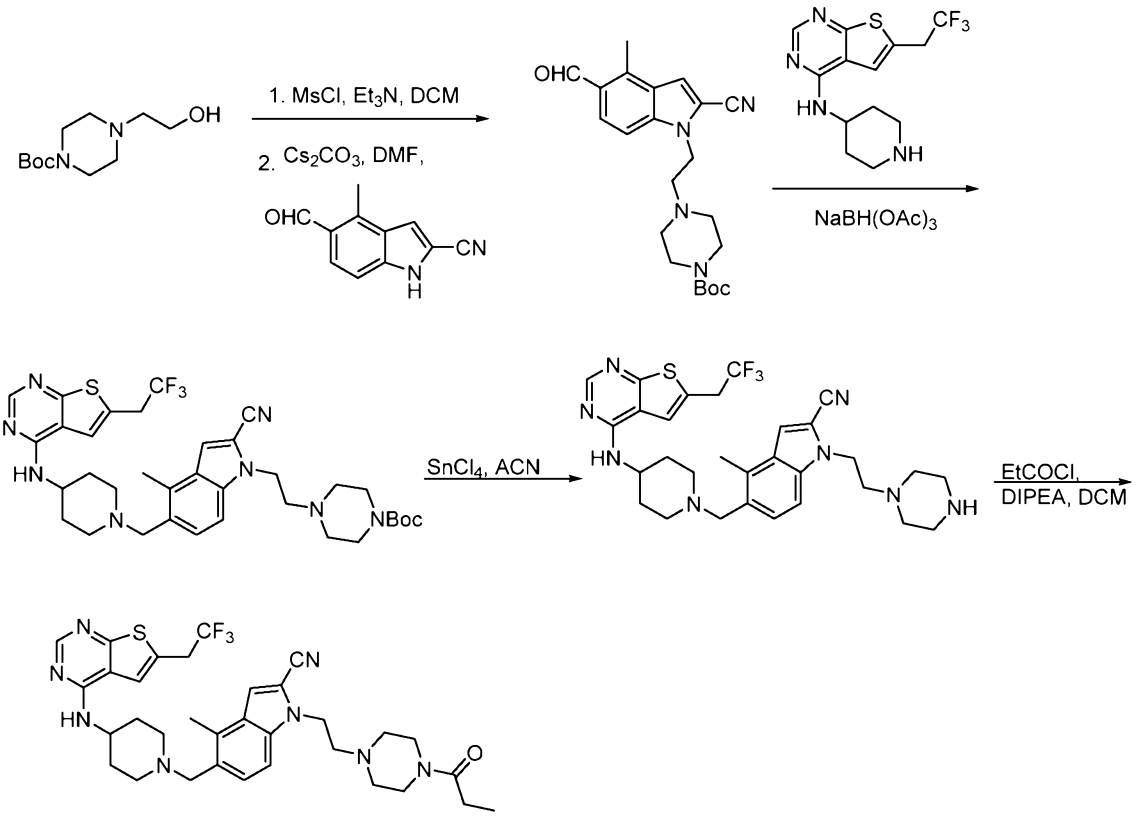
Step 3: 11.09 g of 4-(bromomethyl)-1-trityl-1H-pyrazole (27.5 mmol), 2.53g 5-formyl-4-methyl-1H-indole-2-carbonitrile (13.8 mmol) and 13.6g of cesium carbonate (41.4 mmol) were stirred in 28mL of DMF for 30 minutes. Then reaction was diluted with 300mL of water and 200mL of diethyl ether. After stirring for 4hs the precipitate was filtered off, washed with additional 100ml of water and 100mL of diethyl ether, dried to afford 16.4g of 5-formyl-4-methyl-1-((1-trityl-1H-pyrazol-4-yl)methyl)-1H-indole-2-carbonitrile. ^{1}H NMR (600 MHz, DMSO-d6): 10.02 (s, 1H), 7.85 (s, 1H), 7.82 (d, 1H, J=8.4Hz), 7.77 (d, 1H, J=8.4Hz), 7.58 (s, 1H), 7.50 (s, 1H), 7.36 (m, 9H), 7.00 (m, 6H), 5.47 (s, 2H), 2.83 (s, 3H).). ^{13}C NMR (150 MHz, DMSO-d6): 191.13, 162.28, 142.67, 142.55, 138.52, 132.10, 129.66, 129.54, 127.85, 127.76, 127.14, 126.63, 115.56, 114.89, 109.77, 109.41, 78.46, 78.06, 14.12.

Step 4: 5.5g of 5-formyl-4-methyl-1-((1-trityl-1H-pyrazol-4-yl)methyl)-1H-indole-2-carbonitrile (10.8 mmol) 5.8g of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (16.2 mmol) and 3mL of triethylamine (21.6 mmol) were mixed in 110mL of dry dichloromethane. 4.64 of sodium triacetoxyborohydride (21.6 mmol) was added to it in one portion. After stirring overnight TLC showed absence of starting aldehyde in reaction mixture was transferred in separatory funnel and washed with 100mL of 1M NaOH. Organic phase was evaporated with silica gel and loaded on silica gel column. The product was eluted starting from DCM:MeOH:NH_3*H_2O 40:1:0.1 to 20:1:0.1. Evaporation of solvent gave 6.17g of oily 4-methyl-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1-((1-trityl-1H-pyrazol-4-yl)methyl)-1H-indole-2-carbonitrile. ^{1}H NMR (600 MHz, $CDCl_3$): 8.47 (s, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 7.33 (d, 1H, J=8.4Hz), 7.27 (m, 9H), 7.19 (s, 1H), 7.16 (d, 1H, J=8.4Hz), 7.08 (m, 6H), 7.04 (s, 1H), 5.27 (s, 2H), 5.53 (d, 1H, J=7.7Hz), 4.23 (m, 1H), 3.62 (q, 2H, J=10.5Hz), 3.60 (s, 2H), 2.89 (m, 2H), 2.54 (s, 3H), 2.26 (t, 2H, J=10.6Hz), 2.09 (d, 2H, J=10.3Hz), 1.57 (d, 2H, J=9.9Hz). ^{13}C NMR (150 MHz, $CDCl_3$): 166.83, 156.03, 154.37, 142.89, 138.75, 136.42, 131.63, 131.24, 130.13, 130.08, 129.08, 127.81, 127.74, 127.43, 125.58, 118.35, 116.38, 115.40, 113.83, 112.35, 108.82, 107.36, 78.85, 60.21, 56.24, 52.32, 48.06, 39.90, 35.54 (q, J=32Hz), 32.44, 15.03. HR MS (ESI): $C_{47}H_{41}F_3N_8S$ + H^+ calculated 807.3200; found 807.3197.

Step 5: 6.17g of oily 4-methyl-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1-((1-trityl-1H-pyrazol-4-yl)methyl)-1H-indole-2-carbonitrile was dissolved in 90mL of ethyl acetate methanol 1:1 mixture. 6mL of 4M HCl in dioxane was added. After stirring for 30 minutes the reaction mixture was concentrated and partitioned in DCM:MeOH 10:1 and saturated sodium carbonate solution. Organic phase was separated, evaporated with silica gel and loaded on silica gel column. Gradient elution with DCM:MeOH:NH_3*H_2O 50:1:0.1 to 7:1:0.1 and evaporation of product containing fractions resulted in 4.05g of oil that crystallized upon standing. It was dissolved in 30mL of methanol and 7mL of 1M HCl. Evaporation and drying gave 3.7g of hydrochloride of 1-((1H-pyrazol-4-yl)methyl)-4-methyl-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (**compound 309**). Two rotamers are observed in NMR in approximate ratio 10:1. NMR is reported for the major rotamer. ^{1}H NMR (600 MHz, CD_3OD): 8.36 (s, 1H), 7.63 (m, 5H), 7.43 (s, 1H), 5.45 (s, 2H), 4.53 (s, 2H), 4.46 (m, 1H), 3.86 (q, 2H,

J=10.5Hz), 3.63 (m, 2H), 3.34 (m, 2H), 2.67 (s, 3H), 2.32 (m, 2H), 2.03 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): 165.72, 157.61, 154.23, 138.70, 135.18, 130.91, 130.30, 128.73, 127.51, 125.68, 121.99, 121.12, 118.22, 114.39, 114.04, 111.04, 110.61, 58.83, 52.87, 47.25, 40.50, 35.61 (q, J=32Hz), 29.90, 27.34, 15.89. HR MS (ESI): $C_{47}H_{41}F_3N_8S + H^+$ calculated 807.3200; found 807.3197.

Compound 401



Step 1: 1g of tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (4.3 mmol) and 0.89mL of triethyl amine (6.5 mmol) were dissolved in 14mL of DCM. 0.4mL of MsCl (5.2 mmol) was added slowly and reaction was stirred for 2hs. After that it was washed with brine, dried over anhydrous sodium sulfate and evaporated. That intermediate was dissolved in 4mL of DMF and

368mg of 5-formyl-4-methyl-1H-indole-2-carbonitrile (2 mmol) and 2g of cesium carbonate (6 mmol) were added. After stirring for 18hs TLC showed consumption of aldehyde. The reaction mixture was diluted with 50mL of water and extracted with 2x50mL of DCM. Organics were evaporated with silica gel and loaded on silica gel column. The product was eluted with hexane-ethyl acetate 1:1 to afford 240mg of tert-butyl 4-(2-(2-cyano-5-formyl-4-methyl-1H-indol-1-yl)ethyl)piperazine-1-carboxylate. HR MS (ESI): $C_{22}H_{28}N_4O_3$ + H^+ calculated 397.2234; found 397.2239.

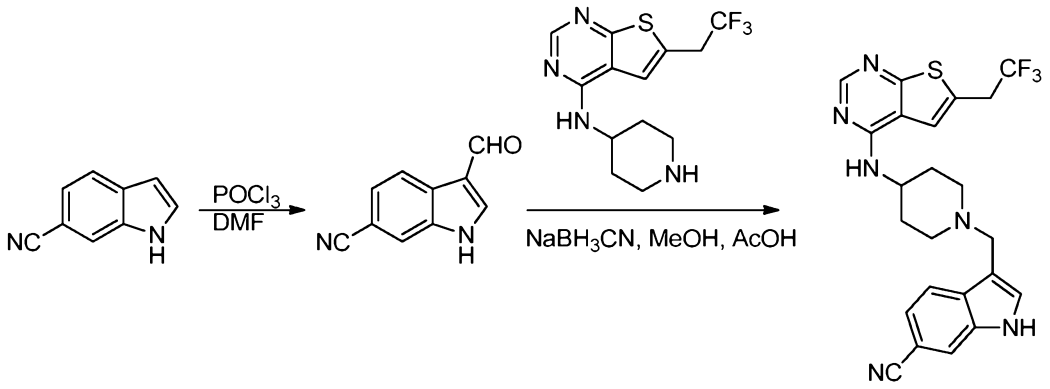
Step 2: 120mg of tert-butyl 4-(2-(2-cyano-5-formyl-4-methyl-1H-indol-1-yl)ethyl)piperazine-1-carboxylate (0.3 mmol) 126mg of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (0.36 mmol) and 0.06mL of triethylamine (0.45 mmol) were mixed in 3mL of dry dichloromethane. 97mg of sodium triacetoxyborohydride (0.45 mmol) was added to it in one portion. After stirring overnight TLC showed absence of starting aldehyde in reaction mixture was transferred in separatory funnel and washed with 20mL of 1M NaOH. Organic phase was evaporated with silica gel and loaded on silica gel column. The product was eluted starting from DCM:MeOH:NH_3*H_2O 40:1:0.1 to 20:1:0.1. Evaporation of solvent gave 180mg of tert-butyl 4-(2-(2-cyano-4-methyl-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indol-1-yl)ethyl)piperazine-1-carboxylate. HR MS (ESI): $C_{35}H_{43}F_3N_8O_2S$ + H^+ calculated 697.3255; found 697.3259.

Step 3: 180mg of tert-butyl 4-(2-(2-cyano-4-methyl-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indol-1-yl)ethyl)piperazine-1-carboxylate (0.26 mmol) was dissolved in 2.6mL of ACN and 0.3mL of $SnCl_4$ (2.6 mmol) was added. The homogenous reaction mixture was stirred for 1h and then all volatiles were removed in vacuo. The residue was quenched ammonia and extracted with ethyl acetate. Combined organic fractions were dried over $MgSO_4$ and concentrated. The residue was purified using preparative TLC to afford 88mg of 4-methyl-1-(2-(piperazin-1-yl)ethyl)-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile. ^{1}H NMR (600 MHz, $CDCl_3$): 8.46 (s, 1H), 7.35 (d, 1H, J=8.4Hz), 7.17 (s, 1H), 7.15 (d, 1H, J=8.4Hz), 7.10 (s, 1H), 5.20 (d, 1H, J=7.7Hz), 4.32 (m, 2H), 4.22 (m, 1H), 3.63 (q, 2H, J=10.5Hz), 3.60 (s, 2H), 2.91, (m, 6H), 2.69 (m, 2H), 2.54 (s, 3H), 2.50 (m, 4H), 2.26 (t, 2H, J=10.6Hz), 2.09 (d, 2H, J=10.3Hz), 1.58 (d, 2H, J=9.9Hz). ^{13}C NMR (150 MHz, $CDCl_3$): 166.79,

156.09, 154.36, 136.37, 131.18, 128.97, 128.65, 127.33, 125.61, 118.62, 116.43, 114.03, 111.64, 109.76, 107.23, 60.14, 57.80, 57.80, 53.86, 52.36, 51.34, 48.05, 45.48, 43.34, 35.53 (q, J=32Hz), 32.39, 15.06. HR MS (ESI): $C_{30}H_{35}F_3N_8S + H^+$ calculated 597.2730; found 597.2727.

Step 4: To a mixture of 20mg of 4-methyl-1-(2-(piperazin-1-yl)ethyl)-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (0.029 mmol) and 0.012mL of DIPEA (0.069 mmol) in 0.3mL of DCM was added 0.0028mL of propionyl chloride (0.032 mmol). After stiring for 30 minutes reaction mixtures was loaded directly on pTLC and developed in DCM-MeOH 15:1. Washing silica gel and evaporating resulted in 19mg of 4-methyl-1-(2-(4-propionylpiperazin-1-yl)ethyl)-5-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (**Compound 401**). It was converted in hydrochloride by dissolving in 0.5mL of methanol, adding 0.03mL of 1M HCl in water and evaporating. ^{1}H NMR (600 MHz, CD_3OD): 8.35 (s, 1H), 7.61 (m, 2H), 7.54 (s, 1H), 7.48 (s, 1H), 4.60 (m, 2H), 4.55 (s, 2H), 3.86 (q, 2H, J=10.5Hz), 3.61 (m, 4H), 3.35 (m, 2H), 2.98 (m, 2H), 2.70 (s, 3H), 2.70 (br, 2H), 2.39 (q, 2H, J=7.6Hz), 2.35 (m, 2H), 1.99 (m, 2H), 1.10 (t, 3H, J=7.36Hz). ^{13}C NMR (150 MHz, CD_3OD): 174.85, 166.81, 157.98, 154.75, 138.82, 135.20, 130.79, 128.81, 127.53, 125.70, 121.77, 121.20, 118.19, 114.42, 112.33, 110.48, 58.85, 54.29, 53.99, 52.94, 47.12, 42.06, 35.63 (q, J=32Hz), 29.98, 27.34, 27.14, 24.24, 15.81, 9.83. HR MS (ESI): $C_{33}H_{39}F_3N_8OS + H^+$ calculated 653.2992; found 653.2988.

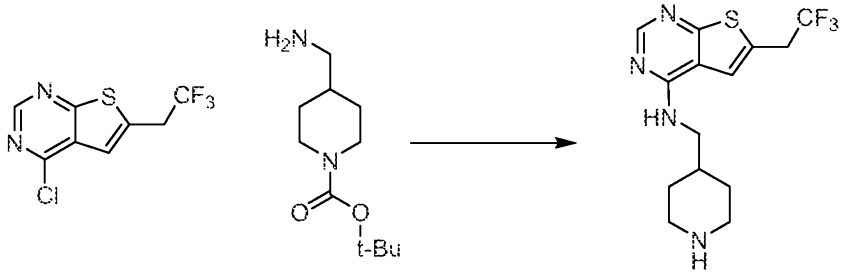
Compound 206



Monohydrochloride salt exists as a mixture of rotomers in approximate ratio 10:1, NMR is described for the major one: ^{1}H NMR (600 MHz, MeOD-d4): 8.56 (s, 1H), 7.94 (d, 1H, J=8.4Hz), 7.89 (m, 2H), 7.70, (s, 1H), 7.46 (d, 1H, J=8.4Hz), 4.60 (s, 2H), 4.54 (m, 1H), 3.93 (q, 2H, J=10.6Hz), 3.67 (m, 2H), 3.28 (m, 2H), 2.35 (m, 2H), 2.04 (m, 2H). ^{13}C NMR (150 MHz, MeOD-d4): δC 157.52, 151.57, 136.80, 134.03, 131.92, 127.24, 125.41, 124.16, 124.12, 122.23, 121.02, 120.49, 118.48, 118.12, 105.91, 104.66, 52.19, 52.06, 47.81, 35.43 (q, J=33Hz), 29.73. ESI MS [MH$^+$]: 471.1576.

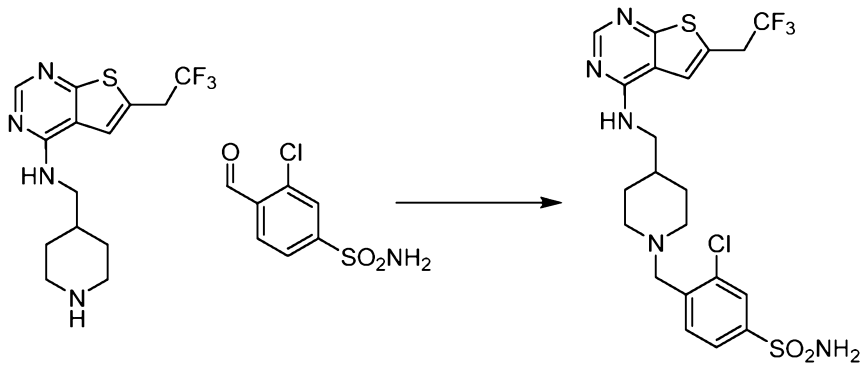
Example 6

Representative procedure for the synthesis of compounds from subscaffold 5



Tert-butyl 4-((6-(2,2,2-trifluoroethyl)thieno[2,3-*d*]pyrimidin-4-ylamino)methyl) piperidine-1-carboxylate. To a solution of 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-*d*]pyrimidine (50 mg, 0.20 mmol) in DMF (1 mL) was added *N,N*-diisopropylethylamine (52 L, 0.30 mmol) and *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (51 mg, 0.30 mmol). The solution was heated to 80 °C for 2 hours. The solution was diluted with EtOAc (10 mL) and washed with 10% $NaHCO_3$ (2 × 5 mL). The organic phase was dried Na_2SO_4 and evaporated *in vacuo* to give the product as a clear oil (103 mg, 80% yield) which was used without further purification. LC-MS: 2.49 min, 431.2 *m/z* [M+H]$^+$, 375.1 *m/z* [M–*t*-Bu+H]$^+$

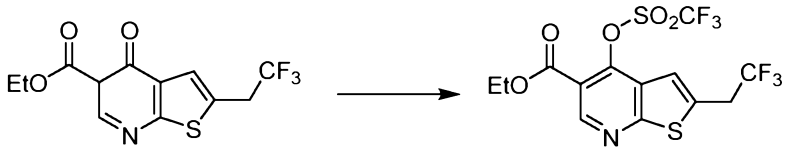
6-(2,2,2-trifluoroethyl)-*N*-((piperidin-4-yl)methyl)thieno[2,3-*d*]pyrimidin-4-amine. *Tert*-butyl 4-((6-(2,2,2-trifluoroethyl)thieno[2,3-*d*]pyrimidin-4-ylamino)methyl) piperidine-1-carboxylate (103 mg, 0.24 mmol) was dissolved in TFA (1 mL). The solution was maintained at room temperature for 2 hours. The solution was then diluted with $CHCl_3$ (10 mL), and washed with 10% $NaHCO_3$ (2 × 5 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to give the product as a clear oil (56 mg, 85% yield). LC-MS: 1.48 min, 331.2 *m/z* [M+H]$^+$.



To a vial containing 6-(2,2,2-trifluoroethyl)-*N*-((piperidin-4-yl)methyl)thieno[2,3-*d*]pyrimidin-4-amine (20 mg, 0.061 mmol) was added 1,2-dichloroethane (300 uL), 3-chloro-4-formylbenzene-1-sulfonamide (17 mg, 0.077 mmol), and sodium tri(acetoxy)borohydride (20 mg, 0.094 mmol). The mixture was stirred at room temperature for 4 hours. The mixture was diluted with EtOAc (5 mL), and washed with 0.1 *N* NaOH (2 × 1 mL). The volatiles were removed *in vacuo*. The resulting residue was purified by reversed-phase preparative HPLC (95:5 – 5:95 MeCN/H_2O with 0.1 % TFA buffer). The product containing fractions were evaporated *in vacuo* to afford the product as a white solid (2.7 mg, 8.4% yield), **Compound 253**. LC-MS: 1.20 min, 534.1 *m/z* $[M+H]^+$

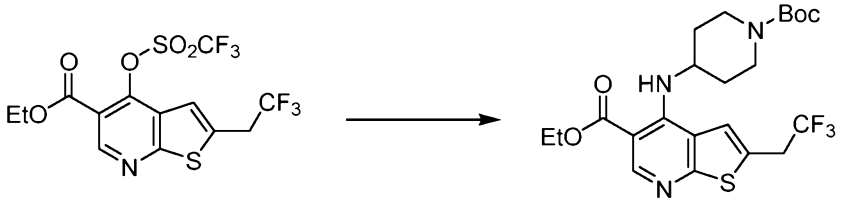
Example 7

Representative procedure for the synthesis of compounds from subscaffold 3 and 4

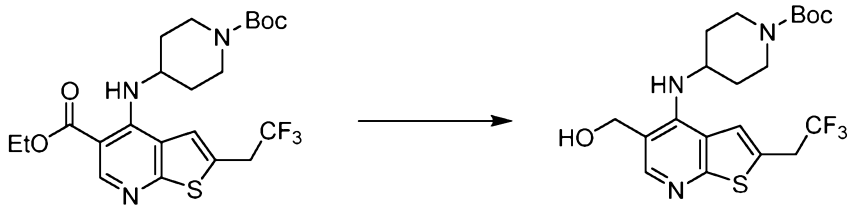


5-(ethoxycarbonyl)-2-(2,2,2-trifluoroethyl)thieno[2,3-*b*]pyridin-4-yl trifluoromethanesulfonate. Ethyl 2-(2,2,2-trifluoroethyl)-4,5-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylate (91 mg, 0.30 mmol) (synthesized using similar procedure described in literature procedure *J. Het. Chem.* 1991, 28(8), 1953-5) was dissolved in dichloromethane (5 mL). *N,N*-diisopropylethylamine (157 uL, 0.90 mmol) was added. Solid *N*-phenyl-bis(trifluoromethanesulfonamide) (214 mg, 0.60 mmol) was added, and the mixture stirred for 10 minutes. The solution was washed with water (5 mL),

dried over Na_2SO_4, and concentrated *in vacuo* to give an orange residue. Purification of the residue by silica gel chromatography (98:2 hexanes/EtOAc) afforded the product as a yellow solid (108 mg, 82% yield). LC-MS 3.22 min 438.2 *m/z* $[M+H]^+$

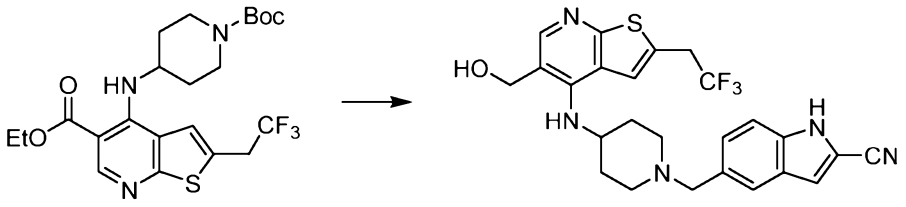


Ethyl 4-(1-(tert-butoxycarbonyl)piperidin-4-ylamino)-2-(2,2,2-trifluoroethyl) thieno[2,3-*b*]pyridine-5-carboxylate. To a solution of 5-(ethoxycarbonyl)-2-(2,2,2-trifluoroethyl)thieno[2,3-b]pyridin-4-yl trifluoromethanesulfonate (108 mg, 0.25 mmol) in THF (2.5 mL) was added *N,N*-diisopropylethylamine (69 uL, 0.40 mmol) and *tert*-butyl 4-aminopiperidine-1-carboxylate (55 mg, 0.27 mmol). The solution was heated to 60 °C for 2 hours. The volatiles were removed *in vacuo*. The residue was dissolved in EtOAc (10 mL), washed subsequently with 0.1 *N* $NaHSO_4$ (2 × 5 mL) and saturated aq. $NaHCO_3$ (1 × 5 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to give the product as a white foam (122 mg), which was used without further purification. LC-MS: 2.73 min, 488.2 *m/z* $[M+H]^+$, 432.1 *m/z* $[M-t\text{-}Bu+H]^+$



*T*ert-butyl 4-(2-(2,2,2-trifluoroethyl)-5-(hydroxymethyl)thieno[2,3-b]pyridin-4-ylamino)piperidine-1-carboxylate. Ethyl 4-(1-(tert-butoxycarbonyl)piperidin-4-ylamino)-2-(2,2,2-trifluoroethyl) thieno[2,3-*b*]pyridine-5-carboxylate (122 mg, 0.25 mmol) was dissolved in THF (2.0 mL). Lithium borohydride (0.5 mL, 2.0 M solution in THF, 1.0 mmol) was added. The solution was heated to reflux under nitrogen for 1 hour. After cooling to room temperature, water (1 mL) was carefully added to the mixture. The mixture was concentrated *in vacuo*. Methanol (10 mL) was added and the solution concentrated to dryness on a rotary evaporator. The addition of methanol and evaporation was repeated three additional times. Purification of the resultant residue by silica gel chromatography (10:1 to 1:1 gradient of hexanes/EtOAc) afforded the

product as a yellow solid (45 mg, 40% yield). LC-MS: 2.35 min, 446.3 *m/z* $[M+H]^+$, 390.3 *m/z* $[M-t\text{-}Bu+H]^+$



Ethyl 4-(1-(tert-butoxycarbonyl)piperidin-4-ylamino)-2-(2,2,2-trifluoroethyl)thieno[2,3-b]pyridine-5-carboxylate (45 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (3 mL). Trifluoroacetic acid (2 mL) was added to the solution. After 2 hours, the solution was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), and washed with a 10% solution of K_2CO_3 (2 × 1 mL), and dried over anhydrous K_2CO_3. The organic phase was concentrated to give tan residue, which was used in the next step without further purification. This residue was dissolved in 1,2-dichloroethane (1 mL). 5-formyl-1*H*-indole-2-carbonitrile (23 mg, 0.14 mmol) and sodium tri(acetoxy)borohydride (32 mg, 0.15 mmol) were added. The mixture was stirred at room temperature for 2 hours. The solution was diluted with EtOAc (10 mL) and washed with 0.1 *N* NaOH (1 × 5 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by reversed-phase preparative HPLC (95:5 – 5:95 MeCN/H_2O with 0.1 % HCl buffer). The product containing fractions were lyophilized to afford the product as a white solid (1.4 mg, 2.5% yield), **Compound 278**. LC-MS: 1.45 min, 500.2 *m/z* $[M+H]^+$.

Example 8

Fluorescence polarization (FP) assay

Fluorescence Polarization Assay. Assays effective in monitoring the inhibition of the MLL binding to menin were developed during experiments performed during the development of embodiments of the present invention. A fluorescein-labeled 12-amino acid peptide derived from MLL containing the high affinity menin binding motif was produced (Yokoyama et al., Cell., 2005.123(2): p. 207-18., herein incorporated by reference in its entirety). Upon binding of the peptide (1.7 kDa) to the much larger menin (- 67 kDa), the rotational correlation time of the fluorophore (peptide labeled with fluorescein at N-terminus) changes significantly, resulting in a

substantial increase in the measured fluorescence polarization and fluorescence anisotropy (excitation at 500 nm, emission at 525 nm). The fluorescence polarization (FP) assay was utilized to determine the K_d for the binding of menin and the MLL peptide using a serial dilution of menin and 50 nM fluorescein-labeled MLL peptide. The titration curve demonstrates nanomolar affinity (K_d =56 nM) for the menin-MLL interaction.

The effectiveness of compounds (IC_{50} values) in inhibiting the menin-MLL interaction was determined in the FP competition experiments. Compounds that inhibit the interaction decrease the fluorescence anisotropy which is being used as a read-out for compound screening and for IC_{50} determination. For validation of the FP assay, a control competition experiment with unlabeled MLL peptide (no fluorescein attached) was performed. The competitive displacement of the fluorescein-labeled MLL peptide from menin by unlabeled MLL peptide was monitored. Using this assay, the IC_{50} value for the MLL peptide with menin: IC_{50} =0.23 μM. In some embodiments of the present invention, the same competition FP assay is used for screening compounds targeting menin and inhibiting the menin-MLL interaction.

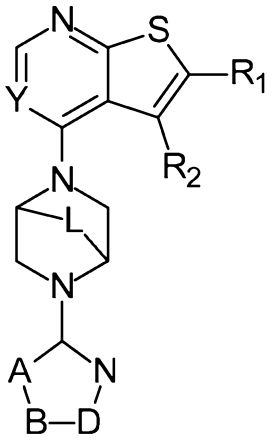
Biological activity of menin-MLL inhibitors is demonstrated in Figures 1-21. The IC_{50} values shown in Tables 1-8 were measured using the above fluorescence polarization (FP) assay.

CLAIMS

What is claimed is:

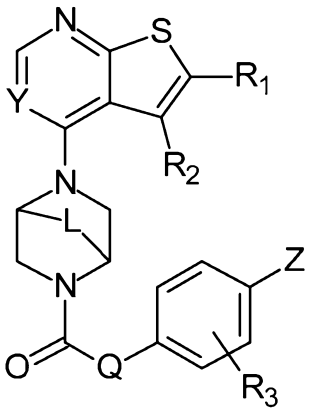
1. A composition comprising a compound having the structure of one of:

Subscaffold 1



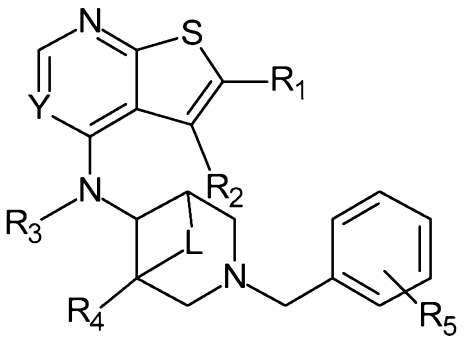
;

Subscaffold 2



;

Subscaffold 3



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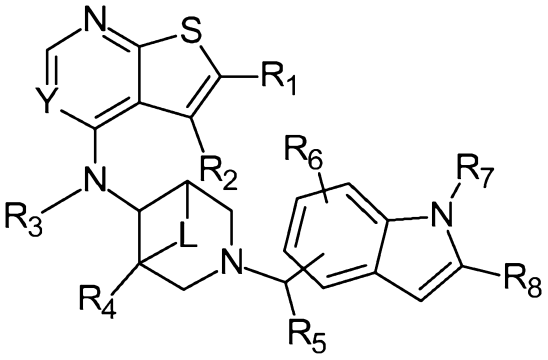
Subscaffold 4



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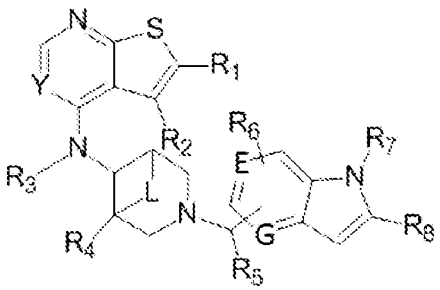
Subscaffold 4b



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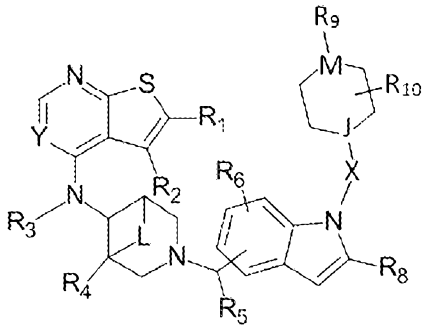
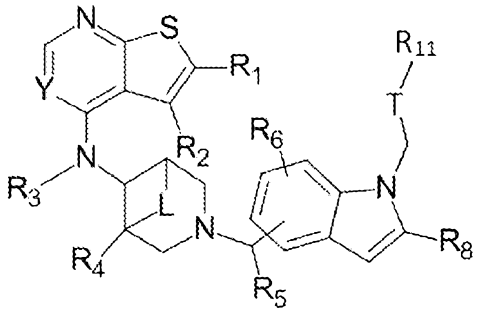
Subscaffold 4c



;

Subscaffold 4d



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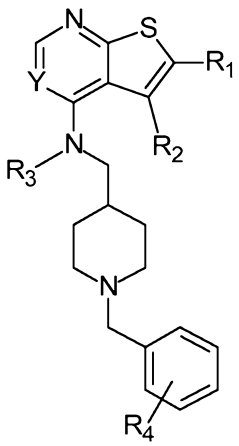
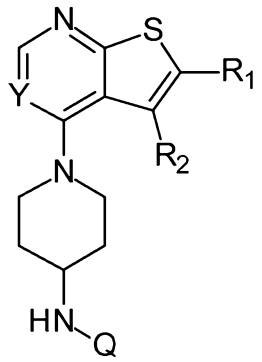
Subscaffold 5



; and

Subscaffold 6



wherein R1-R11, when present, each independently comprise H, C_1-C_{10} straight alkyl, C_1-C_{10} branched alkyl, C_1-C_{10} cycloalkyl, C_1-C_{10} branched cyclic alkyl, halogen-substituted alkyl group, hydroxyl and amino groups, alkoxy group, alcohol, diol, substituted diol, alkylamine, hydroxyalkyl, halogen-substituted cycloalkyl group, alkyl-substituted cycloalkyl group, cycloalkoxy group, cyclolkylamine, halogen, ketone, carboxylic acid and its derivatives, ester, carboxamide), cyano, alkylcyano, alkylocarboxylic acid and its derivatives, alkylester, alkylcarboxamide, amide, alkylamide, carbocyclic ring, aromatic ring, heteroaryl, substituted aromatic ring, heterocyclic aromatic ring, heterocyclic non-aromatic ring, a sulfone-containing group, or multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, alkyl-aryl, alkyl-heteroaromatic ring, alkyl-heterocyclic ring, substituted heterocyclic ring, heterocyclic rings, alkyl chains, and C-, N-, O-, S-, and/or halogen-containing substituents, or combinations thereof;

wherein A, B, D, J, and M, when present, each independently comprise C, N, O, or S, wherein when A, B, D, J, and/or M is O or S, there is no further substitution at that respective position; wherein when A, B, D, J, and/or M is N or C that respective position is optionally substituted, wherein the optional substituent at that respective position comprises: a straight-chain alkyl, a branched alkyl group, a cycloalkyl group, a branched cyclic alkyl, a halogen-substituted alkyl group, hydroxyl and amino groups, alkoxy group, alkylamine, a substituted cycloalkyl group, a halogen, a ketone, carboxylic acid and its derivatives, ester, carboxamide, cyano, alkylcyano, alkylocarboxylic acid and its derivatives, alkylocyano, alkylester, alkylcarboxamide, amide, alkylamide, CO-alkyl, CO-alkenyl, CO-alkynyl, CO-$(CH_2)_{1-6}$-aryl, CO-$(CH_2)_{1-6}$-heteroaryl, CO-$(CH_2)_{1-3}$-trifluoromethane, CO-$(CH_2)_{1-6}$-cycloalkane, alcohol, OH, methanol, ethanol, propanol, $CONH_2$, $CO(CH_2)_{1-6}$, O_2, SO_2NH_2, SO_2-amino-dialkyl, SO_2-NH-alkyl,CO-amino-dialkyl, SO_2-$(CH_2)_{1-6}$, SO_2- alkenyl, SO_2-alkynyl, CO-$(CH_2)_{1-6}$, a carbocyclic ring, an aromatic ring, a substituted aromatic ring, a heterocyclic aromatic ring, a heterocyclic

non-aromatic ring, carbocyclic aromatic ring, or a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, C-, N-, O-, S-, and/or halogen-containing substituents, or combinations thereof;

wherein E and G, when present, each independently comprise C or N, optionally substituted with a R6 substituent;

wherein L is present or absent, and when present comprises an alkylene or oxalkylene group;

wherein Q, when present, comprises an alkyl or heteroalkyl;

wherein T, when present, comprises: a 5- or 6-membered ring comprising carbon atoms and one or more of N, S, and/or O, or a cycloalkane; wherein an R11 substituent optionally extends from the T ring;

wherein X, when present, comprises: an alkyl chain or heteroalkyl chain;

wherein Y, when present, comprises: N or C, and wherein when Y is N or C the Y position may be substituted with R^a, R^a comprising a straight alkyl, branched alkyl, cycloalkyl, heteroalkyl, alkyl-substituted aryl, halo-substituted alkyl, alcohol, alkoxy alkyl-aryl, alkyl-aromatic, alkyl-heterocycle, substituted or non-substituted aryl, aromatic or non-aromatic heterocycle, amine, cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, or combinations thereof;

and wherein Z, when present, comprises: H, straight-chain alkyl, branched alkyl group, cycloalkyl, branched cyclic alkyl, a substituted alkyl group, hydroxyl and amino groups, alkoxy group, alkylamine, thioalkyl, substituted cycloalkyl group, a halogen, a ketone, carboxylic acid and its derivatives, cyano, ester, carboxamide, cyano, alkylcyano, alkylocarboxylic acid and its derivatives, alkylester, alkylcarboxamide, amide, alkylamide, a carbocyclic ring, an aromatic ring, a substituted aromatic ring, a heterocyclic aromatic ring, a heterocyclic non-aromatic ring, carbocyclic or heterocyclic aromatic ring comprising carbon atoms and one or more nitrogen, oxygen and/or sulfur members fused to another aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, halogen-containing substituents, a sulfur-containing group, a group selected from $CHR^4SO_2R^5$ or $NR^4SO_2R^5$, or combinations thereof; and pharmaceutically acceptable salts thereof.

2. The composition of claim 1, wherein R1-R11 and A, B, D, E, G, J, L, M, T, X, Y, and Z are selected from the substituents depicted at the respective positions in Tables 1-8, in any combination.

3. The composition of claim 2, wherein the compound is selected from compounds 1-430 and pharmaceutically acceptable salts thereof.

4. The composition of claim 1, wherein R1-R11, when present, each independently comprise: H, methane, ethane, propane, butane, pentane, hexane, iso-propyl, 2-methyl-hexane, 3-methyl,2-propyl-octane, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane, methylcyclohexane, ethylcyclobutane, propylcyclohexane, trifluoroethane, difluoroethane, monofluoroethane, fluoromethane, difluoromethane, trihalomethane, trifluoromethane, ether, alcohol, ethylamine, iso-butylamine, n-propylamine, sec-butylamine, iso-propylamine, iso-amylamine, methylamine, dimethylamine, n-amylamine, dimethylamine, methylethanolamine, diphenylamine, trimethylamine, triphenylamine, thiolkyl, a substituted cycloalkyl group, halogen-substituted cycloalkyl group, cycloalkoxy group, acyclolkylamine, F, Cl, Br, I, At, a ketone, an amide, an alkylamide, a cyano group, methyl carbonitrile, -SO2CH3 group, sulfonyl group, formyl, acetyl, propanoyl, CO-ethenyl, CO-propenyl, CO-ethynyl, CO-propynyl, CO-(CH2)1-6-aryl, CO-(CH2)1-6-heteroaryl, CO-(CH2)1-3-trifluoromethane, CO-(CH2)1-6-cycloalkane, OH, methanol, ethanol, propanol, CONH2, CO(CH2)1-6, O2, SO2NH2, SO2-amino-dialkyl, SO2-NH-alkyl,CO-amino-dialkyl (, SO2-(CH2)1-6, SO2- alkenyl, SO2-alkynyl, CO-(CH2)1-6, a carbocyclic ring, an aromatic ring, ethylbenzene, methyl benzene, chlorobenzene, fluorobenzene, a a substituted or non-substituted heterocyclic aromatic ring, a substituted or non-substituted heterocyclic non-aromatic ring, a multi-ring system comprising a combination of elements selected from aromatic rings, cycloalkane, heterocyclic rings, alkyl chains, and suitable C-, N-, O-, S-, and/or halogen-containing substituents, or a hydrogen bond donor or a hydrogen bond acceptor, and/or combinations thereof.

5. The composition of claim 1, wherein Y is N or C, and wherein when Y is C the Y position may be substituted with Ra, with Ra consisting of or comprising an isopropyl, propyl, cyclopropyl, methyl propyl ether, ethylbenzene, trifluoromethyl, monofluoroethyl group, difluoroethyl, trifluoroethyl group, trifluoropropyl, trifluorobutyl group, trifluoroisopropyl, 1-

fluoro,2-trifluoroethane, 1-trifluoro,2-ethanol (CH2)nOH, wherein n=0-10, (CH2)n-OR, wherein n=0-10, and R is alkyl, (CH2)n-aryl, (CH2)n-aromatic, or (CH2)n-heterocycle; substituted or non-substituted or substituted aryl, aromatic or non-aromatic heterocycle, cyano, sunlfonyl, methoxy, aldehyde, heterocycle, aromatic, or combinations thereof.

6. The composition of claim 1, wherein the compound comprises subscaffold 1.

7. The composition of claim 1, wherein the compound comprises subscaffold 2.

8. The composition of claim 1, wherein the compound comprises subscaffold 3.

9. The composition of claim 1, wherein the compound comprises subscaffold 4.

10. The composition of claim 1, wherein the compound comprises subscaffold 4b.

11. The composition of claim 1, wherein the compound comprises subscaffold 4c.

12. The composition of claim 1, wherein the compound comprises subscaffold 4d.

13. The composition of claim 1, wherein the compound comprises subscaffold 5.

14. The composition of claim 1, wherein the compound comprises subscaffold 6.

15. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

16. the composition of claim 15, further comprising a second pharmaceutical agent.

17. The composition of claim 15, said compound being in appropriate dose for the treatment of a disease or condition.

18. The method of claim 17, wherein said disease or condition comprises a leukemia, hematologic malignancies, solid tumor cancer, or diabetes.

19. A method for the treatment of a disease or condition comprising: administering a composition of one of claims 1-5 to a subject suffering from said disease or condition.

20. The method of claim 19, wherein said disease or condition comprises a leukemia, hematologic malignancies, solid tumor cancer, or diabetes.

21. The method of claim 20, wherein said leukemia comprises AML, ALL, or Mixed Lineage Leukemia.

22. A method of inhibiting the interaction of menin and one or more of MLL1, MLL2, a MLL fusion protein, and a MLL Patrial Tandem Duplication, comprising administering composition of one of claims 1-5 to said sample comprising MLL and menin.

23. A method of treating a disorder mediated by chromosomal rearrangement on chromosome 11q23, comprising administering to a subject in need thereof a therapeutically effective amount of the composition of one of claims 1-5.

24. A method of treating a disorder mediated by menin interaction with another protein, comparsing administering to a subject in need thereof a therapeutically effective amount of the composition of claim one of claims 1-5.

FIGURE 1

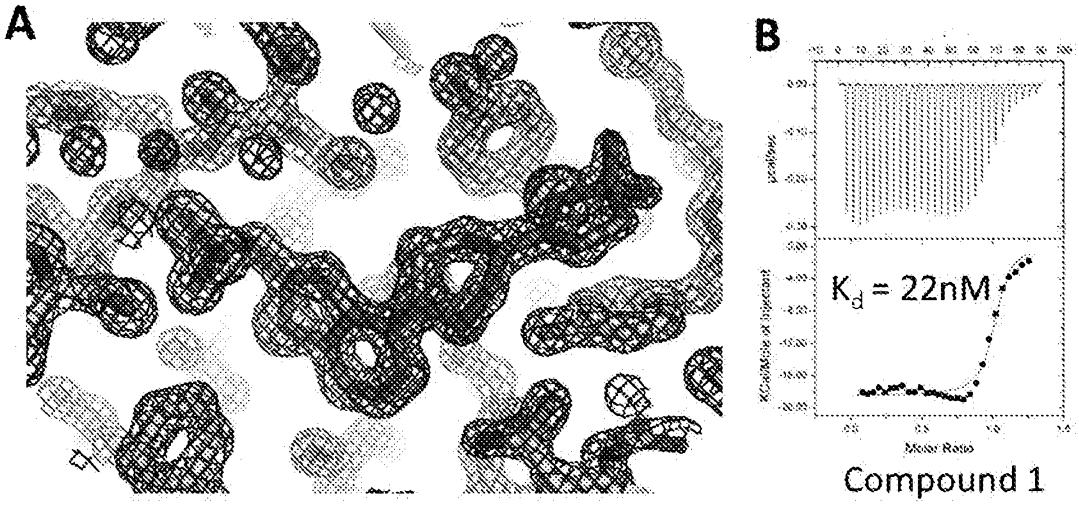


FIGURE 2

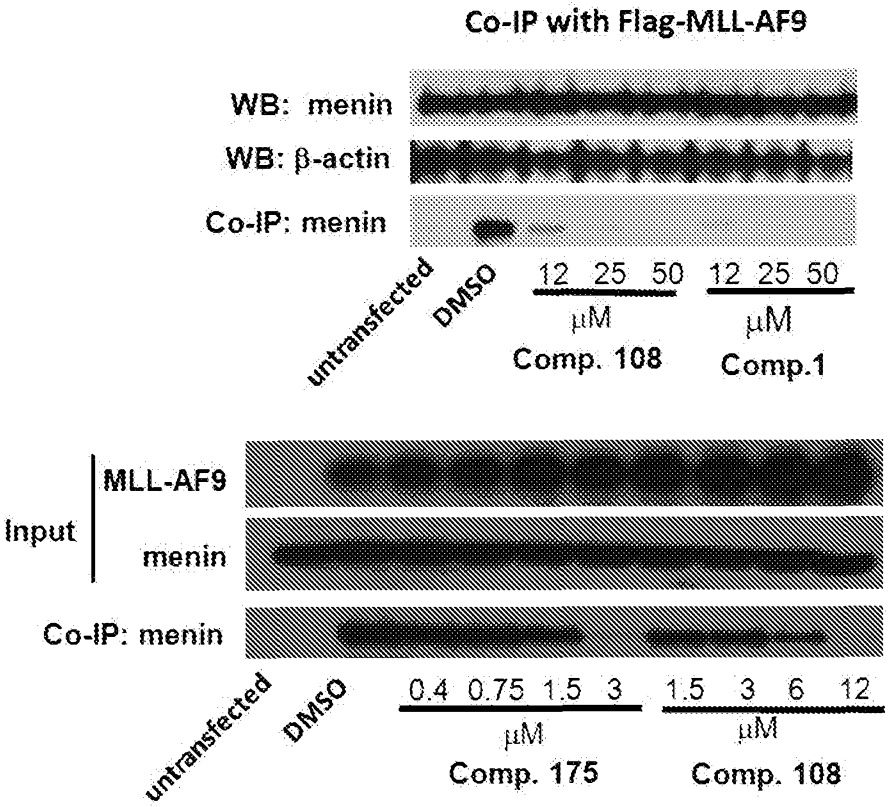

Co-IP with Flag-MLL-AF9
WB: menin
WB: β-actin
Co-IP: menin
untransfected
DMSO
12 25 50
μM
Comp. 108
12 25 50
μM
Comp.1
Input
MLL-AF9
menin
Co-IP: menin
untransfected
DMSO
0.4 0.75 1.5 3
μM
Comp. 175
1.5 3 6 12
μM
Comp. 108

FIGURE 3

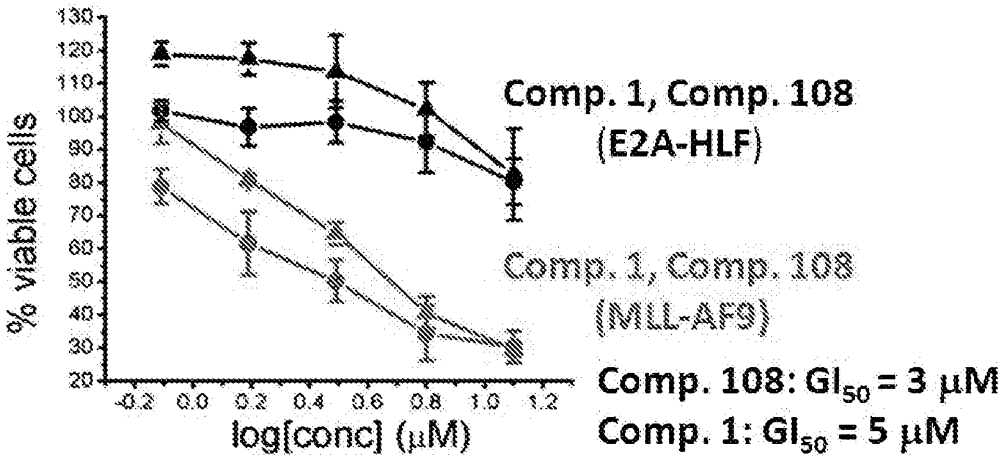

% viable cells
log[conc] (μM)
Comp. 1, Comp. 108
(E2A-HLF)
Comp. 1, Comp. 108
(MLL-AF9)
Comp. 108: GI50 = 3 μM
Comp. 1: GI50 = 5 μM

FIGURE 4

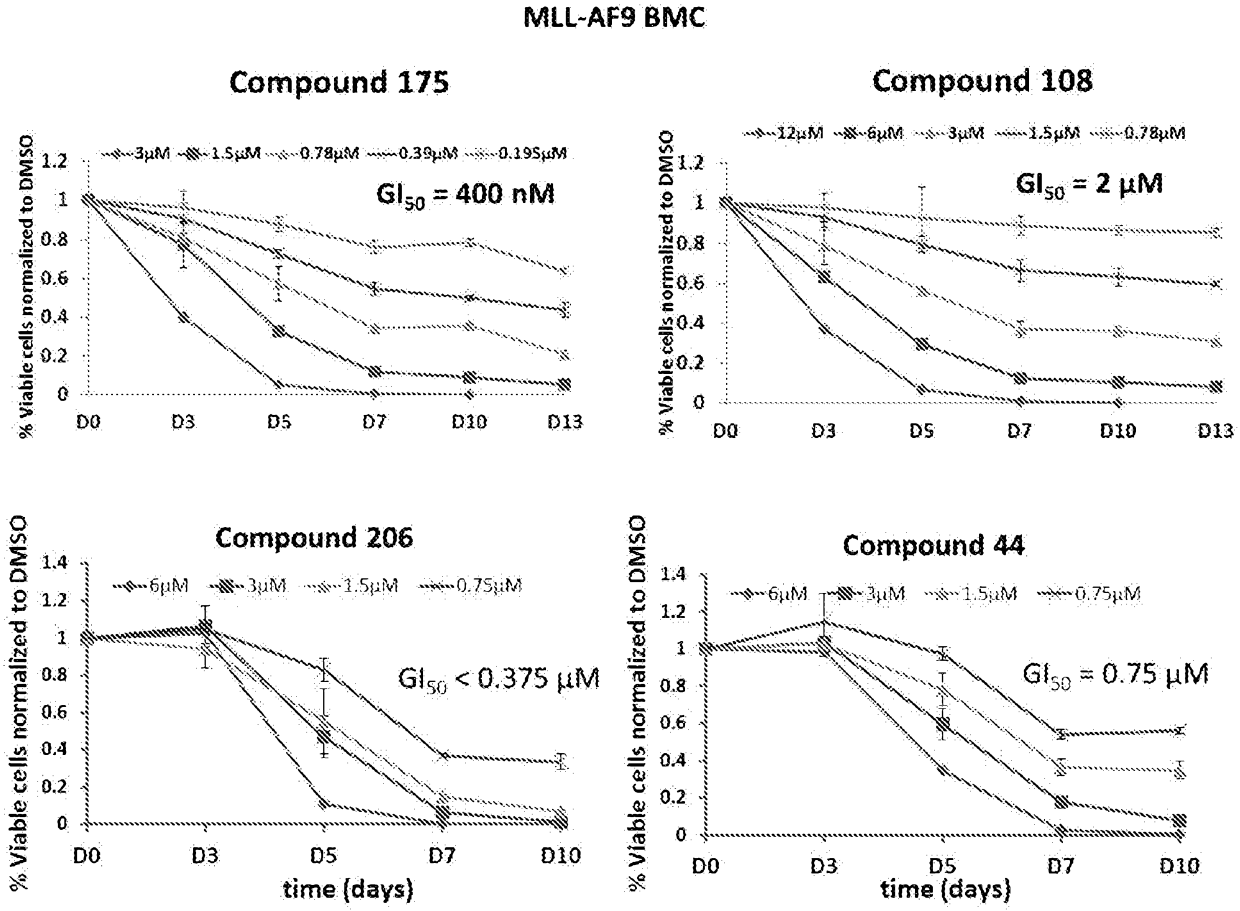

MLL-AF9 BMC
Compound 175
3μM 1.5μM 0.78μM 0.39μM 0.195μM
GI50 = 400 nM
% Viable cells normalized to DMSO
D0 D3 D5 D7 D10 D13
Compound 108
12μM 6μM 3μM 1.5μM 0.78μM
GI50 = 2 μM
% Viable cells normalized to DMSO
D0 D3 D5 D7 D10 D13
Compound 206
6μM 3μM 1.5μM 0.75μM
GI50 < 0.375 μM
% Viable cells normalized to DMSO
D0 D3 D5 D7 D10
time (days)
Compound 44
6μM 3μM 1.5μM 0.75μM
GI50 = 0.75 μM
% Viable cells normalized to DMSO
D0 D3 D5 D7 D10
time (days)

FIGURE 5

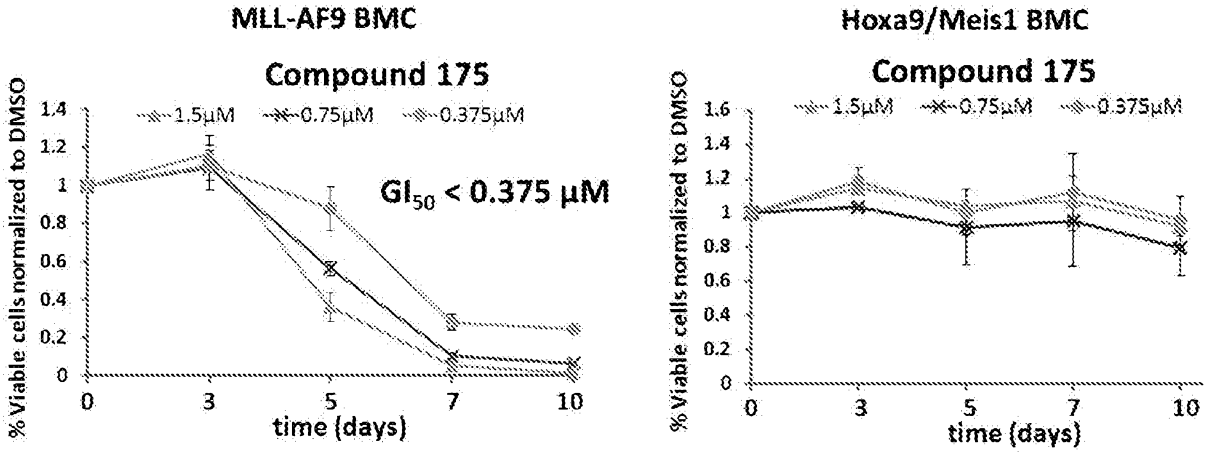

MLL-AF9 BMC
Compound 175
1.5μM
0.75μM
0.375μM
GI50 < 0.375 μM
% Viable cells normalized to DMSO
time (days)
Hoxa9/Meis1 BMC
Compound 175
1.5μM
0.75μM
0.375μM
% Viable cells normalized to DMSO
time (days)

FIGURE 6

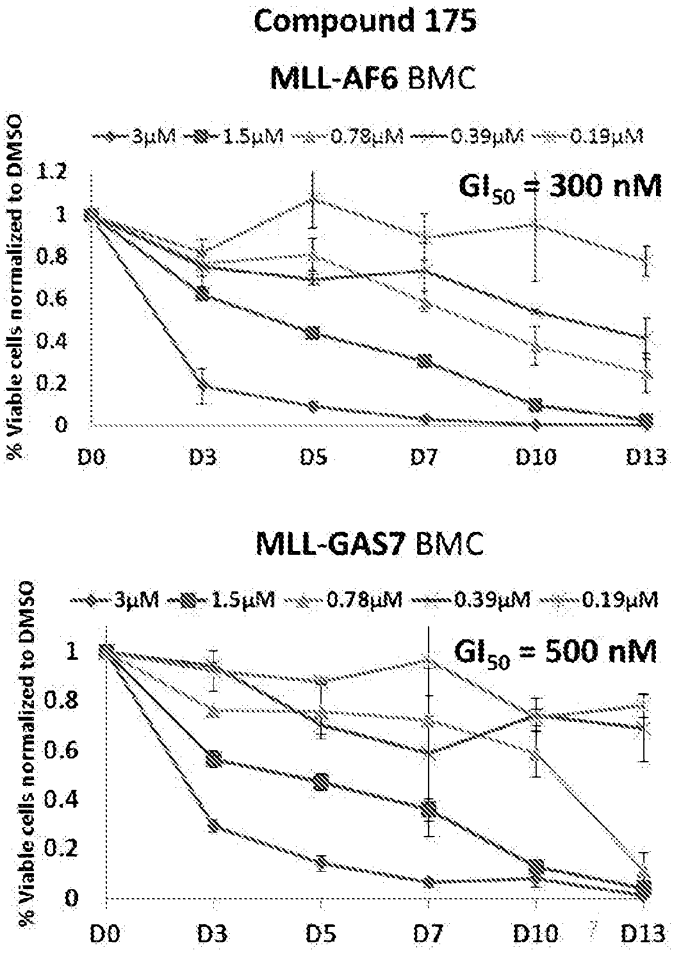

Compound 175
MLL-AF6 BMC
3μM
1.5μM
0.78μM
0.39μM
0.19μM
GI50 = 300 nM
% Viable cells normalized to DMSO
1.2
1
0.8
0.6
0.4
0.2
0
D0
D3
D5
D7
D10
D13
MLL-GAS7 BMC
3μM
1.5μM
0.78μM
0.39μM
0.19μM
GI50 = 500 nM
% Viable cells normalized to DMSO
1
0.8
0.6
0.4
0.2
0
D0
D3
D5
D7
D10
D13

FIGURE 7

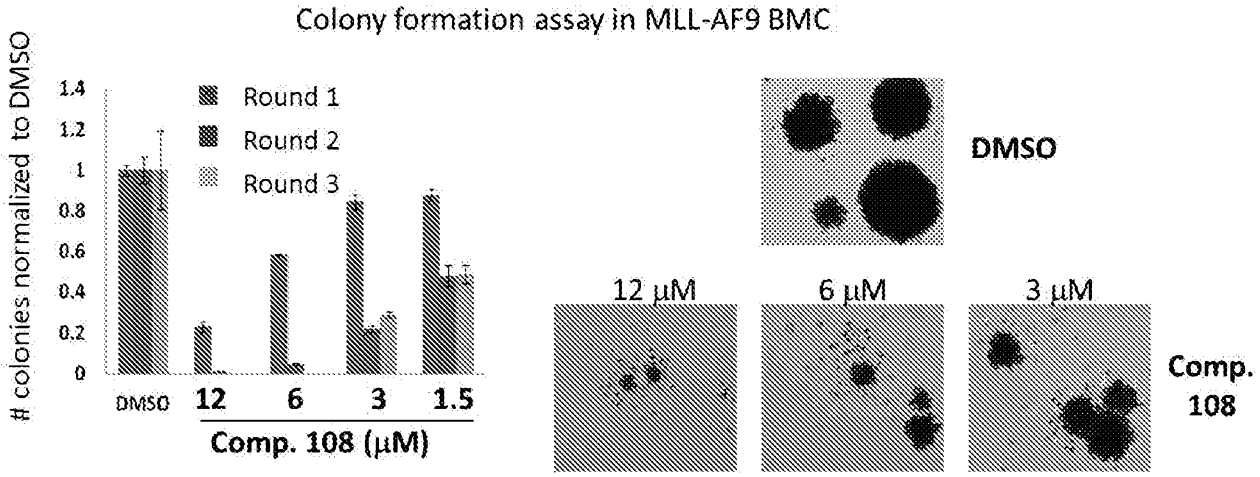

Colony formation assay in MLL-AF9 BMC
colonies normalized to DMSO
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Round 1
Round 2
Round 3
DMSO
12
6
3
1.5
Comp. 108 (μM)
DMSO
12 μM
6 μM
3 μM
Comp. 108

FIGURE 8

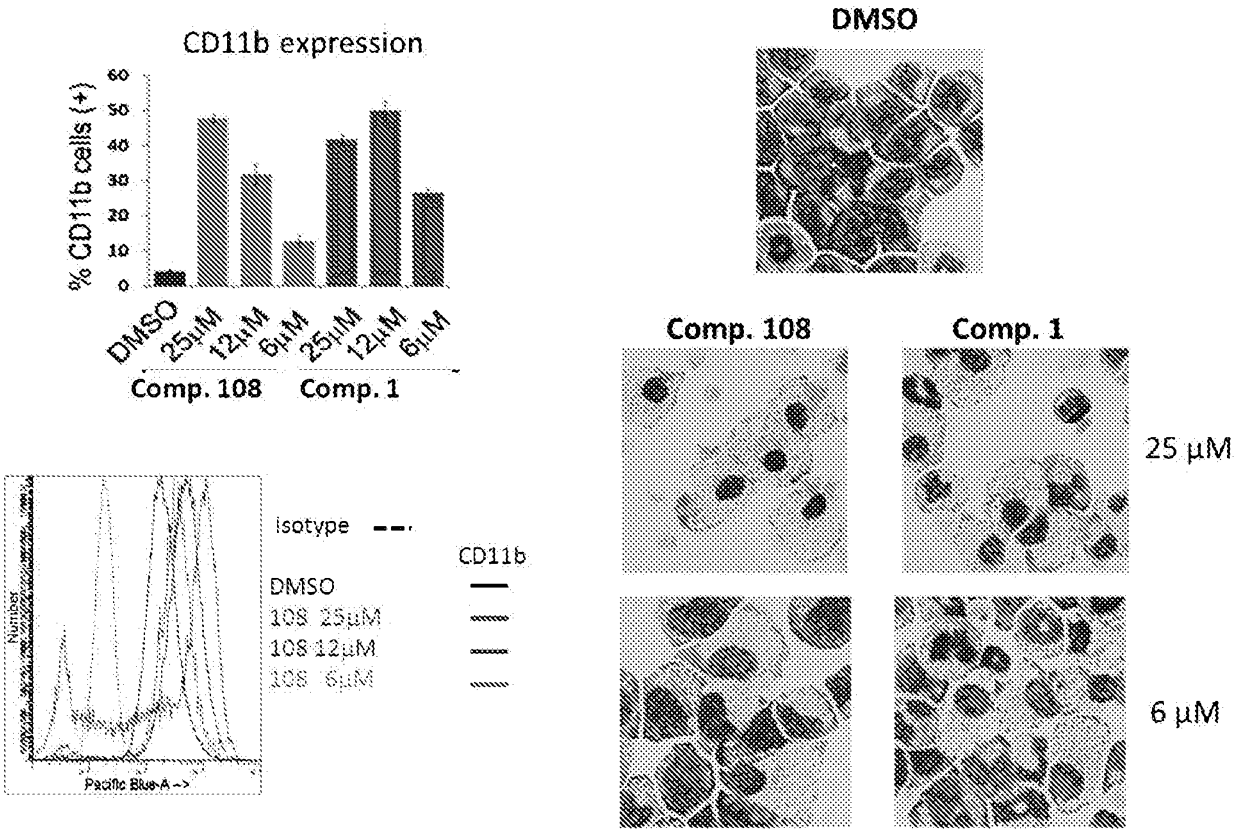

CD11b expression
% CD11b cells (+)
60
50
40
30
20
10
0
DMSO
25μM
12μM
6μM
25μM
12μM
6μM
Comp. 108
Comp. 1
Isotype
CD11b
DMSO
108 25μM
108 12μM
108 6μM
Number
Pacific Blue-A -->
DMSO
Comp. 108
Comp. 1
25 μM
6 μM

FIGURE 9

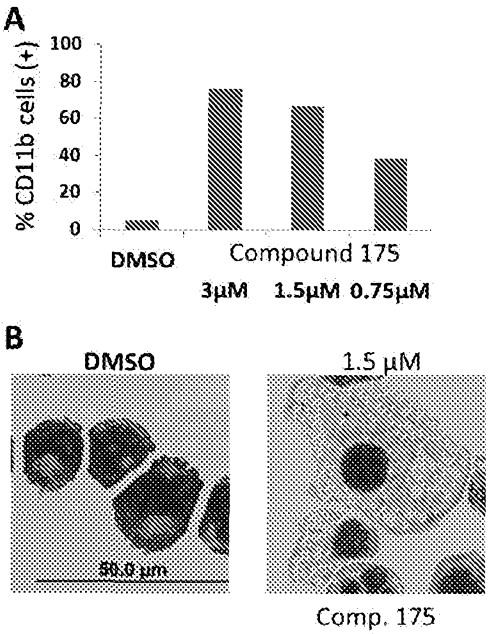

A
% CD11b cells (+)
100
80
60
40
20
0
DMSO
Compound 175
3μM 1.5μM 0.75μM
B
DMSO
1.5 μM
50.0 μm
Comp. 175

FIGURE 10

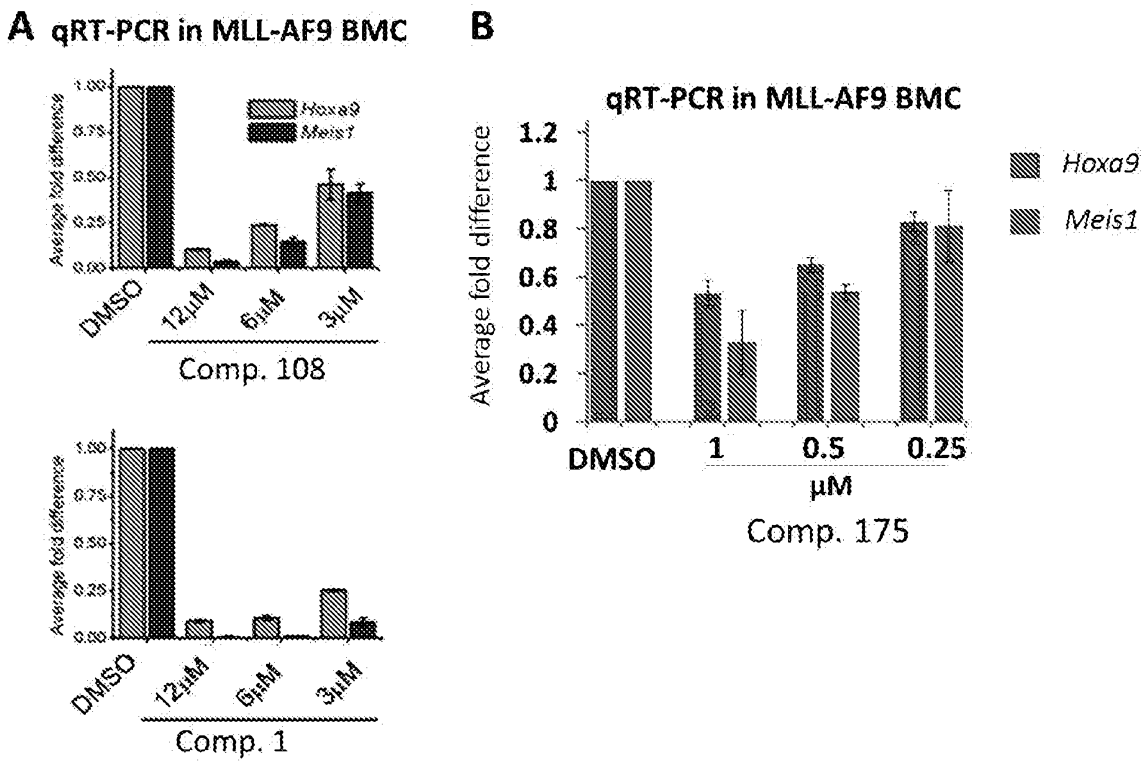

A qRT-PCR in MLL-AF9 BMC
Hoxa9
Meis1
Average fold difference
DMSO
12μM
6μM
3μM
Comp. 108
Comp. 1
B
qRT-PCR in MLL-AF9 BMC
Average fold difference
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
1
0.5
0.25
μM
Comp. 175
Hoxa9
Meis1

FIGURE 11

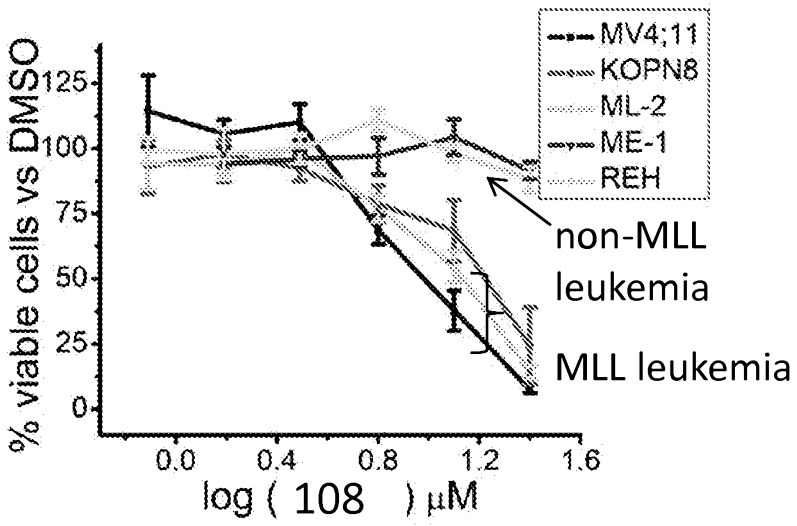

MV4;11
KOPN8
ML-2
ME-1
REH
non-MLL leukemia
MLL leukemia
% viable cells vs DMSO
125
100
75
50
25
0
0.0
0.4
0.8
1.2
1.6
log (108) µM

FIGURE 12

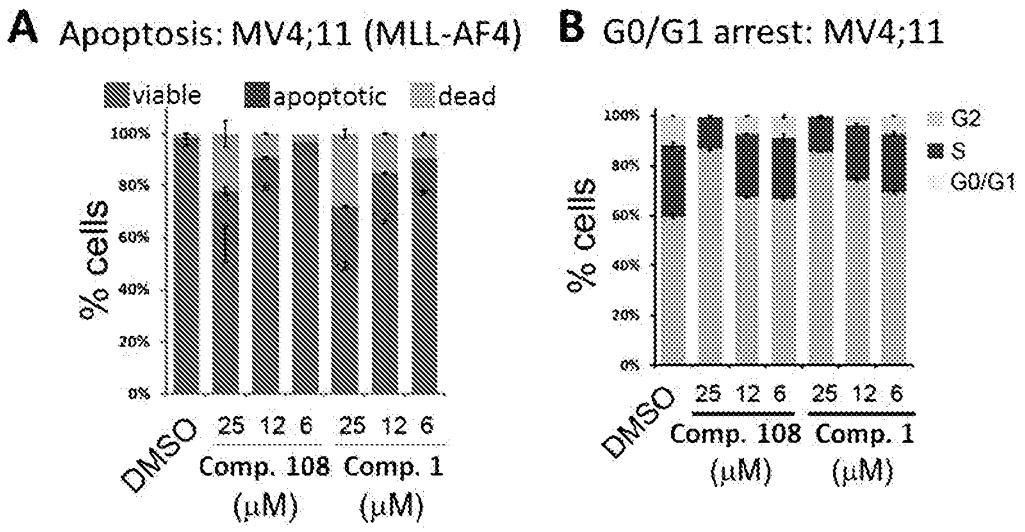

A Apoptosis: MV4;11 (MLL-AF4)
viable
apoptotic
dead
% cells
100%
80%
60%
40%
20%
0%
DMSO
25 12 6
25 12 6
Comp. 108 (μM)
Comp. 1 (μM)
B G0/G1 arrest: MV4;11
G2
S
G0/G1
% cells
100%
80%
60%
40%
20%
0%
DMSO
25 12 6
25 12 6
Comp. 108 (μM)
Comp. 1 (μM)

FIGURE 13

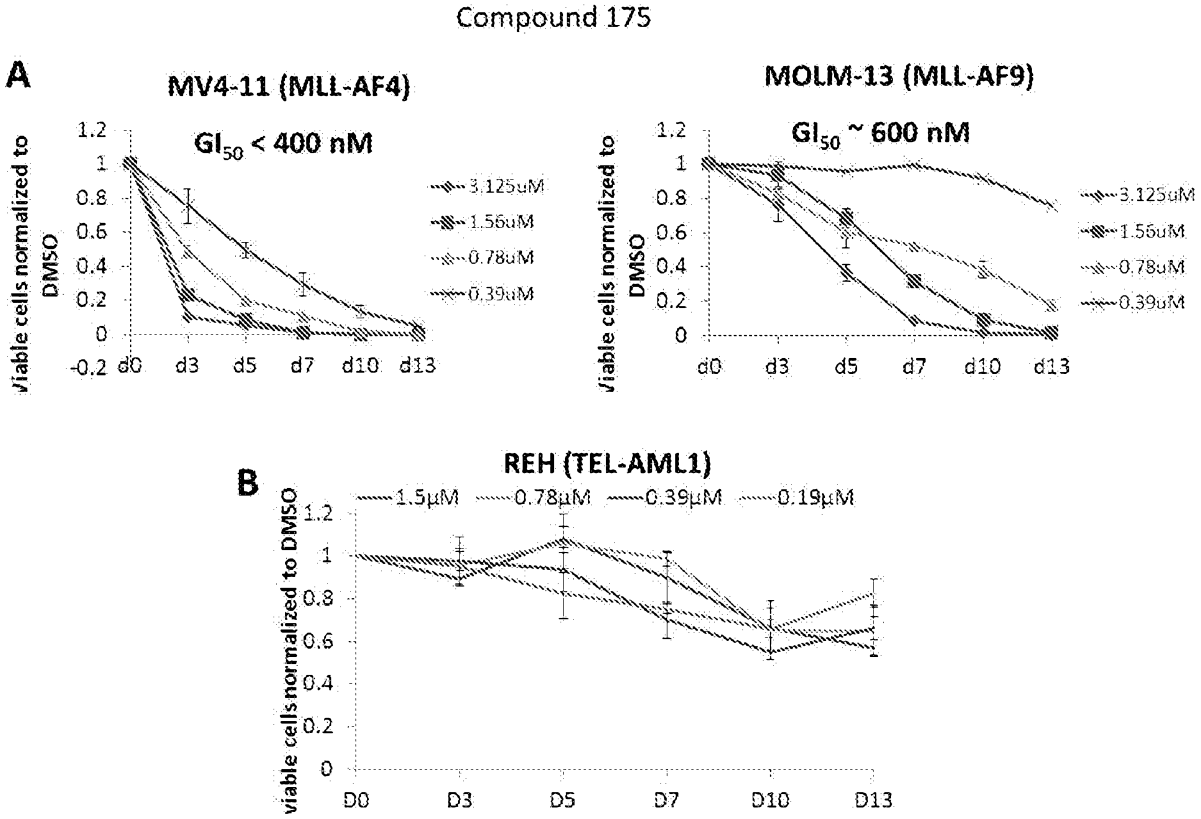
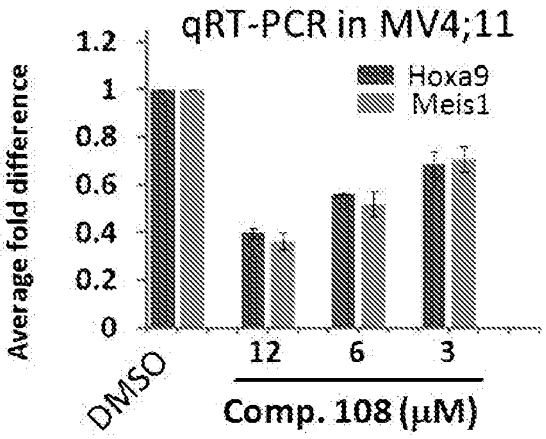

Compound 175
A
MV4-11 (MLL-AF4)
GI50 < 400 nM
Viable cells normalized to DMSO
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
d0
d3
d5
d7
d10
d13
3.125uM
1.56uM
0.78uM
0.39uM
MOLM-13 (MLL-AF9)
GI50 ~ 600 nM
B
REH (TEL-AML1)
1.5µM
0.78µM
0.39µM
0.19µM
viable cells normalized to DMSO
D0
D3
D5
D7
D10
D13

FIGURE 14


qRT-PCR in MV4;11
Hoxa9
Meis1
Average fold difference
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
12
6
3
Comp. 108 (μM)

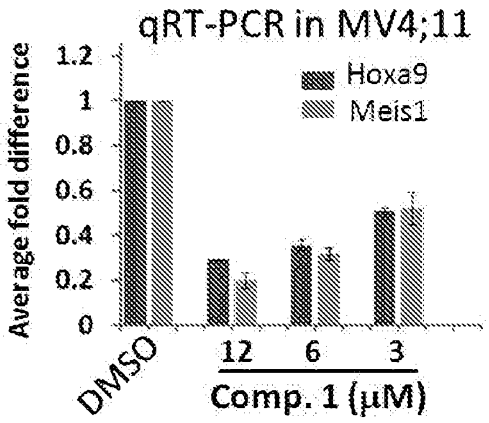

qRT-PCR in MV4;11
Hoxa9
Meis1
Average fold difference
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
12
6
3
Comp. 1 (μM)

FIGURE 15

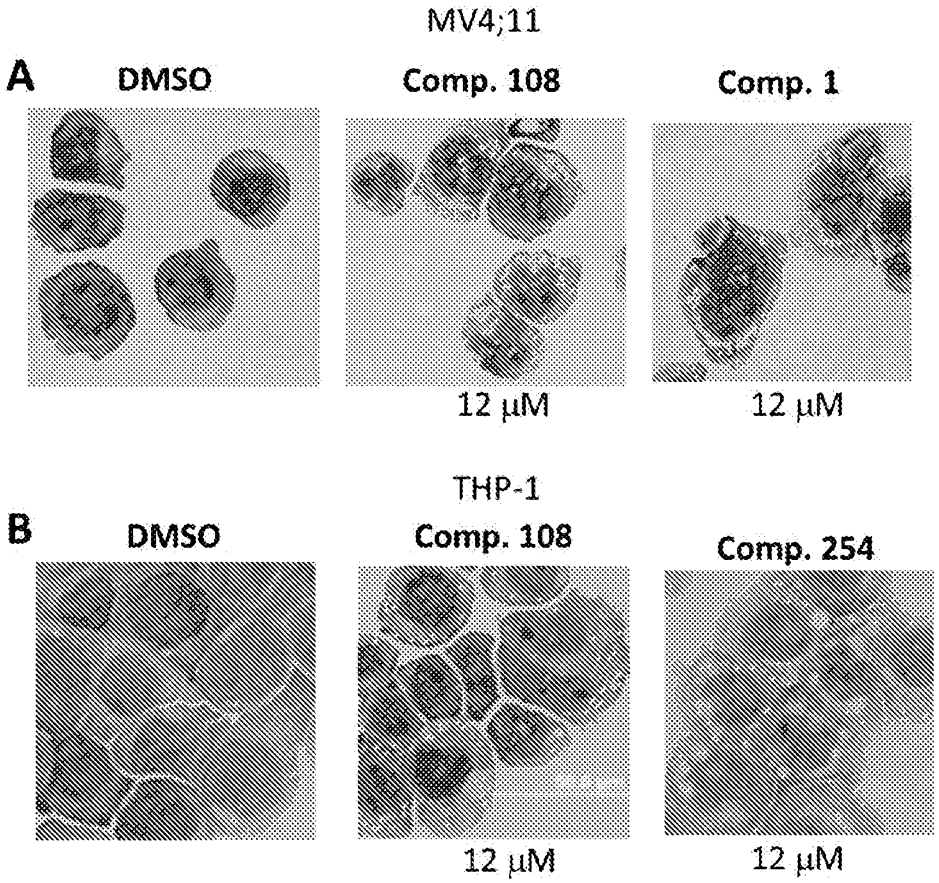
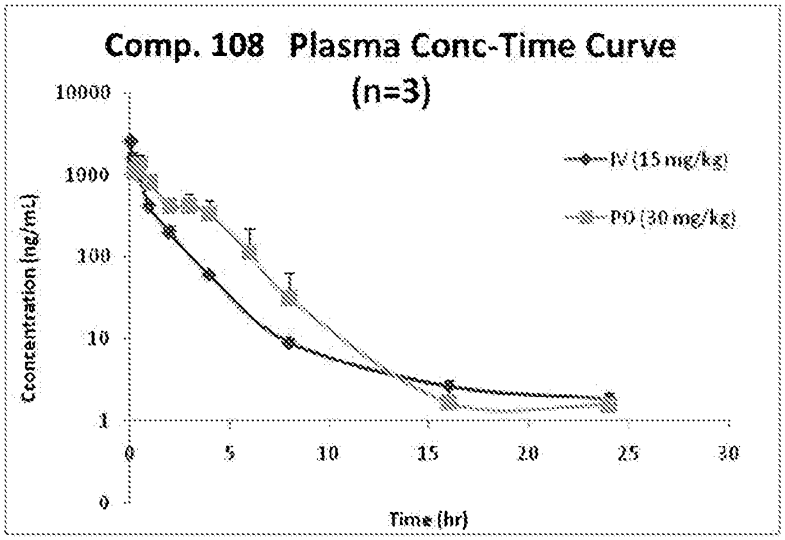

MV4;11
A
DMSO
Comp. 108
Comp. 1
12 μM
12 μM
THP-1
B
DMSO
Comp. 108
Comp. 254
12 μM
12 μM

FIGURE 16

Pharmacokinetic (PK) studies in mice:



Plasma IV 15mg/kg: $T_{1/2}$ = **4.2 h**

Plasma PO 30mg/kg: $T_{1/2}$ = **3.2 h**

Oral bioavailability = 79.4%

FIGURE 17

	Plasma concentration (ng/mL) in mice: IP administration of Comp. 108				
	Single dose		Multiple Dose -once daily for 5 days		Single dose
Sampling Time Point (hr)	30 (mg/kg) PO	15 (mg/kg) IV	30 (mg/kg) by IP	50 (mg/kg) by IP	75 (mg/kg) by IP
0.5	1376	1016	2150	3560	7440
4	335	60.6	372	469	1310

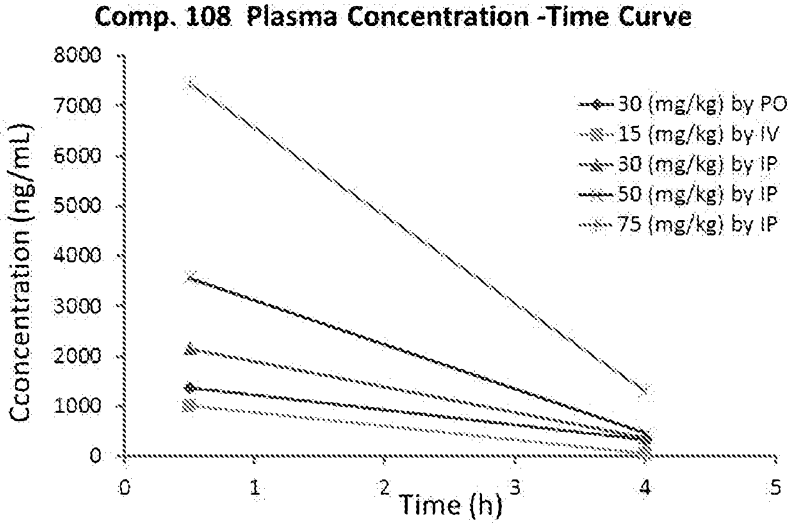


FIGURE 18

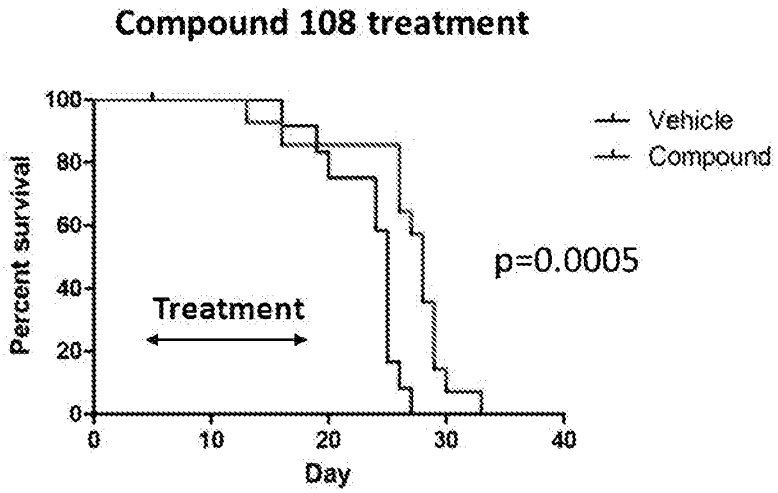

Compound 108 treatment
Percent survival
100
80
60
40
20
0
0
10
20
30
40
Day
Treatment
p=0.0005
Vehicle
Compound

FIGURE 19

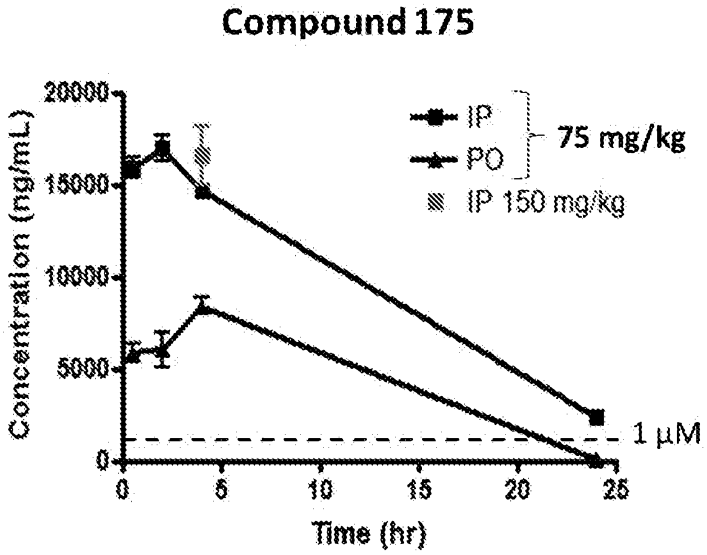

Compound 175
Concentration (ng/mL)
20000
15000
10000
5000
0
0
5
10
15
20
25
Time (hr)
IP
PO
75 mg/kg
IP 150 mg/kg
1 µM

FIGURE 20

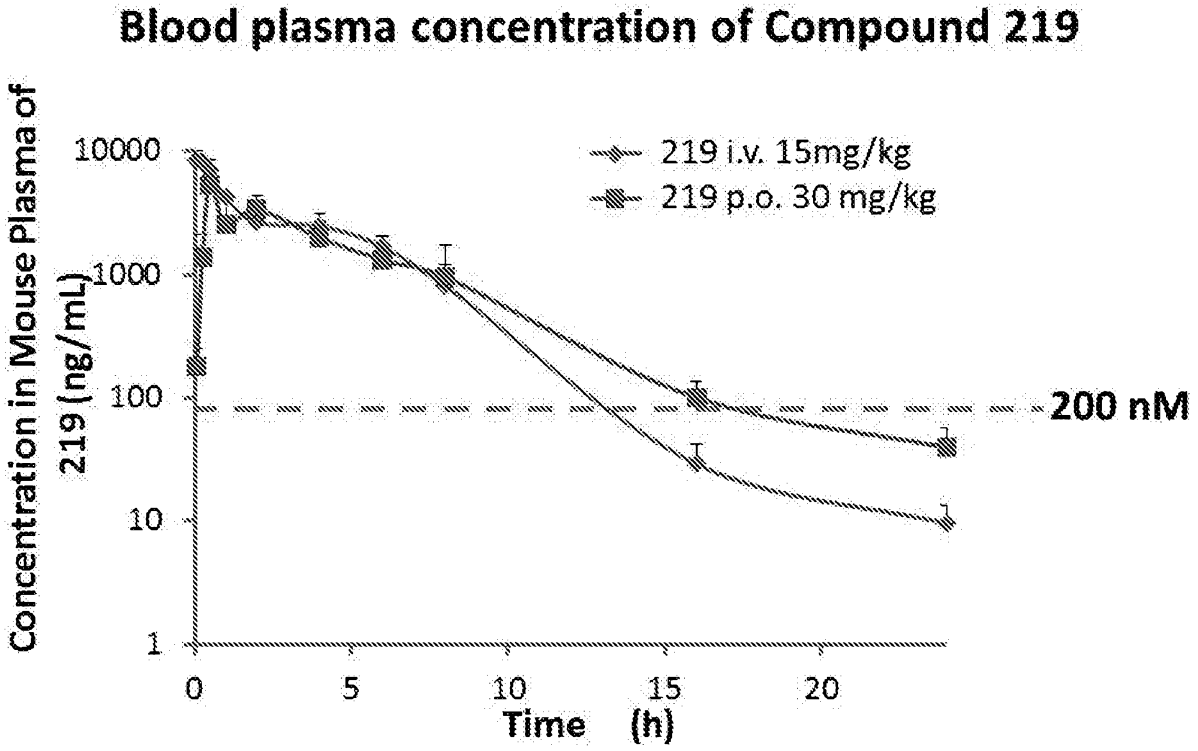
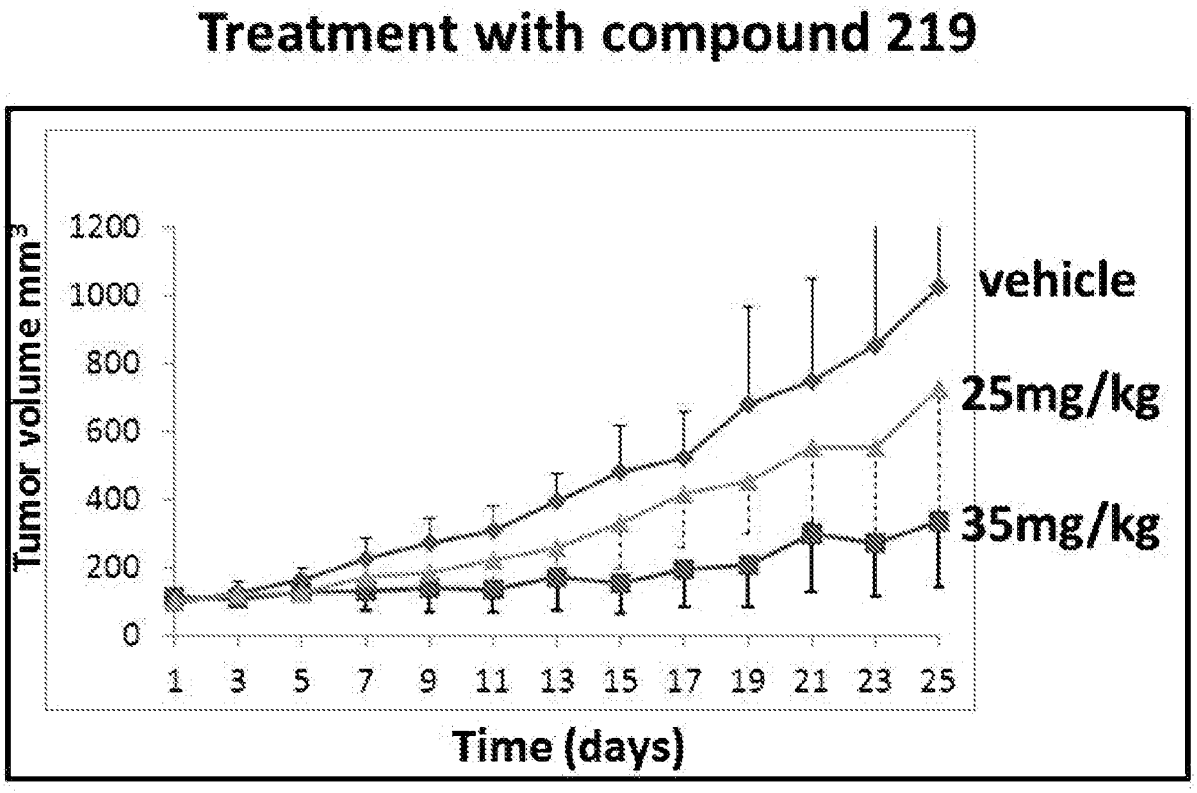

Blood plasma concentration of Compound 219
Concentration in Mouse Plasma of 219 (ng/mL)
10000
1000
100
10
1
0
5
10
15
20
Time (h)
219 i.v. 15mg/kg
219 p.o. 30 mg/kg
200 nM

FIGURE 21


Treatment with compound 219
Tumor volume mm3
1200
1000
800
600
400
200
0
1
3
5
7
9
11
13
15
17
19
21
23
25
Time (days)
vehicle
25mg/kg
35mg/kg