(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 July 2015 (23.07.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/108490 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/SG2015/050005

(22) International Filing Date:
19 January 2015 (19.01.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1400787.6 17 January 2014 (17.01.2014) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

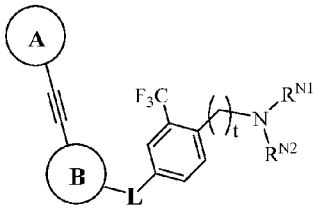
Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: HETEROARYL ALKYNE DERIVATIVES AND USES THEREOF



(I)

(57) Abstract: The present invention relates to certain heteroaryl alkyne compounds of Formula (I) that act as kinase inhibitors. The present invention further relates to pharmaceutical compositions comprising these compounds, and to the use of the compounds for the prevention and treatment of diseases (*e.g.*, proliferative diseases (*e.g.*, cancer), inflammatory diseases, autoimmune disease, metabolic diseases, neurodegenerative diseases (*e.g.*, Alzheimer's disease), or neurodevelopmental disorders (*e.g.*, autism)), as well as methods of treating these diseases.

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HETEROARYL ALKYNE DERIVATIVES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to British Patent Application No. GB1400787.6, filed on 17 January 2014, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The protein kinases represent a large family of proteins and play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. Aberrant kinase activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from the inappropriate activation of the immune and nervous systems.

[0003] The human MAP Kinase-interacting kinases, also known as MAP Kinase signal-integrating kinases, (MNKs), are ubiquitously expressed protein-serine/threonine kinases that are directly activated by ERK or p38 MAP kinases (Buxade, M.; Parra-Palau, J. L.; Proud, C. G. Front Biosci. 2008, 13, 5359-5373; Fukunaga, R.; Hunter, T. EMBO J. 1997, 16, 1921-1933; Waskiewicz, A. J.; Flynn, A.; Proud, C. G.; Cooper, J. A. EMBO J. 1997, 16, 1909-1920). They comprise a group of four proteins derived from two genes (gene symbols: MKNK1 and MKNK2) by alternative splicing. MNK1a/b and MNK2a/b proteins differ at their C-termini, in each case the a-form possessing a longer C-terminal region than the b-form which lacks the MAP Kinase-binding region. The N-termini of all forms contain a polybasic region which binds Importin α and the translation factor scaffold protein eukaryotic Initiation Factor (eIF4G). The catalytic domains of MNK1a/b and MNK2a/b share three unusual features, two short inserts and a DFD tripeptide feature where other kinases have DFG. Mnk isoforms differ markedly in their activity, regulation, and subcellular localization. The best-characterized MNK substrate is eIF4E. Although the cellular role of eIF4E phosphorylation remains unclear, it may promote export of a defined set of mRNAs from the nucleus. Other Mnk substrates bind to AU-rich elements that modulate the stability/translation of specific mRNAs (Buxade, M.; Parra-Palau, J. L.; Proud, C. G. Front Biosci. 2008, 13, 5359-5373). MNK1 is highly expressed in hematological malignancies, and both MNK1 and MNK2 are up-regulated in solid tumors such as gliomas and ovarian cancers (Worch, J.; Tickenbrock, L.; Schwable, J.; Steffen, B.; Cauvet, T.; Mlody, B.; Buerger, H.; Koeffler, H. P.; Berdel, W. E.; Serve, H.; Muller-Tidow, C. Oncogene 2004, 23, 9162-9172; Pellagatti, A.; Esoof, N.; Watkins, F.; Langford, C. F.; Vetrie, D.; Campbell, L. J.; Fidler, C.;

Cavenagh, J. D.; Eagleton, H.; Gordon, P.; Woodcock, B.; Pushkaran, B.; Kwan, M.; Wainscoat, J. S.; Boultwood, J. Br.J.Haematol. 2004, 125, 576-583; Bredel, M.; Bredel, C.; Juric, D.; Harsh, G. R.; Vogel, H.; Recht, L. D.; Sikic, B. I. Cancer Res. 2005, 65, 4088-4096).

[0004] MNK inhibitors can regulate the innate immune response in macrophage. It has been shown that CGP57380, a Mnk inhibitor, inhibits the release of TNF-alpha by macrophage (and not eIF4E) (Buxade, M.; Morrice, N.; Krebs, D. L.; Proud, C. G. J. Biol. Chem. 2008, 283, 57-65). According to PCT publication, WO 2005/003785, MNK kinases are promising targets for anti-inflammatory therapy.

[0005] MNK1/2 were also reported to phosphorylate a number of different proteins in addition to eIF4E. Three of these are hnRNPA1, cPLA2 and Sprouty2 (Guil, S.; Long, J. C.; Caceres, J. F. Mol.Cell Biol. 2006, 26, 5744-5758; Hefner, Y.; Borsch-Haubold, A. G.; Murakami, M.; Wilde, J. I.; Pasquet, S.; Schieltz, D.; Ghomashchi, F.; Yates, J. R., III; Armstrong, C. G.; Paterson, A.; Cohen, P.; Fukunaga, R.; Hunter, T.; Kudo, I.; Watson, S. P.; Gelb, M. H. J.Biol.Chem. 2000, 275, 37542-37551; DaSilva, J.; Xu, L.; Kim, H. J.; Miller, W. T.; Bar-Sagi, D. Mol. Cell Biol. 2006, 26, 1898-1907). Their role and function is still being investigated. Among these substrates, hnRNPA1 is overexpressed in colorectal cancer, and it could contribute to maintenance of telomere repeats in cancer cells with enhanced cell proliferation (Ushigome, M.; Ubagai, T.; Fukuda, H.; Tsuchiya, N.; Sugimura, T.; Takatsuka, J.; Nakagama, H. Int. J. Oncol. 2005, 26, 635-640). It is also reported that the expression levels of hnRNPA/B is deregulated in non-small cell lung cancer (Boukakis, G.; Patrinou-Georgoula, M.; Lekarakou, M.; Valavanis, C.; Guialis, A. BMC.Cancer 2010, 10, 434). Accordingly, MNK inhibitors are potentially useful in the treatment of cancers including breast, protate, hematological malignancies (*e.g.,* CML, AML), head and neck, colon,[1] bladder, prostatic adenocarcinoma, lung, cervical, and lymphomas (Bianchini, A.; Loiarro, M.; Bielli, P.; Busa, R.; Paronetto, M. P.; Loreni, F.; Geremia, R.; Sette, C. Carcinogenesis 2008, 29, 2279-2288; Berkel, H. J.; Turbat-Herrera, E. A.; Shi, R.; De Benedetti, A. Cancer Epidemiol.Biomarkers Prev. 2001, 10, 663-666; Wendel, H. G.; De Stanchina, E.; Fridman, J. S.; Malina, A.; Ray, S.; Kogan, S.; Cordon-Cardo, C.; Pelletier, J.; Lowe, S. W. Nature 2004, 428, 332-337; De Benedetti, A.; Graff, J. R. Oncogene 2004, 23, 3189-3199).

[0006] Abelson (ABL)-family proteins comprise one of the best conserved branches of the tyrosine kinases. Each ABL protein contains an SH3-SH2-TK (Src homology 3–Src homology 2–tyrosine kinase) domain cassette, which confers autoregulated kinase activity and is common among nonreceptor tyrosine kinases. The Abelson non-receptor tyrosine

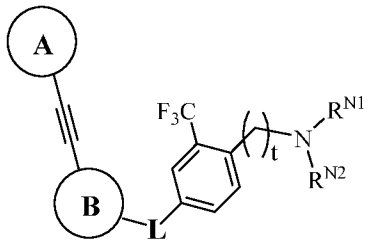
kinase (c-Abl) is involved in signal transduction, via phosphorylation of its substrate proteins. In the cell, c-Abl shuttles between the cytoplasm and nucleus, and its activity is normally tightly regulated through a number of diverse mechanisms. Abl has been implicated in the control of growth-factor and integrin signaling, cell cycle, cell differentiation, neurogenesis, apoptosis, cell adhesion, cytoskeletal structure, and response to DNA damage and oxidative stress.

[0007] Because kinases have been implicated in numerous diseases and conditions, such as cancer, neurodegenerative diseases, or metabolic diseases, there is a need to develop new and potent protein kinase inhibitors that can be used for treating these diseases (Sci. Signal., 2010, 3(139), p. re6).

SUMMARY OF THE INVENTION

[0008] The present invention provides novel compounds that inhibit the activity of one or more protein kinases and are useful in the treatment of kinase-associated diseases. In certain embodiments, the inventive compounds inhibit MAP kinase interacting kinases 1 and 2 (MNK1 and MNK2). In certain embodiments, the inventive compounds inhibit Abelson (Abl) tyrosine kinase. The provided compounds are useful in the prevention and/or treatment of proliferative diseases (*e.g.* cancer including hematological cancers and solid tumors such as gliomas and ovarian cancers), inflammatory conditions, neurodegenerative diseases (*e.g.* Alzheimer's disease), and metabolic disorders (*e.g.* obesity, diabetes).

[0009] In one aspect, the invention provides a compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, Ring B, L, R^{N1}, R^{N2}, and t are as described herein.

[00010] In another aspect, the present invention relates to pharmaceutical compositions comprising an inventive compound and to their use for the prevention and treatment of diseases associated with a dysregulated or dysfunctional kinase pathway or aberrant kinase activity. In another aspect, the present invention relates to methods of using the inventive compound for the prevention and treatment of diseases associated with a dysregulated or

dysfunctional kinase pathway or aberrant kinase activity. In certain embodiments, the disease is asscociated with increased activity of the kinase or the pathway that includes the kinase. In certain embodiments, Mnk1 and Mnk2 play a role in the dysregulated or dysfunctional kinase pathway (*e.g.* Mnk overexpression, eIF4E overexpression, P38 MAPK kinase pathway). In certain embodiments, Abl tyrosine kinase plays a role in the dysfunctional kinase pathway. In certain embodiments, Abl tyrosine kinase has a T315I mutation. In certain embodiments, Abl tyrosine kinase has a E255K mutation.

[00011] In another aspect, the present invention relates to pharmaceutical compositions comprising these compounds for the prevention and/or treatment of diseases such as, but not limited to, cancer, inflammatory conditions, neurodegenerative diseases, and metabolic disorders. In another aspect, the present invention relates to methods of using the provided pharmaceutical compositions comprising these compounds for the prevention and/or treatment of diseases such as, but not limited to, cancer, inflammatory conditions, neurodegenerative diseases, and metabolic disorders. The provided compounds described herein can be used as single agents or in combination with one or more additional agents. In some embodiments, the additional agent is a small molecule or biologic. In some embodiments, the additional agent is a kinase inhibitor. In some embodiments, the additional agent is a monoclonal antibody. In some embodiments, the additional agent is siRNA.

[00012] In another aspect, the invention relates to methods for modulating the activity of a protein kinase comprising contacting the protein kinase with a compound of Formula (**I**). In certain certain embodiments, the protein kinase whose activity is being modulated is Mnk (*e.g.*, Mnk1 or Mnk2). In certain certain embodiments, the protein kinase is Abl tyrosine kinase (*e.g.*, wide type and mutants).

[00013] In yet another aspect, the present invention describes methods for the synthesis of compounds of Formula (**I**).

[00014] In another aspect, the present invention provides kits comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. The provided kits may be useful for the treatment of cancer, inflammatory conditions, neurodegenerative diseases, and metabolic disorders. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (I), or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof. The kits may also include packaging information describing the use or prescribing information for the subject or a health care professional. Such information may be required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). The kit may

also optionally include a device for administration of the compound or composition, for example, a syringe for parenteral administration.

DEFINITIONS

Chemical definitions

[00015] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[00016] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[00017] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[00018] "Alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents. In certain embodiments, the alkyl group is unsubstituted C_{1-10} alkyl (*e.g.*, $–CH_3$). In certain embodiments, the alkyl group is substituted C_{1-10} alkyl.

[00019] "Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds ("C_{2-20} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5),

hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

[00020] "Alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon triple bonds, and optionally one or more double bonds ("C_{2-20} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

[00021] "Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6}

carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-10} carbocyclyl.

[00022] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more

substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_{3-10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_{3-10} cycloalkyl.

[00023] "Heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[00024] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[00025] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl, and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[00026] "Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring

system. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

[00027] "Heteroaryl" refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

[00028] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and

sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted ("unsubstituted heteroaryl") or substituted ("substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

[00029] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[00030] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable

compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[00031] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group $=O$, $=S$, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

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

each instance of R^{bb} is, independently, selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3{}^+X^–$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

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

each instance of R^{ff} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl

or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3^+X^–$, $–NH(C_{1–6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1–6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl$)$, $–N(OH)(C_{1–6}$ alkyl$)$, –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl$)$, $–C(=O)(C_{1–6}$ alkyl$)$, $–CO_2H$, $–CO_2(C_{1–6}$ alkyl$)$, $–OC(=O)(C_{1–6}$ alkyl$)$, $–OCO_2(C_{1–6}$ alkyl$)$, $–C(=O)NH_2$, $–C(=O)N(C_{1–6}$ alkyl$)_2$, $–OC(=O)NH(C_{1–6}$ alkyl$)$, $–NHC(=O)(C_{1–6}$ alkyl$)$, $–N(C_{1–6}$ alkyl$)C(=O)(C_{1–6}$ alkyl$)$, $–NHCO_2(C_{1–6}$ alkyl$)$, $–NHC(=O)N(C_{1–6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1–6}$ alkyl$)$, $–NHC(=O)NH_2$, $–C(=NH)O(C_{1–6}$ alkyl$)$,$–OC(=NH)(C_{1–6}$ alkyl$)$, $–OC(=NH)OC_{1–6}$ alkyl, $–C(=NH)N(C_{1–6}$ alkyl$)_2$, $–C(=NH)NH(C_{1–6}$ alkyl$)$, $–C(=NH)NH_2$, $–OC(=NH)N(C_{1–6}$ alkyl$)_2$, $–OC(NH)NH(C_{1–6}$ alkyl$)$, $–OC(NH)NH_2$, $–NHC(NH)N(C_{1–6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1–6}$ alkyl$)$, $–SO_2N(C_{1–6}$ alkyl$)_2$, $–SO_2NH(C_{1–6}$ alkyl$)$, $–SO_2NH_2$,$–SO_2C_{1–6}$ alkyl, $–SO_2OC_{1–6}$ alkyl, $–OSO_2C_{1–6}$ alkyl, $–SOC_{1–6}$ alkyl, $–Si(C_{1–6}$ alkyl$)_3$, $–OSi(C_{1–6}$ alkyl$)_3$ – $C(=S)N(C_{1–6}$ alkyl$)_2$, $C(=S)NH(C_{1–6}$ alkyl$)$, $C(=S)NH_2$, $–C(=O)S(C_{1–6}$ alkyl$)$, $–C(=S)SC_{1–6}$ alkyl, $–SC(=S)SC_{1–6}$ alkyl, $–P(=O)_2(C_{1–6}$ alkyl$)$, $–P(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(OC_{1–6}$ alkyl$)_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein $X^–$ is a counterion.

[00032] "Halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[00033] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substitutents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[00034] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00035] Amide nitrogen protecting groups (*e.g.*, $-C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine, *o*–nitrobenzamide, and *o*–(benzoyloxymethyl)benzamide.

[00036] Carbamate nitrogen protecting groups (*e.g.*, $-C(=O)OR^{aa}$) include, but are not limited to, methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate (*t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(*N,N*–dicyclohexylcarboxamido)ethyl carbamate, *t*–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl

carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), *m*–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(*o*–nitrophenyl)methyl carbamate, *t*–amyl carbamate, *S*–benzyl thiocarbamate, *p*–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*–decyloxybenzyl carbamate, 2,2–dimethoxyacylvinyl carbamate, *o*–(*N,N*–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(*N,N*–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*–(*p'*–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(*p*–phenylazophenyl)ethyl carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, *p*–(phenylazo)benzyl carbamate, 2,4,6–tri–*t*–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, and 2,4,6–trimethylbenzyl carbamate.

[00037] Sulfonamide nitrogen protecting groups (*e.g.*, $–S(=O)_2R^{aa}$) include, but are not limited to, *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[00038] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl–(10)–acyl derivative, *N'*–*p*–toluenesulfonylaminoacyl derivative, *N'*–phenylaminothioacyl derivative, *N*–benzoylphenylalanyl derivative, *N*–acetylmethionine derivative, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentaacylchromium– or tungsten)acyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3–nitropyridinesulfenamide (Npys).

[00039] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups include, but are not limited to, $–R^{aa}$, $–N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–S(=O)R^{aa}$, $–SO_2R^{aa}$, $–Si(R^{aa})_3$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, and $–P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic*

Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00040] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl (Bn), *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, *p*–methoxyphenyldiphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4′–bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4′,4″–tris(levulinoyloxyphenyl)methyl, 4,4′,4″–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4′,4″–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1′–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodisulfuran–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate

(levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*–nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*–methoxybenzyl carbonate, alkyl 3,4–dimethoxybenzyl carbonate, alkyl *o*–nitrobenzyl carbonate, alkyl *p*–nitrobenzyl carbonate, alkyl *S*–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxyacyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[00041] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00042] As used herein, the term "optionally substituted acyl" refers to an organic functional group having the general formula $R^{OSA}C(=O)$-, wherein R^{OSA} is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

[00043] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The present invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[00044] The term "pharmaceutically acceptable form thereof" as used herein refers to pharmaceutically acceptable salts, solvates, hydrates, prodrugs, tautomers, isomers, enantiomers, diastereomers, and/or polymorphs of a compound of the present invention.

[00045] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" as used herein refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N+(C1–4alkyl)4 salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine

cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00046] In certain embodiments, the pharmaceutically acceptable form is a hydrate or solvate. The term "hydrate" as used herein refers to a compound non–covalently associated with one or more molecules of water. Likewise, the term "solvate" refers to a compound non–covalently associated with one or more molecules of an organic solvent.

[00047] In certain embodiments, the pharmaceutically acceptable form is a prodrug. The term "prodrug" as used herein refers to a derivative of a parent compound that requires transformation within the body in order to release the parent compound. In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The advantage of a prodrug can lie in its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from the digestive tract, or it may enhance drug stability for long–term storage. In recent years several types of bioreversible derivatives have been exploited for utilization in designing prodrugs. Using esters as a prodrug type for compounds containing a carboxyl or hydroxyl functionality is known in the art as described, for example, in *The Organic Chemistry of Drug Design and Drug Interaction* by Richard Silverman, published by Academic Press (1992).

[00048] In certain embodiments, the pharmaceutically acceptable form is a tautomer. The term "tautomer" as used herein includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (e.g., a single bond to a double bond, a triple bond to a single bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (i.e., the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto–to–enol; amide–to–imide; lactam–to–lactim; enamine–to–imine; and enamine–to–(a different) enamine tautomerizations.

[00049] In certain embodiments, the pharmaceutically acceptable form is an isomer. The term "isomer" as used herein includes any and all geometric isomers and stereoisomers (e.g., enantiomers, diasteromers, etc.). For example, "isomer" include cis– and trans–isomers, E– and Z– isomers, R– and S–enantiomers, diastereomers, (D)–isomers, (L)–isomers, racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. For instance, an isomer/enantiomer may, in some embodiments, be provided substantially free of the corresponding enantiomer, and may also be referred to as "optically enriched."

"Optically–enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments the compound of the present invention is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al., Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[00050] In certain embodiments, the pharmaceutically acceptable form is a polymorph. The term "polymorph" as used herein refers to a crystalline compound existing in more than one crystalline form/structure. When polymorphism exists as a result of difference in crystal packing it is called packing polymorphism. Polymorphism can also result from the existence of different conformers of the same molecule in conformational polymorphism. In pseudopolymorphism the different crystal types are the result of hydration or solvation.

[00051] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (e.g, infant, child, adolescent) or adult subject (e.g., young adult, middle–aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, and/or turkeys. In certain embodiments, the subject is an animal. The animal may be of either sex and may be of any stage of development. In certain embodiments, the animal is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent (e.g., mouse, rat), dog, pig, or non-human primate. In certain embodimennts, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal.

[00052] "Treat," "treating" and "treatment" encompasses an action that occurs while a subject is suffering from a condition (*e.g.,* a "MNK1- or MNK2-related" disease, disorder, or condition, *e.g.,* a disease, disorder, or condition in which MNK1 and/or MNK2 is known to play role) which reduces the severity of the condition or retards or slows the progression of the condition ("therapeutic treatment").

[00053] As used herein "inhibition," "inhibiting," and "inhibit", refer to the ability of a compound to reduce, slow, halt or prevent activity of a particular biological process relative to vehicle. In certain embodiments, the biological process is *in vitro* (*e.g.*, a biochemical or cellular assay). In certain embodiments, the biological process is *in vivo.*

[00054] An "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response, *e.g.*, treat the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. In certain embodiments, the effective amount of a compounds refers to an amount sufficient to inhibit the activity of a kinase.

[00055] A "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent. In some embodiments, a therapeutically effective amount is an amount effective to inhibit cell growth or induce cell death.

[00056] A "prophylactically effective amount" of a compound is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[00057] As used herein, the term "kinase" represent a class of enzymes that are able to transfer a phosphate group from a donor molecule to an acceptor molecule, e.g., an amino acid residue of a protein or a lipid molecule. Representative, non-limiting examples of kinases include Abl, ACK, Akt1/PKBα, Akt2/PKBβ, Akt3/PKBγ, ALK1, ALK2, Alk4, AMPKα1/β1/γ1, AMPKα1/β1/γ2, AMPKα1/β1/γ3, AMPKα1/β2/γ1, AMPKα2/β1/γ1, AMPKα2/β2/γ2, Abl2, ARKS, Ask1, Aurora A, Aurora B, Aurora C, Axl, BARK1, Blk, Bmx, B-Raf, Brk, BrSK1, BrSK2, Btk, CaMK1α, CaMK1β, CaMK1γ, CaMK1δ, CAMK2α, CaMK2β, CAMK2δ, CAMK2γ, CAMK4, CAMKK1, CAMKK2, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK9, CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclin E, CDK3/cyclin E, CDK5/p25, CDK5/p35, CDK6/cyclinD3, CDK7/cyclin H/MAT1, CDK9/cyclin T1, CHK1, CHK2, CK1(γ), CK1δ, CK2α1, CK2α2, cKit, c-RAF, CLK1, CLK2, CLK3, COT, Csk, DAPK1, DAPK2, DAPK3, DCAMLK2, DDR2, DMPK, DRAK1, DYRK1A, DYRK2, DYRK3, eEF2K, EGFR, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EphB1, EphB2, EphB3, EphB4, ErbB4, Erk1, Erk2, FAK, Fer, Fes, FGFR1, Flt2, Flt4, FLT3 D835Y, FGFR2, FGFR3, FGFR4, Fgr, Flt1, Flt3, Fms, FRK, FynA, GCK, GPRK5, GRK2, GRK4, GRK6, GRK7, GSK3α, GSK3β, Hck, HER2, HER4, HIPK1, HIPK2, HIPK3, HIPK4, IGF1R, IKKβ, IKKα, IKKε, IR, InsR, IRR, IRAK1, IRAK2, IRAK4, Itk, JAK2, JAK3, JNK1, JNK2, JNK3, KDR, KHS1, Kit, Lck, LIMK1, LKB1, LOK, LRRK2, Lyn A, Lyn B, MAPK1, MAPK2, MAPK12, MAPKAP-K2, MAPKAP-K3, MAPKAPK2, MAPKAPK3, MAPKAPK5, MARK1, MARK2, MARK3, MARK4, MELK, MEK1, MEK2, MEKK2, MEKK3, Mer, Met, MET M1250T, MINK, MKK4, MKK6, MKK7β, MLCK, MLK1, MLK3, MNK1, MNK2, MRCKα, MRCKβ, MSK1, MSK2, MSSK1, STK23, STK4, STK3, STK24, MST1, MST2, MST3, MST4, MUSK, mTOR, MYO3β, MYT1, NDR1, NEK11, NEK2, NEK3, NEK6, NEK7, NEK9, NLK, NUAK2, p38α, p38β, p38δ, p38γ, p70S6K, S6K, SRK, PAK1/CDC42, PAK2, PAK3, PAK4, PAK5, PAK6, PAR-1Bα, PASK, PBK, PDGFRα, PDGFRβ, PDK1, PEK, PHKG2, PI3Kα, PI3Kβ, PI3Kγ, PI3Kδ, Pim1, Pim2, PKAcα, PKAcβ, PKAcγ, PKA(b), PKA, PKBα, PKBβ, PKBγ, PKCα, PKCβ1, PKCβ2, PKCβ11, PKCδ, PKCε, PKCγ, PKCμ, PKCη, PKCι, PKCθ, PKCζ, PKD1, PKD2, PKD3, PKG1α, PKG1B, PKN1, PKN2, PKR, PLK1, PLK2, PLK3, PLK4, Polo, PRAK, PRK2, PrKX, PTK5, PYK2, QIK, Raf1, Ret, RIPK2, RIPK5, ROCK1, ROCK2, RON, ROS, Rse, RSK1, RSK2, RSK3, RSK4, SAPK2a, SAPK2b, SAPK3, SAPK4, SGK1, SGK2, SGK3, SIK, MLCK, SLK, Snk, Src, SRPK1, SRPK2, STK33, SYK, TAK1-TAB1, TAK1, TBK1, TAO1, TAO2, TAO3, TBK1, TEC, TESK1, TGFβR1, TGFβR2, Tie2,

TLK2, TrkA, TrkB, TrkC, TSSK1, TSSK2, TTK, TXK, TYK2, TYRO3, ULK1, ULK2, WEE1, WNK2, WNK3, Yes1, YSK1, ZAK, ZAP70, ZC3, and ZIPK.

[00058] As used herein, "mutant Abl tyrosine kinase" refers to an Abl tyrosine kinase with a single or multiple amino acid changes as compared to the wild-type protein. Mutations in Abl tyrosine kinase act by disrupting critical contact points between protein and inhibitor (for example, Gleevec, and the like), more often, by inducing a transition from the inactive to the active state. Exemplary Abl tyrosine kinase point mutations include: M224V, L248V, G250E, G250R, Q252R, Q252H, Y253H, Y253F, E255K, E255V, D276G, T277A, V289A, F311L, T3151, T315N, F317L, M343T, M315T, E355G, F359V, F359A, V379I, F382L, L387M, L387F, H396P, H396R, A397P, S417Y, E459K, and F486S. Unless otherwise stated for this invention, Abl refers to wild-type and mutant forms of the enzyme.

[00059] As used herein, the term "small molecule" refers to a non-peptidic, non-oligomeric organic compound either synthesized in the laboratory or found in nature. Small molecules, as used herein, can refer to compounds that are "natural product-like", however, the term "small molecule" is not limited to "natural product-like" compounds. Rather, a small molecule is typically characterized in that it contains several carbon-carbon bonds, and has a molecular weight of less than 2000 g/mol, preferably less than 1500 g/mol, although this characterization is not intended to be limiting for the purposes of the present invention. Small molecules are typically characterized by multiple carbon-carbon bonds and may have one or more stereocenters. In certain embodiments, the small molecule is not polymeric or oligomeric. In certain embnodiments, the small molecule is not a nucleic acid, protein, or peptide.

[00060] As used herein the term "biologics" refer to products created by a biological process. Exemplary biologics include, but are not limited to, natural or synthetic growth hormone, natural or synthetic human insulin and its analogues, monoclonal antibodies, receptor constructs, vaccines, antibodies, blood, cells, organs, grafts, or tissues.

[00061] The term "monoclonal antibody" as used in the specification, refers to a composition comprising one or more antibodies obtained from a population of substantially homogeneous antibodies, *i.e.*, a population the individual antibodies of which are identical except for any naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site and generally to a single epitope on an antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of

antibodies, and does not require that the antibody be produced by any particular method or be the only antibody in the composition.

[00062] Antibody as used herein encompasses polyclonal and monoclonal antibodies, and further encompasses antibodies of any class (*e.g.*, IgM, IgG, and subclasses thereof). Antibody also encompasses hybrid antibodies, bispecific antibodies, heteroantibodies, chimeric antibodies, humanized antibodies, and functional fragments thereof which retain antigen binding. The term "antibody" encompasses compositions comprising an antigen-binding protein, individually or as a preparation comprising a plurality thereof, having one or more polypeptides that can be genetically encodable by immunoglobulin genes, or fragments of immunoglobulin genes, or that comprise CDRs obtainted or derived from immunoglobulins, and which bind an antigen of interest. Light chains are classified as either kappa or lambda. Heavy chains can be classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively. Antibody also encompasses single-chain antibodies that contain a heavy chain and a light chain linked together as a single polypeptide, each of such linked heavy or light chains nonetheless being referred to herein as a heavy chain or a light chain. Antibody also encompasses intact immunoglobulins as well antigen-binding fragments of antibodies. Thus, the term "antibody", as used herein also includes an antigen-binding portion of an antibody, which can be produced by the modification of whole antibodies or synthesized de novo using recombinant DNA methodologies.

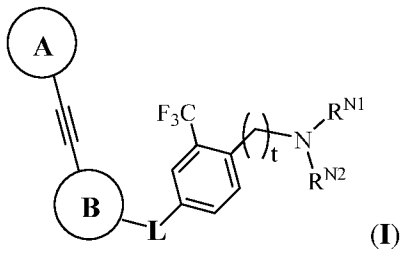
[00063] The term "siRNA" refers to an isolated RNA molecule, preferably greater than 10 nucleotides in length, more preferably greater than 15 nucleotides in length, and most preferably 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length, that functions as a key intermediate in triggering sequence-specific RNA degradation. A range of 19-25 nucleotides is the most preferred size for siRNAs. siRNAs can also include short hairpin RNAs (shRNA) in which both strands of an siRNA duplex are included within a single RNA molecule. Double-stranded siRNAs generally include a sense and anti-sense strand. Single-stranded siRNAs generally consist of only the antisense strand that is complementary to the target gene or mRNA. siRNA includes any form of RNA, preferably dsRNA (proteolytically cleaved products of larger dsRNA, partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA) as well as modified RNA that differs from naturally occurring RNA by the addition, deletion, substitution, and/or alteration of one or more nucleotides (Yair Dorsett; Thomas Tuschl, Nature Reviews Drug Discovery, 2004, 3, 318-329).

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[00064] The invention provides heteroaryl alkyne derivatives as kinase inhibitors. In particular, the provided compounds act as inhibitors of the MAP kinase interacting kinases 1 and 2 (MNK1 and MNK2) and/or Abl-tyrosine kinase. The provided compounds and pharmaceutical compositions thereof are useful in treating diseases associated with aberrant MNK or Abl-tyrosine kinase activity or dysregulation of the corresponding pathway. For example, the provided compounds and pharmaceutical compositions can be used to prevent and/or treat cancer (such as solid tumor and hematological tumor), an inflammatory disease, a neurodegenerative disease (such as Alzheimer's disease), or a metabolic disorder (such as diabetes, hyperlipidemia and obesity).

Compounds

[00065] The provided compounds are heteroaryl alkyne derivatives. In one aspect, the present invention provides a compound of Formula (**I**):



(**I**)

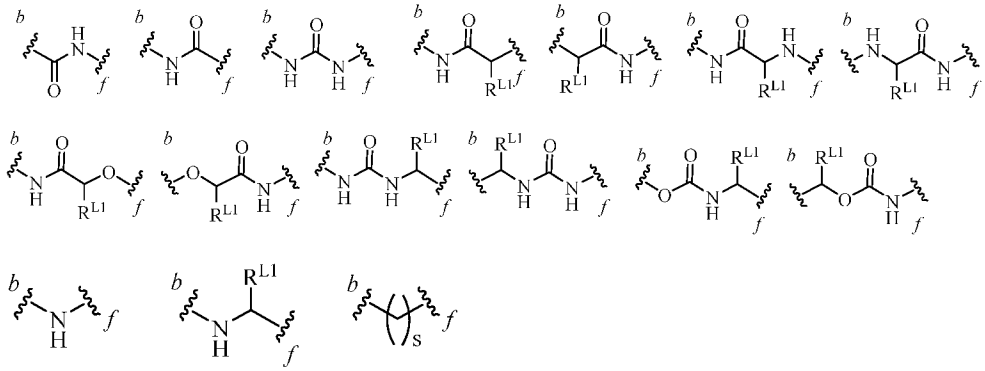
or a pharmaceutically acceptable salt thereof,

wherein

Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, optionally substituted 5,6- or 6,6-bicyclic heteroaryl, or optionally substituted 5,6- or 6,6-bicyclic heterocycle;

Ring B is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl;

L is one of the following formulae:



b indicates the point of attachment to Ring B;

f indicates the point of attachment to *m*-CF_3-Ph;

R^{L1} is hydrogen or optionally substituted C_{1-6} alkyl;

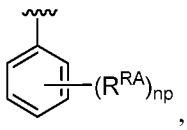
each of R^{N1} and R^{N2} is independently hydrogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} carbocyclyl, or R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted heterocyclic moiety;

t is 1, 2, or 3; and

s is 1, 2, or 3.

[00066] As generally defined herein, Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, optionally substituted 5,6- or 6,6-bicyclic heteroaryl, or optionally substituted 5,6- or 6,6-bicyclic heterocycle. In certain embodiments, Ring A is optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, optionally substituted 5,6- or 6,6-bicyclic heteroaryl, or optionally substituted 5,6- or 6,6-bicyclic heterocycle. In certain embodiments, Ring A is optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6- or 6,6-bicyclic heteroaryl.

[00067] In certain embodiments, Ring A is optionally substituted phenyl of the formula



wherein

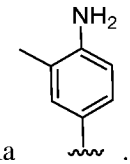
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

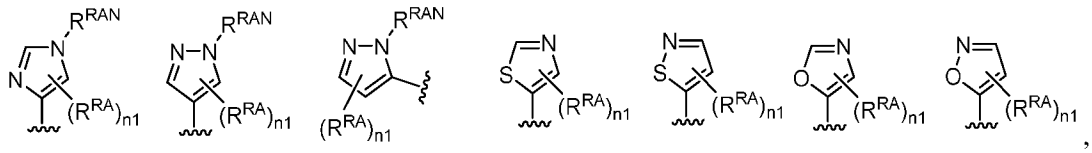
each instance of R^{RAN} and R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{RAN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl, or two R^{AN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl; and

np is 0, 1, 2, 3, 4, or 5.

[00068] In certain embodiments, np is 0. In certain embodiments, np is 1. In certain embodiments, np is 2. In certain embodiments, np is 3. In certain embodiments, np is 4. In certain embodiments, np is 5.

[00069] In certain embodiments, Ring A is of the formula  .

[00070] In certain embodiments, Ring A is optionally substituted five-membered heteroaryl. In certain embodiments, Ring A is optionally substituted five-membered heteroaryl with one heteroatom selected from the group consisting of O, S, and N. In certain embodiments, Ring A is optionally substituted five-membered heteroaryl with two heteroatoms selected from the group consisting of O, S, and N. In certain embodiments, Ring A is one of the following formulae:

 ,

wherein

each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^{RAN} and R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{RAN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl, or two R^{AN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl; and

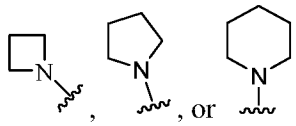
n1 is 0, 1 or 2.

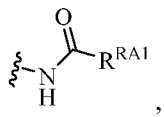
[00071] In certain embodiments, n1 is 0. In certain embodiments, n1 is 1. In certain embodiments, n1 is 2.

[00072] As generally defined herein, each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, -OR^{AO}, or -$N(R^{AN})_2$. In certain embodiments, R^{RA} is hydrogen. In certain embodiments, R^{RA} is halogen. In certain embodiments, R^{RA} is -F, -Cl, -Br, or -I. In certain embodiments, R^{RA} is -CN. In certain embodiments, R^{RA} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RA} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RA} is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In certain embodiments, R^{RA} is substituted C_{1-6} alkyl. In certain embodiments, R^{RA} is -CF_3, -CHF_2, or -CH_2F. In certain embodiments, R^{RA} is optionally substituted acyl. In certain embodiments, R^{RA} is acetyl. In certain embodiments, R^{RA} is -C(=O)NH_2.

[00073] In certain embodiments, R^{RA} is -OR^{AO}, wherein each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group. In certain embodiments, R^{RA} is –OH. In some embodiments, R^{RA} is –OR^{AO}, wherein R^{AO} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group. In certain embodiments, R^{RA} is –OR^{AO}, wherein R^{AO} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RA} is –OR^{AO}, wherein R^{AO} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RA} is –O-methyl, –O-ethyl, –O-propyl, or –O-isopropyl. In certain embodiments, R^{RA} is –OR^{AO}, wherein R^{AO} is optionally substituted heterocyclyl. In certain embodiments, R^{RA} is –OR^{AO}, wherein R^{AO} is optionally substituted aryl. In certain embodiments, R^{RA} is –O-phenyl. In certain embodiments, R^{RA} is –OR^{AO}, wherein R^{AO} is

optionally substituted heteroaryl. In certain embodiments, R^{RA} is $-OR^{AO}$, wherein R^{AO} is an oxygen protecting group. In certain embodiments, R^{RA} is $-OR^{AO}$, wherein R^{AO} is Ac, Boc, TBS, TIPS, Bn, or Bz.

[00074] In certain embodiments, R^{RA} is $-N(R^{AN})_2$, each instance of R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, a nitrogen protecting group, or two R^{RAN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl. In certain embodiments, R^{RA} is $-N(R^{AN})_2$, wherein each instance of R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted acyl, or a nitrogen protecting group. In certain embodiments, R^{RA} is $-NH_2$. In some embodiments, R^{RA} is $-N(R^{AN})_2$. In certain embodiments, R^{RA} is $-NHR^{AN}$, wherein R^{AN} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group. In certain embodiments, R^{RA} is $-NHR^{AN}$, wherein R^{AN} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RA} is $-NHR^{AN}$, wherein R^{AN} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RA} is –NH-methyl, –NH-ethyl, –NH-*n*-propyl, or –NH-*iso*-propyl. In certain embodiments, R^{RA} is $-NHR^{AN}$, wherein R^{AN} is a nitrogen protecting group. In certain embodiments, R^{RA} is $-NHSO_2CH_3$. In certain embodiments, two R^{RAN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl. In certain embodiments, two R^{RAN} are taken with the intervening nitrogen to form an optionally substituted four-, five-, or six-membered heterocyclyl. In certain embodiments, R^{RA} is  .

[00075] In certain embodiments, R^{RA} is of the formula  , wherein R^{RA1} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, $-OR^A$, or $-N(R^B)_2$. In certain embodiments, R^{RA1} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RA1} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RA1} is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In certain embodiments, R^{RA1} is substituted C_{1-6} alkyl. In certain embodiments, R^{RA1} is $-CH_2Cl$, $-CHCl_2$, $-CHF_2$, $-CH_2F$, or $-CF_3$. In certain

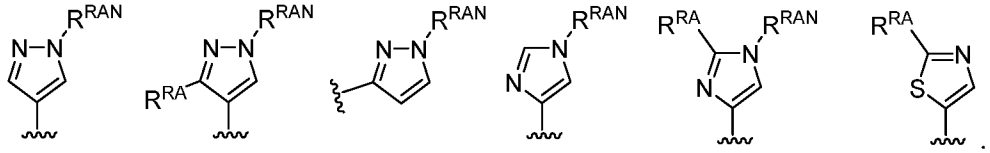
embodiments, R^{RA1} is optionally substituted C_{3-6} carbocyclyl. In certain embodiments, R^{RA1} is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In certain embodiments, R^{RA1} is optionally substituted phenyl. In certain embodiments, R^{RA1} is phenyl. In certain embodiments, R^{RA1} is substituted phenyl. In certain embodiments, R^{RA1} is optionally substituted five- or six-membered heterocyclyl. In certain embodiments, R^{RA1} is optionally substituted five-membered heterocyclyl. In certain embodiments, R^{RA1} is optionally substituted six-membered heterocyclyl. In certain embodiments, R^{RA1} is optionally substituted five- or six-membered heteroaryl. In certain embodiments, R^{RA1} is optionally substituted five-membered heteroaryl. In certain embodiments, R^{RA1} is optionally substituted six-membered heteroaryl. In certain embodiments, R^{RA1} is optionally substituted pyridine. In certain embodiments, R^{RA1} is pyridine.

[00076] In certain embodiments, R^{RA} is optionally substituted four-, five-, or six-membered heterocyclyl. In certain embodiments, R^{RA} is optionally substituted four-membered heterocyclyl. In certain embodiments, R^{RA} is optionally substituted four-membered heterocyclyl with one N, S, and O. In certain embodiments, R^{RA} is optionally substituted five-membered heterocyclyl. In certain embodiments, R^{RA} is optionally substituted five-membered heterocyclyl with one or two heteroatoms each independently selected from the group consisting of N, S, and O. In certain embodiments, R^{RA} is optionally substituted six-membered heterocyclyl. In certain embodiments, R^{RA} is optionally substituted six-membered heterocyclyl with one or two heteroatoms each independently selected from the group consisting of N, S, and O.

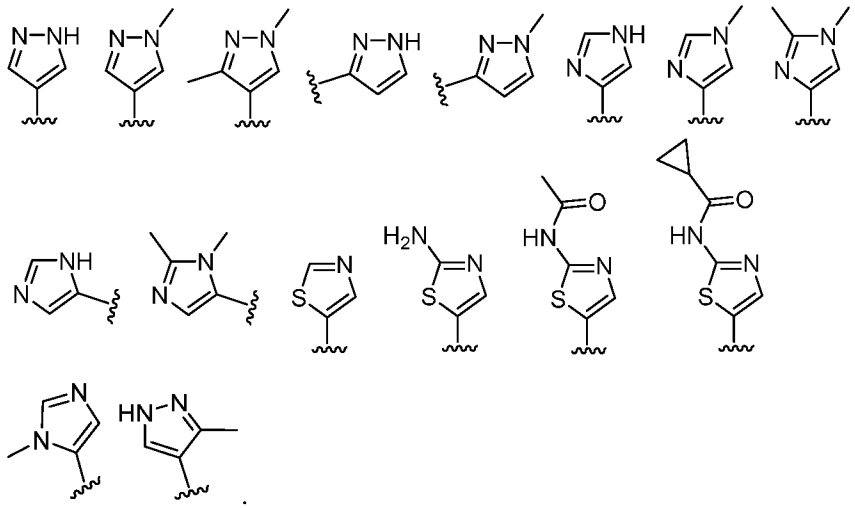
[00077] In certain embodiments, R^{RA} is optionally substituted five- or six-membered heteroaryl. In certain embodiments, R^{RA} is optionally substituted five-membered heteroaryl. In certain embodiments, R^{RA} is optionally substituted five-membered heteroaryl with one N, O, or S. In certain embodiments, R^{RA} is optionally substituted five-membered heteroaryl with two heteroatoms each independently selected from the group consisting of N, S, or O. In certain embodiments, R^{RA} is optionally substituted six-membered heteroaryl. In certain embodiments, R^{RA} is optionally substituted six-membered heteroaryl with one N, O, or S. In certain embodiments, R^{RA} is optionally substituted six-membered heteroaryl with two heteroatoms each independently selected from the group consisting of N, S, or O. In certain embodiments, R^{RA} is substituted pyridine. In certain embodiments, R^{RA} is pyridine.

[00078] In certain embodiments of Ring A being optionally substituted five-membered heteroaryl, R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-NHC(=O)R^{AN1}$. In certain embodiments, R^{RA} is $-NH_2$, -NHAc, or -NHC(=O)-cyclopropyl.

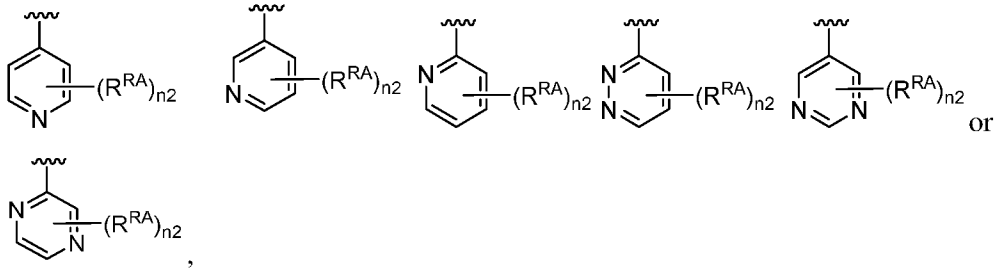
[00079] In certain embodiments, Ring A is one of the following formulae:



[0100] In certain embodiments, Ring A is one of the following formulae:



[00080] In certain embodiments, Ring A is optionally substituted six-membered heteroaryl. In certain embodiments, Ring A is is optionally substituted six-membered heteroaryl with one or two N. In certain embodiments, Ring A is one of the following formulae:



wherein R^{RA} is as defined herein, and each instance of n2 is independently 0, or an integer of 1 to 4, inclusive.

[00081] As generally used herein, each instance of n2 is independently 0 or an integer of 1 to 4, inclusive. In certain embodiments, n2 is 0. In certain embodiments, n2 is 1. In certain embodiments, n2 is 2. In certain embodiments, n2 is 3. In certain embodiments, n2 is 4.

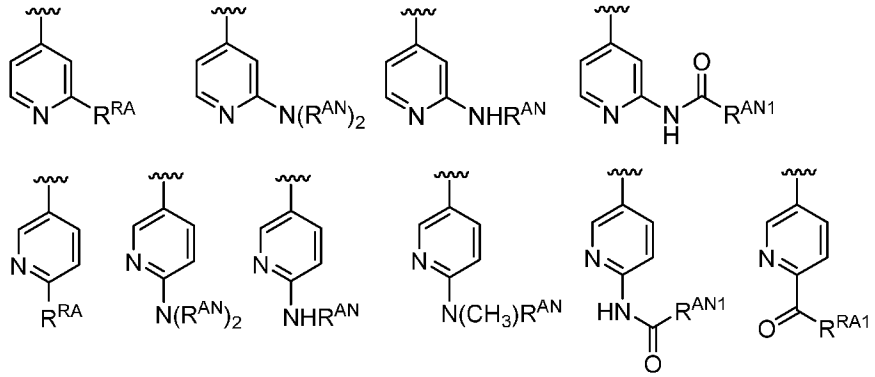
[00082] In certain embodiments wherein Ring A is optionally substituted six-membered heteroaryl, R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-NHC(=O)R^{AN1}$, wherein each instance of R^{AN1} is independently hydrogen, o optionally substituted alkyl, optionally substituted carbocyclyl,

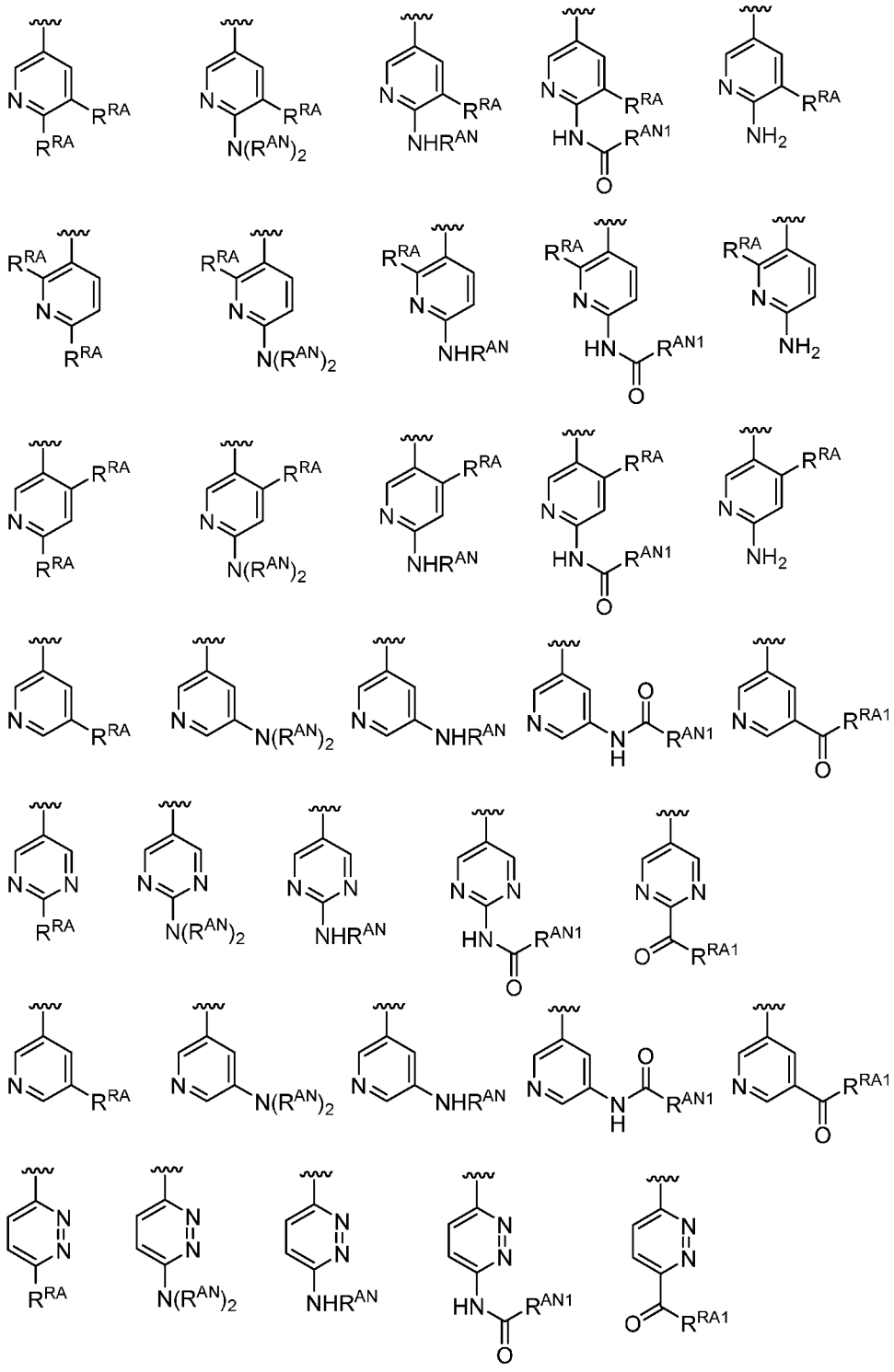
optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

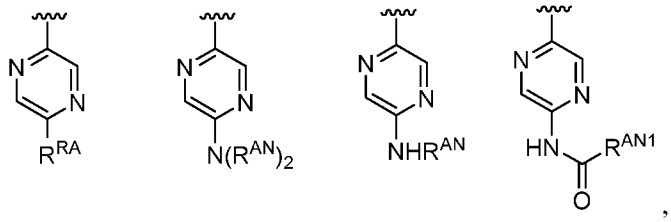
[00083] As generally defined herein, each instance of R^{RN1} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In certain embodiments, R^{RN1} is hydrogen. In certain embodiments, R^{RN1} is optionally substituted alkyl. In certain embodiments, R^{RN1} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RN1} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RN1} is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In certain embodiments, R^{RN1} is substituted C_{1-6} alkyl. In certain embodiments, R^{RN1} is $-CH_2Cl$, $-CHCl_2$, $-CHF_2$, $-CH_2F$, or $-CF_3$. In certain embodiments, R^{RN1} is optionally substituted carbocyclyl. In certain embodiments, R^{RN1} is optionally substituted C_{3-6} carbocyclyl. In certain embodiments, R^{RN1} is cycloproyl, cyclobutyl, cyclopentyl, or cyclohexyl. In certain embodiments, R^{RN1} is optionally substituted aryl. In certain embodiments, R^{RN1} is optionally substituted phenyl. In certain embodiments, R^{RN1} is phenyl. In certain embodiments, R^{RN1} is substituted phenyl. In certain embodiments, R^{RN1} is optionally substituted heterocyclyl. In certain embodiments, R^{RN1} is optionally substituted five- or six-membered heterocyclyl. In certain embodiments, R^{RN1} is optionally substituted heteroaryl. In certain embodiments, R^{RN1} is optionally substituted five- or six-membered heteroaryl.

[00084] In certain embodiments of Ring A being optionally substituted six-membered heteroaryl, R^{RA} is one of the following formulae: -CN, -F, -Cl, $-CH_3$, $-NH_2$, $-NHCH_3$, $-N(C_2H_5)_2$, -NHAc, $-N(CH_3)Ac$, -NHC(=O)-cyclopropyl, or $-C(=O)CH_3$.

[00085] In certain embodiments, Ring A is one of the following formulae:





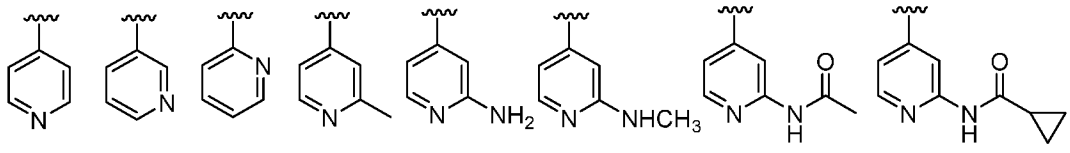


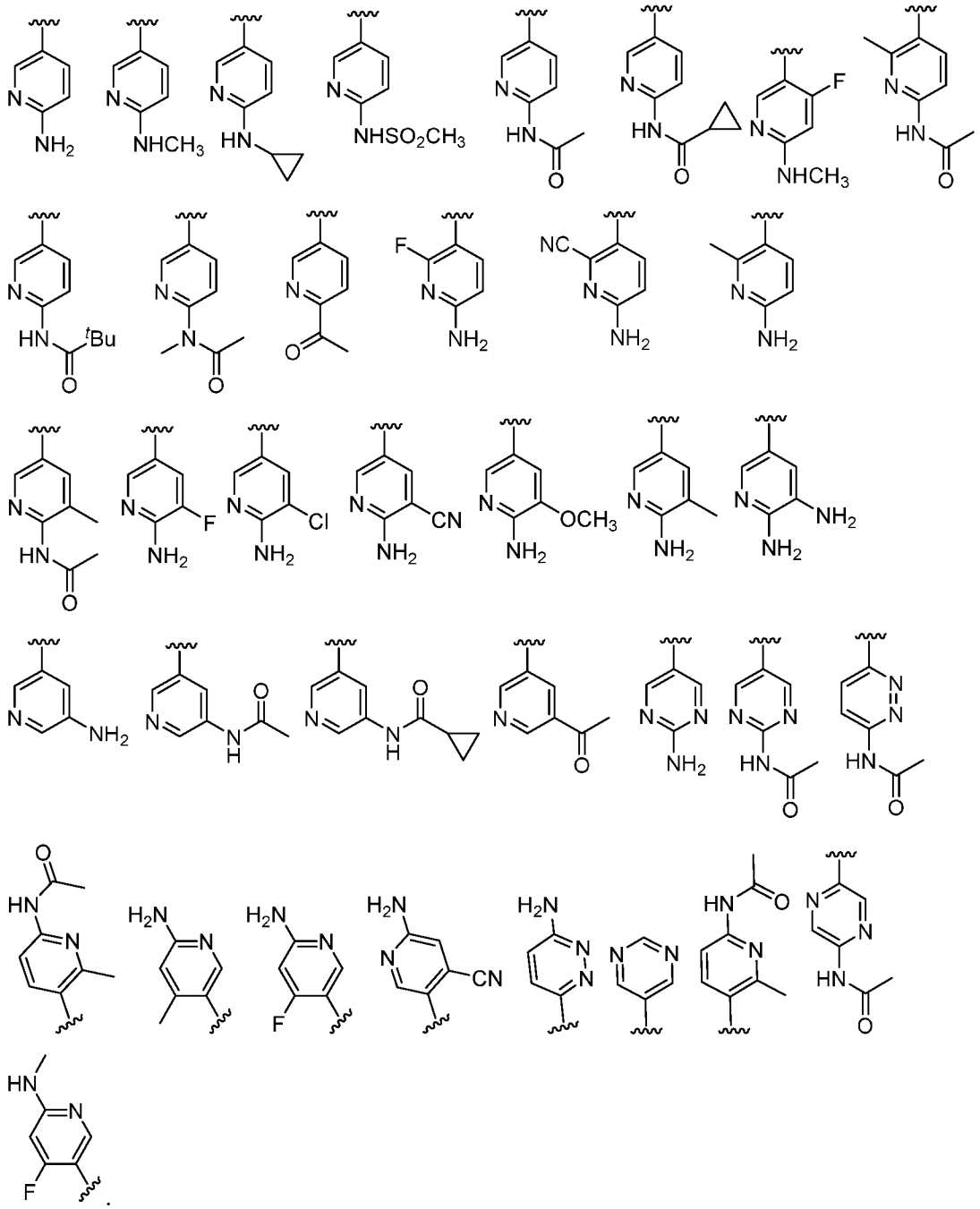
wherein

each instance of R^{RA1} and R^{AN1} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

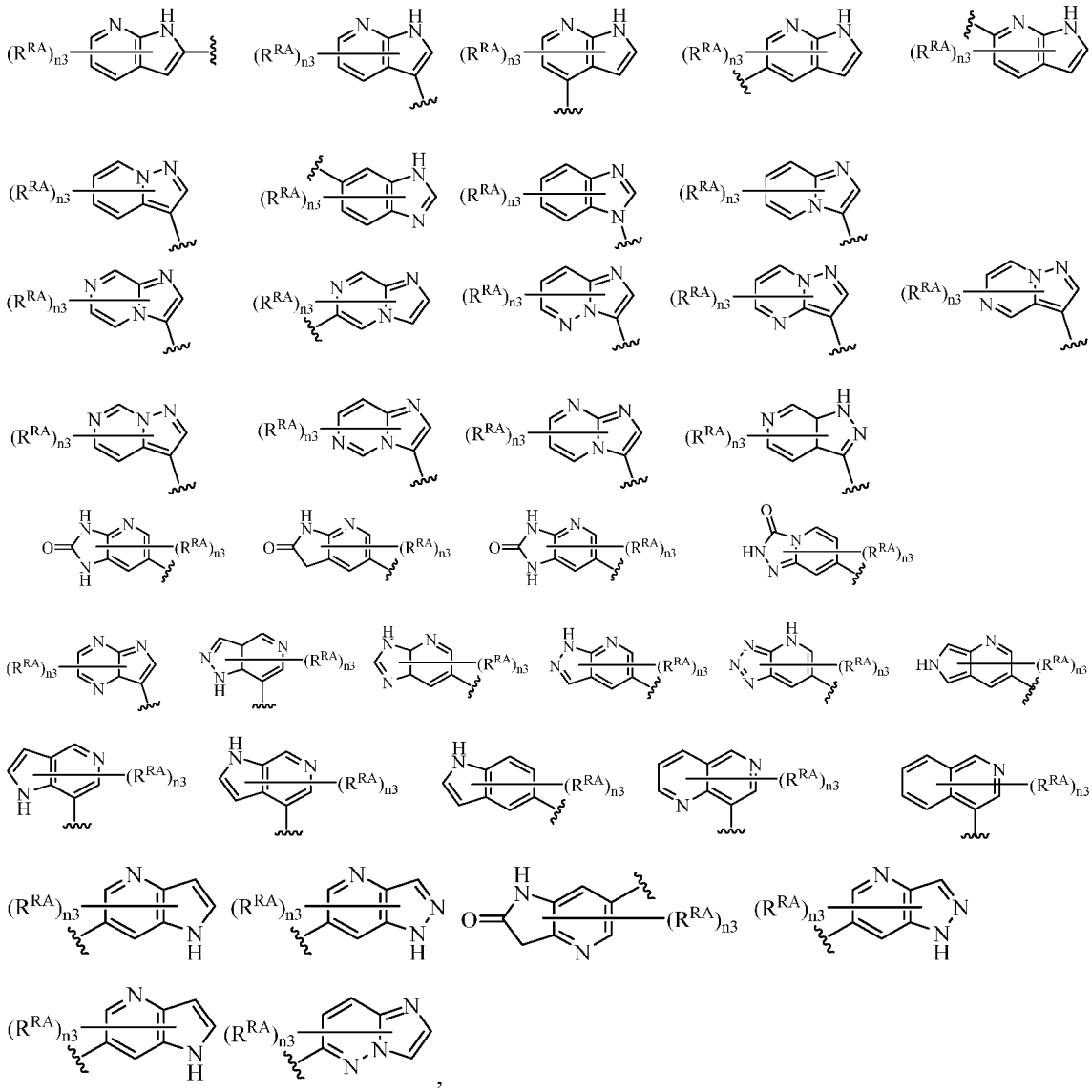
[00086] As generally defined herein, each instance of R^{RA1} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In certain embodiments, R^{RA1} is hydrogen. In certain embodiments, R^{RA1} is optionally substituted alkyl. In certain embodiments, R^{RA1} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RA1} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RA1} is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In certain embodiments, R^{RA1} is substituted C_{1-6} alkyl. In certain embodiments, R^{RA1} is $-CH_2Cl$, $-CHCl_2$, $-CHF_2$, $-CH_2F$, or $-CF_3$. In certain embodiments, R^{RA1} is optionally substituted carbocyclyl. In certain embodiments, R^{RA1} is optionally substituted C_{3-6} carbocyclyl. In certain embodiments, R^{RA1} is cycloproyl, cyclobutyl, cyclopentyl, or cyclohexyl. In certain embodiments, R^{RA1} is optionally substituted aryl. In certain embodiments, R^{RA1} is optionally substituted phenyl. In certain embodiments, R^{RA1} is phenyl. In certain embodiments, R^{RA1} is substituted phenyl. In certain embodiments, R^{RA1} is optionally substituted heterocyclyl. In certain embodiments, R^{RA1} is optionally substituted five- or six-membered heterocyclyl. In certain embodiments, R^{RA1} is optionally substituted heteroaryl. In certain embodiments, R^{RA1} is optionally substituted five- or six-membered heteroaryl.

[00087] In certain embodiments, Ring A is one of the following formulae:





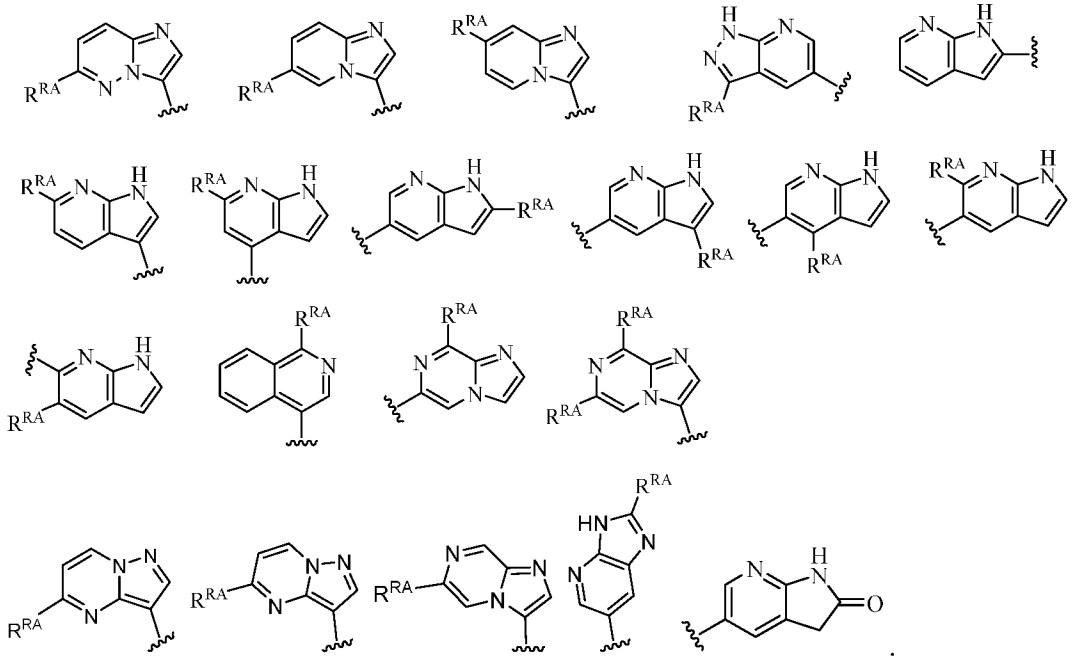
[00088] In certain embodiments, Ring A is optionally substituted 5,6- or 6,6-bicyclic heteroaryl. In certain embodiments, Ring A is optionally substituted 5,6- or 6,6-bicyclic heteroaryl with one, two, or three N. In certain embodiments, Ring A is one of the following formulae:



wherein R^{RA} is as defined herein; each instance of n3 is independently 0 or an integer of 1 to 6, inclusive, as valency permits.

[00089] As generally used herein, each instance of n3 is independently 0 or an integer of 1 to 6, inclusive, as valency permits. In certain embodiments, n3 is 0. In certain embodiments, n3 is 1. In certain embodiments, n3 is 2. In certain embodiments, n3 is 3. In certain embodiments, n3 is 4. In certain embodiments, n3 is 5. In certain embodiments, n3 is 6. In certain embodiments, n3 is an integer of 1 to 6, inclusive, as valency permits. In certain embodiments, n3 is 1 or 2 as valency permits.

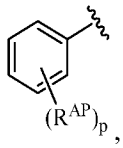
[00090] In certain embodiments, Ring A is one of the following formulae:



[00091] In certain embodiments when Ring A is optionally substituted 5,6- or 6,6-bicyclic heteroaryl, at least one instance of R^{RA} is hydrogen, halogen, optionally substituted C_{1-6} alkyl, $-N(R^{AN})_2$, $-NHR^{AN}$, $-NHC(=O)R^{AN1}$, $-OR^{AO}$, optionally substituted carbocyclyl, or optionally substituted phenyl, wherein R^{AN}, R^{AO} and R^{AN1} are as define herein. In certain embodiments, R^{RA} is hydrogen. In certain embodiments, R^{RA} is halogen. In certain embodiments, R^{RA} is F. In certain embodiments, R^{RA} is Cl. In certain embodiments, R^{RA} is Br. In certain embodiments, R^{RA} is I. In certain embodiments, R^{RA} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RA} is substituted C_{1-6} alkyl. In certain embodiments, R^{RA} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RA} is methyl, ethyl, n-propyl, or iso-propyl.

[00092] In certain embodiments when Ring A is optionally substituted 5,6- or 6,6-bicyclic heteroaryl, at least one instance of R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, $-NHC(=O)R^{AN1}$, $-OR^{AO}$, optionally substituted carbocyclyl, or optionally substituted phenyl, wherein R^{AN}, R^{AO} and R^{AN1} are as define herein.

[00093] In certain embodiments when Ring A is optionally substituted 5,6- or 6,6-bicyclic heteroaryl, at least one instance of R^{RA} is optionally substituted phenyl of the formula:



wherein

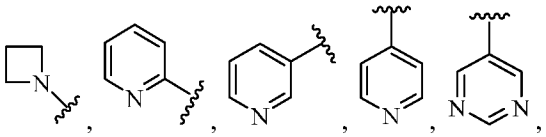
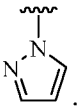
each instance of R^{AP} is independently hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or optionally substituted acyl; and

p is an integer of 1 to 5, inclusive.

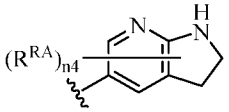
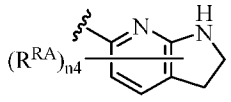
[00094] As generally used herein, p is an integer of 1 to 5, inclusive, as valency permits. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, p is 4. In certain embodiments, p is 5.

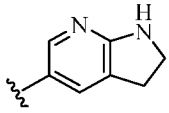
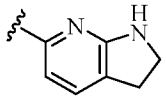
[00095] As generally used herein, each instance of R^{AP} is independently hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or optionally substituted acyl. In certain embodiments, R^{AP} is hydrogen. In certain embodiments, R^{AP} is CN. In certain embodiments, R^{AP} is halogen (*e.g.* F, Cl, Br, or I). In certain embodiments, R^{AP} is optionally substituted alkyl. In certain embodiments, R^{AP} is substituted C_{1-6} alkyl. In certain embodiments, R^{AP} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{AP} is methyl, ethyl, n-propyl, or iso-propyl. In certain embodiments, R^{AP} is optionally substituted acyl of the formula $–C(=O)R^{AP1}$, wherein R^{AP1} is independently optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In certain embodiments, R^{AP} is optionally substituted acyl of the formula $–C(=O)R^{AP1}$, wherein R^{AP1} is optionally substituted heterocyclyl. In certain embodiments, R^{AP} is optionally substituted five-membered heterocyclyl having one N, O, or S. In certain embodiments, R^{AP} is optionally substituted five-membered heterocyclyl having two heteroatoms ech independently selected from the group consisting of N, O, and S. In certain embodiments, R^{AP} is optionally substituted six-membered heterocyclyl having one N, O, or S. In certain embodiments, R^{AP} is optionally substituted six-membered heterocyclyl having two heteroatoms ech independently selected from the group consisting of N, O, and S.

[00096] In certain embodiments when Ring A is optionally substituted 5,6- or 6,6-bicyclic heteroaryl, each instance of R^{RA} is independently -CN, -F, -Cl, $-CH_3$, $-C_2H_5$, $-{}^{i}Pr$, -Ph, , $-O{}^{i}Pr$, $-OCH_3$, $-OC_2H_5$, $-NH_2$, $-NHCH_2{}^{i}Pr$, $-N(CH_3)_2$, $-NHCH_3$, $-N(C_2H_5)_2$, $-NH-(CH_2)_3-OH$, -

$N(CH_3)$-$(CH_2)_2$-OCH_3, -NHC(=O)^{i}Pr, -NHAc,  ,  .

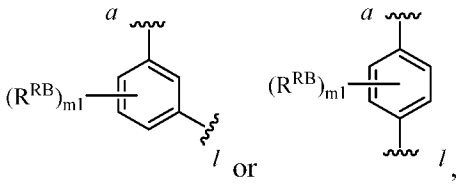
[00097] In certain embodiments, Ring A is optionally substituted 5,6- or 6,6-bicyclic heterocycle. In certain embodiments, Ring A is optionally substituted 5,6- or 6,6-bicyclic heterocycle with one, two, or three N. In certain embodiments, Ring A is one of the following formulae:

 or  , wherein R^{RA} is as defined herein; and each instance of n4 is independently 0 or an integer of 1 to 6, inclusive, as valency permits. In certain embodiments, n4 is 0. In certain embodiments, n4 is 1. In certain embodiments, n4 is 2. In certain embodiments, n4 is 3. In certain embodiments, n4 is 4. In certain embodiments, n4 is 5. In certain embodiments, n4 is 6.

[00098] In certain embodiments, Ring A is of the formula  or  .

[00099] As generally defined herein, Ring B is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl.

[000100] In certain embodiments, Ring B is optionally substituted phenyl of the formula:

 or ,

wherein

each instance of R^{RB} is independently hydrogen, halogen, or optionally substituted C_{1-6} alkyl;

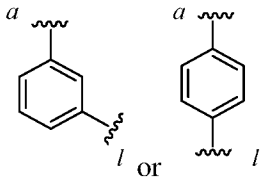
a indicates the point of attachment to alkynyl;

l indicates the point of attachment to L; and

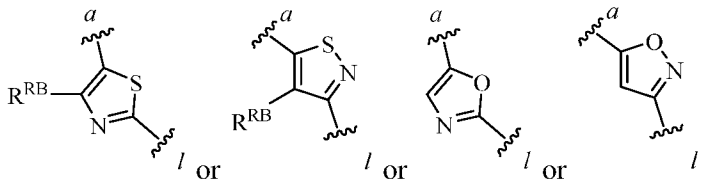
m1 is 1, 2, 3, or 4.

[000101] As generally used herein, m1 is 1, 2, 3, or 4. In certain embodiments, m1 is 1. In certain embodiments, m1 is 2. In certain embodiments, m1 is 3. In certain embodiments, m1 is 4.

[000102] As generally used herein, each instance of R^{RB} is independently hydrogen, halogen, or optionally substituted C_{1-6} alkyl. In certain embodiments, R^{RB} is hydrogen. In certain embodiments, R^{RB} is CN. In certain embodiments, R^{RB} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{RB} is optionally substituted alkyl. In certain embodiments, R^{RB} is substituted C_{1-6} alkyl. In certain embodiments, R^{RB} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{RB} is methyl, ethyl, n-propyl, or iso-propyl.

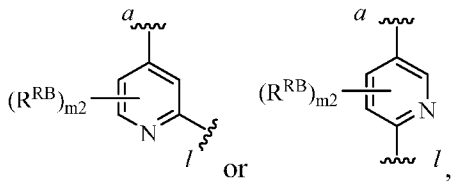
[000103] In certain embodiments, Ring B is of the formula:  or .

[000104] In certain embodiments, Ring B is optionally substituted five-membered heteroaryl. In certain embodiments, Ring B is optionally substituted five-membered heteroaryl with one N, O, or S. In certain embodiments, Ring B is optionally substituted five-membered heteroaryl with two heteroatoms each independently selected from the group consisting of N, O, and S. In certain embodiments, Ring B is of one of the following formulae:



wherein R^{RB} is as defined herein.

[000105] In certain embodiments, Ring B is optionally substituted six-membered heteroaryl. In certain embodiments, Ring B is optionally substituted six-membered heteroaryl with one N, O, or S. In certain embodiments, Ring B is optionally substituted six-membered heteroaryl with two heteroatoms each independently selected from the group consisting of N, O, and S. In certain embodiments, Ring B is of one of the following formulae:



or

,

wherein

a indicates the point of attachment to alkynyl;

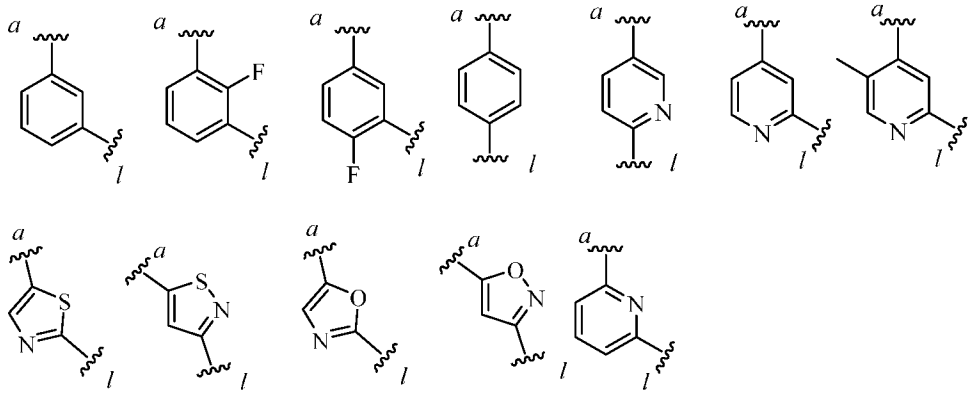
l indicates the point of attachment to L; and

m2 is 1, 2, or 3 and R^{RB} is as defined herein.

[000106] As generally used herein, m2 is 1, 2, or 3. In certain embodiments, m2 is 1. In certain embodiments, m2 is 2. In certain embodiments, m2 is 3.

[000107] In certain embodiments, Ring B is optionally substituted 5,6-bicyclic heteroaryl. In certain embodiments, Ring B is optionally substituted 5,6-bicyclic heteroaryl with one N, O, or S. In certain embodiments, Ring B is optionally substituted 5,6-bicyclic heteroaryl with two heteroatoms each independently selected from the group consisting of N, O, and S.

[000108] In certain embodiments, Ring B is one of the following formulae:

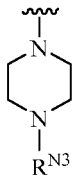


[000109] As generally used herein, R^{N1} is independently hydrogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} carbocyclyl. In certain embodiments, R^{N1} is hydrogen. In certain embodiments, R^{N1} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{N1} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{N1} is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In certain embodiments, R^{N1} is substituted C_{1-6} alkyl. In certain embodiments, R^{N1} is optionally substituted carbocyclyl. In certain embodiments, R^{N1} is optionally substituted C_{3-6} carbocyclyl. In certain embodiments, R^{N1} is cycloproyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[000110] As generally used herein, R^{N2} is independently hydrogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} carbocyclyl. In certain embodiments, R^{N2} is hydrogen.

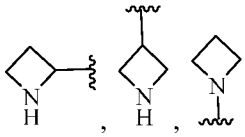
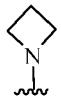
In certain embodiments, R^{N2} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{N2} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{N2} is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In certain embodiments, R^{N2} is substituted C_{1-6} alkyl. In certain embodiments, R^{N2} is optionally substituted carbocyclyl. In certain embodiments, R^{N2} is optionally substituted C_{3-6} carbocyclyl. In certain embodiments, R^{N2} is cycloproyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[000111] In certain embodiments, R^{N1} and R^{N2} each are independently optionally substituted C_{1-6} alkyl. In certain embodiments, R^{N1} and R^{N2} each are independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^{N1} and R^{N2} each are independently methyl, ethyl, n-propyl, or iso-propyl. In certain embodiments, R^{N1} and R^{N2} are the same. In certain embodiments, R^{N1} and R^{N2} are different. In certain embodiments, R^{N1} and R^{N2} are both methyl, ethyl, n-propyl, or iso-propyl.

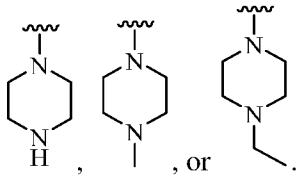
[000112] In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted heterocyclic moiety. In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted three-, four-, five-, or six-membered heterocyclic moiety. In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted six-membered heterocyclic moiety of the formula:  , wherein R^{N3} is independently hydrogen, optionally substituted C_{1-6} alkyl, or a nitrogen protecting group.

[000113] In certain embodiments, R^{N3} is hydrogen. In certain embodiments, R^{N3} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{N3} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{N3} is methyl, ethyl, n-propyl, or iso-propyl. In certain embodiments, R^{N3} is substituted C_{1-6} alkyl. In certain embodiments, R^{N3} is a nitrogen protecting group. In certain embodiments, R^{N3} is Bn, Bz, or Boc.

[000114] In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted four-membered heterocyclic moiety. In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted azetidinyl moiety. In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form one of the following formulae:

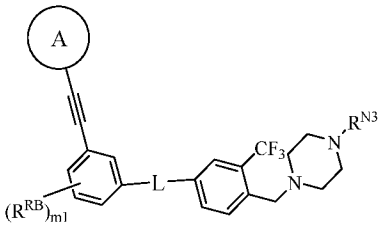

. In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form a formula of  .

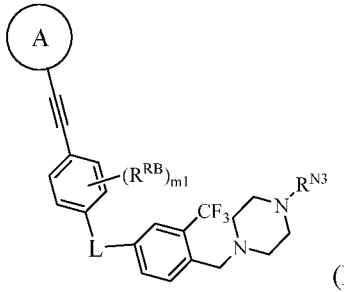
[000115] In certain embodiments, R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted six-membered heterocyclic moiety of the formula:

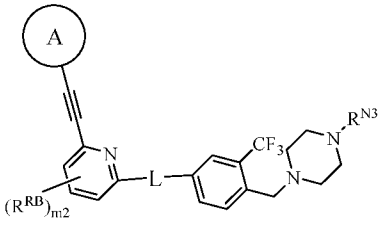


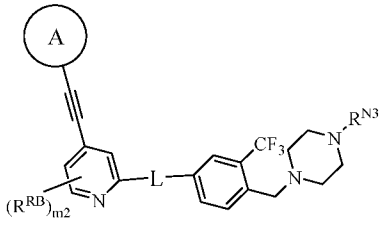
[000116] In certain embodiments, t is 1. In certain embodiments, t is 2. In certain embodiments, t is 3.

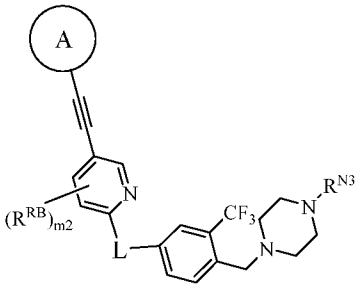
[000117] In certain embodiments, the compound of Formula (**I**) is of one of the following formulae:

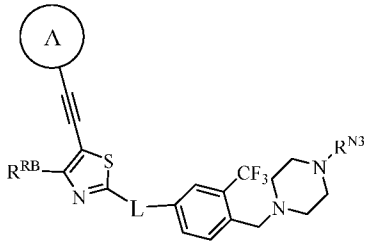

(I-a),


(I-b),


(I-c),

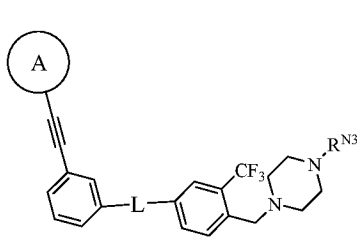

(I-d),


(I-e),

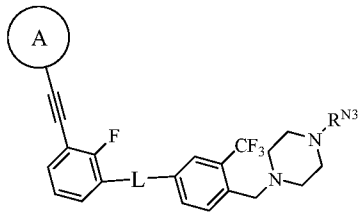

(I-f).

or a pharmaceutically acceptable salt thereof, wherein Ring A, L, R^{RB}, R^{N3}, m1, m2, and m3 are as defined herein.

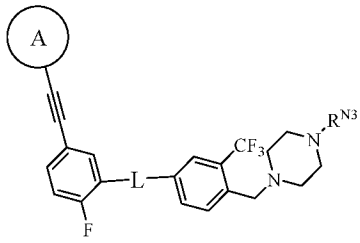
[000118] In certain embodiments, the compound of Formula (**I**) is of one of the following formulae:



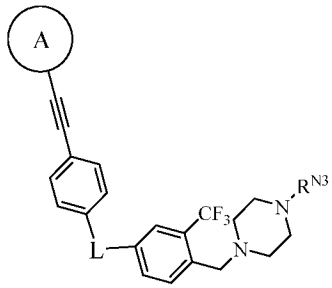
(I-g)



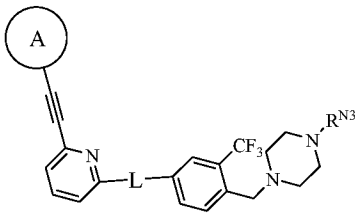
(I-h)



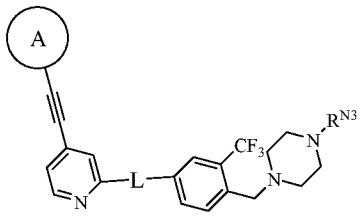
(I-i)



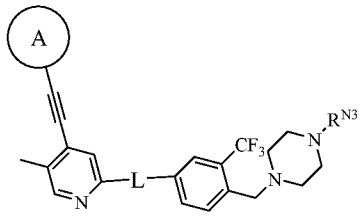
(I-j)



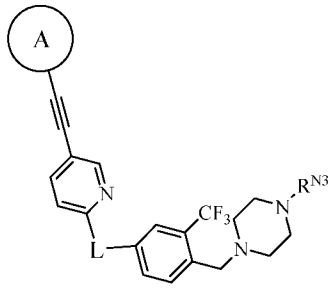
(I-k)



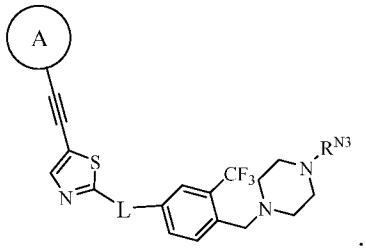
(I-l)



(I-m)



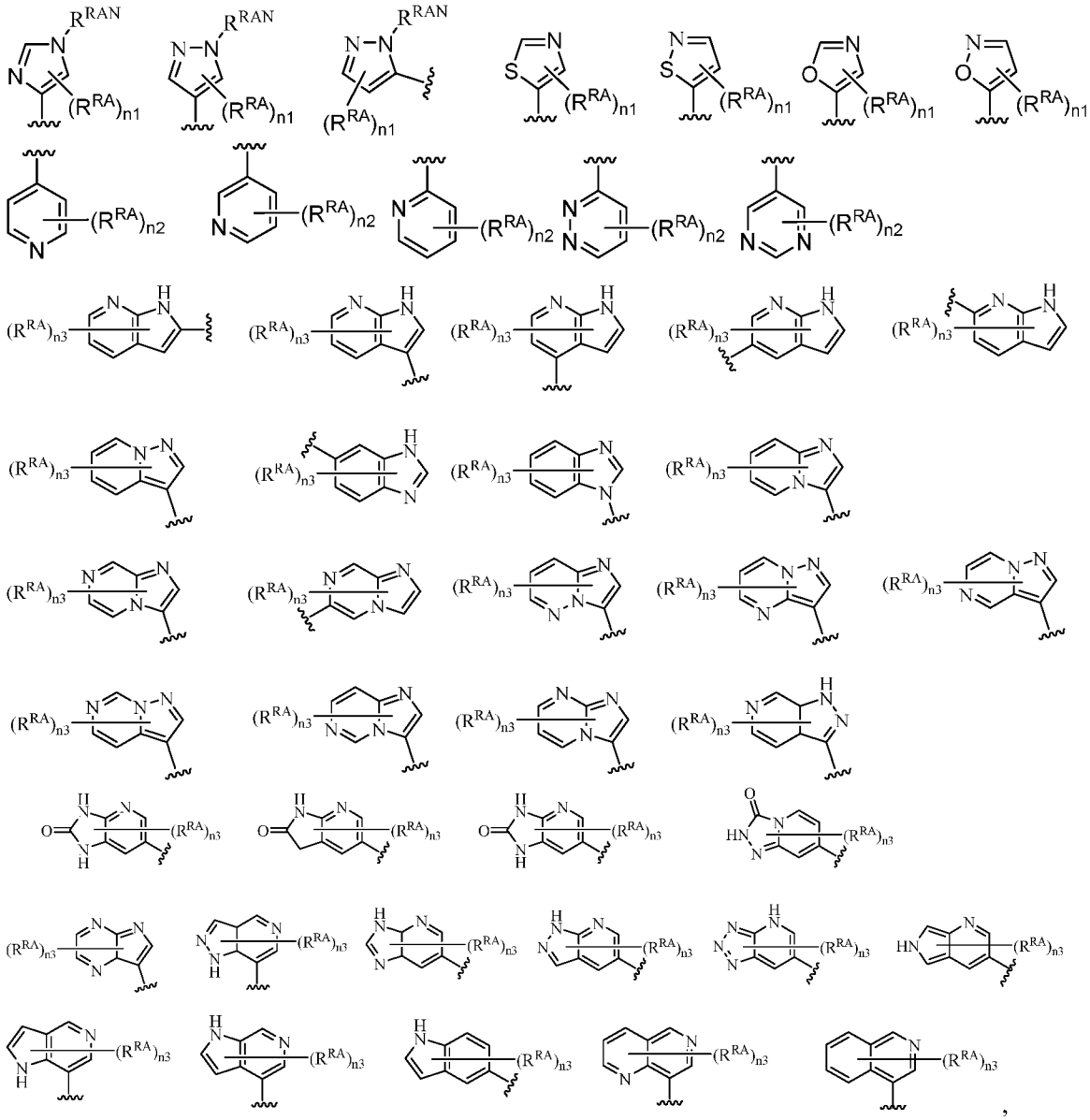
(I-n)



(I-o)

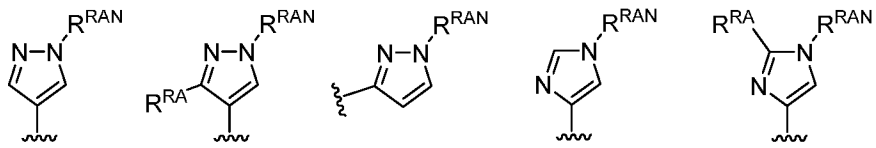
or or a pharmaceutically acceptable salt thereof, wherein Ring A, L, and R^{N3} are as defined herein.

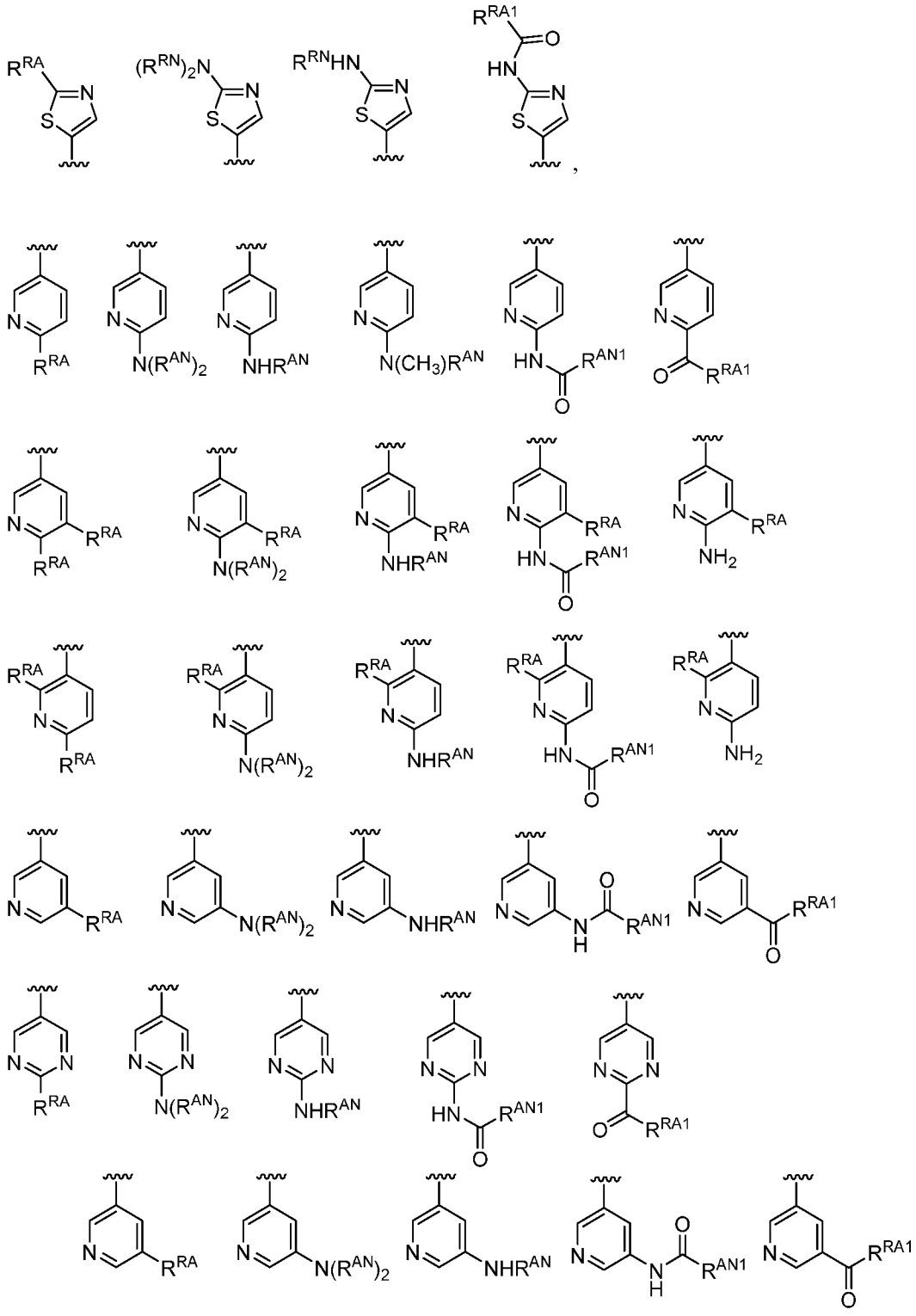
[000119] In certain embodiments, the compound of Formula (**I**) and (**I-a**) to (**I-o**), wherein Ring A is one of the following formulae:

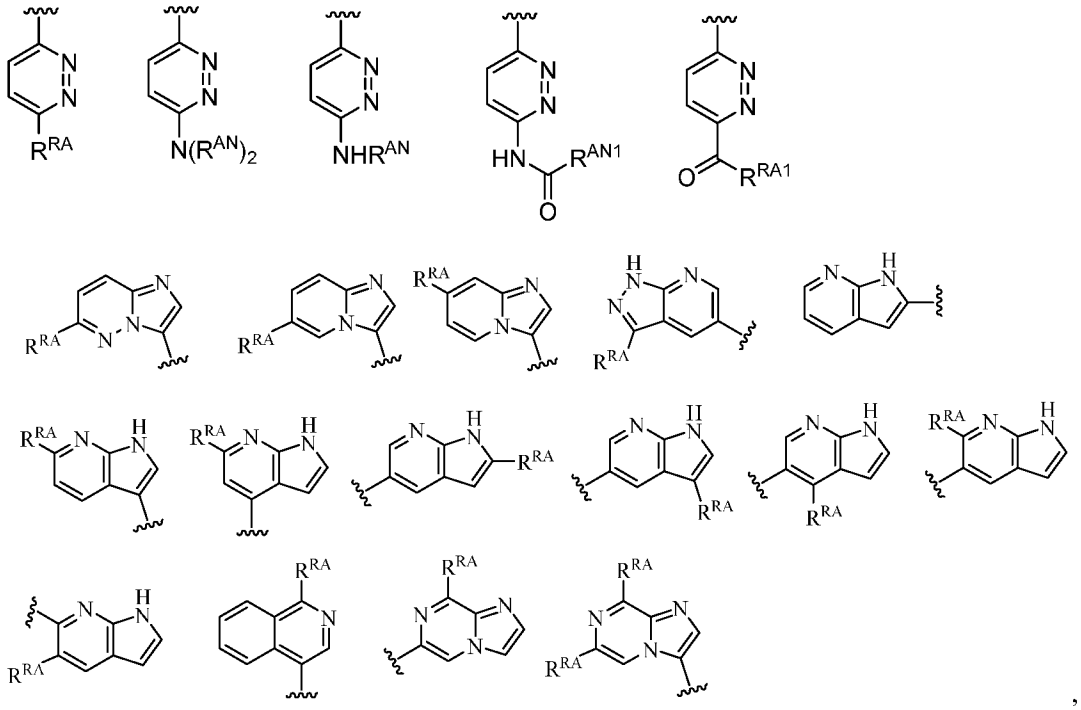


wherein R^{RA}, n1, n2, and n3 are as defined herein.

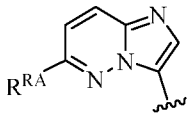
[000120] In certain embodiments, the compound of Formula (**I**) and (**I-a**) to (**I-o**), wherein Ring A is one of the following formulae:

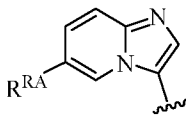


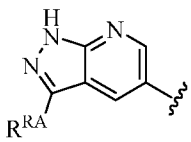




wherein R^{RA} and R^{AN1} are as defined herein.

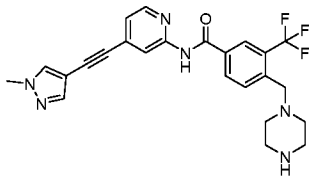
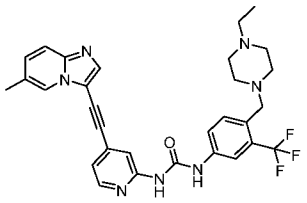
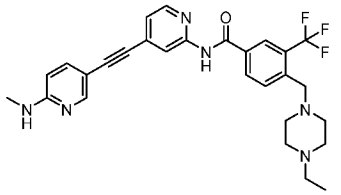
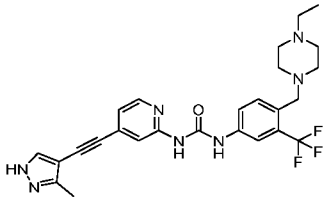
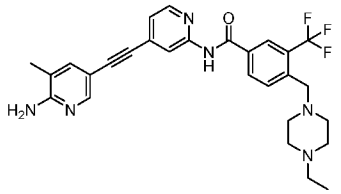
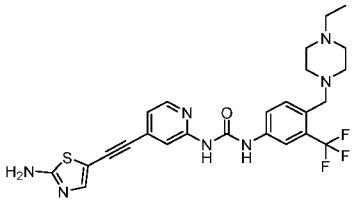
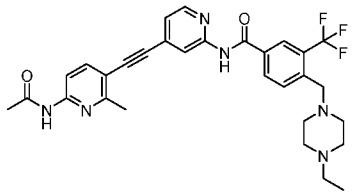
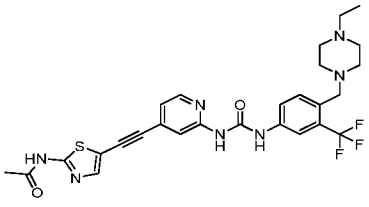
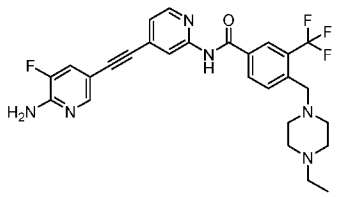
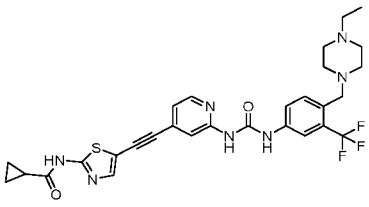
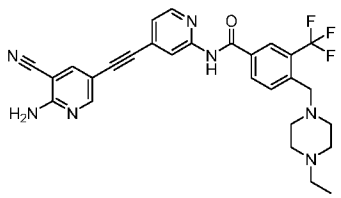
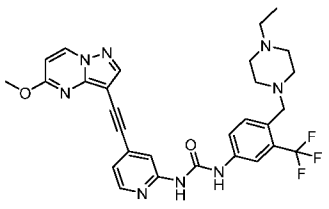
[000121] In certain embodiments, the compound of Formula (**I**) and (**I-a**) to (**I-o**), wherein Ring A is of the formula:  , wherein R^{RA} is as defined herein.

[000122] In certain embodiments, the compound of Formula (**I**) and (**I-a**) to (**I-o**), wherein Ring A is of the formula:  , wherein R^{RA} is as defined herein.

[000123] In certain embodiments, the compound of Formula (**I**) and (**I-a**) to (**I-o**), wherein Ring A is of the formula:  , wherein R^{RA} is as defined herein.

[000124] In certain embodiments, a provided compound is of one of the formulae in Table 1.

Table 1. Exemplified Compounds.

Structure	Structure
	
	
	
	
	
	

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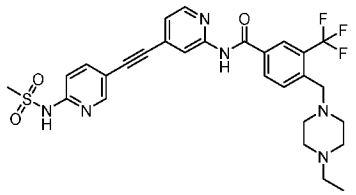	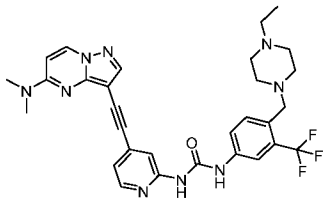
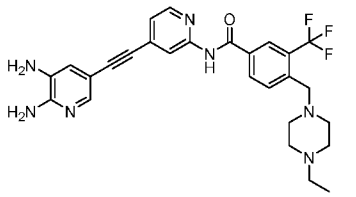	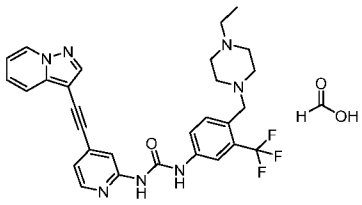
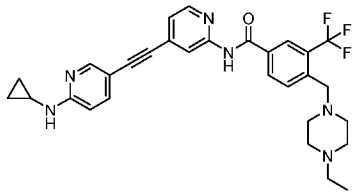	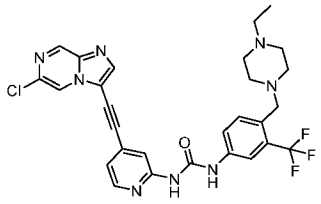
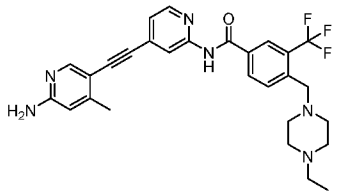	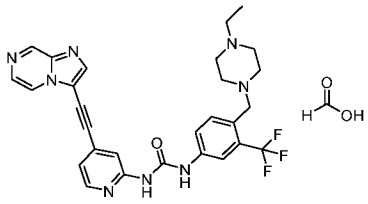
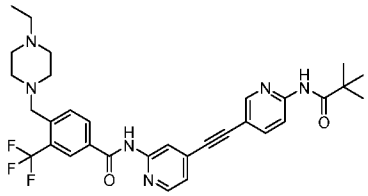	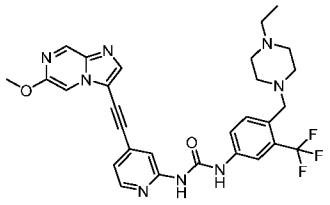
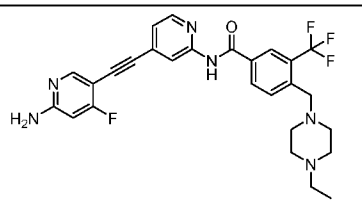	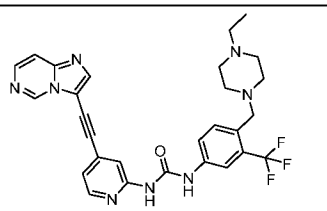

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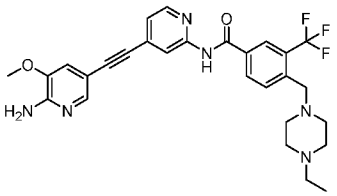	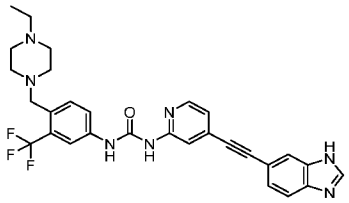
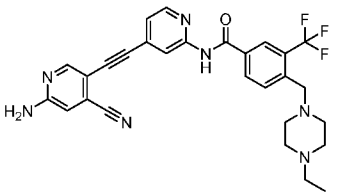	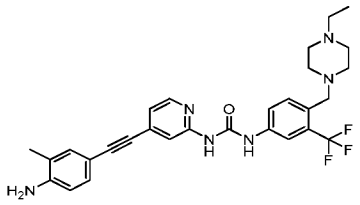
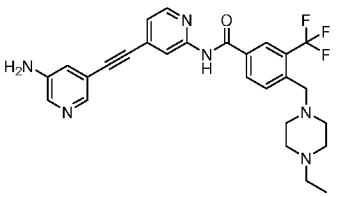	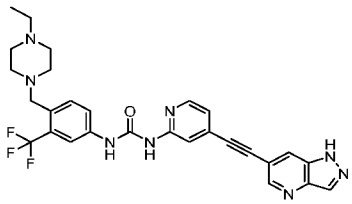
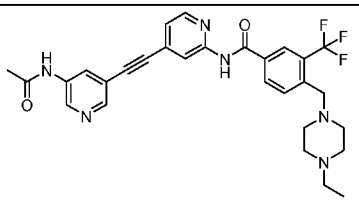	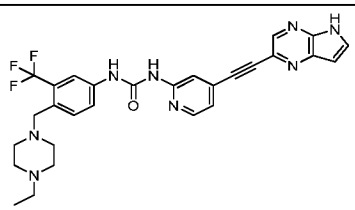
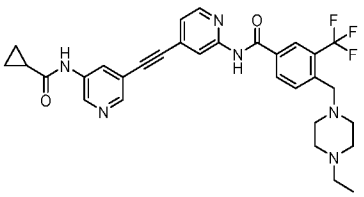	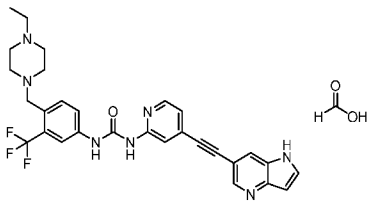
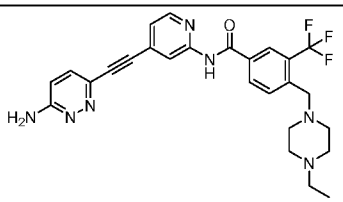	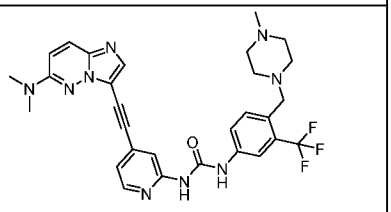

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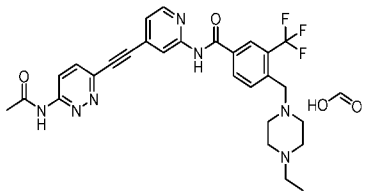	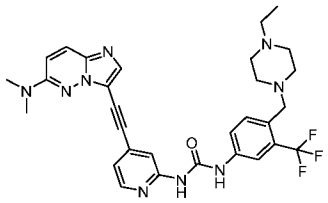
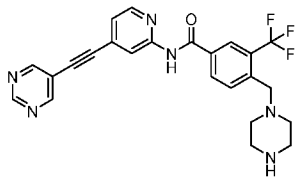	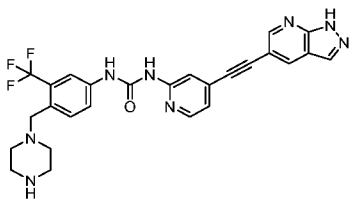
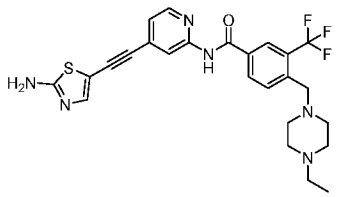	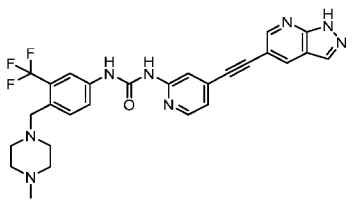
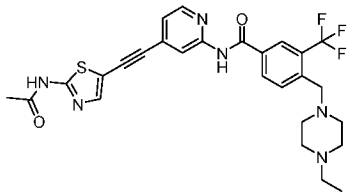	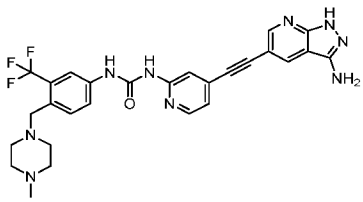
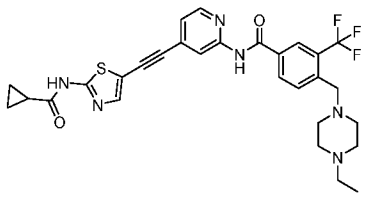	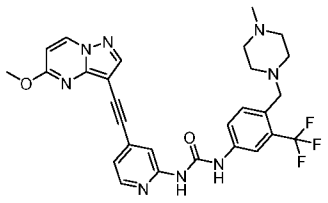
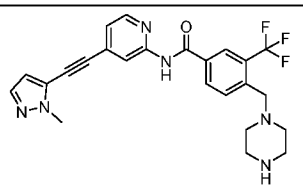	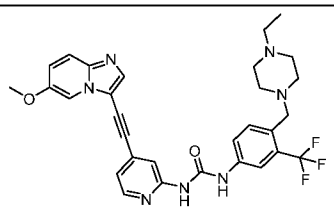

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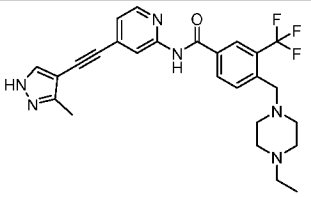	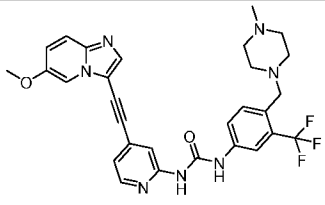
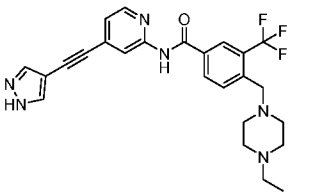	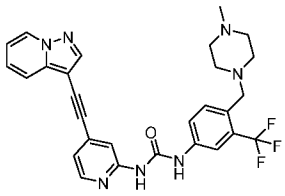
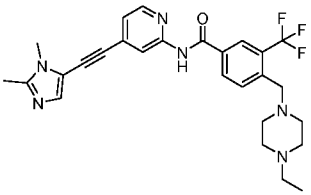	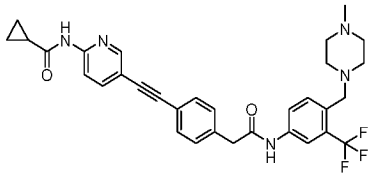
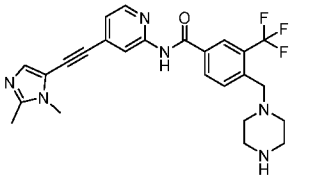	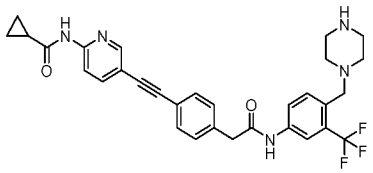
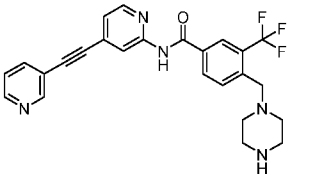	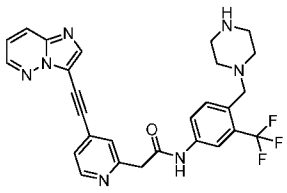
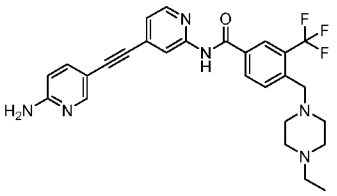	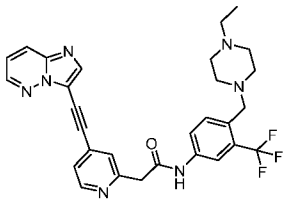

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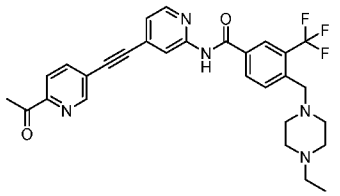	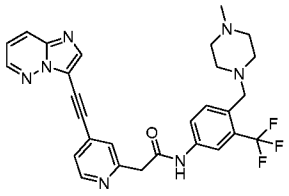
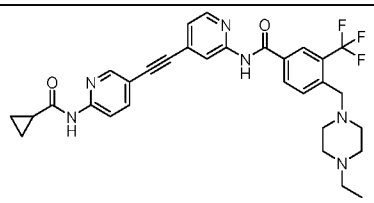	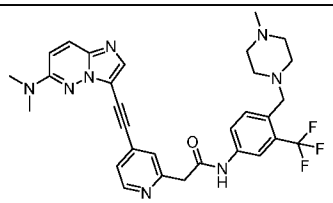
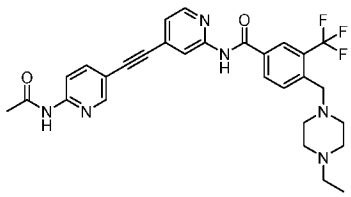	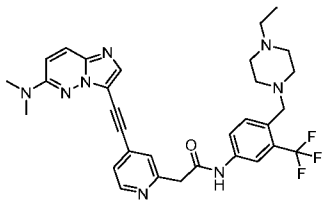
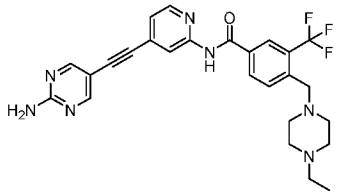	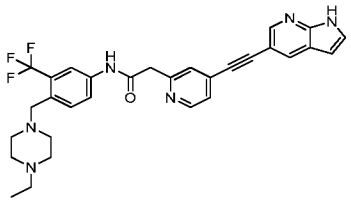
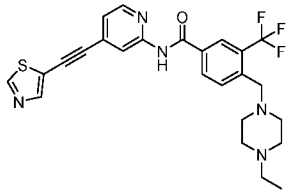	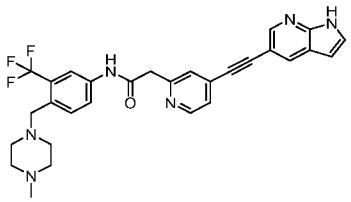
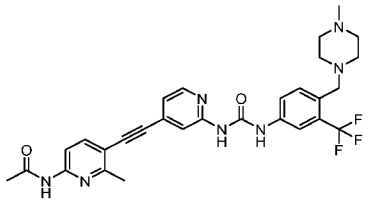	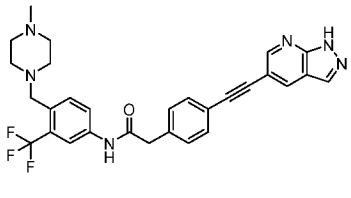

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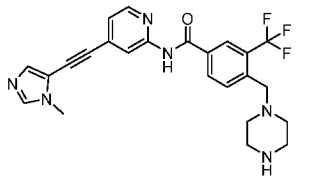	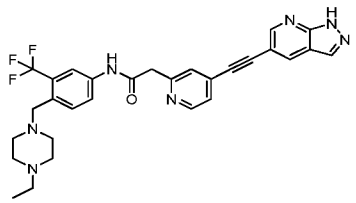
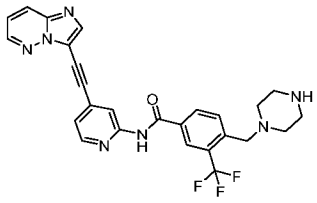	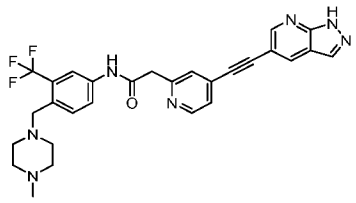
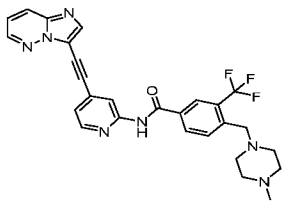	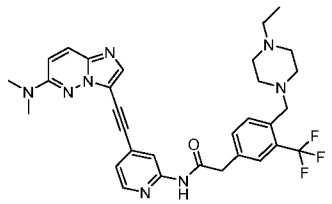
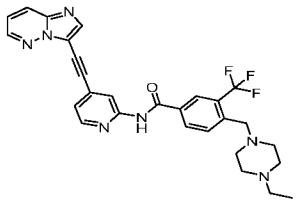	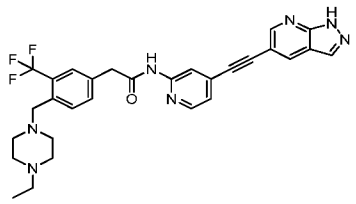
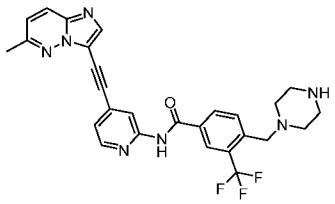	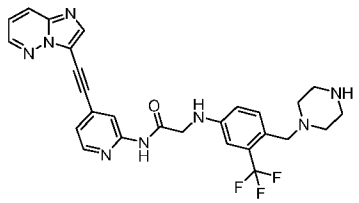
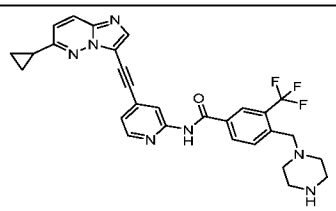	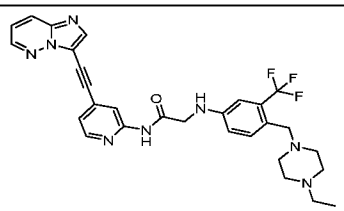

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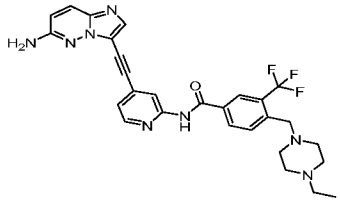	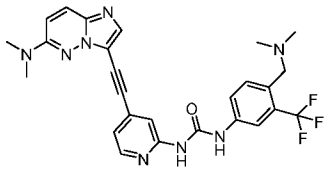
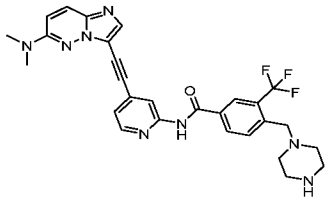	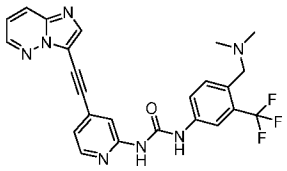
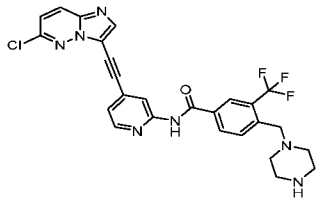	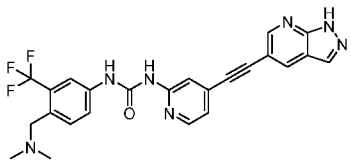
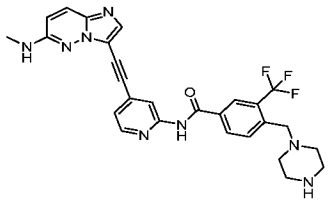	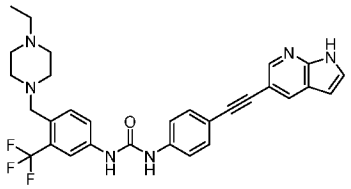
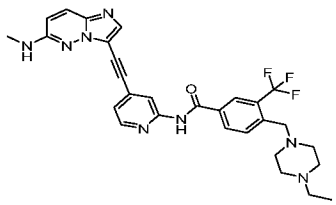	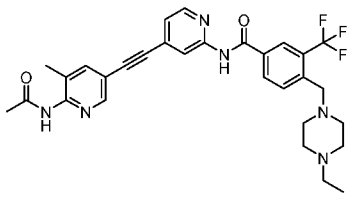
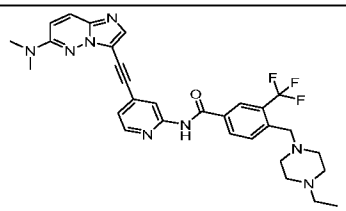	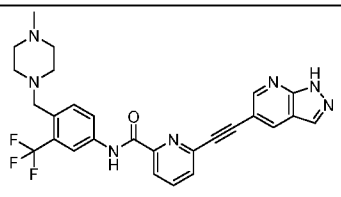

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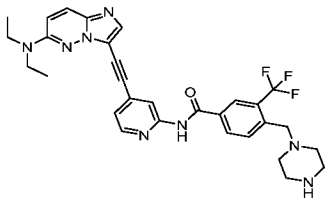	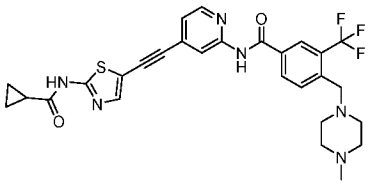
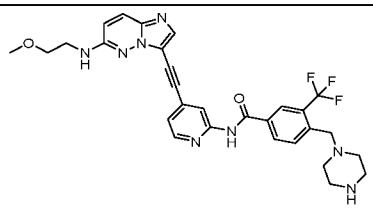	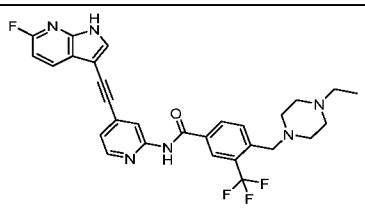
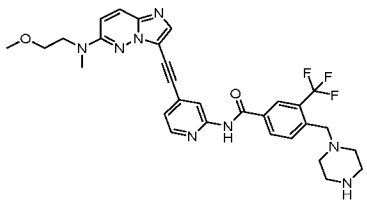	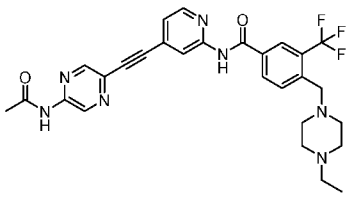
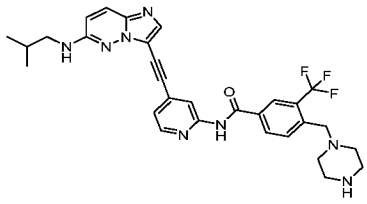	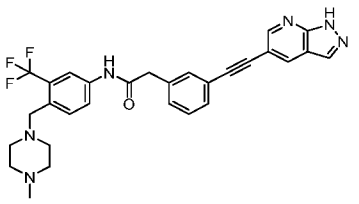
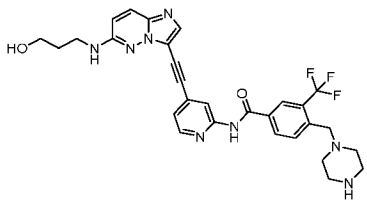	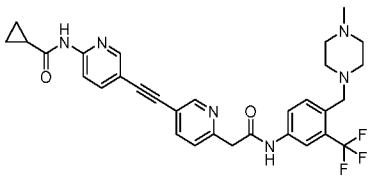
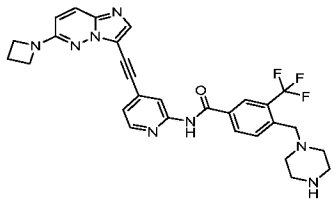	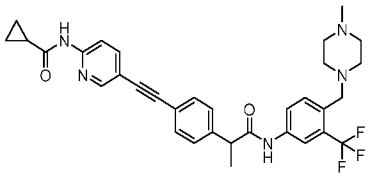

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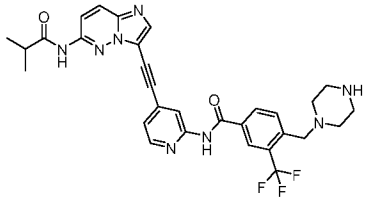	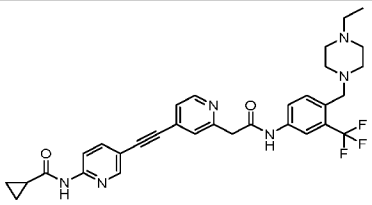
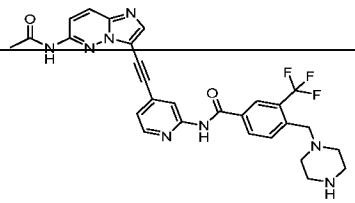	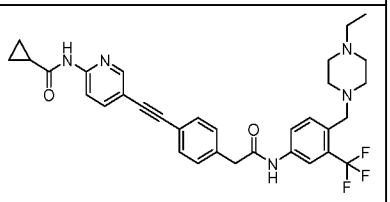
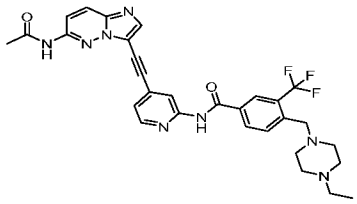	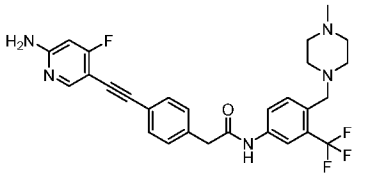
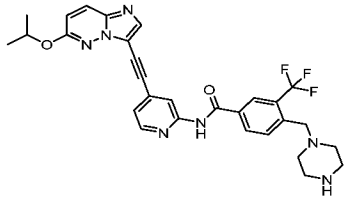	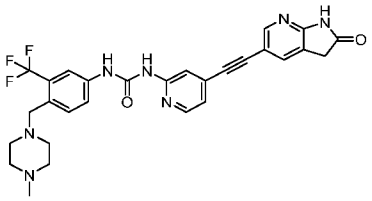
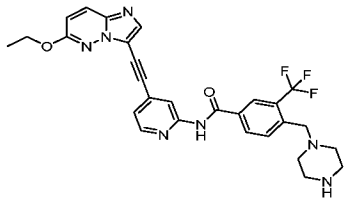	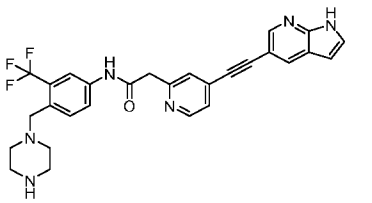
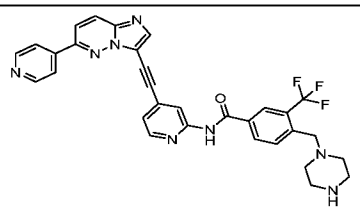	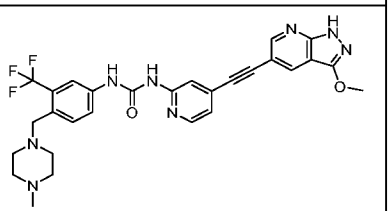

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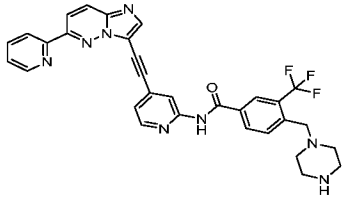	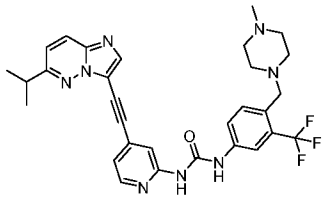
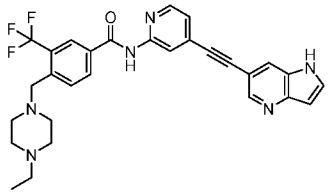	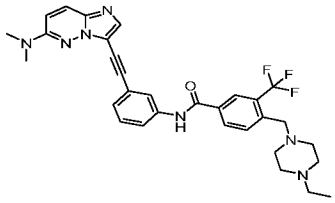
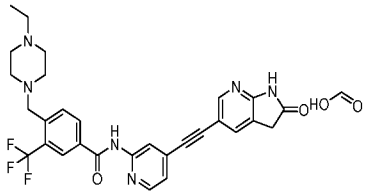	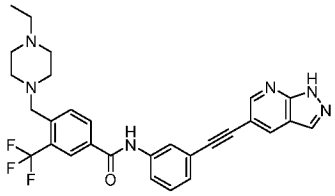
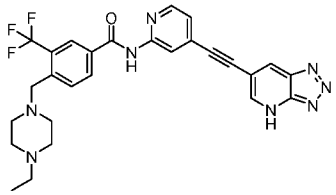	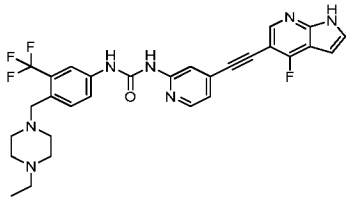
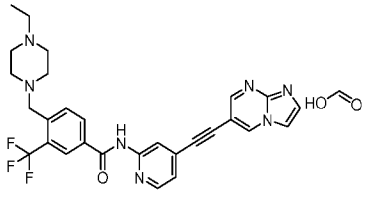	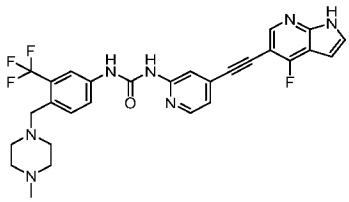
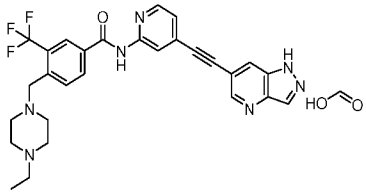	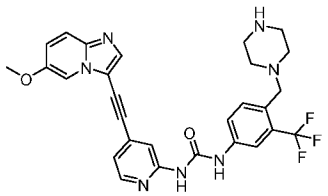

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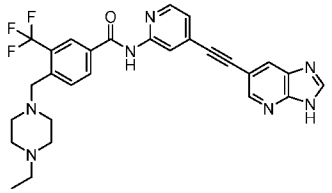	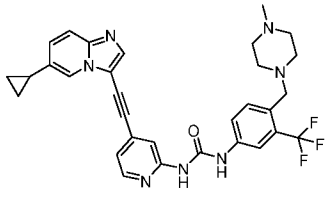
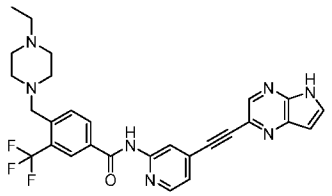	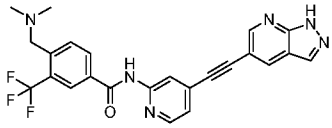
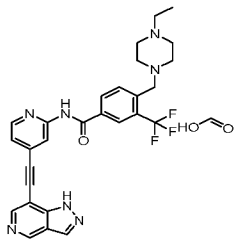	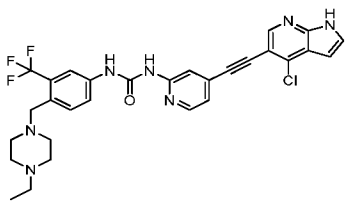
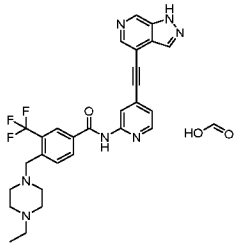	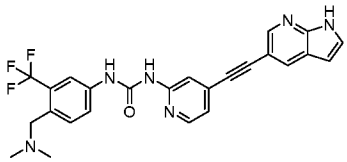
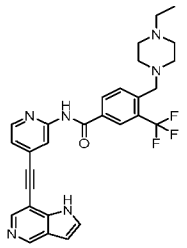	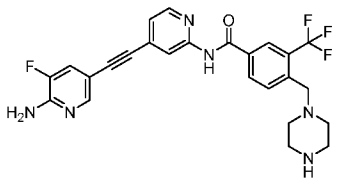
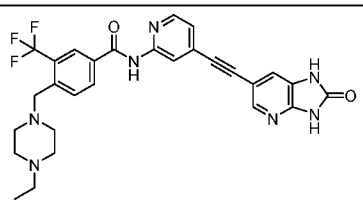	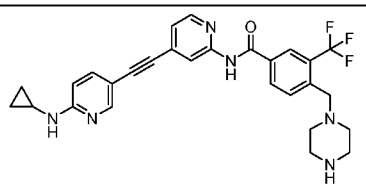

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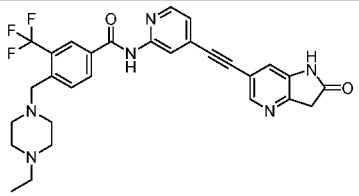	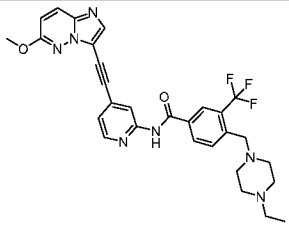
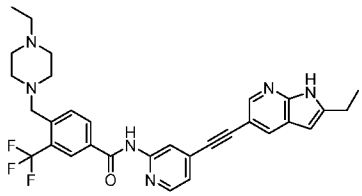	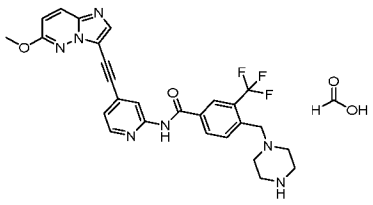
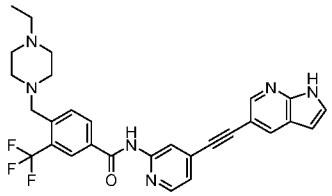	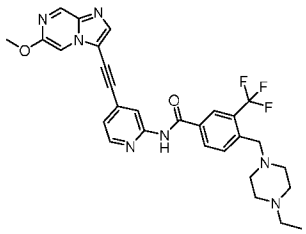
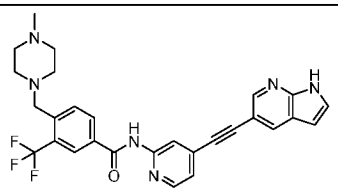	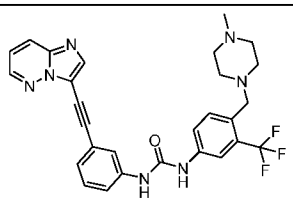
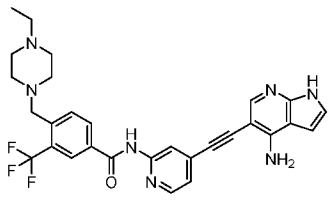	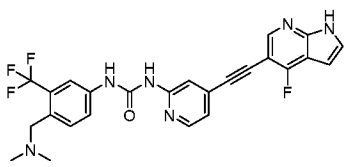
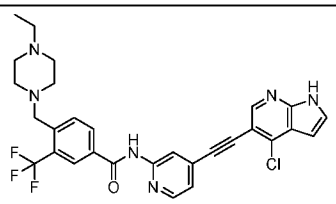	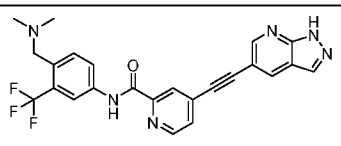

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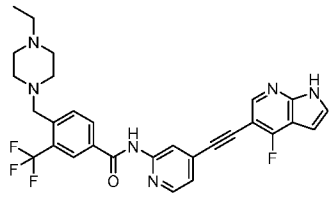	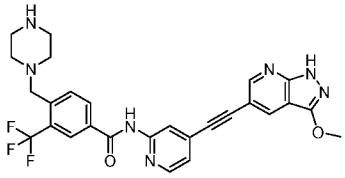
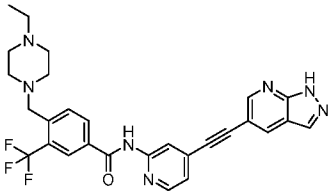	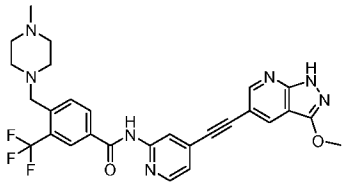
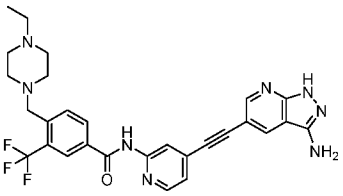	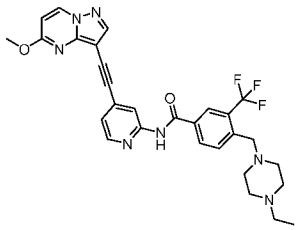
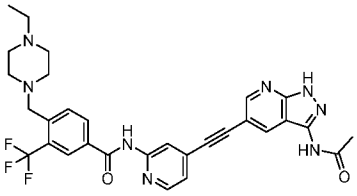	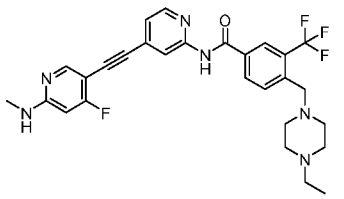
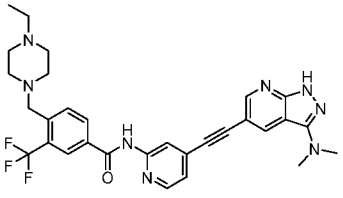	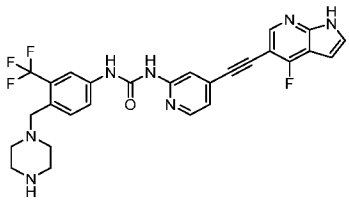
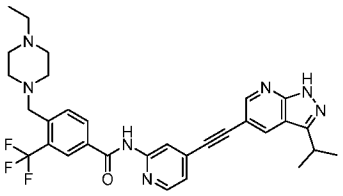	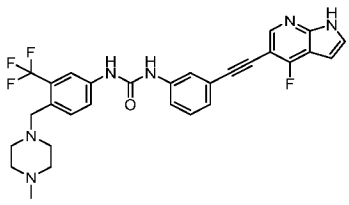

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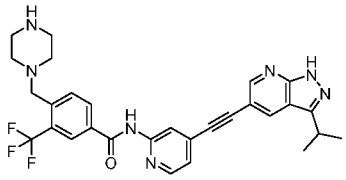	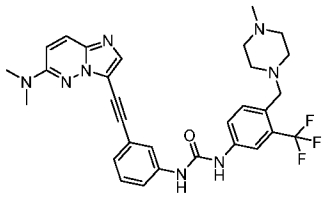
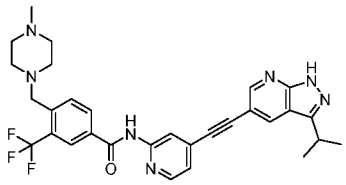	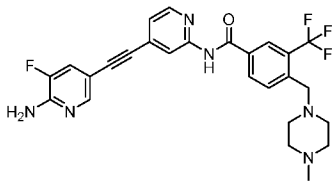
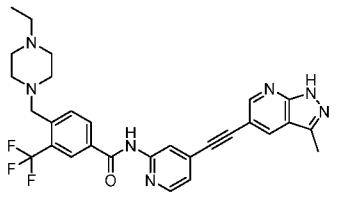	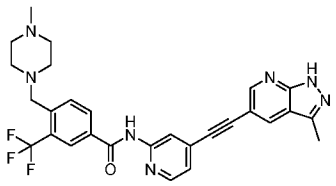
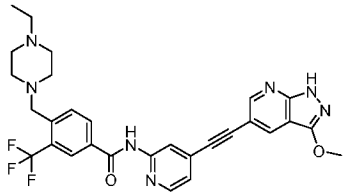	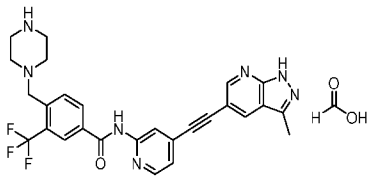
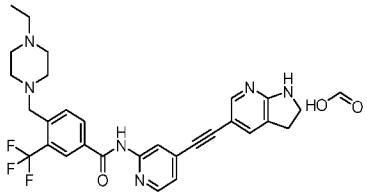	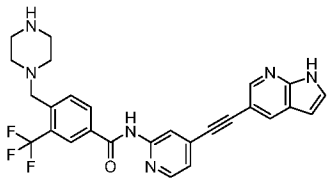
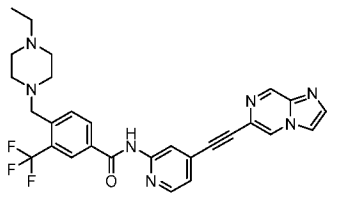	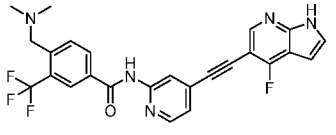

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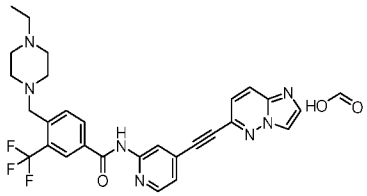	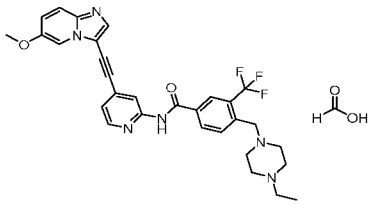
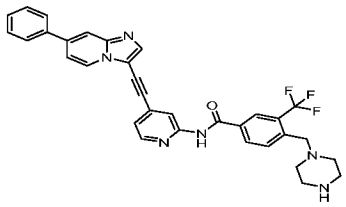	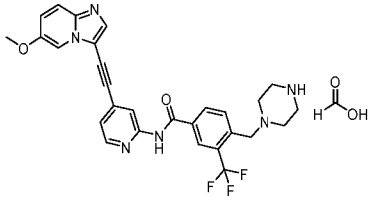
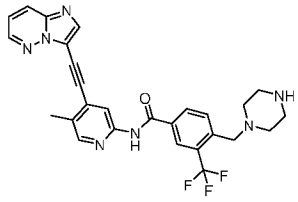	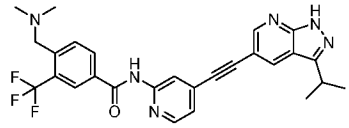
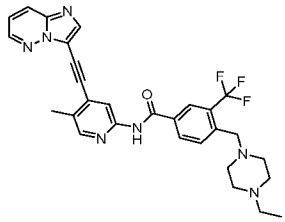	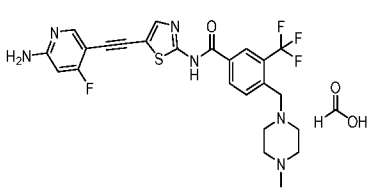
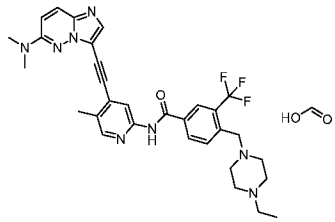	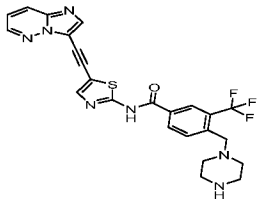
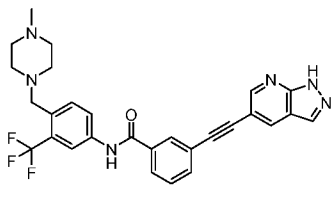	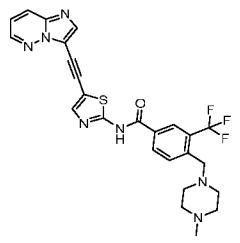

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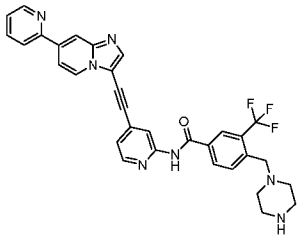	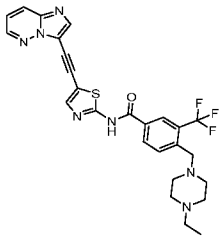
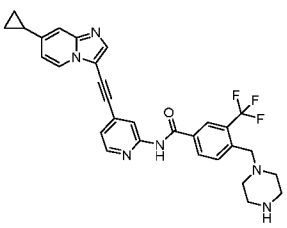	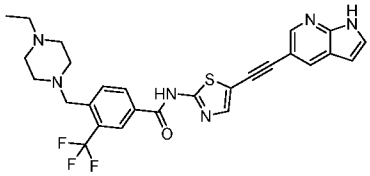
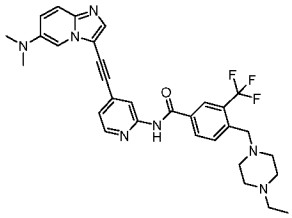	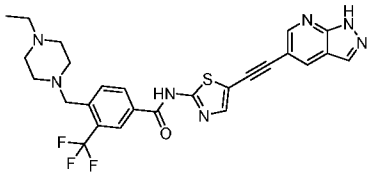
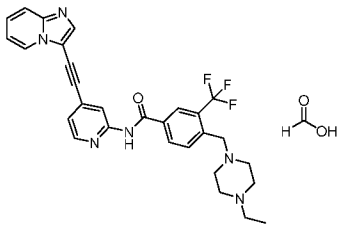	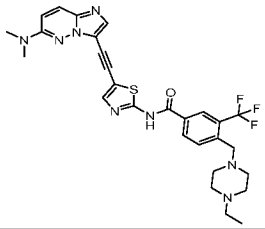
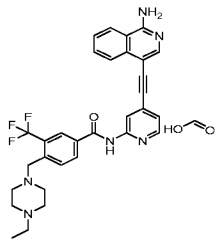	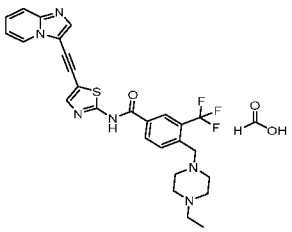
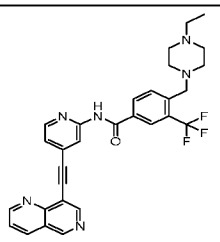	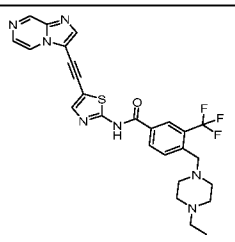

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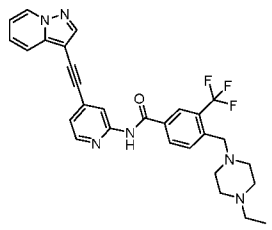	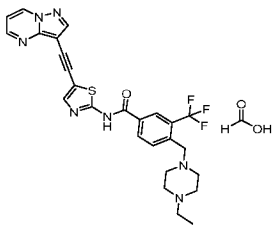
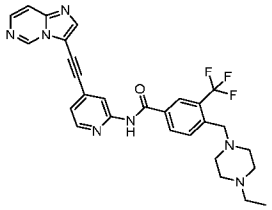	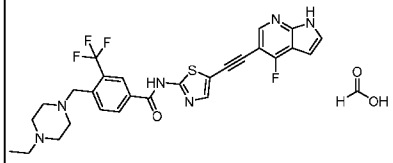
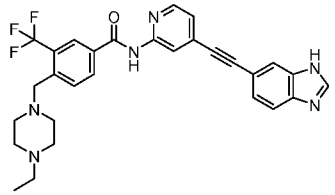	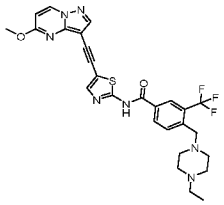
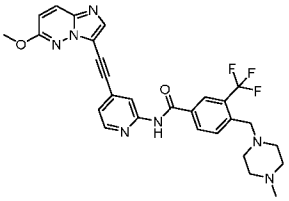	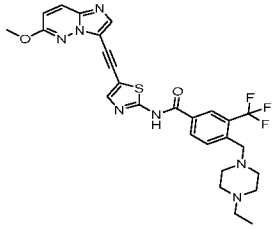
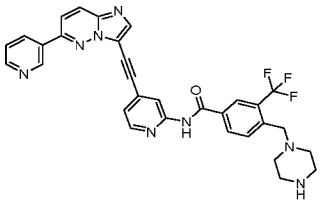	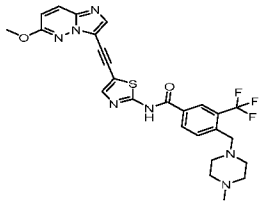
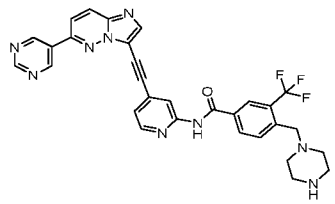	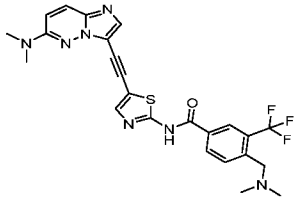

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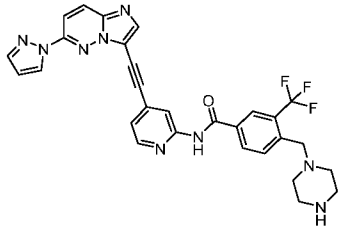	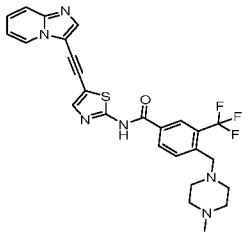
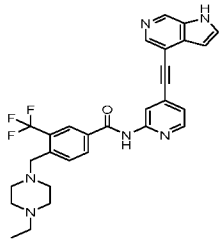	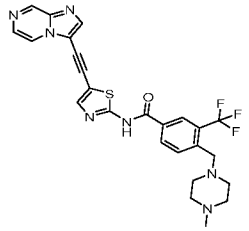
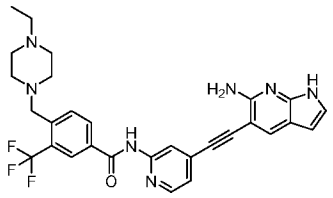	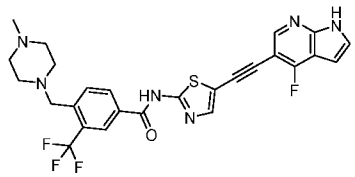
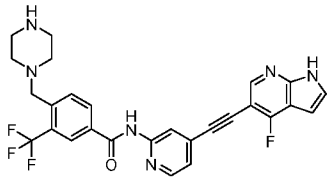	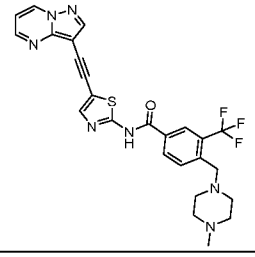
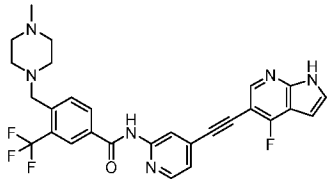	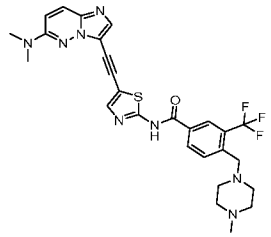
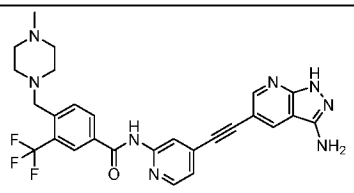	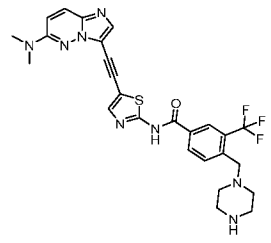

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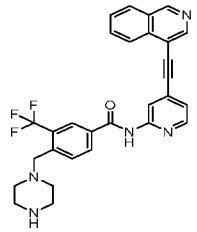	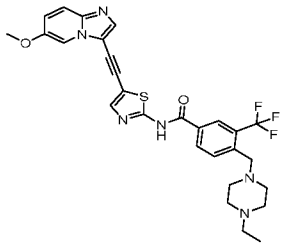
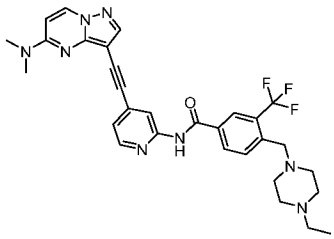	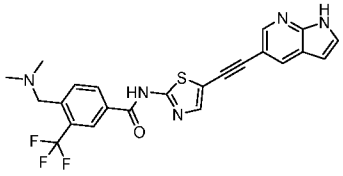
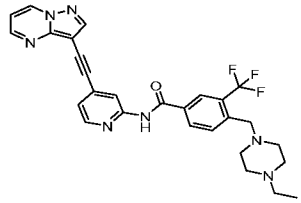	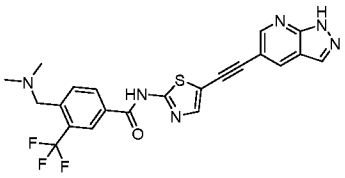
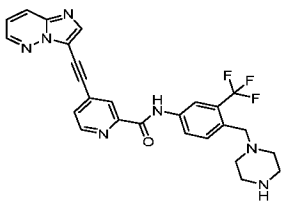	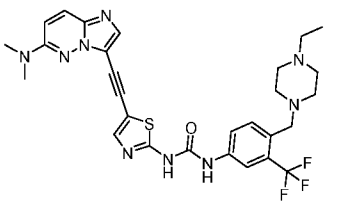
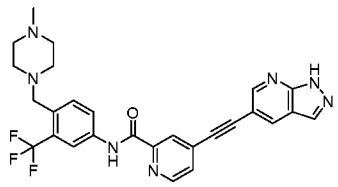	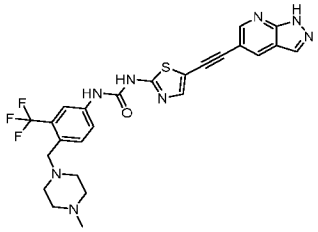
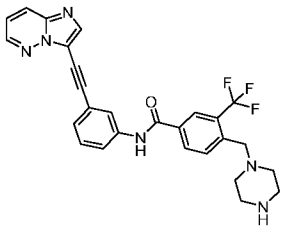	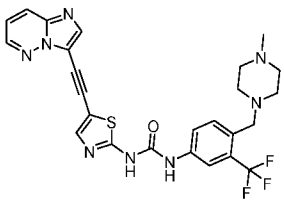

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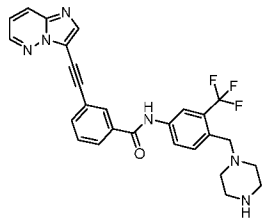	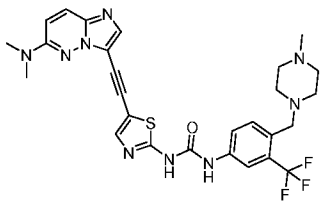
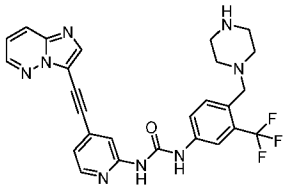	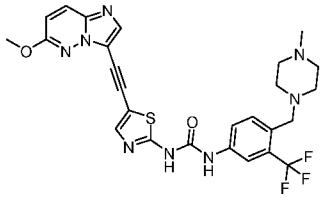
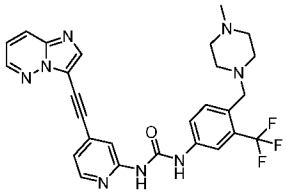	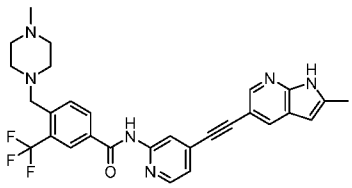
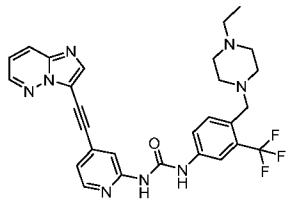	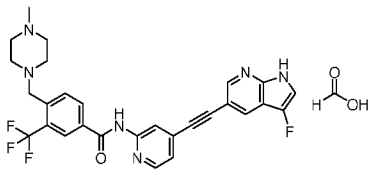
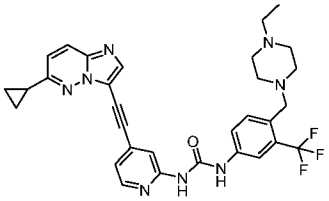	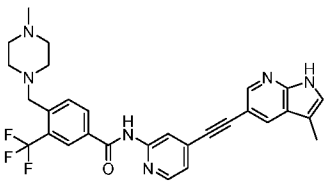
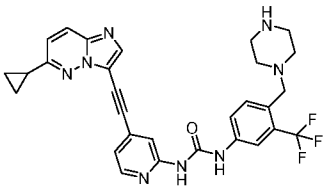	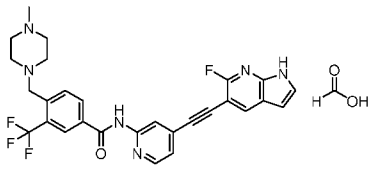

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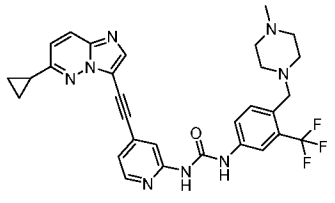	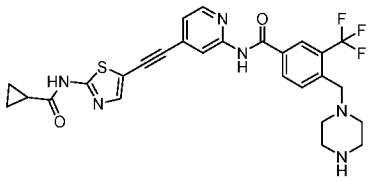
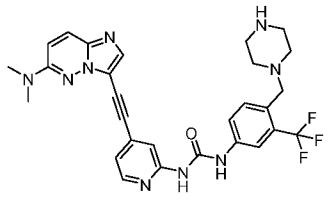	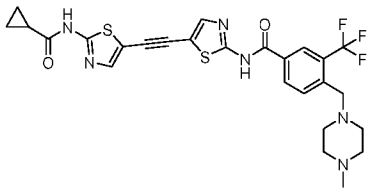
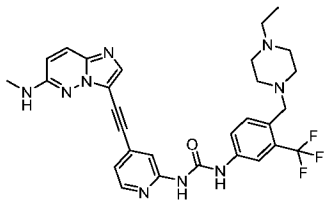	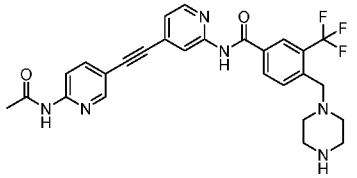
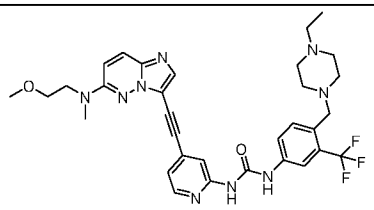	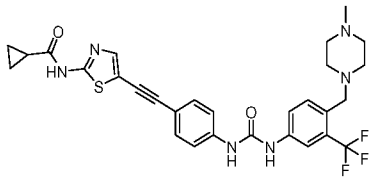
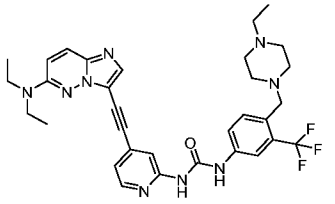	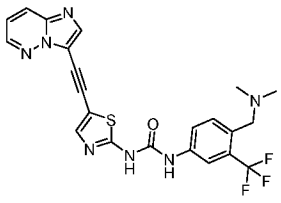
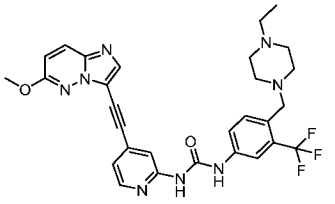	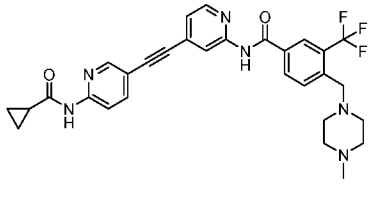

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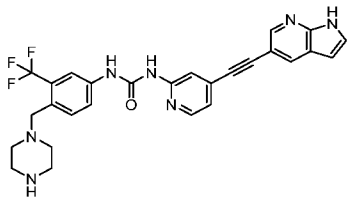	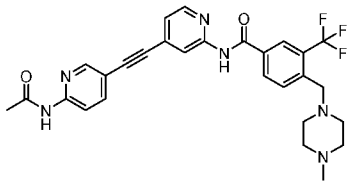
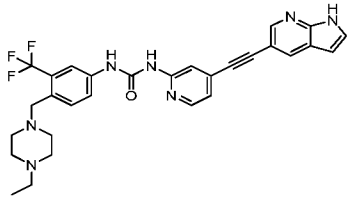	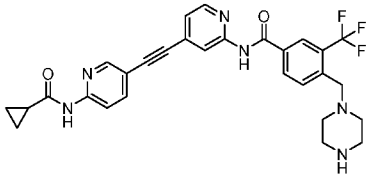
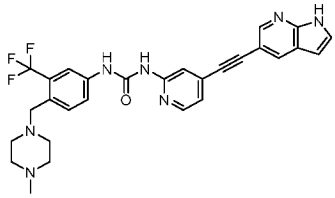	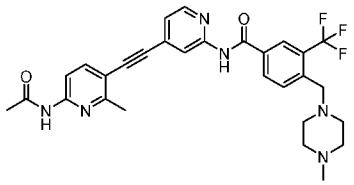
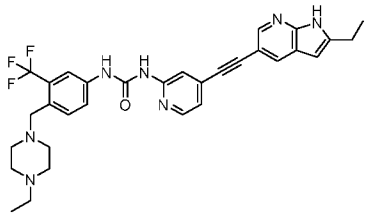	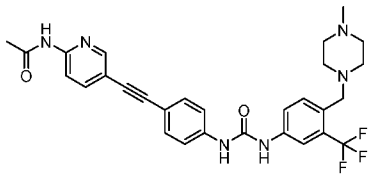
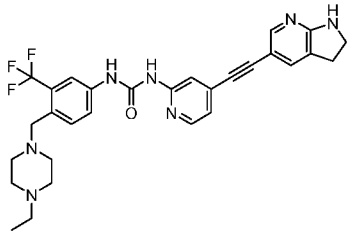	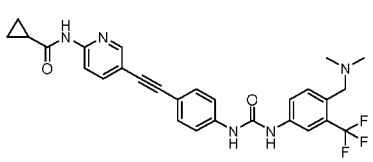
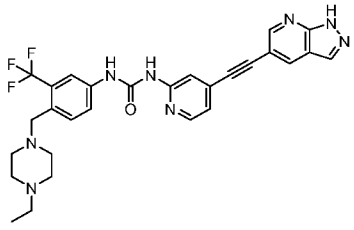	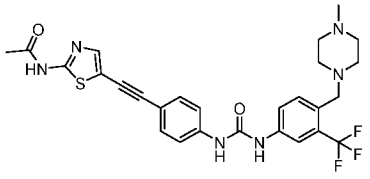

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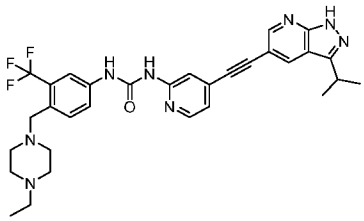	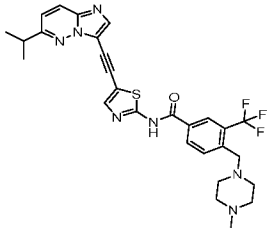
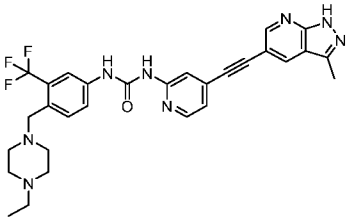	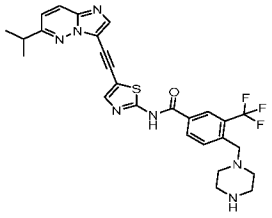
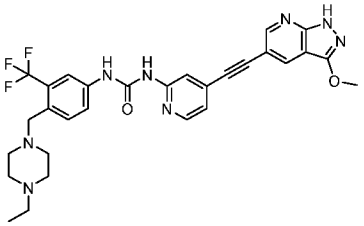	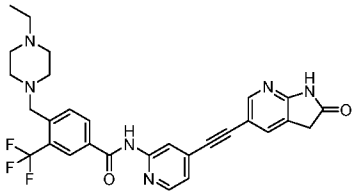
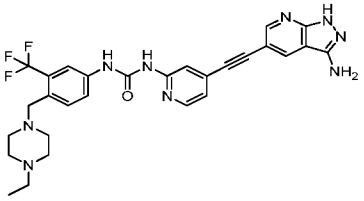	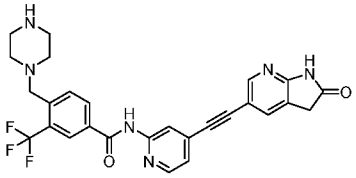
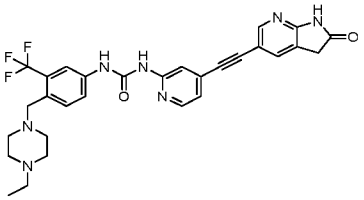	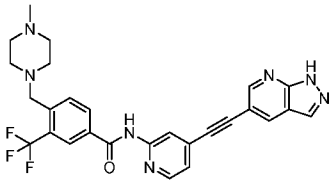
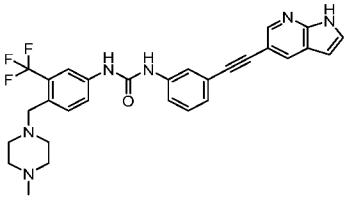	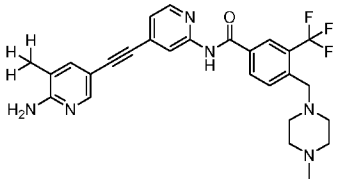

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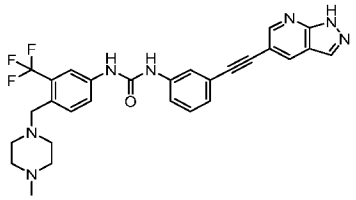	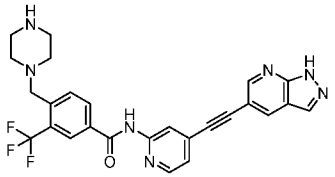
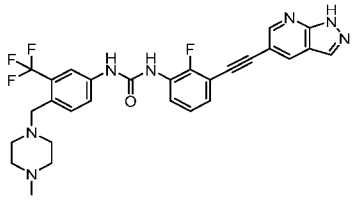	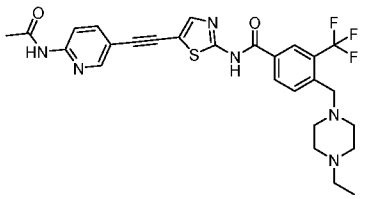
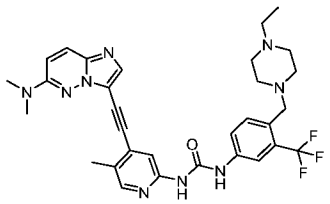	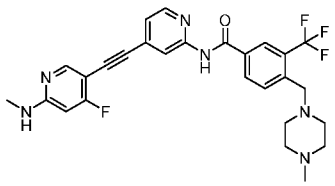
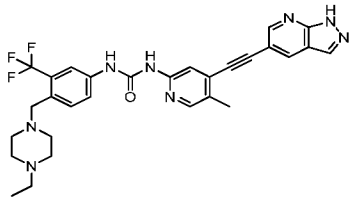	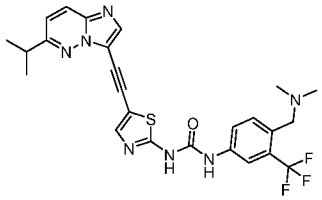
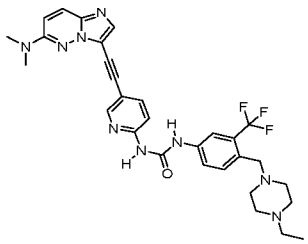	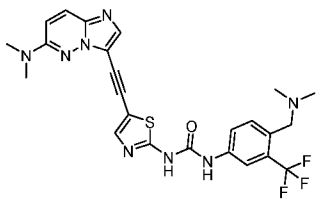
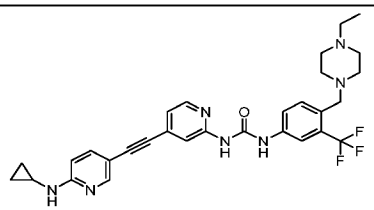	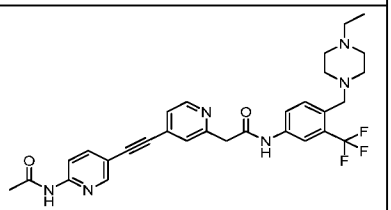

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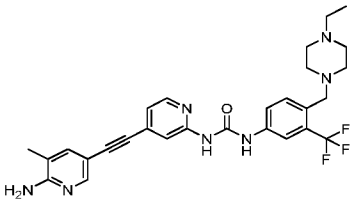	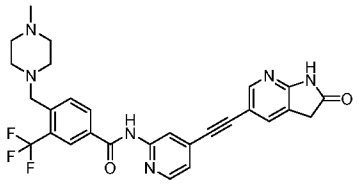
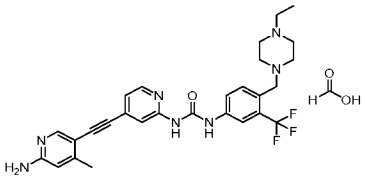	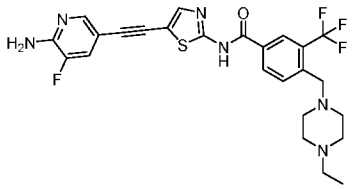
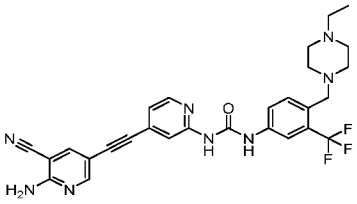	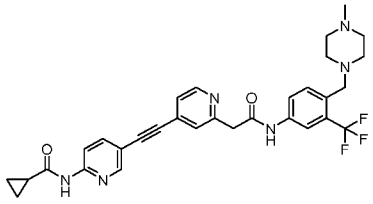
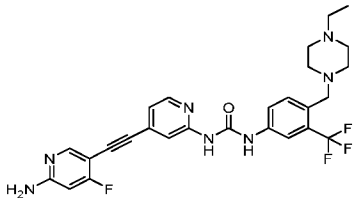	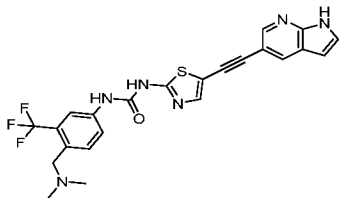
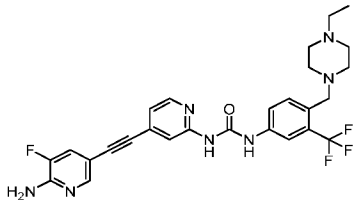	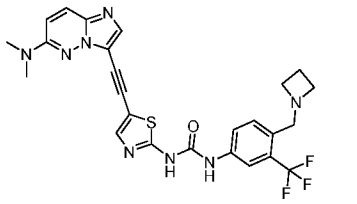
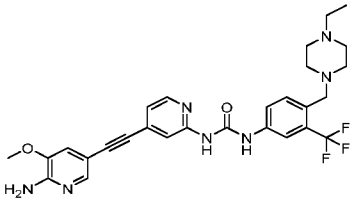	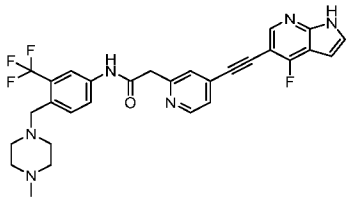

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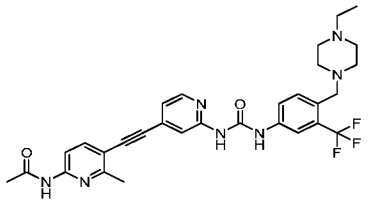	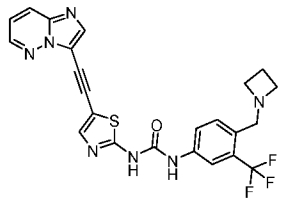
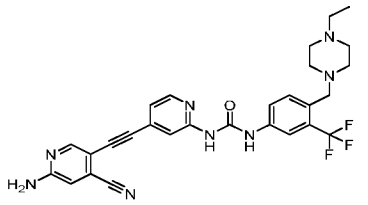	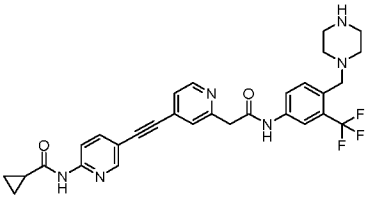
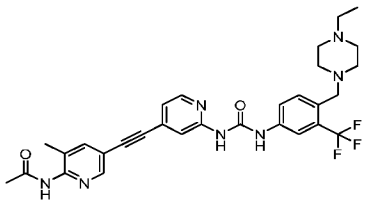	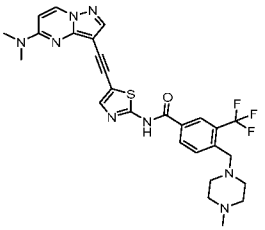
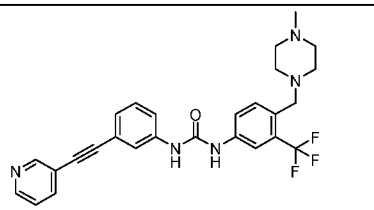	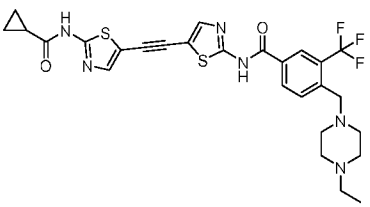
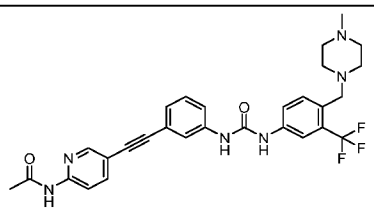	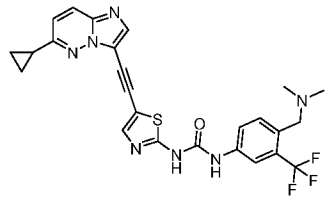
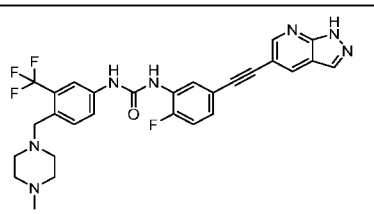	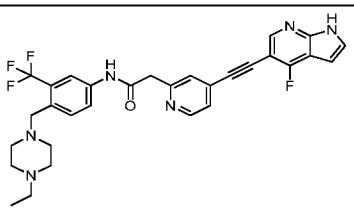

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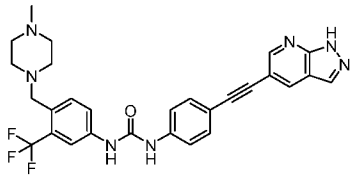
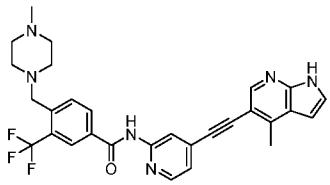
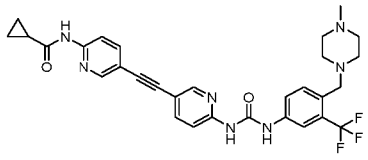
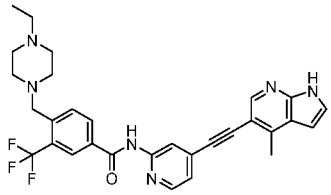
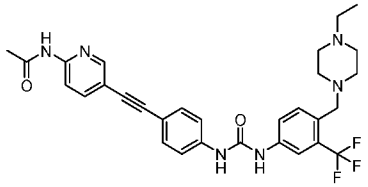
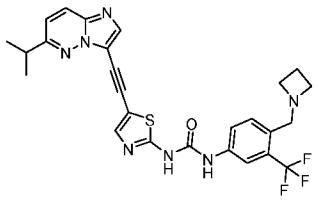
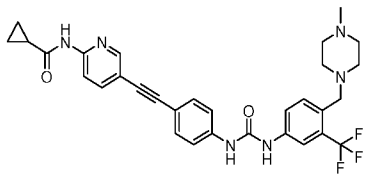
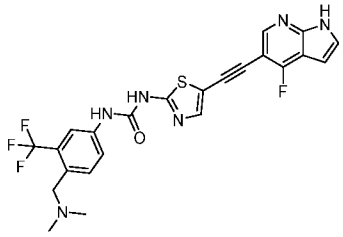
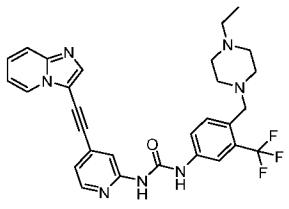
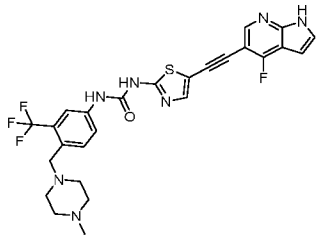
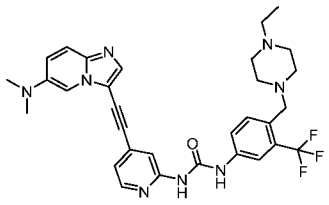
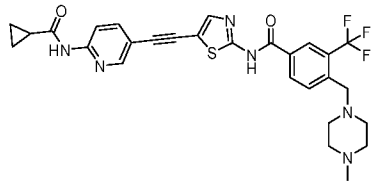
	
	
	
	
	
	

[000125] Enzymatic assays have shown that compounds of Formula (**I**) are inhibitors of Abl-wild type and Abl-T315I with IC_{50} values in the range of approximately 12 μM to lower than approximately 1 nM. In certain embodiments, the provided compounds inhibit Mnk1 and/or Mnk2 with IC_{50} values in the range of approximately 10 μM to lower than approximately 30 nM. In certain embodiments, the provided compounds inhibit Mnk1 and/or Mnk2 with the IC_{50} values in the range of approximately 8 μM to lower than approximately 50 nM. In certain embodiments, the provided compounds inhibit Mnk1 and/or Mnk2 with the IC_{50} values in the range of approximately 5 μM to lower than approximately 100 nM. In certain embodiments, the provided compounds inhibit Mnk1 and/or Mnk2 with the IC_{50} values in the range of approximately 1 μM to lower than approximately 500 nM.

[000126] In certain embodiments, the provided compounds have the IC_{50}s values varying from as low as approximately 7 nM to approximately 16 μM in the phosphorylation inhibition assay in Hela cell line. In certain embodimetns, the provided compounds have IC_{50}s varying from as low as approximately 50 nM to approximately 10 μM in the phosphorylation inhibition assay in Hela cell line. In certain embodimetns, the provided compounds have the IC_{50}s values varying from as low as approximately 100 nM to approximately 5 μM in the phosphorylation inhibition assay in Hela cell line. In certain embodimetns, the provided compounds have IC_{50}s varying from as low as approximately 500 nM to approximately 1 μM in the phosphorylation inhibition assay in Hela cell line.

Pharmaceutical Compositions

[000127] The present invention also provides pharmaceutical compositions comprising an effective amount of a compound described herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salt or prodrug) thereof, and, optionally, a pharmaceutically acceptable excipient.

[000128] Pharmaceutically acceptable excipients include any and all solvents, diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[000129] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of the present invention (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single– or multi–dose unit.

[000130] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one–half or one–third of such a dosage.

[000131] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[000132] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[000133] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, etc., and combinations thereof.

[000134] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl

cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, etc., and combinations thereof.

[000135] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.* CREMOPHOR), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether (Brij 30)), poly(vinyl–pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F-68, Poloxamer P188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof.

[000136] Exemplary binding agents include starch (*e.g.* cornstarch and starch paste), gelatin, sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl–pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, etc., and/or combinations thereof.

[000137] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[000138] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[000139] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[000140] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[000141] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[000142] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[000143] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[000144] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium

chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, etc., and combinations thereof.

[000145] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, etc., and combinations thereof.

[000146] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[000147] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3–butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and

mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as CREMOPHOR, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.

[000148] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[000149] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[000150] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[000151] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention with suitable non–irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[000152] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or

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

[000153] Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[000154] The active ingredients can be in micro–encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[000155] Dosage forms for topical and/or transdermal administration of a compound of this invention may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[000156] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquids to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[000157] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically–administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[000158] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low–boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[000159] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non–ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[000160] Pharmaceutical compositions of the invention formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[000161] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition of the invention. Another formulation suitable for intranasal administration is a coarse powder comprising the active

ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[000162] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[000163] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically–administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

[000164] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

Kits

[000165] Still further encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

[000166] Optionally, a single container may comprise one or more compartments for containing an inventive pharmaceutical composition or compound, and/or a pharmaceutically acceptable excipient for suspension or dilution. In some embodiments, a single container can be appropriate for modification such that the container may receive a physical modification so as to allow combination of compartments and/or components of individual compartments. For example, a foil or plastic bag may comprise two or more compartments separated by a perforated seal which can be broken so as to allow combination of contents of two individual compartments once the signal to break the seal is generated. A kit may thus comprise such multi-compartment containers providing an inventive pharmaceutical composition or compound and one or more pharmaceutically acceptable excipients.

[000167] Optionally, instructions for use are additionally provided in such kits of the invention. Such instructions may provide, generally, for example, instructions for dosage and administration. In other embodiments, instructions may further provide additional detail relating to specialized instructions for particular containers and/or systems for administration. Still further, instructions may provide specialized instructions for use in conjunction and/or in combination with an additional therapeutic agent.

[000168] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the

duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[000169] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra–arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[000170] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[000171] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[000172] In certain embodiments, the compounds of the invention may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[000173] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[000174] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. The compounds or compositions can be administered in combination with additional therapeutically active agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[000175] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[000176] Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In some embodiments, an additional therapeutically active agent is a kinase inhibitor. In some embodiments, an additional kinase inhibitor is Axitinib, Crizotinib, Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Nilotinib, Pazopanib, Ruxolitinib, Sorafenib, Sunitinib, Vandetanib.

[000177] Exemplary additional therapeutically active agents include, but are not limited to, biologics such as naturla of synthetic growth hormone, natural or synthetic human insulin and its analogues, monoclonal antibodies, receptor constructs, vaccines, antibodies, blood, organs or tissues.

[000178] Compounds and compositions described herein are generally useful for the inhibition of one or more kinases. A partial, non-limiting, list of these kinases include: receptor tyrosine kinases such as platelet-derived growth factor receptor kinase (PDGF-R), the nerve growth factor receptor, trkB, Met, and the fibroblast growth factor receptor, FGFR3; non-receptor tyrosine kinases such Abl and the fusion kinase BCR-Abl, Lck, Csk, Fes, Bmx and c-src; and serine/threonine kinases such as b-RAF, c-RAF, sgk, MAP kinases (e.g., MNK1, MNK2, MKK4, MKK6, etc.) and SAPK2α, SAPK2β and SAPK3.

In certain embodiments, compounds and compositions described herein are generally useful for the inhibition of MNK1 and/or MNK2. In certain embodiments, compounds and compositions described herein are generally useful for the inhibition of Abelson (Abl) tyrosine kinase. In certain embodiments, the Abelson (Abl) tyrosine kinase is wild type Abl tyrosine kinase. In certain embodiments, the Abelson (Abl) tyrosine kinase is a mutant Abl tyrosine kinase. In certain embodiments, the Abelson (Abl) tyrosine kinase is a mutant Abl tyrosine kinase having a mutation selected from the group consisting of M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315I, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K and F486S. In certain embodiments, the Abelson (Abl) tyrosine kinase is a mutant Abl tyrosine kinase having the mutation T315I. In certain embodiments, the Abelson (Abl) tyrosine kinase is a mutant Abl tyrosine kinase having the mutation E255K.

[000179] In some embodiments, methods of treating kinase-related disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof), to a subject in need of treatment.

[000180] In some embodiments, methods of treating MNK1- and/or MNK2-related disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof), to a subject in need of treatment. In some embodiments, methods of treating Abl-related disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically

acceptable form thereof), to a subject in need of treatment. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the subject is suffering from a MNK1-related disorder. In certain embodiments, the subject is susceptible to a MNK1-mediated disorder. In certain embodiments, the subject is suffering from a MNK2-related disorder. In certain embodiments, the subject is susceptible to a MNK2-mediated disorder. Exemplary MNK-related disorders include, but are not limited to, metabolic diseases such as obesity, as well as related disorders such as eating disorder, cachexia, diabetes mellitus, hypertension, coronary heart disease, hypercholesterolemia, dyslipidemia, osteoarthritis, gallstones, and sleep apnea, neurodegenerative disorders such as autism, Alzheimer's disease, and cancer such as breast, protate, hematological malignancies (e.g., CML, AML), head and neck, colon, bladder, prostatic adenocarcinoma, lung, cervical, and lymphomas. In certain embodiments, the subject is suffering from an Abl-related disorder. In certain embodiments, the subject is susceptible to a Abl-mediated disorder. In certain embodiments, the subject is suffering from a Abl-related disorder. In certain embodiments, the subject is susceptible to a Abl-mediated disorder. Exemplary Abl-mediated disorders include, but are not limited to, hematopoietic tumor, mammary cancer, uterine body cancer, uterine cervix cancer, prostatic cancer, bladder cancer, renal cancer, gastric cancer, esophageal cancer, hepatic cancer, biliary tract cancer, colon cancer, rectal cancer, pancreatic cancer, lung cancer, oral cavity and pharynx cancer, osteosarcoma, melanoma or brain neoplasm.

[000181] In some embodiments, methods of treating kinase-related disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)) in combination with another agent, to a subject in need of treatment. In certain embodiments, the agent is a small molecule or biologic. In certain embodiments, the agent is a kinase inhibitor. In certain embodiments, the agent is a chemotherapeutic agent. In certain embodiments, the agent is a monoclonal antibody. In certain embodiments, the agent is an siRNA.

[000182] As used herein, the term "kinase-related disorder" means any disease, disorder, or other pathological condition in which a kinase (*e.g.,* MNK1 and/or MNK2 and/or Abl) is known to play a role. In some embodiments, the present disclosure relates to treating or lessening the severity of one or more diseases in which MNK1 and/or MNK2 is known to

play a role. In some embodiments, the present disclosure relates to treating or lessening the severity of one or more diseases in which Abl tyrosine kinase is known to play a role.

[000183] In certain embodiments, the kinase-related condition is selected from the group consisting of proliferative diseases, neurodegenerative diseases, autoimmune diseases, and inflammatory diseases.

[000184] In certain embodiments, a provided compound is useful for treating a proliferative disease, *e.g.*, cancer. In certain embodiments, a provided compound is useful for treating a solid tumor. In certain embodiments, a provided compound is useful for treating a hematological malignancy. Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarinoma); Ewing sarcoma; eye cancer (*e.g.*, intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non–Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B–cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal

marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.,* Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.,* cutaneous T-cell lymphoma (CTCL) (*e.g.,* mycosis fungiodes, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.,* nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.,* hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.,* bronchogenic carcinoma, small cell lung cancer (SCLC), non–small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.,* systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) *e.g.,* polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.,* neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.,* gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*,bone cancer); ovarian cancer (*e.g.,* cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.,* pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.,* Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.,* prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer [*e.g.,* squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)]; small bowel cancer (*e.g.,* appendix cancer); soft tissue sarcoma (*e.g.,* malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma;

testicular cancer (*e.g.,* seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.,* papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.,* Paget's disease of the vulva). In certain embodiments, a provided compound is useful for treating hematopoietic tumor, breast cancer, colon cancer, lung cancer, lymphomas, mammary cancer, uterine body cancer, cervix cancer, prostatic cancer, bladder cancer, renal cancer, gastric cancer, esophageal cancer, hepatic cancer, biliary tract cancer, rectal cancer, pancreatic cancer, lung cancer, gliomas, ovarian cancer, oral cavity and pharynx cancer, osteosarcoma, melanoma or brain neoplasm.

[000185] In certain embodiments, a provided compound is useful for treating a neurodegenerative disease. Exemplary neurodegenerative diseases include, but are not limited to, Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, corticobasal degeneration, frontotemporal lobar degeneration, Pick's disease, Parkinson's disease, Lewy body disease, and amyotropic lateral sclerosis (ALS).

[000186] In certain embodiments, a provided compound is useful for treating a neurodevelopmental disorder. As used herein, the term "neurodevelopmental disorder" refers to impairments of the growth and development of the brain or central nervous system. A neurodevelopmental disorder also refers to a disorder of brain function that affects emotion, learning ability, self-control and memory and that unfolds as the individual grows. Disorders considered neurodevelopmental in origin, or that have neurodevelopmental consequences when they occur in infancy and childhood include, but are not limited to autism and autism spectrum disorders (e.*g.* Asperger syndrome or Mendelsohnn's Syndrome), fetal alcohol spectrum disorder, motor disorders (*e.g.* developmental coordination disorder, stereotypic movement disorder and the tic disorders including Tourette syndrome), traumatic brain injury (*e.g.* congenital injuries), genetic disorders (e.g. fragile-X syndrome, Neurofibromatosis, Tuberous Sclerosis, Rett's Syndrome, Timothy Syndrome, PTEN mutations, or Tourettes), Down syndrome, communication, speech and language disorders, eating disorders (e.g., anorexia nervosa and bulimia nervosa), adjustment disorder, attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, delirium, dementia, multi-infarct dementia, learning and memory disorders (e.g., amnesia and age-related memory loss). In certain embodiments, the neurodevelopmental disorder is autism.

[000187] In certain embodiments, a provided compound is useful for treating an autoimmune disease. Exemplary autoimmune diseases include, but are not limited to, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, degenerative joint diseases such as

osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic arthritis, juvenile arthritis, asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), Still's disease, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Grave's disease, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, antiphospholipid antibody syndrome, autoimmune hepatitis, celiac disease, Goodpasture's syndrome, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, warm autoimmune hemolytic anemia, alopecia universalis, chronic fatigue, dysautonomia, neuromyotonia, vulvodynia and disorders ameliorated by a gastroprokinetic agent (*e.g.*, ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)).

[000188] In certain embodiments, a provided compound is useful for treating an inflammatory disease. The term "inflammatory disease" refers to those conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent. Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[000189] Exemplary inflammatory diseases include, but are not limited to, inflammation associated with acne, asthma, arteritis (*e.g.*, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis, and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, dry eye syndrome, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis), inflammatory bowel syndrome (IBS), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis. In certain embodiments, the inflammatory disorder is selected from arthritis (*e.g.*, rheumatoid arthritis), inflammatory bowel disease, inflammatory bowel syndrome, asthma, psoriasis, endometriosis, interstitial cystitis, prostatistis, appendicitis, Blau syndrome, blepharitis, bronchiolitis, cervicitis, cholangitis, cholecystitis, chronic recurrent multifocal osteomyelitis (CRMO), cryopyrin associated periodic syndrome (CAPS), dacryoadenitis, dermatomyositis, dry eye syndrome, encephalitis, endocarditis, endometritis, enterocolitis, epicondylitis, epididymitis, familial

cold-induced autoinflammatory syndrome, familial Mediterranean fever (FMF), fasciitis, fibrositis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, mevalonate kinase deficiency (MKD), Muckle-Well syndrome, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, inflammatory osteolysis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, pulmonary fibrosis, pyelonephritis, pyoderma gangrenosum and acne syndrome (PAPA), pyogenic sterile arthritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, TNF receptor associated periodic syndrome (TRAPS), tonsillitis, undifferentiated arthropathy, uveitis, vaginitis and vulvitis. In certain embodiments, the inflammatory condition is an acute inflammatory condition (*e.g.*, inflammation resulting from infection). In certain embodiments, the inflammatory condition is a chronic inflammatory condition (*e.g.*, conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds may also be useful in treating inflammation associated with cancer.

[000190] In certain embodiments, a provided compound is useful for treating or lessening the severity of hyperproliferative diseases including, but not limited to, psoriasis or smooth muscle cell proliferation including vascular proliferative disorders, atherosclerosis, and restenosis.

[000191] In certain embodiments, a provided compound is useful for treating or lessening the severity of endometriosis, uterine fibroids, endometrial hyperplasia, and benign prostate hyperplasia.

[000192] In some embodiments, a provided compound is useful for treating or lessening the severity of one or more diseases and conditions, wherein the disease or condition is selected from immune-related conditions or diseases, which include, but are not limited to transplantation, transfusion, anaphylaxis, allergies (*e.g.*, allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[000193] In some embodiments, a provided compound is useful for treating a metabolic disorder (*e.g.*, diabetes, hyperlipidemia and obesity).

Methods of Treatment and Uses

[000194] In some embodiments, the present disclosure provides methods of inhibiting a kinase comprising contacting the kinase with an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof. In some embodiments, the present disclosure provides a method of inhibiting MNK1 comprising

contacting MNK1 with an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof. In some embodiments, the present disclosure provides a method of inhibiting MNK2 comprising contacting MNK2 with an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof. In some embodiments, the present disclosure provides a method of inhibiting Abl tyrosine kinase comprising contacting Abl-tyrosine kinase with an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof. The MNK1, MNK2, Abl tyrosine kinase may be purified, partially purified, isolated, or crude, and may be present in a cell, tissue, or subject. Thus, such methods encompass both inhibition of *in vitro* and *in vivo* MNK1, MNK2, or Abl-tyrosine kinase activity. In certain embodiments, the method is an *in vitro* method, *e.g.*, such as an assay method. It will be understood by one of ordinary skill in the art that inhibition of MNK1, MNK2, or Abl-tyrosine kinase does not necessarily require that all of the MNK1, MNK2, or Abl-tyrosine kinase be inhibited. Exemplary levels of inhibition of MNK1, MNK2, or Abl-tyrosine kinase include at least 10% inhibition, about 10% to about 25% inhibition, about 25% to about 50% inhibition, about 50% to about 75% inhibition, at least 50% inhibition, at least 75% inhibition, about 80% inhibition, about 90% inhibition, and greater than 90% inhibition. Exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 20 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 15 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 10 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 8 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 6 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 4 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 2 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 1 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1

nM to about 0.5 μM. In certain embodiments, the exemplary concentrations of the provided compounds to inhibit MNK1, MNK2, or Abl-tyrosine kinase are from about 1 nM to about 0.1 μM.

[000195] In some embodiments, provided is a method of inhibiting kinase activity in a subject in need thereof (*e.g.*, a subject diagnosed as having a kinase-related disorder) comprising administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof, or a pharmaceutical composition thereof. In some embodiments, provided is a method of inhibiting MNK1 and/or MNK2 and/or Abl-tyrosine kinase activity in a subject in need thereof (*e.g.*, a subject diagnosed as having a MNK1- and/or MNK2- and/or Abl-tyrosine kinase-related disorder) comprising administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable form thereof, or a pharmaceutical composition thereof.

EXAMPLES AND EMBODIMENTS

[000196] The following examples serve to illustrate the invention without limiting the scope thereof.

Abbreviations

ACN: acetonitrile

AcOEt: ethyl acetate

AcOH: acetic acid

AUC: area under the curve

Brine: saturated aqueous solution of NaCl

cat.: catalyst

d: day(s)

DCM: dichloromethane

DIPEA: *N,N*-diisopropylethylamine

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulfoxide

DMSO-d_6: per-deuterated dimethylsulfoxide

dppf: 1,1'- Bis(diphenylphosphino) ferrocene

EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide)

ESI: Electrospray ionisation

Ether: diethylether

Et_3N: triethylamine

EtOH: ethanol

h: hour(s)

HATU: 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium

HBTU: O-Benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate

HOBt: *N*-Hydroxybenzotriazole

HPLC: high pressure liquid chromatography

L: litre(s)

LC-MS: Liquid chromatography–mass spectrometry

mL: milliliter(s)

Me: methyl

MeOH: methanol

min: minute(s)

mp: melting point

MS: mass spectrometry

NBS: *N*-Bromosuccinimide

NIS: *N*-iodosuccinimide

NMM: *N*-methylmorpholine

NMR: Nuclear Magnetic Resonance

$PdCl_2(dppf)_2$•DCM: 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex

$Pd(dppf)Cl_2$: [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)

$Pd(PPh_3)_4$: Tetrakis(triphenylphosphine)palladium(0)

TBAF: Tetra-butyl-ammonium iodide

THF: tetrahydrofuran

TFA: trifluoroacetic acid

TLC: thin layer chromatography

TMS: trimethylsilyl

T_3P: Propylphosphonic Anhydride

Synthesis of compounds

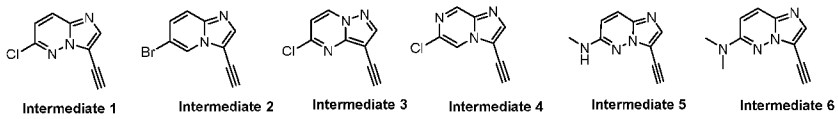
[000197] General procedure A: To a solution of aryl halide in DMF (5.4 mL/mmol) under inert athmosphere were added the aryl alkyne (1.2 eq), $PdCl_2(PPh_3)_2$ (0.13 eq), CuI (0.1 eq), PPh_3 (0.35 eq) and DIPEA (5.4 mL/mmol). The reaction mixture was heated at 80 °C until completion of the reaction. The mixture was then concentrated under reduced pressure and the residue was purified as described.

[000198] General procedure B: To a solution of aryl halide in DMF (5.0 mL/mmol) under inert athmosphere were added the aryl alkyne (3 eq), CuI (0.15 eq), DIPEA (1.5 eq) and $Pd(PPh_3)_4$ (0.05 eq) was heated at 90 °C for 4 h under argon until completion of the reaction. The mixture was diluted with water (20 mL/mmol) and the precipitate was isolated by filtration to give the reaction crude product which was purified as described.

[000199] General procedure C:To a solution of aryl halide in DMF (9.0 mL/mmol) under inert athmosphere were successively added $Pd(PPh_3)_4$ (0.19 eq), PPh_3 (0.19 eq), CuI (0.28 eq), the alkyne (2.9 eq) and DIPEA (9 mL/mmol). The reaction mixture was heated at 80 °C until completion and was diluted with water.The precipitate was isolated by filtration and was purified as described.

[000200] General procedure D: To a solution of Boc-protected derivative in dichloromethane (16 mL/mmol) at a temperature maintained between 0 °C and 5 °C was added TFA (6 mL/mmol). The reaction was stirred for 1 h in most cases while warming to room temperature. The reaction mixture was diluted with water (30 mLmmol) and the pH of the aqueous layer was first adjusted to approximately 9 using saturated aqueous solution of $NaHCO_3$. The aqeous phase was extracted with DCM (30 mL/mmol) or with a mixture of chloroform/methanol (95/5; 30 mL/mmol). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford the reaction crude product was purified as described.

Intermediates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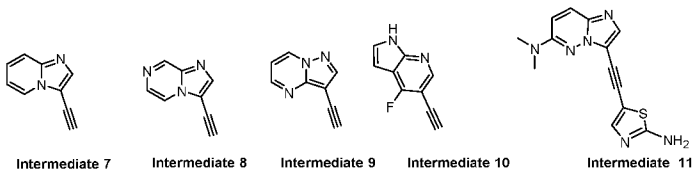
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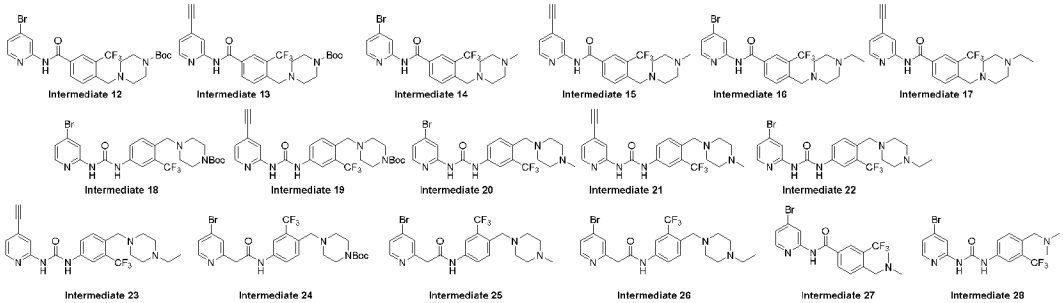
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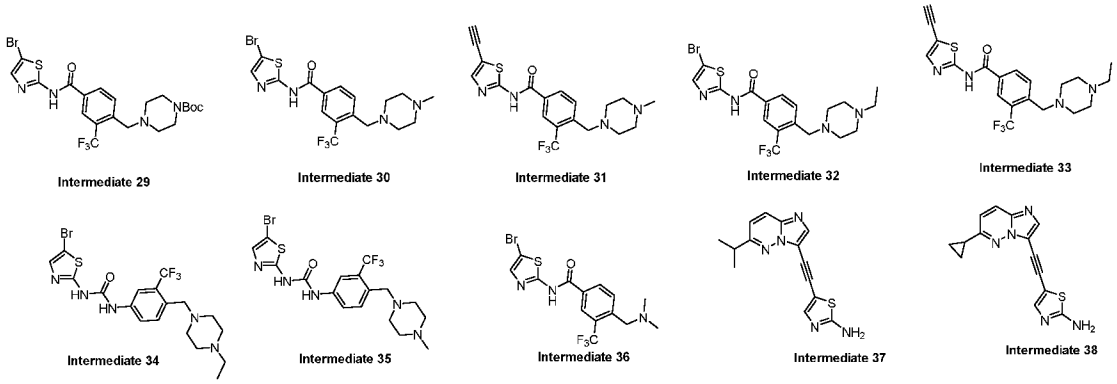
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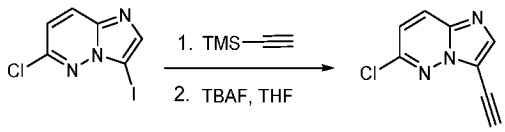
Intermediate 1: 6-chloro-3-ethynylimidazo[1,2-b]pyridazine



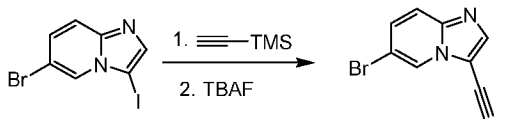
Step 1: Preparation of 6-chloro-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine

[000201] The title compound was prepared following general procedure B and starting from 6-chloro-3-iodoimidazo[1,2-b]pyridazine and ethynyltrimethylsilane. The reaction crude product was purified by column chromatography (silica gel, eluent: hexane/ethyl acetate 50:50) to afford 6-chloro-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (3 g) as a yellow solid. MS (ESI) *m/z* 250.13 $[C_{11}H_{12}ClN_3Si+H]^+$.

Step 2: Preparation of 6-chloro-3-ethynylimidazo[1,2-b]pyridazine

[000202] To a solution of 6-chloro-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (3 g, 12.04 mmol) in THF (30 mL) was added TBAF in THF (15 mL). The reaction mixture at room temperature for 3 h and was concentrated under reduced pressure to afford 6-chloro-3-ethynylimidazo[1,2-b]pyridazine (1.0 g, 47%, AUC HPLC 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99 (s, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.14 (d, J = 9.6 Hz, 1H), 3.80 (s, 1 H); MS (ESI) *m/z* 178.2 $[C_8H_4ClN_3+H]^+$.

Intermediate 2: 6-bromo-3-ethynylimidazo[1,2-a]pyridine



Step 1: Preparation of 6-bromo-3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine

[000203] To a solution of 6-bromo-3-iodoimidazo[1,2-a]pyridine (5 g, 15.5 mmol) and ethynyltrimethylsilane (1.67 g, 17 mmol) in MeCN (150 mL) were added TEA (50 mL), $Pd(PPh_3)Cl_2$ (326 mg, 3% mol) and CuI (147 mg, 5% mol). The mixture was stirred at room temperature for 1 h and then heated to reflux overnight under N_2 atmosphere. The solvent was removed *in vacuo*. The residue was dissolved in DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford the crude 6-bromo-3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine as a black oil which was used without further purification in the next step.

Step 2: Preparation of 6-bromo-3-ethynylimidazo[1,2-a]pyridine

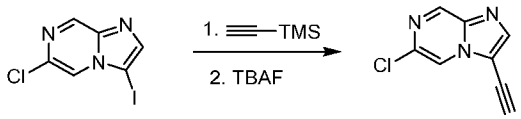
[000204] A solution of crude 6-bromo-3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine and TBAF (5.38 g, 19.34 mmol) in a mixture of THF (60 mL) and H_2O (2 mL) was stirred at room temperature for 1h then was concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 6-bromo-3-ethynylimidazo[1,2-a]pyridine as a brown solid (2.2 g, 64% over two steps). ^{1}HNMR ($CDCl_3$, 400 MHz) δ (ppm): 8.36 (s, 1H), 7.79 (s, 1H), 7.49 (d, J = 9.6 Hz, 1H), 7.27 (dd, J = 9.2 Hz, 0.9 Hz, 1H), 3.77 (s, 1H); LC-MS *m/z* 221 $[C_9H_5BrN_2 + H]^+$.

Intermediate 3: 5-chloro-3-ethynylpyrazolo[1,5-a]pyrimidine

Step 1: Preparation 5-chloro-3-((trimethylsilyl)ethynyl)pyrazolo[1,5-a]pyrimidine

[000205] To a solution of 5-chloro-3-iodopyrazolo[1,5-a]pyrimidine (8.48 g, 30 mmol) and ethynyltrimethylsilane (2.89 g, 30 mmol) in THF (200 mL) were added K_2CO_3 (4.6 g, 33.4 mmol), $Pd(PPh_3)Cl_2$ (640 mg, 0.9 mmol) and CuI (289 mg, 1.5 mmol) and (n-Bu)$_4$NI (350 mg). The mixture was stirred at 68 °C for 8 h under N_2 atmosphere. The solvent was removed *in vacuo* and the residue was dissolved in DCM then washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford black oil which was purified by flash column chromatography on silica gel to afford the 5-chloro-3-((trimethylsilyl)ethynyl)pyrazolo[1,5-a]pyrimidine (4.5 g, 60%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.29 (s, 9H) 6.84–6.88 (m, 1H) 8.23 (s, 1H) 8.51–8.57 (m, 1H)
Step 2: Preparation of 5-chloro-3-ethynylpyrazolo[1,5-a]pyrimidine To a solution of 5-chloro-3-((trimethylsilyl)ethynyl)pyrazolo[1,5-a]pyrimidine (4.5 g) in a mixture of THF (80 mL) and H_2O (4 mL) was added TBAF (5.6 g, 20 mmol) in one portion. The mixture was stirred at room temperature for 1h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel to afford 5-chloro-3-ethynylpyrazolo[1,5-a]pyrimidine as a yellow solid (1 g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.32 (s, 1H) 6.89 (d, J = 7.2 Hz, 1H) 8.24 (s, 1H) 8.56 (d, J = 7.2 Hz, 1H). LC-MS *m/z* 178 $[C_8H_4ClN_3 + H]^+$.

Intermediate 4: 6-chloro-3-ethynylimidazo[1,2-a]pyrazine



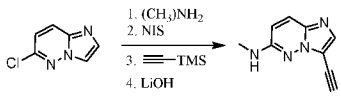
Step 1: Preparation of 6-chloro-3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyrazine

[000206] To a solution of 6-chloro-3-iodoimidazo[1,2-a]pyrazine (5 g, 0.0179 mol) and ethynyltrimethylsilane (1.75 g, 0.017 mmol) in THF (150 mL) were added K_2CO_3 (2.71 g, 0.020 mol), $Pd(PPh_3)Cl_2$ (0.37 g, 0.00053 mol) and CuI (0.17 g, 0.001 mol) and $(n\text{-}Bu)_4NI$ (200 mg). The mixture was stirred at 68 °C for 8 h under N_2 atmosphere. The solvent was removed *in vacuo* and the residue was dissolved in DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford black oil which was purified by chromatography on silica gel to afford 6-chloro-3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyrazine (2.8 g) as a brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.34 (s, 9H), 7.99 (s, 1H) 8.23 (s, 1H) 8.93 (s, 1H).

Step 2: Preparation of 6-chloro-3-ethynylimidazo[1,2-a]pyrazine

[000207] To a solution of 6-chloro-3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyrazine (2.8 g) in a mixture of THF (60 mL) and H_2O (2 mL) was added TBAF (3.92 g, 14.06 mmol) in one portion. The mixture was stirred at room temperature for 1h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel to afford 6-chloro-3-ethynylimidazo[1,2-a]pyrazine as a yellow solid (0.8 g, 40%). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.90 (s, 1H) 8.04 (s, 1H) 8.31 (s, 1H) 8.96 (s, 1H). LC-MS *m/z* 178 $[C_8H_4ClN_3 + H]^+$.

Intermediate 5: 3-ethynyl-N-methylimidazo[1,2-b]pyridazin-6-amine



Step 1: Preparation of *N*-methylimidazo[1,2-b]pyridazin-6-amine

[000208] A solution of 6-chloroimidazo[1,2-b]pyridazine (5 g, 32.67 mmol) and methyl amine in THF (100 mL) in a steel bomb was heated at 180 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the precipitate was isolated by filtration to afford *N*-methylimidazo[1,2-b]pyridazin-6-amine (3.5 g, 73.4%). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.08 (s, 1H), 7.81 (d, J = 9.6 Hz, 1H), 7.68 (s, 1H), 6.91 (t, J = 9.2 Hz, 1H), 2.80 (d, J = 4.4 Hz, 4H); MS (ESI) m/z: 149.0 $[C_7H_8N_4+H]^+$.

Step 2: Preparation of 3-iodo-*N*-methylimidazo[1,2-b]pyridazin-6-amine

[000209] A mixture of solution of *N*-methylimidazo[1,2-b]pyridazin-6-amine (3.5 g, 23.64 mmol) and NIS (6.38 g, 28.37 mmol) in DMF (25 mL) was stirred at room temperature for 4 h and was poured into ice-cold water. The solid that has precipitated was isolated by filtration and dried to afford 3-iodo-*N*-methylimidazo[1,2-b]pyridazin-6-amine (4 g, 51.2%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.22 (d, *J* = 9.6 Hz, 1H), 7.97 (s, 1H), 7.42 (d, *J* = 10.0 Hz, 1H), 2.74 (s, 3H); MS (ESI) m/z: 275.0 $[C_7H_7IN_4+ H]^+$.

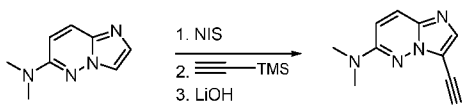
Step 3: preparation of *N*-methyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-amine

To a solution of 3-iodo-*N*-methylimidazo[1,2-b]pyridazin-6-amine (4 g, 14.59 mmol) in THF (50 mL) under argon were successively added TEA (4.15 mL, 29.18 mmol), CuI (415.8 mg, 2.18 mmol), ethynyltrimethylsilane (6.1 mL, 43.77 mmol) and $Pd(PPh_3)_4$ (842 mg, 0.729 mmol). The reaction mixture was heated at 80 °C for 3 h then, was diluted with EtOAc and filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, eluent: hexane/EtOAc 30:70) to afford *N*-methyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-amine (1.5 g, 37.5%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (s, 1H), 7.63 (d, *J* = 10.0 Hz, 1H), 6.45 (d, *J* = 9.6 Hz, 1H), 3.02 (d, *J* = 5.2 Hz, 3H), 0.30 (s, 9H); MS (ESI) m/z: 245 $[C_{12}H_{16}N_4Si+H]^+$.

Step 4: preparation of 3-ethynyl-*N*-methylimidazo[1,2-b]pyridazin-6-amine

[000210] A solution of LiOH in water was added to a solution of *N*-methyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-amine (1.5 g, 6.14 mmol) in THF (15 mL) and the resulting mixture was vigorously stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 90:10) to afford 3-ethynyl-*N*-methylimidazo[1,2-b]pyridazin-6-amine (800 mg) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.02 (d, *J* = 2.8 Hz, 1H), 7.85 (d, *J* = 10.0 Hz, 1H), 7.16 (s, 1H), 6.98–6.95 (m, 1H), 4.93 (s, 1 H), 2.85 (d, *J* = 4.4 Hz, 3H); MS (ESI) *m/z*: 173.19 $[C_9H_8N_4+H]^+$.

Intermediate 6: 3-ethynyl-N,N-dimethylimidazo[1,2-b]pyridazin-6-amine



Step 1: Preparation of 3-iodo-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine

[000211] To a solution of *N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine (15 g, 92.59 mmol) in acetonitrile (100 mL) was added NIS (24.88 g, 111.11 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and the precipitate was isolated by filtration, washed with water and dried to afford 3-iodo-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine 2 (25 g, 93%, LC-MS 96%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.72 (d, J = 10.0 Hz, 2H), 7.55 (s, 1H), 7.04 (d, J = 9.6 Hz, 2H), 3.09 (s, 6H); MS (ESI) *m/z* 289.1 $[C_8H_9IN4 + H]^+$.

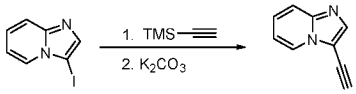
Step 2: Preparation of *N,N*-dimethyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-amine

[000212] A mixture of 3-iodo-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine (5 g, 17.36 mmol), ethynyltrimethylsilane (7.29 mL, 21.36 mmol), $PdCl_2(dppf)_2$•DCM (709 mg, 0.86 mmol), CuI (494.7 mg, 2.60 mmol), and DIPEA (4.47 mL, 26.04 mmol) in 50 mL of THF was stirred at 80 °C under N_2 for 4 h. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/CH_3OH 95:5) to afford *N,N*-dimethyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-amine (3 g) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.84 (d, J = 9.6 Hz, 1H), 7.73 (s, 1H), 7.12 (d, J = 10.4 Hz, 1H), 3.08 (s, 6H), 0.25 (t, J = 3.2 Hz, 9H); MS (ESI) *m/z* 259.13 $[C_{13}H_{18}N_4Si+H]^+$.

Step 3: Preparation of 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine

[000213] To a solution of *N,N*-dimethyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-amine (3 g, 11.62 mmol) in THF (30 mL) at room temperature was added a solution of LiOH (586 mg, 13.95 mmol) in water (10 mL) and MeOH (10 mL). The reaction mixture was stirred for 3 h and was concentrated under reduced pressure to afford 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine, (1.5 g, 71%, AUC HPLC 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.85 (d, J = 10.0 Hz, 1H), 7.74 (s, 1H), 7.12 (d, J = 9.6 Hz, 1H), 4.77 (s, 1 H), 3.10 (s, 6H); MS (ESI) *m/z* 187.1 $[C_{10}H_{10}N_4+H]^+$.

Intermediate 7: Preparation of 3-ethynylimidazo[1,2-a]pyridine



Step 1: Preparation of 3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine

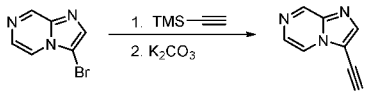
[000214] To a solution of 3-iodoimidazo[1,2-*a*]pyridine (224 mg, 1 mmol) in acetonitrile (3 mL) under inert atmosphere were added ethynyltrimethylsilane (295 mg, 3 mmol),

tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol), copper iodide (29 mg, 0.15 mmol) and DIPEA (1.5 mL) and the resulting mixture was heated at 70 °C for 5 h, then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, Hexane/Ethyl acetate 4:1) to afford 3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyridine (207 mg, 97%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.26 (d, J = 6.7 Hz, 1H), 7.85 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.31–7.21 (m, 1H), 6.98-6.91 (m, 1H), 0.31 (s, 9H); MS (ESI) *m/z* 215 $[C_{12}H_{14}N_2Si + H]^+$.

Step 2: 3-ethynylimidazo[1,2-a]pyridine

[000215] To a solution of 3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyridine (207 mg, 0.97mmol) in methanol (4 mL) was added potassium carbonate (133 mg, 0.97 mmol) and was stirred at room temperature for 3 h before concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, Hexane/Ethyl acetate 4:1) to afford 3-ethynylimidazo[1,2-*a*]pyridine (85 mg, 62%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (dt, J = 6.8, 1.0 Hz, 1H), 7.89 (s, 1H), 7.67 (d, J = 9.1 Hz, 1H), 7.30 (dd, J = 6.8, 1.2 Hz, 1H), 6.95 (td, J = 6.8, 0.8 Hz, 1H), 3.82 (s, 1H); MS (ESI) *m/z* 143$[C_9H_6N_2 + H]^+$.

Intermediate 8: Preparation of 3-ethynylimidazo[1,2-a]pyrazine



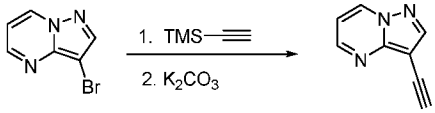
Step 1: Preparation of 3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyrazine

[000216] To a solution of 3-bromoimidazo[1,2-a]pyrazine (198 mg, 1.00 mmol) in DMF (2 mL) under inert atmosphere were added ethynyltrimethylsilane (0.42 ml, 3 mmol), triphenylphophine (91 mg, 0.35 mmol), $Pd(PPh_3)_2Cl_2$ (91 mg, 0.13 mmol), copper iodide (19 mg, 0.1 mmol) and DIPEA (1 mL). The resulting mixture was heated to 80 °C for 5h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hexane/Ethyl acetate 5:1) to afford 3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyrazine (161 mg, 75%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.11 (s, 1H), 8.18 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 4.4 Hz, 1H), 7.96 (s, 1H), 0.33 (s, 9H); MS (ESI) *m/z* 216$[C_{11}H_{13}N_3Si + H]^+$.

Step 2: Preparation of 3-ethynylimidazo[1,2-*a*]pyrazine

[000217] To a solution of 3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyrazine (161 mg, 0.75 mmol) in methanol (4 mL) was added potassium carbonate (103 mg, 0.75 mmol) and was stirred at room temperature for 3 h before concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, Hexane/Ethyl acetate 4:1) to afford 3-ethynylimidazo[1,2-*a*]pyrazine (58 mg, 54%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.14 (d, *J* = 1.3 Hz, 1H), 8.22 (dd, *J* = 4.5, 1.4 Hz, 1H), 8.04 (d, *J* = 4.5 Hz, 1H), 8.00 (s, 1H), 3.86 (s, 1H); MS (ESI) *m/z* 144[$C_8H_5N_3$ + H]$^+$.

Intermediate 9: Preparation of 3-ethynylpyrazolo[1,5-a]pyrimidine



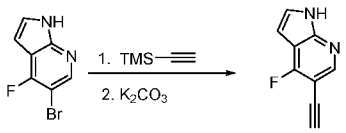
Step 1 : Preparation of 3-((trimethylsilyl)ethynyl)pyrazolo[1,5-a]pyrimidine

[000218] To a mixture of 3-bromopyrazolo[1,5-a]pyrimidine (100 mg, 0.505 mmol), trimethylsilylacetylene (173 µL, 1.21 mmol), $PdCl_2(PPh_3)_2$ (46 mg, 0.0655 mmol), CuI (10 mg, 0.0505 mmol), PPh_3 (46 mg, 0.177 mmol) in THF: DMF (3:1, 1.0 mL) was added Et_3N (1.0 mL). After purging with argon for 10 mins, the resulting mixture was stirred at 90°C for 3 h in a microwave reactor. Upon cooling to room temperature, the solvents were removed *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, eluent EtOAc/ petroleum ether 20:80) to afford 3-((trimethylsilyl)ethynyl)pyrazolo[1,5-a]pyrimidine, which was not further purified and carried forward to the next step. MS (ESI) *m/z* 216 [$C_{11}H_{13}N_3Si$ + H]$^+$

Step 2 : Preparation of 3-ethynylpyrazolo[1,5-a]pyrimidine

[000219] A mixture of 3-((trimethylsilyl)ethynyl)pyrazolo[1,5-a]pyrimidine (60 mg, 0.279 mmol) and K_2CO_3 (38 mg, 0.279 mmol) in MeOH (2 mL) and THF (2 mL) was stirred at room temperature for 1 h. The mixture was filtered through a short pad of celite and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (eluent EtOAc/petroleum ether 50:50) to afford 3-ethynylpyrazolo[1,5-a]pyrimidine (18 mg, 25% over two steps); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.67 (dd, *J* = 7.0, 1.8 Hz, 1H), 8.59 (dd, *J* = 4.0, 1.8 Hz, 1H), 8.25 (s, 1H), 6.91 (dd, *J* = 7.0, 4.0 Hz, 1H), 3.33 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 150.6, 149.5, 147.7, 135.8, 109.1, 93.2, 81.4, 73.5; MS (ESI) *m/z* 144 [$C_8H_5N_3$ + H]$^+$

Intermediate 10: 5-ethynyl-4-fluoro-1H-pyrrolo[2,3-b]pyridine



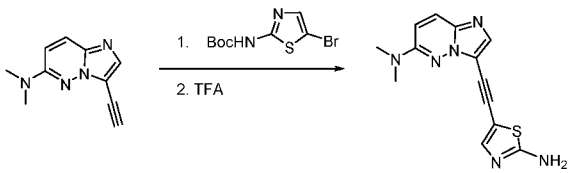
Step 1: Preparation of 4-fluoro-5-((trimethylsilyl)ethynyl)-1*H*-pyrrolo[2,3-b]pyridine

[000220] To a mixture of 5-bromo-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine (200 mg, 0.930 mmol) in a 3:1 mixture of THF and DMF (1.0 mL), were added trimethylsilylacetylene (318 µL, 2.24 mmol), $PdCl_2(PPh_3)_2$ (85 mg, 0.121 mmol), CuI (18 mg, 0.0930 mmol) and PPh_3 (86 mg, 0.326 mmol) and Et_3N (1.0 mL). After purging with Argon for 10 min, the resulting mixture was stirred at 90°C for 3 h in a microwave reactor. Upon cooling to room temperature, the solvents were removed *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, eluent EtOAc/petroleum ether 20:80) to afford 4-fluoro-5-((trimethylsilyl)ethynyl)-1*H*-pyrrolo[2,3-b]pyridine (188 mg, 87%); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.69 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 3.5 Hz, 1H), 6.61 (d, *J* = 3.5 Hz, 1H), 0.30 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 163.6, 161.8, 151.1, 151.0, 147.7, 126.0, 109.4, 109.3, 100.7, 100.6, 97.7, 97.3, 96.1, 0.0; MS (ESI) *m/z* 273 $[C_{12}H_{13}FN_2Si + MeCN]^+$

Step 2: Preparation of 5-ethynyl-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine

[000221] A mixture of 4-fluoro-5-((trimethylsilyl)ethynyl)-1*H*-pyrrolo[2,3-b]pyridine (188 mg, 0.809 mmol) and K_2CO_3 (112 mg, 0.809 mmol) in MeOH (2 mL) and THF (2 mL) was stirred at room temperature for 1 h. The mixture was filtered through a short pad of celite and the filtrate concentrated. The residue was purified by column chromatography (silica gel, eluent EtOAc/ petroleum ether 20 : 80) to afford 5-ethynyl-4-fluoro-1H-pyrrolo[2,3-b]pyridine (84 mg, 65%); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 10.92 (s, 1H), 8.43 (s, 1H), 7.36 (d, *J* = 3.6 Hz, 1H), 6.63 (d, *J* = 3.6 Hz, 1H), 3.35 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 164.0, 162.2, 151.1, 151.0, 147.8, 132.2, 132.2, 128.7, 128.6, 126.0, 97.9, 82.9, 75.3; MS (ESI) *m/z* 161 $[C_9H_5FN_2 + H]^+$

Intermediate 11: 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine



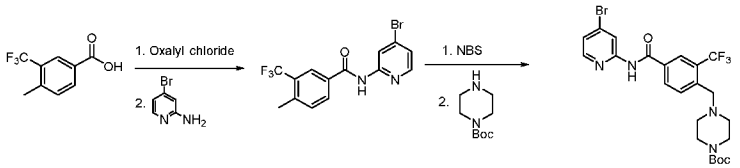
Step 1: Preparation of *tert*-butyl 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate

[000222] To a solution of *tert*-butyl 5-bromothiazol-2-ylcarbamate (600mg, 2.159 mmol) in THF (10.0 mL) were successively added $PdCl_2$(dppf)•DCM (88 mg, 0.107 mmol), dppf (60 mg, 0.107 mmol), CuI (61.5mg, 0.323 mmol), TEA (700 mg, 6.47 mmol) and 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine (400 mg, 2.15 mmol) and the reaction mixture was heated at 80 °C for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (neutral alumina, eluent: dichloromethane/methanol 97:03) to afford *tert*-butyl 5-((6-(dimethylamino) imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (500 mg, 52%, LCMS-86%) as an off white solid. MS (ESI) *m/z*: 384 $[C_{18}H_{20}N_6O_2S]^{+\cdot}$

Step 2: Preparation of 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine

[000223] A solution of *tert*-butyl 5-((6-(dimethylamino) imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (500 mg, 1.30 mmol) and TFA (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was basified with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was washed with diethyl ether to afford 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (200 mg, 37.3%) as a yellow solid. MS (ESI) *m/z*: 284 $[C_{13}H_{12}N_6S]^+$.

Intermediate 12: tert-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate



Step 1: preparation of *N*-(4-bromopyridin-2-yl)-4-methyl-3-(trifluoromethyl)benzamide

[000224] To a solution of 4-methyl-3-(trifluoromethyl)benzoic acid (25 g, 122.5 mmol) in dichloromethane (250 mL) at a temperature maintained between 0-5°C, was added oxalyl chloride (17 mL, 122.5 mmol) and DMF (0.1 mL, cat.) and the mixture was stirred at room temperature for 4 h then was concentrated to dryness under reduced pressure. The residue was dissolved in dichloromethane (250 mL) and cooled to 10 °C prior to the addition of DMAP (14.8g, 122.55 mmol), TEA (24.7g, 245.1 mmol) and 2-amino-4-bromo pyridine (21.1g, 122.55 mmol). The reaction mixture was stirred at room temperature for 15 h then was concentrated under reduced pressure. The residue was diluted with water and the

precipitate that crashed out of solution was isolated by filtration and was purified by flash column chromatography (silica gel, hexanes/EtOAc 8:2) to afford *N*-(4-bromopyridin-2-yl)-4-methyl-3-(trifluoromethyl)benzamide (32.6 g, 74.2 %): ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm): 8.68 (s, 1H), 8.64 (s, 1H), 8.16 (s, 1H), 8.11 (d, J = 5.6 Hz , 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 2.57 (s, 3H), MS (ESI) *m/z* 358.01 $[C_{14}H_{10}BrF_3N_2O]^+$

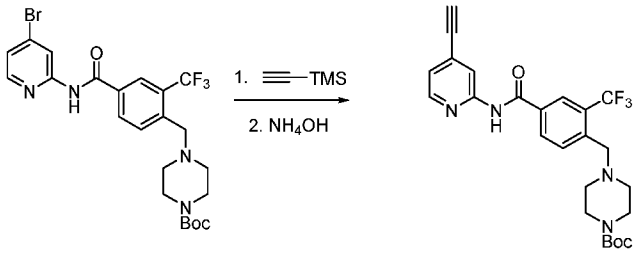
Step 2: preparation of 4-(bromomethyl)-*N*-(4-bromopyridin-2-yl)-3-(trifluoromethyl)

[000225] A solution of *N*-(4-bromopyridin-2-yl)-4-methyl-3-(trifluoromethyl)benzamide (32.6 g, 90.8 mmol), *N*-bromo succinamide (24.2 g, 136.2 mmol) and AIBN (2.9 g, 18.16 mmol) in carbon tetrachloride (350 mL) was heated to reflux for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 filtered and concentrated under reduced pressure to afford 4-(bromomethyl)-*N*-(4-bromopyridin-2-yl)-3-(trifluoromethyl)benzamide (45 g) as pale brown solid. This crude product was used in the next step without further purification.

Step 3: Preparation of *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

[000226] To a cooled solution of *tert*-butyl piperazine-1-carboxylate (31.8 g, 171.2 mmol) in acetonitrile (100 mL) was added dropwise a solution of 4-(bromomethyl)-*N*-(4-bromopyridin-2-yl)-3-(trifluoromethyl)benzamide (25 g, ~57 mmol) in acetonitrile (100 mL). The reaction mixture was stirred at room temperature for 3 h and was concentrated under reduced pressure. The residue was diluted with water then extracted with ethyl acetate (150 mL). The organic phase was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent petroleum ether/EtOAc 80:20) to afford *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (5 g, 16%, AUC HPLC 93.4%) as a yellow solid. m.p: 59-63 °C. ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm): 8.64 (d, J = 1.6 Hz, 1H), 8.57 (s, 1H), 8.17 (s, 1H), 8.13 (d, J = 5.2 Hz , 2H), 8.06–7.99 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 3.73 (s, 2H), 3.46 (t, J = 4.8 Hz, 4H), 2.44 (t, J = 4.8 Hz, 4H), 1.43 (s, 9H); MS (ESI) *m/z* 543.29 $[C_{23}H_{26}BrF_3N_4O_3]^+$.

Intermediate 13: tert-butyl 4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate



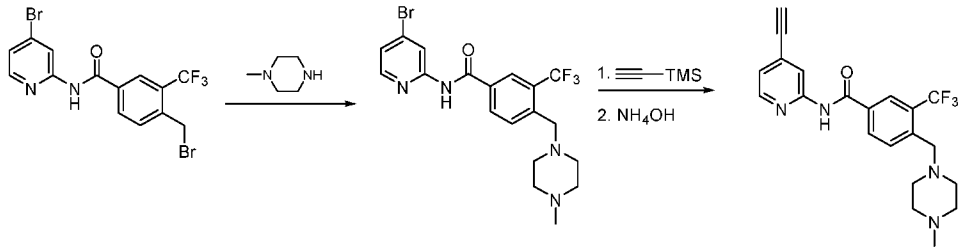
Step 1: Preparation of *tert*-butyl 4-(2-(trifluoromethyl)-4-(4-((trimethylsilyl)ethynyl)pyridin-2-ylcarbamoyl)benzyl)piperazine-1-carboxylate

[000227] The title compound was prepared following similar to general procedure B and starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (1 g, 1.84 mmol) and Ethynyltrimethylsilane. Purification by column chromatography (neutral alumina, eluent: petroleum ether/ethyl acetate 80:20) gave *tert*-butyl 4-(2-(trifluoromethyl)-4-(4-((trimethylsilyl)ethynyl)pyridin-2-ylcarbamoyl)benzyl)piperazine-1-carboxylate (500 mg, 50%) as a brown solid. MS (ESI) *m/z*: 561.2 $[C_{28}H_{35}F_3N_4O_3Si$ +H$]^+$.

Step 2: Preparation *tert*-butyl 4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000228] A solution of *tert*-butyl 4-(2-(trifluoromethyl)-4-(4-((trimethylsilyl)ethynyl)pyridin-2-ylcarbamoyl)benzyl)piperazine-1-carboxylate (500 mg, 0.89 mmol) in a mixture of NH_4OH (20 mL) and THF (20 mL) was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduce pressure, the residue diluted with diethyl ether and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (300 mg, LC-MS 85%) as a off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.81 (s, 1H), 8.50 (s, 1H), 8.25 (d, *J* = 5.2 Hz, 1H), 7.92 (s, 1H), 7.73 (s, 2H), 7.01 (d, *J* = 5.2 Hz ,1H), 6.96 (s, 1H), 3.43 (t, *J* = 4.8 Hz, 4H), 3.33 (s, 2H), 2.41 (s, 4H), 1.46 (s, 9H); MS (ESI) *m/z*: 489.4 (M+H) $C_{25}H_{27}F_3N_4O_3$+ H$]^+$

Intermediate 14 & 15: N-(4-bromopyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and N-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *N*-(4-bromopyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000229] To a solution of *N*-methyl piperazine (34.1 g, 342.4 mmol) in acetonitrile (100 mL) was added a solution of 4-(bromomethyl)-*N*-(4-bromopyridin-2-yl)-3-(trifluoromethyl)benzamide (50 g, 114.15 mmol) in acetonitrile (200 mL) drop wise at room temperature. The reaction mixture was stirred at room temperature for 3 h and was concentrated under reduced pressure. The residue was diluted with ethyl acetate (150 mL) and the resulting solution was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH 90:9.5:0.5) to afford *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (5.23 g, 12%) as an off white solid. m.p: 114–117 °C, ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm): 8.64 (s, 1H), 8.56 (s, 1H), 8.17 (s, 1H), 8.13 (d, *J* = 5.6 Hz , 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.27–7.25 (m, 1H), 3.75 (s, 2H), 2.61–2.55(m, 8H), 2.39 (s, 3H). MS (ESI) m/z 457.1 $[C_{19}H_{20}BrF_3N_4O]^+$.

Step 2: Preparation of 4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl)-*N*-(4-((trimethylsilyl) ethynyl) pyridin-2-yl) benzamide

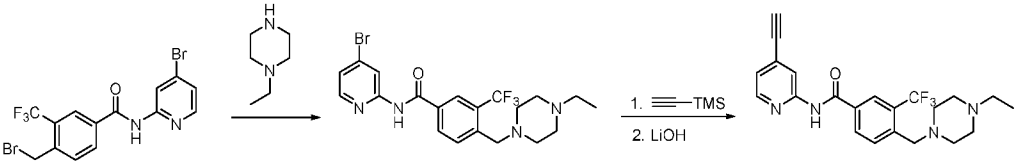
[000230] To a solution of *N*-(4-bromopyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl) benzamide (1 g, 2.18 mmol) in THF (30 mL) under argon were successively were added $PdCl_2(PPh_3)_2$ (74.2 mg, 0.10 mmol), CuI (60.3 mg, 0.31 mmol), Ethynyltrimethylsilane (0.9 mL, 6.54 mmol) and triethyl amine (0.92 mL, 6.54 mmol) and the resulting mixturewas heated at 70 °C for 15 h. The reaction mixture was diluted with EtOAc and washed in turn with water brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (neutral alumina, eluent, ethyl acetate/Petroleum ether 20:80) to afford 4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl)-*N*-(4-((trimethylsilyl) ethynyl) pyridin-2-yl) benzamide (900 mg, 90%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.41 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 8.27 (d, *J* =7.2 Hz, 1H), 8.21 (s, 1H), 7.90 (d, *J* = 8.0

Hz, 1H), 7.60 (bs, 1H), 7.21 (d, *J* = 4.8 Hz, 1H), 3.67 (s , 2H), 2.49–2.35 (m, 8H), 2.16 (s, 3H), 0.27 (s, 9H); MS (ESI) *m/z*: 475.2 $[C_{24}H_{29}F_3N_4OSi + H]^+$

Step 3: Preparation *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl)benzamide

[000231] A mixture of 4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl)-*N*-(4-((trimethylsilyl) ethynyl) pyridin-2-yl)benzamide (900 mg, 1.89 mmol) in THF (20 mL) and aqueous NH_4OH (20 mL) was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduce pressure, and the residue was diluted with diethyl ether then washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl)benzamide (600 mg, 79%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.22 (s, 1H), 8.42 (d, *J* = 5.6 Hz, 1H), 8.32 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.24 (s, 1H), 7.90 (d, *J* = 8 Hz ,1H), 7.25 (dd, *J* = 1.2 Hz, *J* = 1.6 Hz, 1H), 4.61 (s, 1H), 3.67 (s, 2H), 2.50–2.49 (m, 8H), 2.16 (s, 3H); MS (ESI) *m/z*: 403.1 $C_{21}H_{21}F_3N_4O+ H]^+$

Intermediate 16 and 17: N-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000232] To a cooled solution of *N*-ethyl piperazine (26 mL, 207.47 mmol) in acetonitrile (100 mL) was added dropwise a solution of 4-(bromomethyl)-*N*-(4-bromopyridin-2-yl)-3-(trifluoromethyl)benzamide (45 g, 102.73 mmol) in acetonitrile (200 mL). The reaction mixture was stirred at room temperature for 3 h then was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (150 mL). The organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The reaction crude was purified by flash column chromatography (silica gel, eluent DCM/MeOH/NH_4OH) to afford *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (6 g, 12%, AUC HPLC

95.8%) as an off white solid. ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm): 8.64 (s, 1H), 8.53 (s, 1H), 8.17 (s, 1H), 8.14 (d, J = 5.6 Hz , 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 3.75 (s, 2H), 2.61–2.51(m, 10H), 1.14 (t, J = 5.6 Hz, 3H). MS (ESI) *m/z* 471.2 $[C_{20}H_{22}BrF_3N_4O]^+$.

Step 2: Preparation of 4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl)-*N*-(4-((trimethylsilyl) ethynyl) pyridin-2-yl) benzamide

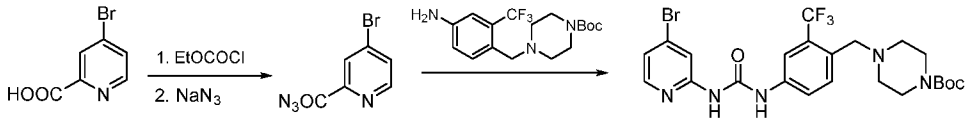
[000233] A solution of *N*-(4-bromopyridin-2yl)4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (20 g, 42.46 mmol) in THF (300 mL) was degassed with argon for 30 min. $PdCl_2(dppf)_2$•DCM (3.5 g, 4.24 mmol), CuI (1.2 g, 6.39 mmol), TEA (17.7 mL, 127 mmol), ethynyltrimethylsilane (8.3 g, 84.92 mmol), were added and the reaction mixture was heated at 80 °C for 15 h. Reaction mixture was cooled to room temperature, filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was triturated with n-hexane. The solid was isolated by filtration and was further purified by column chromatography (neutral alumina, eluent ethyl acetate/hexanes 0/100 to 50/ 100) to afford 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)benzamide as pale brown solid (8 g, 38.6%, LC-MS 91.7%). ^{1}H NMR(400 MHz, $CDCl_3$) δ (ppm): 8.51 (s, 1H) , 8.44 (s, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.18 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.98 (d, J =8.0 Hz, 1H), 7.12 (d, J = 4.4 Hz, 1H), 3.75 (s, 2H), 2.63-2.53 (m, 10H), 1.16-1.15 (m, 3H), 0.27 (s, 9H). MS (ESI) *m/z*:489.23 (M+H) $[C_{25}H_{31}F_3N_4OSi + H]^+$.

Step 3: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide

[000234] A solution of LiOH•H_2O (793 mg, 0.0165 mmol) in water (50 mL) was added to a solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)benzamide (8 g, 16.35 mmol) in THF (50 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with EtOAc and water. The organic layer was washed in turn with water and brine, dried over Na_2SO_4 filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (neutral alumina, eluent EtOAc/hexanes 0/100 to 40/100) to afford 4-((4-ethylpiperazin-1-yl) methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl) benzamide (6 g, 88%, HPLC-95.8%) as pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.23 (s, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.32 (s, 1 H), 8.28 (d, J = 6.4 Hz, 1 H), 8.24 (s, 1H), 7.91 (d, J = 8.0 Hz, 1 H),7.25 (dd, J = 5.6, 1.2

Hz, 1H), 4.61 (s, 1 H), 3.67 (s, 2H), 2.43–2.42 (m, 8 H), 2.31 (q, *J* = 4.0 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 417.2 $[C_{22}H_{23}F_3N_4O+H]^+$.

Intermediate 18: tert-butyl 4-(4-(3-(4-bromopyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate



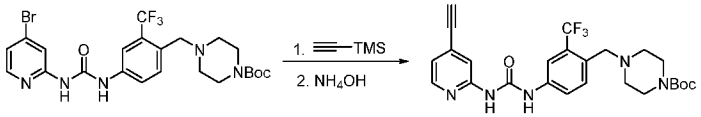
Step 1: Preparation of 4-bromopicolinoyl azide

[000235] To a mixture of 4-bromopicolinic acid (10 g, 49 mmol), triethylamine (6.5 g, 65 mmol) at -10 °C, was added, dropwise, ethyl chloroformate (8 g, 74 mmol) and the resulting mixture was stirred for 2 h. A solution of sodium azide (5.4 g, 84 mmol) in water (25 mL) was added to the above reaction mixture at -10 °C and afterward stirred for 2 h at room temperature. The reaction mixture was poured into ice water (80 mL) and extracted with ethyl acetate (80 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-bromo picolinoyl azide (7 g, 59%) as an off-white solid; MS (ESI) *m/z* 226 $[C_6H_3BrN_4O+H]^+$.

Step 2: Preparation of *tert*-butyl 4-(4-(3-(4-bromopyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

[000236] A solution of 4-bromopicolinoyl azide (20 g, 88.0 mmol) in toluene was refluxed for 1 h then was cooled to room temperature prior to the addition of a solution of *tert*-butyl 4-(4-amino-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (31.5 g, 88.0 mmol) in toluene. The reaction mixture was stirred for 16 h at room temperature and was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent $CHCl_3$/MeOH: 98:2) to afford *tert*-butyl 4-(4-(3-(4-bromopyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (12 g, 24%, AUC HPLC 95%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.70 (s, 1H), 8.78 (s, 1H), 8.11 (d , *J* = 6.0 Hz, 1H), 7.92 (s, 1H), 7.73 (s , 2H), 7.14 (d, *J* = 4.8 Hz, 2H), 3.63 (s, 2H), 3.43 (s, 4H), 2.42 (bs, 4H), 1.46 (s, 9H); *m/z* 473.2 $[C_{23}H_{27}BrF_3N_5O_3+H]^+$.

Intermediate 19: 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) urea



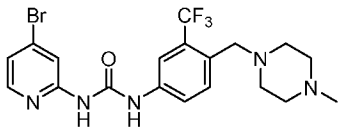
Step 1: *tert*-butyl 4-(2-(trifluoromethyl)-4-(3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)ureido)benzyl)piperazine-1-carboxylate.

[000237] The title compound was prepared in a similar fashion as described in step 1 of intermediate 18 synthesis starting from *tert*-butyl 4-(4-(3-(4-bromopyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (1. 5 g, 2.68 mmol). The crude product was further purified by flash column chromatography (silica gel, eluent: CH_2Cl_2: MeOH 95:5) to afford *tert*-butyl 4-(2-(trifluoromethyl)-4-(3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)ureido)benzyl)piperazine-1-carboxylate (3 g, 58%, LC-MS 90%) as an off white solid

Step 2: Preparation of *tert*-butyl 4-(4-(3-(4-ethynylpyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

[000238] The title compound was prepared in a similar fashion as described in step 2 of intermediate 18 synthesis starting from *tert*-butyl 4-(2-(trifluoromethyl)-4-(3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)ureido)benzyl)piperazine-1-carboxylate (2.3 g, 3.99 mmol). The crude product purified by flash column chromatography (silica gel, eluent: CH_2Cl_2: MeOH 95:5) to afford *tert*-butyl 4-(4-(3-(4-ethynylpyridin-2-yl) ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (2 g, 74%, AUC HPLC 97.5%) as an off white solid. m.p.: 215–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.30 (s, 1H), 9.52 (s, 1H), 8.30 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.69–7.62 (m, 3H), 7.09 (dd, J = 6.8, 2.0 Hz, 1H), 4.58 (s, 1H), 3.56 (s, 2H), 3.32 (bs, 4H), 2.33 (bs, 4H), 1.39 (s, 9H); MS (ESI) *m/z* 504.2 $[C_{25}H_{28}F_3N_5O_3+H]^+$.

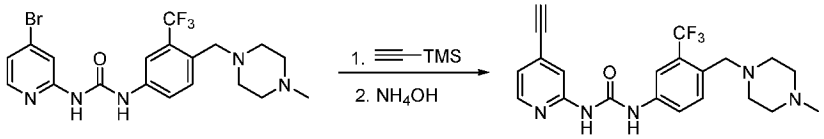
Intermediate 20: 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000239] Preparation of 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea. A solution of 4-bromopicolinoyl azide (10 g, 44.0 mmol) in toluene was refluxed for 1 h then was cooled to room temperature prior to the addition of a solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (12.0 g, 44.0 mmol) in toluene. The resulting mixture was stirred for 16 h at room temperature then, was

concentrated under reduced pressure. The residue was purified by column chromatography (Neutral Alumina, eluent petroleum ether/ethyl acetate 80:20) to afford 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (4.5 g, 21%, LC-MS 98%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.7 (s, 1H), 8.53 (s, 1H), 8.11 (d, *J* = 5.2 Hz, 1H), 7.89 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* =5.2 Hz, 2H), 3.66 (s, 2H), 2.61 (bs, 8H), 2.41 (s, 3H); *m/z* 473.2 $[C_{19}H_{21}BrF_3N_5O+H]^+$.

Intermediate 21: 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) urea

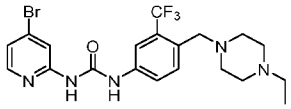


[000240] Step 1: Preparation of 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)urea. The title compound was prepared in a similar fashion as described in step 1 of intermediate 13 synthesis starting from 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (1 g, 2.12 mmol). The crude product was further purified by column chromatography (neutral alumina, eluent: hexanes/EtOAc 8:2) to afford 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)urea (800 mg, 80%, LC-MS 92%) as an off-white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 10.22 (s, 1H), 9.50 (s, 1H), 8.29 (d, *J* = 6.8 Hz, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.64–7.54 (m, 2H), 7.41–7.39 (m, 1H), 7.05 (dd, *J* = 6.8, Hz, 2.0, Hz, 1H), 3.55 (s, 2H), 2.38–2.27 (m, 8H), 2.15 (s, 3H), 0.26 (s, 9 H). MS (ESI) *m/z*:490.11$[C_{24}H_{30}F_3N_5OSi+ H]^+$.

[000241] Step 2: 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea. The title compound was prepared in a similar fashion as described in step 2 of intermediate 13 synthesis starting from 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)urea (800 mg, 1.63 mmol). The crude product was further purified by column chromatography (neutral alumina, eluent: hexanes/EtOAc 8:2:1% NH_4OH) to afford 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (500 mg, 73%, AUC HPLC 94.2 %) as a pale yellow solid. m.p: 176-180°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 9.52 (s, 1H), 8.30 (d, *J* = 6.8 Hz, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.66–7.60 (m,

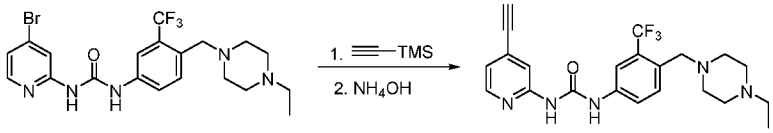
3H), 7.09 (dd, *J* = 6.8, 2.0 Hz, 1H), 4.59 (s, 1H), 3.54 (s, 2H), 2.38–2.32 (m, 8H), 2.15 (s, 3H); MS (ESI) *m/z* 418.15 $[C_{21}H_{22}F_3N_5O+H]^+$.

Intermediate 22: (4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000242] Preparation of 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) urea; A mixture of 4-bromopicolinoyl azide (7 g, 28.8 mmol) in toluene was heated to reflux for 1 h. To the reaction mixture at room temperature was added a solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (8.26 g, 28.8 mmol) in toluene. The reaction mixture was stirred for 16 h and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent $CHCl_3$/MeOH: 98:2) to afford 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) urea (2.5 g, 22%, LC-MS 92%) as an off white solid. m.p.: 161–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 11.72 (s, 1H), 8.94 (s, 1H), 8.10 (d, *J* = 5.6 Hz, 1H), 7.92 (d, *J* = 1.6 Hz, 1H), 7.74–7.67 (m, 2H), 7.18 (s, 1H), 7.14 (dd, *J* = 5.6, 1.2 Hz, 1H), 3.67 (s, 2H); 2.76–2.42 (m, 10H), 1.20 (t, *J* = 7.0 Hz, 3H); *m/z* 488 $[C_{20}H_{23}BrF_3N_5O+H]^+$.

Intermediate 23: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea



Step 1: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)urea

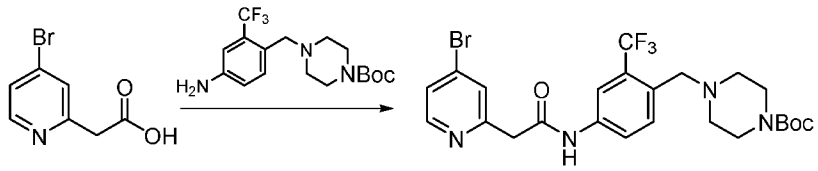
[000243] To a solution of 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (1 g, 2.036 mmol) in THF (15mL) under argon were successively added $PdCl_2(dppf)_2$•CH_2Cl_2 (166 mg, 0.203 mmol), CuI (58 mg, 0.31 mmol), TEA (1.4 mL, 10.28 mmol), ethynyltrimethylsilane (598 mg, 6.11 mmol). The reaction mixture was heated at 80 °C for 15 h and was filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was triturated with n-hexane.

The solid was isolated by filtration and purified by column chromatography (neutral alumina, eluent hexanes/EtOAc 8:2) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)urea (900 mg, 87.7%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.22 (s, 1H), 9.49 (s, 1H), 8.28 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.67–7.59 (m, 3H), 7.05 (d, J = 4.2 Hz, 1H), 3.55 (s, 2H), 2.38–2.33 (m, 10H), 1.02–1.01 (m, 3H), 0.26 (s, 9H). MS (ESI) *m/z*: 504.2 $[C_{25}H_{32}F_3N_5OSi+H]^+$.

Step 2: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea

[000244] A solution of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)urea (3 g, 5.95 mmol) and aqueous ammonia (50 mL) in THF (50 mL) was stirred at room temperature for 15 h. The reaction mixture was concentrated to a smaller volume under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (neutral alumina, eluent: hexanes/EtOAc 8:2) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea (2 g, 80%, AUC HPLC 96.9%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 9.52 (s, 1H), 8.30 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.67–7.59 (m, 3H), 7.05 (d, J = 4.2 Hz, 1H), 4.59 (s, 1H), 3.54 (s, 2H), 2.44–2.27 (m, 10H), 0.97 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 432.19 $[C_{22}H_{24}F_3N_5O + H]^+$.

Intermediate 24: tert-butyl 4-(4-(2-(4-bromopyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

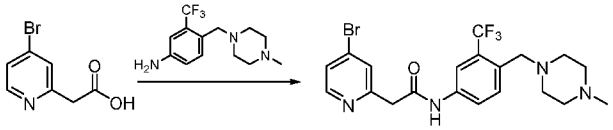


Preparation of tert-butyl 4-(4-(2-(4-bromopyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000245] To a solution of 2-(4-bromopyridin-2-yl) acetic acid (600 mg, 2.77 mmol) and *tert*-butyl 4-(4-amino-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (797 mg, 2.22 mmol in dichloromethane (25 mL) were added TEA (0.392 mL, 2.77 mmol) and Propylphosphonic anhydride (1.22 mL, 4.15 mmol). The reaction mixture was stirred at room

temperature for 16 h then was diluted with dichloromethane and washed in turn with water and brine solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give *tert*-butyl 4-(4-(2-(4-bromopyridin-2-yl) acetamido)-2-(trifluoromethyl) benzyl)piperazine-1-carboxylate (1.5 g).

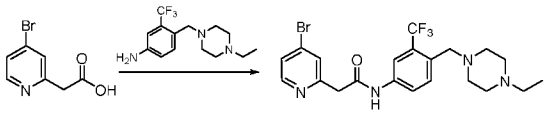
Intermediate 25: 2-(4-bromopyridin-2-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



Preparation of 2-(4-bromopyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide

[000246] To a solution of 2-(4-bromopyridin-2-yl) acetic acid (1.5 g, 6.94 mmol) and 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (2.08 g, 7.63 mmol in dichloromethane (25 mL) were added TEA (1.47 mL, 10.41 mmol) and propylphosphonic anhydride (2.1 g, 10.41 mmol). The reaction mixture was stirred at room temperature for 16 h then was diluted with dichloromethane and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(4-bromopyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) acetamide (1.2 g, LC-MS 88%).

Intermediate 26: 2-(4-bromopyridin-2-yl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide

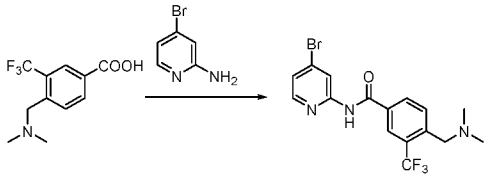


Preparation of 2-(4-bromopyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide

[000247] To a solution of 2-(4-bromopyridin-2-yl) acetic acid (1 g, 4.62 mmol) and 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (1.46 g, 5.09 mmol) in dichloromethane (25 mL) were added TEA (0.98 mL, 6.93 mmol), propylphosphonic anhydride (2.2 mL, 6.93mmol). The reaction mixture was stirred at room temperature for 16 h and was diluted with dichloromethane then washed in turn with water and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to

give 2-(4-bromopyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) acetamide (700 mg, LC-MS 91%).

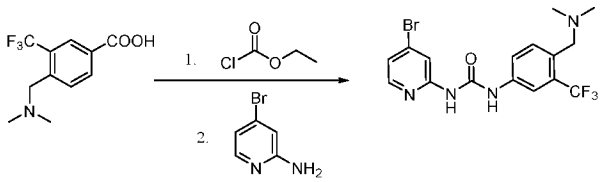
Intermediate 27: 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea



N-(4-bromopyridin-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide

[000248] To a solution of 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoic acid (3) (2.0 g, 8.09 mmol) in anhydrous pyridine (50 mL) at −10 °C, were added 4-bromopyridin-2-amine (1.75 g, 10.12 mmol) and, dropwise, phosphorus oxychloride (3.78 mL, 40.4 mmol) under vigorous agitation. The reaction mixture was stirred at −10 °C for 30 min, then was warmed to room temperature and stirred overnight. The reaction was quenched by adding crushed ice/water (50 mL) and the resulting mixture was extracted with EtOAc (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (neutral alumina, eluent pet-ether/ethyl acetate: 70/30) to afford *N*-(4-bromopyridin-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (1.2 g, 36% AUC HPLC 96%) as an off white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.32 (s, 1H), 8.45 (s, 1H), 8.32–8.27 (m, 3H), 7.91 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 3.60 (s, 2H), 2.22 (s, 6H); MS (ESI) *m/z*: 403.3 (M+H) $[C_{16}H_{15}BrF_3N_3O]^+$.

Intermediate 28: 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoyl azide

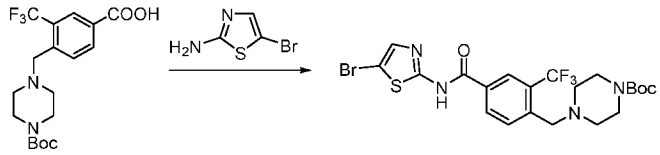
[000249] To a mixture of 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoic acid (4 g, 16.19mmol), triethylamine (3.4 g, 24.29 mmol) in THF (40 mL) at -10 °C, was slowly added ethyl chloroformate (2.27 g, 21.09 mmol). The reaction mixture was stirred for 2 h prior to

the addition of a solution –10 °C, of a solution of NaN_3 (1.78 g, 27.63 mmol) in water (100 mL). The reaction mixture was stirred for 2 h at room temperature and was poured into ice-cold water (80 mL). The aqueous phase was extracted with ethyl acetate (80 mL) and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoyl azide (2.5 g, 56.8 % LC-MS 95%) as yellow liquid *m/z* 273.09 $[C_{11}H_{11}F_3N_4O+H]^+$.

Step 2: Preparation of 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea

[000250] A mixture of 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoyl azide (1 g, 3.67 mmol) and 2-amino 4-bromo pyridine (636 mg, 3.67 mmol) in toluene was heated to reflux for 5 h then was cooled to room temperature. The precipitate was isolated by filtration and dried to afford 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea (1.0 g, 65.35%,) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.19 (s, 1H), 9.59 (s, 1H), 8.94 (s, 1H), 8.20 (d, J = 5.2 Hz, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.67–7.61 (m, 1H), 7.29–7.27 (m, 1H), 3.47 (s, 2H), 2.17 (s, 6H); *m/z* 417.0 $[C_{16}H_{16}BrF_3N_4O+H]^+$.

Intermediate 29: tert-butyl 4-(4-(5-bromothiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

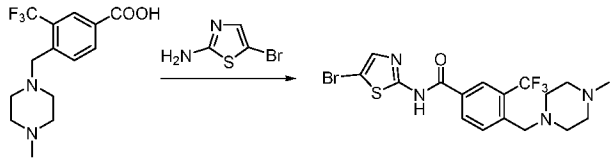


Preparation of *tert*-butyl 4-(4-(5-bromothiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

[000251] To a solution of 4-((4-(*tert*-butoxycarbonyl) piperazin-1-yl) methyl)-3-(trifluoromethyl) benzoic acid (1.5 g, 3.8 mmol) in anhydrous pyridine (100 mL) at −10 °C were added 5-bromothiazol-2-amine (760 mg, 4.25 mmol) and, dropwise, phosphorus oxychloride (1.42 mL, 15.2 mmol) under vigorous agitation. The reaction mixture was stirred at −10 °C for 30 min. The solution was allowed to warm to room temperature and then stirred overnight. The reaction was quenched by adding crushed ice/water (50 mL) and the resulting mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (neutral alumina, eluent petroleum ether/ethyl

acetate 90:10 to afford *tert*-butyl 4-(4-(5-bromothiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (1 g, AUC HPLC 94%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 13.20 (s, 1H), 8.44 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 3.71 (s, 2H), 3.33 (bs , 4H), 2.37 (bs, 4H), 1.39 (s, 9H); MS (ESI) *m/z*: 463.07 (M+H) $[C_{21}H_{24}BrF_3N_4O_3S]^+$

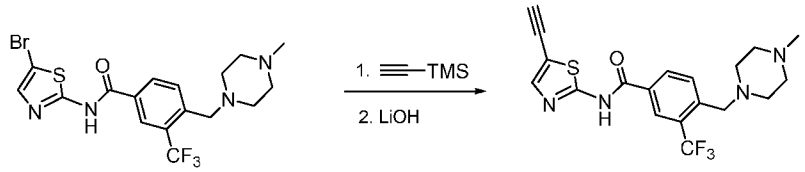
Intermediate 30: N-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000252] To a solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoic acid (15.0 g, 49.66 mmol) in anhydrous pyridine (100 mL) at −10 °C, were 5-bromothiazol-2-amine (10.6 g, 59.60 mmol) and, dropwise, phosphorus oxychloride (18.5 mL, 198.64 mmol) under vigorous agitation. The reaction mixture was stirred at −10 °C for 30 min, was allowed to warm to room temperature and then stirred overnight. The reaction was quenched by additing crushed ice/water (50 mL) followed by a extraction with ethyl acetate (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (neutral alumina, eluent petroleum ether/Ethyl acetate 80/20) to afford *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (6 g, 26%, AUC HPLC 96.75%) as an off white solid. m.p: 190–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.50 (bs, 1H), 8.20 (s, 1H), 8.08–8.03 (m, 2H), 7.25 (s, 1H), 3.74 (s, 2H), 2.54–2.48 (m, 8H), 2.31 (s, 3H); MS (ESI) *m/z*: 463.07 $[C_{17}H_{18}BrF_3N_4OS]^+$

Intermediate 31: N-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



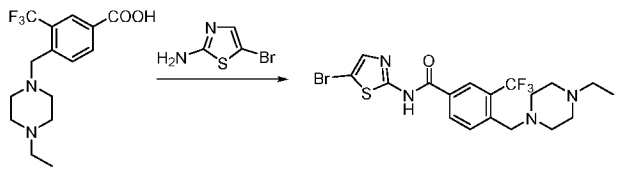
Step 1: preparation of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide

[000253] To a solution of *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (1.5 g, 3.23 mmol) in THF (20 mL) under argon were successively added $PdCl_2(PPh_3)_2$ (113 mg, 0.161 mmol), PPh_3 (42 mg, 0.161 mmol), CuI (92 mg, 0.484 mmol), triethylamine (978 mg, 9.69 mmol), ethynyltrimethylsilane (952 mg, 9.71 mmol). The reaction mixture was heated at 80 °C for 5 h in a sealed tube then was filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and, the residue was purified by column chromatography (neutral alumina, eluent, hexane/ethyl acetate 30:70) to afford 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide (300 mg, 20%, LC-MS 98%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.8 (bs, 1H), 8.43 (s, 1H), 8.34 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.81 (s, 1H), 3.69 (s, 2H), 2.43–2.44 (m, 8H), 2.23 (s, 3H), 0.23 (s, 9H). MS (ESI) *m/z*: 481.11 $[C_{22}H_{27}F_3N_4OSSi + H]^+$.

Step 2: preparation of *N*-(5-ethynylthiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000254] To a solution of $LiOH•H_2O$ (27 mg, 0.63 mmol) in water (5 mL) was added a solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-N-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide (300 mg, 0.625 mmol) in THF (10 mL) and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and residue was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *N*-(5-ethynylthiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (250 mg, 68%, LC-MS 71%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.90 (s, 1H), 8.43 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 4.49 (s, 1H), 3.67 (s, 2H), 2.42–2.38 (m, 8H), 2.18 (s, 3H). MS (ESI) *m/z*: 409.2 $[C_{19}H_{19}F_3N_4OS + H]^+$.

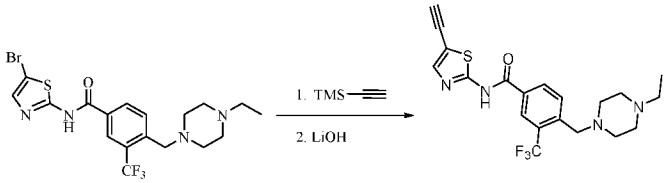
Intermediate 32: N-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000255] To a solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoic acid (10 g, 31.64 mmol) in anhydrous pyridine (100 mL) at−10 °C were successively added 5-bromothiazol-2-amine (6.79 g, 37.97 mmol) and, dropwise under vigorous stirring.phosphorus oxychloride (11.83 mL, 126.56 mmol). The reaction mixture was stirred at −10 °C for 30 min and was stirred overnight while warming to room temperature. The reaction was quenched by adding ice/water (50 mL) and the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (neutral alumina, eluent: ethyl acetate: Petroleum ether 20:80) to afford *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (5 g, 33%, AUC HPLC 96.4%) as an off white solid. m.p: 191–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.80 (bs, 1H), 8.43 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 3.69 (s, 2H), 2.46–2.38 (m, 10H), 1.01 (t, J = 4.0 Hz, 3H); MS (ESI) *m/z*: 477 $[C_{18}H_{20}BrF_3N_4OS]^+$

Intermediate 33: 4-((4-ethylpiperazin-1-yl)methyl)-N-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide

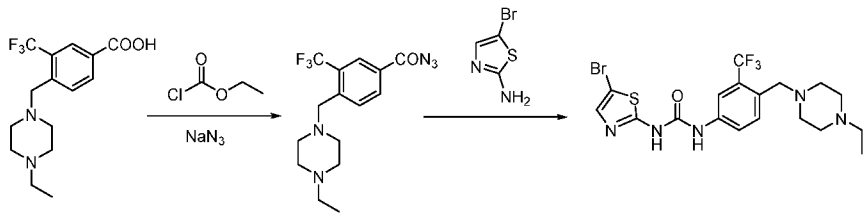
[000256] To a solution of *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (1.4 g, 2.93 mmol) in THF (20 mL) under Argon were successively added $PdCl_2(PPh_3)_2$ (103 mg, 0.146 mmol), PPh_3 (38 mg, 0.146 mmol), CuI (83 mg, 0.44 mmol), triethylamine (1.2 mL, 8.8 mmol) and ethynyltrimethylsilane (862 mg, 8.81 mmol). The reaction mixture was heated in sealed tube at 60 °C for 5 h and was filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (neutral alumina, eluent: hexane/ethyl acetate 20:80) to afford 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide (400 mg, 20%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H), 8.08–8.03 (m, 2H), 7.46 (s, 1H), 3.74 (s, 2H), 2.56–

2.41 (m, 10H), 1.09 (t, *J* = 6.8 Hz, 3H), 0.25 (s, 9H). MS (ESI) m/z: 494.9 [$C_{23}H_{29}F_3N_4OSSi$ + H]$^+$.

Step 2: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl)benzamide

[000257] To a solution of LiOH•H_2O (18 mg, 0.40 mmol) in water (2 mL) was added 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide (200 mg, 0.404 mmol). The reaction mixture was stirred at room temperature for 2 h and was diluted with ethyl acetate. The organic phase was washed in turn with water and brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl)benzamide (160 mg, 94%, LC-MS 95.9.%) as a pale yellow solid.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.42 (s, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 4.35 (s, 1H), 3.65 (s, 2H), 2.41–2.30 (m, 10H), 0.98 (d, *J* = 7.2 Hz, 3H). MS (ESI) m/z:423.3 [$C_{20}H_{21}F_3N_4OS$ + H]$^+$.

Intermediate 34: 1-(5-bromothiazol-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



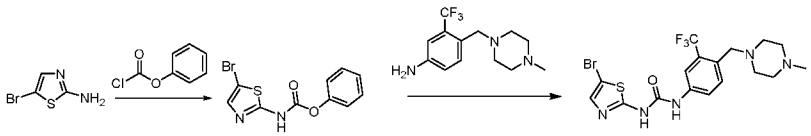
Step 1: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoyl azide

[000258] To a solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoic acid (3.5 g, 11.07 mmol) in THF (50 mL) were successively added TEA (4.8 ml, 32.67 mmol), ethyl chloroformate (4.4 mL, 18.75 mmol) at 0 °C. After 1 h, a solution of NaN_3 (1.4 g, 21.53 mmol) in water (2 mL) at 0 °C was added and was follew by a 2 h stirring at room temperature. To the reaction mixture was added water (50 mL) and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoyl azide (1.1 g, 29.7 %) as colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 1H), 8.15 (d, *J* = 9.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 2H), 2.54–2.43 (m, 10H), 1.08 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z*: 342.15 [$C_{15}H_{18}F_3N_5O$+H]$^+$.

Step 2: Preparation of 1-(5-bromothiazol-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000259] A solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoyl azide 2(1.1 g, 3.22 mmol) and 5-bromothiazol-2-amine (0.8 g, 4.46 mmol) in toluene was heated at 95 °C for16 h. The reaction mixture was concentrated and purified by column chromatography (neutral alumina, eluents: DCM/MeOH 93:7) to afford 1-(5-bromothiazol-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (250 mg,16%) as a brown solid (LC-MS 78.6%). MS (ESI) *m/z*: 592.01 (M+1) $[C_{18}H_{21}BrF_3N_5OS+H]^+$.

Intermediate 35: 1-(5-bromothiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of phenyl 5-bromothiazol-2-ylcarbamate

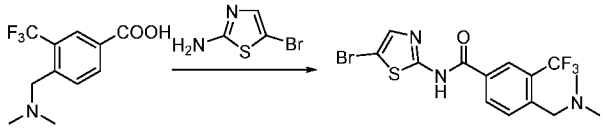
[000260] A solution of 2-amino-5-bromothiazole (5 g, 27.9 mmol) and pyridine (8.81 mL, 111.7 mmol) in dry dichloromethane (120 mL) was stirred under an inert atmosphere prior to the dropwise addition of a solution of phenyl chloroformate (5.22 g, 33.48 mmol) in dichloromethane (20 mL). The resulting reaction mixture and the mixture was stirred for 2 hours then was concentrated under reduced pressure. The residue was suspended in a mixture of hexane and water. The solid that has formed, was isolated by filtration, washed in turn with water and a mixture of hexane/dichloromethane (3:1), then dissolved in THF (100 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under reduced to give phenyl 5-bromothiazol-2-ylcarbamate (7 g, 84.3%, LC-MS 96%). ^{1}H NMR (DMSO-d_6): 7.27 (m, 3H), 7.44 (m, 2H), 7.52 (s, 1H); MS (ESI) m/z: 301 $[C_{10}H_7BrN_2O_2S+H]^+$.

Step 2: Preparation of 1-(5-bromothiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000261] To a solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (2.0 g, 7.35 mmol) and triethylamine (2.81 mL, 20.08 mmol) in anhydrous 1,4-dioxane (20 mL) at room temperature, was added phenyl 5-bromothiazol-2-ylcarbamate (2.0 g, 6.68 mmol). The reaction mixture was stirred at 60 °C under argon atmosphere for 3 hours, then was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent, dichloromethane/MeOH 90:10) to afford 1-(5-bromothiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea as

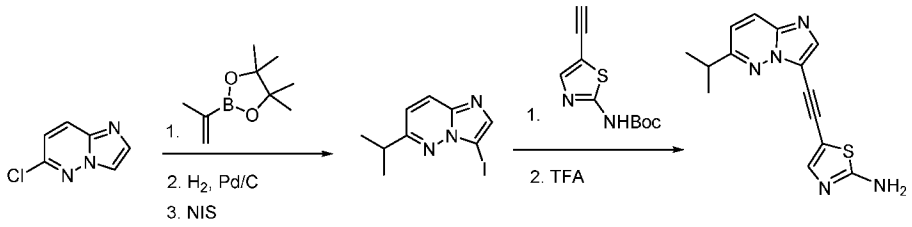
a brown solid (1.5 g, LC-MS 70%); which was used without further purification in the next step.

Intermediate 36: N-(5-bromothiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide



[000262] To a solution of 4-((dimethylamino) methyl)-3-(trifluoromethyl) benzoic acid (2.5 g, 10.12 mmol) in anhydrous pyridine (50 mL) at −10 °C were successively added 5-bromothiazol-2-amine (1.81 g, 10.12 mmol) and, dropwise, phosphorus oxychloride (3.78 mL, 40.4 mmol) under vigorous agitation. The reaction mixture was stirred at −10 °C for 30 min then was warmed to room temperature and stirred overnight. The reaction was quenched by adding crushed ice/water (50 mL) and the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (neutral alumina, eluent petroleum ether/ethyl acetate 60/40) to afford *N*-(5-bromothiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (1.5 g, 36%, AUC HPLC 98%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.09 (s, 1H), 8.43 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 3.62 (s, 2H), 2.22 (s, 6H); MS (ESI) *m/z*: 409.9 (M+H) $[C_{14}H_{13}BrF_3N_3OS]^+$.

Intermediate 37: Synthesis of 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine



[000263] Step 1: Preparation of 6-(prop-1-en-2-yl)imidazo[1,2-b]pyridazine. To a solution of 6-chloroimidazo[1,2-b]pyridazine (4 g, 26.43mmol), K_3PO_4 (11.08 g, 52.28 mmol), and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (5.7 g, 33.98 mmol) in 1,4-dioxan (25 mL) and water (4 mL) under Argon was added $Pd(PPh_3)_4$ (1.5 g, 1.30 mmol). The reaction mixture was heated at 100 °C for 16 h and was filtered through celite. The filtrate

was concentrated, diluted with water and extracted into EtOAc, washed in turn with water and brine. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent petroleum ether/ EtOAc 70:30) to afford 6-(prop-1-en-2-yl)imidazo[1,2-b]pyridazine (3.8 g, 91.5%, LC-MS 91%) as a yellow solid. MS (ESI) *m/z*:159.8 $[C_6H_4ClN_3+H]^+$.

Step 2: Preparation of 6-isopropylimidazo[1,2-b]pyridazine. To a solution of 6-(prop-1-en-2-yl)imidazo[1,2-b]pyridazine(3.8 g) in ethanol(30 mL) was added Pd/C(380 mg, 10% w/w) and stirred under hydrogen (60 psi) for 16 h. The reaction mixture was filtered through celite pad, and the filtrate was concentrated to afford 6-isopropylimidazo[1,2-b]pyridazine (4.0 g, LC-MS 78%) as an orange oil. MS (ESI) *m/z*: 162.2 $[C_9H_9N_3+H]^+$.

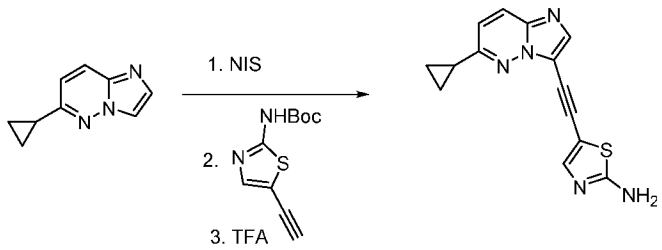
Step 3: Preparation of 3-iodo-6-isopropylimidazo[1,2-b]pyridazine. To a solution of 6-isopropylimidazo[1,2-b]pyridazine (3.5 g 18.63 mmol) in DMF(10 mL) was added *N*-iodosuccinimide and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water, the solid that has precipitated was isolated by filtration and washed several times with water to afford 3-iodo-6-isopropylimidazo[1,2-b]pyridazine(3.5 g, LC-MS 74%) as a yellow solid. MS (ESI) *m/z*: 288.02 $[C_9H_8N_3I+H]^+$

[000264] Step 4: Preparation of *tert*-butyl 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate. To a solution of *tert*-butyl 5-ethynylthiazol-2-ylcarbamate (2.1 g, 9.58 mmol), 3-iodo-6-isopropylimidazo[1,2-b]pyridazine (2.5 g, 8.71 mmol), CuI (248 mg, 0.435 mmol) and DIPEA (4.68 mL, 26.13 mmol) in acetonitrile (50 mL) under argon were added $Pd(PPh_3)_4$ (503 mg, 0.435 mmol). The reaction mixture was heated at 90 °C for 6 h then, was diluted with water and extracted with $CHCl_3$. The organic phase was washeh in turn with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 98:2) to give *tert*-butyl 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (2.5 g, LC-MS 70%) as a yellow solid. MS (ESI) *m/z* 383.9 $[C_{19}H_{21}N_5O_2S+H]$.

[000265] Step 5: Preparation of 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine. To a solution of *tert*-butyl 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (2 g, 5.22 mmol) in dichloromethane (10 mL) and TFA (8 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water and basified with $NaHCO_3$, extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain

5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (400 mg, LC-MS 86%) as a yellow solid. MS (ESI) *m/z* 384.1 [$C_{14}H_{13}N_5S$+H].

Intermediate 38: Synthesis of 5-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine



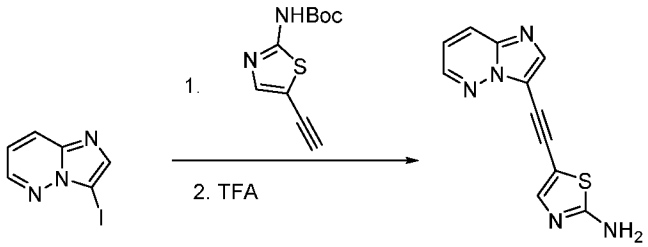
[000266] Step 1: Preparation of 6-cyclopropyl-3-iodoimidazo[1,2-b]pyridazine. A mixture of 6-cyclopropylimidazo[1,2-b]pyridazine (700 mg, 4.4 mmol) and *N*-iodosuccinimide (1 g, 4.84 mmol) in DMF (5 mL) was stirred at room temperature for 2 h.The reaction mixture was diluted with water, the precipitate was washed several times with water to afford 6-cyclopropyl-3-iodoimidazo[1,2-b]pyridazine (800 mg, LC-MS 70%) as a yellow solid. MS (ESI) *m/z*: 286.1 $[C_9H_8IN_3+H]^+$

[000267] Step 2: Preparation of *tert*-butyl 5-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate. To a solution of *tert*-butyl 5-ethynylthiazol-2-ylcarbamate (628 mg, 2.80 mmol), 6-cyclopropyl-3-iodoimidazo[1,2-b]pyridazine (800 mg, 2.80), CuI (80 mg, 0.42 mmol) and DIPEA (1 mL, 5.61 mmol) in acetonitrile (10 mL) under argon were added $Pd(PPh_3)_4$ (162 mg, 0.14 mmol) and PPh_3 (36 mg, 0.14 mmol). The reaction mixture was heated at 80 °C for 6 hand was concentrated under reduced pressure. The residue was diluted with water and extracted with $CHCl_3$. The combined organic layer washed in turn with water and brine, was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/CH_3OH 98:2) to give *tert*-butyl 5-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (600 mg) as a pale yellow solid. MS (ESI) *m/z* 382.2 [$C_{19}H_{19}N_5O_2S$+1].

[000268] Step3: Preparation of 5-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine. A solution of *tert*-butyl 5-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (1.8 g, 4.72 mmol) in dichloromethane (20 mL) and TFA (30 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water and basified with 30% NaOAc solution and extracted with $CHCl_3$. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure to asfford 5-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (700 mg) as a yellow solid. MS (ESI) *m/z* 282.4 $[C_{14}H_{11}N_5S+H]^+$.

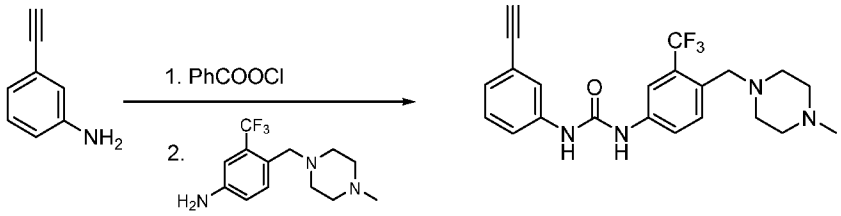
Intermediate 39: Synthesis of 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-amine



[000269] Step 1: Preparation of *tert*-butyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate. To a solution of *tert*-butyl 5-ethynylthiazol-2-ylcarbamate (918 mg, 4.09 mmol), 3-iodoimidazo[1,2-b]pyridazine (1 g, 4.09 mmol), CuI (12 mg, 0.614 mmol) and DIPEA (1.15 mL, 0.614 mmol) in acetonitrile (15 mL) under argon were added $Pd(PPh_3)_4$ (236 mg, 0.204 mmol) and PPh_3 (53 mg, 0.204 mmol). The reaction mixture was heated at 80 °C for 6 h and was concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The combined organic layer was washed in turn with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent CH_2Cl_2/CH_3OH 97:3) to give *tert*-butyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate (700 mg, LC-MS 70%) as a yellow solid. MS (ESI) *m/z* 342.15 $[C_{16}H_{15}N_5O_2S+H]^+$.

[000270] Step 2: Preparation of 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-amine. A solution of *tert*-butyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate (700 mg, 2.05 mmol) in dichloromethane (10 mL) and TFA (15 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water and basified with a 30% aqueous solution of NaOAc and extracted with ethyl acetate. The combined organic layer was washed in turn with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-amine (400 mg) as a yellow solid. MS (ESI) *m/z* 242.12 $[C_{11}H_7N_5S+H]^+$.

Intermediate 40: Synthesis of 1-(3-ethynylphenyl)-3-(4-((4-methylpiperzin-1-yl) methyl)-(trifluoromethyl) phenyl) urea

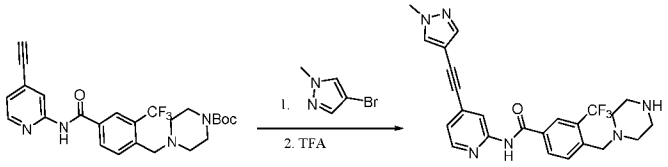


[000271] Step 1: Preparation of phenyl 3-ethynylphenylcarbamate. To an ice-cold solution of 3-ethynylaniline (5 g, 42.73 mmol) and pyridine (2 mL) in dichloromethane (20 mL) was added dropwise phenylchloroformate (3 mL dissolved in 5 mL DCM). The reaction mixture was stirred at room temperature for 4 h and was concentrated under reduce pressure. The residue was diluted with water, solid separated was filtered and washed with n-pentane and dried to afford phenyl 3-ethynylphenylcarbamate as a brown solid (6 g, 78%, LC-MS 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.37 (s, 1H), 7.66 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.45–7.42 (m, 2H), 736–7.33 (m, 1H), 7.28–7.23 (m, 3H), 7.18(d, J = 7.6 Hz, 1H) 4.18 (s, 1H). MS (ESI) m/z: 238.03 $[C_{15}H_{11}NO_2+H]^+$.

[000272] Step 2: Preparation of 1-(3-ethynylphenyl)-3-(4-((4-methylpiperzin-1-yl) methyl)-(Trifluoromethyl) phenyl) urea. A solution of phenyl 3-ethynylphenylcarbamate (1 g, 4.219 mmol) were added 4-((4-methylpiperazin-iyl) methyl)-3-(triflouromethyl) aniline (924 mg, 3.37 mmol) and triethylamine (1.1 mL, 8.43 mmol) in 1,4 dioxane (10 mL) and stirred at 80 °C for 2 h and the reaction mixture was concentrated under reduced pressure. The residue was diluted with water, extracted into ethyl acetate. The ombined organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/MeOH 90:10) to afford 1-(3-ethynylphenyl)-3-(4-((4-methylpiperzin-1-yl) methyl)-(trifluoromethyl) phenyl) urea (800 mg, LC-MS-88%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.02 (s, 1H), 8.84 (s, 1H),7.95 (d, J = 1.6 Hz, 1H), 7.66 (s, 1H), 7.64 (d, J = 14.0 Hz, 1H), 7.55 (dd, J = 8.0, 1.2 Hz, 1H), 7.42 (dd, J = 8.0, 1.2 Hz, 1H). 7.31–7.27 (m, 1H), 7.10 (d, J = 7.6 Hz, 1H), 4.14 (s, 1H), 3.52 (s, 2H), 2.37–2.32 (m, 8H), 2.16 (s, 3H). MS (ESI) m/z: 417.14 $[C_{22}H_{23}F_3N_4O+H]^+$.

Examples

Example 1: N-(4-((1-methyl-1H-pyrazol-4-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide



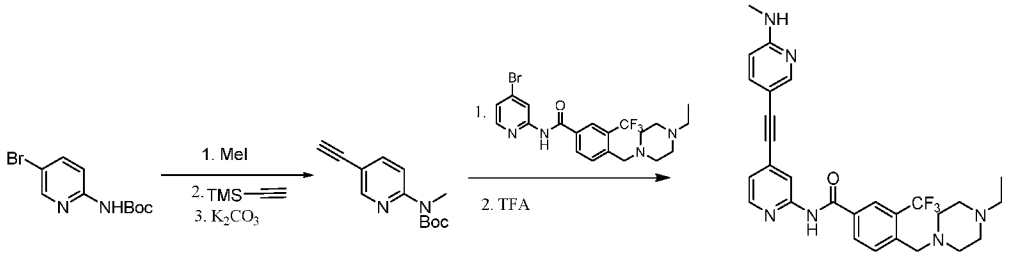
Step 1: Preparation of *tert*-butyl 4-(4-(4-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000273] To a solution of *tert*-butyl 4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (300 mg, 0.56 mmol) in acetonitrile (15 mL) under Argon were successively added $PdCl_2(PPh_3)_2$ (32 mg, 0.028 mmol), CuI (16 mg, 0.83 mmol), 4-bromo-1-methyl-1H-pyrazole (73.5 mg, 0.664 mmol) and DIPEA (143 mg , 1.10 mmol). The reaction mixture was heated at 80 °C for 15 h, was diluted with EtOAc and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel eluent: with dichloromethane/methanol 80:20) to afford *tert*-butyl 4-(4-(4-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (80 mg, 25%, LC-MS 95 %) as a yellow solid.

Step 2: Preparation of *N*-(4-((1-methyl-1*H*-pyrazol-4-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide

[000274] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(4-((1-methyl-1*H*-pyrazol-4-yl)ethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The crude product was purified by flash column chromatography (silica gel, eluent; $CHCl_3/CH_3OH$ 96:4) to give *N*-(4-((1-methyl-1*H*-pyrazol-4-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide (5 mg, 18%, AUC HPLC 96%) as an off-white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.57 (s, 1H), 8.42 (s, 1H), 8.28–8.27 (d, J = 4.4 Hz, 2H), 8.06–8.04 (d, m, 2H), 7.70–7.68 (d, J = 8.0 Hz, 2H), 7.26 (s, 1H), 3.95 (s, 3H), 3.71 (s, 2H), 2.95–2.92 (m, 4H), 2.50–2.46 (m, 4H); MS (ESI) *m/z* 468 $[C_{24}H_{23}F_3N_6O\ H]^+$.

Example 2: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-(methylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 5-bromopyridin-2-yl(methyl)carbamate

[000275] To a suspension of NaH (0.33 g, 13.96 mmol) in DMF (10 mL) cooled to 0-5 °C, was added *tert*-butyl 5-bromopyridin-2-ylcarbamate (1.9 g, 6.98 mmol) portion-wise. After 15 minutes, MeI (1.2 g, 8.38 mmol) was added drop-wise at 0 °C. Reaction mixture was stirred at room temperature for 2 h. Reaction mixture was poured into crushed-ice and extracted into EtOAc. Organic layer was washed with water followed by brine. Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 5-bromopyridin-2-yl(methyl)carbamate (1.8 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.40 (d, *J* = 2.0 Hz, 1H), 7.71–7.65 (m, 2H), 3.37 (s, 3H), 1.52 (s, 9H).

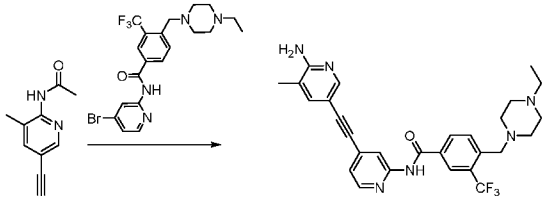
[000276] Step 2: Preparation of *tert*-butyl methyl (5-((trimethylsilyl)ethynyl)pyridin-2-yl)carbamate; The title compound was synthesized from *tert*-butyl 5-bromopyridin-2-yl(methyl) carbamate and ethynyltrimethylsilane following a method similar to general procedure A. The reaction crude product was purified by chromatography (silica gel, eluent hexanes/ethyl acetate 98:2) to afford *tert*-butyl methyl(5-((trimethylsilyl)ethynyl)pyridin-2-yl)carbamate (1.3 g, 68.4%) as a brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (d, *J* = 1.2 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 2, 8.8 Hz, 1H), 3.39 (s, 3H), 1.52 (s, 9H), 0.25 (s, 9H); MS (ESI) *m/z* 305.3 $[C_{16}H_{24}N_2O_2Si+H]^+$.

Step 3: Preparation of *tert*-butyl 5-ethynylpyridin-2-yl(methyl)carbamate; A solution of *tert*-butyl methyl (5-((trimethylsilyl)ethynyl)pyridin-2-yl)carbamate (1.3 g, 4.26 mmol) and K_2CO_3 (1.15 g, 8.52 mmol) in methanol (20 mL) was stirred at room temperature for 3 h and the reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 5-ethynylpyridin-2-yl (methyl)carbamate (900 mg, 90.7%) as a pale brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.47 (d, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 2.4, 8.8 Hz, 1H), 3.40 (s, 3H), 3.15 (s, 1H), 1.53 (s, 9H); MS (ESI) *m/z* 233 $[C_{13}H_{16}N_2O_2+H]^+$.

[000277] Step 4: Preparation of *tert*-butyl 5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)pyridin-2-yl(methyl)carbamate; The title compound was synthesized from *tert*-butyl 5-ethynylpyridin-2-yl(methyl)carbamate and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The crude product was purified by chromatography (silica gel, eluent dichloromethane/CH_3OH 98:2) to afford *tert*-butyl 5-((2-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamido) pyridin-4-yl)ethynyl)pyridin-2-yl(methyl)carbamate (700 mg) as a pale brown semi-solid. MS (ESI) *m/z* 621 $[C_{33}H_{37}F_3N_6O_3+H]^+$.

[000278] Step 5: preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-(methylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)pyridin-2-yl(methyl)carbamate following a method similar to general procedure D. Crude product was purified by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-(methylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (200 mg, HPLC 98.2%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.23 (s, 1H), 8.41 (d, J = 5.2 Hz, 1H), 8.34–8.25 (m, 4H), 7.92 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 4.8 Hz, 1H), 7.16–7.15 (m, 1H), 6.51 (d, J = 8.8 Hz, 1H), 3.67 (s, 2H), 2.82 (d, J = 4.4 Hz, 3H), 2.43–2.29 (m, 10H), 0.98 (t, J = 6.8 Hz, 3H); MS (ESI) *m/z* 523 $[C_{28}H_{29}F_3N_6O+H]^+$.

Example 3: N-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000279] Step 1: Preparation of *N*-(3-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide; The title compound was synthesized from *N*-(5-bromo-3-methylpyridin-2-yl)acetamide and ethynyltrimethylsilane following a method similar to general procedure A. The residue mixture was purified by column chromatography (silica gel, eluents hexanes/EtOAc 4:1) to afford *N*-(3-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (153 mg, 71%) as brown solid.^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (s, 1H), 8.02 (s,

1H), 7.61 (s, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 0.24 (s, 9H); MS (ESI) *m/z* 247 [$C_{13}H_{18}N_2OSi$ + H]$^+$.

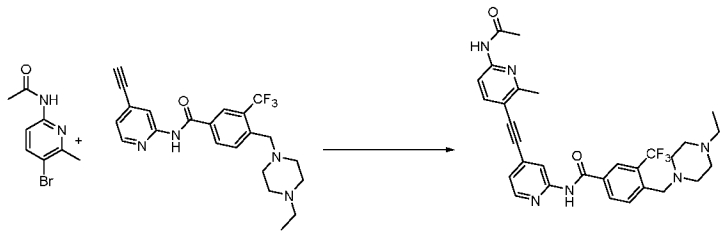
[000280] Step 2: Preparation of *N*-(5-ethynyl-3-methylpyridin-2-yl)acetamide; To a solution of *N*-(3-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (153 mg, 0.62 mmol) in MeOH (10 mL) was added potassium carbonate (300 mg, 3.49 mmol) and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, then diluted with water (100 mL) and extracted with DCM (3×15 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure to afford *N*-(5-ethynyl-3-methylpyridin-2-yl)acetamide (40 mg, 37%,) as brown solid; MS (ESI) *m/z* 175 [$C_{10}H_{10}N_2O$ + H]$^+$.

[000281] Step 3: Preparation of *N*-(4-((6-acetamido-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

The title compound was prepared following a method similar to general procedure A and starting from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and *N*-(5-ethynyl-3-methylpyridin-2-yl)acetamide. A purification by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) gave *N*-(4-((6-acetamido-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (26 mg, 43%, AUC HPLC 98 %) as brown solid and *N*-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (6 mg, 11%, AUC HPLC 99 %) as a yellow solid.

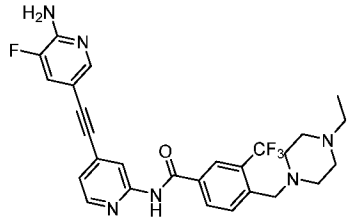
[000282] *N*-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide; m.p. 124 –126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.62 (s, 1H), 8.48 (s, 1H), 8.27 (d, *J* = 4.0 Hz, 1H), 8.20 (s, 2H), 8.07 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* =7.6 Hz, 1H), 7.46 (s,1H), 7.15 (d, *J* = 3.56 Hz, 1H), 4.68 (s, 2H), 3.74 (s, 2H), 2.80 – 2.50 (m, 10H), 2.16 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.17, 157.08, 151.34, 149.83, 147.86, 142.83, 140.38, 134.30, 132.78, 131.00, 130.21, 124.98, 124.92, 121.87, 116.08, 115.81, 109.04, 92.72, 87.69, 57.99, 53.21, 52.83, 52.29, 16.89, 11.95; MS (ESI) *m/z* 523 [$C_{28}H_{29}F_3N_6O$+ H]$^+$.

Example 4: N-(4-((6-acetamido-2-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000283] The title compound was synthesized from4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and *N*-(5-bromo-6-methylpyridin-2-yl)acetamide following a method similar to general procedure A. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((6-acetamido-2-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (10 mg, 15%, AUC HPLC 99%) as white solid; m.p. 65.5–67.4 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.39 (d, J = 5.2 Hz, 1H), 8.37 (s, 1H), 8.31 (s, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.05–7.98 (m, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 5.8 Hz, 1H), 3.80 (s, 2H), 2.68 (s, 3H), 2.51–2.82 (m, 10H), 2.19 (s, 3H),1.16 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 170.71, 165.55, 159.40, 152.09, 151.00, 148.14, 141.78, 141.42, 133.29, 133.16, 130.87, 130.81, 128.70 (q, J = 30.8 Hz), 125.26 (q, J = 5.9 Hz), 124.15 (q, J = 273.6 Hz), 121.42, 116.08, 112.95, 110.66, 91.37, 90.36, 57.58, 52.26, 52.09, 51.85, 22.66, 22.06, 10.08; MS (ESI) *m/z* 565 $[C_{30}H_{31}F_3N_6O_2+H]^+$.

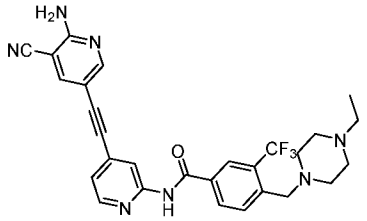
Example 5: N-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000284] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 4-iodo-3-methyl-1*H*-pyrazole following a method similar to general procedure A. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (14 mg, 22%, AUC HPLC 96%) as a white solid; m.p. 77.1–78.5 °C; ^{1}H NMR (400 MHz,

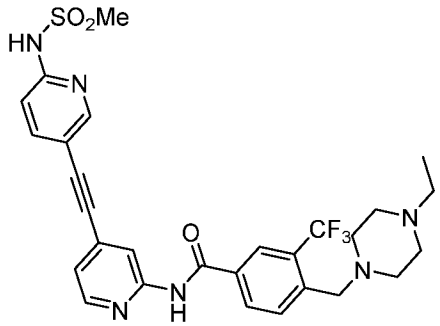
MeOD-d_4) δ (ppm): 8.49 (bs, 1H), 8.34 (d, J = 5.0 Hz, 1H), 8.31 (s, 2H), 8.22 (d, J = 8.2 Hz, 1H), 8.01–7.99 (m, 2H), 7.48 (dd, J = 11.4, 1.6 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 3.84 (s, 2H), 3.10–2.96 (m, 6H), 2.73 (bs, 4H), 1.28 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 169.43, 166.82, 153.40, 151.65, 151.52, 149.46, 147.94 (d, J = 4.9 Hz), 142.41, 135.03, 134.79, 132.36 (d, J = 16.4 Hz), 130.17 (q, J = 30.8 Hz), 126.79 (q, J = 5.6 Hz), 125.54 (q, J = 273.5 Hz), 124.57 (d, J = 16.8 Hz), 122.86, 117.46, 108.31 (d, J = 3.3 Hz), 91.93, 88.32, 58.53, 53.08, 51.88, 10.20; MS (ESI) m/z 527 $[C_{27}H_{26}F_4N_6O + H]^+$.

Example 6: N-(4-((6-amino-5-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



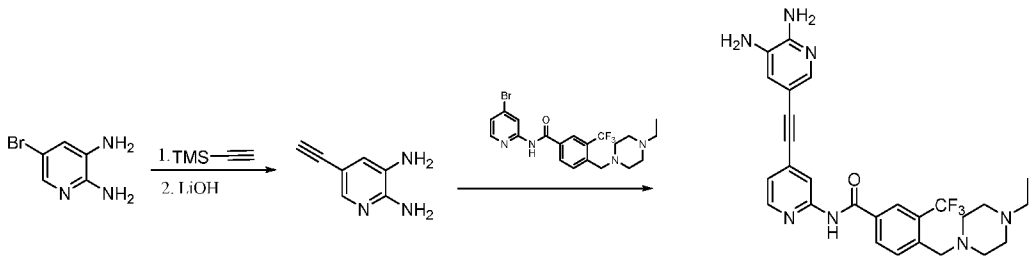
[000285] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 2-amino-5-bromonicotinonitrile following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((6-amino-5-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (14 mg, 22%, AUC HPLC 99%) as brown solid; m.p. 199.6–201.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.28 (bs, 1H), 8.53 (s, 1H), 8.43 (s, 1H), 8.39 (bs, 1H), 8.26 (s, 2H), 8.12 (d, J = 7.9 Hz, 1H), 7.93-7.81 (m, 2H), 7.18 (d, J = 4.8 Hz, 1H), 5.64 (s, 2H), 3.81 (s, 2H), 3.06 (bs, 4H), 2.97 (q, J = 7.2 Hz, 2H), 2.79(bs, 4H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.76, 164.36, 158.42, 155.96, 151.52, 147.41, 144.02, 141.25, 133.71, 133.28, 131.05, 130.61, 129.69, 125.66, 123.77, 121.93, 116.43, 115.38, 108.87, 91.51, 89.82, 88.84, 57.71, 51.49, 51.12, 50.21, 9.36; MS (ESI) m/z 534 $[C_{28}H_{26}F_3N_7O + H]^+$.

Example 7: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-(methylsulfonamido)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000286] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and *N*-(5-bromopyridin-2-yl)methanesulfonamide following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-(methylsulfonamido)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (9 mg, 13%, AUC HPLC 99%) as brown solid; m.p. 102.8-103.2 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.09-8.82(m, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.46 (s, 1H), 8.33 (d, *J* = 5.1 Hz, 1H), 8.23 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.86 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 5.1 Hz, 1H), 3.78 (s, 2H), 3.25 (s, 3H), 3.00-2.61 (m, 8H), 2.79 (q, *J* = 7.3 Hz, 2H) 1.23 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.41, 164.32, 151.48, 151.41, 150.74, 147.90, 142.01, 141.91, 133.42, 133.09, 131.07, 130.45, 129.60, 125.35, 124.43, 122.07, 116.28, 114.00, 111.73, 90.15, 89.58, 57.80, 51.67, 51.62, 51.24, 41.42, 10.22; MS (ESI) *m/z* 587 $[C_{28}H_{29}F_3N_6O_3S + H]^+$.

Example 8: N-(4-((5, 6-diaminopyridin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide



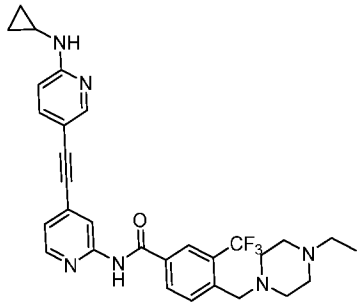
[000287] Step 1: Preparation of 5-((trimethylsilyl) ethynyl) pyridine-2, 3-diamine; The title compound was synthesized from 5-bromopyridine-2,3-diamine and ethynyltrimethylsilane following a method similar to general procedure A. Crude product was purified by column

chromatography (silica gel, methnol/dichloromethane 1:100) to afford 5-((trimethylsilyl)ethynyl)pyridine-2,3-diamine (600 mg, 60 %) as pale brown color solid. MS (ESI) *m/z* 206.3 $[C_{10}H_{15}N_3Si]^+$.

[000288] Step 2: Preparation of 5-ethynylpyridine-2, 3-diamine; A solution of 5-((trimethylsilyl) ethynyl) pyridine-2,3-diamine (600 mg, 2.92 mmol) and LiOH (184 mg,4.39 mmol) in mixture of THF (10 mL) and water (5 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduce pressure, the residue was diluted with EtOAc and washed in turn with water and brine. Organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 5-ethynylpyridine-2, 3-diamine (300 mg, 79 %) as pale brown color solid. MS (ESI) *m/z* 134 $[C_7H_7N_3+H]^+$

[000289] Step 3: Preparation of *N*-(4-((5, 6-diaminopyridin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide; The title compound was synthesized from5-ethynylpyridine-2, 3-diamine and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide following a method similar to general procedure A. Crude product was purified by preparative TLC to afford *N*-(4-((5, 6-diaminopyridin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide (0.05 mg, 25%, LCMS-97%, HPLC Purity?) as off white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.18 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H), 8.31 (s, 1H), 8.28 (d, J = 8.0 Hz, 2H), 8.22 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.22 (d, J = 4.8 Hz, 1H), 6.83 (s, 1H), 6.03 (s, 2H), 4.90 (s, 2H), 3.68 (s, 2H), 2.49–2.32 (m, 10H), 0.99 (t, J = 0.8 Hz, 3H). MS (ESI) *m/z* 524.3 $[C_{27}H_{28}F_3N_7O+H]^+$.

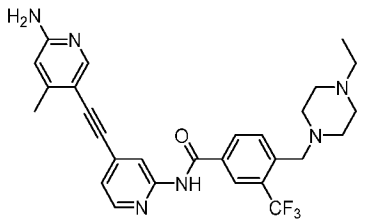
Example 9: N-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000290] The title compound was synthesized from*N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and 5-bromo-*N*-cyclopropylpyridin-2-amine following a method similar to general procedure A. The crude

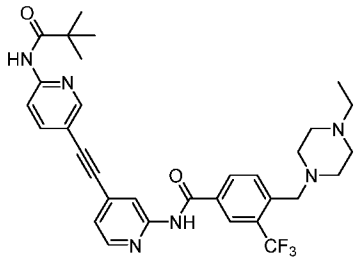
product was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (18 mg, 27%, AUC HPLC 93%) as brown solid; m.p. 83–85 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.34 (d, *J* = 8.0 Hz, 1H), 8.30 (s, 2H), 8.24–8.18 (m, 2H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.66 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 5.2 Hz, *J* = 1.2 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 3.78 (s, 2H), 2.90–2.40 (m, 11H), 1.15 (t, *J* = 7.3 Hz, 3H), 0.82 (m, *J* = 2.9 Hz, 2H), 0.53 (m, *J* = 2.8 Hz, 2H); MS (ESI) *m/z* 549 $[C_{30}H_{31}F_3N_6O+ H]^+$.

Example 10: N-(4-((6-amino-4-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



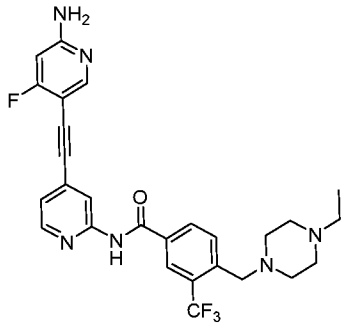
[000291] The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and 5-bromo-4-methylpyridin-2-amine following a method similar to general procedure A. The crude product was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((6-amino-4-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (26 mg, 41%, AUC HPLC 95%) as brown solid; mp 162–164 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.34 (d, *J* = 5.1 Hz, 1H),8.30 (s, 2H), 8.22 (d, *J* = 8.1 Hz, 1H),8.07 (s, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 4.9 Hz,1H), 6.49 (s,1H), 3.81 (s, 2H), 2.87 (s, 4H), 2.78 (q, *J* = 7.2 Hz, 2H), 2.66 (s, 4H), 2.40 (s, 3H),1.21 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 523 $[C_{28}H_{29}F_3N_6O+H]^+$.

Example 11: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-pivalamidopyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000292] The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and *N*-(5-bromopyridin-2-yl)pivalamide following a method similar to general procedure A. The crude product was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-pivalamidopyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (20 mg, 28%, AUC HPLC 98%) as brown solid; mp 100–102°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.11 (s, 1H), 8.54 (s, 1H), 8.46 (d, *J* = 1.5 Hz, 1H), 8.31 (d, *J* = 8.7 Hz, 1H), 8.27 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.87–7.82 (m, 2H), 7.19 (d.d, *J* = 5.2 , 1.6 Hz, 1H), 3.78 (s, 2H), 2.92 (s, 4H), 2.83 (q, *J* = 7.2 Hz, 2H), 2.73 (s, 4H), 1.34 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 593$[C_{32}H_{35}F_3N_6O_2+H]^+$.

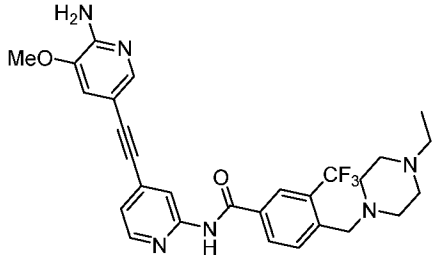
Example 12: N-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000293] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl) and 5-bromo-4-fluoropyridin-2-amine following a method similar to general procedure A. The crude reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford *N*-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (30 mg, 47%, AUC HPLC 96.7%) as yellow solid; m.p. 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.85 (s, 1H), 8.50 (s, 1H), 8.33–8.18 (m, 3H), 8.07

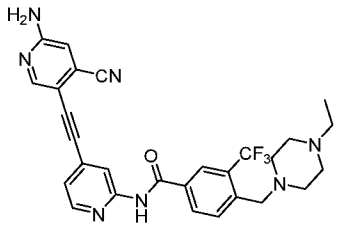
(d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 4.5 Hz, 1H), 6.24 (d, J = 10.2 Hz, 1H), 4.97 (s, 2H), 3.74 (s, 2H), 2.60 (s, 8H), 2.54 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.63, 168.02, 164.29, 160.63, 160.52, 154.40, 151.45, 147.81, 142.59, 133.84, 132.90, 131.00, 130.32, 129.57, 129.27, 125.23, 125.10, 122.51, 121.98, 115.95, 99.30, 94.59, 91.97, 85.78, 57.95, 52.73, 52.51, 52.12, 11.51; MS (ESI) *m/z* 527 $[C_{27}H_{26}F_4N_6O+ H]^+$.

Example 13: N-(4-((6-amino-5-methoxypyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



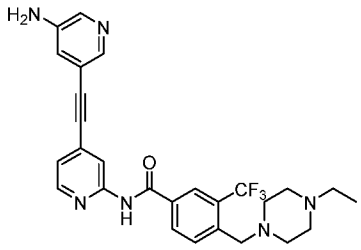
[000294] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 5-bromo-3-methoxypyridin-2-amine following a method similar to general procedure A. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((6-amino-5-methoxypyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (24 mg, 37%, AUC HPLC 99.9%) as white solid; m.p. 69.7–70.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.44 (bs, 1H), 8.54 (s, 1H), 8.39 (bs, 1H), 8.31-8.22 (m, 2H), 8.12 (d, J = 8.1 Hz, 1H), 7.93-7.81 (m, 2H), 7.17 (d, J = 4.9 Hz, 1H), 7.05 (s, 1H), 5.55 (bs, 2H), 3.91 (s, 3H), 3.80 (s, 2H), 3.07(bs, 4H), 2.97 (q, J = 7.3 Hz, 2H), 2.89-2.75 (m, 4H), 1.30 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.81, 164.42, 151.45, 150.74, 147.13, 141.97, 141.79, 141.15, 134.65, 133.39, 131.00, 130.61, 129.65 (q, J = 31.1 Hz), 125.76 (q, J = 5.8 Hz), 123.80 (q, J = 274.3 Hz), 121.80, 117.37, 116.40, 107.81, 93.06, 87.42, 57.71, 55.63, 51.49, 51.13, 50.21, 9.35; MS (ESI) *m/z* 539 $[C_{28}H_{29}F_3N_6O_2 + H]^+$.

Example 14: N-(4-((6-amino-4-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000295] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 2-amino-5-bromoisonicotinonitrile following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((6-amino-4-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (10mg, 16%, AUC HPLC 98%) as yellow solid; m.p. 114.5-116.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.26 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.43 (s, 1H), 8.34 (s, 1H), 8.32-8.27 (m, 2H), 7.92 (d, J = 8.2 Hz, 1H), 7.25 (d, J = 5.0 Hz, 1H), 7.19 (s, 2H), 6.87 (s, 1H), 3.68 (s, 2H), 2.43 (bs, 8H), 2.33 (q, J = 7.1 Hz, 2H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 164.28, 158.84, 152.74, 151.83, 148.03, 141.09, 132.23, 131.21, 129.98, 125.07, 121.78, 120.46, 115.21, 114.93, 110.16, 104.39, 90.73, 88.11, 56.94, 52.30, 51.74, 50.96, 11.38; MS (ESI) *m/z* 534[$C_{28}H_{26}F_3N_7O$ + H]$^+$.

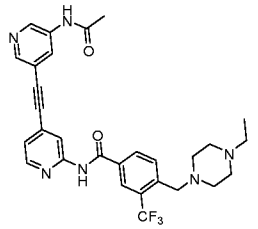
Example 15: N-(4-((5-aminopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000296] The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and 5-bromopyridin-3-amine following a method similar to general procedure A. The crude product was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((5-aminopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (15 mg, 24%, AUC HPLC 98%) as brown solid; mp 63–65 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.50–8.30 (m, 3H), 8.22 (d, J = 7.20 Hz, 1H), 8.20–7.80 (m, 3H), 7.70–7.79 (m,

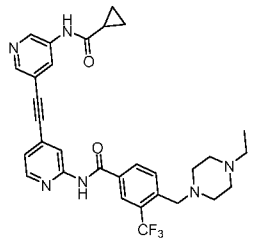
1H), 7.20–7.40 (m, 2H), 3.81 (s, 2H), 2.85 (s, 4H), 2.75 (q, *J* = 7.3 Hz, 2H), 2.66 (s, 4H), 1.20 (t, *J* = 7.3 Hz, 3H); MS (ESI) *m/z* 509 $[C_{27}H_{27}F_3N_6O+ H]^+$.

Example 16: N-(4-(2-(5-acetamidopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000297] The title compound was synthesized from *N*-(5-bromopyridin-3-yl)acetamide and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The crude product was purified by preparative HPLC to afford *N*-(4-(2-(5-acetamidopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (16.3 mg, 25%, AUC HPLC 99%) as a light brown solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.32 (s, 1H), 10.39 (s, 1H), 8.70 (d, *J* = 2.3 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H), 8.48 (d, *J* = 5.1 Hz, 1H), 8.38–8.33 (m, 3H), 8.30 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.73 (s, 2H), 2.11 (s, 3H), 1.09 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 169.3, 164.8, 152.4, 148.7, 146.1, 141.3, 140.8, 135.6, 132.9, 132.0, 131.2, 130.6, 127.8, 127.5, 127.3, 127.1, 126.9, 125.7, 125.0, 123.2, 121.6, 118.0, 116.2, 89.9, 89.5, 57.1, 51.5, 51.1, 23.9, 23.9; MS (ESI) m/z 551 $[C_{29}H_{29}F_3N_6O_2+ H]^+$.

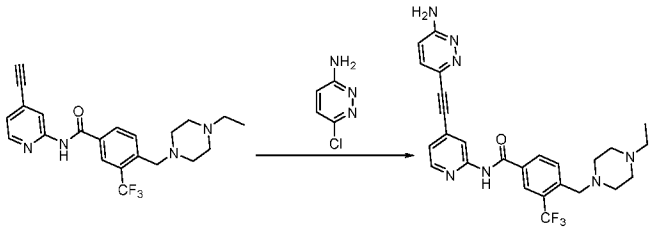
Example 17: N-(4-(2-(5-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000298] The title compound was synthesized from *N*-(5-bromopyridin-3-yl)cyclopropanecarboxamide and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(4-(2-(5-

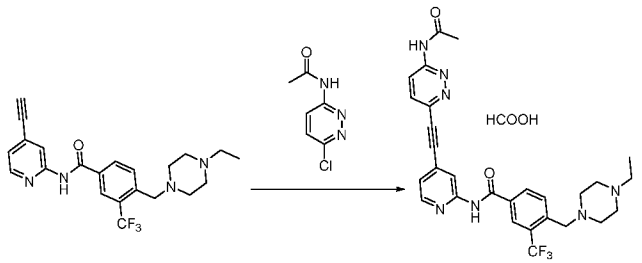
(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (2.2 mg, AUC HPLC 99%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 10.65 (s, 1H), 8.73 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 1.9 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.35 (dd, J = 4.0, 1.8 Hz, 3H), 8.29 (dd, J = 8.2, 1.9 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.38 (dd, J = 5.0, 1.5 Hz, 1H), 3.69 (s, 2H), 2.49–2.29 (m, 8H), 1.85–1.79 (m, 1H), 1.05–0.98 (m, 3H), 0.89–0.83 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 172.6, 164.9, 152.4, 148.7, 146.0, 141.6, 140.8, 135.6, 132.8, 132.0, 131.2, 130.5, 127.9, 127.4, 127.2, 127.07, 126.8, 125.6, 125.0, 123.2, 121.5, 118.0, 116.1, 89.9, 89.5, 57.4, 52.1, 51.4, 14.6, 11.7, 7.7; MS (ESI) m/z 577 $[C_{31}H_{31}F_3N_6O_2+H]^+$.

Example 18: N-(4-(2-(6-aminopyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



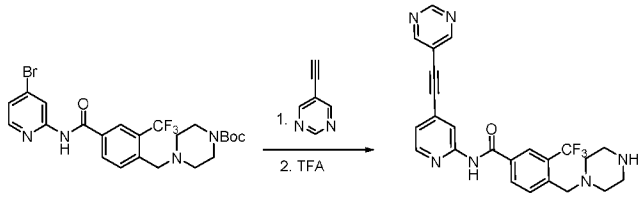
[000299] The title compound was synthesized from 6-chloropyridazin-3-amine and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(4-(2-(6-aminopyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (4.1 mg, AUC HPLC 99%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.29 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.34 (dd, J = 4.5, 1.4 Hz, 2H), 8.29 (dd, J = 8.0, 1.9 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 7.34 (dd, J = 5.0, 1.5 Hz, 1H), 6.95 (s, 2H), 6.79 (d, J = 9.2 Hz, 1H), 3.68 (s, 2H), 2.41 (d, J = 26.3 Hz, 4H), 2.32 (q, J = 7.2 Hz, 2H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 159.5, 152.4, 148.6, 141.7, 136.5, 132.8, 132.0, 131.4, 131.1, 130.5, 127.4, 127.2, 127.0, 126.8, 125.6, 125.0, 123.2, 115.9, 112.6, 91.4, 87.0, 57.5, 52.9, 52.3, 51.5, 12.0; MS (ESI) m/z 510$[C_{26}H_{26}F_3N_7O+ H]^+$.

Example 19: N-(4-(2-(6-acetamidopyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000300] The title compound was synthesized from *N*-(6-chloropyridazin-3-yl)acetamide and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by prep-HPLC to afford *N*-(4-(2-(6-acetamidopyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt (8.0 mg, 11%, AUC HPLC 99%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.43 (s, 1H), 11.34 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.42–8.37 (m, 2H), 8.35 (d, J = 1.9 Hz, 1H), 8.29 (dd, J = 8.1, 1.9 Hz, 1H), 8.20 (s, 1H), 8.01 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 5.0, 1.5 Hz, 1H), 3.68 (s, 2H), 2.46–2.39 (m, 4H), 2.33 (d, J = 7.2 Hz, 2H), 2.18 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 170.4, 164.9, 154.4, 152.4, 148.8, 142.4, 141.7, 132.7, 132.2, 132.0, 130.6, 130.5, 127.4, 127.2, 127.0, 126.8, 125.7, 125.0, 123.2, 121.5, 121.4, 117.3, 116.2, 89.5, 88.8, 57.5, 52.8, 52.3, 51.5, 24.0; MS (ESI) *m/z* 552 $[C_{28}H_{28}F_3N_7O_2 + H]^+$.

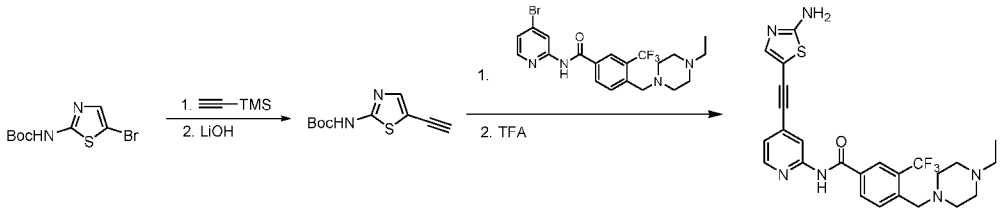
Example 20: 4-(piperazin-1-ylmethyl)-N-(4-(pyrimidin-5-ylethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide



[000301] Step 1: Preparation of *tert*-butyl 4-(4-(4-(pyrimidin-5-ylethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate; The title compound was synthesized from *tert*-butyl4-(4-(4-bromopyridin-2-y5-ethynylpyrimidine carbanoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 5-ethynylpyrimidine in a similar method to that described in general procedure A. The crude product was purified by column chromatography (silica gel, eluent: petroleum ether/EtOAc 1:1) to afford *tert*-butyl 4-(4-(4-(pyrimidin-5-ylethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate as a yellow solid (300 mg, 82%); MS (ESI) *m/z* 567 $[C_{29}H_{29}F_3N_6O_3+H]^+$.

[000302] Step 2: Preparation of 4-(piperazin-1-ylmethyl)-*N*-(4-(pyrimidin-5-ylethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide; The title compound was synthesized from *tert*-butyl 4-(4-(4-(pyrimidin-5-ylethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1- ethynylpyrimidine in a similar method to that described in general procedure D. The crude product was purified by column chromatography (silica gel, eluent $CHCl_3$/MeOH 96:4) to afford 4-(piperazin-1-ylmethyl)-*N*-(4-(pyrimidin-5-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide as an off white solid (170 mg, 69%, LC-MS 96%, AUC HPLC 95.2%); m.p. 135–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (s, 1H), 8.92 (s, 2H), 8.60-8.57 (d, J = 12.8 Hz, 2H), 8.37–8.36 (d, J = 4.4 Hz, 2H), 8.19 (s, 1H), 8.09–8.03 (m, 2H), 7.26–7.23 (m, 1H), 3.72 (s, 2H), 2.94–2.85 (m, 4H), 2.48–2.44 (m, 4H); MS (ESI) *m/z* 467 $[C_{24}H_{21}F_3N_6O+H]^+$.

Example 21: N-(4-((2-aminothiazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



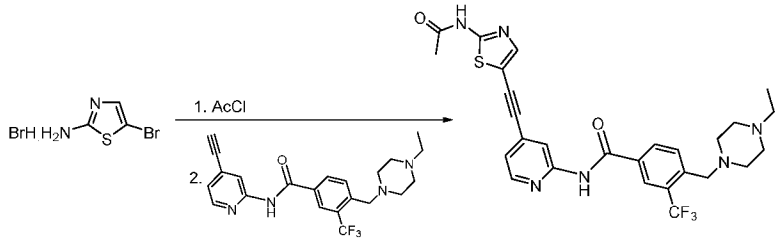
[000303] Step 1: Preparation of *tert*-butyl 5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamate; The title compound was synthesized from *tert*-butyl 5-bromothiazol-2-yl carbamate and Ethynyltrimethylsilane following a method similar to general procedure A. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate 95:5) to afford *tert*-butyl 5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamate (1.4 g). MS (ESI) *m/z* 297.1 $[C_{13}H_{20}N_2O_2SSi+H]^+$.

[000304] Step 2: Preparation of *tert*-butyl 5-ethynylthiazol-2-ylcarbamate; A solution of LiOH in water was added to a solution of *tert*-butyl 5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamate (1.4 g, 5.04 mmol) in THF (15 mL). Reaction was stirred at room temperature for 3 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water, extracted into EtOAc. The extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate 90:10) to afford *tert*-butyl 5-ethynylthiazol-2-ylcarbamate (1 g) as a brown solid.

[000305] Step 3: Preparation of *tert*-butyl 5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)thiazol-2-ylcarbamate; The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and *tert*-butyl 5-ethynylthiazol-2-ylcarbamate following a method similar to general procedure A. To the reaction crude product was added water, and the mixture was extracted with EtOAc. The organic extracts were washed in turn with water and brine then, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)thiazol-2-ylcarbamate. The crude product was used in the next step without further purification. MS (ESI) *m/z* 615.3 $[C_{30}H_{33}F_3N_6O_3S+H]^+$.

[000306] Step 4: Preparation of *N*-(4-((2-aminothiazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)thiazol-2-ylcarbamate in a similar method as described in general procedure D. The reaction crude product was purified by preparative HPLC to afford *N*-(4-((2-aminothiazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamid (18 mg, HPLC 98.7%) as a pale yellow solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 11.23 (s, 1H), 8.38 (d, *J* = 4.8 Hz, 1H), 8.31 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 2H), 7.45 (s, 1H), 7.20 (dd, *J* = 1.2, 4.8 Hz, 1H), 3.65 (s, 2H), 2.42–2.30 (m, 10H), 0.97 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 515.5 $[C_{25}H_{25}F_3N_6OS+H]^+$.

Example 22: N-(4-((2-acetamidothiazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



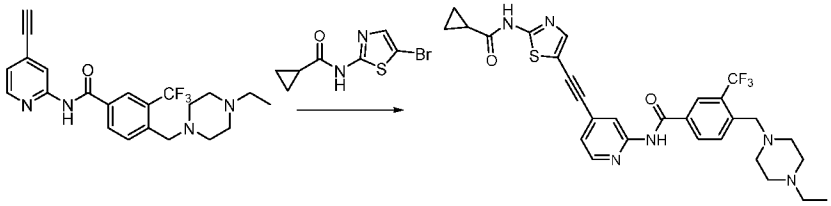
[000307] Step 1: Preparation of *N*-(5-bromothiazol-2-yl)acetamide;

Acetyl chloride (0.14 mL, 1.924 mmol) was added drop wise to a cooled mixture of 5-bromothiazol-2-amine hydrobromide (500 mg, 1.92 mmol) and triethyl amine (0.53 mL, 3.85 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred at room

temperature for 14 h and was diluted with CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, followed by brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc 15:85) to afford *N*-(5-bromothiazol-2-yl) acetamide (340 mg, 80%).

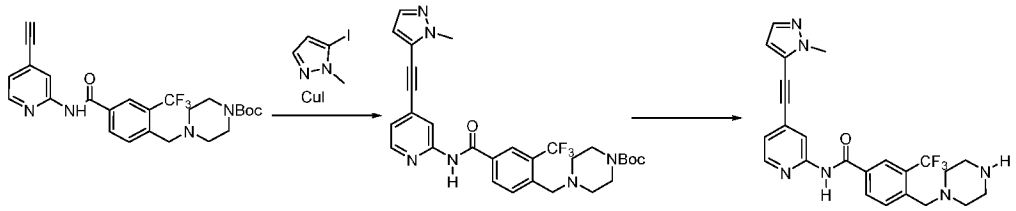
[000308] Step 2: Preparation of *N*-(4-((2-acetamidothiazol-5-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide; The title compound was synthesized from *N*-(5-bromothiazol-2-yl) acetamide and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(4-((2-acetamidothiazol-5-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide (110 mg, AUC HPLC 98.5 %) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.52 (s, 1H), 11.25 (s, 1H), 8.44 (d, J = 5.6 Hz, 1H), 8.34 (s, 1H), 8.28 (s, 2H), 7.94 (s, 1H), 7.91 (d, J = 8.4 Hz,1H), 7.29 (d, J = 1.6 Hz, 1H), 3.68 (s, 2H), 2.42 (m, 8H), 2.32 (q, 2H), 2.19 (s, 3H), 0.98 (t, J = 7.0 Hz, 3H). MS (ESI) *m/z* 557.4 $[C_{27}H_{27}F_3N_6O_2S + H]^+$.

Example 23: N-(4-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000309] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and *N*-(5-bromothiazol-2-yl)cyclopropanecarboxamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(4-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (12 mg, 12.6%, AUC HPLC 95.1%) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.39 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.31–8.29 (m, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.23 (dd, J = 1.6, 5.2 Hz, 1H), 3.77 (s, 2H), 2.60–2.50 (m, 10H), 1.92–1.28 (m, 1H), 1.12 (t, J = 6.8 Hz, 3H), 1.08–0.97 (m, 4H). MS (ESI) *m/z* 583.0 $[C_{29}H_{29}F_3N_6O_2S + H]^+$.

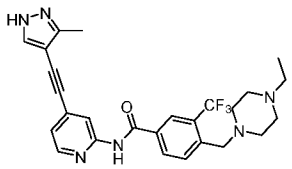
Example 24: N-(4-((1-methyl-1H-pyrazol-5-yl) thinly) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide



[000310] Step 1: Preparation of *tert*-butyl 4-(4-(4-((1-methyl-1*H*-pyrazol-5-yl) ethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate; The title compound was synthesized from *tert*-butyl 4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 5-iodo-1-methyl-1*H*-pyrazole following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel eluent petroleum ether/EtOAc 1:1) to afford *tert*-butyl 4-(4-(4-((1-methyl-1*H*-pyrazol-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as a solid (50 mg, 26%). MS (ESI) *m/z* 569 $[C_{29}H_{31}F_3N_6O_3+ H]^+$

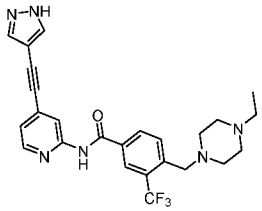
[000311] Step 2: Preparation of *N*-(4-((1-methyl-1*H*-pyrazol-5-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide; The title compound was synthesized from *tert*-butyl 4-(4-(4-((1-methyl-1*H*-pyrazol-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar method as described in general procedure D. The crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3$/MeOH 96:4) to afford 10 mg of *N*-(4-((1-methyl-1*H*-pyrazol-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide as a pale yellow solid (26%, AUC-HPLC 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.58 (s, 1H), 8.53 (s, 1H), 8.35–8.34 (d, *J* = 1.6 Hz, 1H), 8.19 (s, 1H), 8.08–8.03 (m, 2H), 7.50 (s, 1H), 7.21–7.19 (t, *J* = 4.4 Hz, 1H), 6.58–6.57 (d, *J* = 2.0 Hz, 1H), 4.03 (s, 3H), 3.71 (s, 2H), 2.94–2.85 (m, 4H), 2.48–2.20 (m, 4H); MS (ESI) *m/z* 469 $[C_{24}H_{23}F_3N_6O+ H]^+$.

Example 25: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((3-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000312] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 4-iodo-3-methyl-1*H*-pyrazole in a similar method as described in general procedure D. The residue was purified by flash column chromatography (silica gel, DCM/methnol 10:1) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((3-methyl-1*H*-pyrazol-4-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (33 mg, 55%, AUC HPLC 98%) as white solid; m.p. 171.2–173.3 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.33–8.28 (m, 3H), 8.20 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.76 (bs, 1H), 7.20 (d, J = 4.7 Hz, 1H), 3.79 (s, 2H), 2.73 (bs, 8H), 2.65–2.60 (m, 2H), 2.41 (s, 3H), 1.16 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 497 $[C_{26}H_{27}F_3N_6O + H]^+$.

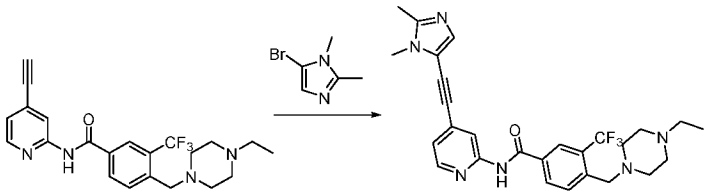
Example 26: N-(4-((1H-pyrazol-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000313] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 4-iodo-1*H*-pyrazole following a method similar to general procedure A. The reaction mixture was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((1*H*-pyrazol-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (18 mg, 22 %, AUC HPLC 95%) as brown solid; mp 124–126 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.33 (d, J = 5.1 Hz, 1H), 8.29 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.91(m, 2H), 7.73 (m, 1H), 7.20 (d, J = 4.7 Hz, 1H), 3.78 (s, 2H), 2.88–2.30 (m, 10H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 152.93, 149.00, 143.55, 135.92, 134.23, 132.29, 132.20, 132.00, 126.67, 123.94, 123.12, 117.79, 103.00,

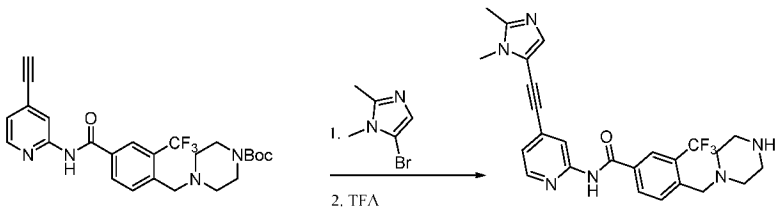
89.30, 87.90, 78.93, 78.61, 78.29, 59.23, 53.89, 53.55, 12.51; MS (ESI) *m/z* 483 $[C_{25}H_{25}F_3N_6O + H]^+$.

Example 27: N-(4-((1,2-dimethyl-1H-imidazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000314] To the mixture of mixture of 5-bromo-1,2-dimethyl-1*H*-imidazole (126 mg, 0.721 mmol), 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide (300 mg, 0.721 mmol), and diisopropyl ethyl amine (1 mL) in DMF (3 mL) under argon, were added $PdCl_2$ $(dppf)_2$ (52 mg, 0.0721 mmol), CuI (20 mg, 0.108 mmol). The reaction mixture was heated at 80 °C for 15 h, was diluted with water and extracted into EtOAc. The organic layer was washed in turn with water and brine then was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford *N*-(4-((1,2-dimethyl-1H-imidazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (45 mg, 12%, AUC HPLC 90%) as an off-white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 11.24 (s, 1H), 8.43 (d, *J* = 5.2 Hz, 1H), 8.35 (s, 1H), 8.30–8.28 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.36 (bs, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 3.70 (s, 2H), 3.64 (s, 3H), 2.45-2.32 (m, 13H), 1.02–1.01 (m, 3H); MS (ESI) *m/z*: 511.1 $[C_{27}H_{29}F_3N_6O+H]^+$.

Example 28: N-(4-((1,2-dimethyl-1H-imidazol-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 4-(4-(4-((1,2-dimethyl-1*H*-imidazol-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

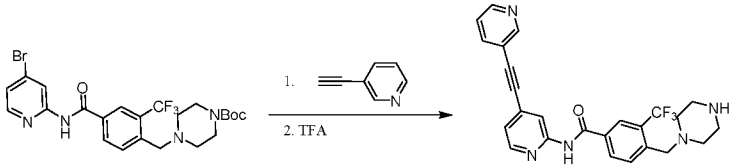
[000315] To a solution of *tert*-butyl 4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate (100 mg, 0.204 mmol) in DMF (2 mL)

under Argon were successively added 5-bromo-1,2-dimethyl-1*H*-imidazole (35 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.1 mg, 0.010 mmol), piperidine (52 mg, 0.61 mmol). The reaction mixture was heated to 80 °C for 15 h and was diluted with EtOAc. The organic phase was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 4-(4-(4-((1,2-dimethyl-1*H*-imidazol-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (180 mg); MS (ESI) *m/z*:583.24 $[C_{30}H_{33}F_3N_6O_3 + H]^+$.The crude product was carried forth to the next step without further purification.

Step 2: preparation of *N*-(4-((1,2-dimethyl-1*H*-imidazol-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000316] A solution of *tert*-butyl 4-(4-(4-((1,2-dimethyl-1*H*-imidazol-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (150 mg) in dichloromethane (5 mL) and TFA (1 mL) was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduce pressure, and the residue was diluted with EtOAc. The organic phase was washed in turn with a saturated aqueous solution of $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford *N*-(4-((1,2-dimethyl-1H-imidazol-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (10 mg, HPLC 98.1%) as pale yellow solid. ^{1}H NMR(400 MHz, CD_3OD) δ (ppm): 8.38 (d, *J* = 5.2 Hz, 1H), 8.33 (s, 1H), 8.29 (s, 1H), 8.22 (d, *J* =8.0 Hz, 1H), 8.03 (d, *J* =8.0 Hz, 1H), 7.28 (s, 1H), 7.24 (dd, *J* =5.2, 1.2 Hz, 1H), 3.78 (s, 2H), 3.71 (s, 3H), 3.02–2.99 (m, 4H), 2.58–2.56(m, 4H), 2.42 (s, 3H). MS (ESI) *m/z*: 483.32 $[C_{25}H_{25}F_3N_6O + H]^+$.

Example 29: 4-(piperazin-1-ylmethyl)-N-(4-(pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 4-(4-(4-(pyridin-3-ylethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate

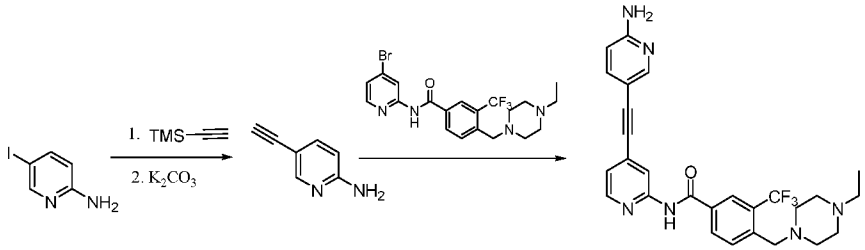
[000317] The title compound was synthesized following a method similar to general procedure B starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynylpyridine. Purification by flash

column chromatography (silica gel eluent: dichloromethane/MeOH 70:30) gave *tert*-butyl 4-(4-(4-(pyridin-3-ylethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate as an off white solid (200mg).

Step 2: Preparation of 4-(piperazin-1-ylmethyl)-*N*-(4-(pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

[000318] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl 4-(4-(4-(pyridin-3-ylethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate. Putification by column chromatography (silica gel, eluent, $CHCl_3/CH_3OH$ 96:4) gave 4-(piperazin-1-ylmethyl)-*N*-(4-(pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (85 mg, 69%, AUC HPLC 96%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.82 (s, 1H), 8.62–8.55 (m, 3H), 8.34–8.33 (d, J = 4.4 Hz, 1H), 8.20 (s, 1H), 8.09–8.02 (m, 2H), 7.88–7.86 (d, J = 7.6 Hz, 1H), 7.36–7.33 (m, 1H), 7.26–7.21 (d, J = 4.4 Hz, 1H), 3.71 (s, 2H), 3.10–2.93 (m, 4H), 2.80–2.49 (m, 4H); MS (ESI) *m/z* 465 $[C_{25}H_{22}F_3N_5O + H]^+$.

Example 30: N-(4-((6-aminopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 5-((trimethylsilyl)ethynyl)pyridin-2-amine.

[000319] The title compound was synthesized following a method similar to general procedure A starting from 5-iodopyridin-2-amine1 and Ethynyltrimethylsilane. The crude product was purified by flash column chromatography (silica gel, eluent dichloromethane/MeOH 99:1) to afford 5-((trimethylsilyl)ethynyl)pyridin-2-amine (750 mg, 86%) as a brown solid. MS (ESI) *m/z*:191 $[C_{10}H_{14}N_2Si + H]^+$.

Step 2: preparation of 5-ethynylpyridin-2-amine

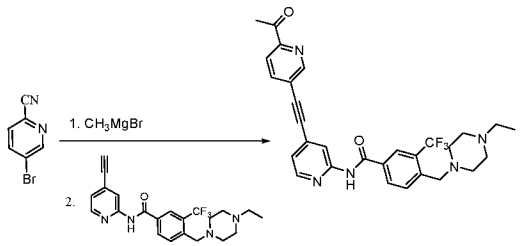
[000320] A mixture of 5-((trimethylsilyl)ethynyl)pyridin-2-amine (750 mg, 3.94 mmol) and K_2CO_3 (1.08 g, 7.89 mmol) in methanol (5 mL) was stirred at room temperature for 2 h then was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 5-

ethynylpyridin-2-amine (450 mg, 96%, LC-MS 98%) as a pale brown solid. MS (ESI) *m/z*:119 $[C_7H_6N_2 + H]^+$.

Step 3: Preparation of *N*-(4-((6-aminopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000321] The title compound was synthesized following a method similar to general procedure A and starting from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and 5-ethynylpyridin-2-amine. The reaction crude product was purified by preparative HPLC to afford *N*-(4-((6-aminopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (90 mg, 21%, AUC HPLC 99.4%) as an off white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.26 (s, 1H), 8.41 (d, *J* = 5.2 Hz 1H), 8.35 (s,1H), 8.30 (d, *J* = 7.6 Hz, 1H), 8.25 (s, 1H),8.21 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 5.6Hz, 1H), 6.62 (s, 2H), 6.47 (d, *J* = 8.8 Hz, 1H), 3.71 (s, 2H), 2.50 (m, 2H), 2.33 (m, 8H), 1.04 (m, 3H); MS (ESI) *m/z*: 509.2 $[C_{27}H_{27}F_3N_6O + H]^+$.

Example 31: N-(4-((6-acetylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 1-(5-bromopyridin-2-yl)ethanone

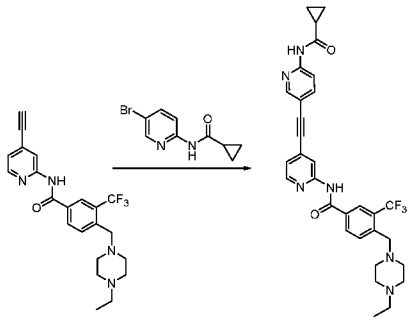
[000322] To a solution of 5-Bromo-2-cyanopyridine (4 g, 21.85 mmol) in anhydrous THF (100 mL) at -20 °C was added dropwise methylmagnesium bromide (21.85 mL, 3M) over 3 hours while maintaining the reaction temperature between -20 °C and -10 °C. The reaction mixture was cooled to -40 °C and a solution of concentrated HCl (4.0 mL) in water (15 mL) was added dropwise. The mixture was stirred for 10 minutes then poured into a potassium phosphate buffer (300 mL, 1M, pH 7). Ethyl acetate (300 mL) was added and the organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent petroleum ether/ethyl acetate 99:1) to give 1-(5-bromopyridin-2-yl)ethanone (3.4 g). ^{1}H NMR (400

MHz, $CDCl_3$) δ (ppm): 8.73 (d, *J* = 1.6 Hz, 1H), 7.96 (dd, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 8.0 Hz, 1H, 2.69 (s, 3H).

Step 2: Preparation of *N*-(4-((6-acetylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000323] To a mixture of 1-(5-bromopyridin-2-yl)ethanone (96 mg, 0.480 mmol), 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide (250 mg, 0.60 mmol), CuI (17.1 mg, 0.09 mmol), and DIPEA (0.154 mL, 0.9 mmol) in DMF (10 mL) was added $Pd(PPh_3)_4$ (40 mg, 0.03 mmol). The reaction mixture was heated at 80 °C for 2 h under argon and was diluted with water (10 mL). The precipitate was isolated byfiltration to give the reaction crude product which was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford *N*-(4-((6-acetylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (55 mg, 21%, AUC HPLC 99%) as a brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H), 8.56 (d, *J* = 5.6 Hz, 2H), 8.36 (d, *J* = 4.8 Hz, 1H), 8.19 (s, 1H), 8.08 (s, 1H), 8.05 (s, 1H), 8.01–7.96 (m, 2H), 7.25–7.20 (m, 1H), 3.75 (s, 2H), 2.74 (s, 3H), 2.71–2.41 (m, 10H), 1.12 (bs, 3H); MS (ESI) *m/z* 536.56 $[C_{29}H_{28}F_3N_5O_2+H]^+$.

Example 32: N-(4-((6-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

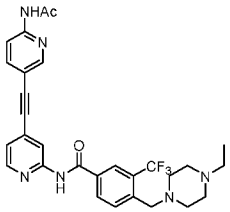


Step 1: Preparation of *N*-(4-((6-(cyclopropanecarboxamido) pyridin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide

[000324] To a solution of *N*-(5-bromopyridin-2-yl) cyclopropanecarboxamide (200 mg, 0.84 mmol) in DMF (2 mL) under argon were successively added $PdCl_2(dppf)_2$ (30.5 mg, 0.041 mmol), CuI (23.8 mg, 0.125 mmol), 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide (350 mg, 0.8361 mmol) and DIPEA (2 mL). The reaction mixture was heated at 100 °C for 15 h and was concentrated under reduced pressure. The syrup was diluted with EtOAc, washed in turn with water and brine. The

organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford *N*-(4-((6-(cyclopropanecarboxamido) pyridin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide (15 mg, 3.1 %, LC-MS 96.63%) as an off-white solid; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.51 (d, *J* = 1.6 Hz, 1H), 8.38 (s, 1H), 8.36 (d, *J* = 4 Hz, 1H), 8.29 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 12 Hz, 1H), 7.92 (dd, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 1.2 Hz, 1H), 3.74 (s, 2H), 2.35–2.57 (m, 10H), 1.92–1.88 (m, 1H), 1.12 (t, *J* = 14.4 Hz, 3H), 1.01–0.98 (m, 2H), 0.93–0.88 (m, 2H); MS (ESI) *m/z*: 577.3 $[C_{31}H_{31}F_3N_6O_2+H]^+$.

Example 33: N-(4-((6-acetamidopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *N*-(5-((trimethylsilyl) ethynyl) pyridin-2-yl) acetamide.

[000325] The title compound was synthesized following a method similar to general procedure B starting from *N*-(5-iodopyridin-2-yl)acetamide and Ethynyltrimethylsilane. The crude product was purified by flash column chromatography (silica gel, eluent CH_2Cl_2/MeOH 99:1) to afford *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (1.3 g, 76.2 %, LCMS-93.5%) as pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.34 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.76 (dd, *J* = 1.6, 8.8 Hz, 1H), 2.21 (s, 3H), 0.25 (s, 9H); MS (ESI) *m/z*: 233.1 $[C_{12}H_{16}N_2OSi+H]^+$.

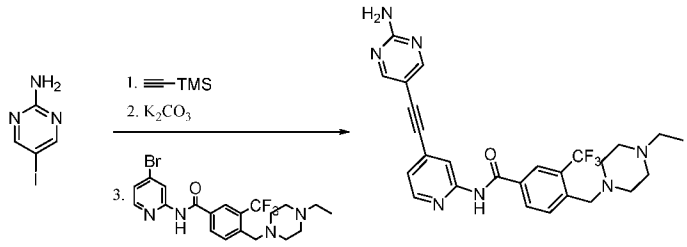
Step 2: Preparation of *N*-(5-ethynylpyridin-2-yl) acetamide.

[000326] A mixture of *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (1.3 g, 5.64 mmol) and K_2CO_3 (1.5 g, 11.29 mmol) in methanol (10 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *N*-(5-ethynylpyridin-2-yl) acetamide (750 mg, 83.2 %) as pale brown solid, that was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.71 (s, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.33 (s, 1H), 2.10 (s, 3H). MS (ESI) *m/z*:161.3 $[C_9H_8N_2O + H]^+$.

Step 3: preparation of *N*-(4-((6-acetamidopyridin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide

[000327] A mixture of *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide (513 mg, 1.086 mmol) in THF (10 mL) under Argon were successively added $PdCl_2(dppf)_2$ (35.5 mg, 0.043 mmol), PPh_3 (56.9 mg, 0.217 mmol), CuI (12.3 mg, 0.0652 mmol), *N*-(5-ethynylpyridin-2-yl)acetamide 3 (350 mg, 2.17 mmol) and triethylamine (2.1 g, 21.5 mmol) and the resulting reaction mixture was heated at 80 °C for 15 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford *N*-(4-((6-acetamidopyridin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide (130 mg, 21.7%, AUC HPLC 96.2%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.29 (s, 1H), 10.79 (s, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 8.47 (d, *J* = 5.6 Hz, 1H) 8.28–8.34 (m, 3H), 8.17 (d, *J* = 8.8 Hz, 1H), 8.05 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* =1.2, 5.2 Hz, 1H), 3.68 (s, 2H), 2.33–2.49 (m, 10H), 2.12 (s, 3H), 0.99 (t, *J* = 6.4 Hz, 3H); MS (ESI) *m/z*: 551.2 $[C_{29}H_{29}F_3N_6O_2 + H]^+$.

Example 34: N-(4-((2-aminopyrimidin-5-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide



Step 1: Preparation of 5-((trimethylsilyl)ethynyl)pyrimidin-2-amine

[000328] To a solution of 5-iodopyrimidin-2-amine (2.0g, 9.0 mmol) in acetonitrile (80 mL) under argon were successively added $PdCl_2(PPh_3)_2$ (0.32g, 0.45 mmol) trimethysillyllalkyne (2.8 mL, 19.0 mmol), CuI (85 mg, 1.30 mmol) and TEA (7.5 mL, 31.5 mmol). The reaction mixture was heated at 80 °C for 3 h and was diluted with EtOAc. The organic phase was washed successively with water and brine, was dried over Na_2SO_4, filtered and concentrated. The residue was purified flash column chromatography (silica gel eluent: petroleum ether/EtOAc 70:30) to afford 5-((trimethylsilyl)ethynyl)pyrimidin-2-amine (1.4 g, LC-MS 88%) as a pale yellow solid.

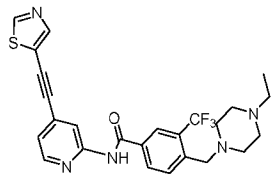
Step 2: Preparation of 5-ethynylpyrimidin-2-amine

[000329] To a solution of 5-((trimethylsilyl)ethynyl)pyrimidin-2-amine (1.4 g, 7.20 mmol) in methanol (80 mL) was slowly added K_2CO_3 at a temperature maintained between 0-5 °C. The resulting heterogeneous mixture was stirred for 1.5 h at room temperature and was filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was washed with a solution of 90:10 methanol/water. The solid thus formed was isolated by filtration and dried under vacuum to afford 5-ethynylpyrimidin-2-amine (700 mg) as a solid.

Step 3: Preparation of *N*-(4-((2-aminopyrimidin-5-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl)benzamide

[000330] To a solution of *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (300 mg, 0.6366 mmol) in acetonitrile (9 mL) under argon were successively added $PdCl_2(PPh_3)_2$ (22 mg, 0.0318 mmol), CuI (18 mg, 0.0947 mmol) and 5-ethynylpyrimidin-2-amine (152 mg, 1.27 mmol) and DIPEA (0.2 mL, 1.28 mmol). The reaction mixture was heated at 80 °C for 3 h and was diluted with EtOAc. The organic phase was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: dichloromethane/methanol 80:20) to afford *N*-(4-((2-aminopyrimidin-5-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl)benzamide (802 mg, 26%, AUC HPLC 97%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.59 (s, 1H), 8.55–8.45 (m, 3H), 8.31–8.30 (d, J = 4.4 Hz, 1H), 8.19 (s, 1H), 8.07–8.0 (m, 2H), 7.17–7.16 (d, J = 4.4 Hz, 1H), 5.30 (s, 2H), 3.73 (s, 2H), 2.56–2.43 (m, 10H), 1.12–1.08 (t, J = 7.6 Hz, 3H); MS (ESI) *m/z* 509 $[C_{26}H_{26}F_3N_7O+ H]^+$.

Example 35: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(thiazol-5-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

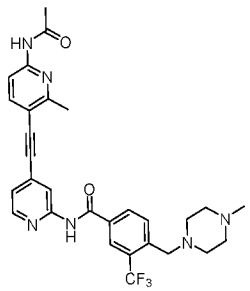


Preparation of 4-((4-ethylpiperazin-1-yl) methyl)-N-(4-(thiazol-5-ylethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamine):

[000331] The title compound was synthesized following a method similar to general procedure B starting from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-

(trifluoromethyl)benzamide (50 mg, 0.63 mmol) and 5-bromothiazole. The reaction crude product was purified by flash column chromatography (silica gel eluent: dichloromethane/methanol 20:80) to afford 4-((4-ethylpiperazin-1-yl) methyl)-*N*-(4-(thiazol-5-ylethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide (5 mg, LC-MS 98 %, AUC HPLC 99%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H), 8.67 (s,1H), 8.52 (s, 1H), 8.35 (s, 1H), 8.23 (s, 1H), 8.15 (bs, 1H), 8.10–8.08 (d, *J* = 7.2 Hz , 1H), 7.81–7.79 (d, *J* = 6.4 Hz, 1H), 7.20 (bs, 1H), 3.85 (s, 2H), 3.48–2.95 (m,10H), 1.58–1.46 (t, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* 499 $[C_{25}H_{24}F_3N_5OS+ H]^+$.

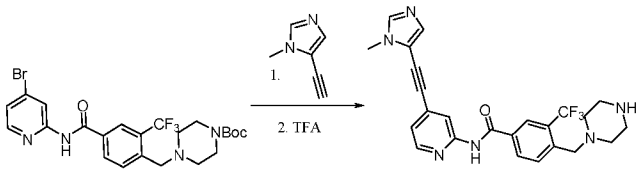
Example 36: N-(4-((6-acetamido-2-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *N*-(6-methyl-5-((2-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)pyridin-2-yl)acetamide

[000332] The title compound was synthesized following a method similar to general procedure B starting from *N*-(5-ethynyl-6-methylpyridin-2-yl)acetamide and 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea. The residue was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 97:3) and by preparative HPLC to give *N*-(6-methyl-5-((2-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)pyridin-2-yl)acetamide (15 mg, AUC HPLC 92.33%) as a pale yellow solid. m.p 226-229 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.31 (d, *J* = 5.2 Hz, 1H), 8.00 (s, 1H), 7.97 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.73–7.70 (m, 2H), 7.41 (s, 1H), 7.11 (d, *J* = 4.8 Hz, 1H), 3.64 (s, 2H), 2.62–2.56 (m, 11 H), 2.35 (s, 3H), 2.17 (s, 3H); MS (ESI) *m/z* 566 $[C_{29}H_{30}F_3N_7O_2+H]^+$.

Example 37: N-(4-((1-methyl-1H-imidazol-5-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide



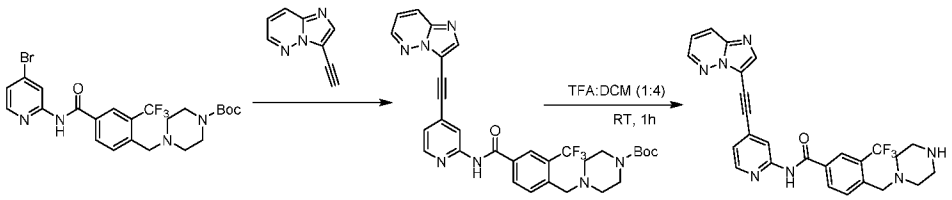
Step 1: Preparation of *tert*-butyl 4-(4-(4-((1-methyl-1*H*-imidazol-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000333] The title compound was synthesized following a method similar to general procedure B starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 5-ethynyl-1-methyl-1*H*-imidazole. The reaction rude product was purified by column chromatography (silica gel, eluent: dichloromethane/methanol 70:30) to afford *tert*-butyl 4-(4-(4-((1-methyl-1*H*-imidazol-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (150 mg, 47%, LC-MS 94.5 %) as an off-white solid.

Step 2: Preparation of of *N*-(4-((1-methyl-1*H*-imidazol-5-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide

[000334] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl 4-(4-(4-((1-methyl-*1H*-imidazol-5-yl) ethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 96:4) to afford *N*-(4-((1-methyl-1*H*-pyrazol-4-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide (50 mg, 40%, LC-MS 95%, AUC HPLC 98%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.65 (bs, 1H), 8.49 (s, 1H), 8.32–8.30 (d, J = 4.8 Hz 1H), 8.20 (s, 1H), 8.08–8.01 (m, 2H), 7.54 (s, 1H), 7.45 (s, 1H), 7.17–7.16 (d, J = 5.2 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 2H), 3.10–2.97 (m, 4H), 2.59–2.45 (m, 4H); MS (ESI) *m/z* 468 $[C_{24}H_{23}F_3N_6O + H]^+$.

Example 38: 3-(trifluoromethyl)-N-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide



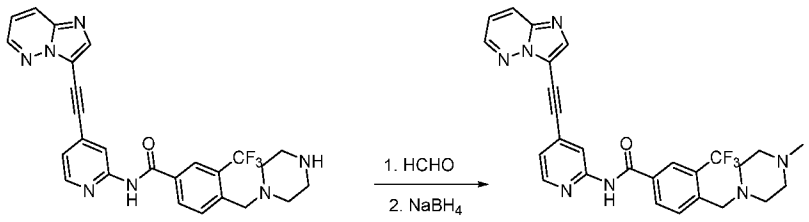
Step 1: Preparation of *tert*-butyl 4-(4-((4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000335] The title compound was prepared following similar to general procedure A and starting from *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynylimidazo[1,2-*b*]pyridazine. Purification by flash column chromatography (silica gel, eluent: EtOAc) gave *tert*-butyl 4-(4-((4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (160 mg, 72%). ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.33 (s, 1H), 8.76 (dd, J = 4.4, 1.5 Hz, 1H), 8.49 (dd, J = 5.1, 0.7 Hz, 1H), 8.40–8.35 (m, 2H), 8.32 (s, 1H), 8.32–8.27 (m, 2H), 7.96 (s, 1H), 7.44 (dd, J = 9.2, 4.4 Hz, 1H), 7.36 (dd, J = 5.1, 1.4 Hz, 1H), 3.71 (s, 2H), 2.42–2.34 (m, 4H), 1.40 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 153.8, 152.4, 148.8, 145.2, 141.3, 140.0, 139.5, 132.9, 132.0, 131.5, 131.4, 131.3, 130.7, 128.8, 128.7, 126.2, 120.8, 119.6, 115.4, 110.9, 96.1, 80.9, 78.8, 57.4, 52.6, 28.0; MS (ESI) *m/z* 606 $[C_{31}H_{30}F_3N_7O_3 + H]^+$

Step 2: Preparation of 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide

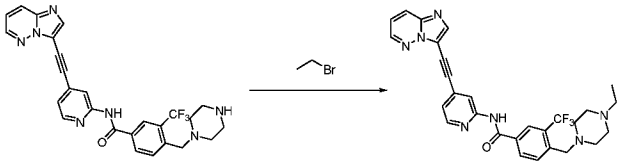
[000336] The title compound was prepared following similar to general procedure D and starting from *tert*-butyl 4-((4-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)phenyl)methyl)piperazine-1-carboxylate. The reaction crude product was purified by column chromatography (eluent DCM/CH_3OH 92:8) to afford 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide (77 mg, 57%, AUC HPLC 100%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.39 (s, 1H), 8.76 (dd, J = 4.4, 1.5 Hz, 1H), 8.49 (dd, J = 5.1, 0.7 Hz, 1H), 8.38 (d, J = 0.7 Hz, 2H), 8.33 (s, 1H), 8.31 (dd, J = 8.5, 1.8 Hz, 1H), 8.30 (dd, J = 9.2, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.44 (dd, J = 9.2, 4.4 Hz, 1H), 7.37 (dd, J = 5.1, 1.4 Hz, 1H), 3.76 (s, 2H), 3.11 (s, 4H), 2.61 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.0, 152.5, 148.7, 145.2, 141.8, 140.0, 139.5, 132.8, 131.9, 131.3, 130.6, 127.3, 126.2, 125.6, 123.2, 120.7, 119.6, 115.4, 110.9, 96.1, 80.8, 58.3, 54.3, 45.6; MS (ESI) *m/z* 506 $[C_{26}H_{22}F_3N_7O + H]^+$.

Example 39: 3-(trifluoromethyl)-N-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)benzamide



[000337] To a solution of 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide (20 mg, 0.039 mmol) and MeOH (1.5 mL) was added formaldehyde (37% wt. aq. solution, 13 mg) and the mixture stirred at 50°C for 30 mins. $NaBH_4$ (4.5 mg) was added and the reaction stirred at rt for 15 min. The reaction was quench with 1N HCl, then the mixture was basified with K_2CO_3, filtered and concentrated *in vacuo*. The residue was purified by preparative TLC (eluent DCM/CH_3OH 4:1) to afford 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (10 mg, 48%, AUC HPLC >99%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 8.76 (dd, J = 4.4, 1.5 Hz, 1H), 8.49 (dd, J = 5.1, 0.7 Hz, 1H), 8.39–8.37 (m, 1H), 8.36 (d, J = 1.5 Hz, 1H), 8.32 (s, 1H), 8.31–8.27 (m, 2H), 7.92 (d, J = 8.2 Hz, 1H), 7.44 (dd, J = 9.2, 4.4 Hz, 1H), 7.36 (dd, J = 5.1, 1.5 Hz, 1H), 3.69 (s, 2H), 2.44 (bs, 8H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 152.4, 148.7, 145.2, 140.0, 139.5, 132.8, 132.0, 131.3, 130.6, 127.3, 126.2, 125.7, 125.0, 120.8, 119.6, 115.4, 110.9, 96.1, 80.9, 57.4, 54.5, 52.5, 45.4; MS (ESI) *m/z* 520 $[C_{27}H_{24}F_3N_7O+ H]^+$.

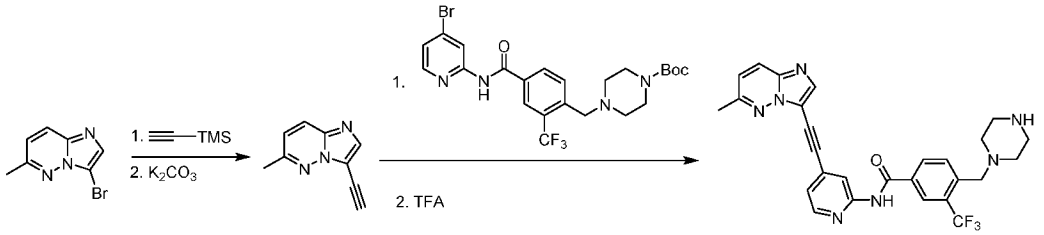
Example 40: 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-N-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)benzamide



[000338] To a solution of 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide (50 mg, 0.099 mmol)in THF (0.5 mL) and CH_2Cl_2 (0.5 mL) was added DIPEA (51.7 µL, 0.297 mmol) followed by bromoethane (14.6 µL, 0.198 mmol) and the mixture stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* and the residue purified by preparative TLC (eluent, DCM/CH_3OH 90:10), to afford 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)benzamide (15

mg, 28.4%, AUC HPLC 97.6%) as a white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1H), 8.76 (dd, J = 4.2, 1.2 Hz, 1H), 8.48 (d, J = 4.8 Hz, 1H), 8. 37–8.32 (m, 3H), 8.30–8.28 (m, 2H), 7.92 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 9.0, 4.2 Hz, 1H), 7.36 (d, J = 5.4 Hz, 1H), 3.67 (s, 2H), 2.43–2.34 (bs, 8H), 2.11 (q, J = 7.2 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 163.4, 153.0, 149.2, 145.7, 142.1, 140.5, 139.9, 133.2, 132.5, 131.7, 131.0, 127.6, 127.4, 126.7, 126.1, 121.2, 120.1, 115.8, 111.3, 96.6, 81.3, 72.9, 63.5, 57.9, 53.3, 52.8, 52.0, 12.5; MS (ESI) m/z 534 $[C_{28}H_{26}F_3N_7O + H]^+$.

Example 41: 3-(trifluoromethyl)-N-(4-(2-(6-methylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide



[000339] Step 1: Preparation of 6-methyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazine; The title compound was synthesized from 3-bromo-6-methylimidazo[1,2-*b*]pyridazine in a similar method to that described in general procedure A. The crude reaction mixture was purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 25:75) to afford 6-methyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazine (62 mg, 93%); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.90 (s, 1H), 7.84 (d, J = 9.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 1H), 2.63 (s, 3H), 0.31 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 153.3, 138.1, 125.2, 120.1, 113.2, 105.3, 90.9, 21.9, 0.0; MS (ESI) m/z 230 $[C_{12}H_{15}N_3Si + H]^+$.

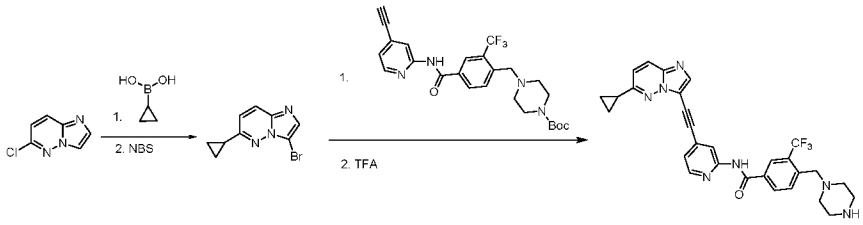
[000340] Step 2: Preparation of 3-ethynyl-6-methylimidazo[1,2-*b*]pyridazine; To a solution of 6-methyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazine (62 mg, 0.270 mmol) in 1:1 THF:MeOH (4 mL) was added K_2CO_3 (45 mg, 0.324 mmol) and stirred at room temperature for 30 minutes. The solvents were removed *in vacuo* and the residue suspended between EtOAc and water. The layers were separated, the organic layer washed with water and the combined aqueous back-extracted with EtOAc. The organics were combined, dried over $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 30:70) to afford 3-ethynyl-6-methylimidazo[1,2-*b*]pyridazine (33 mg, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H), 7.90 (d, J = 9.3 Hz, 1H), 7.02 (d, J = 9.3 Hz, 1H), 3.78 (s, 1H), 2.65 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 153.6, 138.4, 137.9, 125.3, 120.6, 112.2, 87.3, 70.8, 21.9. MS (ESI) m/z 158 $[C_9H_7N_3 + H]^+$.

[000341] Step 3: Preparation of *tert*-butyl 4-(4-((4-((6-methylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from 3-ethynyl-6-methylimidazo[1,2-*b*]pyridazine and *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate following a method similar to general procedure A. The solvents were removed *in vacuo* and purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 75:25) to afford *tert*-butyl 4-(4-((4-((6-methylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (82 mg, 63%); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.87 (s, 1H), 8.60 (s, 1H), 8.30 (d, *J* = 5.0 Hz, 1H), 8.25 (s, 1H), 8.13 (d, *J* = 6.6 Hz, 1H), 8.04 (s, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 3.83 (s, 2H), 3.54 (m, 4H), 2.68 (s, 3H), 2.53 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 164.1, 154.7, 153.5, 151.4, 147.8, 139.3, 135.1, 133.6, 132.2, 132.1, 130.6, 128.6, 128.5, 125.5, 125.4, 124.7, 122.9, 122.0, 120.6, 115.8, 112.2, 96.3, 81.7, 80.1, 57.7, 53.0, 28.5, 21.9; MS (ESI) *m/z* 620 $[C_{32}H_{32}F_3N_7O_3 + H]^+$.

Step 4: Preparation of 3-(trifluoromethyl)-*N*-(4-(2-(6-methylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide;

[000342] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-((4-(4-(2-(6-methylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)phenyl)methyl)piperazine-1-carboxylate. The reaction crude product was purified by preparative TLC (eluent DCM/CH_3OH 90:10) to afford 3-(trifluoromethyl)-*N*-(4-(2-(6-methylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide (36.5 mg, 53.0%, AUC HPLC 100%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.48 (dd, *J* = 5.1, 0.7 Hz, 1H), 8.38–8.33 (m, 2H), 8.31–8.27 (m, 1H), 8.22 (s, 1H), 8.16 (d, *J* = 9.3 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.35 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.33 (d, *J* = 9.3 Hz, 1H), 3.64 (s, 2H), 2.71 (t, *J* = 4.7 Hz, 4H), 2.62 (s, 3H), 2.34 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.0, 154.0, 152.5, 148.7, 141.8, 139.1, 132.8, 131.9, 131.4, 130.6, 127.5, 127.3, 127.1, 126.9, 125.6, 125.0, 123.2, 121.6, 121.4, 120.9, 115.4, 110.6, 95.9, 81.2, 58.3, 54.3, 45.6, 21.3; MS (ESI) *m/z* 520 $[C_{27}H_{24}F_3N_7O + H]^+$.

Example 42: N-(4-(2-(6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)-4-((piperazin-1-yl)methyl)benzamide



Step 1: Preparation of 6-cyclopropylimidazo[1,2-*b*]pyridazine

[000343] To a stirred solution of 6-chloroimidazo[1,2-*b*]pyridazine (2 g, 13.07 mmol), cyclopropylboronic acid (1.68 g, 19.6 mmol), S-Phos (1.6 g, 3.92 mmol) and potassium phosphate (5.5 g, 26.1 mmol) in toluene (20 mL), was added Palladium(II) acetate (440 mg, 1.96 mmol). The reaction mixture was stirred at 150 °C for 2 h in a sealed tube under N_2. The reaction mixture was diluted with DCM and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was purified by column chromatography (silica; heptane/EtOAc 0/100 to 50/50) to afford 6-cyclopropylimidazo[1,2-*b*]pyridazine (1.4 g, 67%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.66 (s, 1H), 6.82 (d, *J* = 9.2 Hz, 1H), 2.09 (t, *J* = 4.8 Hz, 1H), 1.09 (t, *J* = 7.2 Hz, 4H); MS (ESI) *m/z* 160.1 $[C_9H_9N_3+H]^+$.

[000344] Step 2: Preparation of 3-bromo-6-cyclopropylimidazo[1,2-*b*]pyridazine; *N*-bromosuccinimide (214 mg, 1.207 mmol) was added to a solution of 6-cyclopropylimidazo[1,2-*b*]pyridazine (160 mg, 1.006 mmol) in 1:1 acetonitrile:dichloromethane (4 mL) and the mixture stirred at room temperature for 15 minutes. The mixture was then diluted with dichloromethane and washed with water. The layers were separated, the organic layer concentrated and the crude purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 40:60) to afford 3-bromo-6-cyclopropylimidazo[1,2-*b*]pyridazine (190 mg, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.82 (d, *J* = 9.3 Hz, 1H), 7.70 (s, 1H), 6.89 (d, *J* = 9.3 Hz, 1H), 2.19 (tt, *J* = 7.5, 5.5 Hz, 1H), 1.18–1.14 (m, 4H);^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 157.8, 133.2, 125.0, 116.8, 15.5, 9.9. MS (ESI) *m/z* 238 $[C_9H_8BrN_3 + H]^+$.

Step 3: Preparation of *tert*-butyl 4-(4-((4-((6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate;

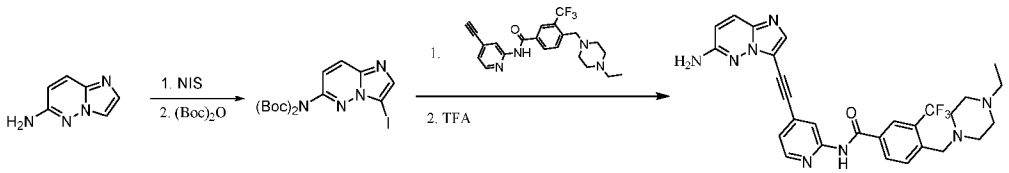
[000345] The title compound was prepared following a method similar to general procedure A and starting from 3-bromo-6-cyclopropylimidazo[1,2-*b*]pyridazine and *tert*-butyl 4-(4-((4-ethynylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The solvents were removed *in vacuo* and the crude purified twice by flash column

chromatography (silica gel, eluent: EtOAc/hexanes 65:35, then EtOAc/diethyl ether 50:50) to afford *tert*-butyl 4-(4-((4-((6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (58 mg, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.87 (s, 1H), 8.57 (s, 1H), 8.29 (d, *J* = 5.1 Hz, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.9 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 2H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.24 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.90 (d, *J* = 9.3 Hz, 1H), 3.73 (s, 2H), 3.50–3.42 (m, 4H), 2.45 (m, 4H), 2.21 (p, *J* = 6.6 Hz, 1H), 1.46 (s, 9H), 1.16 (d, *J* = 6.5 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 164.3, 158.1, 154.8, 151.5, 148.0, 139.0, 133.5, 133.1, 132.9, 131.1, 130.5, 129.7, 129.5, 129.3, 129.1, 125.3, 125.2, 121.9, 118.0, 115.7, 96.3, 81.7, 79.8, 77.3, 77.1, 76.9, 58.1, 53.1, 28.5, 15.6, 10.0; MS (ESI) *m/z* 646 $[C_{34}H_{34}F_3N_7O_3 + H]^+$.

Step 4: Preparation of *N*-(4-(2-(6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)-4-((piperazin-1-yl)methyl)benzamide

[000346] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-((4-(4-(2-(6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)phenyl)methyl)piperazine-1-carboxylate. The reaction crude product was purified by preparative TLC (eluent DCM/CH_3OH 92:8) to afford *N*-(4-(2-(6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)-4-((piperazin-1-yl)methyl)benzamide (9.0 mg, 71.4%, AUC HPLC 98%) as a white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.24 (bs, 1H), 8.49 (d, *J* = 6.0 Hz, 1H), 8.36–8.34 (m, 2H), 8.29 (d, *J* = 6.0 Hz, 1H), 8.19 (s, 1H), 8.12 (d, *J* = 12.0 Hz, 1H), 7.94 (d, *J* = 6.0 Hz, 1H), 7.34 (d, *J* = 6.0 Hz, 1H), 7.24 (d, *J* = 12.0 Hz, 1H), 3.64 (s, 2H), 2.72–2.69 (m, 4H), 2.36–2.28 (m, 5H), 1.15–1.13 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.0, 158.4, 152.5, 148.8, 141.8, 139.4, 138.9, 132.8, 132.0, 131.5, 130.6, 125.7, 125.1, 123.2, 120.8, 118.8, 115.4, 110.7, 96.1, 81.2, 72.5, 63.1, 58.3, 45.6, 15.1 and 9.6; MS (ESI) *m/z* 546 $[C_{29}H_{26}F_3N_7O + H]^+$.

Example 43: N-(4-((6-aminoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 3-iodoimidazo[1,2-*b*]pyridazin-6-amine

[000347] To a solution of imidazo[1,2-*b*]pyridazin-6-amine (2.3 g, 17.16 mmol) in DMF (10 mL) was added NIS (7.68 g, 34.32 mmol) at room temperature. The reaction mixture was stirred for 4 h and was poured into ice-cold water. The solid that has precipitated was isolated by filtration and was dried to afford 3-iodoimidazo[1,2-*b*]pyridazin-6-amine (3.5 g, 79.5 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.69 (d, J = 9.6 Hz, 1H), 7.47 (s, 1H), 6.65 (d, J = 10 Hz, 1H), 6.54 (bs, 2H); MS (ESI) *m/z* 260.9 $[C_6H_5IN_4+ H]^+$.

Step 2: Preparation of 6-bis-Boc-protected (imidazo[1,2-b]pyridazin-6-amine)

[000348] To a solution of 3-iodoimidazo[1,2-*b*]pyridazin-6-amine (500 mg, 1.92 mmol), DMAP (468 mg, 3.84 mmol) and 1,4 dioxane (5 mL), $(Boc)_2O$ (1.2 g, 5.76 mmol) was added drop wise at room temperature. After completion, reaction mixture was concentrated under reduced pressure, diluted with water. The solid was isolated and dried to afford the 6-bis-Boc-protected imidazo[1,2-b]pyridazin-6-amine (500 mg, 56.5%) as an off-white solid. MS (ESI) *m/z* 461.2 $[C_{16}H_{21}IN_4O_4 +H]^+$.

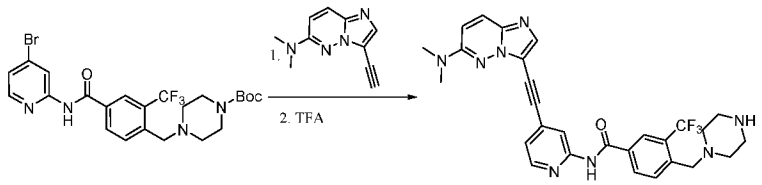
Step 3: Preparation of 6-bis-Boc-protected (*N*-(4-((6-aminoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide;

[000349] The title compound was prepared following a method similar to general procedure A and starting from the product of step 2 above and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide). After completion, reaction mixture was cooled to room temperature, concentrated under reduced pressure and the residue was diluted with water. The solid that has formed was isolated by filtration and dried to afford 6-bis-Boc-protected *N*-(4-((6-aminoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (600 mg). The crude product was used in the next step without further purification. MS (ESI) *m/z* 649.3 $[C_{33}H_{35}F_3N_8O_3 + H]^+$.

[000350] Step 4: Preparation of *N*-(4-((6-aminoimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide; The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 3-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)imidazo[1,2-*b*]pyridazin-6-ylcarbamate. After completion, the reaction mixture was concentrated under reduced pressure, basified with a saturated aqueous of $NaHCO_3$. The precipitate was isolated and purified by preparative HPLC to afford *N*-(4-((6-aminoimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (80 mg, AUC HPLC 98.0%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 8.46 (d, J = 4.8 Hz, 1H), 8.35–8.28 (m, 3H),7.93-7.89 (m, 2H), 7.84 (d, J = 10.0 Hz, 1H), 7.29 (d, J = 5.2 Hz,

1H), 6.78 (d, *J* = 9.6 Hz, 1H), 6.71 (s, 2H), 3.68 (s, 2H), 2.43 (m, 10H), 0.98 (t, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* 548.89 $[C_{28}H_{27}F_3N_8O+H]^+$.

Example 44: N-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



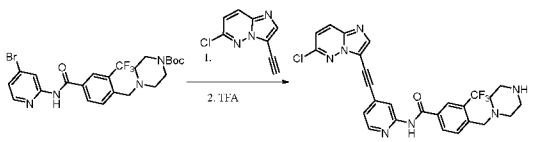
Step 1: Preparation of *tert*-butyl 4-(4-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000351] The title compound was prepared following a method similar to general procedure B and starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine. The reaction crude product was purified by flash chromatography (silica gel, eluent,$CHCl_3$/MeOH 95:5) to afford *tert*-butyl 4-(4-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as a yellow solid (200 mg, LC-MS 71%). MS (ESI) *m/z* 658.3 $[C_{33}H_{35}F_3N_8O_3+H]$.

Step 2: Preparation of *N*-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000352] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purification by preparative HPLC to afford *N*-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (35 mg, AUC HPLC 98.6%) as an off-white solid. m.p: 221–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.59 (s,1H), 8.55 (s,1H), 8.30 (d, *J* = 5.2 Hz, 2H), 8.20 (s, 1H), 8.07 (q, *J* = 8.4 Hz, 2H), 7.84 (s, 1H), 7.71 (d, *J* = 10 Hz,1H), 7.22 (dd, *J* = 1.2 Hz, *J* = 1.2 Hz, 1H), 6.84 (d, *J* = 10 Hz, 1H), 3.71 (s, 2H), 3.21 (s, 6H), 2.94-2.91 (t, *J* = 4.8 Hz, 4H), 2.47 (bs, 4H). MS (ESI) *m/z* 549.15 [M+H] $[C_{28}H_{27}F_3N_8O+H]^+$.

Example 45: N-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



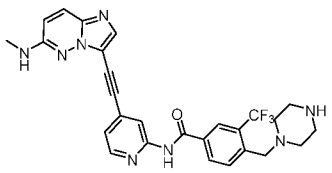
Step 1: Preparation of *tert*-butyl 4-(4-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000353] The title compound was prepared following a method similar to general procedure B and starting from 6-chloro-3-ethynylimidazo[1,2-b]pyridazine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent: dichloromethane/methanol 90:10) to afford *tert*-butyl 4-(4-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (600 mg).

Step 2: Preparation of *N*-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000354] A solution of *tert*-butyl 4-(4-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (600 mg, 0.93 mmol) in dichloromethane (10 mL) and TFA (2 mL) was stirred at room temperature for 2 h and was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford *N*-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (50 mg, LC-MS 91.8% HPLC ?) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1 H), 8.51 (d, J = 4.8 Hz, 1H), 8.39–8.35 (m, 5H), 8.32(d, J = 4.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.39 (dd, J = 1.6 Hz, J =1.6 Hz ,1H), 3.64 (s, 2H), 2.74 (t, J = 4.4 Hz, 4H), 2.33 (d, J = 4.4 Hz, 4H). MS (ESI) *m/z*: 540.12 $[C_{26}H_{21}ClF_3N_7O+H]^+$.

Example 46: N-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



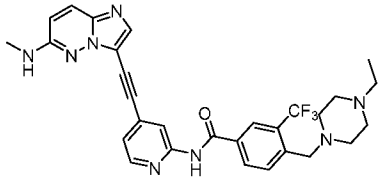
Step 1: preparation of *tert*-butyl 4-(4-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000355] The title compound was prepared following a method similar to general procedure B and starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl)piperazine-1-carboxylate and *tert*-butyl 3-ethynyl-*N*-methylimidazo[1,2-b]pyridazin-6-amine. . The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 4-(4-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (100 mg); MS (ESI) *m/z*:635.1 $[C_{32}H_{33}F_3N_8O_3+H]^+$.

Step 2: preparation of *N*-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000356] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by column chromatography (silica gel, eluent, $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford *N*-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (15 mg, 18%, AUC HPLC 97.8%) as a Brown solid. m.p. 214-217 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm) 11.31 (s, 1H), 8.47 (d, J = 4.8 Hz, 1H), 8.34 (s, 1H), 8.29 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.89 (s,1H), 7.79 (d, J = 9.6 Hz, 1H), 7.30 (d, J = 4.0 Hz, 1H), 7.24 (d, J = 4.4 Hz, 1H), 6.78 (d, J = 9.6 Hz, 1H), 3.66 (s, 2H), 3.89 (d, J = 4.8 Hz, 3H), 2.78–2.70 (m, 4H), 2.38–2.32 (m, 4H); MS (ESI) *m/z* 535.2 $[C_{27}H_{25}F_3N_8O+H]^+$.

Example 47: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

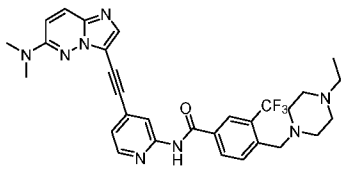


Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

[000357] The title compound was prepared following a method similar to general procedure B starting from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and 3-ethynyl-*N*-methylimidazo[1,2-b]pyridazin-6-amine. The

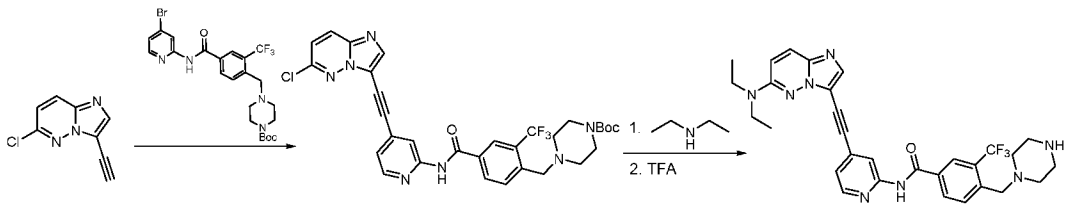
reaction crude product was purified by flash column chromatography (silica gel, eluent: dichloromethane/MeOH 90:10) and preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (30 mg, AUC HPLC 98.7%) as a pale yellow solid. ^{1}H NMR (400 MHz, ($CDCl_3$), δ (ppm): 8.59 (d, *J* = 12.8 Hz, 1H), 8.31 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 1H), 8.08–8.00 (m, 2H), 7.83 (s, 1H), 7.66 (d, *J* = 9.6 Hz, 1H), 7.25–7.23 (m, 1H), 6.53 (d, *J* = 9.6 Hz, 1H), 4.53(d, *J* = 5.2 Hz, 1H), 3.74 (s, 2H), 3.11 (d, *J* = 5.6 Hz, 3H), 2.56–2.42 (m, 10H), 1.10 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z*: 563.2 $[C_{29}H_{29}F_3N_8O+H]^+$.

Example 48: N-(4-((6-(dimethylamino) imidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide



[000358] The title compound was synthesized from 3-ethynyl-*N*, *N*-dimethylimidazo [1, 2-*b*] pyridazin-6-amine and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide in a similar method to that described in general procedure A. The crude product was purified by preparative HPLC to afford *N*-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (90 mg, 25%, AUC HPLC >99%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 8.46 (d, *J* = 4.8 Hz, 1H), 8.35 (m, 2H), 8.29 (d, *J* = 8 Hz, 1H), 7.91–7.96 (m, 3H), 7.30 (dd, *J* = 4.4, 5.6 Hz, 1H), 7.21 (d, *J* = 10 Hz, 1H), 3.68 (s, 2H), 3.13 (s, 6H), 2.31–2.54 (m, 10H), 1.00 (t, *J* = 7.6 Hz, 3H); MS (ESI) *m/z* 576 $[C_{30}H_{31}F_3N_8O+H]^+$.

Example 49: N-(4-((6-(diethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



[000359] Step 1: Preparation of *tert*-butyl 4-(4-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The

title compound was synthesized from 6-chloro-3-ethynylimidazo[1,2-b]pyridazine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate following a method similar to general procedure A. The crude product was purified by column chromatography (silica gel, eluent Hex/EtOAc 5:95) to afford *tert*-butyl 4-(4-(4-((6-chloroimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (18 mg, 16%, AUC HPLC 70%) as an off-white solid. ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.49 (d, *J* = 6.6 Hz, 1H), 8.31 (d, *J* = 7.4 Hz, 2H), 8.42 (s, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 7.95 (t, *J* = 9.2 Hz, 2H), 7.76 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.50–7.41 (m, 4H), 7.22 (d, *J* = 4.0 Hz, 1H), (3.87 (s, 2H), 3.45 (s, 4H), 2.43 (t, *J* = 4.52 Hz, 4H), 1.46 (s, 9H); MS (ESI) *m/z* 640 $[C_{31}H_{29}ClF_3N_7O_3+ H]^+$.

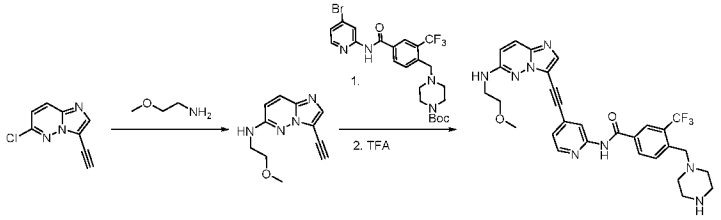
[000360] Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-(diethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; To a solution of *tert*-butyl 4-(4-(4-((6-chloroimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (20 mg, 0.03 mmol) in NMP (3.0 mL) was added diethylamine (2.0 mL). The resulting mixture was heated in a microwave reactor at 160 °C for 1 h followed by a purification by column chromatography (silica gel, eluent Hex/EtOAc 1:3) to afford crude *tert*-butyl 4-(4-(4-((6-(diethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as brown solid. MS (ESI) *m/z* 677 $[C_{35}H_{39}F_3N_8O_3 + H]^+$.

Step 3: Preparation of *N*-(4-((6-(diethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide;

[000361] The title compound was prepared following a method similar to general procedure D and starting from the crude *tert*-butyl 4-(4-(4-((6-(diethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The crude reaction mixture was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((6-(diethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (10 mg, 68%, AUC HPLC 99%) as yellow solid. ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.45 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.33 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.98 (s, 1H), 7.85 (d, *J* = 10.1 Hz, 1H), 7.31 (d, *J* = 10.1 Hz, 1H), 7.28 (q, *J* = 2.1 Hz, 1H), 3.87(s, 2H), 3.68 (q, *J* = 7.1 Hz, 4H), 3.29–3.25 (m, 4H), 3.28 (t, *J* = 5.2 Hz, 4H), 1.33 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 166.84, 155.71, 153.56, 149.64, 142.13, 135.15, 134.04, 133.16,

132.50, 132.34, 126.87, 126.82, 124.62, 122.29, 117.10, 114.99, 97.27, 58.79, 50.86, 45.03, 44.85, 13,13; MS (ESI) *m/z* 577 $[C_{30}H_{31}F_3N_8O_3 + H]^+$.

Example 50: N-(4-((6-(2-methoxyethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



[000362] Step 1: Preparation of 3-ethynyl-*N*-(2-methoxyethyl)imidazo[1,2-*b*]pyridazin-6-amine; A solution of 6-chloro-3-ethynylimidazo[1,2-*b*]pyridazine (60 mg, 0.34 mmol), 2-methoxyethanamine (0.5 mL) and NMP (2 mL) was heated in a microwave reactor at 140 ^oC for 0.5 h. The reaction solution was filtered, concentrated and the residue was purified by flash column chromatography (silica gel, eluents Hex/EA 1:1) to afford 3-ethynyl-*N*-(2-methoxyethyl)imidazo[1,2-b]pyridazin-6-amine (31 mg, 66%) as a brown solid. MS (ESI) *m/z* 217 $[C_{11}H_{12}N_4O + H]^+$.

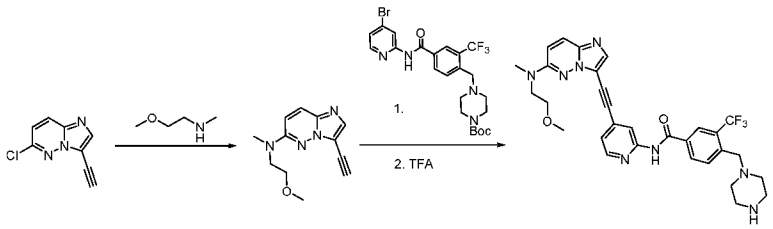
[000363] Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-(2-methoxyethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl) piperazine-1-carboxylate; The title compound was synthesized from 3-ethynyl-*N*-(2-methoxyethyl)imidazo[1,2-*b*]pyridazin-6-amine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate following a method analogous to that described in general procedure A. Purification by preparative HPLC (C18, eluent ACN/H_2O/HCOOH 0.1%) gave *tert*-butyl 4-(4-(4-((6-(2-methoxyethylamino) imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl)piperazine-1-carboxylate (2.5 mg) as off-white solid. MS (ESI) *m/z* 579 $[C_{29}H_{29}F_3N_8O_2 + H]^+$.

Step 3: Preparation of *N*-(4-((6-(2-methoxyethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide;

[000364] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(4-((6-(2-methoxyethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl) piperazine-1-carboxylate. Purification by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) afforded *N*-(4-((6-(2-methoxyethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-

ylmethyl)-3-(trifluoromethyl)benzamide (2.1 mg, AUC HPLC 97%) as off-white solid. ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.55 (s, 1H), 8.41 (s, 1H), 8.38 (d, *J* = 4.9 Hz, 1H), 8.32 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.64 (d, *J* = 9.7 Hz, 1H), 7.26 (d, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 9.7 Hz, 1H), 3.82 (s, 2H), 3.74 (t, *J* = 5.1 Hz, 2H), 3.66 (t, *J* = 5.0 Hz, 2H), 3.42 (s, 3H), 3.14 (s, 4H), 2.66 (s, 4H); ^{13}C NMR (100 MHz, MeOD) δ (ppm): 166.79, 156.16, 153.50, 149.58, 142.54, 136.31, 134.98, 134.98, 132.38, 130.03, 126.82, 126.76, 125.70, 122.25, 117.13, 116.21, 113.14, 96.79, 82.69, 71.61, 59.11, 58.99, 52.28, 45.50, 42.19; MS (ESI) *m/z* 579 $[C_{29}H_{29}F_3N_8O_2 + H]^+$.

Example 51: N-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

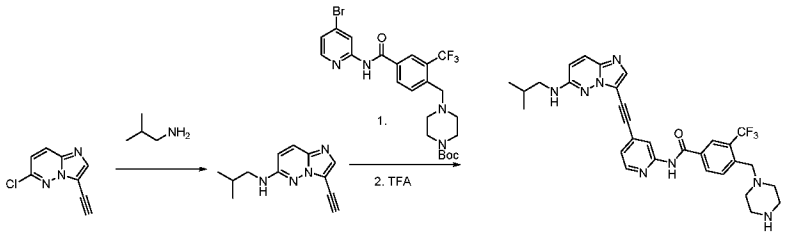


[000365] Step 1: Preparation of 3-ethynyl-*N*-(2-methoxyethyl)-*N*-methylimidazo[1,2-*b*]pyridazin-6-amine; A solution of 6-chloro-3-ethynylimidazo[1,2-b]pyridazine (100 mg, 0.56 mmol) in 2-methoxy-*N*-methylethanamine (2.0 ml) was heated at 140°C in a microwave reactor for 1 h at atmospheric pressure. The reaction mixture was then purified by column chromatography (silica gel, eluent hexanes/EtOAc 1:9) to afford 3-ethynyl-*N*-(2-methoxyethyl)-*N*-methylimidazo[1,2-*b*]pyridazin-6-amine (70 mg, 54%) as brown viscuous sirup. MS (ESI) *m/z* 231 $[C_{12}H_{14}N_4O + H]^+$.

[000366] Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from 3-ethynyl-*N*-(2-methoxyethyl)-*N*-methylimidazo[1,2-b]pyridazin-6-amine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate following a method similar to general procedure A. The reaction mixture was filtered, washed, and purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *tert*-butyl 4-(4-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. MS (ESI) *m/z* 693$[C_{35}H_{39}F_3N_8O_4 + H]^+$.

[000367] Step 3: Preparation of *N*-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide; The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction solution was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) twice to afford *N*-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (7.0 mg, 21%, AUC HPLC 99%) as off-white solid. ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.40 (s, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 8.23 (d,*J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 8.80 (s, 1H), 7.74 (d,*J* = 10.0 Hz, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 7.19 (d, *J* = 10.0 Hz, 1H), 4.90–4.80 (m, 4H), 3.74 (t, *J* = 5.2 Hz, 2H), 3.38 (s, 3H), 3.24 (s, 3H), 3.13 (t, *J* = 4.8 Hz, 4H), 2.66 (s, 4H); MS (ESI) *m/z* 593 $[C_{30}H_{31}F_3N_8O_2+H]^+$.

Example 52: N-(4-((6-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Synthesis of 3-ethynyl-*N*-isobutylimidazo[1,2-*b*]pyridazin-6-amine

[000368] To a solution of 6-chloro-3-ethynylimidazo[1,2-*b*]pyridazine (106 mg, 0.60 mmol) in *N*-methyl-2-pyrrolidone (1 mL) was added isobutylamine (219 mg, 3 mmol). The resulting mixture was heated in a microwave reator at 140 °C for 30 min. The reaction media was purified by column chromatography (silica gel, eluent hexanes/ethyl acetate 1:1) to afford 3-ethynyl-*N*-isobutylimidazo[1,2-*b*]pyridazin-6-amine (85 mg, 66%) as white solid. MS (ESI) *m/z* 215 $[C_{12}H_{14}N_4 + H]^+$.

Step 2: Synthesis of *tert*-butyl 4-(4-((4-((6-(isobutylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

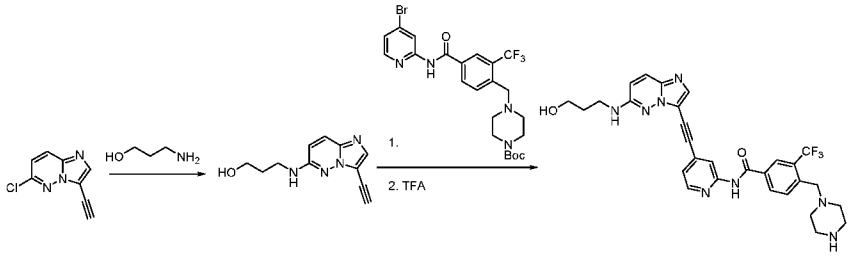
[000369] The title compound was prepared following a method similar to general procedure A and starting from 3-ethynyl-*N*-isobutylimidazo[1,2-*b*]pyridazin-6-amine and *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford *tert*- butyl 4-(4-((4-((6-(isobutylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (38 mg, 28%) as yellow solid; MS (ESI) *m/z* 677[$C_{35}H_{39}F_3N_8O_3$+ H]$^+$.

Step 3: Preparation of *N*-(4-((6-(isobutylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000370] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-((4-((6-(isobutylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/MeOH 95:5 to 90:10) to afford *N*-(4-((6-(isobutylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (9 mg, 52%, AUC HPLC 99%) as white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.41 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H), 7.60 (d, *J* = 9.7 Hz, 1H), 7.24 (d, *J* = 5.0 Hz, 1H), 6.79 (d, *J* = 9.7 Hz, 1H), 3.73 (s, 2H), 3.27 (d, *J* = 6.8 Hz, 2H), 2.89–2.85 (m, 4H), 2.49 (bs, 4H), 2.10 (sept, *J* = 6.7 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 6H); MS (ESI) *m/z* 577 [$C_{30}H_{31}F_3N_8O$ + H]$^+$.

Example 53: N-(4-((6-(3-hydroxypropylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



[000371] Step 1: Preparation of 3-((3-ethynylimidazo[1,2-*b*]pyridazin-6-yl)amino)propan-1-ol.To a solution of 6-chloro-3-ethynylimidazo[1,2-*b*]pyridazine (43 mg, 0.24 mmol) in *N*-methyl-2-pyrrolidone (1 mL) was added 3-aminopropan-1-ol (91 mg, 1.21 mmol). The resulting mixture was heated in a microwave reactor at 140 °C for 30 min. The reaction media was purified by column chromatography (silica gel, eluent CH_2Cl_2/MeOH 95:5 to 90:10) to afford 3-((3-ethynylimidazo[1,2-*b*]pyridazin-6-yl)amino)propan-1-ol (22mg, 42%). MS (ESI) *m/z* 217 [$C_{11}H_{12}N_4O$ + H]$^+$.

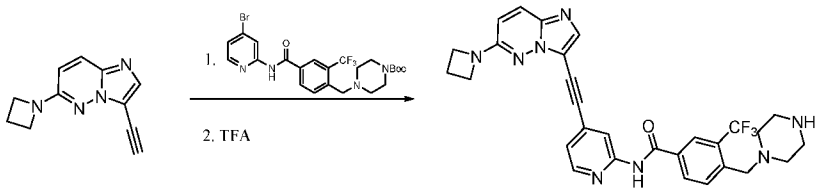
Step 2: Preparation of *tert*-butyl 4-(4-((4-((6-((3-hydroxypropyl)amino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000372] The title compound was prepared following a method similar to general procedure A and starting from 3-((3-ethynylimidazo[1,2-*b*]pyridazin-6-yl)amino)propan-1-ol (22 mg, 0.10 mmol) and *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *tert*-butyl 4-(4-((4-((6-((3-hydroxypropyl)amino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (14 mg, 21%) as yellow solid; MS (ESI) *m/z* 679$[C_{34}H_{37}F_3N_8O_4$+ H$]^+$.

Step 3: Preparation of *N*-(4-((6-(3-hydroxypropylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000373] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(4-((6-(3-hydroxypropylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/MeOH 95:5 to 90:10) to afford *N*-(4-((6-(3-hydroxypropylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (6 mg, 50%, AUC HPLC 99%) as white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.40 (s, 1H), 8.38 (d, *J* = 5.1 Hz, 1H), 8.32 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.74 (s, 1H), 7.62 (d, *J* = 9.7 Hz, 1H), 7.29 (d, *J* = 4.7 Hz, 1H), 6.78 (d, *J* = 9.7 Hz, 1H), 3.85 (s, 2H), 3.74 (t, *J* = 6.3 Hz, 2H), 3.56 (t, *J* = 6.8 Hz, 2H), 3.24 (t, *J* = 5.0 Hz, 4H), 2.77–2.72 (m, 4H), 2.00–1.93 (m, 2H); MS (ESI) *m/z* 579.70 $[C_{29}H_{29}F_3N_8O_2$ + H$]^+$.

Example 54: N-(4-((6-(azetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 6-(azetidin-1-yl)-3-ethynylimidazo [1,2-b]pyridazine

[000374] To a solution of 6-chloro-3-ethynylimidazo[1,2-b]pyridazine (300 mg, 1.69 mmol) in 1,4 dioxane (10 mL) was added azetidine (144.4 mg, 2.53 mmol) and the resultion solution was heated at 100 °C for 2 h. The reaction mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 6-(azetidin-1-yl)-3-ethynylimidazo[1,2-b]pyridazine (200 mg, 59.70%, LC-MS 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (s, 1H), 7.66 (d, *J* = 9.6 Hz, 1H), 6.42 (d, *J* = 9.6 Hz, 1H), 4.15 (t, *J* = 7.6 Hz, 4H), 3.69 (s, 1H), 2.45 (quint, *J* = 7.2 Hz, 2H); MS (ESI) *m/z* 199.09 $[C_{11}H_{10}F_3N_4+H]^+$.

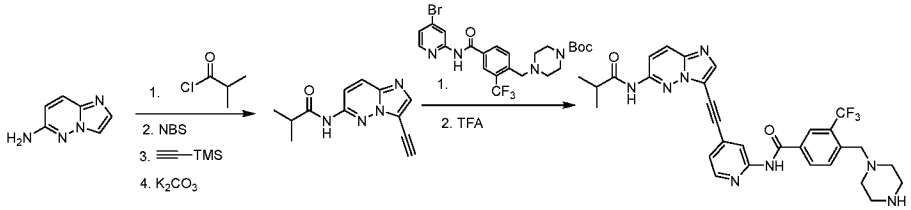
Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-(azetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000375] The title compound was synthesized following a method similar to general procedure B starting from 6-(azetidin-1-yl)-3-ethynylimidazo[1,2-b]pyridazine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 97:3) to afford *tert*-butyl 4-(4-(4-((6-(azetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-trifluoromethyl)benzyl)piperazine-1-carboxylate (150 mg). MS (ESI) *m/z* 661.28 $[C_{34}H_{35}F_3N_8O_3+H]^+$.

Step 3: Preparation of *N*-(4-((6-(azetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000376] To a solution of *tert*-butyl 4-(4-(4-((6-(azetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (150 mg, 0.22 mmol) in dichloromethane (50 mL) was added TFA (10 mL) at 0 °C and the solution was stirred for 3 h while warming to room temperature. The reaction mixture was diluted with $CHCl_3$ and basified with $NaHCO_3$. The organic phase was washed in turn with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 95:5) and by preparative HPLC to afford *N*-(4-((6-(azetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (40 mg, 33%, HPLC-AUC 97.5%) as a yellow solid. m.p-185-190 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 11.31 (s, 1H), 8.46 (d, *J* = 4.8 Hz, 1H), 8.34 (s, 2H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.95 (t, *J* = 6.4 Hz , 3H), 7.30 (d, *J* = 4.8 Hz, 1H), 6.78 (d, *J* = 9.6 Hz, 1H), 4.13 (t, *J* = 6.8 Hz, 4H), 3.66 (s, 2H), 2.78 (s, 4H), 2.38 (s, 7H); MS (ESI) *m/z* 559.2 $[C_{29}H_{27}F_3N_8O+H]^+$.

Example 55: 3-(trifluoromethyl)-N-(4-(2-(6-(isobutyramido)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide



[000377] Step 1: Preparation of *N*-(imidazo[1,2-*b*]pyridazin-6-yl)isobutyramide; To a solution of imidazo[1,2-*b*]pyridazin-6-amine (200 mg, 1.49 mmol), DMAP (91 mg, 0.745 mmol) and triethylamine (623 µL, 4.47 mmol) in anhydrous DCM (3 mL) cooled to 0 °C, was first added a solution of isobutyryl chloride (256 µL, 2.44 mmol) in DCM (1 mL), followed by few drops of DMF. The mixture was stirred at room temperature for 12 h then, was diluted with DCM, washed in turn with water and brine, dried over $MgSO_4$ and concentrated. The crude was purified by flash column chromatography (silica gel, eluent: MeOH/EtOAc 2:98) to afford *N*-(imidazo[1,2-*b*]pyridazin-6-yl)isobutyramide (35 mg, 12%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.52 (s, 1H), 8.13 (d, *J* = 9.9 Hz, 1H), 7.94 (d, *J* = 9.9 Hz, 1H), 7.74 (s, 1H), 7.69 (s, 1H), 2.65 (hept, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H).^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.3, 148.5, 138.1, 133.4, 126.7, 116.3, 112.9, 36.7, 19.4. (ESI) *m/z* 205 $[C_{10}H_{12}N_4O + H]^+$.

[000378] Step 2: Preparation of *N*-(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)isobutyramide; *N*-bromosuccinimide (34 mg, 0.189 mmol) was added to a solution of *N*-(imidazo[1,2-*b*]pyridazin-6-yl)isobutyramide (35 mg, 0.171 mmol) in a mixture of ACN and DCM (1:1, 2 mL) and the mixture stirred at room temperature for 1 h. The mixture was then concentrated and purified by flash column chromatography (silica gel, eluent: EtOAc). The fractions containing desired product was then concentrated and passed through a column of basic alumina and concentrated to afford *N*-(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)isobutyramide (40 mg, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.24 (d, *J* = 9.8 Hz, 2H), 7.94 (d, *J* = 9.9 Hz, 1H), 7.73 (s, 1H), 2.64 (hept, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.2, 149.2, 138.8, 133.9, 127.0, 112.8, 100.0, 36.9, 19.4; MS (ESI) *m/z* 283 $[C_{10}H_{11}BrN_4O + H]^+$.

[000379] Step 3: Preparation of *N*-(3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazin-6-yl)isobutyramide; The title compound was synthesized from *N*-(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)isobutyramide and trimethylsilylacetylene following a similar method as described in general procedure A. The mixture was then concentrated and the crude purified

by flash column chromatography (silica gel, eluent: EtOAc/hexanes 30:70) to afford *N*-(3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazin-6-yl)isobutyramide (95.8 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.24 (d, *J* = 9.7 Hz, 1H), 8.04 (s, 1H), 7.94 (d, *J* = 9.7 Hz, 1H), 2.62 (hept, *J* = 7.0 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H), 0.32 (s, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.1, 149.0, 138.9, 126.9, 121.8, 118.5, 113.4, 105.6, 90.8, 37.0, 19.4, 0.0; MS (ESI) *m/z* 301 $[C_{15}H_{20}N_4OSi+H]^+$.

Step 4: Preparation of *N*-(3-ethynylimidazo[1,2-*b*]pyridazin-6-yl)isobutyramide

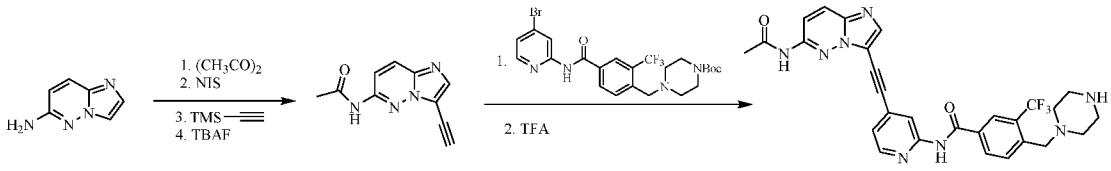
[000380] To a solution of *N*-(3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazin-6-yl)isobutyramide (95 mg, 0.316 mmol) in THF (1.5 mL) and MeOH (1.5 mL) was added potassium carbonate (52 mg, 0.379 mmol). The reaction mixture stirred at room temperature for 1 h. The solvents were removed *in vacuo* and the residue suspended between EtOAc and water. The organic layer washed with water and the combined aqueous back-extracted with EtOAc. The organics were combined, dried over $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 4:6) to afford *N*-(3-ethynylimidazo[1,2-*b*]pyridazin-6-yl)isobutyramide (28 mg, 39%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.27 (d, *J* = 9.8 Hz, 1H), 8.18 (s, 1H), 7.96 (dd, *J* = 9.8, 0.6 Hz, 1H), 7.95 (s, 1H), 3.79 (s, 1H), 2.60 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H);^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.1, 149.1, 138.9, 129.3, 127.1, 113.8, 111.8, 87.3, 70.9, 36.9, 19.4; MS (ESI) *m/z* 229 $[C_{12}H_{12}N_4O + H]^+$.

[000381] Step 5: Preparation of *tert*-butyl 4-(4-((4-((6-isobutyramidoimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from *N*-(3-ethynylimidazo[1,2-*b*]pyridazin-6-yl)isobutyramide and *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate following a method similar to general procedure A. The solvents were removed *in vacuo* and the crude purified by flash column chromatography (silica gel, eluent: EtOAc/dichloromethane 50:50) to afford *tert*-butyl 4-(4-((4-((6-isobutyramidoimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (30 mg, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.00 (s, 1H), 8.78 (s, 1H), 8.51 (s, 1H), 8.37 (d, *J* = 9.8 Hz, 1H), 8.34 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 13.2 Hz, 1H), 7.98 (d, *J* = 4.5 Hz, 2H), 7.23 (dd, *J* = 5.1, 1.4 Hz, 1H), 3.73 (s, 2H), 3.56 – 3.40 (m, 4H), 2.73 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.45 (m, 4H), 1.46 (s, 9H), 1.33 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.6, 164.5, 162.6, 154.8, 151.5, 149.6, 148.0, 139.3, 133.3, 132.2, 132.2, 132.0,

130.4, 128.6, 128.6, 127.2, 125.2, 121.8, 116.0, 114.1, 111.8, 96.6, 81.5, 58.0, 53.1, 36.9, 36.6, 31.5, 28.5, 19.5; MS (ESI) *m/z* 691 $[C_{35}H_{37}F_3N_8O_4 + H]^+$.

[000382] Step 6: Preparation of 3-(trifluoromethyl)-*N*-(4-(2-(6-(isobutyramido)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide: The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-((4-(4-(2-(6-(isobutyramido)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)phenyl)methyl)piperazine-1-carboxylate in. The reaction crude product was purified by preparative TLC (eluent DCM/CH_3OH 90:10) to afford 3-(trifluoromethyl)-*N*-(4-(2-(6-(isobutyramido)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide (15.7 mg, 61%, AUC HPLC 97.6%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.33 (s, 1H), 11.03 (s, 1H), 8.50 (dd, *J* = 5.1, 0.6 Hz, 1H), 8.35 (d, *J* = 0.8 Hz, 2H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.25–8.19 (m, 2H), 8.11 (d, *J* = 9.8 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.4 Hz, 1H), 3.66 (s, 2H), 2.87–2.72 (m, 5H), 2.37 (s, 4H), 1.13 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 177.0, 165.0, 152.4, 149.9, 148.8, 141.7, 139.4, 138.7, 132.7, 132.0, 131.4, 130.7, 127.5, 127.3, 127.1, 126.98, 126.9, 125.08, 123.2, 121.1, 115.4, 115.1, 110.7, 96.0, 81.1, 58.1, 53.74, 45.2, 34.6, 19.2; MS (ESI) *m/z* 591 $[C_{30}H_{29}F_3N_8O_2 + H]^+$.

Example 56: Synthesis of N-(4-((6-acetamidoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: preparation of *N*-(imidazo[1,2-b]pyridazin-6-yl)acetamide

[000383] Acetic anhydride (2.36 mL, 25.06 mmol) was added drop-wise to a cooled mixture of imidazo[1,2-b]pyridazin-6-amine (2.8 g, 20.89 mmol) and 4-dimethylaminopyridine (5.1 g, 41.79 mmol) in pyridine (5 mL). The reaction mixture was stirred at 100 °C for 2 h then was diluted with CH_2Cl_2 and washed in tur with 1N HCl aqueous solution and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: hexane/ethyl acetate 80:20) to afford *N*-(imidazo[1,2-b]pyridazin-6-yl)acetamide (1.2 g, 33%, LC-MS 92%). MS (ESI) *m/z*: 177.2 $[C_8H_8N_4O +$

H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.86 (s, 1H), 8.10 (t, J = 6.0 Hz, 2H), 7.90 (d, J = 9.6 Hz, 1H), 7.70 (s, 1H), 2.13 (s, 3H); MS (ESI) *m/z*: 177.07 [$C_8H_8N_4O$+H]$^+$.

Step 2: Preparation of *N*-(3-iodoimidazo [1,2-b]pyridazin-6-yl)acetamide

[000384] A solution of *N*-(imidazo[1,2-b]pyridazin-6-yl)acetamide (1.2 g, 6.81 mmol) and NIS (1.84 g, 8.18 mmol) in DMF (20 mL) was stirred at room temperature for 4 h. Water (50 mL) was added and the resulting mixture was filtered. The cake was washed with water and dried to afford *N*-(3-iodoimidazo[1,2-b]pyridazin-6-yl)acetamide (1.5 g, 75%, LC-MS 94%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 10.96 (s, 1 H), 8.09 (d, J = 9.6 Hz, 1H), 7.96 (s, 1H), 7.81 (s, 1H), 2.16 (s, 3H); MS (ESI) *m/z*: 302.2 [$C_8H_7IN_4O$+H]$^+$.

Step 3: Preparation of *N*-(3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-yl)acetamide

[000385] The title compound was prepared following a method similar to general procedure B and starting from *N*-(3-iodoimidazo[1,2-b]pyridazin-6-yl)acetamide and ethynyltrimethylsilane. The reaction crude product was purified by flash chromatography (silica gel, eluent: heptane/ethyl acetate 0/100 to 50/50) to afford *N*-(3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-yl)acetamide (900 mg) as a brown solid. MS (ESI) *m/z*: 273.1 [$C_{13}H_{16}N_4OSi$+H]$^+$.

Step 4: Preparation of *N*-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)acetamide

[000386] To a solution of *N*-(3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-yl)acetamide (900 mg, 3.3 mmol) in THF (20 mL) was added LiOH (1667 mg, 3.97 mmol) in water (5 mL) at room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, washed with water and extracted with ethyl acetate (50 mL) to afford *N*-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)acetamide (500 mg) as an brown solid.

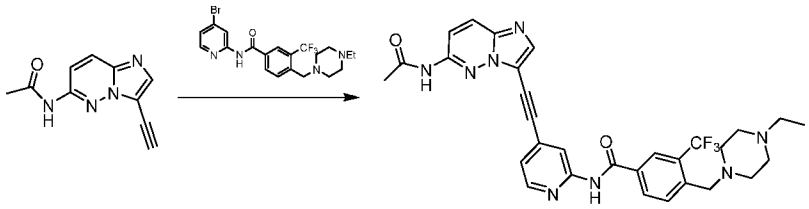
Step 5: Preparation of *tert*-butyl 4-(4-(4-((6-acetamidoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000387] The title compound was prepared following a method similar to general procedure B and starting from *N*-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)acetamide and *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3$/CH_3OH 95:5) to afford *tert*-butyl 4-(4-(4-((6-acetamidoimidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-ylcarbamoyl)-2-trifluoromethyl) benzyl) piperazine-1-carboxylate (150 mg) as a yellow solid.

Step 6: Preparation of *N*-(4-((6-acetamidoimidazo [1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000388] The title compound was prepared following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(4-((6-acetamidoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford *N*-(4-((6-acetamidoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (20 mg, 46%,AUC HPLC 90.8%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 11.35 (s, 1H), 11.11 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.36 (s, 2H), 8.30–8.22 (m, 3H), 8.00 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.36–7.35 (m, 1H), 3.64 (s, 2H), 2.74–2.67 (m, 4H), 2.49–2.34 (m, 4H), 2.18 (s, 3H); MS (ESI) *m/z* 563.55 $[C_{28}H_{25}F_3N_8O_2+H]^+$.

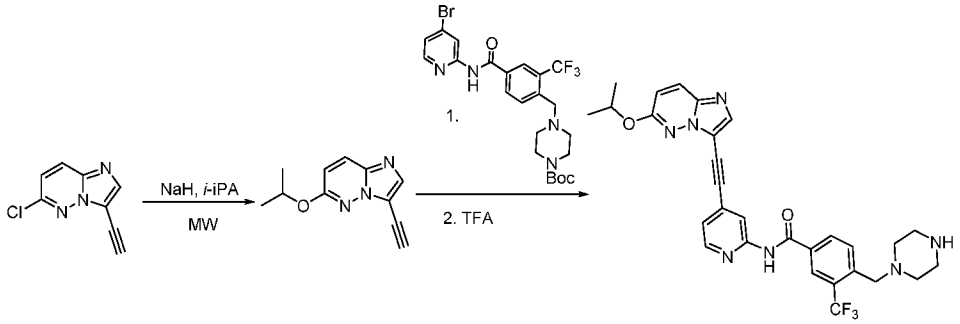
Example 57: Synthesis of N-(4-((6-acetamidoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *N*-(4-((6-acetamidoimidazo [1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000389] *N*-(4-((6-acetamidoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide was prepared using a procedure similar to that described in general procedure B and starting from *N*-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)acetamide and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. The crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 95:5) and by preparative HPLC to afford *N*-(4-((6-acetamidoimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (15 mg, 16%, AUC HPLC 95.6%) as a pale brown solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.42–8.40 (m, 2H), 8.29 (d, J = 9.2 Hz, 2H), 8.22 (d, J = 8.4 Hz, 1H), 8.07–8.01 (m, 3H), 8.30 (d, J = 4.8 Hz, 1H), 3.77 (s, 2H), 2.57–2.44 (m, 10H), 2.22 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 591.62 $[C_{30}H_{29}F_3N_8O_2+H]^+$.

Example 58: N-(4-((6-ethoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



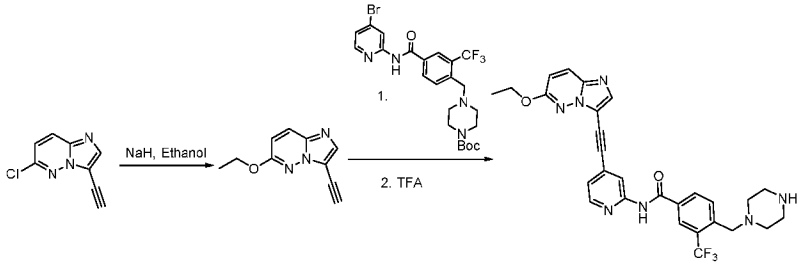
[000390] Step 1: Preparation of 3-ethynyl-6-isopropoxyimidazo[1,2-*b*]pyridazine; A mixture of 6-chloro-3-ethynylimidazo[1,2-*b*]pyridazine (50 mg, 0.28 mmol), Sodium hydride (23 mg, 0.56 mmol) in isopropanol (5 mL) was heated at 150 °C in a microwave reactor for 2 h. The reaction solution was filtered, concentrated and purified by column chromatography (silica gel, eluents hexanes/EtOAc 9:1) to afford 3-ethynyl-6-isopropoxyimidazo[1,2-*b*]pyridazine (33 mg, 75 %) as a brown solid. MS (ESI) *m/z* 202 $[C_{11}H_{11}N_3O+H]^+$.

[000391] Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-isopropoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from 3-ethynyl-6-isopropoxyimidazo[1,2-*b*]pyridazine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate following a method similar to general procedure A. The residue mixture filtered washed was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford to *tert*-butyl 4-(4-(4-((6-isopropoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as off-white solid. MS (ESI) *m/z* 664 $[C_{34}H_{36}F_3N_7O_4+H]^+$.

[000392] Step 3: Preparation of 4-(4-((6-isopropoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 4-(4-(4-((6-isopropoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar method as described in general procedure D. The crude product was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford 4-(4-((6-isopropoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (3 mg, AUC HPLC 95%) as off-white solid.^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.60 (s, 1H), 8.53 (t, *J* = 3.8 Hz, 1H), 8.33 (s, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 9.7 Hz, 1H), 7.90 (s, 1H), 7.42 (dd, *J* = 5.2, 1.2 Hz, 1H),

6.96 (d, J = 9.7 Hz, 1H), 5.34 (q, J = 6.2 Hz, 1H), 3.83 (s, 2H), 3.17–3.13 (m, 4H), 2.68 (s, 4H), 1.48 (d, J = 6.2 Hz, 6H); MS (ESI) *m/z* 564 $[C_{29}H_{28}F_3N_7O_2 + H]^+$.

Example 59: N-(4-((6-ethoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 6-ethoxy-3-ethynylimidazo[1,2-*b*]pyridazine;

[000393] A solution of 6-chloro-3-ethynylimidazo[1,2-*b*]pyridazine (78.0 mg, 0.44 mmol) in EtOH (5.0 mL) was added sodium hydride (12.65 mg, 0.53 mmol). The reaction mixture was subjected to microwave condition at 100°C for 30 min and purified by column chromatography (silica gel, eluents hexanes/EtOAc 9:1) to afford 6-ethoxy-3-ethynylimidazo[1,2-*b*]pyridazine (23.0 mg, 0.123 mmol) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.78 (d, J = 9.6 Hz, 1H), 6.73 (d, J = 9.6 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.69 (s, 1H), 1.46 (t, J = 7.1 Hz, 3H); MS (ESI) *m/z* 188 $[C_{10}H_9N_3O + H]^+$.

Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-ethoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

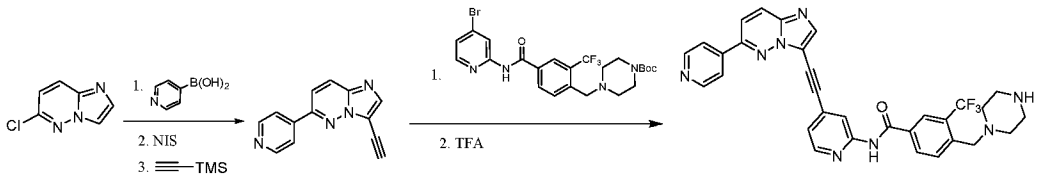
[000394] The title compound was synthesized from 6-ethoxy-3-ethynylimidazo[1,2-*b*]pyridazine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate following a method similar to general procedure A. The residue mixture filtered washed was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford to *tert*-butyl 4-(4-(4-((6-ethoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as off-white solid. MS (ESI) *m/z* 650 $[C_{33}H_{34}F_3N_7O_4 + H]^+$.

Step 3: Preparation of *N*-(4-((6-ethoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000395] The title compound was synthesized from *tert*-butyl 4-(4-(4-((6-ethoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar method as described in general

procedure D. The reaction solution was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((6-ethoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (3.2 mg, AUC HPLC 97%) as off-white solid.^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.45 (s, 1H), 8.41 (d, *J* = 4.9 Hz, 1H), 8.31 (d, *J* = 10.5 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 3.2 Hz, 1H), 7.92 (s, 1H), 7.29 (d, *J* = 2.1 Hz, 1H), 6.99 (d, *J* = 9.6 Hz, 1H), 4.60–4.55 (m, 2H), 3.81 (s, 2H), 3.13–3.09 (m, 4H), 2.64 (s, 4H), 1.53 (t, *J* = 7.04 Hz, 3H); MS (ESI) *m/z* 550 $[C_{28}H_{26}F_3N_7O_2+H]^+$.

Example 60: Synthesis of r4-(piperazin-1-ylmethyl)-N-(4-((6-(pyridin-4-yl) imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000396] Step 1: Preparation of 6-(pyridin-4-yl) imidazo [1,2-*b*]pyridazine; A mixture of 3 g of 6-chloroimidazo[1,2-*b*] pyridazine in 1,4- dioxane/water (30 mL) was treated with pyridin-4-ylboronic acid (2.65 g, 21.5 mmol) and potassium phosphate (8.3 g, 39.2 mmol). The reaction mixture was degassed with argon for 30 min. $Pd(PPh_3)_4$ (1.12 g, 0.1 mmol) was added and degassed with argon for another 30 min. The mixture was heated at 100 °C for 4 h. The solvent was removed and water was added to the reaction mixture; the solid was filtered to afford 6-(pyridin-4-yl) imidazo[1,2-*b*]pyridazine (1.8 g, 48%) as a pale yellow solid. MS (ESI) *m/z* 197 $[C_{11}H_8N_4+H]$.

[000397] Step 2: Preparation of 3-iodo-6-(pyridin-4-yl) imidazo [1,2-*b*]pyridazine; A solution of 6-(pyridin-4-yl)imidazo[1,2-*b*]pyridazine (1.8 g) in DMF (18 mL) was treated with *N*-iodosuccinamide (4.2 g, 18.3 mmol) and heated to 90 °C for 3 h. The reaction mixture was cooled to room temperature then poured into ice cold water, extracted with ethyl acetate and washed the organic layer with water. The solvent was evaporated to dryness under vacuum to afford 3-iodo-6-(pyridin-4-yl) imidazo [1, 2-*b*] pyridazine (2.5 g, 86%) as a brown solid. MS (ESI) *m/z* 322 $[C_{11}H_7IN_4+H]$.

[000398] Step 3: Preparation of 6-(pyridin-4-yl)-3-((trimethylsilyl) ethynyl) imidazo [1, 2-*b*] pyridazine; The title compound was synthesized from 3-iodo-6-(pyridin-4-yl)imidazo[1,2-*b*]pyridazine and trimethylsilyl acetylene following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel eluent petroleum

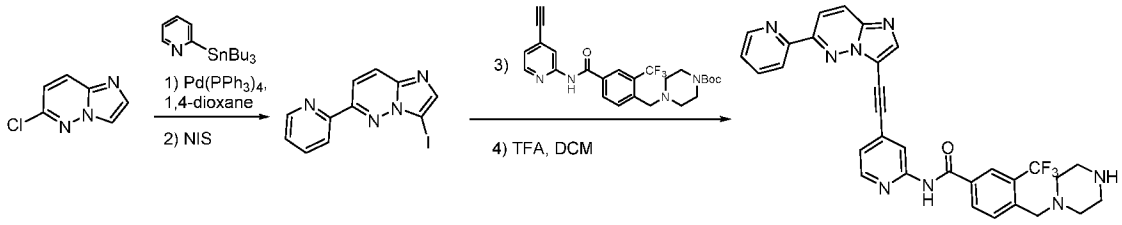
ether/EtOAc1:1) to afford 6-(pyridin-4-yl)-3-((trimethylsilyl) ethynyl)imidazo[1,2-*b*]pyridazine as a yellow solid (500 mg, 86%); MS (ESI) *m/z* 293 [$C_{16}H_{16}N_4Si$+H].

[000399] Step 4: Preparation of 3-ethynyl-6-(pyridin-4-yl) imidazo [1, 2-*b*] pyridazine; A mixture of 6-(pyridin-4-yl)-3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazine (0.5 g, 6.1 mmol) and LiOH (0.14 mg, 3.42 mmol) in THF (10 mL) and H_2O (2 mL) was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue was diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (20 mL). The organic layer was washed in turn water and brine (10 mL) then concentrated to dryness under reduced pressure to afford 3-ethynyl-6-(pyridin-4-yl)imidazo[1,2-*b*]pyridazine (300 mg, 86%, LC-MS 92%) as a light brown solid; (ESI) *m/z* 221 [$C_{13}H_8N_4$+H].

[000400] Step 5: Preparation of *tert*-butyl 4-(4-(4-((6-(pyridin-4-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from *tert*-butyl4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynyl-6-(pyridin-4-yl)imidazo[1,2-*b*]pyridazine following a method similar to general procedure A. The crude product was purified by flash chromatography (silica gel, eluted: petroleum ether/EtOAc 1:1) to afford *tert*-butyl 4-(4-(4-((6-(pyridin-4-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as a pale yellow solid (340 mg, 77%); MS (ESI) *m/z* 683 [$C_{36}H_{33}F_3N_8O_3$+H].

[000401] Step 6: 4-(piperazin-1-ylmethyl)-*N*-(4-((6-(pyridin-4-yl) imidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide; The title compound was synthesized from *tert*-butyl 4-(4-(4-((6-(pyridin-4-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar method as described in general procedure D. The crude product was purified by column chromatography to afford 4-(piperazin-1-ylmethyl)-N-(4-((6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (43%, AUC HPLC 96.4%) as a pale yellow solid; m.p. 234–237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.87–8.86 (d, *J* = 1.4 Hz, 2H), 8.67–8.64 (d, *J* = 12.3Hz, 2H), 8.38–8.37 (d, *J* = 4.9 Hz, 1H), 8.21–8.00 (m, 7H), 7.67–7.65 (d, *J* = 9.7 Hz,1H), 7.31–7.29 (d, *J* = 1.4 Hz, 1H), 3.72 (s, 2H), 2.95–2.93 (t, *J* = 4.8 Hz, 4H), 2.48 (m, 4H); MS (ESI) *m/z* 583 $[C_{31}H_{25}F_3N_8O$+H$]^+$.

Example 61: Synthesis of tert-butyl 4-(4-(4-((6-(pyridin-2-yl) imidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate



Step 1: Preparation of 6-(pyridin-2-yl) imidazo[1,2-*b*]pyridazine

[000402] To a solution of 6-chloroimidazo [1,2-*b*]pyridazine (1 g, 6.5 mmol) in 1,4-dioxane (10 mL) were added 2-(tributylstannyl)pyridine (2.5 g, 6.5 mmol) and $Pd(PPh_3)_4$ (0.3 g, 0.33 mmol). The reaction mixture was heated at 100 °C for 4 h, then was concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent ethyl acetate/petroleum ether (3:7)) to afford 6-(pyridin-2-yl) imidazo[1,2-*b*]pyridazine (0.8 g, 62%) as yellow solid. MS (ESI) *m/z* 197 $[C_{11}H_8N_4+ H]^+$.

Step 2: Preparation of 3-iodo-6-(pyridin-2-yl) imidazo[1,2-*b*]pyridazine

[000403] A mixture of 6-(pyridin2-yl) imidazo[1,2-*b*] pyridazine (0.8 g, 4.0 mmol) and *N*-iodo succinamide (1.3 g, 18.3 mmol) in DMF (8 mL) was heated at 90 °C for 4 h. The reaction mixture was cooled to room temperature and poured into ice cold water (20 mL). The aqueous phase was extracted with ethyl acetate (15 mL) and the organic phase was washed with water (5 mL) and concentrated under reduced pressure to afford 3-iodo-6-(pyridin-2-yl)imidazo[1,2-*b*]pyridazine (1 g, 77%) as an light brown solid; MS (ESI) *m/z* 322 $[C_{11}H_7IN_4+ H]^+$.

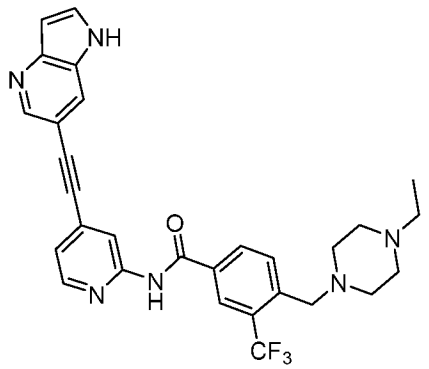
Step 3: Preparation of *tert*-butyl 4-(4-(4-((6-(pyridin-2-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000404] The title compound was synthesized from *tert*-butyl4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-iodo-6-(pyridin-2-yl)imidazo[1,2-*b*]pyridazine in a similar manner as described in general procedure A. The crude product was purified by column chromatography (silica gel eluent CH_2Cl_2/MeOH 96:4) to afford *tert*-butyl 4-(4-(4-((6-(pyridin-2-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (300 mg, 71%) as a yellow solid; MS (ESI) *m/z* 683 $[C_{36}H_{33}F_3N_8O_3+ H]^+$.

[000405] Step 4: Preparation of 4-(piperazin-1-ylmethyl)-*N*-(4-((6-(pyridin-2-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 4-(4-(4-((6-(pyridin-2-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-

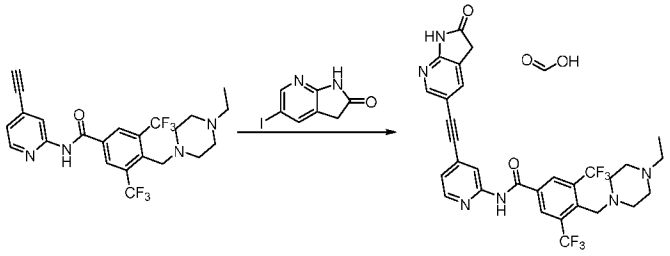
carboxylate in a similar fashion as described in general procedure D. The crude reaction was purified by flash column chromatography to afford 4-(piperazin-1-ylmethyl)-*N*-(4-((6-(pyridin-2-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (60 mg, 46%, AUC HPLC 96.2) as a pale yellow solid; m.p. 219–224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.75–8.74 (d, *J* = 4.4 Hz, 1H), 8.68–8.60 (m, 3H), 8.39–8.34 (dd, *J* = 9.3Hz, *J* = 7.5 Hz, 2H), 8.23 (s, 1H), 8.12–7.96 (m, 5H), 7.45–7.42 (dd, *J* = 4.9 Hz, *J* = 5.3 Hz, 1H), 7.31–7.30 (dd, *J* = 1.4 Hz, 0.9 Hz, 1H), 3.72 (s, 2H), 2.94 (m, 4H), 2.48(m, 4H); MS (ESI) *m/z* 584 $[C_{31}H_{25}F_3N_8O+H]^+$.

Example 62: N-(4-((1H-pyrrolo[3,2-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



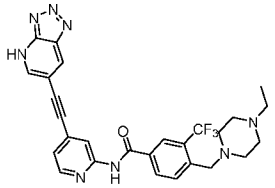
[000406] The title compound was prepared in the amount of 250 mg (11.3%, over 2 steps, AUC HPLC 98.40%) as an off-white solid in a similar fashion as described for Example 297 synthesis starting from Intermediate 17**.** mp: 208–211 °C**.** ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.63 (s, 1H), 11.26 (s, 1H), 8.56 (d, *J* = 1.2 Hz, 1H), 8.47 (d, *J* = 4.8 Hz, 1H), 8.33–8.26 (m, 3H), 8.11 (d, *J* =1.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 3.2 Hz, 1H), 7.37 (dd, *J* = 4.0, 1.2 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 3.67 (s, 2H), 2.53–2.21 (m, 10H), 1.00 (t, *J* = 6.8 Hz, 3H). MS (ESI) *m/z* 533.22 $[C_{29}H_{27}F_3N_6+H]^+$.

Example 63: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt



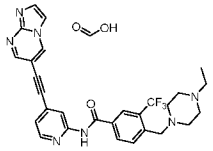
[000407] The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and 5-iodo-1*H*-pyrrolo[2,3-*b*]pyridin-2(3H)-one following a method similar to general procedure A. The crude product was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide fomate salt (3.0 mg, AUC HPLC >99 %) as white solid; m.p. 111-113 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.62 (s, 1H), 8.52 (s, 1H), 8.38 (t, *J* = 0.9 Hz, 1H), 8.32 (dd, *J* = 4.8 Hz, *J* = 0.8 Hz, 1H), 8.20 (s, 1H), 8.10–8.60 (m, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 0.9 Hz, 1H), 7.18 (dd, *J* = 5.2 Hz, *J* = 1.6 Hz, 1H), 3.74 (s, 2H), 3.63 (s, 2H), 2.57 (s, 8H), 2.47 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 549 $[C_{29}H_{27}F_3N_6O_2 + H]^+$.

Example 64: N-(4-((4H-[1,2,3]triazolo[4,5-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



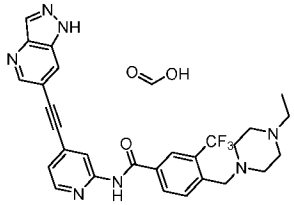
[000408] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 6-bromo-4*H*-[1,2,3]triazolo[4,5-*b*]pyridine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((4*H*-[1,2,3]triazolo[4,5-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (7 mg, 11%, AUC HPLC 97%) as brown solid; m.p. 132.2-134.2 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.81(s, 1H), 8.56 (s, 1H), 8.50-8.28 (m, 3H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 1H), 3.84 (s, 2H), 3.40-3.20 (m, 4H), 3.17 (q, *J* = 7.2 Hz, 2H), 2.78 (bs, 4H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 167.89, 166.80, 153.56, 153.43, 152.49, 149.69, 142.16, 135.08, 134.00, 133.00, 132.53, 132.28, 130.19, 129.23, 126.86, 125.55, 123.16, 117.82, 116.88, 91.46, 90.32, 58.38, 53.09, 52.91, 51.34, 9.78; MS (ESI) *m/z* 535 $[C_{27}H_{25}F_3N_8O + H]^+$.

Example 65: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(imidazo[1,2-a]pyrimidin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt



[000409] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 6-bromo-imidazo[1,2-*a*]pyrimidine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(imidazo[1,2-*a*]pyrimidin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide fomate salt (25 mg, 39%, AUC HPLC >99%) as yellow solid; m.p. 155.1–155.6 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 9.23 (d, J = 2.3 Hz, 1H), 8.71 (d, J = 2.3 Hz, 1H), 8.47–8.36 (m, 3H), 8.32 (s, 1H), 8.24 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 1.4 Hz, 1H), 7.79 (d, J = 1.4 Hz, 1H), 7.32 (dd, J = 5.1; 1.4 Hz, 1H), 3.86 (s, 2H), 3.21 (bs, 4H), 3.10 (q, J = 7.3 Hz, 2H), 2.76(bs, 4H), 1.32 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 168.47, 166.92, 153.65, 153.47, 149.80, 148.40, 142.35, 139.50, 135.92, 135.10, 133.65, 132.53, 132.35, 130.25, 126.88, 125.58, 123.04, 117.72, 113.96, 107.28, 91.53, 87.59, 58.49, 53.13, 53.03, 51.63, 9.99; MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O + H]^+$.

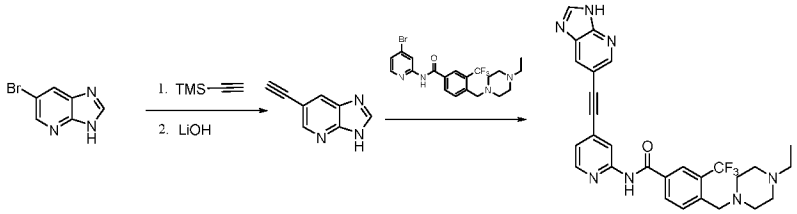
Example 66: N-(4-((1H-pyrazolo[4,3-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt



[000410] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 6-bromo-1*H*-pyrazolo[4,3-*b*]pyridine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((1*H*-pyrazolo[4,3-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt (23mg, 36%, AUC HPLC >99%) as yellow solid. m.p: 63.0–65.6 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.70 (d, J = 1.6 Hz, 1H), 8.50–8.38 (m, 3H), 8.33 (bs, 1H), 8.31–8.26 (m, 2H), 8.24 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 4.5 Hz,

1H), 3.86 (s, 2H), 3.15(bs, 4H), 3.04 (q, *J* = 7.3 Hz, 2H), 2.75(bs, 4H), 1.30 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 168.88, 166.94, 153.61, 149.75, 148.90, 142.43, 141.17, 135.08, 134.00, 132.52, 132.34, 130.24, 126.87, 125.59, 123.18, 117.87, 117.61, 91.74, 90.60, 58.55, 53.16, 53.11, 51.83, 10.16; MS (ESI) *m/z* 534 [$C_{28}H_{26}F_3N_7O$ + H]$^+$.

Example 67: N-(4-((3H-imidazo [4,5-b] pyridin-6-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide



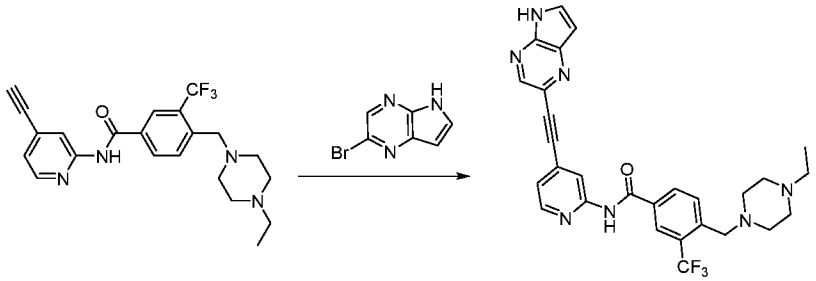
[000411] Step 1: Preparation of 6-((trimethylsilyl) ethynyl)-3*H*-imidazo [4,5-*b*] pyridine; The title compound was synthesized from 6-bromo-3*H*-imidazo [4,5-*b*] pyridine and trimethyl silyl acetylene following a method similar to general procedure A. Crude product was purified by column chromatography (silica gel, eluent dichloromethane/MeOH 100/1) to afford 6-((trimethylsilyl) ethynyl)-3*H*-imidazo [4,5-*b*] pyridine (300 mg, 55 %) as a brown color solid. MS (ESI) *m/z* 216.3 [$C_{11}H_{13}N_3Si$+H]$^+$.

[000412] Step 2: Preparation of 6-ethynyl-3*H*-imidazo [4,5-*b*] pyridine; A solution of 6-((trimethylsilyl) ethynyl)-3*H*-imidazo [4,5-*b*] pyridine (250 mg, 5.81 mmol) and LiOH (366 mg, 8.72 mmol) in THF (10 mL) and water (5 mL) was stirred at room temperature for 3 h and was concentrated under reduce pressure. The residue was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 6-ethynyl-3*H*-imidazo [4,5-*b*] pyridine (100 mg, 55 %) as brown color solid. MS (ESI) *m/z* 144 [$C_8H_5N_3$ +H]$^+$.

[000413] Step 3: Preparation of *N*-(4-((3*H*-imidazo [4,5-*b*] pyridin-6-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide; The title compound was synthesized from6-ethynyl-3*H*-imidazo [4,5-*b*] pyridine and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide following a method similar to general procedure A. Crude product was purified by preparative HPLC to afford *N*-(4-((3*H*-imidazo[4,5-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (50 mg, 22%, AUC HPLC 98.3% as off white solid. ^{1}H NMR(400 MHz, CD_3OD) δ (ppm): 8.61 (s, 1H), 8.51 (s, 1H), 8.41 (d, *J* = 1.2 Hz, 2H), 8.32

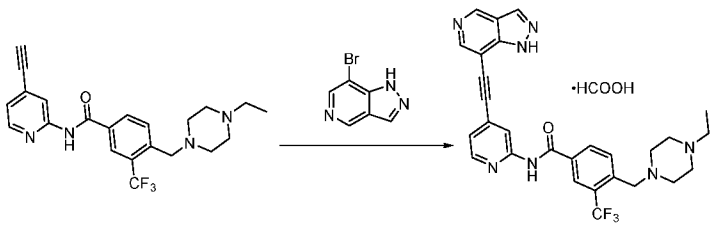
(s, 1H), 8.29 (s, 1H), 8.22 (d, *J* = 0.8 Hz, 1H), 8.10 (d, *J* = 1.2 Hz, 1H), 7.32 (dd, *J* = 1.2,5.2 Hz, 1H), 3.75 (s, 2H), 2.41-2.85 (m, 10H), 1.82 (t, *J* = 0.8 Hz, 3H); MS (ESI) *m/z* 532 $[C_{28}H_{26}F_3N_7O+ H]^+$

Example 68: N-(4-((5H-pyrrolo[3,2-b]pyrazin-2-yl)ethynyl)pyridin-2-yl)-4-((4-tethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



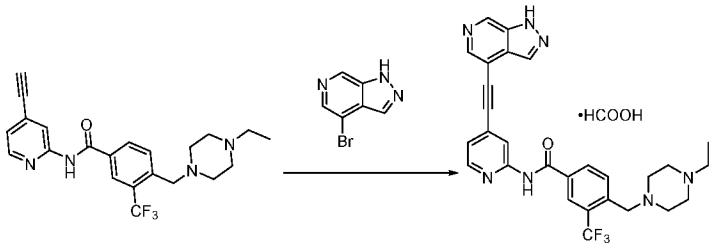
[000414] The title compound was synthesized from from4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 2-ethynyl-5*H*-pyrrolo[3,2-*b*]pyrazine following a method similar to general procedure A. The reaction mixture was purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((5*H*-pyrrolo[3,2-*b*]pyrazin-2-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (56 mg, 50 %, AUC HPLC 98%) as off white solid; m.p. 226 – 228 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.54 (s, 1H), 8.44 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 3.64 Hz, 1H), 7.33 (q, *J* = 2.1 Hz, 1H), 6.66 (d, *J* = 3.6 Hz, 1H), 3.84 (s, 2H), 3.20–3.00 (m, 6H), 2.76 (s, 4H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 169.43, 166.80, 153.56, 149.69, 142.30, 142.03, 141.82, 140.41, 135.00, 134.36, 133.76, 132.48, 132.34, 132.26, 130.30, 129.99, 126.84, 126.80, 124.17, 123.14, 117.83, 101.80, 92.25, 88.30, 58.47, 53.09, 52.99, 51.62, 10.02; MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O + H]^+$.

Example 69: N-(4-((1H-pyrazolo[4,3-c]pyridin-7-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt



[000415] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 7-bromo-1*H*-pyrazolo[4,3-*c*]pyridine following a method similar to general procedure A. The crude product was purified by flash column chromatography (eluent CH_2Cl_2/CH_3OH 90:10) followed by preparative HPLC to afford *N*-(4-((1H-pyrazolo[4,3-c]pyridin-7-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formic acid salt (12.0 mg, 17%, AUC HPLC >99%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 9.19 (s, 1H), 8.64 (s, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.49 (s, 1H), 8.47 (s, 1H), 8.37 (d, *J* = 1.9 Hz, 1H), 8.31 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.16 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 4.8 Hz, 1H), 3.69 (s, 2H), 2.45 (m, 4H), 2.36 (q, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.8, 163.3, 152.3, 148.5, 146.6, 145.8, 142.3, 141.7, 135.0, 132.8, 132.0, 131.6, 130.6, 127.4, 127.2, 127.0, 126.8, 125.6, 123.2, 121.7, 120.1, 116.2, 100.8, 93.6, 86.6, 57.5, 52.7, 52.2, 51.5, 11.9; MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O+ H]^+$

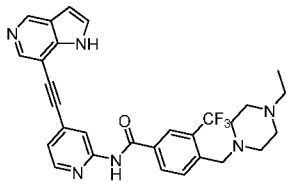
Example 70: N-(4-((1H-pyrazolo[3,4-c]pyridin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt



[000416] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 4-bromo-1*H*-pyrazolo[3,4-*c*]pyridine following a method similar to general procedure A. The residue was purified by flash column chromatography (eluent CH_2Cl_2/CH_3OH 90:10) followed by preparative HPLC to afford *N*-(4-((1*H*-pyrazolo[3,4-*c*]pyridin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate (17.8 mg, 26%, AUC HPLC 99.2%) as a light yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 9.15 (s, 1H), 8.55 – 8.49 (m, 2H), 8.47 (s, 1H), 8.42 (d, *J* = 1.3 Hz, 1H), 8.36 (d, *J* = 1.9 Hz, 1H), 8.30 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.16 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.49 (dd, *J* = 5.1, 1.4 Hz, 1H), 3.69 (s, 2H), 2.48 – 2.42 (m, 4H), 2.38 (q, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 163.2, 152.4, 148.7, 141.7, 141.6, 136.3, 136.1, 132.8, 132.0, 131.4,

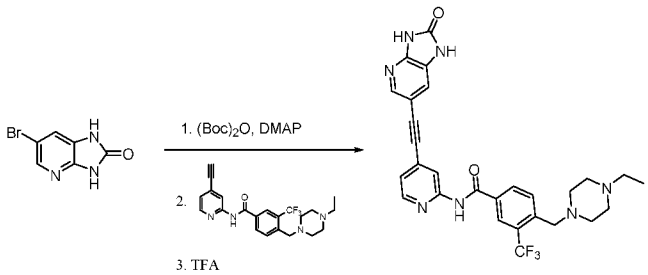
130.6, 127.5, 127.3, 127.1, 126.8, 126.4, 125.7, 125.0, 123.2, 121.8, 116.2, 109.0, 92.3, 88.5, 57.4, 52.6, 52.2, 51.5, 11.7; MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O+ H]^+$

Example 71: N-(4-((1H-pyrrolo[3,2-c]pyridin-7-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000417] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 7-bromo-1*H*-pyrrolo[3,2-*c*]pyridine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((1*H*-pyrrolo[3,2-*c*]pyridin-7-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (16 mg, 25%, AUC HPLC 99%) as yellow solid; m.p. 114.1-114.7 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.92 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.33 (s, 1H), 8.32–8.19 (m, 4H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 3.3 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.86 (d, *J* = 3.3 Hz, 1H), 3.87 (s, 2H), 3.40-3.21 (m, 4H), 3.20 (q, *J* = 7.3 Hz, 2H), 2.80 (bs, 4H), 1.35 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 165.42, 165.31, 152.09, 148.22, 141.13, 140.72, 140.40, 140.35, 133.67, 132.60, 131.08, 130.91, 128.80, 128.57, 125.44, 124.11, 121.82, 116.48, 102.52, 92.88, 85.85, 56.92, 51.57, 51.32, 49.70, 8.17; MS (ESI) *m/z* 533 $[C_{29}H_{27}F_3N_6O + H]^+$.

Example 72: N-(4-((6-aminoimidazo [1,2-b] pyridazin-3-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide



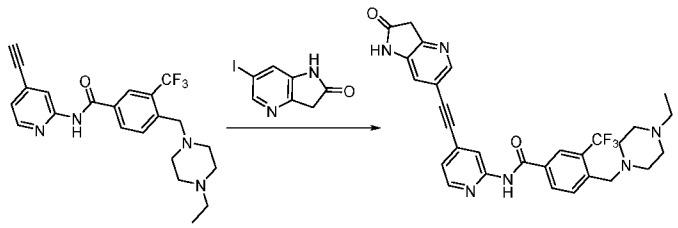
[000418] Step 1: Preparation of di-*tert*-butyl 6-bromo-2-oxo-1*H*-imidazo[4,5-*b*] pyridine-1, 3(2*H*)-dicarboxylate; To a solution of 6-bromo-1*H*-imidazo [4, 5-b] pyridin-2(3*H*)-one (500

mg, 2.34 mmol) and DMAP (568 mg, 4.69 mmol) in THF (20 mL), was added $(Boc)_2O$ (2 g, 9.388 mmol) at room temperature. After completion, reaction mixture was concentrated under reduce pressure and purified by column chromatography using (silica gel, eluent: petroleum ether/ethyl acetate 80:20) to afford di-*tert*-butyl 6-bromo-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-1,3(2*H*)-dicarboxylate (800 mg, 88%) as white solid. MS (ESI) *m/z* 413 $[C_{16}H_{20}BrN_3O_5+H]^+$.

[000419] Step 2: Preparation of di-*tert*-butyl 6-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-1,3(2*H*)-dicarboxylate; The title compound was synthesized from di-*tert*-butyl 6-bromo-2-oxo-1*H*-imidazo [4,5-*b*] pyridine-1,3(2*H*)-dicarboxylate and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. Crude product was directly used in next step to afford di-*tert*-butyl 6-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-2-oxo-1*H*-imidazo[4,5-b]pyridine-1,3(2H)-dicarboxylate (300 mg) as brown color solid. MS (ESI) *m/z* 750 $[C_{38}H_{42}F_3N_7O_6+H]^+$

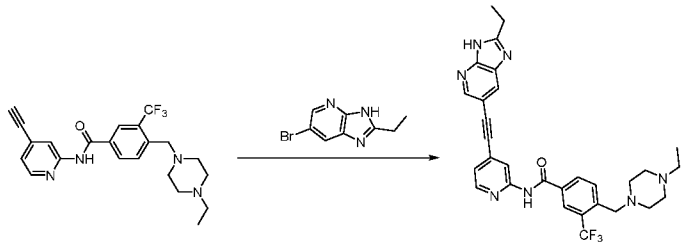
[000420] Step 3: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide; The title compound was prepared following similar to general procedure D and starting from di-*tert*-butyl-6-((2-(4-((4-ethyl piperazin-1-yl) methyl)-3-(trifluoromethyl) benzamido)pyridine-4-yl)ethynyl)-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-1,3(2*H*)-dicarboxylate. The crude product was purified by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (50 mg, 25%, AUC HPLC 95.2%) as off-white color solid.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.66 (s, 1H), 11.24 (s, 1H), 11.08 (s, 1H), 8.45 (d, *J* = 4.8, 1H), 8.35 (s, 1H), 8.29 (d, *J* = 11.6 Hz, 2H), 8.19 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H),7.44 (s, 1H), 7.32 (d, *J* = 1.2 Hz, 1H), 3.69 (s, 2H), 2.51-2.33 (m, 10H), 1.10 (t, *J* = 0.8 Hz, 3H). MS (ESI) *m/z* 550 $[C_{28}H_{26}F_3N_7O_2 + H]^+$

Example 73: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000421] The title compound was synthesized from from4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 6-iodo-1,3-dihydro-2*H*-pyrrolo[3,2-*b*]pyridin-2-one following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, DCM/methanol 10:1) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((2-oxo-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (10 mg, 15%, AUC HPLC 99.9%) as brown solid; m.p. 196.0–197.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (s, 1H), 8.54 (s, 1H), 8.42 (d, *J* = 1.6 Hz, 1H), 8.34 (dd, *J* = 5.1, 0.6 Hz, 1H), 8.19 (s, 1H), 8.07 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H), 7.20 (dd, *J* = 5.1, 1.3 Hz, 1H), 3.74 (s, 2H), 3.71 (s, 2H), 2.56 (bs, 8H), 2.45 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.29, 151.48, 148.30, 148.16, 146.32, 143.07, 136.98, 133.00, 132.59, 131.07, 130.20, 129.14, 127.28, 124.93, 122.08, 118.32, 117.54, 116.15, 90.47, 89.89, 57.99, 53.27, 52.86, 52.32, 37.55, 11.99; MS (ESI) *m/z* 549 $[C_{29}H_{27}F_3N_6O_2 + H]^+$.

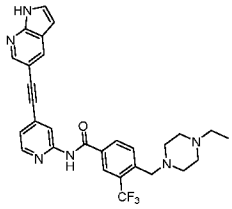
Example 74: N-(4-((2-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000422] The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and 5-bromo-2-ethyl-1H-pyrrolo[2,3-*b*]pyridine following a method similar to general procedure A. The crude product was purified by preparative HPLC (C18, eluent ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (16 mg, 23%, AUC HPLC 97%) as yellow solid; mp 98–100°C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.45–8.30 (m, 2H), 8.31 (s, 2H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.06 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 5.1 Hz, 1H), 6.26 (s, 1H),

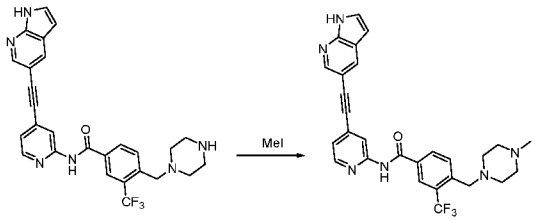
3.78 (s, 2H), 2.83 (q, *J* = 7.3 Hz, 2H), 2.80–2.40 (m, 10H), 1.36 (t, *J* = 7.5 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 167.02, 153.50, 149.50, 146.56, 145.37, 135.16, 134.82, 132.29, 131.96, 126.76, 123.01, 122.84, 117.67, 111.53, 98.00, 94.09, 87.95, 59.09, 53.75, 53.61, 53.32, 22.45, 13.50, 11.58; MS (ESI) *m/z* 561 $[C_{31}H_{30}F_3N_6O+ H]^+$

Example 75: N-(4-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was synthesized from Intermediate 17 and 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, DCM/methanol 10:1) to afford *N*-(4-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (1065 mg, 83%, AUC HPLC 97.36%) as yellow solid. mp: 232.7-233.9 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 12.00 (s, 1H), 11.16 (s, 1H), 8.48–8.45 (m, 2H), 8.35-8.28 (m, 4H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 5.6 Hz, 1H), 7.33 (dd, *J* = 4.0, 1.2 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 3.68 (s, 2H), 2.49-2.39 (m, 10H) 0.98 (t, *J* = 7.6 Hz, 3H) MS (ESI) *m/z* 533.05 $[C_{29}H_{27}F_3N_6O +H]^+$..

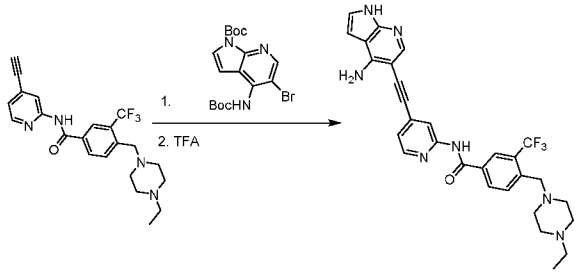
Example 76: N-(4-(2-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide



[000423] To a solution of *N*-(4-(2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)-4-((piperazin-1-yl)methyl)benzamide (17 mg, 0.0336 mmol) and DMF (1.0 mL) was added K_2CO_3 (14 mg, 0.101 mmol) followed by MeI (2.0 µL, 0.0336 mmol). The resulting mixture was stirred at room temperature for 12 h. DMF was then removed *in vacuo*

and the resulting residue was purified by preparative TLC (DCM/MeOH 85:15) to afford *N*-(4-(2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (7.2 mg, 41%, AUC HPLC 95.7%) as a brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.00 (s, 1H), 11.25 (s, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.35 (d, *J* = 1.8 Hz, 1H), 8.33 (d, *J* = 1.3 Hz, 1H), 8.31–8.28 (m, 2H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.60–7.57 (m, 1H), 7.34 (dd, *J* = 5.1, 1.5 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.69 (s, 2H), 2.48–2.43 (m, 4H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 152.3, 148.5, 147.8, 145.5, 141.5, 132.9, 132.3, 132.0, 131.6, 130.6, 127.9, 125.7, 125.0, 123.2, 121.4, 119.2, 115.9, 109.3, 100.5, 93.0, 87.2, 57.4, 54.4, 52.3, 45.3; MS (ESI) *m/z* 520 $[C_{28}H_{25}F_3N_6O + H]^+$

Example 77: Synthesis of N-(4-((4-amino-1H-pyrrolo [2, 3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide



Step 1: Preparation of *tert*-butyl 4-(*tert*-butoxycarbonylamino)-5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate

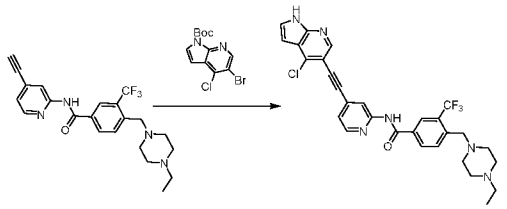
[000424] The title compound was prepared following similar to general procedure A and starting from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and the *tert*-butyl 5-bromo-4-((tert-butoxycarbonyl)amino)-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate. The crude product was purified by flash column chromatography (silica gel, eluent: dichloromethane/methanol 80:20) to afford *tert*-butyl 4-((*tert*-butoxycarbonyl)amino)-5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate (150 mg) as a brown solid.

Step 2: Preparation of *N*-(4-((4-amino-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000425] The title compound was prepared following similar to general procedure D and starting from *tert*-butyl 4-((*tert*-butoxycarbonyl)amino)-5-((2-(4-((4-ethylpiperazin-1-

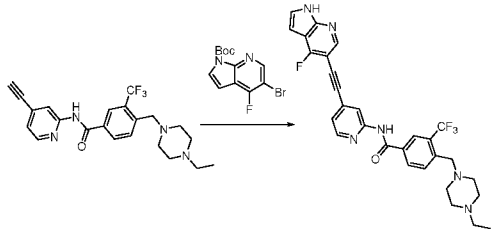
yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate. The crude product was purified by preparative HPLC to afford *N*-(4-((4-amino-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (1.2 mg, AUC HPLC 89.5%) as a pale brown solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.33–8.30 (m, 3H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.05–8.00 (m, 2H), 7.32 (d, *J* = 4.0 Hz, 1H), 7.11 (d, *J* = 3.6 Hz, 1H), 6.62 (d, *J* =3.2 Hz,1H), 3.77 (s, 2H), 2.68–2.48 (m, 10H), 1.13 (d, *J* = 7.2 Hz, 3H). MS (ESI) *m/z*: 548.3 $[C_{29}H_{28}F_3N_7O + H]^+$.

Example 78: N-(4-((4-chloro-1H-pyrrolo [2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



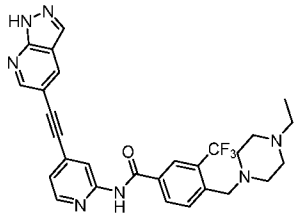
[000426] Preparation of *N*-(4-((4-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 5-bromo-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate and 4-((4-ethylpiperazin-1-yl) methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl) benzamide following a method similar to general procedure A. The crude product was purified by preparative HPLC to afford *N*-(4-((4-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (2.6 mg, HPLC 96.2 %) as pale brown solid; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.44 (s, 1H), 8.41–8.39 (m, 2H), 8.30 (s, 1H), 8.23 (d, *J* = 10.8 Hz, 1H), 8.03 (d, *J* = 10.8 Hz, 1H), 7.53 (d, *J* = 4.8 Hz, 1H), 7.32 (dd, *J* = 6.8, 2.0 Hz, 1H), 6.65 (d, *J* = 4.8 Hz, 1H), 3.78 (s, 2H), 2.59–2.48 (m, 10H),1.13 (t, *J* = 9.6 Hz, 3H); MS (ESI) *m/z* 567 $[C_{29}H_{26}ClF_3N+H]^+$.

Example 79: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



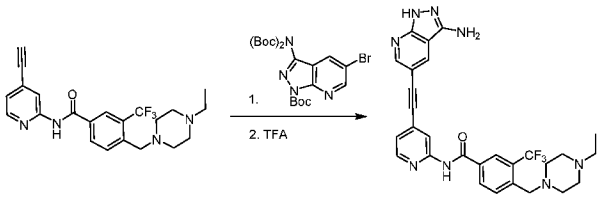
[000427] Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 5-bromo-4-fluoro-1*H*-pyrrolo [2,3-*b*]pyridine-1-carboxylate and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (41 mg, 36.4%, AUC HPLC 96.9%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.35 (s, 1H), 11.26 (s, 1H), 8.51–8.46 (m, 2H), 8.35–8.28 (m, 3H), 7.93 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H),7.35 (d, J = 5.2 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 3.68 (s, 2H), 2.44–2.29 (m, 10H), 0.98 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 551.0 $[C_{29}H_{26}F_4N_6O+ H]^+$.

Example 80: N-(4-((1H-pyrazolo [3, 4-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide



[000428] The title compound was synthesized from 5-ethynyl-1*H*-pyrazolo [3, 4-*b*] pyridine and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (50 mg, 16%, AUC HPLC 97.9%) as light yellow color solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 14.01 (s, 1H), 11.31 (s, 1H), 8.77 (d, J = 2 Hz, 1H), 8.61 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.36–8.24 (m, 4H), 7.92 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 4.8 Hz, 1H), 3.68 (s, 2H) 2.50 ,–2.31 (m, 10H), 0.99 (t, J = 6.8 Hz, 3H); MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O+H]^+$

Example 81: N-(4-((3-amino-1H-pyrazolo [3, 4-b] pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation *tert*-butyl 3-(*tert*-butoxycarbonylamino)-5-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate

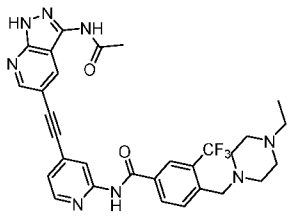
[000429] The title compound was prepared following similar to general procedure A and starting from

The boc-protected aza-indazole and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide. The reaction crude product was purified by column chromatography (silica gel, eluent :dichloromethane/methanol/NH_4OH 95:4:1) to afford a mixture of boc-protected products as a brown solid. MS (ESI) *m/z*: 749.53 (M+H) di-boc and 649.41 (M+H) mono-boc.

Step 2: Preparation *N*-(4-((3-amino-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide:

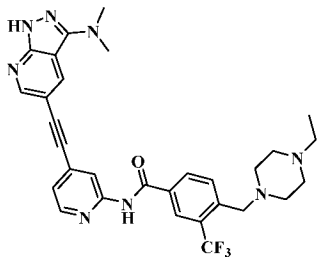
[000430] A solution of the above products (300 mg) in a mixture of TFA (5.0 mL) and dichloromethane (15 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ and extracted into EtOAc. The organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol 80:20) to afford *N*-(4-((3-amino-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (75 mg, 34.2%, AUC HPLC >99%) as yellow solid; m.p. 129.0–130.1 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.59 (s, 1H), 8.45–8.30 (m, 5H), 8.23 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 3.86 (s, 2H), 3.24 (bs, 4H), 3.13 (q, *J* = 7.2 Hz, 2H), 2.77 (bs, 4H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 166.86, 153.51, 153.33, 149.59, 142.25, 135.00, 134.74, 132.52, 132.35, 130.26 (q, *J* = 29.3 Hz), 126.88 (q, *J* = 5.6 Hz), 125.58 (q, *J* = 273.4 Hz), 123.02, 117.67, 110.71, 107.70, 92.86, 88.60, 58.45, 53.12, 52.98, 51.50, 9.90; MS (ESI) *m/z* 549 $[C_{28}H_{27}F_3N_8O + H]^+$.

Example 82: N-(4-((3-acetamido-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000431] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and *N*-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)acetamide following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((3-acetamido-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (4 mg, AUC HPLC 97%) as a yellow solid; m.p. 144.5-145.6 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.71 (s, 1H), 8.67 (d, J = 1.6 Hz, 1H), 8.45-8.25 (m, 5H), 8.24 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 5.2 Hz, 1H), 3.87 (s, 2H), 3.40–3.22 (m, 4H), 3.18 (q, J = 7.3 Hz, 2H), 2.79 (bs, 4H), 2.24 (s, 3H), 1.34 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 171.78, 167.10, 166.84, 153.52, 153.21, 152.19, 149.63, 142.15, 141.59, 138.13, 135.19, 134.57, 132.57, 132.35, 130.25, 126.88, 125.58, 123.09, 117.74, 112.49, 109.12, 92.47, 88.86, 58.39, 53.11, 52.92, 51.32, 22.95, 9.75; MS (ESI) *m/z* 591[$C_{30}H_{29}F_3N_8O_2$ + H]$^+$.

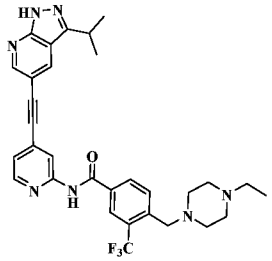
Example 83: N-(4-(2-(3-(dimethylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000432] The title compound was synthesized from 5-bromo-*N*,*N*-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(4-(2-(3-(dimethylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (5.4 mg, AUC HPLC 98.8%) as a yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.33 (d, J = 15.2 Hz, 1H), 8.75 (d, J = 2.3 Hz,

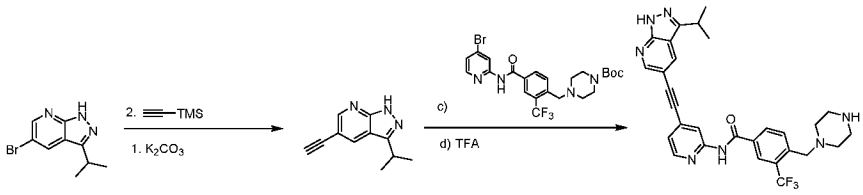
1H), 8.50 (d, *J* = 5.1 Hz, 1H), 8.43 – 8.31 (m, 2H), 8.28 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.23 (d, *J* = 2.3 Hz, 1H), 7.92 (dd, *J* = 8.2, 4.6 Hz, 1H), 7.36 (dd, *J* = 5.0, 1.4 Hz, 1H), 3.97 (s, 1H), 3.68 (s, 2H), 3.03 (s, 2H), 2.85 (s, 2H), 2.43 (m, 5H), 2.32 (q, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 164.5, 152.4, 152.2, 148.8, 145.9, 141.7, 139.8, 132.7, 132.5, 132.0, 130.9, 130.6, 127.4, 127.2, 127.0, 126.8, 125.6, 121.5, 118.1, 116.1, 91.3, 88.3, 57.5, 52.9, 52.3, 51.6, 37.6, 34.2, 12.0; MS (ESI) *m/z* 557 $[C_{30}H_{31}F_3N_8O+ H]^+$.

Example 84:4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((3-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000433] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridine following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (21.8 mg, 32%, AUC HPLC 97.9%) as a cream solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 13.53 (s, 1H), 11.27 (s, 1H), 8.71 (d, *J* = 2.0 Hz, 1H), 8.68 (d, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 5.0 Hz, 1H), 8.38–8.36 (m, 1H), 8.35 (d, *J* = 1.9 Hz, 1H), 8.29 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.35 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.68 (s, 2H), 2.43 (m, 5H), 2.32 (q, *J* = 7.2 Hz, 2H), 1.38 (d, *J* = 6.9 Hz, 6H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 152.4, 151.5, 151.1, 148.6, 141.7, 133.8, 133.7, 132.8, 132.0, 130.6, 127.4, 127.2, 127.0, 126.8, 125.6, 125.0, 123.2, 121.4, 115.9, 111.9, 109.8, 91.9, 87.8, 57.5, 52.9, 52.3, 51.6, 27.4, 21.9, 12.0; MS (ESI) *m/z* 577 $[C_{31}H_{32}F_3N_7O+ H]^+$.

Example 85: 3-(trifluoromethyl)-N-(4-(2-(3-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide



[000434] Step 1: Preparation of 3-isopropyl-5-((trimethylsilyl)ethynyl)-1*H*-pyrazolo[3,4-*b*]pyridine;_The title compound was synthesized from 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridine and trimethylsilylacetylene following a method similar to general procedure A. The mixture was then concentrated to dryness and the crude purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 30:70) to afford 3-isopropyl-5-((trimethylsilyl)ethynyl)-1*H*-pyrazolo[3,4-*b*]pyridine (111 mg, 86%); MS (ESI) *m/z* 258 $[C_{14}H_{19}N_3Si + H]^+$.

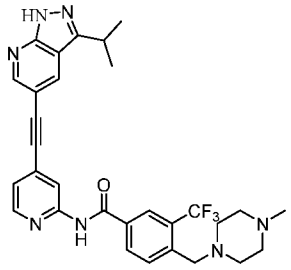
[000435] Step 2: Preparation of 5-ethynyl-3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridine; To a solution of 3-isopropyl-5-((trimethylsilyl)ethynyl)-1*H*-pyrazolo[3,4-*b*]pyridine (111 mg, 0.431 mmol) and 1:1 THF:MeOH (5 mL) was added K_2CO_3 (71 mg, 0.517 mmol) and stirred at room temperature for 1 h. The solvents were removed *in vacuo* and the crude purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 30:70) to afford 5-ethynyl-3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridine (43.4 mg, 54%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H), 8.31 (s, 1H), 3.42-3.40 (m, 1H), 3.18 (s, 1H), 1.47 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 152.34, 151.20, 150.81, 134.61, 113.46, 111.69, 80.88, 79.10, 28.43, 22.14

[000436] Step 3: Preparation of *tert*-butyl 4-(4-((4-((3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from 5-ethynyl-3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridine and *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate following a method similar to general procedure A. The solvents were removed *in vacuo* and purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 75:25) to afford *tert*-butyl 4-(4-((4-((3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (104 mg, 58%); MS (ESI) *m/z* 648 $[C_{34}H_{36}F_3N_7O_3 + H]^+$.

[000437] Step 4: Preparation of 3-(trifluoromethyl)-*N*-(4-(2-(3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide; The title compound was synthesized from *tert*-butyl 4-(4-(4-(2-(3-isopropyl-1*H*-pyrazolo[3,4-

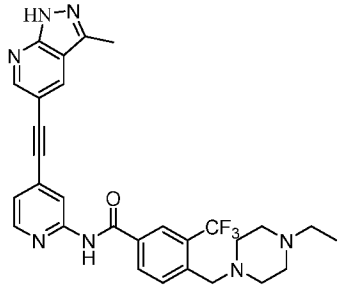
b]pyridin-5-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar method as described in general procedure D. The reaction crude product was purified by preparative HPLC to afford 3-(trifluoromethyl)-*N*-(4-(2-(3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide (28.5 mg, 41%, AUC HPLC: 96.6%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 8.72 (d, *J* = 1.9 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 8.48 (dd, *J* = 5.1, 0.9 Hz, 1H), 8.37 (q, *J* = 1.2 Hz, 2H), 8.30 (dd, *J* = 8.0, 1.9 Hz, 1H), 8.28 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 5.0, 1.5 Hz, 1H), 3.70 (s, 2H), 3.40-3.38 (m, *J* = 6.9 Hz, 1H), 2.91 (t, *J* = 4.9 Hz, 4H), 2.49–2.44 (m, 4H), 1.39 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, DMSO) δ (ppm): 164.8, 152.3, 151.5, 151.1, 150.8, 148.60, 141.2, 133.7, 132.9, 132.0, 130.6, 127.1, 125.7, 125.0, 123.2, 121.4, 115.9, 111.8, 109.8, 91.9, 87.8, 57.7, 51.9, 44.2, 27.4, 21.9; MS (ESI) *m/z* 549 $[C_{29}H_{28}F_3N_7O + H]^+$.

Example 86: N-(4-((3-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000438] To a solution of *N*-(4-((3-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (30 mg, 0.0548 mmol) in 1:1 THF:DMF (2 mL), was added K_2CO_3 (7.6 mg, 0.055 mmol) and stirred for 15 min. iodomethane (1.7 µL, 0.0274 mmol) dissolved in THF (40µL) was then added and the mixture stirred for 1.2 h at room temperature and was concentrated *in vacuo*. The residue was purified by preparative TLC to give *N*-(4-((3-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (6.2 mg, 20%, AUC HPLC: 97.8%) as a light yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 13.53 (s, 1H), 11.28 (s, 1H), 8.72 (d, *J* = 1.9 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 8.49–8.46 (m, 1H), 8.38–8.34 (m, 2H), 8.30 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.69 (s, 2H), 2.43 (s, 4H), 2.19 (s, 3H), 1.39 (d, *J* = 6.9 Hz, 6H); MS (ESI) *m/z* 563 $[C_{30}H_{30}F_3N_7O + H]^+$.

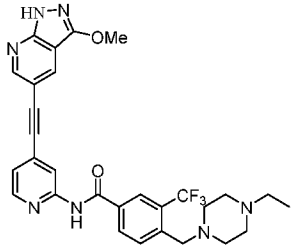
Example 87: 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-N-(4-(2-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)benzamide



[000439] Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-(2-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)benzamide

The title compound was synthesized from 5-bromo-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a protocol similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-(2-(3-methyl-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)benzamide (17.1 mg, 26%, AUC HPLC: >99%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 13.55 (s, 1H), 11.27 (s, 1H), 8.72 (d, J = 1.9 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.38–8.33 (m, 2H), 8.29 (dd, J = 8.2, 1.9 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.34 (dd, J = 5.1, 1.5 Hz, 1H), 3.68 (s, 2H), 2.53 (s, 3H), 2.46–2.39 (m, 4H), 2.32 (q, J = 7.2 Hz, 2H), 0.98 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO) δ (ppm): 164.9, 152.4, 151.4, 151.1, 148.7, 141.7, 133.6, 132.8, 132.0, 130.6, 127.1, 125.7, 125.0, 123.2, 121.4, 115.9, 113.6, 109.9, 91.8, 87.8, 57.5, 52.9, 52.4, 51.6, 12.1, 12.0, 11.9; MS (ESI) *m/z* 549 $[C_{29}H_{28}F_3N_7O + H]^+$

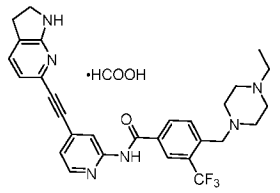
Example 88: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((3-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000440] Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((3-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 5-bromo-3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine following general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and followed by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (16 mg, 12%, AUC HPLC 97%) as white solid; m.p. 66.3–67.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.46 (s, 1H), 8.67 (d, *J* = 1.4 Hz, 1H), 8.60 (s, 1H), 8.40-8.26 (m, 3H), 8.25 (d, *J* = 1.9 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.24 (dd, *J* = 5.2, 1.4 Hz, 1H), 4.12 (s, 3H), 3.82 (s, 2H), 3.11 (bs, 4H), 3.01 (q, *J* = 7.3 Hz, 2H), 2.84-2.76 (m, 4H), 1.32 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.36, 164.62, 156.16, 152.59, 151.59, 151.29, 146.78, 140.89, 134.52, 133.39, 133.37, 130.99, 130.80, 129.66 (q, *J* = 31.2 Hz), 126.02 (q, *J* = 5.8 Hz), 123.80 (q, *J* = 274.4 Hz), 122.03, 119.71, 116.93, 110.85, 104.92, 92.42, 88.10, 57.67, 56.16, 51.59, 51.11, 49.85, 9.09; MS (ESI) *m/z* 564.20$[C_{29}H_{28}F_3N_7O_2 + H]^+$.

Example 89: N-(4-((2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt

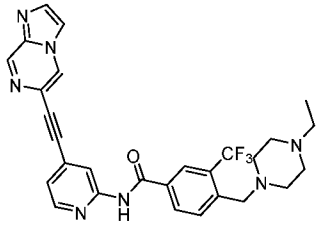


N-(4-((2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideformate

[000441] The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and 6-bromo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine following general procedure A. The reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford *N*-(4-((2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt, (18.7 mg, 29%, AUC HPLC 98.6%) as off-white solid; m.p. 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.08 (s, 1H), 8.47 (s, 1H), 8.41 (s, 1H), 8.23 (s, 1H), 8.22 (s, 1H), 8.09 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 8.00 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 1.6 Hz, 1H), 7.13 (dd, *J* = 5.2 Hz, *J* = 1.2 Hz, 1H), 3.78 (s, 2H), 3.73 (t, *J* = 8.4 Hz, 2H), 3.12 (t, *J* = 8.4 Hz, 2H), 2.90 (bs, 4H), 2.81 (q, *J* = 7.3 Hz, 2H),

2.75–2.65 (m, 4H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.22, 164.28, 163.92, 151.40, 149.62, 147.49, 141.64, 134.59, 133.92, 133.29, 131.00, 130.46, 130.03, 129.73, 129.42, 129.11, 127.91, 125.47, 125.41, 125.18, 122.46, 121.84, 116.01, 107.43, 93.49, 87.36, 57.79, 51.61, 51.49, 51.03, 44.33, 29.71, 27.08, 10.03; MS (ESI) *m/z* 535 $[C_{29}H_{29}F_3N_6O+ H]^+$.

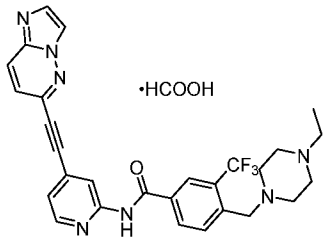
Example 90: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(imidazo[1,2-a]pyrazin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(imidazo[1,2-a]pyrazin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

[000442] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 6-bromoimidazo[1,2-*a*]pyrazine following general procedure A. The reaction crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(imidazo[1,2-*a*]pyrazin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (7.0 mg, 11%, AUC HPLC 99%) as white solid; m.p. 94.3–94.6 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 9.03 (s, 1H), 8.95 (d, J = 1.2 Hz, 1H), 8.45 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.11 (s, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 7.33 (d, J = 4.9 Hz, 1H), 3.84 (s, 2H), 3.04(bs, 4H), 2.93 (q, J = 7.2 Hz, 2H), 2.71 (bs, 4H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 166.98, 153.66, 149.80, 144.09, 142.60, 137.19, 135.02, 133.62, 132.49, 132.33, 130.23 (q, J = 30.5 Hz), 126.85 (q, J = 6.5 Hz), 126.04, 125.61 (q, J = 274.6 Hz), 124.88, 123.09, 117.81, 116.99, 90.43, 88.25, 58.65, 53.25, 53.20, 52.22, 10.47; MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O + H]^+$.

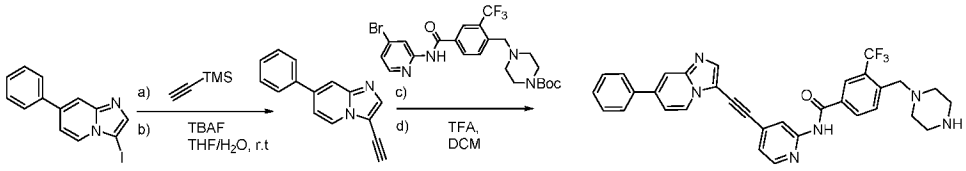
Example 91: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(imidazo[1,2-b]pyridazin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt



Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(imidazo[1,2-b]pyridazin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt

[000443] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 6-bromoimidazo[1,2-*b*]pyridazine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(imidazo[1,2-*b*]pyridazin-6-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt (34 mg, 53%, AUC HPLC 99%) as white solid; m.p. 157.1-157.3 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.48(s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.20 (s, 1H), 8.08 (d, *J* = 9.4 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.85 (s, 1H), 7.48 (d, *J* = 9.4 Hz, 1H), 7.37 (dd, *J* = 5.1, 1.2 Hz, 1H), 3.86 (s, 2H), 3.20(bs, 4H), 3.08 (q, *J* = 7.3 Hz, 2H), 2.76(bs, 4H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 168.55, 166.98, 153.75, 149.98, 142.40, 139.70, 139.41, 135.33, 135.07, 132.72, 132.55, 132.35, 130.26 (q, *J* = 30.9 Hz), 126.90 (q, *J* = 5.9 Hz), 126.20, 125.53 (q, *J* = 272.7 Hz), 123.27, 122.66, 118.83, 118.06, 89.93, 89.27, 58.53, 53.15, 53.07, 51.71, 10.06; MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O + H]^+$.

Example 92: N-(4-((7-phenylimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



[000444] Step 1: Preparation of 7-phenyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine; The title compound was synthesized from 3-iodo-7-phenylimidazo[1,2-*a*]pyridine and ethynyltrimethylsilane following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, eluents Hex/EtOAc 1:1) to afford 7-phenyl-3-

((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyridine (35 mg, 18%) as a yellow solid. MS (ESI) *m/z* 291[$C_{18}H_{18}N_2Si$+H]$^+$.

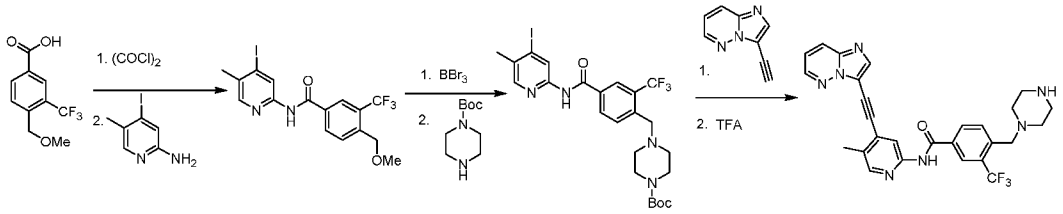
[000445] Step 2: Preparation of 3-ethynyl-7-phenylimidazo[1,2-*a*]pyridine; To a solution of 7-phenyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyridine (35 mg, 0.12 mmol) in THF (2 mL) was added TBAF solution (2 ml, 1M in THF) and stirred at r.t for 18 h. The reaction mixture was concentrated under reduced pressure, then diluted with water (20 mL) and extracted with DCM (3×10 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluents Hex/EtOAc 9:1) to afford 3-ethynyl-7-phenylimidazo[1,2-*a*]pyridine (15 mg, 57%) as brown solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.41 (d, *J* = 6.8 Hz, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.50–7.93 (m, 2H), 7.41–7.37 (m, 2H), 4.43 (s, 1H); MS (ESI) *m/z* 219 [$C_{15}H_{10}N_2$ + H]$^+$.

[000446] Step 3: Preparation of *tert*-butyl 4-(4-(4-((7-phenylimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from 3-ethynyl-7-phenylimidazo[1,2-*a*]pyridine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate following a method similar to general procedure A. The residue mixture was purified by column chromatography (silica gel, eluent Hex/EtOAc 1:9) to afford *tert*-butyl 4-(4-(4-((7-phenylimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (34 mg, 73%, AUC HPLC 97%) as yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.49 (d, *J* = 6.6 Hz, 1H), 8.31 (d, *J* = 7.4 Hz, 2H), 8.42 (s, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 7.95 (t, *J* = 9.2 Hz, 2H), 7.76 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.50–7.41 (m, 4H), 7.22 (d, *J* = 4.0 Hz, 1H), 3.87 (s, 2H), 3.45 (s, 4H), 2.43 (t, *J* = 4.52 Hz, 4H), 1.46 (s, 9H); MS (ESI) *m/z* 681 [$C_{38}H_{35}F_3N_6O_3$+ H]$^+$.

[000447] Step 4: Preparation of *N*-(4-((7-phenylimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 4-(4-(4-((7-phenylimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a method similar to general procedure D. The residue was purified by column chromatography (silica gel, eluents MeOH/DCM 1:9) to afford *N*-(4-((7-phenylimidazo [1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide (24 mg, 83%, AUC HPLC 99%) as yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.68 (d, *J* = 7.1 Hz, 1H), 8.45 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.05 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.91 (s, 1H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.57–7.44 (m, 4H), 7.38 (q, *J* = 2.2 Hz,

1H), 3.87 (s, 2H), 3.30 – 3.26 (m, 4H), 2.76 (t, J = 4.66 Hz, 4H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 166.74, 163.66, 163.31, 162.62, 153.42, 149.58, 142.38, 139.78, 138.83, 134.93, 133.71, 132.47, 132.26, 130.62, 130.33, 130.13, 130.00, 129.70, 127.98, 127.04, 126.85, 126.80, 124.16, 122.25, 119.70, 116.80, 115.36, 114.17, 113.89, 98.63, 81.41, 58.78, 50.83, 44.96; MS (ESI) *m/z* 581 $[C_{33}H_{27}F_3N_6O+ H]^+$.

Example 93: 3-(trifluoromethyl)-N-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide



[000448] Step 1: Preparation of *N*-(4-iodo-5-methylpyridin-2-yl)-4-(methoxymethyl)-3-(trifluoromethyl)benzamide; Oxalyl chloride (395 µL, 4.596 mmol) was added dropwise to a solution of 4-(methoxymethyl)-3-(trifluoromethyl)benzoic acid (200 mg, 0.707 mmol) dissolved in anhydrous DCM (2.5 mL), followed by 2 drops of DMF and the mixture was stirred at room temperature for 5h. The mixture was then concentrated *in vacuo* and the crude acid chloride redissolved in dry dichloromethane (2.5 mL). To a solution of 4-iodo-5-methylpyridin-2-amine (182 mg, 0.777 mmol) in DCM (2 mL) at 0°C was added DMAP (22 mg, 0.177 mmol) and triethylamine (148 µL, 1.059 mmol). The solution of acid chloride was then added dropwise and the mixture stirred at room temperature for 12 h. The mixture was then diluted with DCM, washed in turn with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 25:75) to afford *N*-(4-iodo-5-methylpyridin-2-yl)-4-(methoxymethyl)-3-(trifluoromethyl)benzamide (142 mg, 37%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.34 (s, 1H), 9.05 (s, 1H), 8.26 (d, J = 1.8 Hz, 1H), 8.18 (dd, J = 8.2, 1.9 Hz, 1H), 8.03 (s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 4.75–4.67 (m, 2H), 3.49 (s, 3H), 2.41 (d, J = 0.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 164.1, 148.5, 143.8, 142.3, 134.4, 132.6, 130.7, 129.1, 128.5, 128.2, 128.0, 127.8, 125.4, 125.3, 125.3, 125.3, 124.8, 122.9, 116.6, 70.1, 70.1, 70.1, 70.1, 59.0, 24.2; MS (ESI) *m/z* 451 $[C_{16}H_{14}F_3IN_2O_2+ H]^+$.

[000449] Step 2: Preparation of 4-(bromomethyl)-*N*-(4-iodo-5-methylpyridin-2-yl)-3-(trifluoromethyl)benzamide; A solution of *N*-(4-iodo-5-methylpyridin-2-yl)-4-(methoxymethyl)-3-(trifluoromethyl)benzamide (142 mg, 0.316 mmol) in dichloromethane (2

mL) was cooled to -78°C and BBr_3 (3.16 mL, 3.16 mmol) was added slowly dropwise and the reaction stirred at room temperature for 12 h. The mixture was quenched by cooling to 0°C, followed by the addition of saturated $NaHCO_3$. The aqueous was extracted with DCM (3x5 mL), the organic extracts were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 50:50) to afford 4-(bromomethyl)-*N*-(4-iodo-5-methylpyridin-2-yl)-3-(trifluoromethyl)benzamide (45 mg, 28%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.50 (s, 1H), 9.06 (s, 1H), 8.27 (s, 1H), 8.21 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.03 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 4.66 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm):163.7, 148.2, 143.4, 140.8, 134.6, 133.6, 131.2, 129.3, 129.2, 129.1, 127.1, 126.0, 125.9, 125.9, 125.8, 124.9, 124.5, 122.6, 117.1, 27.3, 24.2; MS (ESI) *m/z* 498 $[C_{15}H_{11}BrF_3IN_2O+ H]^+$.

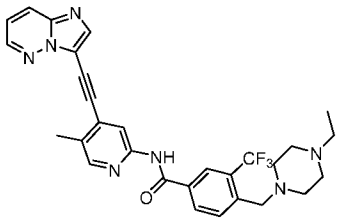
[000450] Step 3: Preparation of *tert*-butyl 4-(4-((4-iodo-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; 4-(bromomethyl)-*N*-(4-iodo-5-methylpyridin-2-yl)-3-(trifluoromethyl)benzamide (45 mg, 0.0904 mmol) was added to a solution of *N*-Boc piperazine (169 mg, 0.908 mmol) in ACN (1.5 mL), followed by DMF (0.5 mL) and the mixture stirred at room temperature for 4 h. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 40:60) to afford *tert*-butyl 4-(4-((4-iodo-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (55 mg, quant.).^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.92 (s, 1H), 8.65 (s, 1H), 8.21 (s, 1H), 8.12 – 8.06 (m, 1H), 8.05 (s, 1H), 3.78 (s, 2H), 3.51 (m, 4H), 2.50 (m, 4H), 2.39 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 163.9, 154.7, 149.1, 148.7, 146.5, 134.2, 131.3, 130.5, 129.8, 125.2, 124.7, 124.0, 122.9, 121.1, 114.4, 114.2, 53.0, 28.5, 24.1; MS (ESI) *m/z* 605 $[C_{24}H_{28}F_3IN_4O_3+ H]^+$.

[000451] Step 4: Preparation of *tert*-butyl 4-(4-((4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from *tert*-butyl 4-(4-((4-iodo-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynylimidazo[1,2-*b*]pyridazine following a method similar to general procedure A. The solvents were removed *in vacuo* and the crude purified by flash column chromatography (silica gel, eluent: EtOAc/hexanes 80:20) to afford *tert*-butyl 4-(4-((4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (32 mg, 49%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.84 (s, 1H), 8.58 (s, 1H), 8.51 (d, *J* = 4.2 Hz, 1H), 8.32–8.07 (m, 5H), 8.08–7.97 (m, 2H), 7.18 (dd, *J* = 9.0, 4.4 Hz, 1H), 3.82 (s, 2H), 3.53 (m, 4H), 2.53

(m, 7H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 164.0, 162.6, 154.7, 149.2, 147.8, 144.1, 139.4, 133.3, 132.2, 132.2, 132.0, 130.8, 130.6, 128.6, 128.5, 126.1, 125.3, 124.8, 122.9, 118.3, 115.5, 95.6, 84.9, 80.1, 53.0, 28.5, 17.3; MS (ESI) *m/z* 620 $[C_{32}H_{32}F_3N_7O_3 + H]^+$.

[000452] Step 5: Preparation of 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide; The title compound was synthesized from *tert*-butyl 4-((4-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)phenyl)methyl)piperazine-1-carboxylate in a similar method as described in general procedure D. The reaction crude product was purified by preparative TLC (eluent DCM/CH_3OH 90:10) to afford 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide (12.2 mg, 51.9%, AUC HPLC 97%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.19 (s, 1H), 8.75 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.39 (s, 1H), 8.31–8.26 (m, 5H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.68 (s, 2H), 2.89–2.87 (m, 4H), 2.48-2.38 (m, 7H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.1, 150.6, 149.0, 145.7, 141.6, 140.5, 139.7, 133.4, 132.3, 131.6, 131.1, 129.8, 120.0, 115.4, 111.5, 95.6, 84.8, 58.2, 52.5, 44.8, 17.0; MS (ESI) *m/z* 520 $[C_{27}H_{24}F_3N_7O + H]^+$.

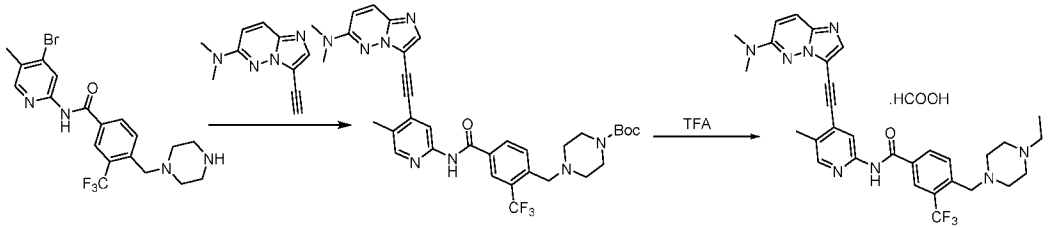
Example 94: 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-N-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)benzamide



[000453] The title compound was synthesized by alkylating 3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-((piperazin-1-yl)methyl)benzamide with bromoethane in a similar method as described for 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)benzamide. The reaction crude product was purified by preparative TLC (eluent DCM/CH_3OH 90:10) to afford 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)benzamide (10 mg, 68%, AUC HPLC 97%) as a white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.19 (s, 1H), 8.76 (dd, *J* = 4.2, 1.2 Hz, 1H), 8.40 (s, 1H), 8. 34– 8.31 (m, 3H),

8.28 (m, 2H), 7.91 (d, J = 7.8 Hz, 1H), 7.42 (dd, J = 9.0, 4.2 Hz, 1H), 3.67 (s, 2H), 2.48 (s, 3H), 2.46–2.32 (m, 8H), 2.31 (q, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.7, 150.2, 148.6, 145.3, 141.6, 140.1, 139.3, 132.8, 131.9, 130.6, 129.4, 126.2, 125.6, 119.6, 114.9, 111.1, 95.2, 84.3, 72.5, 63.1, 57.5, 52.9, 52.3, 51.6, 16.6, 12.0; MS (ESI) m/z 548 $[C_{29}H_{28}F_3N_7O + H]^+$.

Example 95: N-(4-(2-(6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



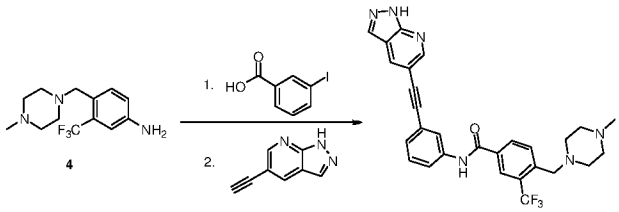
[000454] Step 1: Preparation of *tert*-butyl 4-(4-((4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from *tert*-butyl 4-(4-((4-iodo-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynyl-*N*,*N*-dimethylimidazo[1,2-*b*]pyridazin-6-amine following a method similar to general procedure A. The solvents were removed *in vacuo* and the crude purified by flash column chromatography (silica gel, eluent: EtOAc) to afford *tert*-butyl 4-(4-((4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (37 mg, 19%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ (ppm): 8.81 (s, 1H), 8.53 (s, 1H), 8.23 (s, 2H), 8.10 (t, J = 12.5 Hz, 2H), 7.77 (s, 1H), 6.87 (s, 1H), 3.78 (s, 2H), 3.50 (m, 4H), 3.18 (s, 6H), 2.53 (s, 3H), 2.49 (m, 4H), 1.46 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.0, 155.3, 154.8, 149.2, 133.9, 133.3, 132.2, 132.2, 132.0, 131.3, 130.5, 129.6, 129.4, 128.6, 128.6, 126.6, 125.7, 125.3, 125.2, 125.2, 125.2, 124.8, 123.0, 115.1, 110.2, 95.4, 80.0, 57.9, 53.1, 38.8, 28.5, 17.2; MS (ESI) m/z 663 $[C_{34}H_{37}F_3N_8O_3 + H]^+$.

[000455] Step 2: Preparation of *N*-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide; The title compound was synthesized from *tert*-butyl 4-(4-((4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar method as described in general

procedure D. The crude product was directly used in next step without further purification. MS (ESI) *m/z* 563 $[C_{29}H_{29}F_3N_8O + H]^+$.

[000456] Step 3: Preparation of *N*-(4-(2-(6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide: The title compound was synthesized from *N*-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide in a similar method as described for 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)benzamide. The reaction crude product was purified by preparative HPLC to afford *N*-(4-(2-(6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate (8.9 mg, 26%, AUC HPLC 99%) as a white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.22 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 8.29 (m, *J* = 4.4 Hz, 2H), 8.15 (s, 1H), 7.99 (s, 1H), 7.94 (d, *J* = 9.9 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 10.0 Hz, 1H), 3.71 (s, 3H), 3.13 (s, 6H), 1.24 (d, *J* = 6.4 Hz, 2H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.6, 163.3, 155.4, 150.2, 148.5, 141.3, 136.8, 133.0, 132.0, 131.7, 130.6, 129.1, 127.3, 127.0, 125.7, 125.1, 123.2, 114.4, 110.5, 95.0, 86.0, 57.2, 51.8, 51.3, 38.2, 18.8, 16.5, 11.2; MS (ESI) m/z 591.2 $[C_{31}H_{33}F_3N_8O + H]^+$.

Example 96: Synthesis of 3-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide

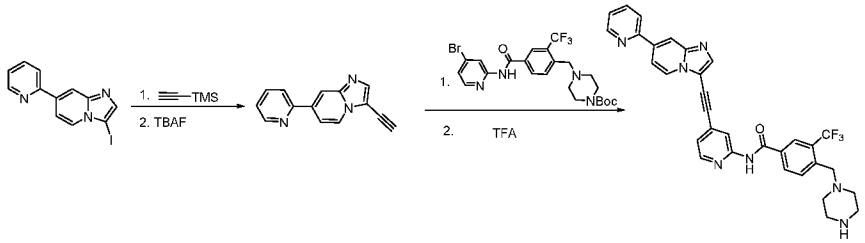


[000457] Step 1: Synthesis of 3-iodo-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide; To a solution of 3-iodobenzoic acid (90 mg, 0.36 mmol) in anhydrous *N,N*-dimethylformamide (2 mL) was added HATU (278 mg, 0.78 mmol) and the mixture was stirred at room temperature for 30 minutes. A solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (100 mg, 0.36 mmol) and triethylamine (74 mg, 0.73 mmol) in anhydrous *N,N*-dimethylformamide (1 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was then

partitioned between H_2O (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2x50 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuum. The residue was purified by flash column chromatography (silica gel, eluent DCM/MeOH 19:1) to afford 3-iodo-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide (182 mg, 98% yield) as brown amorphous solid. MS (ESI) *m/z* 504.1 $[C_{20}H_{21}F_3IN_3O+H]^+$.

[000458] Step 2: Synthesis of 3-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide; To a round bottom flask equipped with a reflux condenser was added 3-iodo-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide (100 mg, 0.19 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.019 mmol), copper(I) iodide (3.7 mg, 0.019 mmol) and 5-ethynyl-1*H*-pyrazolo[3,4-*b*]pyridine (31 mg, 0.21 mmol) in anhydrous triethylamine (5 mL). The reaction mixture was purged with nitrogen for 5 minutes. The mixture was heated at 80 °C for 16 hours. The solution was cooled to room temperature, filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, DCM/MeOH/ammonium hydroxide 96:3.6:0.4) to afford 3-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide (24.2 mg, 23% yield, AUC HPLC 95.7%) as an off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.93 (s, 1H), 10.61 (s, 1H), 8.72 (d, *J* = 1.9 Hz, 1H), 8.51 (d, *J* = 1.9 Hz, 1H), 8.22–8.21 (m, 3H), 8.06 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 3.57 (s, 2H), 2.39–2.32 (m, 8H), 2.16 (s, 3H); MS (ESI) *m/z* 519.2 $[C_{28}H_{25}F_3N_6O+H]^+$;

Example 97: 4-(piperazin-1-ylmethyl)-N-(4-((7-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000459] Step 1: Preparation of 3-ethynyl-7-(pyridin-2-yl)imidazo[1,2-*a*]pyridine; 3-iodo-7-(pyridin-2-yl)imidazo[1,2-*a*]pyridine and ethynyltrimethylsilane subjected to Sonogashira coupling reaction following a method similar to general procedure A. The residue was

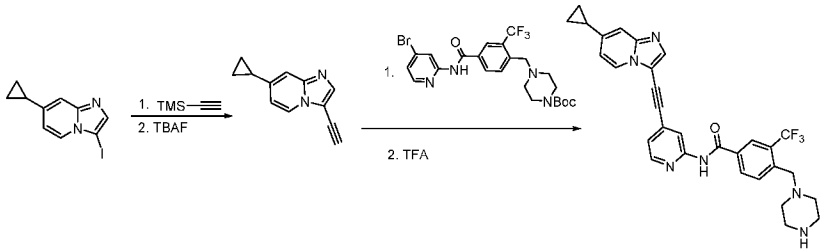
purified by flash column chromatography (silica gel, eluents Hex/EtOAc 2:3) to afford 7-(pyridin-2-yl)-3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyridine as yellow solid.

[000460] Step 2: Preparation of 3-ethynyl-7-(pyridin-2-yl)imidazo[1,2-*a*]pyridine. The intermediate was dissolved in THF (2 ml) followed by addition of TBAF solution (2 ml, 1M) and the mixture was stirred for18 h at room temperature. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, eluents Hex/EtOAc 1:1) to afford 3-ethynyl-7-(pyridin-2-yl)imidazo[1,2-*a*]pyridine (18 mg, 57 % 2 steps) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.67 (m, J = 1.1 Hz, 1H), 8.48 (q, J = 2.7 Hz, 1H), 8.24 (q, J = 0.87 Hz, 1H), 8.01–7.86 (m, 3H), 7.79 (q, J = 2.9 Hz, 1H), 7.40 (m, J = 1.9 Hz, 1H), 4.45 (s, 1H); MS (ESI) *m/z* 220 $[C_{14}H_9N_3+H]^+$.

[000461] Step 2: Preparation of 4-(piperazin-1-ylmethyl)-*N*-(4-((7-(pyridin-2-yl)imidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide; 3-ethynyl-7-(pyridin-2-yl)imidazo[1,2-*a*]pyridine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate subjected to Sonogashira coupling reaction in a similar fahion as described in general procedure A. The residue mixture was purified by column chromatography (silica gel, eluents Hex/EtOAc 3:7) to afford *tert*-butyl 4-(4-(4-((7-(pyridin-2-yl)imidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

Step 3: Synthesis of 4-(piperazin-1-ylmethyl)-*N*-(4-((7-(pyridin-2-yl)imidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide. The intermediate from the step above was added to a solution of TFA in DCM (6 ml, 50%) and stirred at room temperature for 18 h before purification by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford 4-(piperazin-1-ylmethyl)-*N*-(4-((7-(pyridin-2-yl)imidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (25 mg, 52%, AUC HPLC 99%) as yellow solid; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.49 (d, J = 6.6 Hz, 1H), 8.31 (d, J = 7.4 Hz, 2H), 8.42 (s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.95 (t, J = 9.2 Hz, 2H), 7.76 (s, 1H), 7.70 (d, J = 7.5 Hz, 2H), 7.50–7.41 (m, 4H), 7.22 (d, J = 4.0 Hz, 1H), (3.87 (s, 2H), 3.45 (s, 4H), 2.43 (t, J = 4.5 Hz, 4H), 1.46 (s, 9H); MS (ESI) *m/z* 681 $[C_{38}H_{35}F_3N_6O_3+ H]^+$.

Example 98: N-(4-((7-cyclopropylimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

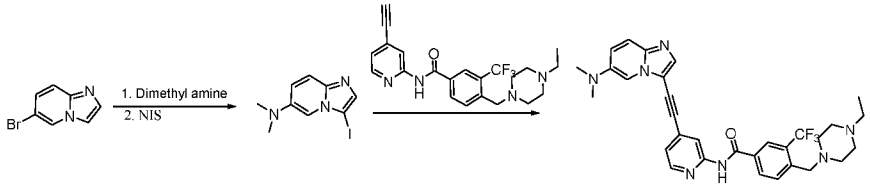


[000462] Step 1: Preparation of 7-cyclopropyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*a*]pyridine; 7-cyclopropyl-3-iodoimidazo[1,2-*a*]pyridine and ethynyltrimethylsilane subjected to Sonogashira coupling reaction in a similar methodas described in general procedure A. The reaction mixture was purified by column chromatography (silica gel, eluents Hex/EtOAc 7:3) to afford 7-cyclopropyl-3-((trimethylsilyl)ethynyl)imidazo[1,2]pyridine (11.4 mg) as brown viscous liquid. MS (ESI) *m/z* 246 $[C_{15}H_{18}N_2Si + H]^+$.

The intermediate 7-cyclopropyl-3-((trimethylsilyl)ethynyl)imidazo[1,2]pyridine was subjected to silyl deportation by using TBAF in THF. The reaction mixture was purified by column chromatography to afford 7-cyclopropyl-3-ethynylimidazo[1,2-*a*]pyridine.

[000463] Step 2: Preparation of *N*-(4-((7-cyclopropylimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide; 7-cyclopropyl-3-ethynylimidazo[1,2-*a*]pyridine and *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate subjected to Sonogashira coupling reaction following a method similar to general procedure A. The residue mixture was purified by flash column chromatography (silica gel, eluents Hex/EtOAc 1:9) to afford crude *tert*-butyl 4-(4-(4-((7-cyclopropylimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate which was then dissolved in DCM (2 ml) and TFA was added (2 ml). The reaction solution was stirred at 80 ^oC overnight and neutralized with a saturated aqueous olution of $NaHCO_3$ followed by an aqueous work-up then a purification by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford *N*-(4-((7-cyclopropylimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (0.8 mg, AUC HPLC 97%) as yellow solid. ^1H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.45 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H), 8.33 (s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.98 (s, 1H), 7.85 (d, J = 10.1 Hz, 1H), 7.31 (d, J = 10.1 Hz, 1H), 7.28 (q, J = 2.1 Hz, 1H), 3.87(s, 2H), 3.68 (q, J = 7.1 Hz, 4H), 3.29–3.25 (m, 4H), 3.28 (t, J = 5.2 Hz, 4H), 1.33 (t, J = 7.1 Hz, 6H); MS (ESI) *m/z* 577 $[C_{30}H_{31}F_3N_8O_3 + H]^+$.

Example 99: N-(4-((6-(dimethylamino)imidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *N,N*-dimethylimidazo[1,2-*a*]pyridin-6-amine

[000464] A mixture of 6-bromoimidazo[1,2-*a*]pyridine (2 g, 10.1 mmol), potassium *tert*-butoxide (2.27 g, 20.3 mmol), X-Phos (48.1 mg, 0.10 mmol), dimethyl amine in THF (2 M, 10 mL) and $Pd(dba)_2$ (57.5 mg, 0.10 mmol) in xylene was heated at 180 °C for 4 h in a sealed tube. The reaction mixture was diluted with a mixture of EtOAc and THF and washed in turn with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) of *N,N*-dimethylimidazo[1,2-*a*]pyridin-6-amine (1.2 g, 73%) as a solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 (s, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 2.4 Hz, 1H), 2.84 (s, 6H); MS (ESI) *m/z*:162.2 $[C_9H_{11}N_3+H]^+$.

Step 2: Preparation of 3-iodo-*N,N*-dimethylimidazo[1,2-*a*]pyridin-6-amine

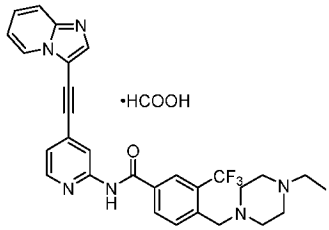
[000465] To a solution of *N,N*-dimethylimidazo[1,2-*a*]pyridin-6-amine (1.2 g, 7.45 mmol) in ACN (20 mL) was added NIS (2.01 g, 8.94 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (50 mL) and filtered. The organic phase was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 3-iodo-*N,N*-dimethylimidazo[1,2-*a*]pyridin-6-amine. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.58 (s, 1H), 7.48 (d, *J* = 9.6 Hz, 1H), 7.32 (d, *J* =1.6 Hz, 1H), 7.28 (dd, *J* = 2.0 Hz, 1H), 2.84 (s, 6H); MS (ESI) *m/z*: 286.1 $[C_9H_{10}IN_3+H]^+$.

Step 3: Preparation of *N*-(4-((6-(dimethylamino)imidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000466] The title compound was synthesized from 3-iodo-*N,N*-dimethylimidazo[1,2-*a*]pyridin-6-amine and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction mixture was purified by flash coloum chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) to afford *N*-(4-((6-(dimethylamino)imidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (50 mg, 25%, AUC HPLC 90%) as a yellow solid; m.p. 160–165 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.54 (d, *J* =

12.0 Hz, 1H), 8.33 (d, *J* = 4.8 Hz, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.62 (s, 1H), 7.58 (d, *J* = 9.6 Hz, 1H), 7.21–7.16 (m, 2H), 3.80 (s, 2H), 3.00 (s, 6H), 2.82–2.77 (m, 10H), 1.29 (t, *J* = 4.0 Hz, 3H); MS (ESI) *m/z* 576.4 $[C_{31}H_{32}F_3N_7O+H]^+$.

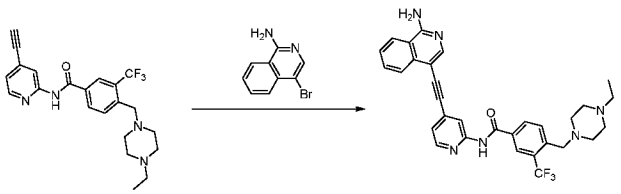
Example 100: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(imidazo[1,2-a]pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt



Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(imidazo[1,2-a]pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt

[000467] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 3-iodoimidazo[1,2-*a*]pyridine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, DCM/methnol 10:1) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(imidazo[1,2-*a*]pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formate salt (32 mg, 25%, AUC HPLC 99%) as a yellow solid. m.p. 50.2–51.6 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.51 (d, *J* = 6.8 Hz, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.32 (d, *J* = 5.1 Hz, 1H), 8.27 (s, 1H), 8.19 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.96–7.89 (m, 2H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.49–7.42 (m, 1H), 7.25 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.17–7.12 (m, 1H), 3.83 (s, 2H), 3.35–3.24 (m, 4H), 3.20 (q, *J* = 7.3 Hz, 2H), 2.79 (bs, 4H), 1.35 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 168.03, 166.59, 153.39, 149.54, 147.29, 142.12, 139.67, 134.90, 133.78, 132.44, 132.19, 130.09, 128.92, 126.97, 126.82, 125.49, 121.42, 118.09, 116.78, 115.63, 109.30, 98.54, 81.57, 58.35, 52.92, 52.67, 51.11, 9.60; MS (ESI) *m/z* 533.70 $[C_{29}H_{27}F_3N_6O + H]^+$.

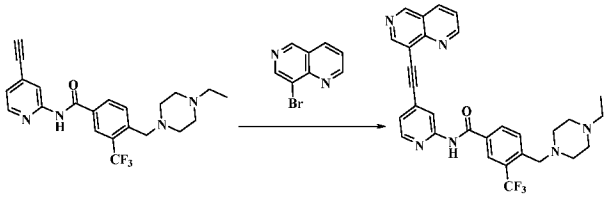
Example 101: N-(4-((1-aminoisoquinolin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate



Preparation of *N*-(4-((1-aminoisoquinolin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate

[000468] The title compound was synthesized from *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine and 4-bromoisoquinolin-1-amine following a method similar to general procedure A. The reaction mixture was purified twice by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford *N*-(4-((1-aminoisoquinolin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (5 mg, AUC HPLC 98.9%) as an off-white solid; m.p. 99–101 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.94 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 8.31 (d, *J* = 5.2 Hz, 1H), 8.26 (t, *J* = 3.9 Hz, 2H), 8.20 (s, 1H), 8.11 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.94–7.81 (m, 3H), 7.68–7.60 (m, 1H), 7.30–7.28 (m, 1H), 6.60–6.20 (bs, 2H), 3.79 (s, 2H), 3.91 (s, 4H), 2.82 (q, *J* = 7.3 Hz, 2H), 2.73 (s, 4H), 1.25 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 166.90, 164.25, 156.49, 151.43, 147.64, 144.56, 136.68, 134.43, 133.19, 132.01, 131.07, 130.41, 127.45, 125.93, 125.44, 125.38, 122.89, 122.09, 116.87, 116.00, 105.73, 91.85, 90.69, 57.80, 51.60, 51.49, 51.05, 10.04; MS (ESI) *m/z* 593 $[C_{31}H_{29}F_3N_6O + H]^+$.

Example 102: N-(4-(2-(1,6-naphthyridin-8-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

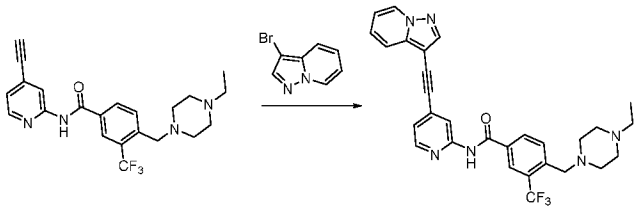


Preparation of *N*-(4-(2-(1,6-naphthyridin-8-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000469] The title compound was synthesized from 8-bromo-1,6-naphthyridine and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The reaction crude product was purified by column chromatography (eluent DCM/CH_3OH 90:10) to afford *N*-(4-(2-(1,6-naphthyridin-8-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (11.9 mg, 18%, AUC HPLC 99%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.32 (s, 1H), 9.49 (s, 1H), 9.30 (dd, *J* = 4.2, 1.8 Hz, 1H), 9.09 (s, 1H), 8.70 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 8.43 (d, *J* = 1.3 Hz, 1H), 8.36 (d, *J* = 1.8 Hz, 1H),

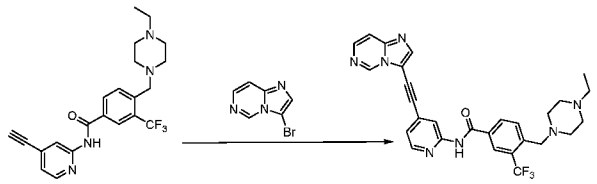
8.30 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.85 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.42 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.47 – 2.39 (m, 4H), 2.32 (q, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ (ppm): 164.9, 156.1, 154.1, 152.4, 150.5, 149.1, 148.7, 141.7, 136.9, 132.8, 132.0, 131.7, 130.5, 127.4, 127.2, 127.0, 126.8, 125.6, 125.0, 124.1, 123.2, 123.0, 121.5, 116.1, 93.9, 88.7, 57.5, 52.9, 52.3, 51.5, 11.9; MS (ESI) *m/z* 545.15 [$C_{30}H_{27}F_3N_6O$+ H]$^+$.

Example 103: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(pyrazolo[1,5-a]pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000470] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 3-bromopyrazolo[1,5-*a*]pyridine following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH 100:0 to 90:10) and by preparative HPLC (CH_3CN/H_2O/0.1% Formic acid) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(pyrazolo[1,5-*a*]pyridin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (4.9 mg, AUC HPLC 98.7%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm): 11.22 (s, 1H), 8.84 (d, 1H, *J* = 6.9 Hz), 8.43–8.42 (m, 2H), 8.35 (s, 1H), 8.31–8.29 (m, 2H), 7.93–7.90 (m, 2H), 7.53–7.48 (m, 1H), 7.33–7.32 (m, 1H), 7.12–7.09 (m, 1H), 3.68 (s, 2H), 2.49–2.43 (m, 8H), 2.32 (q, 2H, *J* = 7.2 Hz), 0.98 (t, 3H, *J* = 7.2 Hz); MS (ESI) *m/z* 533.2 [$C_{29}H_{27}F_3N_6O$+H]$^+$;

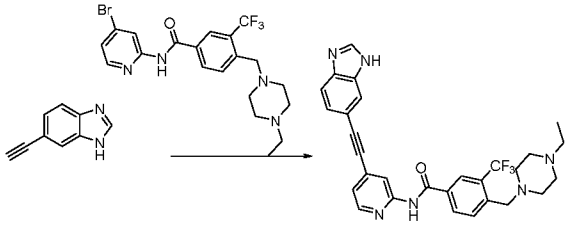
Example 104: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(imidazo[1,2-c]pyrimidin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000471] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 3-bromoimidazo[1,2-c]pyrimidine

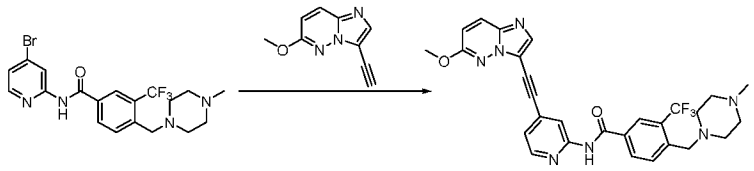
following a method similar to general procedure A. The residue was purified by flash column chromatography (silica gel, eluent DCM/MeOH 9:1) and the product thus obtained was triturated in MeOH, isolated by centrifugation and dried to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(imidazo[1,2-*c*]pyrimidin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (21 mg, 33.1%, AUC HPLC 97.5%) as white powder; mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.25 (s, 1H), 8.80 (s, 1H), 8.58 (s, 1H), 8.34 (d, *J* = 5.0 Hz, 1H), 8.21 (s, 1H), 8.08 (d, *J* = 6.4 Hz, 2H), 8.01 (d, *J* = 7.3 Hz, 2H), 7.60 (d, *J* = 6.3 Hz, 1H), 7.23 (d, *J* = 4.8 Hz, 1H), 3.74 (s, 2H), 2.75–2.30 (m, 10H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.37, 151.65, 148.27, 145.83, 142.99, 140.92, 138.87, 132.68, 132.52, 131.10, 130.29, 129.63, 129.32, 129.01, 125.24, 125.04, 124.98, 122.51, 121.44, 115.48, 112.95, 106.38, 97.40, 79.79, 58.01, 53.11, 52.82, 52.33, 11.87; MS (ESI) *m/z* 534.60[$C_{28}H_{26}F_3N_7O$ + H]$^+$.

Example 105: N-(4-((1H-benzo[d]imidazol-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000472] The title compound was synthesized from 6-ethynyl-1*H*-benzo[*d*]imidazole and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide following a method similar to general procedure A. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((1*H*-benzo[*d*]imidazol-6-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (69 mg, 24%, AUC HPLC 99%) as white solid; m.p. 248.2-250.7 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.36-8.35 (m, 2H), 8.28 (d, *J* = 1.6 Hz, 1H), 8.26 (s, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.86 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.26 (dd, *J* = 2.8; 1.4 Hz, 1H), 3.75 (s, 2H), 2.56 (bs, 8H), 2.45 (q, *J* = 7.3 Hz, 2H), 1.10 (t, *J* = 7.3 Hz, 3H); MS (ESI) *m/z* 533 [$C_{29}H_{27}F_3N_6O$ + H]$^+$.

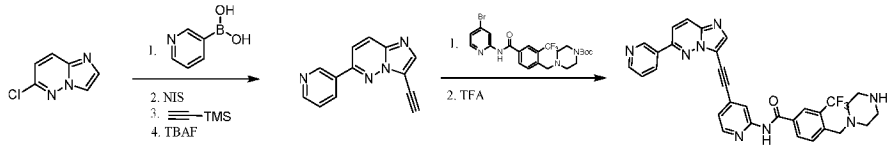
Example 106: N-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide.

[000473] The title compound was synthesized following a method similar to general procedure B starting from *N*-(4-bromopyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and 3-ethynyl-6-methoxyimidazo[1,2-b]pyridazine. The reaction crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 97:3) to give *N*-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (100 mg, 41%, AUC HPLC 94.6%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 11.27 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 8.13 (d, J = 4.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.35 (dd, J = 1.2 Hz, J = 1.6 Hz, 1H), 7.07 (d, J = 9.6 Hz, 1H), 4.07 (s, 3H), 3.68 (s, 2H), 2.42–2.32 (m, 8H), 2.17 (s, 3H); MS (ESI) *m/z* 550.1 $[C_{28}H_{26}F_3N_7O_2+H]^+$.

Example 107: 4-(piperazin-1-ylmethyl)-N-(4-((6-(pyridin-3-yl) imidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-yl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 6-(pyridin-3-yl) imidazo[1,2-b]pyridazine

[000474] To a solution of 6-chloroimidazo[1,2-b] pyridazine (2.0 g, 13 mmol) in a mixture of 1,4-dioxane and water (25 mL) under argon were successively added pyridin-3-ylboronic acid (1.80 g, 14 mmol), potassium phosphate (5.6 g, 26 mmol), $Pd(PPh_3)_4$ (0.75 g, 0.6 mmol). The resulting reaction mixture was heated at 80 °C for 16 h, was concentrated under reduced pressure and the residue was diluted with water (20 mL). The precipitate was isolated by filtration and dried to afford 6-(pyridin-3-yl) imidazo[1,2-b]pyridazine as a yellow solid (1.4 g).

Step 2: Preparation of 3-iodo-6-(pyridin-3-yl) imidazo[1,2-b]pyridazine):

[000475] To a solution of 6-(pyridin3-yl) imidazo[1,2-b] pyridazine (1.5 g, 7.65 mmol) in DMF (5 mL) was added *N*-iodo succinamide (2.6 g, 11.4 mmol). The reaction mixture was

heated at 90 °C for 2 h, poured into ice cold water (20 mL) and extracted with ethyl acetate (15 mL). The organic phase washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 3-iodo-6-(pyridin-3-yl)imidazo[1,2-b]pyridazine (1 g, 41%, LC-MS 75%) as a brown solid.

Step 3: Preparation of 6-(pyridin-3-yl)-3-((trimethylsilyl) ethynyl)imidazo[1,2-b]pyridazine:

[000476] To a solution of 3-iodo-6-(pyridin-3-yl)imidazo[1,2-b]pyridazine (2.0g, 6.2 mmol) in DMF (5 mL) under argon were successively added $Pd(PPh_3)_4$ (0.36 g, 0.31 mmol), trimethysillyllalkyne (0.73 g, 7.4 mmol), CuI (58 mg, 0.31 mmol) and DIPEA (1.6 g, 12.4 mmol). The resulting reaction mixture was stirred for 3 h at room temperature, diluted with EtOAc and washed in turn with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel eluent: petroleum ether/EtOAc 70:30) to afford 6-(pyridin-3-yl)-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (1.5 g, 83%).

Step 4: Preparation of 3-ethynyl-6-(pyridin-3-yl) imidazo [1, 2-b] pyridazine:

[000477] To a solution of 6-(pyridin-3-yl)-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (1 g, 3.4 mmol) in a mixture of THF (10 mL) and H_2O (2 mL) was added LiOH (210 mg, 0.005 mol). The reaction mixture was stirred at room temperature for 2 h, was concentrated under reduced pressure and the residue was diluted with ethyl acetate (15 mL). The organic phase was washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 3-ethynyl-6-(pyridin-3-yl)imidazo[1,2-b]pyridazine (400 mg, 53%, LC-MS 89%) as a yellow solid.

Step 5: Preparation of *tert*-butyl 4-(4-(4-((6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate:

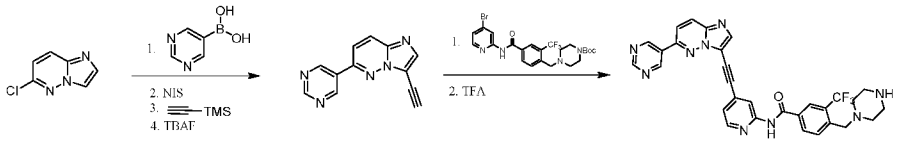
[000478] The title compound was synthesized following a method similar to general procedure B starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynyl-6-(pyridin-3-yl)imidazo[1,2-b]pyridazine. The reaction crude product was purified by flash column chromatography (silica gel eluent: dichloromethane/ methanol 98:2) to afford *tert*-butyl 4-(4-(4-((6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (80 mg, LC-MS 84%) as a yellow solid.

Step 6: 4-(piperazin-1-ylmethyl)-*N*-(4-((6-(pyridin-3-yl) imidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide:

[000479] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl 4-(4-(4-((6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-

yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 96:4) to give 4-(piperazin-1-ylmethyl)-*N*-(4-((6-(pyridin-3-yl) imidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide (60 mg, 69%, AUC HPLC 98%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.28–9.28 (d, *J* = 1.6 Hz, 1H), 8.79–8.77 (dd, *J* = 4.8, *J* = 1.2 Hz, 1H), 8.63–8.62 (d, *J* = 5.6 Hz , 2H), 8.37–8.35 (d, *J* = 5.2 Hz, 1H), 8.21 (s, 1H), 8.15–8.06 (m, 4H), 7.66–7.63 (d, *J* = 11.2 Hz, 1H), 7.60–7.56 (m, 1H), 7.31–7.29 (m, 1H), 3.72 (s, 2H), 2.94–2.92 (m, 4H), 2.50–2.42 (m, 4H); MS (ESI) *m/z* 583 $[C_{31}H_{25}F_3N_8O+H]^+$.

Example 108: 4-(piperazin-1-ylmethyl)-N-(4-((6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine

[000480] To a solution of 6-chloroimidazo[1,2-b] pyridazine (2 g, 13.07 mmol) in a mixture of 1,4- dioxane and water (30 mL) under argon, were successively added $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol), pyrimidin-5-ylboronic acid (1.94 g, 15.68 mmol), potassium phosphate (5.54 g, 26.14 mmol). The reaction mixture was heated at 100 °C for 4 h and was concentrated to afford 6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine (2.5 g, 48%, LC-MS 98%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.45 (s, 2H), 9.35 (s, 1H), 8.44 (s, 1H), 8.35 (d, *J* = 9.6 Hz,1H), 7.94 (d, *J* = 9.6 Hz, 1H), 7.89 (s, 1H). MS (ESI) *m/z* 198 $[C_{10}H_7N_5+H]$.

Step 2: Preparation of 3-iodo-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine

[000481] To a solution of 3-iodo-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine (2.5 g, 12.69 mmol) in DMF (18 mL) was added *N*-iodosuccinamide (3.42 g, 15.22 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 3-iodo-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine (2.8 g) as a pale brown solid. (ESI) *m/z* 324 $[C_{10}H_6IN_5+H]$.

Step 3: Preparation of 6-(pyrimidin-5-yl)-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine

[000482] The title compound was synthesized following a method similar to general procedure A starting from 3-iodo-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine (2.8 g, 2.18

mmol) and ethynyltrimethylsilane. The reaction crude product was purified by column chromatography (neutral alumina, eluent: Petroleum ether/ethyl acetate 80:20) to afford 6-(pyrimidin-5-yl)-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (1.5 g, 60%, LC-MS 90%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.40 (s, 2H), 9.36 (s, 1H), 8.44 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 7.56 (d, J = 9.2 Hz, 1H), 0.34 (s, 9H). MS (ESI) *m/z* 294.1 [$C_{15}H_{15}N_5Si$+H].

Step 4: Preparation of 3-ethynyl-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine

[000483] To a solution of 6-(pyrimidin-5-yl)-3-((trimethylsilyl) ethynyl) imidazo [1, 2-b] pyridazine (1.5 g, 5.11 mmol) in THF (20 mL) and H_2O (5 mL) was added LiOH (257.5 mg, 6.13 mmol) at room temperature and stirred for 6 h. The reaction mixture was concentrated under reduce pressure. The residue was diluted with diethyl ether then washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 3-ethynyl-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine (800 mg, 61%, LC-MS 95%) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.46 (s, 2H), 9.37 (s, 1H), 8.44 (d, J = 9.2 Hz, 1H), 8.21 (s, 1H), 8.07 (d, J = 9.6 Hz, 1H), 5.03 (s, 1H). MS (ESI) *m/z* 222.1 [$C_{12}H_7N_5$+H].

Step 5: Preparation of tert-butyl 4-(4-(4-((6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

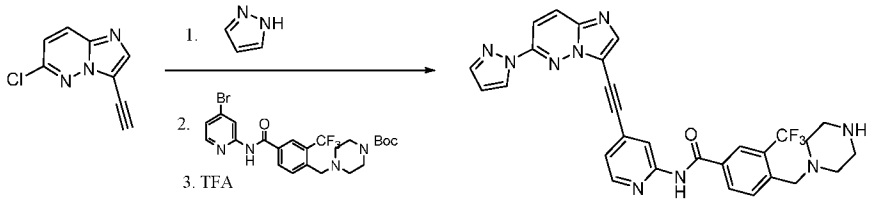
[000484] The title compound was synthesized following a method similar to general procedure A starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynyl-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazine. The crude product was purified by column chromatography (neutral alumina, eluent: Petroleum ether /ethyl acetate 80:20) to afford *tert*-butyl 4-(4-(4-((6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg, 53%, LC-MS 88%) as an off-white solid.

Step 6: 4-(piperazin-1-ylmethyl)-*N*-(4-((6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

[000485] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl tert-butyl 4-(4-(4-((6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by column chromatography (neutral alumina, eluent: petroleum ether/ethyl acetate 70:30) to afford 4-(piperazin-1-ylmethyl)-*N*-(4-((6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-

(trifluoromethyl)benzamide (30 mg, 17%, LC-MS 97%, AUC HPLC 99%) as a yellow solid. m.p.: 260–263 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1H), 9.55 (s, 2H), 9.38 (s, 1H), 8.51 (d, J = 7.6 Hz, 2H), 8.42 (s, 2H), 8.36 (s, 1H), 8.29 (s, 1H), 8.16 (d, J = 10.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 3.75 (s, 2H), 2.91 (t, J = 4.0 Hz, 4H), 2.51–2.49 (m, 4H). MS (ESI) *m/z* 582.1 $[C_{30}H_{24}F_3N_9O+H]^+$.

Example 109: N-(4-((6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 3-ethynyl-6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazine

[000486] To a solution of 1*H*-pyrazole (154 mg, 2.26 mmol) in DMF (5 mL) under argon was added NaH (108 mg, 4.52 mmol) in portions wise and the mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C prior to the addition of 6-chloro-3-ethynylimidazo [1, 2-b]pyridazine (400 mg, 2.26 mmol). The reaction mixture was heated at 80 °C for 4 h, was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 80:20) to afford 3-ethynyl-6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazine (120 mg, 25%, LC-MS 85%) $[C_{11}H_7N_5+ H]^+$.

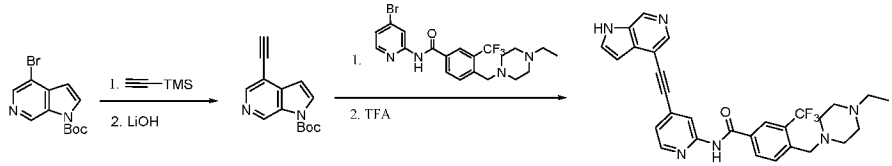
Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000487] The title compound was synthesized following a method similar to general procedure B starting from *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (250 mg, 0.46mmol) and 3-ethynyl-6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazine. The reaction crude product was purified by preparative HPLC to afford *tert*-butyl 4-(4-(4-((6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (100 mg, 31%, AUC HPLC 90%) as a yellow semi solid. MS (ESI) m/z: 670.2 $[C_{34}H_{32}F_3N_9O_3+H]^+$.

Step 3: Preparation of *N*-(4-((6-(1H-pyrazol-1-yl) imidazo [1, 2-b] pyridazin-3-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide

[000488] To a solution of *tert*-butyl 4-(4-(4-((6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (100 mg, 0.148 mmol) in dichloromethane (3 mL) at 0 °C was added TFA (2 mL). The reaction mixture was stirred at room temperature for 2 h, was concentrated under reduce pressure, diluted with EtOAC then washed in turn with a saturated aqueous solution of $NaHCO_3$, water and brine. The organic layer was concentrated to dryness and afforded *N*-(4-((6-(1H-pyrazol-1-yl)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (26 mg, 30%, AUC HPLC 98.0%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1H), 8.74 (d, *J* = 2.4 Hz, 1H), 8.54–8.52 (d, *J* = 5.2 Hz, 2H), 8.44 (t, *J* = 3.6 Hz 1H), 8.37–8.30 (m, 3H), 8.04 (d, *J* = 10.4 Hz, 1H), 8.0 (s, 1H), 7.95(d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 5.2 Hz, 1H), 6.75 (s, 1H), 3.64 (s, 2H), 2.74–2.70 (m, 4H), 2.38–2.34 (m, 4H). MS (ESI) m/z: 572.4 $[C_{29}H_{24}F_3N_9O+H]^+$.

Example 110: N-(4-((1H-pyrrolo[2,3-c]pyridin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 4-((trimethylsilyl)ethynyl)-1*H*-pyrrolo[2,3-c]pyridine-1-carboxylate

[000489] The title compound was synthesized following a method similar to general procedure A starting from *tert*-butyl 4-bromo-1*H*-pyrrolo[2,3-c]pyridine-1-carboxylate and ethynyltrimethylsilane. The reaction crude product was purified by column chromatography (silica gel, eluent: hexane/ethyl acetate 60:40) to afford *tert*-butyl 4-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (500 mg) as an off-white solid. MS (ESI) *m/z* 259.13 $[C_{17}H_{22}N_2O_2Si+H]^+$.

Step 2: Preparation of *tert*-butyl 4-ethynyl-1*H*-pyrrolo[2,3-c]pyridine-1-carboxylate

[000490] A solution of *tert*-butyl 4-((trimethylsilyl)ethynyl)-1*H*-pyrrolo[2,3-c]pyridine-1-carboxylate (500 mg, 1.59 mmol) and LiOH (80.2 mg, 1.91 mmol) in THF (10 mL) and water (2 mL) was and stirred at room temperature for 2 h and was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with water and brine. The

organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 4-ethynyl-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (300 mg, 78%, LC-MS 98%) as a brown solid; MS (ESI) m/z: 243.2 $[C_{14}H_{14}N_2O_2+H]^+$.

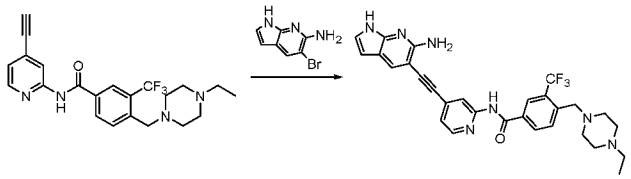
Step 3: Preparation of *tert*-butyl 4-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-1H-pyrrolo[2,3-c]pyridine-1-carboxylate

[000491] The title compound was synthesized following a method similar to general procedure A starting from *tert*-butyl 4-ethynyl-1H-pyrrolo[2,3-c]pyridine-1-carboxylate and *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. The reaction crude product was purified by column chromatography (silica gel eluent: dichloromethane/methanol 95:5) to afford *tert*-butyl 4-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (200 mg) as a brown solid. (ESI) *m/z*: 633.2 $[C_{34}H_{35}F_3N_6O_3+H]^+$.

Step 4: Preparation of *N*-(4-((*1H*-pyrrolo[2,3-c]pyridin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000492] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl 4-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-*1H*-pyrrolo[2,3-c]pyridine-1-carboxylate. The reaction crude product was purified by preparative TLC (dichloromethane/methanol 80:20) to afford *N*-(4-((1H-pyrrolo[2,3-c]pyridin-4-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (50 mg, 34.2%, HPLC AUC 99.1%) as an off-white solid. mp:119–125°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H), 8.70 (s, 1H), 8.61 (d, *J* = 6.0 Hz, 2H), 8.52 (s, 1H),, 8.35(d, *J* = 4.8 Hz, 1H), 8.21 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.02(d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 2.8 Hz, 1H), 7.28 (d, *J* = 9.6 Hz, 1H), 6.84 (s, 1H), 3.74 (s, 2H), 2.59–2.50 (bs, 8H), 2.46 (q, *J* = 7.0 Hz, 2H), 1.10 (t, *J* = 6.8 Hz, 3H). MS (ESI) *m/z*: 533.2 $[C_{29}H_{27}F_3N_6O+ H]^+$.

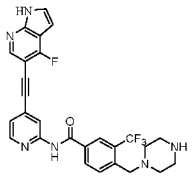
Example 111: N-(4-((6-amino-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step1: preparation of *N*-(4-((6-amino-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000493] The title compound was synthesized following a method similar to general procedure A starting from 5-bromo-1*H*-pyrrolo [2,3-b]pyridin-6-amine (152 mg, 0.721 mmol) and 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide. The reaction crude product was purified by preparative HPLC to afford *N*-(4-((6-amino-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (60 mg, 15.2%, AUC HPLC 93.43 %) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.15 (s, 1H), 11.06 (s, 1H), 8.41 (d, J = 4.8 Hz, 1H), 8.35 (s, 1H), 8.31–8.28 (m, 2H), 7.93–7.91 (m,2H), 7.41 (dd, J = 5.2, 1.2 Hz, 1H), 7.05–7.04 (m, 1H), 6.23–6.22 (m, 1H), 6.06 (bs, 2H), 3.68 (s, 2H), 2.49–2.32 (m, 10H), 0.99 (t, J = 6.8 Hz, 3H). MS (ESI) *m/z*:548.1 $[C_{29}H_{28}F_3N_7O+ H]^+$.

Example 112: N-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 5-((2-(4-((4-(tert-butoxycarbonyl) piperazin-1-yl) methyl)-3-(trifluoromethyl) benzamido) pyridin-4-yl) ethynyl)-4-fluoro-1*H*-pyrrolo [2, 3-b] pyridine-1-carboxylate

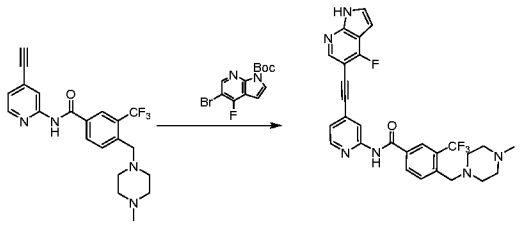
[000494] To a solution of *tert*-butyl 5-bromo-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate (129 mg, 0.409 mmol) in DMF (1 mL) under argon were successively added $PdCl_2$(dppf) (30 mg, 0.040 mmol), CuI (11.7 mg, 0.061 mmol), dppf (11.4 mg, 0.020 mmol), *tert*-butyl 4-(4-(4-ethynylpyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg, 0.409 mmol) and DIPEA (1 mL). The reaction mixture was heated at 100 °C for 16 h and was diluted with water (30 mL). The precipitate was isolated by filtration to afford *tert*-butyl 5-((2-(4-((4-(tert-butoxycarbonyl) piperazin-1-yl) methyl)-3-(trifluoromethyl) benzamido) pyridin-4-yl) ethynyl)-4-fluoro-1*H*-pyrrolo [2, 3-b] pyridine-1-carboxylate (140 mg, LC-MS 86%). The crude product was used in the next step without further purification. MS (ESI) *m/z*: 723 $[C_{37}H_{38}F_4N_6O_5 + H]^+$.

Step 2: Preparation of *N*-(4-((4-fluoro-1H-pyrrolo [2, 3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide

[000495] The title compound was synthesized following a method similar to general procedure B starting from *tert*-butyl 5-((2-(4-((4-(*tert*-butoxycarbonyl) piperazin-1-yl)

methyl)-3-(trifluoromethyl) benzamido) pyridin-4-yl) ethynyl)-4-fluoro-1*H*-pyrrolo [2, 3-b] pyridine-1-carboxylate. The reaction crude product was purified by preparative TLC plate to afford *N*-(4-((4-fluoro-1H- pyrrolo [2, 3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) benzamide (15 mg, HPLC AUC 96%) as an off white solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.42 (s, 1H), 8.40 (s, 1H), 8.39–8.37 (d, *J* = 8.0 Hz, 2H), 8.32–8.30 (d, *J* = 2.0 Hz, 1H), 8.23–8.21 (d, *J* = 8 Hz, 1H), 7.46–7.44 (dd, *J* = 7.6 Hz, 1.5 Hz, 1H), 7.31–7.29 (d, *J* = 6.4 Hz, 1H), 6.64–6.62 (d, *J* = 3.2 Hz, 1H), 3.77 (s, 2H), 2.98–2.95 (m, 4H), 2.60–2.51 (m, 4H): MS (ESI) *m/z*: 523.1 $[C_{27}H_{22}F_4N_6O+H]^+$.

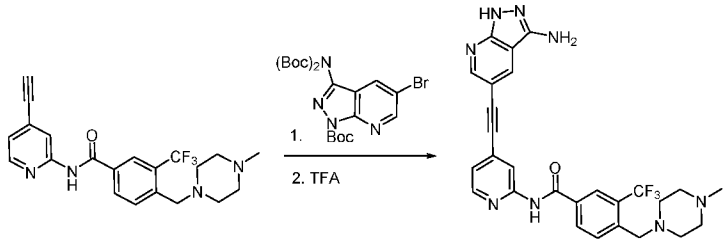
Example 113: N-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(4-((4-fluoro-1*H*-pyrrolo [2, 3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) benzamide

[000496] To a solution of *tert*-butyl 5-bromo-4-fluoro-1*H*-pyrrolo [2, 3-b] pyridine-1-carboxylate (250 mg, 0.7936 mmol) in DMF (2 mL) under argon were successively added $PdCl_2(dppf)_2$ (29 mg, 0.039 mmol), dppf (22 mg, 0.0396 mmol), CuI (22.6 mg, 0.119 mmol), *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl)benzamide (318.3 mg, 0.7936 mmol) and DIPEA (2 mL). The reaction mixture was heated at 100 °C for 15 h and was concentrated under reduced pressure. The residue was diluted with EtOAc and washed in turn with water and brine. The extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford *N*-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (10 mg, 2.1%, AUC HPLC 96.2%) as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.42 (s, 2H), 8.40 (s, 1H), 8.38 (s, 1H), 8.30 (s, 1H), 8.21 (d, *J* = 6.4 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 3.6 Hz, 1H), 6.64 (d, *J* = 3.6 Hz, 1H), 3.77 (s, 2H), 2.56–2.52 (m, 8H), 2.31 (s, 3H); MS (ESI) *m/z*: 537.1 $[C_{28}H_{24}F_4N_6O+H]^+$.

Example 114: N-(4-((3-amino-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



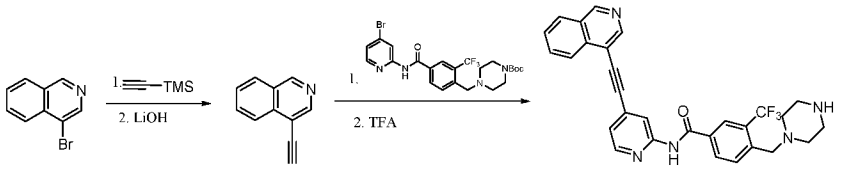
Step 1: Preparation of *tert*-butyl 3-(*tert*-butoxycarbonylamino)-5-((2-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate

[000497] The title compound was synthesized following a method similar to general procedure A starting from *tert*-butyl 3-(bis(*tert*-butoxycarbonyl)amino)-5-bromo-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate and *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. Purification by flash column chromatography (silica gel, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95:4:1) gave a mixture boc protected products (250 mg, LC-MS 28% triBoc, 14% diBoc and 15% monoBoc) as a brown solid.

Step 2: preparation of *N*-(4-((3-amino-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide.

[000498] A solution of the products from step (250 mg, 0.34 mmol) in a mixture of TFA (5.0 mL) and dichloromethane (10 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the crude product was basified with a saturated aqueous solution of $NaHCO_3$ and then extracted with EtOAc. The extracts were washed in turn with water and brine, dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to afford *N*-(4-((3-amino-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (30 mg, 18.6%, AUC HPLC 97.2%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.32 (s, 1H), 11.24 (s, 1H), 8.58 (d, J = 2.4 Hz, 1H), 8.47–8.44 (m, 2H), 8.35–8.33 (m, 2H), 8.29 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 5.2, 1.2 Hz, 1H), 5.77 (s, 2H), 3.68 (s, 2H), 2.43–2.32 (m, 8H), 2.18 (s, 3H); MS (ESI) *m/z*: 535.41 $[C_{27}H_{25}F_3N_8O+H]^+$.

Example 115: N-(4-(isoquinolin-4-ylethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 4-((trimethylsilyl)ethynyl)isoquinoline

[000499] To a solution of 4-bromoisoquinoline (2 g, 9.7 mmol) and ethynyltrimethylsilane (2.0 mL, 14.56 mmol) in THF (30 mL) under Argon were successively added $PdCl_2(PPh_3)_2$ (340 mg, 0.485 mmol), CuI (276 mg, 1.45 mmol) and DIPEA (2.5 mL, 14.55 mmol) and the mixture was heated to 80 °C for 10 h. The reaction mixture was concentrated under reduced pressure and then purified by column chromatography (silica gel eluent petroleum ether/ethyl acetate 80:20) to afford 4-((trimethylsilyl)ethynyl)isoquinoline (1.8 g, 85%) as an off-white solid. (ESI) *m/z*:226.10 $[C_{14}H_{15}NSi + H]^+$.

Step 2: Preparation of 4-ethynylisoquinoline

[000500] To a solution of 4-((trimethylsilyl)ethynyl)isoquinoline (1.8 g, 7.99 mmol) in a mixture of THF (10 mL) and water (2 mL) was added LiOH (0.403 g, 9.59 mmol) and the mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with EtOAc and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-ethynylisoquinoline (1 g, 83%, LCMS-98%) as a brown color solid. ^{1}H NMR(400 MHz, $CdCl_3$) δ: 9.22 (s, 1H), 8.74 (s, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.62–7.60 (m, 1H), 7.31-7.24 (m, 1H), 3.55 (s, 1H); (ESI) *m/z*:154.01 $[C_{11}H_7N+H]^+$.

Step 3: Preparation of *tert*-butyl 4-(4-(4-(isoquinolin-4-ylethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

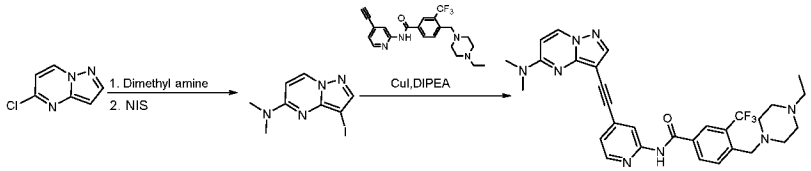
[000501] To a solution of 4-ethynylisoquinoline (127 mg, 0.83 mmol) in DMF (10 mL) under argon was successively added *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg, 0.55 mmol), $PdCl_2(PPh_3)_2$ (19 mg, 0.027 mmol), CuI (15.6 mg, 0.08 mmol) and DIPEA (0.141 mL, 0.825 mmol). The mixture was heated at 90 °C for 6 h and was poured in cold water. The precipitate was isolated by filtration and was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) to give *tert*-butyl 4-(4-(4-(isoquinolin-4-ylethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (150 mg, 16%, LC-MS 96.8%) as a yellow solid. ^{1}H NMR(400 MHz, $CDCl_3$) δ (ppm): 9.30 (bs, 1H), 8.83 (bs, 1H), 8.64 (d, *J* = 5.6 Hz, 2H), 8.38 (d, *J* = 4.8 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 8.05 (d, *J* = 7.6 Hz, 2H),

7.73 (t, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 5.2 Hz, 2H), 3.74 (s, 2H), 3.48–3.44 (m, 4H), 2.48–2.44.(m, 4H), 1.10 (9H, s); (ESI) *m/z*: 614.1 $[C_{34}H_{32}F_3N_5O_3\text{-}H]^+$.

Step 3: Preparation of *N*-(4-(isoquinolin-4-ylethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000502] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl 4-(4-(4-(isoquinolin-4-ylethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford *N*-(4-(isoquinolin-4-ylethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (40 mg, 41%, HPLC AUC 99.5%) as an off-white solid. m.p-197-201°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.27 (s, 1H), 8.83 (s, 1H), 8.66 (d, *J* = 5.6 Hz, 2H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 2H), 8.22 (s,1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.88 (t, *J* = 7.2 Hz, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 5.6 Hz, 1H) 3.72 (s, 2H), 2.93 (t, *J* = 5.2 Hz, 4H), 2.48 (s, 4H); MS (ESI) *m/z* 516.3 $[C_{29}H_{24}F_3N_5O\text{+}H]^+$.

Example 116: N-(4-((5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *N, N*-dimethylpyrazolo[1,5-*a*]pyrimidin-5-amine

[000503] A solution of 5-chloropyrazolo[1,5-*a*]pyrimidine (1 g, 6.536 mmol) in dimethyl amine (15 mL) was heated in a sealed tube at 60 °C for 4 h. The reaction mixture was concentrated and the precipitate was isolated by filtration and washed with n-pentane to afford *N,N*-dimethylpyrazolo[1,5-*a*]pyrimidin-5-amine (1 g, 95%). MS (ESI) *m/z* 163.0 $[C_8H_{10}N_4\text{+}H]^+$.

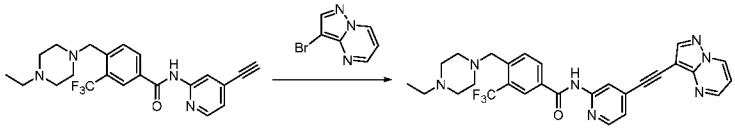
[000504] Step 2: Preparation of 3-iodo-*N,N*-dimethylpyrazolo[1,5-*a*]pyrimidin-5-amine; A solution of *N,N*-dimethylpyrazolo[1,5-*a*]pyrimidin-5-amine (1 g, 6.172 mmol) and NIS (2.5 g, 11.11 mmol) in DMF (3 mL) was stirred for 3 h at room temperature. The reaction mixture was poured into ice-cold water and extracted into ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The solid was washed with n-pentane to afford 3-iodo-*N,N*-dimethylpyrazolo[1,5-

a]pyrimidin-5-amine (1.68 g, 94 %) as a pale brown solid. MS (ESI) *m/z* 289.02 [$C_8H_9IN_4$+ H]$^+$.

Step 3: Preparation of *N*-(4-((5-(dimethylamino)pyrazolo[1,5-*a*]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

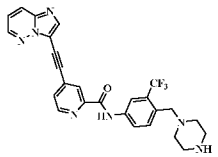
[000505] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide 3-iodo-*N,N*-dimethylpyrazolo[1,5-*a*]pyrimidin-5-amine following a method similar to general procedure A. The crude product was purified by preparative HPLC to afford *N*-(4-((5-(dimethylamino)pyrazolo[1,5-*a*]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (20 mg, AUC HPLC 95%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.16 (s, 1H), 8.68 (d, *J* = 8.0 Hz, 1H), 8.38 (d, *J*= 5.2 Hz, 1H), 8.33 (s, 1H), 8.30 (d, *J*= 4.8 Hz, 1H), 8.27 (s, 1H), 8.23 (s, 1H), 8.17 (s,1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.70 (d, *J* = 7.6 Hz 1H), 3.68 (s, 2H), 3.21 (s, 6H), 2.45–2.43 (m, 8H), 2.32 (q, 2H), 0.98 (t, *J* = 7.0 Hz, 3H). MS (ESI) *m/z* 577.36 [$C_{30}H_{31}F_3N_8O$ + H]$^+$.

Example 117: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-(pyrazolo[1,5-a]pyrimidin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



[000506] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 3-bromopyrazolo[1,5-*a*]pyrimidine following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 0-20%) and by preparative HPLC (CH_3CN/H_2O/0.1% formic acid) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-(pyrazolo[1,5-*a*]pyrimidin-3-ylethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (3.4 mg, AUC HPLC 98.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.24 (s, 1H), 9.26 (dd, 1H, *J* = 1.6, 7.2 Hz), 8.75 (dd, *J* = 1.6, 4.2 Hz, 1H), 8.62 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 8.35 (s, 1H), 8.32 (s, 1H), 8.30–3.28 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.29–7.25 (m, 2H), 3.68 (s, 2H), 2.43–2.29 (m, 10H), 0.98 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 534.2 [$C_{28}H_{26}F_3N_7O$+H]+

Example 118: 4-(imidazo[1,2-b]pyridazin-3-ylethynyl)-N-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)picolinamide



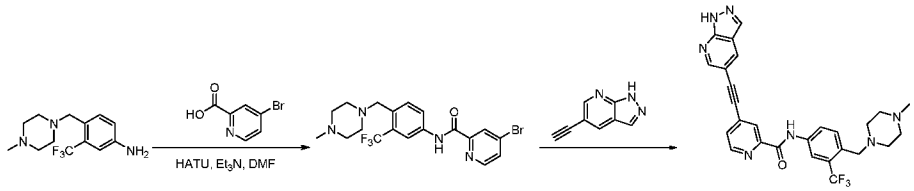
Step 1: Preparation of *tert*-butyl 4-(4-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)picolinamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000507] The title compound was synthesized following a method similar to general procedure B starting from *tert*-butyl 4-(4-(4-bromopicolinamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynylimidazo[1,2-b]pyridazine. The reaction crude product was purified by flash column chromatography (silica gel, eluent dichloromethane/MeOH 90:10) to afford *tert*-butyl 4-(4-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)picolinamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg) as an off-white solid.

Step 2: Preparation of 4-(imidazo[1,2-b]pyridazin-3-ylethynyl)-*N*-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)picolinamide

[000508] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl 4-(4-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)picolinamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by preparative HPLC to afford 4-(imidazo[1,2-b]pyridazin-3-ylethynyl)-*N*-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)picolinamide (25 mg, AUC HPLC 97.5%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.07 (s, 1H), 8.64 (d, *J* = 5.8 Hz, 1H), 8.53 (d, *J* = 2.8 Hz, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 8.06–7.99 (m, 3H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 4.8 Hz, 1H), 7.21 (q, *J* = 4.4 Hz, 1H), 3.63 (s, 2H), 2.92 (t, *J* = 4.4 Hz, 4H), 2.46 (bs, 4H). MS (ESI) m/z: 548.29 $[C_{26}H_{22}F_3N_7O + H]^+$.

Example 119: 4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide

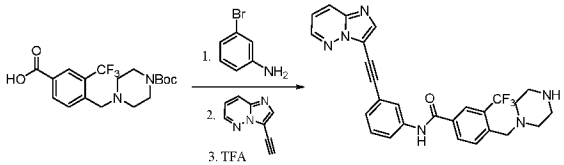


[000509] Step 1: Synthesis of 4-bromo-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide; To 4-bromopicolinic acid (74 mg, 0.36 mmol) in anhydrous DMF (2 mL) was treated HATU (278 mg, 0.78 mmol) and the mixture was stirred

at room temperature for 30 minutes. A solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (100 mg, 0.36 mmol) and triethylamine (74 mg, 0.73 mmol) in anhydrous DMF (1 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was then partitioned between H_2O (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuum. The residue was purified by flash chromatography (silica gel, eluent 19:1 DCM/MeOH) to afford 4-bromo-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide (131 mg, 78%, AUC HPLC) as brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.04 (s, 1H), 8.64 (d, J = 5.2 Hz, 1H), 8.38 (d, J = 1.7 Hz, 1H), 8.30 (d, J = 1.7 Hz, 1H), 8.37 (dd, J = 1.5 and 8.5 Hz, 1H), 8.00–7.99 (m, 1H), 7.71 (d, J = 8.5 Hz, 1H), 3.64 (s, 2H), 2.93 (s, 3H), 2.69 (s, 8H); MS (ESI) *m/z* 458 $[C_{19}H_{20}BrF_3N_4O+H]^+$

[000510] Step 2: Synthesis of 4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide; The title compound was synthesized from 4-bromo-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide and 5-ethynyl-1*H*-pyrazolo[3,4-*b*]pyridine following a method similar to general procedure A. The residue was purified by preparative HPLC (C18, acetonitrile/water/0.1% formic acid) to afford 4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide (6.5 mg, AUC HPLC 98.9%) as yellow amorphous solid. mp: 90.6–91.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 14.00 (bs, 1H), 11.02 (s, 1H), 8.82–8.79 (m, 2H), 8.62 (s, 1H), 8.39 (s, 1H), 8.26 (d, J = 2.6 Hz, 2H), 8.17 (d, J = 8.3 Hz, 1H), 7.85 (dd, J = 5.0; 1.4 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 3.57 (s, 2H), 2.39–2.32 (m, 8H), 2.17 (s, 3H); MS (ESI) *m/z* 520 $[C_{27}H_{24}F_3N_7O+H]^+$;

Example 120: N-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenyl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 4-(4-(3-bromophenylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000511] To a solution of 4-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)benzoic acid (1.4 g, 3.60 mmol) in DMF (25 mL) were successively added HATU (2.05 g, 5.41mmol), 3-bromoaniline (743 mg, 4.32 mmol) and DIPEA (0.92 mL, 5.41 mmol). The resultant reaction mixture was stirred at room temperature under inert atmosphere for 16 h. The reaction mixture was diluted with EtOAc (75 mL) and washed with water (15 mL) and brine. The organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: ethyl acetate/petroleum ether 50:50) to afford *tert*-butyl 4-(4-(3-bromophenylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (900 mg)

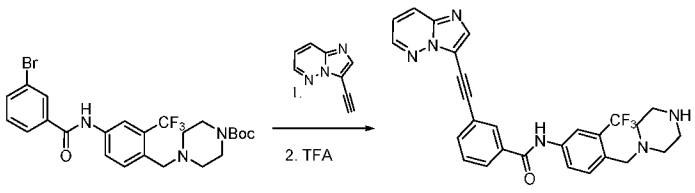
Step 2: Preparation of *tert*-butyl 4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

[000512] The title compound was synthesized following a method similar to general procedure B starting from 3-ethynylimidazo[1,2-b]pyridazine (126.6 mg, 0.88 mmol) in acetonitrile (10 mL) and *tert*-butyl 4-(4-(3-bromophenylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 97:3) to afford *tert*-butyl 4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg). MS (ESI) *m/z* 605.2 $[C_{32}H_{31}F_3N_6O_3 + H]^+$.

Step 3: Preparation of *N*-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenyl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide.

[000513] The title compound was synthesized following a method similar to general procedure D starting from *tert*-butyl 4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to give *N*-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenyl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (45 mg, 30%, AUC HPLC 95.9%) as a yellow solid. m.p 115–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.49 (s, 1H), 8.14 (s, 1H), 8.05 (s, 1H), 8.02–7.99 (m, 6H), 7.73 (d, J = 8.0 Hz, 1H), 7.45–7.39 (m, 2H), 7.14 (q, J = 4.4 Hz, 1H), 3.70 (s, 2H), 2.93 (t, J = 4.4 Hz, 4H), 2.47 (bs, 4H); MS (ESI) *m/z* 503.3 $[C_{27}H_{23}F_3N_6O+H]^+$.

Example 121: 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-N-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)benzamide



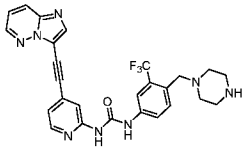
Preparation of *tert*-butyl 4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)benzamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000514] The title compound was synthesized following a method similar to general procedure B starting from *tert*-butyl 4-(4-(3-bromobenzamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynylimidazo[1,2-b]pyridazine. The reaction crude product was purified by column chromatography to afford 4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)benzamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg) as a white solid.

Step 2: Preparation of 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-*N*-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)benzamide

[000515] To a solution of 4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)benzamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg, 0.33 mmol) in dichloromethane (10 mL) was added TFA (5 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-*N*-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)benzamide (20 mg, AUC HPLC 92.5%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.64 (d, *J* = 2.8 Hz, 1H), 8.20 (s, 1H), 8.15 (s, 1H) 8.11 (d, *J* = 9.2 Hz, 1H), 8.07 (s, 1H), 8.00 (t, *J* = 9.2 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 4.4 Hz, 1H), 3.75 (s, 2H), 3.28–3.24 (m, 4H), 2.78–2.74 (m, 4H). MS (ESI) m/z: 548.29 $[C_{27}H_{23}F_3N_6O + H]^+$.

Example 122: 1-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea

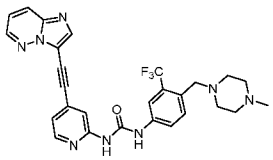


[000516] Step 1: Preparation of *tert*-butyl 4-(4-(3-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from 3-ethynylimidazo[1,2-*b*]pyridazine and *tert*-butyl 4-(4-(3-

(4-bromopyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate following a method similar to general procedure A. The crude product was purified by flash chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 95:5) to afford *tert*-butyl 4-(4-(3-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as a brown solid (150 mg).

[000517] Step 2: Preparation of 1-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea; The title compound was synthesized from *tert*-butyl-4-(4-(3-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar method as described in general procedure D.. The crude product was purified by column chromatography (silica gel, eluent $CHCl_3$/MeOH 95:5) of 1-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (90 mg, 75%, AUC HPLC 93.3%) as a brick-red solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.82 (s, 1H), 9.94 (s, 1H), 8.77 (dd, J = 1.2 Hz, 1H), 8.35–8.26 (m, 3H), 8.04 (s, 1H), 7.94 (s, 1H), 7.67 (d, J = 9.2 Hz, 2H), 7.45 (dd, J = 5.6 Hz, 1H), 7.17 (d, J = 6.8 Hz, 1H), 3.52 (bs, 2H), 3.33 (bs, 2H), 2.73–2.69 (m, 2H), 2.27 (bs, 4H); MS (ESI) *m/z* 521.2 $[C_{26}H_{23}F_3N_8O+H]^+$.

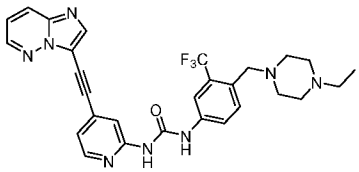
Example 123: 1-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000518] The title compound was synthesized from 3-ethynylimidazo[1,2-*b*]pyridazine and 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by flash chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 95:5) to afford 1-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (100 mg, 90%, AUC HPLC 98.5%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.86 (s, 1H), 8.52 (dd, J = 1.6 Hz, 2H), 8.12 (s, 1H), 8.05 (d, J = 10.0 Hz, 2H),7.82 (d, J = 7.6 Hz, 2H), 7.64–7.60 (m, 1H),7.40 (s, 1H),

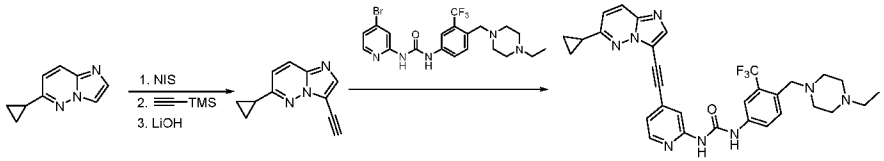
7.22–7.15 (m, 2H), 6.96 (s, 1H), 3.68 (s, 2H), 2.72 (bs, 8H), 2.52 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 535.25 $[C_{27}H_{25}F_3N_8O+H]^+$.

Example 124: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)urea



[000519] The title compound was synthesized from 3-ethynylimidazo[1,2-*b*]pyridazine and 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by flash chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 95:5) to afford 100 mg of material, which was further purified by preparative TLC to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)urea (50 mg, 46%, AUC HPLC 96.0%) as a pale yellow solid; m.p. 221-223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.45 (s, 1H), 9.65 (s, 1H), 8.75 (d, J = 1.6 Hz, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.30–8.27 (m, 2H), 8.03 (s, 1H), 7.86 (s, 1H), 7.69 (t, J = 12.8 Hz, 2H), 7.45 (dd, J = 4.4 Hz, 1H), 7.20–7.18 (m, 1H), 3.64 (s, 2H), 3.45–3.34 (m, 2H), 3.19–2.8 (m, 6H), 2 .46 (s, 2H), 1.23–1.22 (m, 3H); MS (ESI) *m/z* 549.5 $[C_{28}H_{27}F_3N_8O+H]^+$.

Example 125: 1-(4-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of 6-cyclopropyl-3-iodoimidazo[1,2-b]pyridazine

[000520] A solution of 6-cyclopropylimidazo[1,2-b]pyridazine (1.4 g, 8.8 mmol) and NIS (2.36 g, 10.5 mmol) in DMF (20 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with water (50 mL) and was filtered. The organic phasewas washed with water and dried to afford 6-cyclopropyl-3-iodoimidazo[1,2-*b*]pyridazine (2.1 g, 84%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.84 (d, J = 9.2 Hz, 1H), 7.70 (s, 1H),

6.99 (d, J = 9.6 Hz, 1H), 2.19 (q, J = 6.4 Hz, 1H), 1.09 (t, J = 7.2 Hz, 4H); MS (ESI) *m/z*: 286.1 $[C_9H_8IN_3+H]^+$.

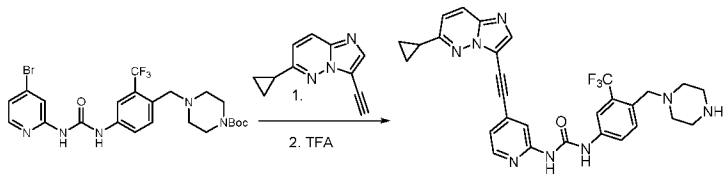
Step 2: Preparation of 6-cyclopropyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazine

[000521] The title compound was synthesized from 6-cyclopropyl-3-iodoimidazo[1,2-*b*]pyridazine and ethynyltrimethylsilane following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel; heptane/ethyl acetate 100/0 to 50/50) to afford 6-cyclopropyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazine (1.3 g, 73%) as a brown solid. ^{1}H NMR(400 MHz, $CDCl_3$) δ (ppm): 8.01 (d, J = 9.2 Hz, 1H),7.95 (s, 1H), 6.89 (d, J = 9.2 Hz, 1H), 2.17 (d, J =7.2 Hz, 1H), 1.09 (t, J = 7.2 Hz, 4H), 0.31 (s, 9H); MS (ESI) *m/z* 256.59 $[C_{14}H_{17}N_3Si+H]^+$.

[000522] Step 3: Preparation of 6-cyclopropyl-3-ethynylimidazo[1,2-*b*]pyridazine; an heterogneous solution of 6-cyclopropyl-3-((trimethylsilyl)ethynyl)imidazo[1,2-*b*]pyridazine (1.3 g, 5.09 mmol) and LiOH (256 g, 6.11 mmol) in THF (20 mL) and water (5 mL) was stirred at room temperature and stirred for 2 h and was concentrated under reduced pressure. The residue was diluted with water and the resulting solution was extracted with ethyl acetate (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 6-cyclopropyl-3-ethynylimidazo[1,2-*b*]pyridazine (500 mg, 50%) as an off-white solid.

[000523] Step 4: Preparation of 1-(4-((6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea; The title compound was synthesized from 6-cyclopropyl-3-ethynylimidazo[1,2-*b*]pyridazine and Intermediate 22 following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford 1-(4-((6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (40 mg, 16%, AUC HPLC 96.08%) as a brown solid; m.p. 221–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.81 (s, 1H), 8.30 (d, J = 5.2 Hz, 1H), 8.00 (s, 1 H), 7.87–7.84 (m, 2H), 7.78 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.12 (t, J = 1.2 Hz, 1H), 6.99–6.93 (m, 2H), 3.62 (s, 2H), 2.52–2.39 (m, 10H), 2.21 (q, J = 7.2 Hz, 1H), 1.16 (t, J = 3.2 Hz, 4H), 1.09 (t, J = 7.2 Hz, 4H); MS (ESI) *m/z* 589.6 $[C_{31}H_{31}F_3N_8O+H]^+$.

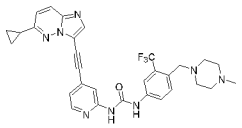
Example 126: 1-(4-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea



[000524] Step 1: Preparation of *tert*-butyl 4-(4-(3-(4-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from 6-cyclopropyl-3-ethynylimidazo[1,2-b]pyridazine and Intermediate 18 following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent: ethyl acetate/petroleum ether 70:30) to afford (174 mg) *tert*-butyl 4-(4-(3-(4-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

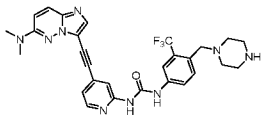
[000525] Step 2: Preparation of 1-(4-((6-cyclopropylimidazo [1, 2-*b*] pyridazin-3-yl) ethynyl) pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) phenyl)urea; The title compound was synthesized from *tert*-butyl 4-(4-(3-(4-((6-cyclopropylimidazo [1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar procedure as described in general procedure D. *tert*-butyl 4-(4-(3-(4-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (150 mg, 0.22 mmol) and TFA (2 mL) in DCM (10 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with water and basified with $NaHCO_3$. The aqueous pase was extracted with $CHCl_3$.The extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain 1-(4-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (40 mg, 16%, AUC HPLC 96.1%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (bs, 1H), 9.59 (s, 1H), 8.36 (d, J = 4.8 Hz ,1H), 8.17 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.04 (brs, 2H), 7.78 (s, 1H), 7.67–7.65 (m, 2H), 7.25 (d, J = 9.6 Hz, 1H), 7.16 (d, J = 4.8 Hz, 1H), 1.14–1.16 (m, 4H), 2.36–2.40 (m, 5H), 2.84 (bs, 4H), 3.55 (brs, 2H); MS (ESI) *m/z* 560.23 $[C_{29}H_{27}F_3N_8O+H]^+$.

Example 127: Synthesis of 1-(4-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000526] The title compound was synthesized from 6-cyclopropyl-3-ethynylimidazo[1,2-*b*]pyridazine and Intermediate 20 following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford 1-(4-((6-cyclopropylimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (12 mg, 57%, AUC HPLC 98.1%) as a off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.34 (s, 1H), 9.59 (s, 1H), 8.36 (d, J = 4.8 Hz 1H), 8.17 (s, 1H), 8.11 (d, J = 9.6 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 7.78 (s, 1H), 7.68–7.61 (m, 2H), 7.25 (d, J = 9.2 Hz ,1H), 7.16 (d, J = 5.2 Hz, 1H), 3.54 (s, 2H), 2.38-2.27 (m, 9H), 2.16 (s, 3H), 1.16–1.07 (m, 4H); MS (ESI) *m/z* 575.24 $[C_{30}H_{29}F_3N_8O+H]^+$.

Example 128: Synthesis of 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea

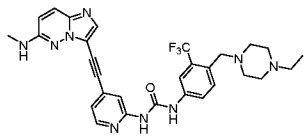


[000527] Step 1: Preparation of *tert*-butyl 4-(4-(3-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized starting from 3-ethynyl-*N*,*N*-dimethylimidazo[1,2-*b*]pyridazin-6-amine and Intermediate 18 following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 95:5) to afford *tert*-butyl-4-(4-(3-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (200 mg) as a brown solid.

[000528] Step 2: Preparation of 1-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea; The title compound was synthesized from *tert*-butyl 4-(4-(3-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate in a similar procedure as described in general procedure D. The crude product was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH/NH_4OH$ 95:4:1) to afford 1-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-

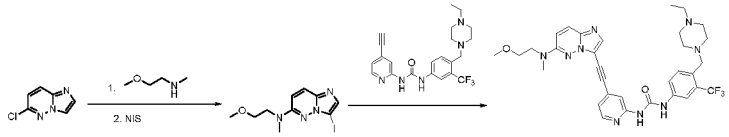
yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (110 mg, 68%, AUC HPLC 95.7%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.46 (s, 1H), 9.62 (s, 1H), 8.33 (d, J = 6.8 Hz, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.90 (s, 1H), 7.75 (s, 1H), 7.70–7.65 (m, 2H), 7.20 (d, J = 13.6 Hz, 1H), 7.12 (dd, J = 6.8 Hz, 1H), 3.56 (bs, 2H), 3.15 (s, 6H), 2.86 (s, 4H), 2.42 (s, 4H); MS (ESI) *m/z* 564.29 $[C_{28}H_{28}F_3N_9O+H]^+$.

Example 129: Synthesis of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea



[000529] The title compound was prepared following generale produre B and starting from Intermediate 22 and 3-ethynyl-*N*-methylimidazo[1,2-b]pyridazin-6-amine. The reaction crude product was purified by preparative TLC (dichloromethane/MeOH 80:20) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea (45 mg, 19.5%, AUC HPLC 98.6%) as an off white solid. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 10.40 (s, 1H), 9.50 (s, 1H), 8.33 (d, J = 5.2 Hz, 1H), 8.04 (s, 1H), 7.85 (s, 1H), 7.77 (d, J = 10.0 Hz, 2H) 7.68–7.65 (m, 2H), 7.17 (d, J = 4.4 Hz, 1H), 7.13 (d, J = 4.4 Hz, 1H), 6.77 (d, J = 9.60 Hz, 1H), 3.55 (s, 2H), 2.90 (d, J = 4.80 Hz, 3H), 2.40 (bs, 10H), 1.00 (s, 3H); MS (ESI) *m/z*: 578.42 $[C_{29}H_{30}F_3N_9O + H]^+$.

Example 130: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea

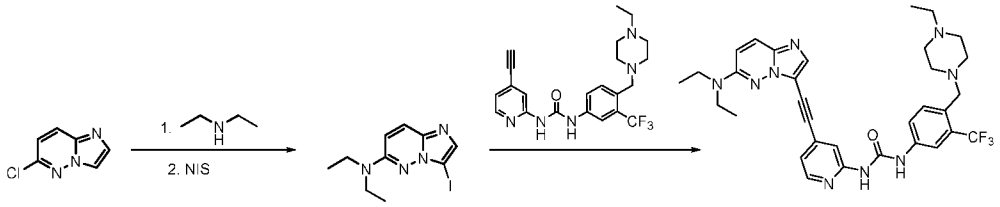


[000530] Step 1: Preparation of *N*-(2-methoxyethyl)-*N*-methylimidazo[1,2-*b*]pyridazin-6-amine; A solution of 6-chloroimidazo[1,2-*b*]pyridazine (300 mg, 1.95 mmol) in NMP (3.00 mL) was added 2-methoxy-*N*-methylethanamine (830 mg, 9.05 mmol). The reaction mixture was heated in a microwave reactor at 150 °C for 60 min then was diluted with ACN (30.0 mL) and acidified with TFA prior to the addition of 1-iodopyrrolidine-2,5-dione (440 mg, 1.95 mmol) and the resultingmixture was further stirred for 3 h. The reaction mixture was purified by flash column chromatography (silica gel, eluents Hex/EtOAc 95:5) to afford 3-

iodo-*N*-(2-methoxyethyl)-*N*-methylimidazo[1,2-*b*]pyridazin-6-amine (211 mg, 32.5%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 9.9 Hz, 1H), 7.56 (s, 1H), 6.77 (d, *J* = 9.9 Hz, 1H), 3.71 (t, *J* = 5.1 Hz, 1H), 3.65 (t, *J* = 5.1 Hz, 1H), 3.37 (s, 3H), 3.17 (s, 1H); MS (ESI) *m/z* 333 $[C_{10}H_{13}IN_4O+ H]^+$.

[000531] Step 2: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea; The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 3-iodo-*N*-(2-methoxyethyl)-*N*-methylimidazo[1,2-*b*]pyridazin-6-amine following a method similar to general procedure A. The crude reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-((2-methoxyethyl)(methyl)amino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea (24 mg, 32%, AUC HPLC 97.9 %) as brown solid; m.p. 93–95 °C; ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.31 (d, *J* = 5.2 Hz, 1H), 7.99 (d, *J* = 1.28 Hz, 1H), 7.89–7.62 (m, 4H), 7.46 (s, 1H), 7.19 (d, *J* = 9.9 Hz, 1H), 7.11 (d, *J* = 4.7 Hz, 1H), 3.82 (t, *J* = 5.3 Hz, 2H), 3.72 (t, *J* = 5.3 Hz, 2H), 3.65 (s, 2H), 3.37 (s, 3H), 3.23 (s, 3H), 2.80–2.30 (m, 10H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ (ppm): 154.95, 152.94, 146.52, 138.24, 135.41, 133.27, 131.42, 130.35, 129.04, 128.74, 128.43, 125.71, 124.33, 123.00, 122.38, 118.46, 116.51, 116.45, 112.83, 111.70, 95.35, 81.43, 69.83, 57.85, 57.03, 54.41, 51.60, 50.22, 50.00, 46.96, 42.35, 36.35, 11.70, 8.66; MS (ESI) *m/z* 636.70 $[C_{32}H_{36}F_3N_9O_2+H]^+$.

Example 131: 1-(4-((6-(diethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of *N*,*N*-diethyl-3-iodoimidazo[1,2-*b*]pyridazin-6-amine

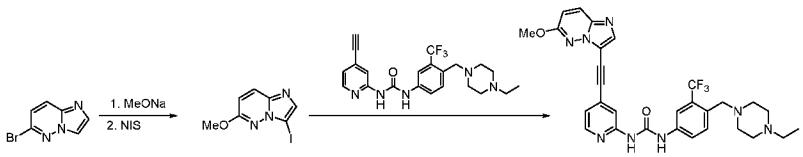
[000532] A solution of 6-chloroimidazo[1,2-*b*]pyridazine (300 mg, 1.95 mmol) and diethylamine (707 mg, 4.95 mmol) in NMP (3.00 mL) was heated at 150°C for 60 min in a microwave reactor. The reaction mixture was diluted with ACN (30.0 mL) and acidified with TFA before adding 1-iodopyrrolidine-2,5-dione (440 mg, 1.95 mmol). The reaction mixture

was stirred for 3 h and was purified by flash column chromatography (silica gel, eluents hexanes/EtOAc 3:7) to afford *N,N*-diethyl-3-iodoimidazo[1,2-*b*]pyridazin-6-amine (309 mg, 50 %) as an yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 (d, *J* = 9.9 Hz, 1H), 7.66 (s, 1H), 6.82 (d, *J* = 9.6 Hz, 1H), 3.57 (q, *J* = 7.1 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 1H); MS (ESI) *m/z* 317 $[C_{10}H_{13}IN_4 + H]^+$.

Step 2: Preparation of 1-(4-((6-(diethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000533] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and *N,N*-diethyl-3-iodoimidazo[1,2-*b*]pyridazin-6-amine following a method similar to general procedure A. The crude reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((6-(diethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (9.5 mg, 13%, AUC HPLC 97.1 %) as brown solid; mp 110–112 °C; ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.31 (d, *J* = 5.2 Hz, 1H), 8.01 (d, *J* = 1.7 Hz, 1H), 7.85–7.62 (m, 4H), 7.47 (s, 1H), 7.20-7.00 (m, 2H), 3.75–3.60 (m, 6H), 2.90–2.40 (m, 10H), 1.31 (t, *J* = 7.0 Hz, 6H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ (ppm): 153.78, 153.05, 146.63, 138.39, 131.43, 130.81, 129.06, 128.76, 125.73, 124.57, 123.02, 122.42, 118.49, 116.55, 116.50, 112.87, 111.56, 95.20, 57.24, 54.41, 51.76, 51.11, 11.86, 11.74, 9.36; MS (ESI) *m/z* 620.70 $[C_{32}H_{36}F_3N_9O_2+H]^+$.

Example 132: Preparation 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea



Step 1: Preparation of 6-methoxyimidazo[1,2-*b*]pyridazine

[000534] A solution of 6-bromoimidazo[1,2-*b*]pyridazine (198 mg, 1.00 mmol) in methanol (2 mL) and sodium methoxide (108 mg, 2.00 mmol) was heated at 100 °C for 1 hr in a microwave reactor and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent; hexane/ethyl acetate 5:1) to afford 6-methoxyimidazo[1,2-*b*]pyridazine (100 mg, 67%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (pm) 7.77 (d, *J* = 9.6 Hz, 1H), 7.74 (s, 1H), 7.60 (d, *J* = 1.0 Hz, 1H), 6.67 (d, *J* = 9.6 Hz, 1H), 3.98 (s, 3H); MS (ESI) *m/z* 150 $[C_7H_7N_3O + H]^+$.

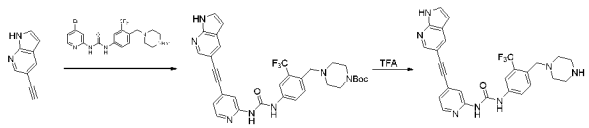
Step 2: Preparation of 3-iodo-6-methoxyimidazo[1,2-*b*]pyridazine

[000535] A solution of 6-methoxyimidazo[1,2-*b*]pyridazine (100 mg, 0.67 mmol) and *N*-iodosuccinimide (302 mg, 1.34 mmol) in acetonitrile (8 mL) was stirred at room temperature for 8 h and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent hexane/ethyl acetate 5:1) to afford 3-iodo-6-methoxyimidazo[1,2-*b*]pyridazine (140 mg, 76%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.89 (d, J = 9.6 Hz, 1H), 7.64 (s, 1H), 6.84 (d, J = 9.6 Hz, 1H), 4.09 (s, 3H); MS (ESI) *m/z* 276 $[C_7H_6IN_3O + H]^+$.

Step 3: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea

[000536] The title compound was synthesized following a method similar to general procedure B starting from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 3-iodo-6-methoxyimidazo[1,2-*b*]pyridazine. The reaction crude product was purified by flash column chromatography (silica gel, DCM/methanol 10:1) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)urea (12 mg, 17%, AUC HPLC 98%) as yellow solid; m.p. 204.8–206.0 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.30 (s, 1H), 8.02–7.84 (m, 3H), 7.73–7.65 (m, 2H), 7.44 (s, 1H), 7.12 (s, 1H), 6.98 (d, J = 8.8 Hz, 1H), 4.13 (s, 3H), 3.72 (s, 2H), 3.27 (bs, 4H), 3.16 (q, J = 7.0 Hz, 2H), 2.74 (bs, 4H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d4) δ (ppm): 162.68, 154.52, 148.15, 139.77, 138.09, 134.35, 132.96, 131.66, 130.43, 128.25, 125.79, 123.95, 120.06, 118.06, 115.77, 114.56, 97.13, 91.87, 81.78, 58.34, 55.65, 53.05, 52.92, 51.19, 9.72; MS (ESI) m/z 580 $[C_{29}H_{29}F_3N_8O_2 + H]+$.

Example 133: 1-(4-((1H-pyrrolo [2,3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl) phenyl) urea



Step 1: Preparation of di-*tert*-butyl 6-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-1,3(2*H*)-dicarboxylate

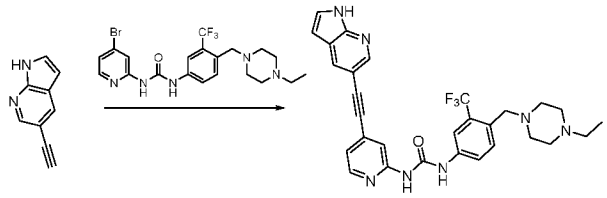
[000537] The title compound was synthesized from 5-ethynyl-1*H*-pyrrolo [2,3-*b*] and *tert*-butyl 4-(4-(3-(4-bromopyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-

carboxylate following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent: dichloromethane/methanol 10:1) to afford di-*tert*-butyl 6-((2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-1,3(2*H*)-dicarboxylate (150 mg, 53%) as an off-white color solid. MS (ESI) *m/z* 621 $[C_{32}H_{32}F_3N_7O_3+H]^+$.

Step 2: Preparation of 1-(4-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea

[000538] The title compound was synthesized starting from di-*tert*-butyl6-((2-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoro methyl) benzamido) pyridin-4-yl) ethynyl)-2-oxo-1*H*-imidazo [4,5-*b*]pyridine-1,3(2*H*)-dicarboxylate in a similar method as described in general procedure D. After completion, reaction mixture was concentrated under reduce pressure, basified with saturated aqueous solution of $NaHCO_3$ resulted solid was separated, filtered and dried to afford 1-(4-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (70 mg, 56%, AUC HPLC 95.3%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.978 (s, 1H), 10.339 (s, 1H), 9.55 (s, 1H), 8.45 (d, *J* = 2 Hz, 1H), 8.33 (d, *J* = 5.6 Hz, 1H), 8.26 (d, *J* = 2 Hz, 1H), 8.03 (s, 1H), 7.75 (s, 1H),7.68 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H),7.59 (d, *J* = 8.8 Hz, 2H), 7.17 (dd, *J* = 1.2, 4 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H), 3.51 (s, 2H), 2.69 (m, 4H), 2.30 (m, 4H); MS (ESI) *m/z* 520 $[C_{27}H_{24}F_3N_7O+H]^+$.

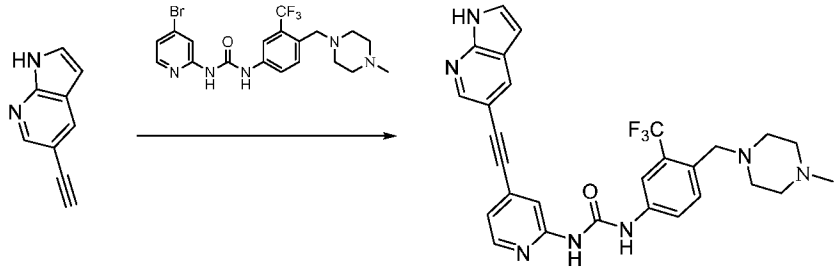
Example 134: 1-(4-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl



[000539] The title compound was prepared from 5-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine and 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by flash chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford 1-(4-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (80 mg, 21%, AUC HPLC 96.2%) as an off-white

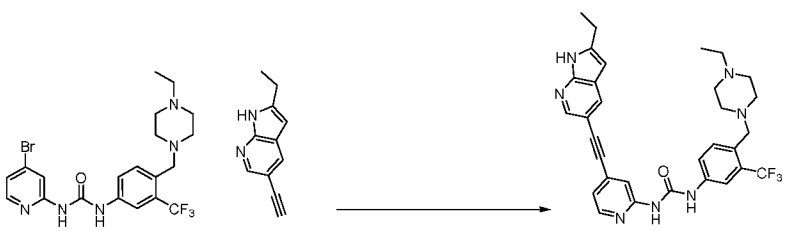
solid; m.p. 268-271 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.97 (s, 1H), 10.32 (s, 1H), 9.53 (s, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 1.6 Hz, 1H), 7.75 (s, 1H), 7.68–7.57 (m, 3H), 7.17 (q, *J* = 4.8 Hz, 1H), 6.52 (q, *J* = 1.6 Hz, 1H), 3.54 (s, 2H), 2.39–2.28 (m, 10H), 0.99 (t, *J* = 7.6 Hz, 3H); MS (ESI) *m/z* 548.26 $[C_{29}H_{28}F_3N_7O+H]^+$.

Example 135: 1-(4-((1H-pyrrolo [2, 3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) urea



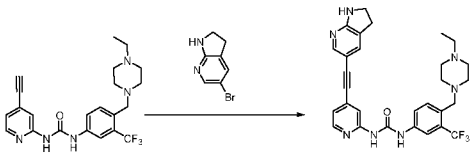
[000540] The title compound was prepared from 5-ethynyl-1*H*-pyrrolo [2, 3-*b*] pyridine and 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent: dichloromethane/methanol 10:1) to afford 1-(4-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1yl)methyl)3(trifluoromethyl)phenyl)urea (100 mg, 45%, HPLC 99.8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.98 (s, 1H), 10.33 (s, 1H), 9.54 (s, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 8.03 (d, *J* = 1.6 Hz, 1H), 7.75 (s, 1H),7.57–7.67 (m, 3H), 7.17 (dd, *J* = 0.8, 4.8 Hz, 1H), 7.17 (dd, *J* = 1.6, 3.2 Hz, 1H), 3.60 (s, 2H), 2.32 (s, 3H), 2.33–2.62 (m, 8H); MS (ESI) *m/z* 534 $[C_{28}H_{26}F_3N_7O+H]^+$.

Example 136: 1-(4-((2-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



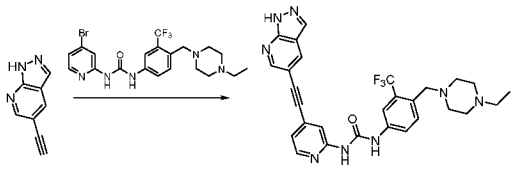
[000541] The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 2-ethyl-5-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine following a method similar to general procedure A. The reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (4.8 mg, AUC HPLC 99.8 %) as brown solid; m.p. 260–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.84 (s, 1H), 10.38 (s, 1H), 9.58 (s, 1H), 8.35 (d, *J* = 1.72 Hz, 1H), 8.32 (d, *J* = 5.12 Hz, 1H), 8.10 (d, *J* = 1.5 Hz, 1H), 8.04 (s, 1H), 7.74 (s, 1H), 7.70–7.60 (m, 2H), 7.16 (d, *J* = 5.1 Hz, 1H), 6.23 (s, 1H), 3.55 (s, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.50–2.20 (m, 10H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 576.65 $[C_{31}H_{32}F_3N_7O+H]^+$.

Example 137: 1-(4-((2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



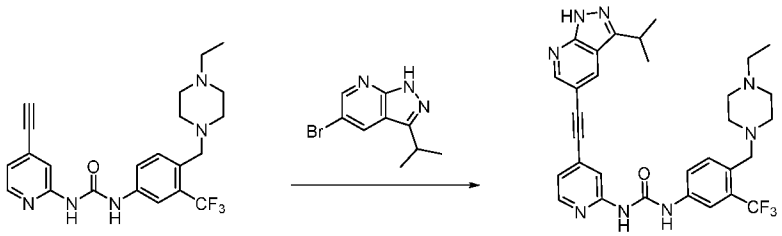
[000542] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-bromo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine following a method similar to general procedure A. The crude product was washed in MeOH (1.0 ml x 3) and the precipitate was isolated by centrifugation to afford 1-(4-((2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (6.1 mg, AUC HPLC 97.7%) as white powder; mp 223–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.20 (s, 1H), 10.21 (s, 1H), 8.21 (d, *J* = 5.3 Hz, 1H), 8.17 (s, 1H), 7.85–7.74 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.52 (s, 1H), 7.32 (s, 1H), 6.98 (d, *J* = 5.2 Hz, 1H), 6.94 (s, 1H), 3.78 (t, *J* = 8.4 Hz, 2H), 3.64 (s, 2H), 3.78 (t, *J* = 8.4 Hz, 2H), 2.75–2.30 (m, 10H), 1.11 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 550.65$[C_{29}H_{30}F_3N_7O + H]^+$.

Example 138: 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000543] The title compound was prepared from 5-ethynyl-1*H*-pyrazolo[3,4-*b*]pyridine and 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by flash chromatography (silica gel, eluent $CHCl_3/CH_3OH/NH_4OH$ 95:4:1) and then it was further purified by preparative HPLC to afford 1-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (10 mg, 21%, AUC HPLC 98%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 10.42 (s, 1H), 9.61 (s, 2H), 8.75 (d, J = 1.6 Hz, 1H), 8.58 (s, 1H), 8.35 (d, J = 4.8 Hz, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.67 (s, 2H), 7.20 (d, J = 5.2 Hz, 1H), 3.65 (s, 2H), 3.44 (d, J = 11.6 Hz, 2H), 3.13–2.89 (m, 6H), 2.44–2.32 (m, 2H), 1.23 (t, J = 7.6 Hz, 3H); MS (ESI) *m/z* 549.26 $[C_{28}H_{27}F_3N_8O+H]^+$.

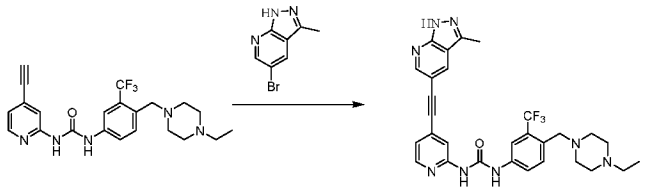
Example 139: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea



[000544] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridine following a method similar to general procedure A. The resulting residue was purified by flash column chromatography (eluent CH_2Cl_2/CH_3OH 85:15) followed by preparative HPLC to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-isopropyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)urea (3.2 mg, AUC HPLC 98.6%) as an off white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.32 (s, 1H), 9.61 (s, 1H), 8.70 (d, J = 1.9 Hz, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.82 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.61 (dd, J = 8.4, 2.3 Hz, 1H), 7.21–7.16 (m, 1H), 3.54 (s, 2H), 2.42–2.35 (m, 4H), 2.31 (q, J = 7.2 Hz, 2H), 1.38 (d, J = 6.9 Hz, 6H), 0.98 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ

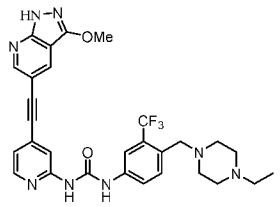
(ppm): 152.8, 152.1, 151.5, 151.1, 147.9, 138.0, 133.7, 132.2, 131.4, 130.9, 127.9, 127.7, 127.5, 127.3, 125.2, 123.4, 122.2, 119.3, 115.5, 113.1, 111.9, 109.8, 91.8, 87.7, 57.4, 52.8, 52.4, 51.6, 27.4, 21.9, 12.0; MS (ESI) *m/z* 591 $[C_{31}H_{32}F_3N_8O + H]^+$

Example 140: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea



[000545] The title compound was synthesized from 5-bromo-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine and 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea following a method similar to general procedure A. The reaction crude was purified by flash column chromatography (eluent CH_2Cl_2/CH_3OH 85:15) and by preparative HPLC to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea (4.0 mg, AUC HPLC: 98.7%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 13.54 (s, 1H), 10.33 (s, 1H), 9.63 (s, 1H), 8.71 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 8.05 (d, *J* = 2.2 Hz, 1H), 7.81 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.62 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.18 (dd, *J* = 5.2, 1.5 Hz, 1H), 3.54 (s, 2H), 2.53 (s, 3H), 2.43–2.35 (m, 4H), 2.31 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 152.8, 152.1, 151.4, 151.1, 147.9, 138.0, 133.5, 132.1, 131.4, 130.9, 127.9, 127.7, 127.5, 127.3, 125.2, 123.4, 122.1, 119.2, 115.5, 113.6, 113.1, 109.8, 91.7, 87.7, 57.4, 52.8, 52.3, 51.5, 12.1, 12.0; MS (ESI) *m/z* 564 $[C_{29}H_{29}F_3N_8O + H]^+$

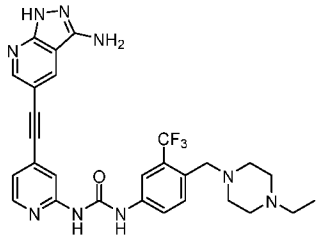
Example 141: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea



[000546] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-bromo-3-methoxy-1*H*-

pyrazolo[3,4-*b*]pyridine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)urea (12 mg, AUC HPLC 98%) as white solid; m.p. 224.0-225.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.94 (s, 1H), 10.36 (s, 1H), 9.63 (s, 1H), 8.70 (d, *J* = 1.8 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 8.34 (d, *J* = 5.1 Hz, 1H), 8.05 (s, 1H), 7.80 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 5.1 Hz, 1H), 4.04 (s, 3H),), 3.55 (s, 2H), 2.41 (bs, 8H), 2.34 (q, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 154.89, 152.78, 152.31, 152.04, 150.89, 147.78, 138.00, 132.59, 132.04, 131.34, 130.78, 127.54, 124.24, 122.10, 119.25, 115.44, 113.07, 109.44, 103.05, 91.41, 87.72, 57.30, 55.73, 52.59, 52.22, 51.44, 11.78; MS (ESI) *m/z* 579.70[$C_{29}H_{29}F_3N_8O_2$ + H]$^+$.

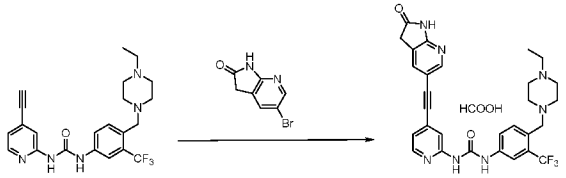
Example 142: 1-(4-((3-amino-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000547] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine in following a method similar to general procedure A. The residue was purified blash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((3-amino-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (4 mg, AUC HPLC 95%) as white solid; m.p. 210.0–211.2 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.59 (d, *J* = 1.9 Hz, 1H), 8.39 (d, *J* = 1.9 Hz, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 8.01 (d, *J* = 1.5 Hz, 1H), 7.78-7.71 (m, 2H), 7.43 (s, 1H), 7.16 (dd, *J* = 5.2, 1.2 Hz, 1H), 3.74 (s, 2H), 3.15 (bs, 4H), 3.04 (q, *J* = 7.3 Hz, 2H), 2.72 (bs, 4H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 167.66, 153.11, 153.06, 151.85, 151.02, 148.87, 146.61, 138.25, 133.65, 133.52, 131.52, 130.44, 129.00 (q, *J* = 31.4 Hz),

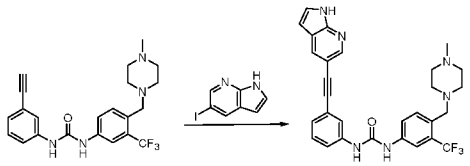
124.35 (q, J = 273.9 Hz), 122.61, 119.16, 116.70 (q, J = 6.1 Hz), 113.45, 109.14, 106.21, 91.51, 86.84, 56.98, 51.68, 50.20, 8.64; MS (ESI) *m/z* 564.65[$C_{28}H_{28}F_3N_9O$ + H]$^+$.

Example 143: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea formate



[000548] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one following a method similar to general procedure A. The reaction mixture was purified twice by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea formate (4.6 mg, AUC HPLC 90.2%) as purple solid; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.52 (s, 1H), 8.34–8.38 (m, 2H), 7.98 (s, 1H), 7.76–7.65 (m, 4H), 7.39 (s, 1H), 7.11 (dd, J = 5.2, 1.6 Hz, 1H), 3.69 (s, 2H), 3.00–2.50 (m, 12H), 1.22 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 564 [$C_{29}H_{28}F_3N_7O_2$ + H]$^+$.

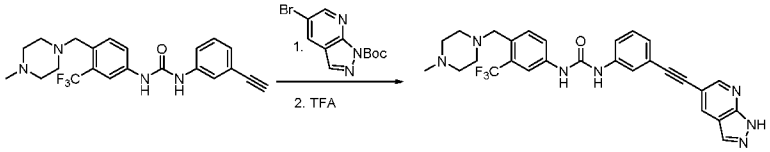
Example 144: 1-(3-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000549] The title compound was synthesized from Intermediate 40 and 5-iodo-1*H*-pyrrolo[2,3-*b*]pyridine following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 1-(3-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (20.3 mg, 32%, AUC HPLC 99%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.53 (s, 1H), 9.12 (s, 1H), 8.94 (s, 1H), 8.50 (bs, 1H), 7.97 (d, J= 4.8 Hz, 2H), 7.80 (s, 1H), 7.75 (t, J= 2.7 Hz, 1H), 7.64–7.56 (m, 2H), 7.41–7.32 (m, 2H), 7.20 (d, J= 7.3 Hz,

1H), 6.61 (s, 1H), 3.53 (s, 2H), 2.38□–2.33 (m, 8H), 2.16 (s, 3H); MS (ESI) *m/z* 533.15 $[C_{29}H_{27}F_3N_6O+H]+$;

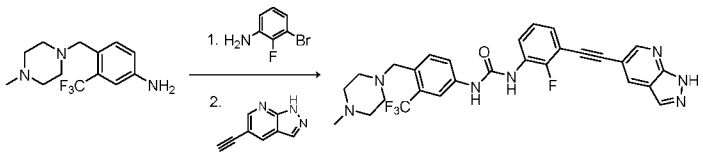
Example 145: 1-(3-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000550] Step 1: Synthesis of *tert*-butyl 5-((3-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate; The title compound was synthesized from Intermediate 40 and *tert*-butyl 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate following a method similar to general procedure A. The reaction crude product was purified by flash chromatography (silica gel, dichloromethane/ methanol/ NH_4OH 94:5.4:0.6) to afford *tert*-butyl 5-((3-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (92 mg) as brow visquous liquid MS (ESI) *m/z* 634.2 $[C_{33}H_{34}F_3N_7O_3$ +H]+.

[000551] Step 2: Synthesis of 1-(3-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea; A solution of *tert*-butyl 5-((3-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (90 mg, 0.14 mmol) in TFA (65 mg, 0.56 mmol) and DCM (3 mL) was stirred at room temperature for 16 h and was concentrated under reduced pressure. The residue was purified by preparative HPLC (65:35 water with 0.1% formic acid/ acetonitrile with 0.1% formic acid) to afford 3 1-(3-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (16.7 mg, 17% yield over 2 steps, AUC HPLC 99.3%) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.90 (s, 1H), 9.09 (s, 1H), 8.93 (s, 1H), 8.69 (d, *J* = 1.9 Hz, 1H), 8.49 (s, 1H), 8.20 (s, 1H), 7.99 (d, *J* = 1.8 Hz, 1H), 7.83 (s, 1H), 7.64–7.56 (m, 2H), 7.41–7.33 (m, 2H), 7.21 (d, *J* = 7.4 Hz, 1H), 3.53 (s, 2H), 2.38–2.32 (m, 8H), 2.15 (s, 3H); MS (ESI) *m/z* 534.2 $[C_{28}H_{26}F_3N_7O+H]^+$.

Example 146: 1-(3-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



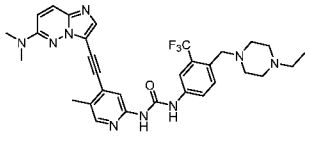
Step 1: Synthesis of 1-(3-bromo-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000552] To a solution of 3-Bromo-2-fluoroaniline (69.5 mg, 0.365 mmol) in DCM (3.0 mL) were added triethylamine (0.05 mL, 0.365 mmol) and triphosgene (35.7 mg, 0.120 mmol) at 0°C. The reaction was stirred for 30 min while warming to room temperature prior to the addition of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (100 mg, 0.365 mmol) and was further stirred for 16 h. The reaction diluted with methanol and was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH 20:1) to afford 1-(3-bromo-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (176 mg, 98%). MS (ESI) *m/z* 492.0 $[C_{20}H_{21}BrF_4N_4O+H]^+$.

Step 2: Synthesis of 1-(3-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000553] The title compound was synthesized from 5-ethynyl-1*H*-pyrazolo[3,4-*b*]pyridine and 1-(3-bromo-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent CH_2Cl_2:MeOH 100:0 to 80:20) and by preparative HPLC (CH_3CN:H_2O, 0.1% formic acid) to afford 1-(3-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (3.0 mg, AUC HPLC 99.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.94 (s, 1H), 9.70 (s, 1H), 8.97 (s, 1H), 8.70 (d, 1H, *J* = 1.9 Hz), 8.52 (d, 1H, *J* = 1.9 Hz), 8.27 (s, 1H), 8.22 (s, 1H), 8.14 (t, 1H, *J* = 7.6 Hz), 7.99 (d, 1H, *J* = 2.0 Hz), 7.31–7.56 (m, 2H), 3.32–3.23 (m, 2H), 2.38–2.32 (m, 8H), 2.15 (s, 3H); MS (ESI) *m/z* 552.2 $[C_{28}H_{25}F_4N_7O+H]+$.

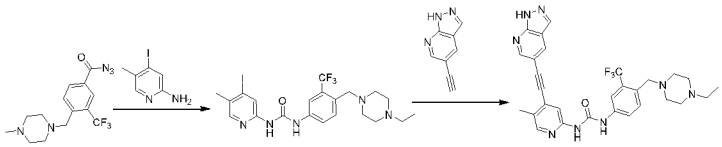
Example 147: 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000554] Step 1: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-iodo-5-methylpyridin-2-yl)urea; A solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoyl azide (25 mg, 0.0733 mmol) in dry toluene (2 mL) was refluxed under argon for 2 h. When the reaction was completed, 4-iodo-5-methylpyridin-2-amine (17 mg, 0.0733 mmol) was added and the mixture heated at 100 °C for 2 h. The solvents were then removed *in vacuo* and the crude purified by flash column chromatography (silica gel, eluent DCM/MeOH 95/5) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-iodo-5-methylpyridin-2-yl)urea (8.9 mg, 22%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.57 (s, 1H), 8.84 (s, 1H), 8.02 (s, 1H), 7.88 (d, *J* = 2.6 Hz, 1H), 7.75 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.65–7.53 (m, 2H), 3.68 (d, *J* = 3.9 Hz, 2H), 2.76 (m, 4H), 2.35 (s, 3H), 1.41 (q, *J* = 7.0 Hz, 1H), 1.29 (m, 4H), 0.97 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 153.3, 150.8, 144.5, 137.9, 131.7, 131.1, 129.4, 125.2, 123.4, 122.9, 122.1, 117.7, 114.4, 59.1, 57.8, 52.3, 51.0, 13.7; MS (ESI) *m/z* 548 $[C_{20}H_{23}F_3IN_5O + H]^+$.

[000555] Step 2: Preparation of 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea; The title compound was synthesized from 3-ethynyl-*N*,*N*-dimethylimidazo[1,2-*b*]pyridazin-6-amine and 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-iodo-5-methylpyridin-2-yl)urea following a method similar to general procedure A. The resulting residue was purified by flash column chromatography (eluent CH_2Cl_2/CH_3OH 85:15) followed by preparative HPLC to afford 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)-5-methylpyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (10.1 mg, 33%, AUC HPLC 97.9%) as a yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.32 (s, 1H), 9.48 (s, 1H), 8.25 (s, 1H), 8.04 (d, *J* = 2.2 Hz, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 9.9 Hz, 1H), 7.72 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.60 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.20 (d, *J* = 9.9 Hz, 1H), 3.54 (s, 2H), 3.13 (s, 6H), 2.44 (s, 3H), 2.42–2.34 (m, 4H), 2.31 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 155.3, 152.1, 150.7, 147.5, 138.1, 136.9, 136.7, 132.1, 131.4, 130.7, 127.7, 126.6, 125.6, 125.2, 122.0, 115.4, 111.7, 111.5, 110.5, 94.8, 85.8, 57.4, 52.7, 52.3, 51.5, 38.1, 16.2, 11.9; MS (ESI) *m/z* 607 $[C_{31}H_{34}F_3N_9O + H]^+$.

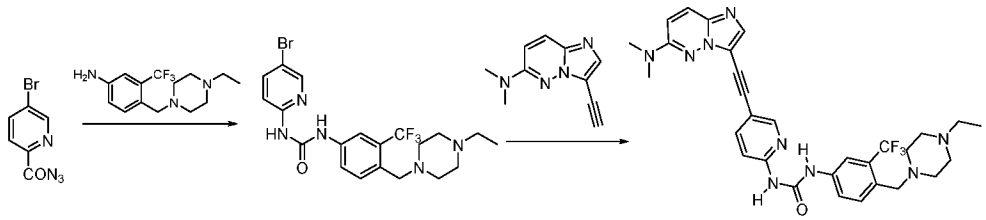
Example 148: 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-5-methylpyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000556] Step 1: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-iodo-5-methylpyridin-2-yl)urea; A solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoyl azide (25 mg, 0.0733 mmol) in dry toluene (2 mL) was refluxed under argon for 2 h. 4-iodo-5-methylpyridin-2-amine (17 mg, 0.0733 mmol) was added and the mixture heated at 100°C for 2 h. The solvents were then removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, eluent: MeOH/dichloromethane 5:95) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-iodo-5-methylpyridin-2-yl)urea (8.9 mg, 22%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.57 (s, 1H), 8.84 (s, 1H), 8.02 (s, 1H), 7.88 (d, *J* = 2.6 Hz, 1H), 7.75 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.65–7.53 (m, 2H), 3.68 (d, *J* = 3.9 Hz, 2H), 2.76 (m, 4H), 2.35 (s, 3H), 1.41 (q, *J* = 7.0 Hz, 1H), 1.29 (m, 4H), 0.97 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3, 150.8, 144.5, 137.9, 131.7, 131.1, 129.4, 125.2, 123.4, 122.9, 122.1, 117.7, 114.4, 59.1, 57.8, 52.3, 51.0, 13.7; MS (ESI) *m/z* 548 $[C_{20}H_{23}F_3IN_5O + H]^+$.

[000557] Step 2: Preparation of 1-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-5-methylpyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea; The title compound was synthesized from 5-ethynyl-1*H*-pyrazolo[3,4-*b*]pyridine and 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-iodo-5-methylpyridin-2-yl)urea following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-5-methylpyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (6.1 mg, 20%, AUC HPLC 97.7%) as an off-white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 13.98 (s, 1H), 10.25 (s, 1H), 9.49 (s, 1H), 8.77 (d, *J* = 2.0 Hz, 1H), 8.61 (d, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 8.24 (s, 1H), 8.03 (d, *J* = 2.3 Hz, 1H), 7.79 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.60 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.54 (s, 2H), 2.41 (s, 3H), 2.40–2.33 (m, 4H), 2.30 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 152.6, 151.7, 151.2, 151.2, 148.1, 138.6, 134.3, 132.4, 131.8, 131.2, 128.3, 128.1, 128.0, 127.9, 127.7, 125.7, 123.9, 122.5, 115.8, 114.4, 113.3, 111.4, 95.5, 87.1, 57.8, 53.3, 52.8, 52.0, 16.9, 12.5; MS (ESI) *m/z* 564 $[C_{29}H_{29}F_3N_8O + H]^+$

Example 149: Synthesis of 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



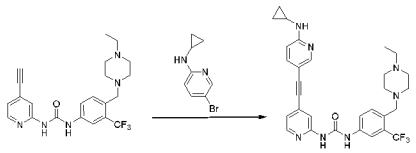
Step 1: Preparation of 1-(5-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) urea

[000558] A mixture of 5-bromopicolinoyl azide (1.5 g, 6.6 mmol) in toluene was refluxed for 1 h then cooled to room temperature. A solution of 4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) aniline (2.0 g, 6.9 mmol) in toluene was slowly added to the reaction mixture at room temperature and the resulting solution was stirred for an additional 16 h. The reaction mixture was concentrated to a smaller volume under reduced pressure and the residue was purified by column chromatography (silica gel, eluent $CHCl_3$/MeOH 98:2) to afford 1-(5-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (78%, LC-MS 86%) as an off white solid; MS (ESI) *m/z* 486 $[C_{20}H_{23}BrF_3N_5O+ H]^+$.

Step 2: Preparation of 1-(5-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

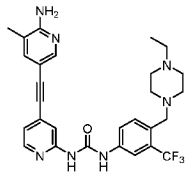
[000559] The title compound was synthesized from 1-(5-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 3-ethynyl-*N,N*-dimethylimidazo[1,2-*b*]pyridazin-6-amine following a method similar to general procedure A. The solvent was evaporated and the residue was purified by preparative HPLC to afford 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (23 mg, AUC HPLC 98.8%) as a yellow solid. m.p. 192–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.72 (s, 1H), 8.94 (s, 1H), 8.10 (d, *J* = 5.6 Hz, 1H), 7.92 (d, *J* = 1.6 Hz, 1H), 7.74-7.67 (m, 2H), 7.18 (s, 1H), 7.14 (dd, *J* = 5.6 Hz, 1.2 Hz, 1H), 3.67 (s, 2H), 2.76-2.42 (m, 10 H), 1.20 (t, *J* = 7.0, Hz, 2H); MS (ESI) *m/z* 592 $[C_{30}H_{32}F_3N_9O+ H]^+$.

Example 150: 1-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000560] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-bromo-*N*-cyclopropylpyridin-2-amine following a method similar to general procedure A. The reaction mixture was purified by column chromatography (silica gel, eluents DCM/MeOH 9:1) to afford a yellow solid which was triturated in MeOH (3X1.0 ml) and the solid was isolated by centrifugation to afford 1-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (6.5 mg, AUC HPLC 99.5%) as a white powder; mp 238–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.12 (s, 1H), 9.39 (s, 1H), 8.38 (d, *J* = 1.7 Hz, 1H), 8.23 (d, *J* = 5.3 Hz, 1H), 7.93 (s, 1H), 7.80–7.70 (m, 2H), 7.66 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.31 (s, 1H), 7.02 (d, *J* = 5.4 Hz, 1H), 6.87 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 3.64 (s, 2H), 2.65–2.30 (m, 11H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 5.1 Hz, 2H), 0.67 (d, *J* = 2.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.29, 153.70, 152.94, 151.86, 145.96, 140.91, 137.33, 134.55, 132.37, 131.30, 123.10, 119.16, 117.57, 113.09, 106.92, 105.79, 93.57, 87.19, 73.65, 57.95, 53.15, 52.96, 52.34, 23.96, 11.99, 7.35; MS (ESI) *m/z* 564.25 $[C_{30}H_{32}F_3N_7O + H]^+$.

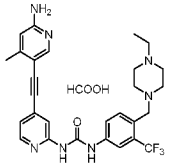
Example 151: 1-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000561] The title compound was synthesized from1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-iodo-3-methylpyridin-2-amine following a method similar to general procedure A. The reaction mixture was purified twice by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (5.2 mg, AUC HPLC > 99%) as white solid; m.p. 210 –212 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.27 (d, *J* = 5.3 Hz, 1H), 8.03 (s, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 7.76–7.63 (m, 2H), 7.48 (s, 1H), 7.30 (s, 1H), 7.06 (dd, *J* = 5.2, 1.6 Hz, 1H), 3.65 (s, 2H), 2.85–2.25 (m, 10H), 2.14 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz,

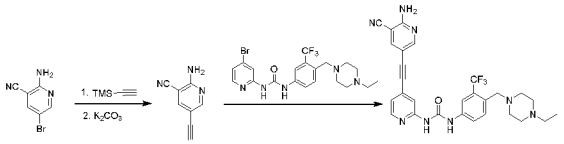
DMSO-d_6) δ (ppm): 159.11, 153.29, 152.62, 149.97, 148.11, 139.60, 138.56, 133.39, 132.04, 131.90, 129.12, 128.26, 122.68, 119.41, 116.29, 113.18, 105.74, 93.63, 87.58, 67.91, 57.91, 53.31, 52.88, 52.05, 42.95, 38.58, 30.28, 28.83, 23.74, 22.85, 17.17; MS (ESI) *m/z* 538.65 $[C_{28}H_{30}F_3N_7O+ H]^+$.

Example 152: 1-(4-((6-amino-4-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea formate



[000562] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-iodo-4-methylpyridin-2-amine following a method similar to general procedure A. The reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((6-amino-4-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea formate (7.6 mg, 12.2%, AUC HPLC 99.4 %) as pale-yellow solid; m.p. 199–201 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.42 (s, 1H), 8.27 (d, *J* = 5.3 Hz, 1H), 8.04 (s, 1H), 7.98 (s, 1H), 7.77–7.65 (m, 2H), 7.30 (s, 1H), 7.06 (dd, *J* = 5.2, 1.6 Hz, 1H), 6.48 (s, 1H), 3.73 (s, 2H), 3.31–3.00 (m, 6H), 2.73 (s, 4H), 2.38 (s, 3H), 1.32 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 159.68, 153.17, 153.04, 150.98, 150.66, 146.43, 137.86, 134.21, 131.39, 128.73, 122.54, 118.88, 113.02, 90.83, 90.18, 57.52, 52.31, 52.18, 51.86, 18.93, 10.20; MS (ESI) *m/z* 538.30 $[C_{28}H_{30}F_3N_7O+ H]^+$.

Example 153: 1-(4-((6-amino-5-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of 2-amino-5-((trimethylsilyl)ethynyl)nicotinonitrile

[000563] The title compound was synthesized following a method similar to general procedure B starting from 2-amino-5-bromonicotinonitrile and ethynyltrimethylsilane. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate 5:1) to afford 2-amino-5-((trimethylsilyl)ethynyl)nicotinonitrile (176 mg, 82%) as white solid. ^{1}H

NMR (400 MHz, $CDCl_3$) δ (ppm): 8.34 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 5.32 (s, 2H), 0.24 (s, 9H); MS (ESI) *m/z* 216[$C_{11}H_{13}N_3Si$ + H]$^+$.

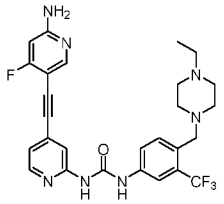
Step 2: Preparation of 2-amino-5-ethynylnicotinonitrile

[000564] To a solution of 2-amino-5-((trimethylsilyl)ethynyl)nicotinonitrile (176 mg, 0.82 mmol) in methanol (4 mL) was added potassium carbonate (226 mg, 1.63 mmol) and was stirred at room temperature for 3 h and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, Hexane/Ethyl acetate 1:1) to afford 2-amino-5-ethynylnicotinonitrile (120 mg, 99.9%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.36 (d, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 5.34 (s, 2H), 3.11 (s, 1H); MS (ESI) *m/z* 144 [$C_8H_5N_3$ + H]$^+$.

Step 3: Preparation of 1-(4-((6-amino-5-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea;

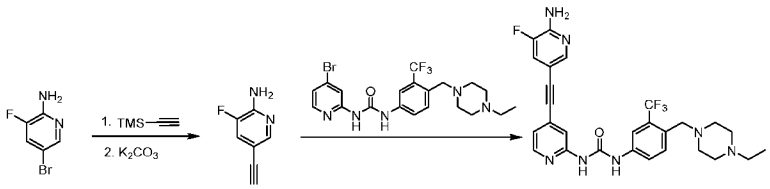
[000565] To a solution of 2-amino-5-ethynylnicotinonitrile (17 mg, 0.12 mmol) in DMF (1 mL) under inert atmosphere was added 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (58 mg, 0.12 mmol), triphenylphophine (11 mg, 0.042 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), copper iodide (2.3 mg, 0.012 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((6-amino-5-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (15 mg, 23%, AUC HPLC 98%) as white solid; m.p. 224.0–225.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.31 (s, 1H), 9.57 (s, 1H), 8.46 (s, 1H), 8.31 (d, *J* = 5.0 Hz, 1H), 8.20 (s, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.73 (s, 1H), 7.69–7.58 (m, 2H), 7.50 (s, 2H), 7.10 (d, *J* = 4.7 Hz, 1H), 3.55 (s, 2H), 2.80–2.15 (m, 10H), 1.00 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.68, 158.66, 155.65, 152.23, 151.50, 147.24, 144.47, 137.48, 131.59, 130.86, 130.25, 127.06, 123.74 , 121.59, 118.52, 115.29, 114.94, 112.37, 104.94, 89.66, 88.83, 87.24, 56.77, 51.98, 51.66, 50.90, 11.18; MS (ESI) *m/z* 549.65[$C_{28}H_{27}F_3N_8O$+ H]$^+$.

Example 154: 1-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000566] The title compound was synthesized from from4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 5-bromo-4-fluoropyridin-2-amine following a method similar to general procedure A. The reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (9.3 mg, 14.8%, AUC HPLC 95.8 %) as brown solid; mp 172–174 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.28 (d, J = 5.4 Hz, 1H), 8.14 (d, J = 10.0 Hz, 1H), 7.97 (s, 1H), 7.71 (s, 2H), 7.32 (s, 1H), 7.07 (dd, J = 5.2, 1.2 Hz, 1H), 6.33 (d, J = 11.6 Hz, 1H), 3.66 (s, 2H), 2.90 –2.40 (m, 10H), 1.16 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 153.70, 153.14, 153.06, 146.51, 137.96, 133.71, 131.43, 131.13, 122.58, 118.88, 116.66, 113.13, 93.62, 90.69, 57.37, 53.37, 52.13, 51.81, 51.62, 9.75; MS (ESI) *m/z* 542.60 $[C_{27}H_{27}F_4N_7O+H]^+$.

Example 155: 1-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of 3-fluoro-5-((trimethylsilyl)ethynyl)pyridin-2-amine

[000567] The title compound was synthesized following a method similar to general procedure A starting from 5-bromo-3-fluoropyridin-2-amine and ethynyltrimethylsilane. The crude product was purified by column chromatography (silica gel, Hexane/Ethyl acetate 5:1) to afford 3-fluoro-5-((trimethylsilyl)ethynyl)pyridin-2-amine (125 mg, 60%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78 (s, 1H), 7.05 (dd, J = 11.1, 1.6 Hz, 1H), 4.58 (s, 2H), 0.02 (s, 9H); MS (ESI) *m/z* 209$[C_{10}H_{13}FN_2Si + H]^+$.

Step 2: Preparation of 5-ethynyl-3-fluoropyridin-2-amine

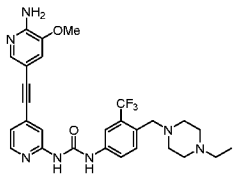
[000568] To a solution of 3-fluoro-5-((trimethylsilyl)ethynyl)pyridin-2-amine (125 mg, 0.60mmol) in methanol (4 mL) was added potassium carbonate (166 mg, 1.20 mmol) and

was stirred at room temperature for 3 h before concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, Hexane/Ethyl acetate 1:1) to afford 5-ethynyl-3-fluoropyridin-2-amine (78 mg, 95%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (s, 1H), 7.29 (dd, *J* = 11.0, 1.6 Hz, 1H), 4.79 (s, 2H), 3.06 (s, 1H); MS (ESI) *m/z* 137[$C_7H_5FN_2$ + H]$^+$.

Step 3: Preparation of 1-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000569] The title compound was synthesized following a method similar to general procedure A starting from 5-ethynyl-3-fluoropyridin-2-amine and 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea. The reaction crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (12 mg, 18%, AUC HPLC 99%) as white solid. m.p: 195.5–196.6 °C; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ (ppm): 8.28 (d, *J* = 5.2 Hz, 1H), 8.02–7.96 (m, 2H), 7.76-7.69 (m, 2H), 7.46 (dd, *J* = 11.4, 1.7 Hz, 1H), 7.33 (s, 1H), 7.08 (dd, *J* = 5.3, 1.0 Hz, 1H), 3.73 (s, 2H), 3.16 (bs, 4H), 3.07 (q, *J* = 7.3 Hz, 2H), 2.72 (bs, 4H), 1.30 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-*d*$_4$) δ (ppm): 168.96, 154.58, 154.48, 151.73, 151.60, 148.00, 147.06, 139.72, 135.21, 132.98, 131.86, 130.45, 125.80, 124.56, 124.08, 120.50, 118.20, 114.72, 108.21, 92.09, 88.06, 58.42, 53.11, 51.57, 10.03; MS (ESI) *m/z* 542.65 [$C_{27}H_{27}F_4N_7O$ + H]$^+$.

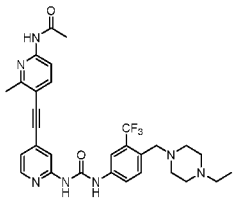
Example 156: 1-(4-((6-amino-5-methoxypyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000570] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 5-bromo-3-methoxypyridin-2-amine following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((6-amino-5-methoxypyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

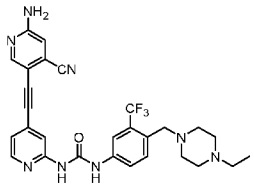
(5 mg, AUC HPLC 99%) as white solid; m.p. 211.1-212.1 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.27 (s, 1H), 7.99 (s, 1H), 7.82-7.66 (m, 3H), 7.32 (s, 1H), 7.15 (s, 1H), 7.07 (d, J = 3.7 Hz, 1H), 3.90 (s, 3H), 3.74 (s, 2H), 3.45-3.25 (m, 4H), 3.18 (q, J = 7.2 Hz, 2H), 2.74 (bs, 4H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 165.73, 153.00, 151.52, 146.40, 141.98, 138.34, 134.11, 131.54, 130.20, 129.00, 124.33, 122.62, 119.02, 116.70, 116.67, 113.16, 92.28, 86.20, 56.86, 54.80, 51.61, 51.47, 49.68, 8.23; MS (ESI) *m/z* 554.65 $[C_{28}H_{30}F_3N_7O_2 + H]^+$.

Example 157: N-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)-6-methylpyridin-2-yl)acetamide



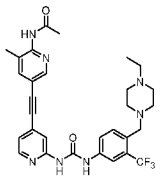
[000571] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and *N*-(5-bromo-6-methylpyridin-2-yl)acetamide following a method similar to general procedure A. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)-6-methylpyridin-2-yl)acetamide (8 mg, 12%, AUC HPLC 98%) as white solid; m.p. 201.2–202.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.69 (s, 1H), 10.36 (s, 1H), 9.58 (s, 1H), 8.33 (d, J = 4.6 Hz, 1H), 8.18 (s, 1H), 8.07-7.91 (m, 3H), 7.75 (s, 1H), 7.70-7.59 (m, 2H), 7.16 (d, J = 4.3 Hz, 1H), 3.55 (s, 2H), 2.61 (s, 3H), 2.60-2.20(m, 10H), 2.11 (s, 3H), 1.00 (t, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 170.12, 163.88, 159.52, 153.33, 152.58, 151.88, 148.35, 142.31, 138.52, 132.60, 131.96, 131.30, 128.13, 124.78, 122.73, 119.69, 116.08, 113.52, 112.14, 110.83, 91.98, 91.08, 57.79, 52.90, 52.65, 51.94, 24.41, 23.28, 12.11; MS (ESI) *m/z* 581.05 $[C_{30}H_{32}F_3N_7O_2 + H]^+$.

Example 158: 1-(4-((6-amino-4-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000572] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 2-amino-5-bromoisonicotinonitrile following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((6-amino-4-cyanopyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (8 mg, 12%, AUC HPLC 98%) as yellow solid. m.p: 203.4–204.2 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.31 (s, 2H), 7.98 (s, 1H), 7.77–7.68 (m, 2H), 7.36 (s, 1H), 7.11 (d, *J* = 4.6 Hz, 1H), 6.86 (s, 1H), 3.73 (s, 2H), 3.21 (bs, 4H), 3.11 (q, *J* = 7.3 Hz, 2H), 2.73 (bs, 4H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 160.98, 154.55, 154.15, 148.03, 139.73, 134.64, 133.00, 131.83, 130.47 (q, *J* = 30.2 Hz), 125.80 (q, *J* = 273.2 Hz), 125.03, 124.13, 120.47, 118.21 (q, *J* = 6.1 Hz), 116.64, 114.71, 112.35, 108.03, 92.35, 89.57, 58.41, 53.12, 53.06, 51.44, 9.92; MS (ESI) *m/z* 549.75 $[C_{28}H_{27}F_3N_8O + H]^+$.

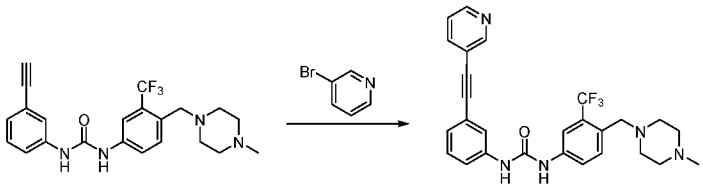
Example 159: N-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)-3-methylpyridin-2-yl)acetamide



[000573] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and *N*-(5-bromo-3-methylpyridin-2-yl)acetamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford *N*-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)-3-methylpyridin-2-yl)acetamide (22.4 mg, 33.3%, AUC HPLC 99.7%) as brown solid; m.p. 110–112 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.47 (s, 1H), 8.32 (d, *J* = 5.2 Hz, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.78–7.63 (m, 2H), 7.43 (s, 1H), 7.14 (dd, *J* = 5.2, 0.8 Hz, 1H), 3.65 (s, 2H), 2.80–2.40 (m, 10H), 2.29 (s, 3H), 2.20 (s, 3H),1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C

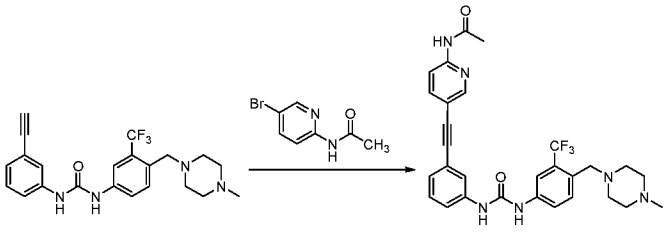
NMR (100 MHz, CD_3OD) δ (ppm): 170.97, 167.70, 153.06, 153.02, 149.69, 148.23, 146.73, 142.16, 138.28, 132.98, 131.52, 130.32, 129.65, 129.12, 128.85, 128.52, 125.69, 122.98, 122.57, 119.23, 117.07, 116.69, 116.63, 113.70, 89.51, 88.88, 56.92, 51.58, 51.48, 49.85, 29.33, 21.78, 16.29, 8.36; MS (ESI) *m/z* 580.35 $[C_{30}H_{32}F_3N_7O_2 + H]^+$.

Example 160: 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(3-(pyridin-3-ylethynyl)phenyl)urea



[000574] The title compound was synthesized from 1-(3-ethynylphenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 3-bromopyridine following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC (acetonitrile/water/ 0.1% formic acid) to afford 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(3-(pyridin-3-ylethynyl)phenyl)urea (20.3mg, 32%, AUC HPLC 99.3%) as a yellow solid; mp: 68.6–69.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.90 (s, 1H), 8.93 (s, 1H), 8.77 (s, 1H), 8.06–8.05 (m, 1H), 8.01–7.98 (m, 2H), 7.83 (s, 1H), 7.62 (d, *J*= 8.4 Hz, 1H), 7.58–7.55 (m, 1H), 7.48–7.34 (m, 4H), 7.21 (d, *J*= 7.6 Hz, 1H), 3.53 (s, 2H), 2.37–2.32 (m, 8H), 2.15 (s, 3H); MS (ESI) *m/z* 494.2 $[C_{27}H_{26}F_3N_5O+H]+$.

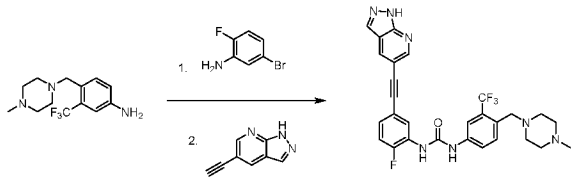
Example 161: N-(5-((3-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)acetamide



[000575] The title compound was synthesized from 1-(3-ethynylphenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and *N*-(5-bromopyridin-2-yl)acetamide following a method similar to general procedure A. The residue was purified by preparative HPLC (75:35 water with 0.1% formic acid/ acetonitrile with 0.1% formic acid) to afford *N*-(5-((3-(3-(4-((4-methylpiperazin-1-yl)methyl)-3

(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)acetamide (21 mg, 31%, AUC HPLC 98.3%) as yellow solid; mp: 105.9–106.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.70 (s, 1H), 9.13 (s, 1H), 8.96 (s, 1H), 8.52 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.98–7.94 (m, 2H), 7.80 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.40–7.32 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 3.52 (s, 2H), 2.38–2.32 (m, 8H), 2.15 (s, 3H), 2.11 (s, 3H); MS (ESI) m/z 551.2 $[C_{29}H_{29}F_3N_6O_2+H]+$.

Example 162: 1-(5-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of 1-(5-bromo-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

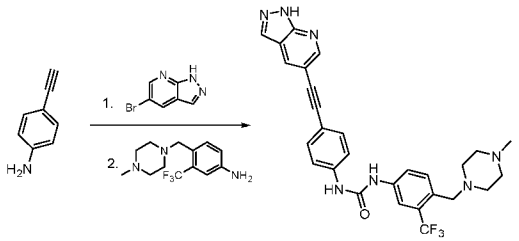
[000576] To a solution of 5-Bromo-2-fluoroaniline (69.5 mg, 0.365 mmol) in dichloromethane (3.0 mL) was added triethylamine (0.05 mL, 0.365 mmol), followed by triphosgene (35.7 mg, 0.120 mmol) at 0 °C. The reaction was then allowed to stir at room temperature for 30 minutes. 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (100 mg, 0.365 mmol) was added to the reaction mixture and stirred at room temperature for 16 hours. The reaction mixture was quenched with methanol and concentrated in vacuo. The crude product was purified by flash column chromatography (Redisep silica gel, CH_2Cl_2:MeOH 20:1) to afford 1-(5-bromo-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (179 mg, 99.9%).

Step 2: Preparation of 1-(5-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000577] The title compound was synthesized from 5-ethynyl-1*H*-pyrazolo[3,4-*b*]pyridine and 1-(5-bromo-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by flash column chromatography (Silica gel, CH_2Cl_2:MeOH, 0-20%), the product collected was further recrystallised with MeOH/Hexane to afford 1-(5-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (6.9 mg, AUC HPLC 97.2%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.89 (s, 1H), 9.57 (s, 1H), 8.81 (s, 1H), 8.74–8.69 (m, 1H), 8.50 (d, J = 1.6 Hz,

1H), 8.39–8.37 (m, 1H), 8.19 (m, 1H), 8.00 (d, 1H, *J* = 2 Hz), 7.65–7.57 (m, 2H), 7.37–7.25 (m, 2H), 3.62 (s, 2H), 2.71–2.66 (m, 8H), 2.33–2.32 (m, 3H); MS (ESI) *m/z* 552.2 $[C_{28}H_{25}F_4N_7O+H]+$;

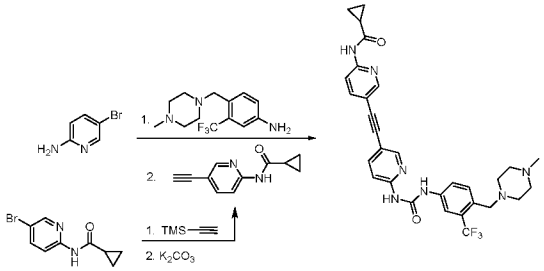
Example 163: 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000578] Step 1: Synthesis of 4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)aniline; The title compound was synthesized from 4-ethynylaniline and 5-Bromo-1*H*-pyrazolo[3,4-*b*]pyridine following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 0-10%) to afford 4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)aniline (23 mg, 38%). MS (ESI) *m/z* 235.1 $[C_{14}H_{10}N_4+H]^+$.
Step 2: Synthesis of 1-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000579] To a solution of 5-((1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)ethynyl)-1*H*-pyrazolo[3,4-*b*]pyridine (23 mg, 0.0982 mmol) in DCM (1.0 mL) was added triethylamine (0.01 mL, 0.0982 mmol), followed by triphosgene (9.6 mg, 0.032 mmol) at 0 °C. The reaction was stirred at room temperature for 15 minutes prior to the addition of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (26.8 mg, 0.0982 mmol) and the resulting mixture was stirred for an additional 2 h at room temperature. The reaction was quenched by adding methanol and the mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography (Silica gel, eluent: CH_2Cl_2:MeOH 20:1), followed by re-crystallization in a mixture of methanol and hexane to afford 1-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (6.1 mg, 11%, AUC HPLC 92.1%). mp 163.4–164.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.86 (s, 1H), 9.16 (s, 1H), 9.09 (s, 1H), 8.65 (d, 1H, *J* = 2.0 Hz), 8.43 (d, 1H, *J* = 1.8 Hz), 8.18 (s, 1H), 7.96 (d, 1H, *J* = 1.8 Hz), 7.64–7.54 (m, 7H), 3.56 (s, 2H), 2.67–2.66 (m, 3H), 2.33–2.20 (m, 8H); MS (ESI) *m/z* 533.9 $[C_{28}H_{26}F_3N_7O+H]+$;

Example 164: N-(5-((6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



[000580] Step 1: Preparation of *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide; The title compound was synthesized from *N*-(5-bromopyridin-2-yl)cyclopropanecarboxamide and ethynyltrimethylsilane following a method similar to general procedure A. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate 19:1) to afford *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (806 mg, 75%) as yellow solid. MS (ESI) *m/z* 259.0 $[C_{14}H_{18}N_2OSi + H]^+$.

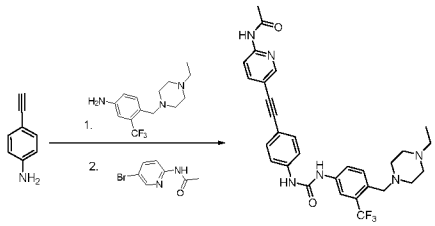
[000581] Step 2: Preparation of *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide; A solution of *N*-(5-ethynylpyridin-2-yl)cyclopropanecarboxamide (800 mg, 0.30 mmol) in anhydrous methanol (10 mL) was treated with potassium carbonate (231 mg, 0.15 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was poured into a mixture of water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (50x2 mL) and the combined organic extracts were washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced. The residue was purified by flash chromatography (silica gel, dichloromethane/ethyl acetate 99:1) to afford *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (297 mg, 51% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.96 (s, 1H), 8.42 (d, *J* = 2.1 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.85 (dd, *J* = 8.6; 2.1Hz, 1H), 4.29 (s, 1H), 2.04–1.98 (m, 1H), 0.83–0.81 (m, 4H); MS (ESI) *m/z* 187.9 $[C_{11}H_{10}N_2O+H]^+$;

[000582] Step 3: Preparation of 1-(5-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea; To a solution of 5-bromopyridin-2-amine (50 mg, 0.28 mmol) in anhydrous dichloromethane (5 mL) was added triethylamine (29 mg, 0.28 mmol) and triphosgene (28 mg, 0.095 mmol) at 0 °C. The mixture was stirred at room temperature for 15 minutes before adding 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (78 mg, 0.28 mmol). The reaction mixture was stirred at room

temperature for 16 h and was quenched with methanol and concentrated under reduced pressure. The residue was purified by flash chromatography (Silica gel, dichloromethane/methanol 9:1) to afford 1-(5-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (58 mg) with 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline as crude brown oil. MS (ESI) *m/z* 473.8 $[C_{19}H_{21}BrF_3N_5O+H]^+$;

[000583] Step 4: Preparation of *N*-(5-((6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide; The title compound was synthesized from 1-(5-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and *N*-(5-ethynylpyridin-2-yl)cyclopropanecarboxamide following a method similar to general procedure A. The filtrate was concentrated under vacuum and the residue was purified by preparative HPLC (acetonitrile/water/0.1% formic acid/ with 0.1% formic acid) to afford *N*-(5-((6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (11.3 mg) to afford a yellow amorphous solid which was subjected to saturated bicarbonate wash and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a yellow solid (9.3 mg) which was freeze dried with water and methanol to afford *N*-(5-((6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (4.4 mg, AUC HPLC 97.5%) as yellow amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.55–8.47 (m, 2H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.02 (s, 1H), 7.94–7.89 (m, 2H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.65 (s, 2H), 3.54 (s, 2H), 2.38–2.32 (m, 8H), 2.15 (s, 3H), 2.05–1.99 (m, 1H), 0.84 (m, 4H); MS (ESI) *m/z* 578.3 $[C_{30}H_{30}F_3N_7O_2+H]^+$.

Example 165: N-(5-((4-(3-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) ureido) phenyl) ethynyl) pyridin-2-yl) acetamide

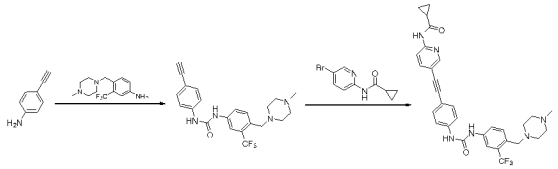


[000584] Step 1: Preparation of 1-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl)-3-(4-ethynylphenyl) urea; To a solution of Triphosgene (7.60 g, 25.62 mmol) in

dichloromethane was added 4-ethynylaniline (3 g, 25.62 mmol), triethyl amine (18 mL, 150 mmol) and stirred for 30 minutes at 0 °C. To this reaction mixture was added 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (7.35 g, 25.62 mmol) and the mixture was heated at 40 °C for 3 h. The reaction mixture was diluted with saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane. Theorganic layer was concentrated and purified by column chromatography (DCM/MeOH 95:5) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylphenyl)urea (5 g, 89%) as an off white solid. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 9.05 (s, 1H), 8.97 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.64–7.62 (d, J = 8.4 Hz, 1H), 7.57–7.55 (d, J = 8.4 Hz, 1H), 7.49–7.47 (m, 2H), 7.40–7.38 (m, 2H), 4.06 (s, 2H), 3.34 (s, 1H), 2.37–2.33 (m, 10H), 0.99–0.96 (t, J = 6.8 Hz, 3H); MS (ESI) *m/z* 430.5 $[C_{23}H_{25}F_3N_4O + H]^+$.

[000585] Step 2: Preparation of *N*-(5-((4-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)acetamide; The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylphenyl)urea and *N*-(5-bromopyridin-2-yl)acetamide following a method similar to general procedure A. Purification of the reaction crude product by preparative HPLC gave *N*-(5-((4-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)acetamide (130 mg, LC-MS 97.98%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 9.08 (s, 1H), 9.01 (s, 1H), 8.47 (s, 1H), 8.13–8.10 (d, J = 8.8 Hz, 1H), 7.97–7.89 (m, 2H), 7.64–7.46 (m, 6H), 3.52 (s, 2H), 2.38–2.27 (m, 10H), 2.11 (s, 3H), 0.99–0.96 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 565.3 $[C_{30}H_{31}F_3N_6O_2 + H]^+$.

Example 166: N-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



Step 1: Preparation of 1-(4-ethynylphenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

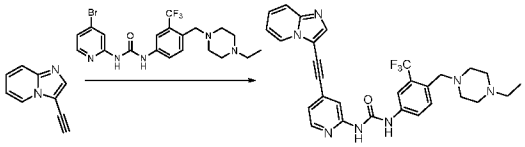
[000586] To a solution of 4-ethynylaniline (150 mg, 1.28 mmol) in dichloromethane (6.0 mL) were successively added triethylamine (0.18 mL, 1.28 mmol) and triphosgene (125 mg, 0.422 mmol) at 0 °C. The reaction was stirred at room temperature for 15 minutes prior to the

addition of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (150 mg, 1.28 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with methanol and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH 20:1) to afford 1-(4-ethynylphenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (531 mg, 99%). MS (ESI) *m/z* 417.2 $[C_{22}H_{23}F_3N_4O+H]^+$.

Step 2: Preparation of *N*-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide

[000587] The title compound was synthesized from *N*-(5-bromopyridin-2-yl)cyclopropanecarboxamide and 1-(4-ethynylphenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The residue was purified by flash column chromatography (silica gel, dichloromethane/ methanol/ ammonium hydroxide 85:15:1%) and by preparative HPLC (acetonitrile/water/0.1% formic acid) to afford *N*-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (6.9 mg, AUC HPLC 99.5%) as pale brown amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.97 (s, 1H), 9.49 (s, 1H), 9.41 (s, 1H), 8.47 (d, *J*= 1.6 Hz, 1H), 8.11 (d, *J*= 8.6 Hz, 1H), 7.98 (s, 1H), 7.89 (dd, *J*= 2.2; 8.6 Hz, 1H), 7.61 (s, 1H), 7.55 (d, *J*= 8.8 Hz, 1H), 7.46 (d, *J*= 8.8 Hz, 1H), 3.52 (s, 2H), 2.37–2.32 (m, 8H), 2.15 (s, 3H), 2.03–2.00 (m, 1H), 0.84–0.82 (m, 4H); MS (ESI) *m/z* 577.9 $[C_{31}H_{31}F_3N_6O_2+H]$+;

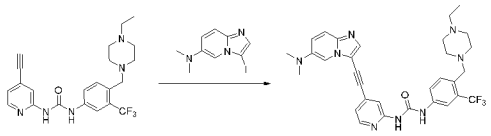
Example 167: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-a]pyridin-3-ylethynyl)pyridin-2-yl)urea



[000588] The title compound was synthesized from 3-ethynylimidazo[1,2-*a*]pyridine and 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The crude product was purified by column chromatography (silica gel, eluent $CHCl_3$/CH_3OH 96:4) and by preparative TLC to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-*a*]pyridin-3-ylethynyl)pyridin-2-yl)urea (80 mg, 46%, AUC HPLC 96.1%) as a brown solid; m.p. 206-209 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.45 (s, 1H), 9.98 (s, 1H), 9.61

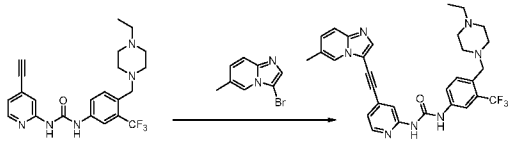
(s, 1H), 8.71 (d, *J* = 6.8 Hz, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.15 (s, 1H), 8.04 (s, 1H), 7.85 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.67–7.64 (m, 2H), 7.51–7.47 (m, 1H), 7.31 (dd, *J* = 4.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 3.66 (s, 2H), 3.47–2.90 (m ,10H), 1.25 (t, *J* = 4.0 Hz, 3H); MS (ESI) *m/z* 548.2 $[C_{29}H_{28}F_3N_7O+H]^+$.

Example 168: 1-(4-((6-(dimethylamino)imidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000589] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 3-iodo-*N,N*-dimethylimidazo[1,2-*a*]pyridin-6-amine following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 1-(4-((6-(dimethylamino)imidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (27.1 mg, 40%, AUC HPLC: 98.9%) as a light yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) : 10.42 (s, 1H), 9.59 (s, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.05 (d, *J* = 2.2 Hz, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 9.1, 3.9 Hz, 2H), 7.40 (dd, *J* = 9.8, 2.4 Hz, 1H), 7.24 (dd, *J* = 5.3, 1.5 Hz, 1H), 3.55 (s, 2H), 2.95 (s, 6H), 2.42–2.32 (m, 6H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 152.8, 152.1, 147.8, 141.7, 141.1, 139.0, 138.0, 132.0, 131.5, 130.9, 128.0, 127.8, 127.6, 127.4, 125.2, 123.4, 122.3, 120.7, 118.5, 117.2, 115.6, 112.3, 106.5, 106.2, 97.8, 82.2, 57.4, 52.6, 52.3, 51.6, 11.8; MS (ESI) *m/z* 591 $[C_{31}H_{33}F_3N_8O + H]^+$.

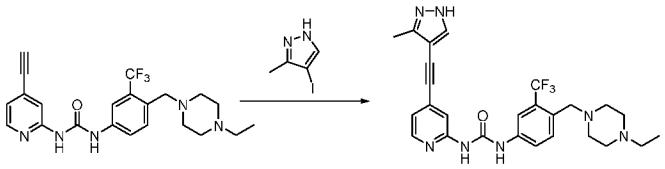
Example 169: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methylimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)urea



[000590] The title compound was synthesized from1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 3-bromo-6-methylimidazo[1,2-*a*]pyridine following a method similar to general procedure A. The reaction crude rpoduct was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methylimidazo[1,2-

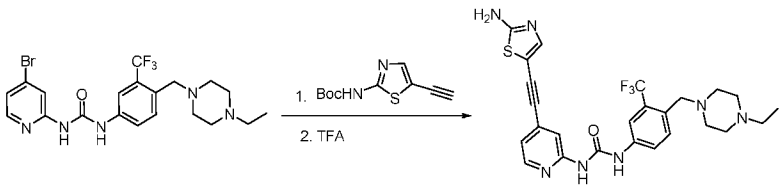
a]pyridin-3-yl)ethynyl)pyridin-2-yl)urea (14.8 mg, 22.6%, AUC HPLC 97.8%) as brown solid; m.p. 205-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.37 (s, 1H), 9.61 (s, 1H), 8.51 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.25–8.00 (m, 2H), 7.81 (s, 1H), 7.75–7.60 (m, 3H), 7.40–7.30 (m, 2H), 3.55 (s, 2H), 2.50 –2.10 (m, 13H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 152.22, 151.52, 147.16, 137.46, 131.33, 130.85, 130.36, 129.47, 123.23, 12.94, 121.62, 118.27, 116.32, 114.98, 111.75, 96.57, 56.82, 52.25, 51.81, 50.98, 16.90, 11.42; MS (ESI) *m/z* 562.65 [$C_{30}H_{30}F_3N_7O$ + H]$^+$.

Example 170: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-2-yl)urea



[000591] The title compound was synthesized from1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 4-iodo-3-methyl-1*H*-pyrazole following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, DCM/methanol 10:1) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((3-methyl-1*H*-pyrazol-4-yl)ethynyl)pyridin-2-yl)urea (10 mg, 15%, AUC HPLC 95%) as brown solid.^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.26 (dd, *J* = 5.3, 0.5 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 7.79–7.64 (m, 3H), 7.30 (s, 1H), 7.05 (dd, *J* = 5.3, 1.3 Hz, 1H), 3.64 (s, 2H), 2.54(bs, 8H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.40 (s, 3H), 1.11 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.62, 154.47, 147.85, 139.29, 135.81, 132.83, 130.32, 125.83, 123.98, 120.34, 118.01, 114.47, 101.80, 90.28, 87.45, 58.97, 53.78, 53.72, 53.32,11.72 ; MS (ESI) *m/z* 512.65 [$C_{26}H_{28}F_3N_7O$ + H]$^+$.

Example 171: tert-butyl 5-((2-(3-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) ureido) pyridin-4-yl) ethynyl) thiazol-2-ylcarbamate



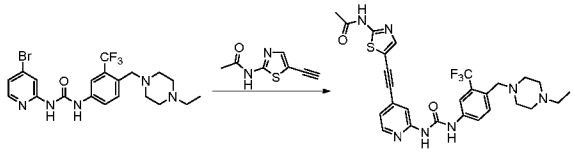
Step 1: Preparation of tert-butyl (5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)thiazol-2-yl)carbamate

[000592] The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl) urea and *tert*-butyl (5-ethynylthiazol-2-yl)carbamate following a method similar to general procedure A. The crude reaction mixture was diluted with water, extracted with EtOAc. The combined organic layer were washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)thiazol-2-ylcarbamate (200 mg, LC-MS 78%) MS (ESI) *m/z* 630.1 $[C_{30}H_{34}F_3N_7O_3S + H]^+$.

Step 2: Preparation of 1-(4-((2-aminothiazol-5-yl) ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000593] A solution of *tert*-butyl 5-((2-(3-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)thiazol-2-ylcarbamate (200 mg, 1.01 mmol, 78%) and TFA (5 mL) in DCM (15 mL) was stirred at room temperature for 2 h. After completion, reaction mixture was concentrated under reduce pressure, basified with a saturated aqueous solution of $NaHCO_3$. The solid was isolated by filtration and purified by preparative TLC to afford 1-(4-((2-aminothiazol-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (20 mg, AUC HPLC 95.1%) as brown solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 9.52 (s, 1H), 8.01 (s, 1H), 7.67–7.60 (m, 4H), 7.54 (s, 1H), 7.45 (s, 1H),7.02 (d, J = 4.0 Hz, 1H), 3.56 (s, 2H), 3.54 (s, 2H), 2.44–2.27 (m, 10H), 0.97 (t, J = 7.6 Hz, 3H); MS (ESI) *m/z* 530.16 $[C_{25}H_{26}F_3N_7OS + H]^+$.

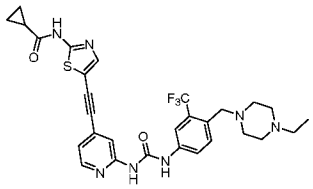
Example 172: N-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)thiazol-2-yl)acetamide



[000594] The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl) urea and *N*-(5-ethynylthiazol-2-yl)acetamide following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)thiazol-2-yl)acetamide (18 mg, LC-MS

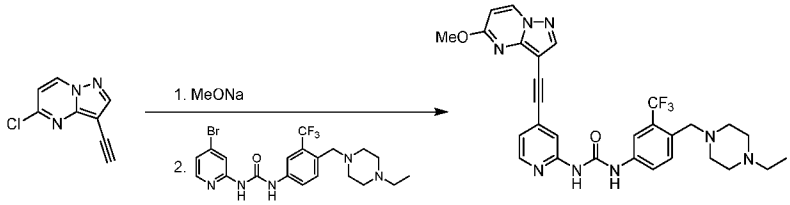
89.5%,) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.52 (s, 1H), 10.29 (s, 1H), 9.54 (s,1H), 8.31 (d, J = 5.6 Hz, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 7.71 (s, 1H), 7.67–7.60 (m, 3H), 7.13 (d, J = 4.8 Hz, 1H), 3.55 (s, 2H), 2.40–2.32 (m, 10H), 2.18 (s, 3H) 0.99 (t, J = 6.4 Hz, 3H). MS (ESI) m/z 472.1 $[C_{27}H_{28}F_3N_7O_2S + H]^+$.

Example 173: N-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide



[000595] The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl) urea and *N*-(5-ethynylthiazol-2-yl)cyclopropanecarboxamide (118.7 mg, 0.618 mmol) following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford *N*-(5-((2-(3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide (90 mg, AUC HPLC 99.8%) as an off-white solid; m.p. 254–258 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.34 (s,1H), 9.53 (s, 1H), 8.29 (d, J = 5.6 Hz, 1H), 8.02 (d, J = 1.6 Hz, 1H), 7.86 (s, 1H), 7.67–7.60 (m, 3H),7.10 (d, J = 4.8 Hz, 1H), 3.54 (s, 2H), 2.38-2.27 (m, 8H), 1.88 (bs, 3H) 0.99(t, J = 7.2 Hz, 3H), 0.88 (bs, 4H); MS (ESI) m/z 598.2 $[C_{29}H_{30}F_3N_7O_2S + H]$.

Example 174: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)urea



Step 1: Preparation of 3-ethynyl-5-methoxypyrazolo[1,5-*a*]pyrimidine

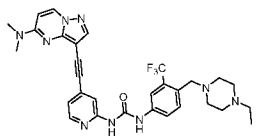
[000596] A solution of 5-chloro-3-ethynylpyrazolo[1,5-*a*]pyrimidine (50 mg, 0.28 mmol) and sodium methoxide (30 mg, 0.56 mmol)in methanol (2 mL) was heated at 100 °C for 1 h in a microwave reactor and was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent hexane/ethyl acetate 5:1) to

afford 3-ethynyl-5-methoxypyrazolo[1,5-*a*]pyrimidine (34 mg, 70%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.4 Hz, 1H), 8.07 (s, 1H), 6.38 (d, *J* = 7.4 Hz, 1H), 4.09 (s, 3H), 3.26 (s, 1H); MS (ESI) *m/z* 174 $[C_9H_7N_3O + H]^+$.

Step 2: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((5-methoxypyrazolo[1,5-*a*]pyrimidin-3-yl)ethynyl)pyridin-2-yl)urea

[000597] To a solution of 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (58 mg, 0.12 mmol) in DMF (1 mL) under inert atmosphere was added 3-ethynyl-5-methoxypyrazolo[1,5-*a*]pyrimidine (21 mg, 0.12 mmol), triphenylphophine (11 mg, 0.042 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), copper iodide (2.3 mg, 0.012 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((5-methoxypyrazolo[1,5-*a*]pyrimidin-3-yl)ethynyl)pyridin-2-yl)urea (15 mg, 22%, AUC HPLC 98%) as white solid; m.p. 220.0–221.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.46 (s, 1H), 9.56 (s, 1H), 9.00 (d, *J* = 7.4 Hz, 1H), 8.40 (s, 1H), 8.31 (d, *J* = 5.3 Hz, 1H), 8.03 (d, *J* = 1.7 Hz, 1H), 7.70-7.61 (m, 3H), 7.11 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.73 (d, *J* = 7.4 Hz, 1H), 4.06 (s, 3H), 3.55 (s, 2H), 2.46-2.28 (m, 10H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.14, 152.76, 152.06, 147.69, 147.56, 147.02, 138.82, 137.96, 132.88, 131.34, 130.79, 127.55, 124.23, 122.17, 118.71, 115.52, 112.61, 101.54, 89.89, 89.11, 85.73, 62.70, 57.28, 54.18, 52.57, 52.21, 51.43, 11.76; MS (ESI) *m/z* 579.2 $[C_{29}H_{29}F_3N_8O_2 + H]^+$.

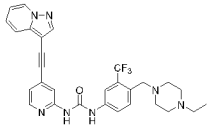
Example 175: 1-(4-(2-(5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000598] The title compound was synthesized from 3-ethynyl-*N,N*-dimethylpyrazolo[1,5-*a*]pyrimidin-5-amine and 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 1-(4-(2-(5-

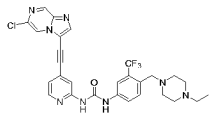
(dimethylamino)pyrazolo[1,5-*a*]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (40.1 mg, 46%, AUC HPLC 94.4) as a pale yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.63 (s, 1H), 9.60 (s, 1H), 8.68 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 5.5 Hz, 1H), 8.17 (s, 1H), 8.05 (s, 1H), 7.66 (q, *J* = 8.7 Hz, 2H), 7.60 (s, 1H), 7.05 (d, *J* = 5.4 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 3.55 (s, 2H), 3.21 (s, 6H), 2.42 (m, 4H), 2.36 (q, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 156.7, 152.8, 152.2, 149.4, 147.5, 146.6, 138.1, 136.1, 133.6, 131.5, 130.9, 127.9, 127.7, 127.5, 127.4, 125.2, 123.4, 122.3, 118.6, 115.6, 112.3, 97.9, 89.6, 88.0, 85.9, 57.4, 52.6, 52.3, 51.5, 11.9; MS (ESI) *m/z* 592 $[C_{30}H_{32}F_3N_9O+H]^+$.

Example 176: 1-(4-((6-chloroimidazo[1,2-a]pyrazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



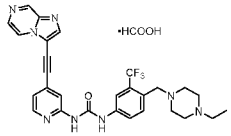
[000599] The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 3-ethynylpyrazolo[1,5-*a*]pyridine following a method similar to general procedure A. The reaction crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((6-chloroimidazo[1,2-*a*]pyrazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (10 mg, 14%, AUC HPLC 97%) as white solid; m.p. 191–192 ^{o}C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.62 (d, *J* = 7.0 Hz, 1H), 8.38 (s, 1H), 8.28 (d, *J* = 5.3 Hz, 1H), 8.19 (s, 1H), 7.99 (d, *J* = 1.8 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.77–7.68 (m, 2H), 7.46 (ddd, *J* =8.8, 6.8, 0.8 Hz, 1H), 7.36 (s, 1H), 7.12 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.05 (td, *J* = 7.0, 1.1 Hz, 1H), 3.73 (s, 2H), 3.25 (bs, 4H), 3.15 (q, *J* = 7.3 Hz, 2H), 2.74 (bs, 4H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.75, 153.17, 152.99, 146.42, 144.40, 141.60, 138.33, 134.35, 131.54, 130.24, 129.10, 129.00, 126.26, 124.34 122.61, 118.85, 117.00, 116.70, 113.74, 112.88, 92.34, 89.76, 85.38, 56.91, 51.62, 51.52, 49.81, 8.33; MS (ESI) *m/z* 548 $[C_{29}H_{28}F_3N_7O+H]^+$.

Example 177: 1-(4-((6-chloroimidazo[1,2-a]pyrazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000600] The title compound was synthesized from1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 6-chloro-3-ethynylimidazo[1,2-*a*]pyrazine following a method similar to general procedure A. The reaction crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((6-chloroimidazo[1,2-*a*]pyrazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (10 mg, 14%, AUC HPLC 98%) as white solid; m.p. 225.2–227.8 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.96 (d, J = 1.0 Hz, 1H), 8.75 (d, J = 1.0 Hz, 1H), 8.37 (d, J = 5.1 Hz, 1H), 8.21 (s, 1H), 7.98 (s, 1H), 7.77–7.69 (m, 2H), 7.57 (s, 1H), 7.28 (d, J = 4.8 Hz, 1H), 3.73 (s, 2H), 3.21 (bs, 4H), 3.12 (q, J = 7.3 Hz, 2H), 2.74 (bs, 4H), 1.32 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 584 $[C_{28}H_{26}ClF_3N_8O + H]^+$.

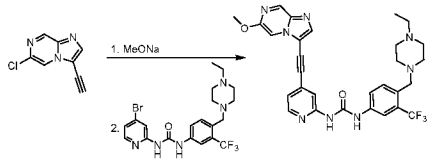
Example 178: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-a]pyrazin-3-ylethynyl)pyridin-2-yl)urea formate



[000601] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 3-bromoimidazo[1,2-*a*]pyrazine following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-*a*]pyrazin-3-ylethynyl)pyridin-2-yl)urea formate (60 mg, 46%, AUC HPLC 97%) as white solid; m.p. 189.4–190.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 1H), 9.62 (s, 1H), 9.23 (d, J = 1.4 Hz, 1H), 8.80 (dd, J = 4.5, 1.4 Hz, 1H), 8.39 (dd, J = 5.2, 0.5 Hz, 1H), 8.34 (s, 1H), 8.16 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.90 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.4, 2.0 Hz, 1H), 7.34 (dd, J = 5.2, 1.4 Hz, 1H), 3.56 (s, 2H), 2.42 (bs, 8H), 2.38 (q, J = 7.2 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.21, 152.76, 151.99, 147.92, 143.18, 140.62, 140.51, 137.99, 131.38, 131.12, 130.84, 130.75, 127.57 (q, J = 29.6 Hz), 124.24 (q, J

= 274.1 Hz), 122.08, 119.33, 118.99 115.43 (q, *J* = 5.9 Hz), 112.64, 108.16, 97.58, 79.38, 57.25, 52.44, 52.14, 51.39, 11.64; MS (ESI) *m/z* 549.75 $[C_{28}H_{27}F_3N_8O + H]^+$.

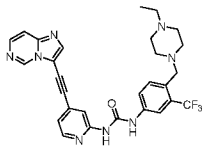
Example 179: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-a]pyrazin-3-yl)ethynyl)pyridin-2-yl)urea



[000602] Step 1: Preparation of 3-ethynyl-6-methoxyimidazo[1,2-*a*]pyrazine; A solution of 6-chloro-3-ethynylimidazo[1,2-a]pyrazine (100 mg, 0.563 mmol) and sodium methoxide (60 mg, 1.26 mmol)in MeOH (5.00 mL) was heated at 140°C for 1 h in a microwave reactor. Purification by flash column chromatography (silica gel, eluents Hex/EtOAc 9:1) gave 3-ethynyl-6-methoxyimidazo[1,2-*a*]pyrazine (12.5 mg, 12.8 %) as an yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.84 (d, *J* = 1.3 Hz, 1H), 7.95 (s, 1H), 7.78 (d, *J* = 1.3 Hz, 1H), 4.01 (s, 3H), 3.88 (s, 1H), 1.46(t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 174 $[C_9H_7N_3O+ H]^+$.

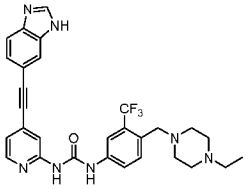
[000603] Step 2: Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-*a*]pyrazin-3-yl)ethynyl)pyridin-2-yl)urea; The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 3-ethynyl-6-methoxyimidazo[1,2-*a*]pyrazine following a method similar to general procedure A. The filtrate was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-*a*]pyrazin-3-yl)ethynyl)pyridin-2-yl)urea (9 mg, 30.3%, AUC HPLC 99.7 %) as brown solid; mp 154–156 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.83 (s, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 8.16–8.03 (m, 2H), 7.96 (d, *J* = 1.7 Hz, 1H), 7.76–7.62 (m, 2H), 7.49 (s, 1H), 7.22 (dd, *J* = 5.2, 0.8 Hz, 1H), 4.05 (s, 3H), 3.63 (s, 2H), 2.80–2.30 (m, 10H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, MeOD-d_4) δ (ppm): 154.93, 153.07, 152.97, 146.87, 140.65, 139.14, 137.83, 131.37, 129.02, 128.72, 122.43, 118.64, 116.46, 113.07, 102.04, 98.05, 78.86, 57.49, 54.47, 52.31, 52.16, 51.86, 10.18; MS (ESI) *m/z* 579.55 $[C_{29}H_{29}F_3N_8O_2+H]^+$.

Example 180: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-c]pyrimidin-3-ylethynyl)pyridin-2-yl)urea



[000604] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 3-bromoimidazo[1,2-*c*]pyrimidine following a method similar to general procedure A. The reaction crude product was purified by column chromatography (silica gel, eluents DCM/MeOH 9:1) to afford a yellow crude product. This crude product was triturated in MeOH and the solid was isolated by centrifugation to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-*c*]pyrimidin-3-ylethynyl)pyridin-2-yl)urea (14.7 mg, 23.1 %, AUC HPLC 97.3%) as white solid mp 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.44 (s, 1H), 8.36 (d, *J* = 5.0 Hz, 1H), 8.15 (d, *J* = 6.4 Hz, 1H), 8.06 (s, 1H), 7.99 (s, 1H), 7.72 (s, 2H), 7.67 (d, *J* = 5.3 Hz, 1H), 7.53 (s, 1H), 7.25 (d, *J* = 4.1 Hz, 1H), 3.72 (s, 2H), 3.30–2.40 (m, 10H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.07, 153.00, 46.90, 145.83, 141.26, 139.59, 138.29, 132.40, 131.54, 130.35, 128.86, 122.58, 118.77, 116.71, 113.13, 111.84, 106.71, 96.49, 78.75, 56.91, 51.69, 51.63, 49.96, 8.45; MS (ESI) *m/z* 549.60 $[C_{28}H_{27}F_3N_8O + H]^+$.

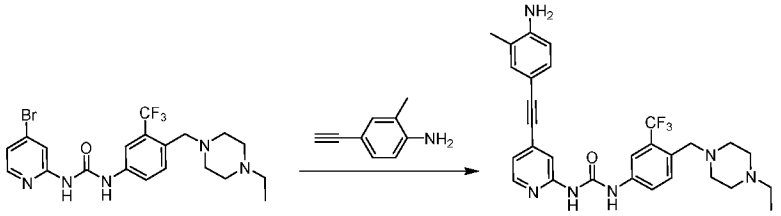
Example 181: 1-(4-((1H-benzo[d]imidazol-6-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000605] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 6-iodo-1*H*-benzo[*d*]imidazole following a method similar to general procedure A. The reaction crude product was purified by column chromatography (silica gel, DCM/methanol 10:1) to afford 1-(4-((1*H*-benzo[*d*]imidazol-6-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (41 mg, 62%, AUC HPLC 93%) as brown solid.^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.29 (dd, *J* = 5.3, 0.5 Hz, 1H), 8.27 (s, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 7.84 (s, 1H), 7.74-7.61(m, 3H), 7.47 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.36 (s, 1H), 7.11 (dd, *J* = 5.3, 1.3 Hz, 1H), 3.63 (s, 2H), 2.55(bs, 8H), 2.50 (q, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.2 Hz, 3H);

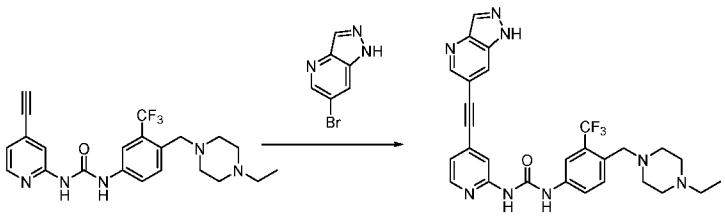
^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 153.15, 153.06, 146.46, 143.05, 137.86, 134.04, 131.37, 128.86, 126.37, 124.38, 122.52, 119.19, 116.56, 115.92, 113.48, 94.51, 84.93, 57.50, 52.29, 52.13, 51.86, 10.17; MS (ESI) *m/z* 548.65[$C_{29}H_{28}F_3N_7O$ + H]$^+$.

Example 182: N-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



[000606] The title compound was synthesized from1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 4-ethynyl-2-methylaniline following a method similar to general procedure A. The reaction mixture was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((4-amino-3-methylphenyl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (16 mg, 24%, AUC HPLC 99.3%) as brown solid; m.p. 273.1–275.7 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.22 (d, *J* = 5.3 Hz, 1H), 7.97 (s, 1H), 7.70 (d, *J* = 2.3 Hz, 1H), 7.23 (s, 1H), 7.21–7.15 (m, 2H), 7.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 1H), 3.66 (s, 2H), 2.90–2.30 (m, 10H), 2.14 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.68, 153.76, 152.63, 146.40, 145.52, 138.00, 135.37, 134.37, 131.69, 131.40, 130.51, 129.48, 125.54, 123.13, 122.81, 121.98, 119.51, 118.10, 118.04, 114.51, 113.73, 110.63, 96.92, 84.63, 60.42, 57.68, 51.48, 51.11, 49.74, 19.28, 17.10, 14.21, 9.13; MS (ESI) *m/z* 537 [$C_{29}H_{31}F_3N_6O$+ H]$^+$

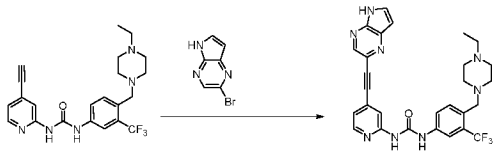
Example 183: 1-(4-((1H-pyrazolo[4,3-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000607] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 6-bromo-1*H*-pyrazolo[4,3-

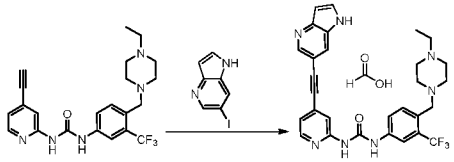
b]pyridine following a method similar to general procedure A. The reaction crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 1-(4-((1*H*-pyrazolo[4,3-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (18 mg, 27%, AUC HPLC 99%) as white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.68 (s, 1H), 8.35 (d, J = 5.1 Hz, 1H), 8.29 (s, 1H), 8.26 (s, 1H), 7.99 (s, 1H), 7.79-7.69 (m, 2H), 7.49 (s, 1H), 7.20 (d, J = 4.4 Hz, 1H), 3.74 (s, 2H), 3.40-3.15 (bs, 4H), 3.14 (q, J = 7.3 Hz, 2H), 2.73 (bs, 4H), 1.33 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 164.46, 153.08, 153.03, 147.41, 146.80, 139.70, 138.32, 133.55, 132.88, 132.21, 131.54, 130.21, 129.00, 124.32, 122.58, 121.95, 119.31, 116.69, 116.05, 113.79, 90.38, 88.86, 56.85, 51.60, 51.44, 49.60, 8.17; MS (ESI) *m/z* 549.65 [$C_{28}H_{27}F_3N_8O$ + H]$^+$.

Example 184: 1-(4-((5H-pyrrolo[3,2-b]pyrazin-2-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



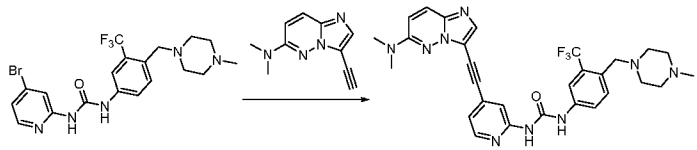
[000608] The title compound was synthesized from 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea and 2-bromo-5*H*-pyrrolo[2,3-*b*]pyrazine following a method similar to general procedure A. The filtrate was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((5*H*-pyrrolo[3,2-*b*]pyrazin-2-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (9.9 mg, 15.5%, AUC HPLC 99.4%) as brown solid; m.p. 262–264 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.38 (s, 1H), 10.37 (s, 1H), 9.65 (s, 1H), 8.59 (s, 1H), 8.37 (d, J = 5.3 Hz, 1H), 8.10–8.00 (m, 2H), 7.82 (s, 1H), 7.65–7.60 (m, 2H), 7.23 (dd, J = 5.2, 1.6 Hz, 1H), 6.68 (d, J = 3.7 Hz, 1H), 3.55 (s, 2H), 2.55–2.20 (m, 10H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 153.42, 152.62, 148.47, 140.91, 140.51, 139.59, 138.54, 133.92, 132.01, 131.90, 131.42, 131.18, 122.72, 119.81, 113.96, 101.16, 92.24, 86.97, 57.90, 53.31, 52.88, 52.05, 12.48; MS (ESI) *m/z* 549.65 [$C_{28}H_{27}F_3N_8O$+ H]$^+$.

Example 185: 1-(4-((1H-pyrrolo[3,2-b]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000609] The title compound was synthesized from 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide and 6-iodo-1*H*-pyrrolo[3,2-*b*]pyridine following a method similar to general procedure A. The crude reaction product was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea formate, (13.7 mg, 21.6 %, AUC HPLC 98.4 %) as an off-white solid; mp 228–230 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.48 (s, 1H), 8.31 (d, *J* = 5.2 Hz, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 7.90–7.76 (m, 1H), 7.74–7.70 (m, 3H), 7.40 (s, 1H), 7.16–7.12 (m, 1H), 6.68 –6.65 (m, 1H), 3.66 (s, 2H), 2.90 –2.45 (m, 10H), 1.18 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 153.07, 146.59, 145.71, 144.70, 138.08, 135.29, 134.54, 134.44, 133.68, 131.64, 131.46, 130.85, 130.31, 130.18, 128.79, 128.34, 122.57, 121.95, 119.17, 116.67, 116.61, 113.48, 110.84, 101.62, 92.09, 87.23, 57.20, 51.94, 51.76, 51.03, 9.29; MS (ESI) *m/z* 548.60 $[C_{29}H_{28}F_3N_7O+H]^+$.

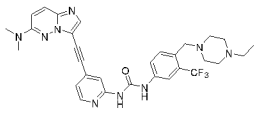
Example 186: 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000610] The title compound was synthesized following a method similar to general procedure B and starting from 1-(5-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine. The reaction crude product was purified by preparative HPLC to afford 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (8 mg, AUC HPLC 96%) as a pale yellow solid. mp 247-250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.72 (s, 1H), 8.27 (d , *J* = 5.2 Hz, 1H), 7.84–7.79 (m, 3H), 7.74–7.71 (m, 2H), 7.43 (bs, 1H), 7.08 (d, *J* = 5.2

Hz, 1H), 6.87–6.83 (m, 2H), 3.62 (s, 2H), 3.18 (s, 6H), 2.51-2.46 (m, 8H), 2.30 (s, 3H); MS (ESI) *m/z* 577 $[C_{29}H_{30}F_3N_9O+ H]^+$.

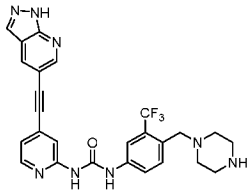
Example 187: 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Preparation of 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000611] The title compound was synthesized following a method similar to general procedure B and starting from 1-(4-bromopyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (150 mg, 0.306 mmol)and 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine. The reaction crude product was purified by preparative TLC (eluent: dichloromethane/methanol 80:20) to afford 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (7.3 mg, AUC HPLC 96%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.42 (s, 1H), 9.82 (s, 1H), 8.35 (s, 1H), 8.13 (s, 1H), 8.00–7.98 (d, *J* = 8.0 Hz, 2H), 7.78 (s, 1H), 7.65–7.62 (m, 3H), 7.10 (d, *J* = 1.8 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 3.65 (s, 3H); 3.25 (s, 6H), 3.15–2.84 (m, 4H), 2.62–2.38 (m, 4H), 1.05 (t, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* 592 $[C_{30}H_{32}F_3N_9O+ H]^+$.

Example 188: 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of *tert*-butyl 4-(4-(3-(4-((1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

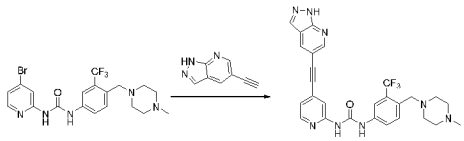
[000612] The title compound was synthesized following a method similar to general procedure B and starting from 5-bromo-1*H*-pyrazolo[3,4-b]pyridine and *tert*-butyl 4-(4-(3-(4-ethynylpyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The crude product was purified by flash column chromatography (neutral alumina eluent

CH_2Cl_2/CH_3OH 95:5) to afford *tert*-butyl 4-(4-(3-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (300 mg, 83.3%) as a yellow solid. MS (ESI) *m/z* 621.32 $[C_{31}H_{31}F_3N_8O_3+H]^+$.

Step 2: Synthesis of 1-(4-((1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea

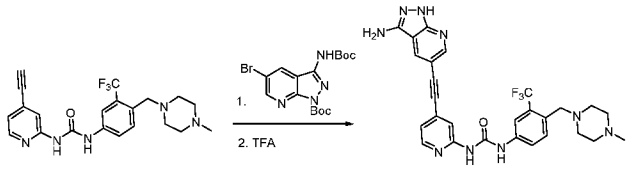
[000613] The title compound was synthesized following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(3-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reactiob crude product was purified by preparative HPLC to afford 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (30 mg, 12%, AUC HPLC >99%) as a brown solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 13.90 (s, 1H), 10.35 (s, 1H), 9.64 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.34 (d, J = 6.8 Hz, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.81 (s, 1H), 7.69–7.60 (m, 2H), 7.19 (d, J = 5.6 Hz, 1H), 3.50 (s, 2H), 2.69 (bs, 4H), 2.29 (bs, 4H); MS (ESI) *m/z*: 521.25 $[C_{26}H_{23}F_3N_8O+H]^+$.

Example 189: 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000614] The title compound was synthesized following a method similar to general procedure B and starting from 1-(4-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl)phenyl)urea and 5-ethynyl-1H-pyrazolo[3,4-b]pyridine. The reaction crude product was purified by flash column chromatography (silica gel, eluent: dichloromethane/MeOH/ammonia 87:10:3) to afford 1-(4-((1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (150 mg, 26.7%, AUC HPLC 95.74%) as an off white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 10.27 (s, 1H), 9.55 (s, 1H), 8.75 (s, 1H), 8.58 (s, 1H), 8.35 (d, J = 4.8 Hz, 1H), 8.25 (s, 1H), 8.03 (s, 1H), 7.80 (s, 1H), 7.67–7.60 (m, 2H), 7.19 (d, J = 4.8 Hz, 1H), 3.55 (s, 2H), 2.39–2.19 (m, 11H). MS (ESI) *m/z*: 535.34 $[C_{27}H_{25}F_3N_8O+H]^+$.

Example 190: 1-(4-((3-amino-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



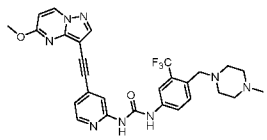
Step 1: Preparation of *tert*-butyl 3-(*tert*-butoxycarbonylamino)-5-((2-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate.

[000615] The title compound was synthesized following a method similar to general procedure A and starting from *tert*-butyl 5-bromo-3-(tert-butoxycarbonylamino)-1*H*-pyrazolo [3, 4-b] pyridine-1-carboxylate and 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) urea. The crude product was used in the next step without further purification. MS (ESI) *m/z*: 750 $[C_{37}H_{42}F_3N_9O_5+H]^+$.

Step 2: Preparation 1-(4-((3-amino-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000616] The title compound was synthesized following a method similar to general procedure D and starting from *tert*-butyl 3-(tert-butoxycarbonylamino)-5-((2-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-4-yl)ethynyl)-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate. The reaction crude product was purified by preparative HPLC to afford 1-(4-((3-amino-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (2.1 mg, AUC HPLC 95.4%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.32 (s, 1H), 10.31 (s, 1H), 9.54 (s, 1H), 8.56 (d, J = 9.6 Hz, 1H), 8.45 (d, J = 1.6 Hz, 1H), 8.31 (d, J = 5.6 Hz, 1H), 8.03 (s, 1H), 7.75 (s, 1H), 7.68–7.63 (m, 2H), 7.15 (d, J = 4.4, 1H), 5.77 (bs, 2H), 3.55 (s, 2H), 2.38–2.35 (m, 8H), 2.15 (s, 3H): MS (ESI) *m/z*: 550 $[C_{27}H_{26}F_3N_9O+H]^+$.

Example 191: 1-(4-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

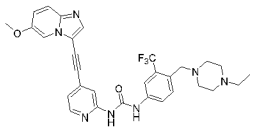


Preparation of 1-(4-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000617] The title compound was synthesized following a method similar to general procedure B and starting from 3-iodo-5-methoxypyrazolo[1,5-a]pyrimidine and 1-(4-

ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea. The eaction crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and preparative HPLC to give 1-(4-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (50 mg, 20%, AUC HPLC 96.36%) as an off-white solid. mp: 225–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.50 (s, 1H), 9.57 (s, 1H), 9.48 (s, 1H), 8.99 (d, J = 7.6 Hz, 1H), 8.39 (s, 1H), 8.30 (d, J = 5.2 Hz, 1H), 8.02 (s, 1H), 7.67–7.63 (m, 3H), 7.11 (q, J = 1.2 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 4.05 (s, 3H), 3.62 (s, 2H), 2.95 (s, 4H), 2.66–2.50 (m, 6H); MS (ESI) *m/z*: 565.35 $[C_{28}H_{27}F_3N_8O_2+H]^+$.

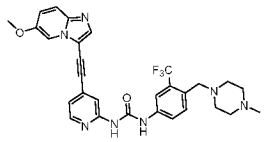
Example 192: 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)urea



Preparation of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)urea

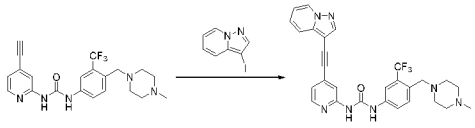
[000618] To a mixture of 3-iodo-6-methoxyimidazo[1,2-a]pyridine (190 mg, 0.696 mmol) and TEA (0.3mL) in acetonitrile (5 mL) under argon were successively added 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea (200 mg, 0.464 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.0232 mmol) and CuI (17 mg, 0.092 mmol) and heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography followed by preparative HPLC to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)urea (10 mg, AUC HPLC 96 %) as an off-white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 10.35 (s, 1H), 9.60 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.15 (d, J = 2 Hz, 1H), 8.12 (s, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.75–7.66 (m, 3H), 7.35–7.25 (m, 2H), 3.92 (s, 3H), 3.55 (s, 2H), 2.40(m, 10H), 1.00 (t, 3H); MS (ESI) *m/z*: 578.2 $[C_{30}H_{30}F_3N_7O_2+H]^+$.

Example 193: 1-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000619] To a solution of 3-iodo-6-methoxyimidazo[1,2-a]pyridine (247 mg, 0.903 mmol) and TEA (0.4 mL) in acetonitrile (5 mL) under argon were successively added 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (250 mg, 0.602 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.0301 mmol) and CuI (22 mg, 0.12 mmol) and the resulting mixture was heated at 80 °C for 2 h. The reaction mixture was diluted with EtOAc and filtered through a short pad of celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography and by preparative HPLC to afford 1-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (14 mg, AUC HPLC 96%) as an off-white solid. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 10.34 (s, 1H), 9.65 (s, 1H), 8.70 (d, J = 5.2 Hz, 1H), 8.35 (d, J = 2 Hz, 1H), 8.12 (s, 1H), 8.05 (d, J = 2 Hz, 1H), 7.80 (s, 1H), 7.72–7.65 (m, 3H), 7.35-7.25 (m, 2H), 3.90 (s, 3H), 3.55 (s, 2H), 2.42 (m, 8H), 2.21 (s, 3H); MS (ESI) *m/z*: 564.23 $[C_{29}H_{28}F_3N_7O_2+H]^+$.

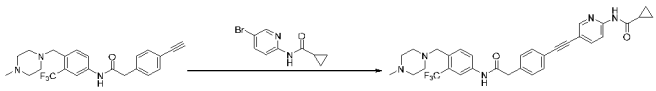
Example 194: 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(pyrazolo[1,5-a]pyridin-3-ylethynyl)pyridin-2-yl)urea



Step 1: Preparation 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(pyrazolo[1,5-a]pyridin-3-ylethynyl)pyridin-2-yl)urea.

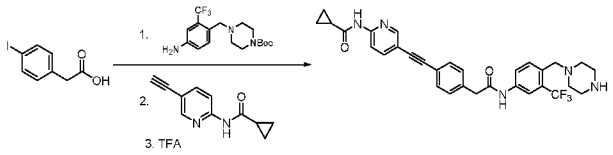
[000620] The title compound was synthesized following a method similar to general procedure B and starting from 3-iodopyrazolo[1,5-a]pyridine and 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea. The reaction crude product was purified by preparative TLC to afford 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(pyrazolo[1,5-a]pyridin-3-ylethynyl)pyridin-2-yl)urea (50 mg, 20%, AUC-HPLC 98.2%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.41 (s, 1H), 9.81 (s, 1H), 8.83 (d, J = 6.8 Hz, 1H), 8.40 (s, 1H), 8.30 (d, J = 6.0 Hz, 1H), 8.03 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.74 (s, 1H), 7.76 (dd, J = 8.8 Hz, J = 8.4 Hz, 2H), 7.51 (t, J = 6.8 Hz, 1H), 7.20–7.15 (m, 1H), 7.12–7.08 (m, 1H), 3.54 (s, 2H), 2.30–2.15 (m, 8H), 2.15 (s, 3H); MS (ESI) *m/z*: 534.37 $[C_{28}H_{26}F_3N_7O+H]^+$.

Example 195: N-(5-((4-(2-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



[000621] The title compound was synthesized from 2-(4-ethynylphenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide and *N*-(5-bromopyridin-2-yl)cyclopropanecarboxamide following a method similar to general procedure A. The residue was purified by column chromatography (Silica gel, dichloromethane/methanol/ammonium hydroxide 84:14.4:1.6) and by preparative HPLC (acetonitrile/water/0.1% formic acid) to afford *N*-(5-((4-(2-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)ethynyl)pyridin-2-yl)cyclopropane carboxamide (13.3 mg, 19%, AUC HPLC 99.0%) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.00 (s, 1H), 10.51 (s, 1H), 8.50 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.04 (s, 1H), 7.93–7.90 (m, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 3.71 (s, 2H), 3.52 (s, 2H), 2.36–2.32 (m, 8H), 2.14 (s, 3H), 2.03–2.00 (m, 1H), 0.84–0.82 (m, 4H); MS (ESI) *m/z* 576.2 $[C_{32}H_{32}F_3N_5O_2+H]^+$;

Example 196: N-(5-((4-(2-oxo-2-((4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)ethyl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



Step 1: Preparation of *tert*-butyl 4-(4-(2-(4-iodophenyl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000622] To a solution of 2-(4-iodophenyl) acetic acid (1 g, 3.81 mmol) in DMF (30 mL) were added *tert*-butyl 4-(4-amino-2-(trifluoromethyl) benzyl) piperazine-1-carboxylate (1.36 g, 3.81 mmol), HATU (2.17 g, 5.71 mmol), and TEA (0.8 mL, 5.71 mmol) and the mixture was stirred for 4 h at room temperature. The reaction mixture was poured in to ice-cold water (100 mL) and the precipitate was isolated by filtration and product was purified by flash column chromatography (silica gel, eluent: dichloromethane/CH_3OH 95:5) to afford *tert*-

butyl 4-(4-(2-(4-iodophenyl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (500 mg, 21%, LC-MS 78%) as an off-white solid. MS (ESI) m/z: 604.12 $[C_{25}H_{29}F_3IN_3O_3+H]^+$.

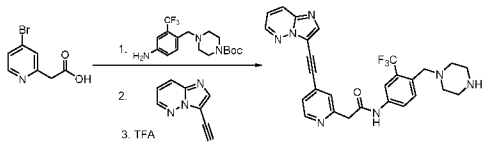
Step 2: Preparation of *tert*-butyl 4-(4-(2-(4-((6-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)phenyl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000623] The title compound was synthesized following a method similar to general procedure B and starting from *tert*-butyl 4-(4-(2-(4-iodophenyl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and *N*-(5-ethynylpyridin-2-yl)cyclopropanecarboxamide. The reaction crude product was purified by flash column chromatography (silica gel, eluent: dichloromethane/methanol 95:5) to afford *tert*-butyl 4-(4-(2-(4-((6-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)phenyl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (400 mg, 45%, LC-MS 70%) as a pale brown solid. MS (ESI) *m/z*: 662.29 $[C_{36}H_{38}F_3N_5O_4+H]^+$.

Step 3: Preparation of *N*-(5-((4-(2-oxo-2-((4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)ethyl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide

[000624] The title compound was synthesized following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(2-(4-((6-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)phenyl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The residue was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 96:4) to afford *N*-(5-((4-(2-oxo-2-((4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)ethyl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (50 mg, 16%, AUC HPLC 98.6%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 10.98 (s, 1H), 10.46 (s, 1H), 8.49 (t, J = 1.2 Hz, 1H), 8.11 (d, J = 9.2 Hz, 1H), 8.02 (s, 1H), 7.92 (d, J = 2.4 Hz, J = 2.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 3.71 (s, 2H), 3.64 (d, J = 5.2 Hz, 2H), 3.38–3.36 (m, 1H), 3.62–2.56 (m, 3H), 2.45–2.32 (m, 2H), 2.22–2.18 (m, 1H), 2.08–1.99 (m, 2H), 1.42–1.40 (m, 1H), 0.86–0.82 (3, J = 4.0 Hz, 4H); MS (ESI) *m/z* 562.2 $[C_{31}H_{30}F_3N_5O_2+H]^+$.

Example 197: Synthesis of 2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-N-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)acetamide



Step 1: Preparation *tert*-butyl 4-(4-(2-(4-bromopyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

[000625] To a solution of 2-(4-bromopyridin-2-yl)acetic acid (600 mg, 2.77 mmol) in dichloromethane (25 mL) were added *tert*-butyl 4-(4-amino-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (797 mg, 2.22 mmol, TEA (0.392 mL, 2.77 mmol) and Propylphosphonic anhydride (1.22 mL, 4.15 mmol). The reaction mixture was stirred at room temperature for 16 h and was diluted with dichloromethane. The organic phase was washed with water and brine, was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain *tert*-butyl 4-(4-(2-(4-bromopyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (1.5 g, LC-MS 78%) as a solid.

Step 2: Preparation of *tert*-butyl 4-(4-(2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

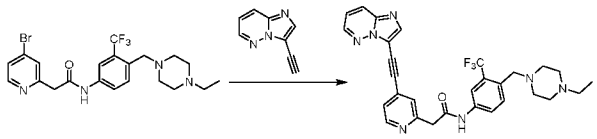
[000626] The title compound was synthesized following a method similar to general procedure B and starting from 3-ethynylimidazo[1,2-b]pyridazine and *tert*-butyl 4-(4-(2-(4-bromopyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by flash column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 97:3) gave *tert*-butyl 4-(4-(2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (250 mg, LC-MS 91%). MS (ESI) *m/z* 620.6 $[C_{32}H_{32}F_3N_7O_3 + H]^+$.

Step 3: Preparation of 2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-*N*-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)acetamide

[000627] The title compound was synthesized following a method similar to general procedure D and starting from *tert*-butyl 4-(4-(2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)acetamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The reaction crude product was purified by column chromatography (silica gel, eluent: $CHCl_3/CH_3OH$ 96:4) and preparative HPLC to give 2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-*N*-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)acetamide (60 mg, 30%, AUC HPLC 98.1%) as a yellow solid. m.p 93-96; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 10.53 (s, 1H), 8.73 (d, J = 4.0 Hz, 1H), 8.58 (d, J = 4.8 Hz, 2H), 8.27 (d, J = 5.2 Hz,

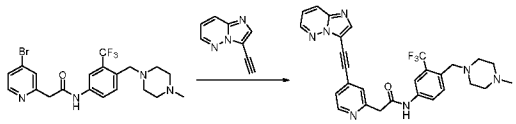
2H), 8.07 (s,1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H),7.46–7.40 (m,2 H), 3.93 (s, 2H), 3.50 (s, 2H), 2.79–2.65 (m, 4H), 2.38–2.22 (m, 4H) ; MS (ESI) *m/z* 520.5 $[C_{27}H_{24}F_3N_7O+H]^+$.

Example 198: Synthesis of N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)acetamide



[000628] The title compound was synthesized from 3-ethynylimidazo[1,2-b]pyridazine and 2-(4-bromopyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide carboxylate following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, eluent ($CHCl_3$/CH_3OH 97:3) and by preparative HPLC to afford *N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)acetamide (60 mg, 18%, AUC HPLC 99%) as a off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.89 (s, 1H), 8.64 (d, *J* = 4.8 Hz, 1H), 8.32 (d, *J* = 4.4 Hz, 1H), 8.11(s, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.70 (d, *J* = 8.0 Hz ,1H), 7.50 (s, 1H), 7.44 (d, *J* = 5.2 Hz, 1H),7.19–7.16 (m, 1H) 3.90 (s, 2H), 3.61 (s, 2H) 2.54 (brs, 10H), 1.10 (brs, 3H); MS (ESI) *m/z* 548.3 $[C_{29}H_{28}F_3N_7O$ +H$]^+$.

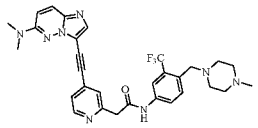
Example 199: Synthesis of 2-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000629] The title compound was synthesized from 3-ethynylimidazo[1,2-*b*]pyridazine and 2-(4-bromopyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3$/CH_3OH 96:4) and by preparative HPLC to afford 2-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (25 mg, AUC HPLC 96.2%) as a yellow solid. m.p.78–82 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.88 (s, 1H), 8.64 (d, *J* = 5.2 Hz 1H), 8.51(d, *J* =

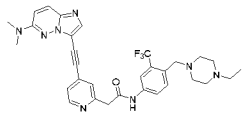
5.2 Hz 1H), 8.10 (s, 1H), 8.03 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz , 1H), 7.74 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.44 (m, 1H), 7.19 (d, *J* = 4.4 Hz ,1H), 3.90 (s, 2H), 3.60 (s, 2H), 2.43 (bs, 8H), 2.28 (s, 3H); MS (ESI) *m/z* 534.1 $[C_{28}H_{26}F_3N_7O +H]^+$.

Example 200: 2-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000630] The title compound was synthesized from 3-ethynyl-*N*,*N*-dimethylimidazo[1,2-*b*]pyridazin-6-amine and 2-(4-bromopyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide following a method similar to general procedure A. The reaction crude product was first purified by column chromatography (silica gel, eluent ($CHCl_3$/CH_3OH 95:5) and by preparative TLC gave 2-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3 (trifluoromethyl)phenyl)acetamide (20 mg, AUC HPLC 97%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.53 (s, 1H), 8.55 (d, *J* = 5.2 Hz, 1H), 8.07 (s, 1H), 7.90 (t, *J* = 6.0 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 7.39 (d, *J* = 5.2 Hz, 1H), 7.18(dd, *J* = 10.0 Hz,7.4 Hz, 1H), 3.91 (s, 2H), 3.53 (s, 2H), 3.11 (s, 6H), 2.36 (brs, 8H), 2.14 (s, 3H); MS (ESI) *m/z* 577.1 $[C_{30}H_{31}F_3N_8O +H]^+$.

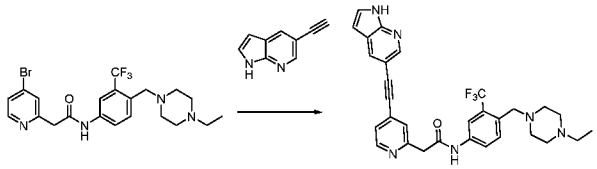
Example 201: 2-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000631] The title compound was synthesized from 3-ethynyl-*N*,*N*-dimethylimidazo[1,2-*b*]pyridazin-6-amine and 2-(4-bromopyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3(trifluoromethyl)phenyl)acetamide following a method similar to general procedure A. The reaction crude product was purified by column chromatography (silica gel, eluent $CHCl_3$/CH_3OH 96:4) and by preparative HPLC to afford 2-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (10 mg, AUC HPLC 91.9%) as a off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.53 (d, *J* = 5.2 Hz 1 H), 7.99 (s, 1H), 7.79–

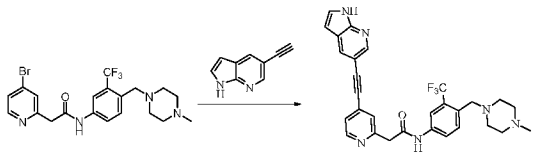
7.71 (m, 5H), 7.56(s, 1H), 7.43 (d, *J* = 5.2 Hz 1 H), 7.15 (d, *J* = 10 Hz, 1H), 3.95 (s, 2H), 3.63 (s, 2H), 3.18 (s, 6H), 2.53-2.46 (m, 10H), 1.10 (t, *J* = 5.6 Hz, 3H); MS (ESI) *m/z* 591.31 $[C_{31}H_{33}F_3N_8O + H]^+$.

Example 202: 2-(4-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000632] The title compound was synthesized from 5-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine and 2-(4-bromopyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 90:10) and by preparative TLC to give 2-(4-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (25 mg, AUC HPLC 98.5%) as a yellow solid; m.p. 114–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.97 (s, 1H), 10.53 (s, 1H), 8.54 (d, *J* = 5.6 Hz, 1H), 8.44 (d, *J* = 1.6 Hz, 1H), 8.24 (s, 1H), 8.07 (s, 1H), 7.78 (d, *J* = 7.6 Hz 1H), 7.66 (q, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 2.8 Hz, 1H), 7.42 (d, *J* = 5.2 Hz, 1H), 6.52 (d, *J* = 1.6 Hz, 1H), 3.90 (s, 2H), 3.53 (s, 2H), 2.44–2.32 (m, 10H), 0.97 (t, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* 547.36 $[C_{30}H_{29}F_3N_6O + H]^+$.

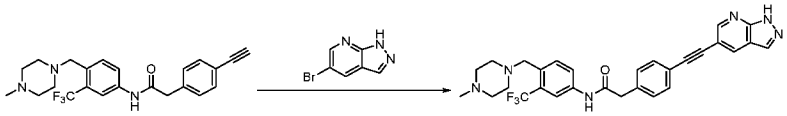
Example 203: 2-(4-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000633] The title compound was synthesized from 5-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine and 2-(4-bromopyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide following a method similar to general procedure A. The reaction crude product was purified by column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 96:4) and by preparative HPLC to afford 2-(4-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-

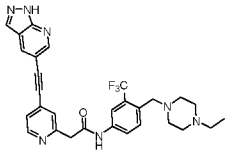
(trifluoromethyl)phenyl)acetamide (10 mg, AUC HPLC 96.1%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.53 (s, 1H), 8.54 (d, J = 5.2 Hz, 1H), 8.44 (s, 1H), 8.24 (s, 2H), 8.07 (s, 1H), 7.78 (d, J = 8.4 Hz 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 4.0 Hz, 1H), 7.55 (s, 1H), 7.55 (s, 1H), 7.42 (dd, J = 3.6 Hz,2.4 Hz, 1H), 3.90 (s, 2H), 3.53 (s, 2H), 2.36 (bs, 8H), 2.14 (s, 3H); MS (ESI) *m/z* 533.32[$C_{29}H_{27}F_3N_6O$ +H]$^+$.

Example 204: Synthesis of 2-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)phenyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000634] The title compound was synthesized from 2-(4-ethynylphenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide and 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine following a method similar to general procedure A. The residue was purified by preparative HPLC to afford 2-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)phenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (9.7 mg, 15% yield, AUC HPLC 99%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.89 (s, 1H), 10.52 (s, 1H), 8.67 (s, 1H), 8.46 (s, 1H), 8.19 (s, 1H), 8.05 (d, J = 1.7 Hz, 1H), 7.78 (d, J= 8.9 Hz, 1H), 7.65 (d, J= 8.5 Hz, 1H), 7.55 (d, J= 8.1 Hz, 2H), 7.40 (d, J= 8.2 Hz, 2H), 3.72 (s, 2H), 3.52 (s, 2H), 2.36-2.32 (m, 8H), 2.14 (s, 3H); MS (ESI) *m/z* 533.2 [$C_{29}H_{27}F_3N_6O$+H]$^+$.

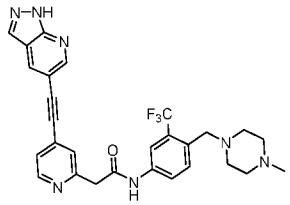
Example 205: 2-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000635] The title compound was synthesized from Intermediate 26 following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent $CHCl_3$/CH_3OH 96:4) and by preparative HPLC to give 2-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (10 mg, AUC HPLC 99%) as an off-white solid; m.p. 158–162 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.70 (d, J = 2.0 Hz 1H), 8.54 (t, J = 5.2 Hz, 1H), 8.47 (d, J = 2.0 Hz, 1H), 8.17 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.78 (d, J

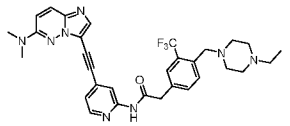
= 8.4 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.60 (s, 1H), 7.47(dd, *J* = 4.0, 2.8 Hz, 1H), 3.95 (s, 2H), 3.63 (s, 2H) 2.52 (bs, 8H), 2.46 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 548.3 $[C_{29}H_{28}F_3N_7O + H]^+$.

Example 206: 2-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



[000636] The title compound was synthesized from Intermediate 24 following a method similar to general procedure A. The crude product was purified by flash column chromatography (silica gel, eluent ($CHCl_3$/CH_3OH 96:4) and by preparative HPLC to give 2-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (15 mg, AUC HPLC 98.3%) as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.70 (d, *J* = 1.6 Hz, 1H), 8.53 (d, *J* = 1.6 Hz 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 8.17 (s, 1H), 7.99 (s,1H), 7.78 (dd, *J* = 10.0 Hz, 1.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.60 (s ,1H), 7.46 (dd, *J* = 3.6 Hz,2.4 Hz, 1H), 3.96 (s, 2H), 3.63 (s, 2H), 2.52 (bs, 8H), 2.30 (s, 3H); MS (ESI) *m/z* 534.5$[C_{28}H_{26}F_3N_7O + H]^+$.

Example 207: N-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



Step 1: Preparation of (4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)methanol.

[000637] To a suspension of $LiAlH_4$ (0.77 g, 22.64 mmol) in THF (50 mL) was added methyl 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoate (5 g, 15.15 mmol) in THF (5 mL) at 0 °C dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 6 h, was then cooled to 0 °C, quenched with saturated Na_2SO_4 and the mixture thus obtained was filtered through a short pad of celite. The filtrate was dried over anhydrous Na_2SO_4, filtered and dried under vacuum to afford (4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)methanol (4.3 g, 95%, AUC HPLC 96%) as a pink

liquid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 7.68 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 5.31 (t, J = 5.6 Hz, 1H), 4.54 (d, J = 5.6 Hz, 2H), 3.57 (s, 2H), 2.37–2.29 (m, 10H), 0.97 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z* 303.1 $[C_{15}H_{21}F_3N_2O+H]^+$.

Step 2: Preparation of 1-(4-(chloromethyl)-2-(trifluoromethyl)benzyl)-4-ethylpiperazine 4.

[000638] To a solution of (4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)methanol 3 (4.3 g, 14.23 mmol) in dichloromethane (40 mL) was added TEA (5.7 g, 56.43 mmol) at 0 °C and the resulting mixture was stirred for 20 minutes at room temperature, then was cooled to 0 °C prior to the addition of mesyl chloride (4.0 g, 35.08 mmol). The reaction mixture was stirred at room temperature for 16 h and was diluted with EtOAC then washed in turn with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and dried under vacuum to afford 1-(4-(chloromethyl)-2-(trifluoromethyl)benzyl)-4-ethylpiperazine (3.2 g, 71%, AUC HPLC 97%) as a pink color liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.6–7.66 (m, 2H), 7.55 (d, J = 8.4 Hz, 1H), 4.59 (s, 2H), 3.72 (s, 2H), 2.81–2.77 (m, 10H), 1.30 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z* 321.1 $[C_{15}H_{20}ClF_3N_2+H]^+$.

Step 3: Preparation of 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-trifluoromethyl)phenyl)acetonitrile.

[000639] To a solution of 1-(4-(chloromethyl)-2-(trifluoromethyl)benzyl)-4-ethylpiperazine 4 (3.2 g, 10.0 mmol) in DMSO (40 mL) was added NaCN (0.98 g, 20.0 mmol) and the mixture was heated at 100 °C for 16 h. The reaction mixture was diluted with EtOAc and washed in turn with water (1 x 25 mL) and brine (1 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and dried under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent dichloromethane/methanol 95:5) to afford 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetonitrile (3.0 g, 96.4%, LC-MS 88%) as a pink liquid. MS (ESI) *m/z* 312 $[C_{16}H_{20}F_3N_3+H]^+$.

Step 4: Preparation of 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetic acid hydrochloride

[000640] A solution of 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetonitrile (3.0 g, 9.64 mmol) in 6N HCl (75 mL) was heated at 90 °C for 14 h was cooled to 0 °C and was diluted with methanol (3 mL) and diethyl ether. The solid was isolated by filtration and dried under to afford 2-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) acetic acid hydrochloride salt (2.0 g, 52.6%, LC-MS 85%) as a white solid. MS (ESI) *m/z* 331 $[C_{16}H_{22}ClF_3N_2O_2+H]^+$.

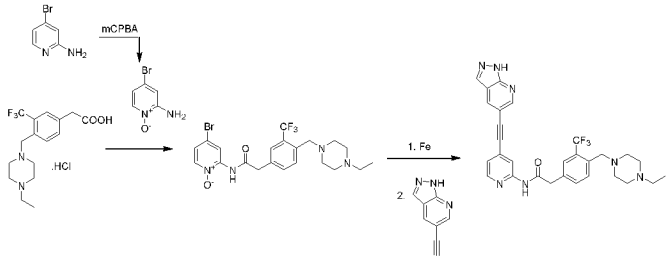
Step 5: Preparation of 3-((2-aminopyridin-4-yl)ethynyl)-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine

[000641] The title compound was synthesized following a method similar to general procedure A and starting from 4-iodopyridin-2-amine and 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine. The crude product was purified by flash column chromatography (silica gel, eluent dichloromethane/methanol 97:3) to afford 3-((2-aminopyridin-4-yl)ethynyl)-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine (250 mg, 86%, LC-MS 65%) as a pale yellow solid. MS (ESI) *m/z* 279 $[C_{15}H_{14}N_6+H]^+$.

Step 6: *N*-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide.

[000642] To a solution of 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetic acid hydrochloride salt (170 mg, 0.51 mmol) in pyridine (1.7 ml) were successively added 3-((2-aminopyridin-4-yl)ethynyl)-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine A (140 mg, 0.50 mmol), $POCl_3$ (1.2 mL) at 0 °C and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc and basified with aqueous $NaHCO_3$. The organic layer was washed in turn with water and brine then, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol 90:10) to afford *N*-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (5 mg, AUC HPLC 98.61%) as a yellow solid. ^{1}H NMR(400 MHz, $CDCl_3$) δ (ppm): 8.36 (s, 1H), 8.22 (d, *J* = 5.6 Hz, 1H), 7.83–7.81 (m, 2H), 7.71–7.62 (m, 3H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 4.0 Hz, 1H), 6.83 (d, *J* = 10.0 Hz, 1H), 3.78 (s, 2H), 3.74 (s, 2H), 3.18 (s, 6H), 2.99–2.60 (m, 10H), 1.33 (bs, 3H), MS (ESI) *m/z*: 591.3 $[C_{31}H_{33}F_3N_8O+H]^+$.

Example 208: Synthesis of N-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



Step 1: Preparation 2-amino-4-bromopyridine 1-oxide

[000643] To a solution of 4-bromopyridin-2-amine (4.0 g, 23.12 mmol) in dichloromethane (20 mL) was added *m*CPBA (7.9 g, 45.93 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and was concentrated to a smaller volume. The residue was purified by flash column chromatography (silica gel, eluent, dichloromethane/MeOH 96:4) to afford 2-amino-4-bromopyridine 1-oxide (4 g, 93%, LC-MS 90%) as a white solid. ^{1}H NMR(400 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 6.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H) 6.75 (dd, *J* = 2.4, 7.2 Hz, 1H), 5.75 (s, 2H); MS (ESI) *m/z* 189 $[C_5H_5BrN_2O+H]^+$

Step 2: Preparation of 4-bromo-2-(2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamido)pyridine 1-oxide

[000644] To a solution of 2-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) acetic acid hydrochloride (300 mg, 0.909 mmol) in DMF (10 mL) was added HATU (260 mg, 1.631 mmol), DIPEA (0.67 ml, 3.636 mmol) and 2-amino-4-bromopyridine 1-oxide (260 mg, 1.375 mmol). The reaction mixture was stirred at room temperature for 16 h and was diluted with EtOAc. The organic layer was washed with water and brine then was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane/CH_3OH 95:5) to afford 4-bromo-2-(2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamido)pyridine-1-oxide (200 mg, 44.4%, LC-MS 40%) as a pale yellow solid. MS (ESI) *m/z* 501 $[C_{21}H_{24}BrF_3N_4O_2+H]^+$.

Step 3: Preparation of *N*-(4-bromopyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide

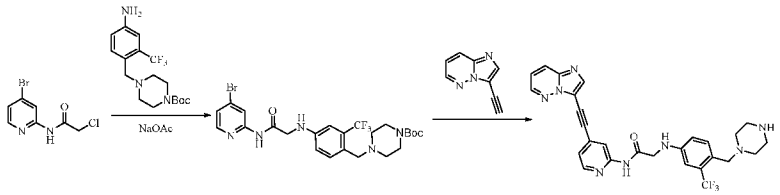
[000645] A slurry constituted of solution of 4-bromo-2-(2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamido)pyridine-1-oxide (200 mg, 0.399 mmol) and iron (110 mg, 1.964 mmol) in AcOH (5 mL) was heated at 95 °C for 1 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: dichloromethane/MeOH 95:5) to afford *N*-(4-bromopyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (80 mg, 42%); MS (ESI) *m/z* 487 $[C_{21}H_{24}BrF_3N_4O+3]^+$.

Step 4: Preparation of *N*-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide

[000646] The title compound was synthesized following a method similar to general procedure A and starting from *N*-(4-bromopyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-

3-(trifluoromethyl)phenyl)acetamide and 5-ethynyl-1H-pyrazolo[3,4-b]pyridine. The reaction crude product was purified by preparative TLC (dichloromethane/MeOH 80:20) to afford *N*-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (30 mg, 33.3%, AUC HPLC 96.2%) as an off white solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.69 (s, 1H), 8.46 (s, 1H), 8.31 (d, *J* = 4.8 Hz, 1H), 8.22 (s, 1H), 8.16 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H) 7.69 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 5.2 Hz, 1H), 3.84 (s, 2H), 3.67 (s, 2H), 2.55–2.48 (m, 10H), 1.10 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z*: 548.33 $[C_{29}H_{28}F_3N_7O + H]^+$.

Example 209: N-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-2-((4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)acetamide



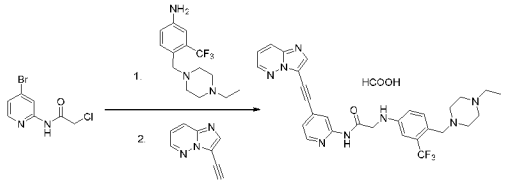
[000647] Step 1: Preparation of *tert*-butyl 4-(4-((2-((4-bromopyridin-2-yl)amino)-2-oxoethyl)amino)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; A solution of *N*-(4-bromopyridin-2-yl)-2-chloroacetamide (50 mg, 0.200 mmol), *tert*-butyl 4-(4-amino-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (108 mg, 0.300 mmol), NaOAc (33 mg, 0.400 mmol) in EtOH (5 mL) was refluxed at 90°C for 15 h. The solvents were then removed *in vacuo* and the crude purified by flash column chromatography (silica gel, eluent: EtOAc) to afford *tert*-butyl 4-(4-((2-((4-bromopyridin-2-yl)amino)-2-oxoethyl)amino)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (55 mg). MS (ESI) *m/z* 573 $[C_{24}H_{29}BrF_3N_5O_3 + H]^+$.

[000648] Step 2: Preparation of *tert*-butyl 4-(4-((2-((4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)amino)-2-oxoethyl)amino)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate; The title compound was synthesized from *tert*-butyl 4-(4-((2-((4-bromopyridin-2-yl)amino)-2-oxoethyl)amino)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 3-ethynylimidazo[1,2-b]pyridazine following a method similar to general procedure A. The crude was purified by flash column chromatography (silica gel, eluent: EtOAc/MeOH 95:5) to afford *tert*-butyl 4-(4-((2-((4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)amino)-2-oxoethyl)amino)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (54 mg, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.10 (s, 1H), 8.50 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.48 (s, 1H), 8.24

(dd, *J* = 5.1, 0.9 Hz, 1H), 8.10 (s, 1H), 8.03 (dd, *J* = 9.2, 1.7 Hz, 1H), 7.23 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.17 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.84 (s, 1H), 4.02 (d, *J* = 5.5 Hz, 2H), 3.51 (s, 4H), 2.76 (s, 1H), 2.48 (s, 4H), 1.44 (s, 9H), 1.28 – 1.19 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 177.7, 168.8, 162.6, 154.56, 151.00, 147.98, 144.17, 139.70, 134.62, 134.14, 133.15, 132.91, 126.20, 125.08, 123.26, 121.97, 118.36, 116.34, 115.73, 110.84, 96.60, 81.11, 52.60, 48.94, 36.63, 31.58, 29.77, 28.49. MS (ESI) *m/z* 635 $[C_{32}H_{33}F_3N_8O_3 + H]^+$.

[000649] Step 3: Preparation of *N*-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-2-((4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)acetamide; The title compound was synthesized following a method similar to general procedure D and starting from *tert*-butyl 4-(4-((2-((4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)amino)-2-oxoethyl)amino)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The crude productwas purified by preparative HPLC to afford *N*-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)-2-((4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)acetamide (25.1 mg, 55%, AUC HPLC: 99.0%) as a red solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.77 (s, 1H), 8.74 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.41 (dd, *J* = 5.0, 0.9 Hz, 1H), 8.30 (s, 1H), 8.28 (dd, *J* = 9.2, 1.6 Hz, 1H), 8.22 (s, 1H), 7.43 (dd, *J* = 9.2, 4.5 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.5 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.54 (t, *J* = 6.4 Hz, 1H), 4.06 (d, *J* = 6.3 Hz, 2H), 3.44 (s, 2H), 2.93–2.83 (m, 4H), 2.41 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 170.2, 152.0, 148.9, 147.5, 145.2, 140.1, 139.5, 132.1, 131.4, 128.0, 126.2, 125.6, 122.9, 120.3, 119.6, 114.9, 114.0, 110.9, 109.4, 96.1, 80.9, 57.6, 51.1, 46.4, 43.9; MS (ESI) *m/z* 536 $[C_{27}H_{25}F_3N_8O + H]^+$

Example 210: 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-N-(4-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)acetamide

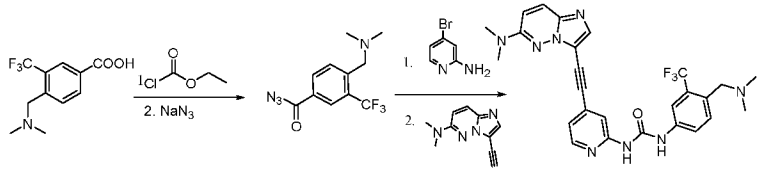


[000650] Step 1: Preparation of 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-*N*-(4-bromopyridin-2-yl)acetamide and 3-ethynylimidazo[1,2-*b*]pyridazine; A solution of *N*-(4-bromopyridin-2-yl)-2-chloroacetamide (50 mg, 0.20 mmol), 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (86 mg, 0.300 mmol), NaOAc (33 mg, 0.40 mmol) in EtOH (5 mL) was refluxed at 90°C for 15 h. The solvents were then

removed *in vacuo* and the crude purified by flash column chromatography (silica gel, eluent: dichloromethane/MeOH 85:15) and by preparative HPLC to afford *N*-(4-bromopyridin-2-yl)-2-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)acetamide (30 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.28 (s, 1H), 8.53 (s, 1H), 8.40 (s, 2H), 8.04 (d, *J* = 5.3 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 5.3, 1.8 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.99 (s, 2H), 3.60 (s, 2H), 2.97 (q, *J* = 7.1 Hz, 2H), 2.74 (m, 4H), 1.30 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 169.2, 167.1, 151.5, 148.2, 146.2, 135.0, 132.7, 130.6, 130.4, 130.2, 130.0, 123.7, 117.4, 115.5, 111.5, 57.6, 51.6, 51.2, 49.7, 49.0, 34.8, 9.3. (ESI) *m/z* 500 $[C_{21}H_{25}BrF_3N_5O + H]^+$.

[000651] Step 2: Preparation of 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)acetamide; The title compound was synthesized from 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-*N*-(4-bromopyridin-2-yl)acetamide and 3-ethynylimidazo[1,2-*b*]pyridazine following a method similar to general procedure A. The reaction crude product was purified by preparative HPLC to afford 2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-*N*-(4-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)acetamide formic acid salt (5.1 mg, 17%, AUC HPLC 95.4%) as a brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.70 (s, 1H), 8.75–8.71 (m, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 8.29 (s, 1H), 8.28–8.25 (m, 1H), 8.22 (s, 1H), 8.14 (s, 1H), 7.42 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.28 (dd, *J* = 4.5, 1.0 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.48 (t, *J* = 6.4 Hz, 1H), 4.05 (d, *J* = 6.2 Hz, 2H), 2.48–2.33 (m, 6H), 1.01 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 170.2, 163.1, 151.9, 148.8, 147.4, 145.2, 140.0, 139.4, 131.9, 131.4, 127.8, 126.2, 125.5, 123.7, 123.4, 120.3, 119.6, 115.0, 114.0, 110.9, 109.3, 96.1, 80.8, 57.3, 52.0, 51.3, 46.5, 39.9, 11.3; MS (ESI) *m/z* 564 $[C_{29}H_{29}F_3N_8O + H]^+$.

Example 211: 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea



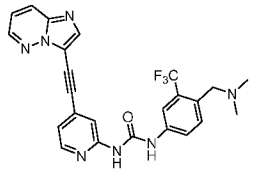
[000652] Step 1: 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoyl azide; To a mixture of 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoic acid (4 g, 16.19 mmol),

triethylamine (3.4 g, 24.29 mmol) in THF (40 mL) was added dropwise ethyl chloroformate (2.27 g, 21.09 mmol) slowly at -10 °C. The resulting mixture was stirred for 2 h prior to the addition of a solution of NaN_3 (1.78 g , 27.63 mmol) in water (100 mL). The resulting mixture was stirred for 2 h at room temperature, was poured into ice-cold water (80 mL) and extracted into ethyl acetate (80 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoyl azide (2.5 g, 56.8 %) as a yellow liquid; MS (ESI) *m/z* 273.09 $[C_{11}H_{11}F_3N_4O+H]^+$.

[000653] Step 2: 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea; A mixture of 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoyl azide (1 g, 3.67 mmol) and 2-amino 4-bromo pyridine (636 mg, 3.67 mmol) in toluene was refluxed for 5 h. The reaction mixture was cooled to room temperature and the precipitate was isolated by filtration and dried to afford 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea (1.0 g, 65.35%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.19 (s, 1H), 9.59 (s, 1H), 8.94 (s, 1H), 8.20 (d , J = 5.2 Hz, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.67–7.61 (m, 1H), 7.29–7.27 (m, 1H), 3.47 (s, 2H), 2.17 (s, 6H) ; MS (ESI) *m/z* 417.0 $[C_{16}H_{16}BrF_3N_4O+H]^+$.
Step 3: 1-(4-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea

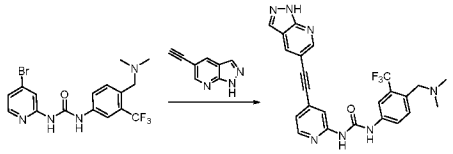
[000654] The title compound was synthesized startinf from 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea and 3-ethynyl-*N*,*N*-dimethylimidazo[1,2-*b*]pyridazin-6-amine following a method similar to general procedure A. The reaction crude product was purified by flash column chromatography (silica gel, eluent DCM/CH_3OH 95/5) and by preparative TLC to afford 1-(4-((6-(dimethylamino)imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea (70 mg, AUC HPLC 97.1%) as a pale yellow solid; m.p. 224–226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.41 (s, 1H), 9.59 (s, 1H), 8.35 (d, J = 5.6 Hz, 1H), 8.04 (s, 1H), 7.93–7.90 (m, 2H), 7.74 (s, 1H), 7.68–7.62 (m,. 2H), 7.20 (d, J = 9.6 Hz, 1H), 7.11 (d, J = 4.0 Hz 1H), 3.47 (s, 2H), 3.15 (s, 6H), 2.17 (s, 6H); MS (ESI) *m/z*: 523.0 $[C_{26}H_{25}F_3N_8O]^+$.

Example 212: Synthesis of 1-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-b]pyridazin-3-ylethynyl)pyridin-2-yl)urea



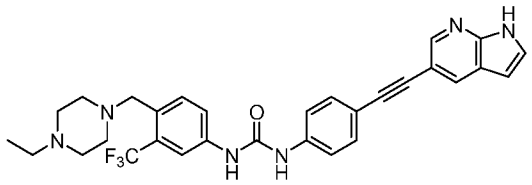
[000655] The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino) methyl)-3-(trifluoromethyl)phenyl)urea and 3-ethynylimidazo[1,2-*b*]pyridazine following a method similar to general procedure A. The crude product was purified by flash column chromatography (CH_2Cl_2/CH_3OH 98:2 to 97:3) to afford 1-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)pyridin-2-yl)urea (20 mg, AUC HPLC 95.0%) as a yellow solid; m.p. 223–226 °C; ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 10.26 (s, 1H), 9.57 (s, 1H) 8.75 (d, *J* = 3.2 Hz, 1H), 8.36 (d, *J* = 4.8 Hz, 1H), 8.31–8.27 (m, 2H) 8.02 (s, 1H), 7.81 (s, 1H), 7.67–7.65 (m, 2H), 7.44–7.74 (m, 1H), 7.19 (d, *J* = 4.8 Hz, 1H), 3.48 (s, 2H), 2.18 (s, 6H); MS (ESI) *m/z* 480.09 $[C_{24}H_{20}F_3N_7O+H]^+$.

Example 213: 1-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea



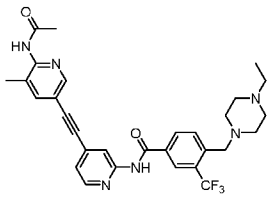
[000656] The title compound was synthesized from 1-(4-bromopyridin-2-yl)-3-(4-((dimethylamino) methyl)-3-(trifluoromethyl) phenyl) urea and 5-ethynyl-1*H*-pyrazolo [3, 4-*b*]pyridine following a method similar to general procedure A. The crude product was purified by preparative HPLC to afford 1-(4-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea (130 mg, 11%, AUC HPLC 94.1%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.90 (s, 1H), 10.28 (s, 1H), 9.55 (s, 1H), 8.75 (d, *J* = 2 Hz, 1H), 8.58 (d, *J* = 1.6 Hz, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.23 (s, 1H), 8.02 (s,1H), 7.79 (s, 1H), 7.68-7.61 (m, 2H), 7.19 (d, *J* = 3.6 Hz, 1H), 3.47 (s, 2H), 2.17 (s, 6H); MS (ESI) *m/z* 480.1 $[C_{24}H_{20}F_3N_7O+H]^+$.

Example 214, Preparation of 1-(4-((1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



A solution of **Intermediate 23** (500 mg, 1.16 mmol), 5-Bromo-7-azaindole (270 mg, 1.39 mmol) and DIPEA (0.31 mL, 1.74 mmol) in DMF (5 mL) was degassed with argon. To the reaction mixture $Pd(PPh_3)_4$ (67 mg, 0.058 mmol), and CuI (33 mg, 0.17 mmol) were added and degassed again with argon. The reaction mixture was heated at 80 °C for 3 h under argon and was diluted with water and extracted with EtOAc. The organic layer was washed with water, brine dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using 5% MeOH in dichloromethane to afford 160 mg of 1-(4-((1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea as an off white solid (25.23%, AUC HPLC 95.43%.). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.09 (s, 1H), 9.65 (bs, 1H), 9.40 (bs, 1H), 9.29 (s, 1H), 8.37 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 7.97 (s, 1H), 7.63–7.48 (m, 6H), 6.48 (s, 1H), 3.61 (s, 2H), 3.28–2.67 (m, 6H), 2.45–2.33 (m, 4H), 1.18 (t, J = 7.2 Hz, 3H). LC-MS: m/z 547.31 (M+H)

Examples 215: Preparation of N-(4-((6-acetamido-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and N-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



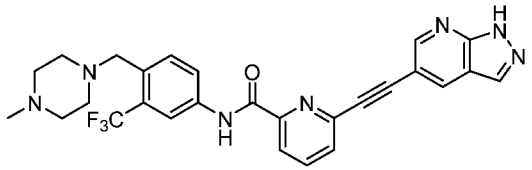
Step 1: Preparation of *N*-(3-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide. To a solution of *N*-(5-bromo-3-methylpyridin-2-yl)acetamide (200 mg, 0.87 mmol) in DMF (2.0 mL) was added tetrakis (53 mg, 0.04 mmol), cupper iodide (13 mg, 0.07 mmol) and degassed with N_2 for 20 min before DIPEA (228 □L, 1.31 mmol) and ethynyltrimethylsilane (616 □L. 4.36 mmol) were added and stirred at 80 °C for 18h. The residue mixture was purified by column chromatography (silica gel, eluents Hex/EtOAc 4:1) to afford *N*-(3-methyl-5-

((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (153 mg, 71%, AUC HPLC 94 %) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.02 (s, 1H), 7.61 (s, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 0.24 (s, 9H); MS (ESI) *m/z* 247 $[C_{13}H_{18}N_2OSi + H]^+$.

Step 2: Preparation of *N*-(5-ethynyl-3-methylpyridin-2-yl)acetamide. To a solution of *N*-(3-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (153 mg, 0.62 mmol) in MeOH (10 mL) was added potassium carbonate (300 mg, 3.49 mmol) and stirred at rt for 4h. The residue mixture was concentrated under reduced pressure, then diluted with water (100 mL) and extracted with DCM (3×15 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure to afford *N*-(5-ethynyl-3-methylpyridin-2-yl)acetamide (40 mg, 37%) as brown solid; MS (ESI) *m/z* 175 $[C_{10}H_{10}N_2O + H]^+$.

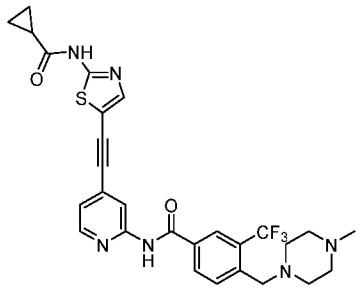
Step 3: Preparation of *N*-(4-((6-acetamido-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. To a solution of *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamideamine (50 mg, 0.106 mmol) in DMF (2.0 mL) was added *N*-(5-ethynyl-3-methylpyridin-2-yl)acetamide (40 mg, 0.230 mmol), bis(triphenylphosphine) palladium(II) dichloride (9.7 mg, 0.014mmol), cupper iodide (2.0 mg, 0.011 mmol), triphenyl phosphate (9.7 mg, 0.037 mmol) and degassed with N_2 for 20 min before DIPEA (0.5 ml, 2.87 mmol) was added and stirred at 80 ^{o}C for 18h. The reaction mixture was filtrated and purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford the de-acteylated product *N*-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (6 mg, AUC HPLC 99 %) as a yellow solid; m.p 124 –126 °C and the desired product *N*-(4-((6-acetamido-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (26 mg, 43%, AUC HPLC 98 %) as brown solid; mp 109 – 111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.64 (s, 1H), 8.53 (s, 1H), 8.42 (s, 1H), 8.32 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.56 (s, 1H), 7.19 (t, *J* = 3.1 Hz, 1H), 3.75 (s, 2H), 2.80 – 2.50 (m, 10H), 2.35 (s, 3H), 2.30 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.24, 151.45, 149.50, 148.76, 148.02, 142.68, 142.33, 133.39, 132.75, 131.03, 130.27, 129.61, 125.07, 125.01, 122.06, 116.15, 90.54, 89.61, 57.92, 52.69, 52.47, 52.10, 24.15, 17.94, 11.48; MS (ESI) *m/z* 565 $[C_{30}H_{31}F_3N_6O_2 + H]^+$.

Example 216, Preparation of 6-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide



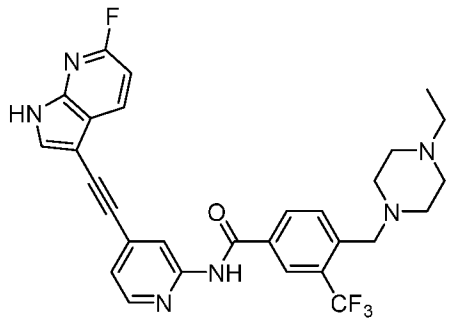
Intermediate 14 (178 mg, 0.391 mmol), 5-ethynyl-1*H*-pyrazolo[3,4-b]pyridine (84 mg, 0.586 mmol), Bis(triphenylphosphine)palladium(II) dichloride (16.5 mg, 0.0235 mmol), triphenylphosphine (35.8 mg, 0.137 mmol) and copper iodide (7.4 mg, 0.391 mmol) was dissolved in anhydrous DMF (2.0 mL), followed by the addition of triethylamine (2.0 mL, 14.3 mmol). The reaction mixture was heated to 80°C for 2 hours and was filtered through celite. The filtrate was concentrated under reduced pressure and purified by preparative HPLC to afford 6-((1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)picolinamide as off-white solid (10 mg, 0.0193 mmol, 4.9%, AUC HPLC 99.90%;) mp: 112.4-113.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.00 (s, 1H), 10.83 (s, 1H), 8.78 (d, 1H, *J* = 1.9 Hz), 8.60 (d, 1H, J = 1.9 Hz), 8.38-8.37 (m, 1H), 8.26-8.23 (m, 1H), 8.19-8.12 (m, 3H), 7.97-7.95 (m, 1H), 7.72 (d, 1H, *J* = 8.5 Hz), 3.58 (s, 1H), 2.40-2.32 (m, 8H), 2.16 (s, 3H); ESI-MS, m/z 520.2 $[C_{27}H_{24}F_3N_7O+H]^+$

Example 217, Preparation of N-(4-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



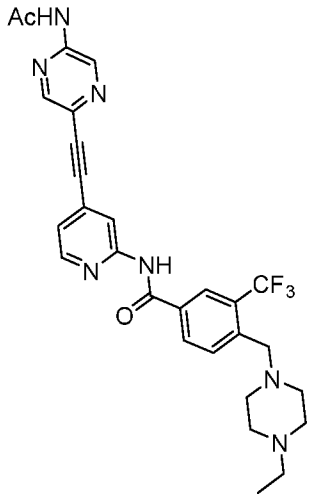
The title compound was prepared in the amount of 110 mg (15.5%, AUC HPLC 99%) as an off-white solid using general procedure B and Intermediate 15. mp: 214–216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.81 (s, 1H), 11.26 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 8.34–8.28 (m, 3H), 7.65–7.90 (m, 2H), 7.70 (d, *J* = 3.0 Hz, 1H), 3.67 (s, 2H), 2.50–2.36 (m, 8H), 2.17 (s, 3H), 1.99–1.96 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 4 H). MS (ESI) m/z: 569.01 $[C_{28}H_{27}F_3N_6O_2S+H]^+$.

Example 218: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



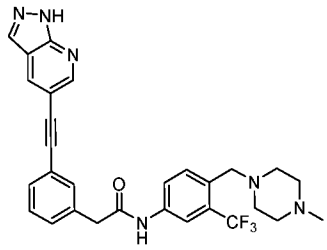
To a solution of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide (70 mg, 0.168 mmol) in DMF (2.0 mL) was added 6-fluoro-3-iodo-1*H*-pyrrolo[2,3-b]pyridine (88 mg, 0.336 mmol), bis(triphenylphosphine)palladium(II) dichloride (15.3 mg, 0.022 mmol), cupper iodide (3.2 mg, 0.017 mmol), triphenyl phosphate (15.4 mg, 0.059 mmol) and degassed with N_2 for 20 min before DIPEA (0.5 ml, 2.87 mmol) was added and stirred at 80 °C for 18 h. The reaction mixture was filtered and rinsed with MeOH before purified by preparative HPLC (C18, eluents ACN/H_2O/HCOOH 0.1%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-fluoro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (15 mg, 16 %, AUC HPLC 95 %) as brown solid; m.p 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.45 (s, 1H), 8.69 (s, 1H), 8.54 (s, 1H), 8.29 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.20 (q, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.75 (s, 2H), 2.58 (s, 8H), 2.50 (q, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.26, 159.85, 151.39, 147.90, 144.29, 142.78, 134.36, 133.12, 132.77, 131.03, 130.22, 128.84, 125.05, 124.99, 121.84, 118.24, 115.79, 103.05, 97.27, 89.24, 87.36, 57.97, 53.01, 52.70, 52.23, 11.76; MS (ESI) *m/z* 551 $[C_{29}H_{26}F_4N_6O + H]^+$.

Example 219, Preparation of N-(4-((5-acetamidopyrazin-2-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



To a solution of *N*-(5-bromopyrazin-2-yl)acetamide (100 mg, 0.462 mmol) and DIPEA (0.18mL) in DMF (0.5 mL) under argon were successively added Intermediate 17 (211 mg, 0.509 mmol), $PdCl_2(dppf)_2$ (16.8 mg, 0.0231 mmol) and CuI (13.1 mg, 0.069 mmol) and heated at 80 °C for 15 h. The reaction mixture was diluted with water (30 mL) extracted into EtOAc (50 mL), washed in turn with water and brine. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent CH_2Cl_2/MeOH 95:5) to afford *N*-(4-((5-acetamidopyrazin-2-yl)ethynyl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (55 mg, 21.5%, AUC HPLC 98.45%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO–d_6) δ: 11.30 (s, 1H), 11.06 (s, 1H), 9.37 (s, 1H), 8.74 (s, 1H), 8.49 (d, J = 4.8 Hz, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 3.68 (s, 2H), 2.45–2.29 (m, 10H), 2.17 (s, 3H), 0.98 (t, J = 7.0 Hz, 3H). MS (ESI) *m/z*: 552.3 $[C_{28}H_{28}F_3N_7O_2+H]^+$

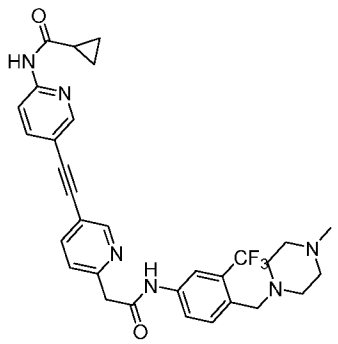
Example 220, Preparation of 2-(3-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)phenyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



Step 1: Preparation of 2-(3-bromophenyl)-*N*-(4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl)acetamide. To a solution of 4-((4-methylpiperazin-1-yl) methyl)-3-(trifluoromethyl) aniline (300 mg, 1.094 mmol) in DMF (5 mL) was added DIPEA (0.3 mL, 1.641 mmol) and HATU (831 mg, 2.188 mmol). The mixture was stirred at room temperature for 30 min, prior to the addition of 2-(3-bromophenyl) acetic acid (282 mg, 1.313 mmol). The reaction mixture was stirred for 6 h, was diluted with EtOAc and washed in turn with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent $CHCl_3/CH_3OH$ 95:5) to afford 2-(3-bromophenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (300 mg, LC-MS-78%) as a yellow solid. MS (ESI) *m/z* 470.1, 472.12 (Bromo pattern) $[C_{21}H_{23}BrF_3N_3O+H]^+$

Step 2: Preparation of 2-(3-((7,7a-dihydro-4a*H*-pyrrolo[3,4-b]pyridin-3-yl)ethynyl)phenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide. The title compound was prepared from 2-(3-bromophenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide in the amount of 20 mg (5.8%, AUC HPLC 96%) as an off-white solid using a Sonogashira coupling conditions similar to general procedure B. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 13.91 (s, 1H), 10.61 (s, 1H), 8.68 (s, 1H), 8.48 (s, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.41 (d, J = 5.6 Hz, 2H), 3.73 (s, 2H), 3.60 (s, 2H), 3.15–2.97 (m, 4H), 2.68–2.61 (m, 7H). MS (ESI) *m/z* 533.35 $[C_{29}H_{27}F_3N_6O+H]^+$

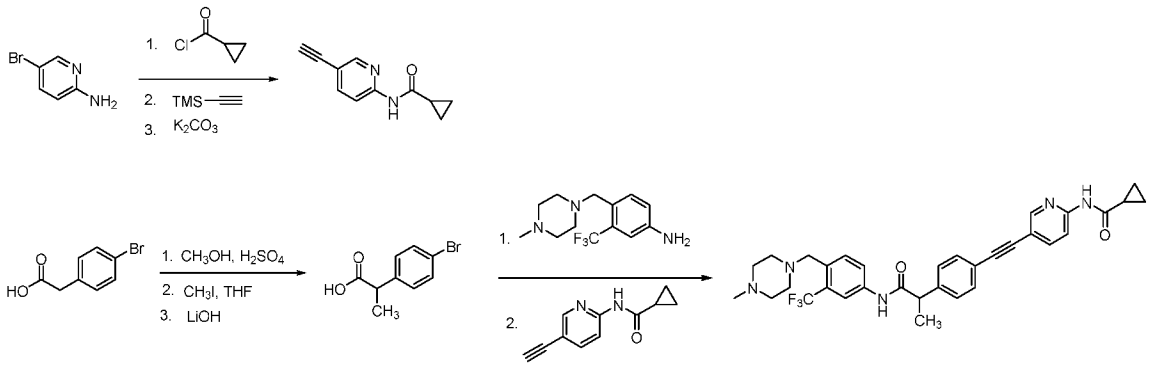
Example 221, Preparation of N-(5-((6-(2-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)pyridin-3-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



Step 1: 2-(5-bromopyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide. To a solution of 2-(5-bromopyridin-2-yl)acetic acid (500 mg, 2.31 mmol), HATU (1.75 g, 4.62 mmol) and DIPEA (0.79 mL, 4.62 mmol) in THF (20 mL) was added 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (696 mg, 2.54 mmol). The reaction mixture was stirred at room temperature for 6 h, was concentrated under reduced pressure, diluted with water, extracted with EtOAc. The combined organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-(5-bromopyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (700 mg). MS (ESI) *m/z* 471.2 $[C_{20}H_{22}BrF_3N_4O+H]^+$

Step 2: Synthesis of *N*-(5-((6-(2-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)pyridin-3-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide. The title compound was prepared from intermediate 2-(5-bromopyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide in the amount of 40 mg (4.6%, AUC HPLC 99.33%) as a pale brown solid using Sonogashira coupling conditions similar to general procedure B. mp: 222–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.94 (s, 1H), 10.56 (s, 1H), 8.69 (d, *J* = 1.2 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.06 (s, 1H), 7.97–7.93 (m, 2H), 7.77 (d, *J* = 9.6 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 2H), 3.53 (s, 2H), 2.37–2.35 (m, 8H), 2.16 (s, 3H), 2.04–2.01 (m, 1H), 0.84–0.83 (m, 4H). MS (ESI) *m/z* 577.25 $[C_{31}H_{31}F_3N_6O_2+H]^+$

Example 222: Preparation of N-(5-((4-(1-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-1-oxopropan-2-yl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



Step 1: synthesis of *N*-(5-bromopyridin-2-yl)cyclopropanecarboxamide. To 5-bromopyridin-2-amine (2.00 g, 11.5 mmol) in anhydrous dichloromethane (20 mL) was treated with cyclopropanecarbonyl chloride (1.20 g, 11.5 mmol) dropwise at -78 °C. The reaction mixture was stirred at rt for 16 hours and ice water was added. The aqueous layer was extracted with ethyl acetate (100 mL x 2). The combined organic extracts were washed with brine (200 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography (Redisep silica gel, 9:1 hexanes/ ethyl acetate) to afford *N*-(5-bromopyridin-2-yl)cyclopropanecarboxamide (1.68 g, AUC HPLC 95.86%; 60% yield) as pale green amorphous solid. ESI MS, m/z 240.90 and 242.80 (1: 1) ($[C_9H_9BrN_2O]^+$, Br isotopes).

Step 2: synthesis of *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide. To a round bottom flask with reflux condenser was added *N*-(5-bromopyridin-2-yl)cyclopropanecarboxamide (1.00 g, 4.14 mmol), $PdCl_2(PPh_3)_2$ (291 mg, 0.41 mmol), copper(I) iodide (79 mg, 0.41 mmol) and ethynyltrimethylsilane (0.44 g, 4.56 mmol) in anhydrous triethylamine (8 mL). The reaction mixture was purged with nitrogen gas for 5 minutes. The mixture was then heated at 80 °C for 4 hours. The solution was cooled to room temperature, filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 19:1 hexanes/ ethyl acetate) to afford *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (806 mg, 75%) as yellow solid. ESI MS, m/z 259.0 $[C_{14}H_{18}N_2OSi+H]^+$.

Step 3: Synthesis of *N*-(5-ethynylpyridin-2-yl)cyclopropanecarboxamide. To *N*-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide (800 mg, 0.30 mmol) in anhydrous methanol (10 mL) was treated with potassium carbonate (231 mg, 0.15 mmol). The mixture was stirred at room temperature for 2 hours. Reaction was completed and

methanol was evaporated under reduced pressure. The residue was dissolved in a mixture was poured into water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL x2). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced. The residue was purified by flash chromatography (Redisep silica, 99:1 dichloromethane/ ethyl acetate) to afford *N*-(5-ethynylpyridin-2-yl)cyclopropanecarboxamide (66.8 mg, AUC HPLC 98.8%: 16% yield) as off- white amorphous solid. ESI MS, m/z 187.1 $[C_{11}H_{10}N_2O+H]^+$

Step 4: Synthesis of Methyl 2-(4-bromophenyl)acetate. A solution of 2-(4-bromophenyl)acetic acid (300 mg, 1.39 mmol) in anhydrous methanol (5 mL) was treated with catalytic amount of concentrated sulfuric acid. The mixture was heated at reflux for 16 hours before cooling to room temperature. The clear solution was then poured into water (50 mL) and extracted dichloromethane (50 mL x 2). The combined organic layer was washed with saturated bicarbonate (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford methyl 2-(4-bromophenyl)acetate (332 mg, AU HPLC 99.6%) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.51 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 3.68 (s, 2H), 3.61 (s, 3H); ESI MS, m/z 230.9 $[C_9H_9BrO_2+H]^+$

Step 5: Synthesis of methyl 2-(4-bromophenyl)propanoate. To a solution of LDA in 2M THF/heptane/ethylbenzene (0.76 mL, 1.53 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with methyl 2-(4-bromophenyl)acetate (270 mg, 1.17 mmol) dropwise at −78 °C. The red clear solution was stirred for 30 minutes before warming to 0 °C. Methyl iodide (0.12 mL, 1.88 mmol) was added dropwise and the mixture was stirred at 0 °C for 30 minutes. It was then stirred at room temperature for 2 hours. The reaction mixture was poured into ice water, acidifed with 2M HCl and extracted with ethyl acetate (30 mL x2). The combined organic was dried over sodium sulfate and concentrated under vacuum to afford methyl 2-(4-bromophenyl)propanoate (174 mg, AUC HPLC 92.3%, 60% yield) as pale green oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.71–3.66 (m, 4H), 1.48 (d, *J* = 7.2 Hz, 3H); ESI MS, m/z 242.9 and 244.9 (1: 1) ($[C_{10}H_{11}BrO_2]^+$, Br isotopes).

Step 6: Synthesis of 2-(4-bromophenyl)propanoic acid. To methyl 2-(4-bromophenyl)propanoate (170 mg, 0.69 mmol) in anhydrous tetrahydrofuran (2 mL) and water (2 mL) was treated with lithium hydroxide (64 mg, 2.79 mmol). The mixture was stirred at room temperature for 2 hours. Upon completion of reaction, tetrahydrofuran was evaporated under reduced pressure. The residue was acidified with 2M HCl and extracted

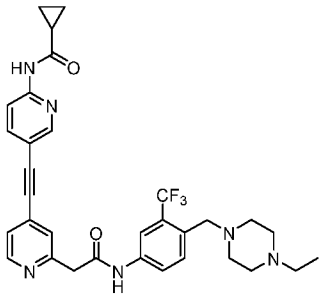
with ethyl acetate (40 mL x2). The combined organic was dried over sodium sulfate and concentrated under vacuum to afford 2-(4-bromophenyl)propanoic acid (152 mg, AUC HPLC 94.9%; 95% yield) as colorless oil which solidified upon standing at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.71 (q, *J* = 7.1 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H); ESI MS, m/z 226.9 and 229.0 (1: 1) ($[C_9H_9BrO_2]^-$, Br isotopes)

Step 7: Synthesis of 2-(4-bromophenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)propanamide. A solution of 2-(4-bromophenyl)propanoic acid (42 mg, 0.18 mmol) in anhydrous *N,N*-dimethylformamide (3 mL) was treated HATU (139 mg, 0.36 mmol) and the mixture was stirred at room temperature for 5 minutes. 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (50 mg, 0.18 mmol) and triethylamine (37 mg, 0.36 mmol) were added. The reaction mixture was stirred at room temperature for an hour. Upon completion of reaction, the mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layers was washed with brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Redisep silica gel, 97:3 dichloromethane/ methanol) to afford 2-(4-bromophenyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)propanamide (81 mg, AUC HPLC 86.0%; 92% yield) as green oil. ESI MS, m/z 484.1 and 486.1 (1: 1) ($[C_{22}H_{25}BrF_3N_3O]^+$, Br isotopes)

Step 8: Synthesis of *N*-(5-((4-(1-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-1-oxopropan-2-yl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide. To 2-(4-bromophenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)propanamide (80 mg, 0.16 mmol) in anhydrous *N,N*-dimethylformamide (1 mL) was treated with *N*-(5-ethynylpyridin-2-yl)cyclopropanecarboxamide (37 mg, 0.19 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 0.016 mmol), copper(I) iodide (3.1 mg, 0.016 mmol) and anhydrous triethylamine (2 mL). The reaction mixture was purged with nitrogen gas for 5 minutes. The mixture was heated at 80 °C for 6 hours. The solution was cooled to room temperature, filtered through celite and washed with ethyl acetate. The filtrate was then concentrated under reduced pressure. The residue was purified by flash chromatography [Redisep silica gel, 87:13 dichloromethane/ (dichloromethane/ methanol/ ammonium hydroxide)] and preparative HPLC (40:60 water/ acetonitrile) followed by lyophilization to afford *N*-(5-((4-(1-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-1-oxopropan-2-yl)phenyl)ethynyl)pyridin-2-

yl)cyclopropanecarboxamide (14.2 mg, AUC HPLC 99.48%14% yield) as yellow amorphous solid, mp: 228.1-228.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.99 (s, 1H), 10.39 (s, 1H), 8.49–8.48 (m, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 8.04 (s, 1H), 7.90 (m, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 3.87 (q, *J* = 6.9 Hz, 1H), 3.51 (s, 2H), 2.34–2.32 (m, 8H), 2.14 (s, 3H), 2.05–1.98 (m, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 0.84–0.81 (m, 4H); ESI MS, m/z 590.20 [$C_{33}H_{34}F_3N_5O_2$+H]

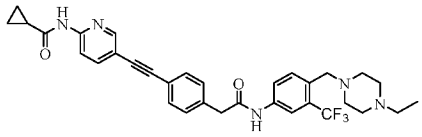
Example 223, Preparation of N-(5-((2-(2-((3-bromo-4-((4-ethylpiperazin-1-yl)methyl)phenyl)amino)-2-oxoethyl)pyridin-4-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



Synthesis of *N*-(5-((2-(2-(3-bromo-4-((4-ethylpiperazin-1-yl)methyl)phenylamino)-2-oxoethyl)pyridin-4-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide

The title compound was prepared in the amount of 150 mg (15.3%, AUC HPLC 97%) as a pale brown solid following general procedure B and using Intermediate **26**. mp; 192–196 °C. ^{1}H NMR (400 MHz, DMSO–d_6) δ(ppm): 11.08 (s, 1H), 10.56 (s, 1H), 8.58–8.55 (m, 2H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 8.00 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.79–7.76 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.55 (s, 1H), 7.43–7.42 (m, 1H), 3.09 (s, 2H), 3.56 (s, 2H), 2.45–2.32 (m, 10H), 2.04–2.01 (m, 1H), 1.1–1.0 (m, 3H), 0.85–0.83 (m, 4H). MS (ESI) *m/z*: 591.24 [$C_{32}H_{33}F_3N_6O_2$+H]$^+$.

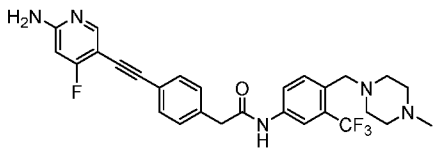
Example 224, Preparation of N-(5-((4-(2-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



Step 1: Synthesis of *N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(4-iodophenyl)acetamide. To a solution of 2-(4-iodophenyl)acetic acid (1 g, 3.83 mmol), HATU (2.18 g, 5.74 mmol) and DIPEA (1.4 mL, 7.64 mmol) in DMF (5 mL) was added 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (1 g, 3.83 mmol). The reaction mixture was stirred at room temperature for 6 h, diluted with water (30 mL), extracted with EtOAc (3 x 50 mL). The combined organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-(5-bromopyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (1 g, LC-MS 78%). MS (ESI) *m/z* 531.95 $[C_{22}H_{25}F_3IN_3O+H]^+$

Step 2: Synthesis of *N*-(5-((4-(2-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide. The title compound was prepared in the amount of 15 mg (4.5%, AUC HPLC 99%) as an off-white solid following general procedure B and using the product of step 1 as starting material. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 10.98 (s, 1H), 10.47 (s, 1H), 8.50 (d, *J* = 1.6 Hz, 1H), 8.12 (d, *J* = 9.2 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.90 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 3.71 (s, 2H), 3.53 (s, 2H), 2.45–2.28 (m, 10H), 2.03–2.00 (m, 1H), 0.97 (t, *J* = 6.4 Hz, 3H), 0.84–0.82 (m, 4H). MS (ESI) *m/z*: 590.41 $[C_{33}H_{34}F_3N_5O_2+H]^+$

Example 225, Preparation of 2-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)phenyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



Step 1: 2-(4-iodophenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide-(4-iodophenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide was prepared in a similar fashion as described in Step 1 of Example 224.

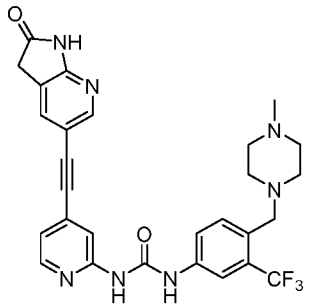
Step 2: *N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(4-((trimethylsilyl)ethynyl)phenyl)acetamide; *N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(4-((trimethylsilyl)ethynyl)phenyl)acetamide was prepared from 2-(4-iodophenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (800 mg, LC-MS 80%) as an off-white solid via using conditions similar to general procedure C.

Step 3: Synthesis of 2-(4-ethynylphenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide; To a solution of N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(4-((trimethylsilyl)ethynyl)phenyl)acetamide (800 mg, 1.64 mmol) in THF (5 mL) was added $LiOH.H_2O$ (69 mg, 1.64 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 5 h and was concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted into EtOAc (3 x 50 mL). The combined organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-(4-ethynylphenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (500 mg, LC-MS 75%) as a pale borwn solid.

Step 4: Synthesis of *tert*-butyl 4-fluoro-5-((4-(2-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-2-oxoethyl)phenyl)ethynyl)pyridin-2-ylcarbamate. To a solution of *tert*-butyl-bromo-4-fluoropyridin-2-ylcarbamate (252 mg, 0.86 mmol) and DIPEA (186 mg, 1.44 mmol) in acetonitrile (20 mL) under argon were successively added 2-(4-ethynylphenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (300 mg, 0.722 mmol), $Pd(PPh_3)_4$ (41 mg, 0.0361 mmol), PPh_3 (9 mg, 0.0361 mmol) and CuI (20 mg, 0.106 mmol) and heated at 80 °C for 6 h. The reaction mixture was diluted with water (30 mL) extracted into EtOAc (50 mL), washed in turn with water and brine. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent CH_2Cl_2/MeOH 95:5) to afford *tert*-butyl 4-fluoro-5-((4-(2-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-2-oxoethyl)phenyl)ethynyl)pyridin-2-ylcarbamate (280 mg, LC-MS 82%).

Step 5: Synthesis of 2-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)phenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide. A mixture of *tert*-butyl 4-fluoro-5-((4-(2-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-2-oxoethyl)phenyl)ethynyl)pyridin-2-ylcarbamate (280 mg, 0.448 mmol) and 1.6M HCl in dioxane (10 mL) was stirred at room temperature for 3 h and the reaction mixture was concentrated under reduced pressure. The residue was basified with a saturated aqueous solution of $NaHCO_3$ and extracted into EtOAc (50 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford 2-(4-((6-amino-4-fluoropyridin-3-yl)ethynyl)phenyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (42.5%, 100 mg, AUC HPLC 98.73%) as an off-white solid. mp: 212–215 °C. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 10.47 (s, 1H), 8.16 (d, *J* = 10.8 Hz, 1H), 8.04 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.71 (s, 2H), 6.28 (d, *J* = 12.4 Hz, 1H), 3.69 (s, 2H), 3.52 (s, 2H), 2.38–2.32 (m, 8H), 2.14 (s, 3H). MS (ESI) *m/z*: 526.1 $[C_{28}H_{27}F_4N_5O+H]^+$.

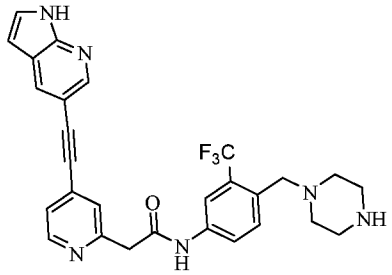
Example 226: Preparation 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea



To a solution of 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea (50 mg, 0.116 mmol) in DMF (2.0 mL) was added 5-bromo-1*H*-pyrrolo[2,3-b]pyridin-2(3H)-one (62 mg, 0.240 mmol), bis (triphenylphosphine)palladium(II) dichloride (10.6 mg, 0.015 mmol), cupper iodide (2.21 mg, 0.012 mmol), triphenylphosphine (10.6 mg, 0.041 mmol) and DIPEA (0.5 ml, 2.47 mmol). The reaction mixture was stirred at 80 °C for 18 h then, was filtered and the cake was rinsed with CH_3OH. The filtrate was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((2-oxo-2,3-dihydro-1*H*-

pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea (17 mg, 25.8 %, AUC HPLC 93.5 %) as purple solid; mp 178–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 10.31 (s, 1H), 9.58 (s, 1H), 8.38-8.34 (m, 1H), 8.33 (d, J = 5.2 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.75 (s, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.61 (dd, J = 8.4, 1.6 Hz, 1H), 7.14 (dd, J = 5.2, 1.2 Hz, 1H), 3.60 (s, 2H), 3.54 (s, 2H), 2.50–2.20 (m, 8H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 175.10,158.13, 152.24, 151.49, 149.52, 147.26, 137.44, 133.46, 131.53, 130.86, 127.20, 126.91, 122.37, 121.61, 120.22, 118.65, 114.92, 112.49, 110.78, 90.69, 87.51, 56.77, 54.10, 52.01, 45.05, 34.50; MS (ESI) *m/z* 550.90 $[C_{28}H_{26}F_3N_7O_2 + H]^+$.

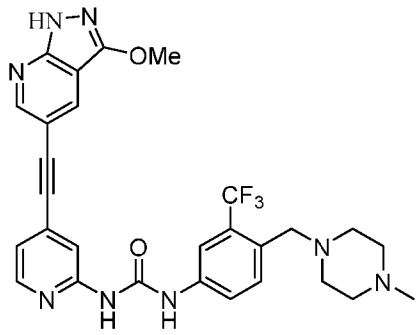
Example 227, Preparation of 2-(4-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-N-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)acetamide



Step 1: Synthesis of 2-(4-((1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-*N*-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)acetamide

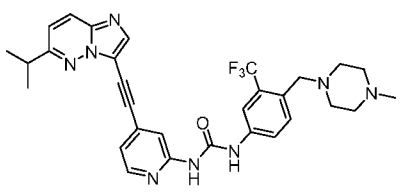
The title compound was prepared in the amount of 17 mg (11.3%, AUC HPLC 95.41%) as a pale brown solid starting form **Intermediate 24 and** following general Procedures B then D**.** mp: 138–142 °C**.** ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 11.97 (s, 1H), 10.52 (s, 1H), 8.55 (d, J = 5.6 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 8.07 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.58–7.56 (m, 2H), 7.43–7.42 (m, 1H), 6.52 (d, J = 1.6 Hz, 1H), 3.90 (s, 2H), 3.50 (s, 2H), 2.72–2.69 (m, 4H), 2.31–2.28 (m, 4H). MS (ESI) *m/z*: 519.13 $[C_{28}H_{25}F_3N_6O+H]^+$.

Example 228: Preparation of 1-(4-((3-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



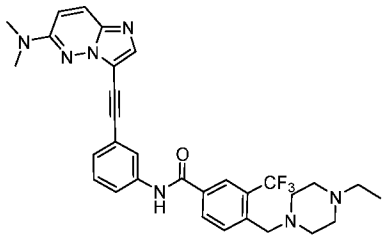
To a solution of 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (100 mg, 0.24 mmol) in DMF (1 mL) under inert atmosphere was added 5-bromo-3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (55 mg, 0.24 mmol), triphenylphophine (22 mg, 0.084 mmol), $Pd(PPh_3)_2Cl_2$ (22 mg, 0.032 mmol), copper iodide (4.6 mg, 0.024 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford 1-(4-((3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (31 mg, 23%, AUC HPLC 95%) as white solid. mp: 215.5-217.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.94 (s, 1H), 10.29 (s, 1H), 9.56 (s, 1H), 8.70 (d, *J* = 2.0 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.04 (d, *J* = 1.8 Hz, 1H), 7.78 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.18 (dd, *J* = 5.2, 1.3 Hz, 1H), 4.04 (s, 3H),), 3.56 (s, 2H), 2.42 (bs, 8H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 154.88, 152.74, 152.31, 151.98, 150.88, 147.76, 137.98, 132.59, 132.08, 131.41, 130.69, 127.59 (q, *J* = 31.7 Hz), 124.24 (q, *J* = 273.5 Hz), 122.12, 119.27, 115.47 (q, *J* = 6.1 Hz), 113.04, 109.42, 103.05, 91.45, 87.70, 57.18, 55.73, 54.40, 52.16, 45.15; MS (ESI) *m/z* 565.75$[C_{28}H_{27}F_3N_8O_2 + H]^+$.

Example 229, Preparation of 1-(4-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



The title compound was prepared in 53.3% yield (1.1 g, AUC HPLC 99.53 %) as an off-white solid using general procedure B starting from **Intermediate 21**. mp: 213–216 °C. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 10.35 (s, 1H), 9.60 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 8.21–8.16 (m, 2H), 8.04 (s, 1H), 7.17 (d, J = 4.8 Hz, 1H), 7.79 (s, 1H), 7.66–7.63 (m, 2H), 7.45 (d, J = 4.58 Hz, 1H), 3.55 (s, 2H), 3.24–3.21 (m, 1H), 2.39–2.30 (m, 8H), 2.17 (s, 3H), 1.37 (d, J = 7.2 Hz, 6H). MS (ESI) *m/z*: 577.1 $[C_{30}H_{31}F_3N_8O+H]^+$.

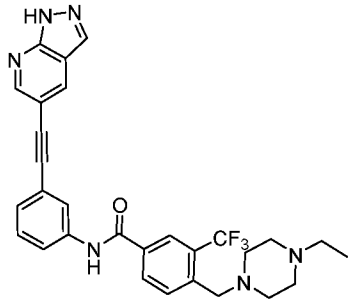
Example 230, Preparation of N-(3-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)phenyl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1 Preparation of *N*-(3-bromophenyl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. A solution of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoic acid (2 g, 6.32 mmol), HATU (3.6 g, 9.49 mmol), DIPEA (2.26 mL, 12.65 mmol) and 3-bromo aniline (1 g, 6.32 mmol) in DMF (10 mL) was stirred at room temperature for 15 h. The reaction mixture was diluted with water and extracted into EtOAc (3 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH 95:5) to afford *N*-(3-bromophenyl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (1.2 g, LC-MS 92%) as pale brown solid.

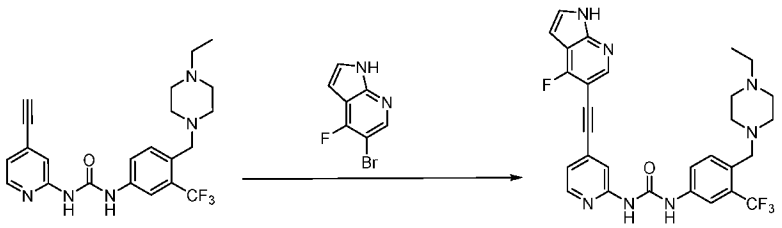
Step 2: *N*-(3-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)phenyl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. The title compound was prepared in 9.8% yield (48 mg, AUC HPLC 96.97%) as a yellow solid gollowing general procedure B and using *N*-(3-bromophenyl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. mp: 115–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (s, 1H), 8.00–7.99 (m, 2H), 7.82–7.80 (m, 2H), 7.77 (s, 1H), 7.70–7.67 (m, 2H), 7.39–7.38 (m, 2H), 6.81 (d, J = 9.6 Hz, 1H), 3.73 (s, 2H), 3.17 (s, 6H), 2.55–2.42 (m, 10H), 1.0 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z*: 576.1 $[C_{31}H_{32}F_3N_7O+H]^+$.

Example 231: Preparation of N-(3-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)phenyl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 7.9 % yield (36 mg, AUC HPLC 96.61%) as a white solid in a fashion similar as **Example 230** synthesis using *N*-(3-bromophenyl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. mp: 230–233 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.90 (s, 1H), 10.53 (s, 1H), 8.70 (s, 1H), 8.50 (s, 1H), 8.26–8.20 (m, 3H), 8.07 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.47–7.43 (m, 1H), 7.36 (d, J = 7.6 Hz, 1H), 3.68 (s, 2H), 2.43–2.29 (m, 10H), 0.98 (t, J = 7.0 Hz, 3H). MS (ESI) *m/z*: 533.1 $[C_{29}H_{27}F_3N_6O+H]^+$

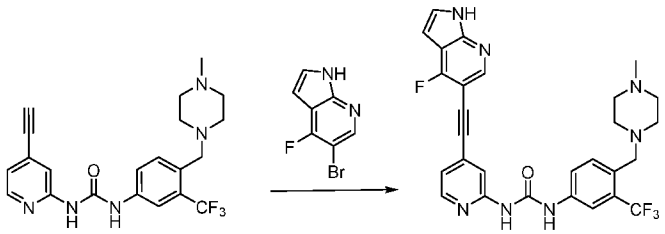
Example 232: Preparation 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea



To a solution of 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea (50 mg, 0.116 mmol) in DMF (2.0 mL) was added 5-bromo-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine (50 mg, 0.232 mmol), bis (triphenylphosphine)palladium(II) dichloride (10.6 mg, 0.015 mmol), cupper iodide (2.21 mg, 0.012 mmol), triphenylphosphine (10.6 mg, 0.041 mmol) and DIPEA (0.5 ml, 2.47 mmol). The reaction mixture was stirred at 80 °C for 18 h then was concentrated under reducedpressure. The residue was purified by flash column chromatography (silica gel, eluent

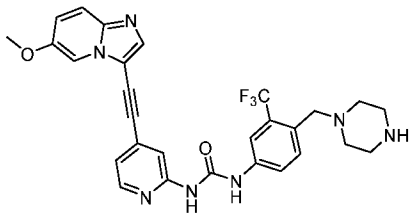
DCM/MeOH 9:1) and triturated with MeOH (1.0 ml x 3). The desired product was isolated by centrifugation to afford 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((4-fluoro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)urea (11 mg, 16.8 %, AUC HPLC 97.9 %) as white solid; mp 195–197 °C; ^{1}H NMR (400 MHz, CD_3OH) δ (ppm): 8.39 (d, *J* = 8.9 Hz, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 7.99 (d, *J* = 1.7 Hz, 1H), 7.78–7.68 (m, 2H), 7.47 (d, *J* = 3.4 Hz, 1H), 7.41 (s, 1H), 7.16 (dd, *J* = 5.6, 1.2 Hz, 1H), 6.63 (d, *J* = 3.6 Hz, 1H), 3.72 (s, 2H), 3.30–2.90 (m, 6H), 2.89–2.45 (m, 4H), 1.28 (t, *J* = 7.30 Hz, 3H); MS (ESI) *m/z* 567 $[C_{29}H_{27}F_4N_7O + H]^+$.

Example 233: Preparation 1-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



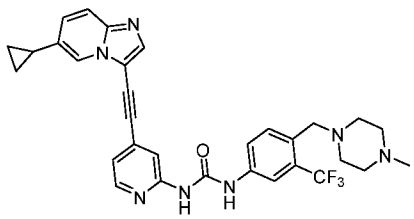
To a solution of 1-(4-ethynylpyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (50 mg, 0.120mmol) in DMF (2.0 mL) was added 5-bromo-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine (50 mg, 0.240 mmol), bis (triphenylphosphine)palladium(II) dichloride (10.9 mg, 0.015 mmol), cupper iodide (2.28 mg, 0.012 mmol), triphenylphosphine (11.0 mg, 0.041 mmol) and DIPEA (0.5 ml, 2.39 mmol. The reaction mixture was stirred at 80 °C for 18 h then concentrated in reduced vacuum. The residue was purified by column chromatography (silica gel, eluent DCM/MeOH 9:1) to afford a yellow crude product. This crude product was triturated in MeOH (1.0 ml x 3) and a solid was isolated by centrifugation to afford 1-(4-((4-fluoro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (6 mg, 9.1 %, AUC HPLC 95.2 %) as yellow solid; mp 187–189 °C; ^{1}H NMR (400 MHz, CD_3OH) δ (ppm): 8.39 (d, *J* = 8.9 Hz, 1H), 8.33(d, *J* = 5.2 Hz, 1H), 7.98 (s, 1H), 7.78–7.68 (m, 2H), 7.46 (d, *J* = 3.6 Hz, 1H), 7.41 (s, 1H), 7.15 (dd, *J* = 5.6, 1.2 Hz, 1H), 6.63 (d, *J* = 3.6 Hz, 1H), 3.65 (s, 2H), 2.70–2.45 (m, 8H), 2.37 (s, 3H); MS (ESI) *m/z* 552 $[C_{28}H_{25}F_4N_7O + H]^+$.

Example 234, Preparation of 1-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea



The title compound was prepared in 50% yield (42 mg, AUC HPLC 98.66 %) as described for Example 227 synthesis starting from **Intermediate 19**. mp: 170–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 10.39 (s, 1H), 9.61 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 1.6 Hz, 1H), 8.07–8.04 (m, 2H), 7.80 (s, 1H),7.69–7.67 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.31–7.25 (m, 2H), 3.94 (s, 3H), 3.50 (s, 2H), 2.70–2.68 (m, 4H), 2.31–2.29 (m, 4H). MS (ESI) *m/z*: 550.55 $C_{28}H_{26}F_3N_7O_2$+H]$^+$.

Example 235, Preparation of 1-(4-((6-cyclopropylimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

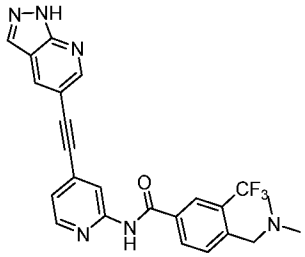


Step 1: preparation of 6-cyclopropyl-3-iodoimidazo[1,2-a]pyridine. A solution of 6-bromoimidazo[1,2-a]pyridine (1 g, 6.32 mmmol) and *N*-Iodo succinamide (1.4 g, 6.32 mmol) in DMF (5mL) was stirred at room temperature for 5 h. Reaction mixture was diluted with water, solid separated was filtered and dried to afford 6-cyclopropyl-3-iodoimidazo[1,2-a]pyridine (1.3 g) as a pale brown solid.

Step 2: synthesis of 1-(4-((6-cyclopropylimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea. The title compound was prepared in 19.3% yield (78 mg, AUC HPLC 97.8%) as an off-white solid following conditions similar to **general procedure B** and starting from **Intermediate 21**. mp: 196–199 °C.^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 10.33 (s, 1H), 9.55 (s, 1H), 8.45 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 7.79 (s, 1H), 7.68–7.61 (m, 3H), 7.32 (d, *J* =

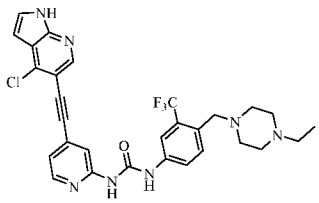
4.0 Hz, 1H), 7.15 (d, *J* = 10.0 Hz, 1H), 3.54 (s, 2H), 2.32–2.38 (m, 8H), 2.15–2.12 (m, 4H), 1.01 (q, *J* = 8.4 Hz, 2H), 0.81 (q, *J* = 6.4 Hz, 2H). MS (ESI) *m/z*: 574 $[C_{31}H_{30}F_3N_7O+H]^+$.

Example 236: Preparation of N-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared with a yield of 16% (55 mg, AUC HPLC 97.8%) as off-white using Sonogashira coupling conditions similar to general procedure B using **Intermediate-27**. mp: 233–236 °C. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 13.96 (s, 1H), 11.27 (s, 1H), 8.77 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 1.6 Hz, 1H), 8.48 (d, *J* = 4.8 Hz, 1H), 8.34–8.35 (m, 2H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.24 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 5.2 Hz, 1H), 3.61 (s, 2H), 2.22 (s, 6H). MS (ESI) *m/z*: 465.0 $[C_{24}H_{19}F_3N_6O+H]^+$.

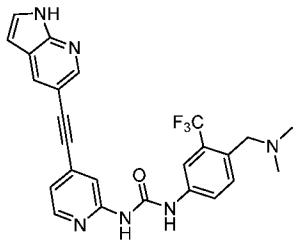
Example 237: Preparation of 1-(4-((4-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



To a solution of 1-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-ethynylpyridin-2-yl)urea (103 mg, 0.24 mmol) in DMF (1 mL) under inert atmosphere was added 5-bromo-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (56 mg, 0.24 mmol), triphenylphophine (22 mg, 0.084 mmol), $Pd(PPh_3)_2Cl_2$ (22 mg, 0.032 mmol), copper iodide (4.6 mg, 0.024 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford 1-(4-((4-chloro-1*H*-pyrrolo[2,3-

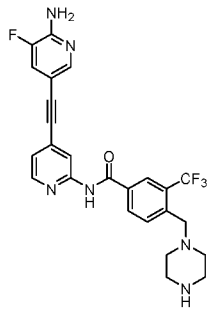
b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (7 mg, 5%, AUC HPLC 95%) as white solid. m.p: 254.4-255.0 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.37 (s, 1H), 10.31 (s, 1H), 9.57 (s, 1H), 8.53 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.03 (d, *J* = 1.9 Hz, 1H), 7.80 (s, 1H), 7.72-7.69 (m, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.63 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.20 (dd, *J* = 5.2, 1.3 Hz, 1H), 6.61 (d, *J* = 2.7 Hz, 1H), 3.55 (s, 2H), 2.39 (bs, 8H), 2.31 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 152.80, 151.98, 148.09, 147.84, 146.27, 137.89, 135.90, 131.90, 131.35, 130.89, 128.79, 127.54 (q, J = 31.0 Hz), 124.25 (q, J = 273.4Hz), 122.18, 119.18, 118.42, 115.52 (q, J = 5.8 Hz), 113.00, 109.28, 98.86, 91.68, 88.83, 57.31, 52.73, 52.30, 51.48, 11.91; MS (ESI) *m/z* 583.50[$C_{29}H_{27}ClF_3N_7O$ + H]$^{+}$.

Example 238: Preparation of 1-(4-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea



The title compound was prepared in 30.4% yield (86 mg, AUC HPLC 99.83%) as a white solid via using experimental conditions similar to general procedure B with Intermediate 28 as starting material. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 11.98 (s, 1H), 10.43 (s, 1H), 9.58 (s, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 4.4 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 1.6 Hz, 1H), 7.77 (s, 1H), 7.67–7.64 (m, 2H), 7.59–7.57 (m, 1H), 7.17 (d, *J* = 4.8 Hz, 1H), 6.53–6.51 (m, 1H), 3.47 (2H), 2.17 (s, 6H). MS (ESI) *m/z*: 478.76 [$C_{25}H_{21}F_3N_6O$+H] $^{+}$.

Example 239: Preparation of N-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



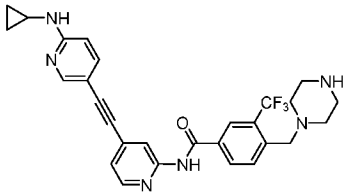
Step 1: Preparation of *tert*-butyl 4-(4-((4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

To a solution of 5-ethynyl-3-fluoropyridin-2-amine (49 mg, 0.36 mmol) in DMF (1 mL) under inert atmosphere was added *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (196 mg, 0.36 mmol), triphenylphophine (33 mg, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (33 mg, 0.048 mmol), copper iodide (6.9 mg, 0.036 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) afford *tert*-butyl 4-(4-((4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (181 mg, 84%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (s, 1H), 8.49 (s, 1H), 8.29 (d, J = 5.6 Hz, 1H), 8.20 (s, 1H), 8.11 (d, J = 0.7 Hz, 1H), 8.08 (dd, J = 8.1, 1.5 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 11.0, 1.7 Hz, 1H), 7.16 (dd, J = 5.1, 1.4 Hz, 1H), 4.88 (s, 2H), 3.74 (s, 2H), 3.50-3.43 (m, 4H), 2.50-2.40 (m, 4H), 1.47 (s, 9H); MS (ESI) *m/z* 599.2$[C_{30}H_{30}F_4N_6O_3 + H]^+$.

Step 2: N-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide. A solution of *tert*-butyl 4-(4-((4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (181 mg, 0.30 mmol) and TFA (0.5 mL) in DCM (4 mL) was stirred at room temperature for 3 h before concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/MeOH 95:5–90:10) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (97 mg, 65%, AUC HPLC 96%) as yellow solid, mp:193.9–195 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.45 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 8.36–8.32 (m, 2H), 8.25 (dd, J = 8.2, 1.3 Hz, 1H),

8.06-8.01 (m, 2H), 7.51 (dd, *J* = 11.4, 1.8 Hz, 1H), 7.26 (dd, *J* = 5.2, 1.3 Hz, 1H), 3.89 (s, 2H), 3.29 (t, *J* = 5.1 Hz, 4H), 2.81–152.73 (m, 4H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 166.74, 166.47, 153.33, 151.52(d, *J* = 13.3 Hz), 149.40, 147.89 (d, *J* = 4.9 Hz), 146.99 (d, *J* = 253.2 Hz), 142.12, 135.02, 134.75, 132.46, 132.25, 130.15 (q, *J* = 30.9Hz), 126.80 (q, *J* = 5.9 Hz), 125.50 (q, *J* = 273.5 Hz), 124.56 (d, *J* = 16.8 Hz), 122.84, 117.43, 108.30(d, *J* = 3.3 Hz), 91.91(d, *J* = 1.6 Hz), 88.34, 58.76, 50.84, 44.91; MS (ESI) *m/z* 499.55 $[C_{25}H_{22}F_4N_6O+H]^+$.

Example 240: Preparation N-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

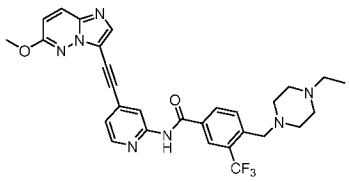


Step 1: Preparation N-cyclopropyl-5-ethynylpyridin-2-amine. To a solution of 5-bromo-*N*-cyclopropylpyridin-2-amine (200 mg, 0.94 mmol) in DMF (2.0 mL) was added ethynyltrimethylsilane (663 uL, 4.63 mmol), tetrakis (triphenylphosphine) palladium (0) (57 mg, 0.05 mmol), cupper iodide (14.3 mg, 0.08 mmol) and *N,N*-diisopropylethylamine (0.5ml, 371 mg, 2.87 mmol) and stirred at 80 °C for 18h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, eluents Hex/EtOAc 9:1) to afford *N*-cyclopropyl-5-((trimethylsilyl)ethynyl)pyridin-2-amine (~250 mg) as brown solid. This crude intermediate was dissolved in MeOH (20 mL) and potassium carbonate (250 mg, 1.81 mmol) and stirred for 3 h, then was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluents Hex/EtOAc 85:15) to afford *N*-cyclopropyl-5-ethynylpyridin-2-amine (67 mg, 45.1%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 1.7 Hz, 1H), 7.57 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.68 (dd, *J* = 8.4, 0.8 Hz, 1H), 5.52 (s, 1H), 3.06 (s, 1H), 2.51 (m, 1H), 0.81 (m, 2H), 0.56 (m, 2H); MS (ESI) *m/z* 159$[C_{10}H_{10}N_2+H]^+$.

Step 2: Preparation N-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide. To a solution of *tert*-butyl 4-(4-(4-bromopyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (50 mg, 0.120 mmol) in DMF (2.0 mL) was added *N*-cyclopropyl-5-ethynylpyridin-2-amine (50 mg, 0.240 mmol), bis-(triphenylphosphine)palladium(II) dichloride (10.9 mg, 0.015 mmol),

cupper iodide (2.28 mg, 0.012 mmol), triphenylphosphine (11.0 mg, 0.041 mmol) and DIPEA (0.5 ml, 2.39 mmol) and the mixture was stirred at 80 °C for 18 h. The reaction mixture was stirred at 80 °C for 18 h then was concentrated in reduced pressure. The residue was purified by flash column chromatography (silica gel, eluents DCM/MeOH 9:1) to afford *tert*-butyl 4-(4-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. This intermediate was stirred in a mixture of TFA and DCM for 4 h. The desired product was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford *N*-(4-((6-(cyclopropylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (6.30 mg, 9.7 %, AUC HPLC 97.8 %) as yellow solid; mp 110–111 °C; ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.60–8.30 (m, 3H), 8.29–8.17 (m, 2H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.98 (dd, *J* = 9.6, 2.0 Hz, 1H), 7.31 (bs, 1H), 7.07 (d, *J* = 9.3 Hz, 1H), 3.87 (s, 2H), 3.31–3.25 (m, 4H), 2.88–2.65 (m, 5H), 1.02 (m, 2H), 0.74 (m, 2H); MS (ESI) *m/z* 521.60[$C_{28}H_{27}F_3N_6O$ + H]$^+$.

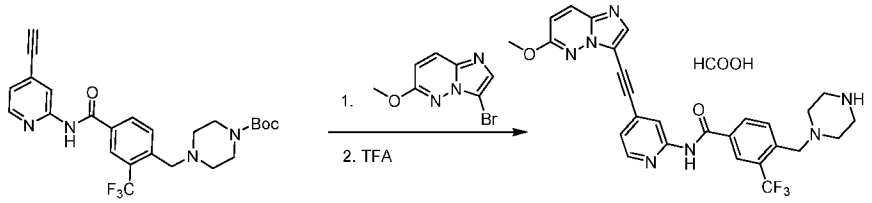
Example 241: Preparation of afford 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



To a solution of 3-bromo-6-methoxyimidazo[1,2-b]pyridazine (30 mg, 0.132 mmol), Intermediate 17 (50 mg, 0.120 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.0156 mmol), CuI (2.3 mg, 0.0120 mmol) and PPh_3 (11 mg, 0.0420 mmol) and DMF (1.0 mL), DIPEA (1.0 mL) was added. After purging with Ar for 10 mins, the resulting mixture was stirred at 90°C for 3h in a microwave. Upon cooling to room temperature, DMF was then removed *in vacuo* and the resulting residue was purified by preparatory HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (16.5 mg, 24%, AUC HPLC: 96.9%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 8.50 – 8.46 (m, 1H), 8.39 – 8.37 (m, 1H), 8.35 (d, *J* = 1.8 Hz, 1H), 8.29 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.14 (d, *J* = 9.6 Hz, 1H), 8.12 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.35 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.08 (d, *J* = 9.6 Hz, 1H), 4.07 (s, 3H), 3.69 (s, 2H), 2.48 – 2.43 (m, 4H), 2.39 (q, *J* = 7.1 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 160.6, 152.4, 148.7, 141.6, 138.2, 137.9, 132.8,

132.0, 131.4, 130.5, 128.0, 127.4, 127.2, 127.0, 126.8, 125.6, 125.0, 120.7, 115.3, 113.9, 111.2, 96.3, 81.1, 57.4, 54.7, 52.6, 52.2, 51.5, 11.7; MS (ESI) *m/z* : 564 $[C_{29}H_{28}F_3N_7O_2 + H]^+$

Example 242: Preparation of N-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt

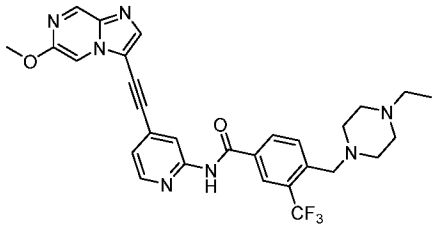


Step 1: Preparation of *tert*-butyl 4-(4-((4-((6-methoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. To a solution of 3-bromo-6-methoxyimidazo[1,2-b]pyridazine (25 mg, 0.111 mmol), *tert*-butyl 4-(4-((4-ethynylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (54 mg, 0.110 mmol), $PdCl_2(PPh_3)_2$ (8.4 mg, 0.0120 mmol), CuI (2 mg, 0.0092 mmol) and PPh_3 (8.4 mg, 0.0322 mmol) and DMF (1.0 mL), DIPEA (1.0 mL) was added. After purging with argon for 10 mins, the resulting mixture was stirred at 90°C for 3 h in a microwave. The reaction mixture was concentrated to dryness under reduced pressure . The resulting residue was purified by preparatory column chromatography to afford of *tert*-butyl 4-(4-((4-((6-methoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (25.2 mg, 43%); MS (ESI) *m/z* : 636 $[C_{32}H_{32}F_3N_7O_4 + H]^+$

Step 2: Preparation of To a solution of tert-butyl 4-(4-((4-((6-methoxyimidazo[1,2-*b*]pyridazin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (25.2 mg, 0.0396 mmol) in CH_2Cl_2 (2.4mL), trifluoroacetic acid (0.6mL) was added. The mixture was stirred at rt for 1h. TFA was then removed *in vacuo* and the resulting residue was redissolved in CH_2Cl_2/CH_3OH, followed by the addition of solid $NaHCO_3$ and 10 drops of water. The mixture was stirred at rt for 15 mins. The solids were filtered off and the filtrate concentrated and purified by preparatory HPLC to afford *N*-(4-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt (7.2 mg, 31%) as a brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 8.50–8.47 (m, 1H), 8.39–8.37 (m, 1H), 8.35 (d, *J* = 1.9 Hz, 1H), 8.29 (dd, *J* = 8.1, 2.0 Hz, 2H), 8.15 (d, *J* = 9.7 Hz, 1H), 8.13 (s, 1H), 7.94 (d, *J*=8.2 Hz, 1H), 7.35 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.08 (d, *J* = 9.6 Hz, 1H), 4.07 (s, 3H), 3.67 (s,

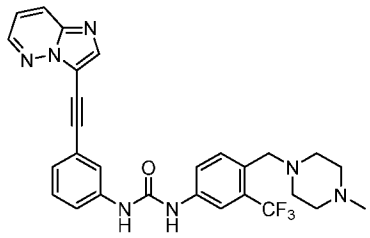
2H), 2.82 (t, J = 4.8 Hz, 4H), 2.41 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.97, 160.64, 152.44, 148.74, 141.51, 138.25, 137.98, 132.86, 132.01, 131.48, 130.64, 128.10, 127.49, 127.29, 127.09, 126.89, 125.69, 125.04, 123.22, 120.74, 115.36, 113.98, 111.23, 96.30, 81.16, 57.98, 54.73, 53.03, 44.85; MS (ESI) m/z 537 $[C_{27}H_{24}F_3N_7O_2 + H]^+$

Example 243: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-methoxyimidazo[1,2-a]pyrazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



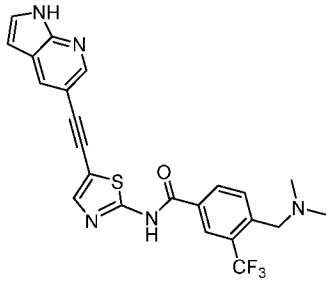
To a solution of 3-bromo-6-methoxyimidazo[1,2-*a*]pyrazine (30 mg, 0.132 mmol), 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide (50 mg, 0.120 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.0156 mmol), CuI (3 mg, 0.0120 mmol) and PPh_3 (11 mg, 0.0420 mmol) and DMF (1.0 mL), DIPEA (1.0 mL) was added. After purging with argon for 10 mins, the resulting mixture was stirred at 90°C for 3h in a microwave. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparatory HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-methoxyimidazo[1,2-a]pyrazin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (4.2 mg, AUC HPLC: 98.4%) as an off-white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.30 (s, 1H), 8.83 (s, 1H), 8.48 – 8.46 (m, 1H), 8.38 – 8.36 (m, 1H), 8.35 (d, J = 1.8 Hz, 1H), 8.29 (dd, J = 8.0, 1.9 Hz, 1H), 8.25 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.76 (s, 1H), 7.31 (dd, J = 5.1, 1.5 Hz, 1H), 4.29 (s, 3H), 3.68 (s, 2H), 2.41 (m, 4H), 2.32 (q, J = 7.2 Hz, 2H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 165.0, 152.4, 148.7, 147.2, 142.3, 141.8, 141.7, 135.3, 132.8, 132.0, 131.7, 130.5, 127.0, 125.6, 123.2, 120.2, 115.1, 110.2, 106.3, 94.1, 83.2, 58.0, 57.5, 52.9, 52.3, 51.5, 12.0; MS (ESI) m/z : 564 $[C_{29}H_{28}F_3N_7O_2 + H]^+$

Example 244: Preparation of 1-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



To a solution of Intermediate 40 (400 mg, 0.961 mmol) and 3-bromoimidazo[1,2-b]pyridazine (287 mg, 1.442 mmol) in acetonitrile were added diisopropylethylamine (0.5 mL, 2.88 mmol), triphenylphosphine (12.5 mg, 0.048 mmol), $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) and CuI (27.5 mg, 0.144 mmol). The reaction mixture was heated at 80 °C for 3 h under argon and was concentrated to a smaller volume under reduced pressure. The residue was extracted with EtOAc and the organic phase was washed in turn with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/MeOH 90:10) to afford *1-(3-(imidazole(1,2-bipyridazin-3-ylethylphynyl)-3-(4((4-methylpiperazin-1yl)methyl)-3-(trifluoromethyl)phenyl)urea* (100 mg, 19%, AUC HPLC 98%) as a pale yellow solid. mp:199–202 °C. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 9.06 (s, 1H), 8.92 (s, 1H), 8.71 (dd, J = 16.0 Hz, J = 4.4 Hz,1H), 8.24 (dd, J = 12.0 Hz, J = 12.0 Hz, 1H), 8.2 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.8 (s, 1H), 7.66–7.55 (m, 2H), 7.45–7.34 (m, 3H), 7.29–7.20 (m, 1H), 3.50 (s, 2H), 2.46–2.23 (m, 7H), 2.16 (s, 3H). MS (ESI) *m/z*: 533.9 $[C_{28}H_{26}F_3N_7O+H]^{+\cdot}$

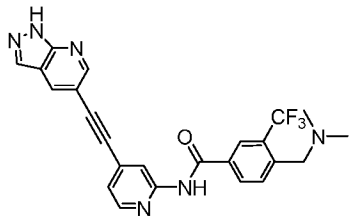
Example 245, Preparation of N-(5-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 13.1% yield (120 mg, AUC HPLC 97.8%) as a yellow solid following experimental conditions similar to general procedure B with Intermediate 36 as starting material. mp: 258–261 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 13.17 (s, 1H), 11.92 (s, 1H), 8.46 (s, 1H), 8.39–8.36 (m, 2H), 8.18 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H),

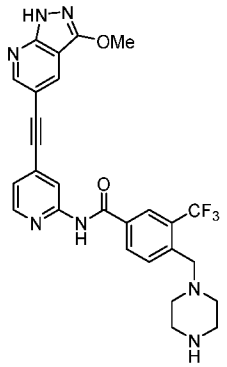
7.89 (s, 1H), 7.56 (s, 1H), 6.50 (s, 1H), 3.62 (s, 2H), 2.22 (s, 6H). MS (ESI) *m/z*: 470.09 $[C_{23}H_{18}F_3N_5OS+H]^+$.

Example 246, Preparation of 4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)picolinamide



Step 1: Synthesis of 4-bromo-*N*-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)picolinamide. To an ice-cold solution of 4-bromopicolinic acid (1 g, 4.95 mmol) and 4-((dimethylamino)methyl)-3-(trifluoromethyl)aniline (1g, 4.95 mmol) and TEA (3.47 mL, 24.75 mmol) in dichloromethane (15 mL) was added dropwise T_3P (2.3 g, 7.42 mmol, 50% in EtOAc). The reaction mixture was stirred at room temperature for 15 h, was diluted with dichloromethane, wahsed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silicagel, eluent CH_2Cl_2:MeOH 98:2) to afford 4-bromo-*N*-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)picolinamide (800 mg, LC-MS 76%).
Step 2: Synthesis of 4-((1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-*N*-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)picolinamide. The title compound was prepared in 27.7% yield (160 mg, AUC HPLC 94.48%) as an off-white solid using coupling conditions similar to general procedure B with 4-bromo-*N*-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)picolinamide from Step 1. mp: 225–229 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 14.05 (s, 1H), 11.12 (s, 1H), 8.82 (d, J = 4.0 Hz, 1H), 8.80 (d, J = 2.4 Hz, 1H), 8.62 (d, J = 1.2 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.26 (bs, 2H), 8.17 (t, J = 8.8 Hz, 1H), 7.86 (dd, J = 1.2, 1.6 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 3.50 (s, 2H), 2.18 (s, 6H). MS (ESI) m/z: 465.09 $[C_{24}H_{19}F_3N_6O+H]^+$.

Example 247: Preparation of N-(4-((3-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



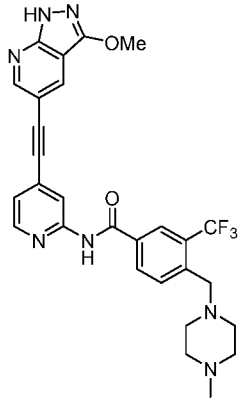
Step 1: Preparation of *tert*-butyl 4-(4-((4-((3-methoxy-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. To a solution of 5-ethynyl-3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (62 mg, 0.36 mmol) in DMF (1 mL) under inert atmosphere was added *tert*-butyl 4-(4-((4-bromopyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (196 mg, 0.36 mmol), triphenylphophine (33 mg, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (33 mg, 0.048 mmol), copper iodide (6.9 mg, 0.036 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) afford *tert*-butyl 4-(4-((4-((3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (115 mg, 50%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.89 (s, 1H), 8.68 (d, *J* = 1.6 Hz, 1H), 8.64 (s, 1H), 8.54 (s, 1H), 8.33 (d, *J* = 5.1 Hz, 1H), 8.22 (d, *J* = 9.3 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.21 (dd, *J* = 5.1, 1.0 Hz, 1H), 4.12 (s, 3H), 3.74 (s, 2H), 3.55-3.39 (m, 4H), 2.50-2.40 (m, 4H), 1.47 (s, 9H); MS (ESI) *m/z* 636.2 $[C_{32}H_{32}F_3N_7O_4 + H]^+$.

Step 2: Preparation of *N*-(4-((3-methoxy-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

To a solution of *tert*-butyl 4-(4-((4-((3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (115 mg, 0.18 mmol) in DCM (4 mL) was added TFA (0.5 mL) and was stirred at room temperature for 3 h before concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/MeOH 95:5~90:10) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-

(trifluoromethyl)benzamide (88 mg, 91%, AUC HPLC 97%) as yellow solid. mp 204.0–205.9 °C; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ (ppm): 8.66 (s, 1H), 8.43-8.37 (m, 2H), 8.37-8.29 (m, 3H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 3.9 Hz, 1H), 4.11 (s, 3H), 3.88 (s, 2H), 3.31-3.25 (m, 4H), 2.77 (bs, 4H); ^{13}C NMR (100 MHz, MeOD-*d*$_4$) δ (ppm): 167.34, 166.70, 157.12, 153.73, 153.42, 152.37, 149.49, 142.15, 135.02, 134.52, 134.05, 132.50, 132.26, 130.17 (q, *J* = 30.8 Hz), 126.84 (q, *J* = 5.9 Hz), 125.55 (q, *J* = 273.4 Hz), 123.03, 117.63, 111.83, 105.36, 92.42, 88.95, 58.82, 56.63, 50.90, 44.97; MS (ESI) *m/z* 536.55 $[C_{27}H_{24}F_3N_7O_2+ H]^+$.

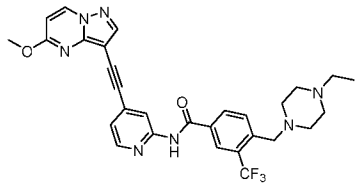
Example 248: Preparation of N-(4-((3-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



To a solution of 5-ethynyl-3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (40 mg, 0.23 mmol) in DMF (1 mL) under inert atmosphere was added *N*-(4-bromopyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (105 mg, 0.23 mmol), triphenylphophine (21 mg, 0.03 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 0.081 mmol), copper iodide (4.4 mg, 0.023 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((3-methoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (32 mg, 25%, AUC HPLC 99%) as white solid. m.p: 102.2-102.8 °C; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ (ppm): 8.65 (d, *J* = 1.4 Hz, 1H), 8.41-8.36 (m, 2H), 8.35-8.29 (m, 3H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 5.4 Hz, 1H), 4.10 (s, 3H), 3.86 (s, 2H),

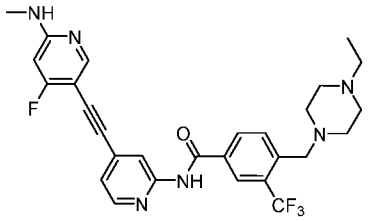
3.22 (bs, 4H), 2.82 (s, 3H), 2.75 (bs, 4H); ^{13}C NMR (100 MHz, MeOD-d_4) δ (ppm): 167.96, 166.61, 157.07, 153.70, 153.37, 152.31, 149.44, 142.12, 134.96, 134.47, 134.02, 132.46, 132.20, 130.11 (q, J = 30.8 Hz), 126.81 (q, J = 6.0 Hz), 125.50 (q, J = 273.3 Hz), 122.99, 117.59, 111.79, 105.32, 92.41, 88.95, 58.33, 56.62, 54.91, 51.22, 43.61; MS (ESI) *m/z* 550.55[$C_{28}H_{26}F_3N_7O_2$ + H]$^+$.

Example 249: 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



To a solution of 3-ethynyl-5-methoxypyrazolo[1,5-*a*]pyrimidine (25 mg, 0.144 mmol), *N*-(4-bromopyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (68 mg, 0.144 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.0187 mmol), CuI (2.7 mg, 0.0144 mmol) and PPh_3 (13 mg, 0.0504 mmol) and DMF (1.0 mL), DIPEA (1.0 mL) was added. After purging with argon for 10 mins, the resulting mixture was heated in microwave apparatus at 90 °C for 3 h. DMF was then removed *in vacuo* and the residue was purified by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (26.1 mg, 32%, AUC HPLC: 98.3%) as an off-white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.24 (s, 1H), 9.00 (d, J = 7.4 Hz, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.42 (s, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.31 – 8.27 (m, 2H), 7.92 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 5.1, 1.5 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 4.05 (s, 3H), 3.68 (s, 2H), 2.43 (m, 4H), 2.33 (q, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 164.8, 163.2, 152.3, 148.4, 147.7, 147.1, 141.6, 138.9, 132.8, 132.7, 131.9, 130.5, 127.4, 127.2, 127.0, 126.8, 125.6, 125.0, 120.9, 115.4, 101.6, 90.0, 89.2, 85.8, 57.5, 54.3, 52.8, 52.3, 51.5, 11.9; MS (ESI) *m/z* : 564 [$C_{29}H_{28}F_3N_7O_2$ + H]$^+$

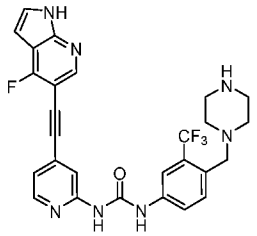
Example 250: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((4-fluoro-6-(methylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of 5-bromo-4-fluoro-*N*-methylpyridin-2-amine. To a solution of *5-bromo-4-fluoropyridin-2-amine* (50 mg, 0.262 mmol) in dioxane (2.0 mL) was added Copper (II) acetate (119 mg, 0.655 mmol), pyridine (73 □L, 0.910 mmol) and stirred for 15 min prior to the addition of methylboronic acid (39 mg, 0.655 mmol). The reaction mixture was heated to reflux for 18 h, cooled to room temperature and purified by flash column chromatography (silica gel, eluents Hex/EtOAc 85:15) to afford 5-bromo-4-fluoro-*N*-methylpyridin-2-amine (23 mg, 43%); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (d, *J* = 9.7 Hz, 1H), 6.14 (d, *J* = 10.7 Hz, 1H), 4.80 (s, 1H), 2.89 (d, *J* = 5.2 Hz, 3H); MS (ESI) m/z 206 $[C_6H_6BrFN_2+H]^+$.

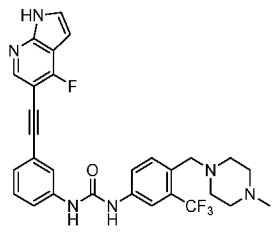
Step 2: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((4-fluoro-6-(methylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide. To a solution of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide (46 mg, 0.112 mmol) in DMF (2.0 mL) was added 5-bromo-4-fluoro-N-methylpyridin-2-amine (23 mg, 0.112 mmol), bis (triphenylphosphine)palladium(II) dichloride (10.2 mg, 0.015 mmol), cupper iodide (2.1 mg, 0.011 mmol), triphenylphosphine (10.3 mg, 0.035 mmol) and DIPEA (0.5 ml, 2.39 mmol). The reaction mixture was stirred at 80 °C for 18 h then was concentrated under reduced pressure. The residue was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((4-fluoro-6-(methylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (2.0 mg, AUC HPLC 98.7 %) as white solid; mp 153–155 °C; ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.35 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 2H), 8.25–8.15 (m, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 5.2 Hz, 1H), 6.29 (d, *J* = 11.9 Hz, 1H), 3.77 (s, 2H), 2.91 (s, 3H), 2.80–2.40 (m, 10H), 1.13 (t, *J* = 7.2 Hz, 3H); MS (ESI) m/z 541.2 $[C_{28}H_{28}F_4N_6O + H]^+$.

Example 251: Preparation 1-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea



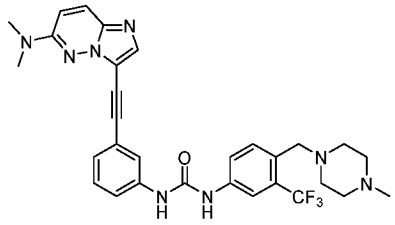
To a solution of *tert*-butyl 4-(4-(3-(4-ethynylpyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (50 mg, 0.099 mmol) in DMF (2.0 mL) was added 5-bromo-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine (64 mg, 0.298 mmol), bis (triphenylphosphine)palladium(II) dichloride (9.6 mg, 0.013 mmol), cupper iodide (1.98 mg, 0.010 mmol), triphenylphosphine (9.1 mg, 0.035 mmol) and DIPEA (0.5 ml, 2.39 mmol). The reaction mixture was stirred at 80 °C for 18 h then was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluents DCM/MeOH 9:1) to afford *tert*-butyl 4-(4-(3-(4-((4-fluoro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)ureido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (16 mg, 25.3%). A solution of the boc protected intermediate in a mixture of TFA (2 ml) in DCM (2 ml) was stirred at room temperature for 4 h then was concentrated under pressure. The crude product was purified by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.1%) to afford 1-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (3.0 mg, 5.6 % over 2 steps, AUC HPLC 95.86 %) as white solid; mp 167–169 °C; ^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.39 (d, *J* = 8.8 Hz, 1H), 8.33 (d, *J* = 5.8 Hz, 1H), 7.99 (d, *J* = 1.6 Hz, 1H), 7.78–7.70 (m, 2H), 7.47 (d, *J* = 3.6 Hz, 1H), 7.41 (s, 1H), 7.16 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.63 (d, *J* = 3.6 Hz, 1H), 3.71 (s, 2H), 3.17 (t, *J* = 5.0 Hz, 4H), 2.67 (s, 4H); MS (ESI) m/z 538.60 $[C_{27}H_{23}F_4N_7O + H]^+$.

Example 252, Preparation of 1-(3-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



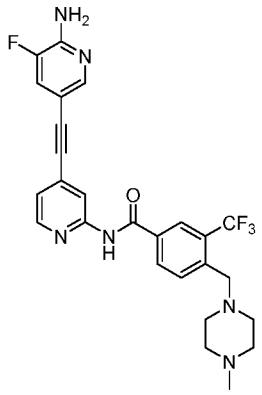
The title compound was prepared in 27% yield (70 mg, AUC HPLC 99%) as an off-white solid using Sonogashira coupling conditions similar to **general procedure B** using Intermediate 40 as starting material. mp: 201–208 °C.^{1}H NMR (400 MHz, DMSO–d_6 δ (ppm):12.26 (s, 1H), 10.15 (s, 1H), 9.99 (s, 1H), 8.46 (t, J = 9.2 Hz, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.60 (s, 1H), 7.49 (d, J = 8.0 Hz , 1H), 7.34 (t, J = 7.0 Hz, 1H), 7.17 (d, J = 7.0 Hz, 2H), 6.62 (s, 1H), 3.52 (s, 2H), 2.4–2.2 (m, 8H), 2.15 (s, 1H). MS (ESI) *m/z*: 551.21 (M+H) $[C_{29}H_{26}F_4N_6O+H]^+$

Example 253, Preparation of 1-(3-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



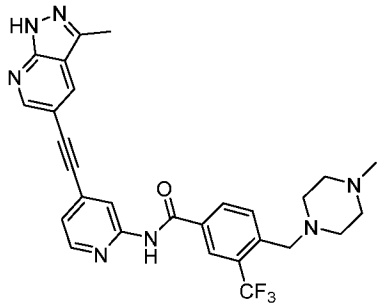
The title compound prepared (12 mg, AUC HPLC 95%) as an off-white solid using coupling conditions similar to **general procedure B** using intermediate 40 as starting material. mp: 181–186 °C. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 10.1–9.38 (m, 1H), 8.0 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.83 (s, 2H), 7.60 (s, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.16–7.13 (m, 2H), 3.52 (s, 1H), 3.13 (s, 6H): 2.37–2.32 (m, 8H), 2.15 (s, 3H). MS (ESI) *m/z*: 577.0 $[C_{30}H_{31}F_3N_8O+H]^{+\cdot}$

Example 254: Preparation of N-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



To a solution of 5-ethynyl-3-fluoropyridin-2-amine (49 mg, 0.36 mmol) in DMF (1 mL) under inert atmosphere was added *N*-(4-bromopyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (165 mg, 0.36 mmol), triphenylphophine (33 mg, 0.048 mmol), $Pd(PPh_3)_2Cl_2$ (33 mg, 0.126 mmol), copper iodide (6.9 mg, 0.036 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 8 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford *N*-(4-((6-amino-5-fluoropyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (90 mg, 49%, AUC HPLC 95%) as yellow solid. m.p: 208.7-210.9 °C; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ (ppm): 8.42-8.28 (m, 3H), 8.22 (d, *J* = 8.3Hz, 1H), 8.05-7.97 (m, 2H), 7.49 (dd, *J* = 11.3, 1.5 Hz, 1H), 7.28-7.20 (m, 1H), 4.57(s, 2H), 3.82 (s, 2H), 2.95 (bs, 4H), 2.67 (bs, 4H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, MeOD-*d*$_4$) δ (ppm): 166.88, 153.42, 151.66, 151.53, 149.48, 147.98, 147.07 (d, *J* = 252.9 Hz), 142.61, 134.89 (d, *J* = 16.1 Hz), 132.44, 132.31, 130.17 (q, J = 30.1 Hz), 126.78 (q, *J* = 5.9 Hz), 125.59 (q, *J* = 273.6 Hz), 124.68, 124.51, 122.89, 117.50, 108.37, 91.94, 88.37, 58.64, 55.51, 52.35, 44.70; MS (ESI) *m/z* 513.14[$C_{26}H_{24}F_4N_6O$+ H]$^+$.

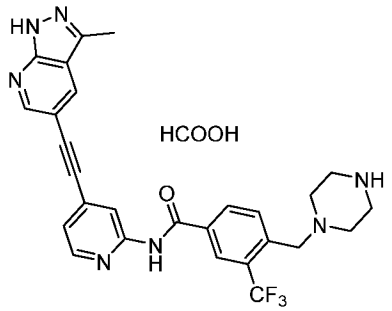
Example 255: *N-(4-((3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide*



To a solution of *N*-(4-((3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (11 mg, 0.0194 mmol) in 1:1 THF:DMF (2 mL), potassium carbonate (2.7 mg, 0.0194 mmol) was added and stirred for 15 min. Iodomethane (0.66 µL, 0.0106 mmol) in DMF was then added and the mixture stirred for 12 h at rt. The reaction was quenched by adding water (2 drops) and the solvents were removed *in vacuo*. The residue was then purified by preparative TLC to give *N*-(4-((3-methyl-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-

yl)methyl)-3-(trifluoromethyl)benzamide (3.0 mg, 29%, AUC HPLC: 95.6%) as a yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 13.55 (s, 1H), 11.28 (s, 1H), 8.72 (d, J = 2.0 Hz, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.47 (dd, J = 5.0, 0.9 Hz, 1H), 8.38 – 8.33 (m, 2H), 8.30 (dd, J = 8.1, 1.9 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 5.0, 1.5 Hz, 1H), 3.68 (s, 2H), 2.53 (s, 3H), 2.46 – 2.37 (m, 4H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 152.4, 151.3, 151.1, 148.6, 141.7, 133.6, 132.8, 132.0, 131.9, 130.6, 127.4, 127.2, 127.0, 126.8, 125.6, 125.0, 123.2, 121.3, 115.9, 113.6, 109.8, 91.8, 87.7, 57.5, 54.7, 52.7, 45.7, 12.1; MS (ESI) m/z 535 $[C_{28}H_{26}F_3N_7O + H]^+$

Example 256: *N-(4-((3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt*

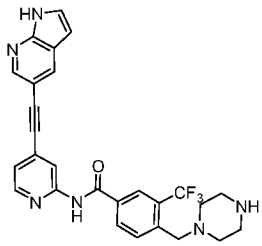


Step 1: Preparation of *tert*-butyl 4-(4-((4-((3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. To a solution of 5-bromo-3-methyl-1*H*-pyrazolo[3,4-b]pyridine (42 mg, 0.197 mmol), *tert*-butyl 4-(4-((4-ethynylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (80 mg, 0.164 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.012 mmol), CuI (3 mg, 0.016 mmol) and PPh_3 (15 mg, 0.057 mmol) and DMF (1.0 mL), DIPEA (1.0 mL) was added. After purging with Ar for 10 mins, the resulting mixture was stirred at 90°C for 3h in a microwave. Upon cooling to room temperature, DMF was then removed *in vacuo* and the resulting residue was purified by preparatory column chromatography to afford of *tert*-butyl 4-(4-((4-((3-methyl-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (48 mg, 47%); MS (ESI) *m/z*: 620 $[C_{32}H_{32}F_3N_7O_3 + H]^+$

Step 2: Synthesis of *N*-(4-((3-methyl-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt. To a solution of *tert*-butyl 4-(4-((4-((3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-

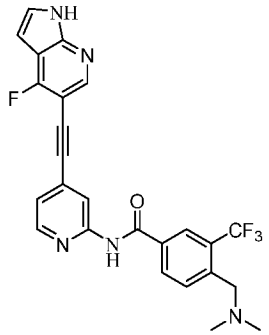
(trifluoromethyl)benzyl)piperazine-1-carboxylate (48 mg, 0.0775 mmol) in CH_2Cl_2 (2.4 mL), trifluoroacetic acid (0.6mL) was added. The mixture was stirred at rt for 1h. TFA was then removed *in vacuo* and the resulting residue was redissolved in CH_2Cl_2/CH_3OH, followed by adding solid $NaHCO_3$ and 15 drops of water. The mixture was stirred at rt for 15 mins. The solids were filtered off and the filtrate concentrated and purified by preparatory HPLC twice to afford *N*-(4-((3-methyl-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt (15.1 mg, 34%, AUC HPLC: 97.5%) as a brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 13.56 (s, 1H), 11.29 (s, 1H), 8.72 (d, *J* = 1.9 Hz, 1H), 8.62 (d, *J* = 2.0 Hz, 1H), 8.50 – 8.46 (m, 1H), 8.36 (d, *J* = 1.1 Hz, 2H), 8.30 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.28 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.35 (dd, *J* = 5.0, 1.5 Hz, 1H), 3.69 (s, 2H), 2.90 – 2.82 (m, 4H), 2.53 (s, 3H), 2.44 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.8, 164.2, 152.4, 151.4, 151.1, 148.6, 141.9, 141.4, 133.6 132.8, 132.0, 130.6, 127.3, 127.1, 125.7, 125.0, 123.2, 121.3, 115.9, 113.6, 109.8, 91.8, 87.7, 57.8, 52.5, 44.5, 12.1; MS (ESI) *m/z* 521 $[C_{27}H_{24}F_3N_7O + H]^+$

Example 257, Preparation of N-(4-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 60.6% yield (400 mg, AUC HPLC 96.05%) as an off-white solid in a fashion similar to **Example 227** synthesis starting from **Intermediate 12**. mp: 159–162 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.01 (s, 1H), 11.27 (s, 1H), 8.48–8.45 (m, 2H), 8.34 (d, *J* = 4.4 Hz, 2H), 8.28 (d, *J* = 2.4 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 2.4 Hz, 1H), 7.34 (dd, *J* = 1.2 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 3.64 (s, 2H), 2.74–2.71 (m, 4H), 2.35–2.34 (m, 4H). MS (ESI) *m/z*: 505.3 $[C_{27}H_{23}F_3N_6O+H]^+$.

Example 258: Preparation of 4-((dimethylamino)methyl)-N-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



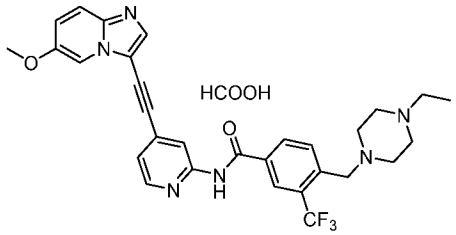
Step 1: *tert*-butyl 5-((2-aminopyridin-4-yl) ethynyl)-4-fluoro-1H-pyrrolo [2, 3-b] pyridine-1-carboxylate. The title compound was prepared in the amount of 300 mg (73%, LC-MS 98%) as a pale yellow solid using Sonogashira coupling conditions similar to **general procedure B** using 4-ethynylpyridin-2-amine. MS (ESI) *m/z*: 353 $[C_{19}H_{17}FN_4O_2+ H]^+$.

Step 2: Synthesis of *tert*-butyl 5-((2-(4-((dimethylamino) methyl)-3-(trifluoromethyl) benzamido) pyridin-4-yl) ethynyl)-4-fluoro-1*H*-pyrrolo[2, 3-b]pyridine-1-carboxylate. To a solution of *tert*-butyl 5-((2-aminopyridin-4-yl)ethynyl)-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate (282 mg, 0.79 mmol) in pyridine (5 ml) were successively added 4-((dimethylamino)methyl)-3-(trifluoromethyl)benzoic acid (300mg, 0.99 mmol), $POCl_3$ (0.5 mL) at 0 °C and then stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc and basified with aqueous $NaHCO_3$. The organic layer was washed in turn with water and brine then dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 5-((2-(4-((dimethylamino) methyl)-3-(trifluoromethyl) benzamido) pyridin-4-yl) ethynyl)-4-fluoro-1*H*-pyrrolo [2, 3-b] pyridine-1-carboxylate (120 mg, LC–MS 44%) as a pale brown solid. MS (ESI) m/z: 582.1 $[C_{30}H_{27}F_4N_5O_3+H]^+$.

Step 3: Synthesis of 4-((dimethylamino) methyl)-*N*-(4-((4-fluoro-1*H*-pyrrolo [2, 3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide. A solution of *tert*-butyl 5-((2-(4-((dimethylamino) methyl)-3-(trifluoromethyl) benzamido) pyridin-4-yl) ethynyl)-4-fluoro-1*H*-pyrrolo [2, 3-b] pyridine-1-carboxylate (120 mg) and 6N HCl in 1, 4-dioxane (2 mL) was stirred at room temperature for 2 h. The reaction mixture was basified with saturated $NaHCO_3$ and extracted with EtOAc (10 mL). The organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford of 4-((dimethylamino) methyl)-*N*-(4-((4-fluoro-1H-pyrrolo [2, 3-b] pyridin-5-yl) ethynyl) pyridin-2-yl)-3-(trifluoromethyl) benzamide (20 mg, 20.2%, AUC HPLC 97.7%) as an off-white solid. mp: 223–226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.35 (s, 1H), 11.27 (s, 1H), 8.47–8.52 (m, 2H), 8.35 (s, 1H), 8.31

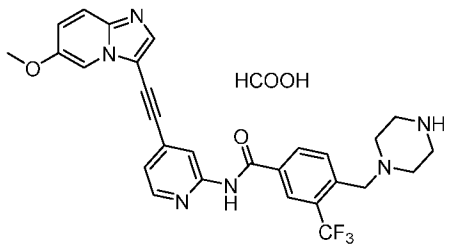
(d, *J* = 8 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 2.8 Hz, 1H), 7.35 (dd, *J* = 1.2, 4.8 Hz, 1H), 6.65–6.62 (m, 1H), 3.61 (s, 2H), 2.22(s, 6H). MS (ESI) m/z: 481.9 $[C_{25}H_{19}F_4N_5O+H]^+$.

Example 259: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formic acid salt



To a solution of 3-bromo-6-methoxyimidazo[1,2-*a*]pyridine (25 mg, 0.110 mmol), 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-ethynylpyridin-2-yl)-3-(trifluoromethyl)benzamide (46 mg, 0.110 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 0.0143 mmol), CuI (2 mg, 0.0110 mmol) and PPh_3 (10 mg, 0.0385 mmol) and DMF (1.0 mL), DIPEA (1.0 mL) was added. After purging with argon for 10 min, the resulting mixture was heated in a microwave apparatus at 90 °C for 3 h. The DMF was then removed *in vacuo* and the resulting residue was purified preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide formic acid salt (16.0 mg, 24%, AUC HPLC 99.8%) as a light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.28 (s, 1H), 8.48 (d, *J* = 5.1 Hz, 1H), 8.38 (d, *J* = 1.2 Hz, 1H), 8.35 (d, *J* = 1.9 Hz, 1H), 8.29 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.17 (s, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 8.09 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 9.7 Hz, 1H), 7.47 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.28 (dd, *J* = 9.7, 2.4 Hz, 1H), 3.94 (s, 3H), 3.68 (s, 2H), 2.44 (m, 4H), 2.34 (q, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): δ 164.9, 163.2, 152.3, 149.9, 148.5, 142.7, 141.6, 139.8, 132.8, 132.0, 131.7, 130.5, 127.4, 127.2, 127.0, 126.8, 125.6, 123.2, 121.6, 120.9, 117.9, 115.2, 107.8, 107.6, 97.7, 81.5, 57.5, 56.4, 52.8, 52.3, 51.5, 11.9; MS (ESI) *m/z* : 564 $[C_{30}H_{29}F_3N_6O_2 + H]^+$, m.p 186-188°C.

Example 260: Preparation of N-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt

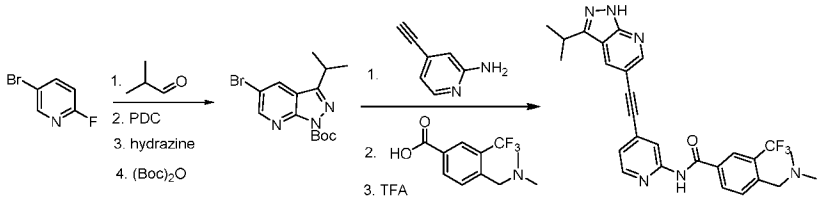


Step 1: Preparation of *tert*-butyl 4-(4-((4-((6-methoxyimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. To a solution of 3-bromo-6-methoxyimidazo[1,2-*a*]pyridine (25 mg, 0.110 mmol), *tert*-butyl 4-(4-((4-ethynylpyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (54 mg, 0.110 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 0.0143 mmol), CuI (2 mg, 0.0110 mmol) and PPh_3 (10 mg, 0.0385 mmol) and DMF (1.0 mL), DIPEA (1.0 mL) was added. After purging with argon for 10 mins, the resulting mixture was heated at 90°C for 3h in a microwave apparatus. Upon cooling to room temperature, DMF was then removed *in vacuo* and the resulting residue was purified by cloumn chromatography to afford tert-butyl 4-(4-((4-((6-methoxyimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (52.0 mg, 82%); MS (ESI) *m/z* : 635 $[C_{33}H_{33}F_3N_6O_4 + H]^+$,

Step 2: Preparation of *N*-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt. To a solution of tert-butyl 4-(4-((4-((6-methoxyimidazo[1,2-*a*]pyridin-3-yl)ethynyl)pyridin-2-yl)carbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (57 mg, 0.0898 mmol) in CH_2Cl_2 (2.4mL), trifluoroacetic acid (0.6mL) was added. The mixture was stirred at RT for 1h. TFA was then removed *in vacuo* and the resulting residue was redissolved in CH_2Cl_2/CH_3OH, followed by adding solid $NaHCO_3$ and 10 drops of water. The mixture was stirred at RT for 15 mins. The solids were filtered off and the filtrate concentrated and purified by preparative HPLC to afford *N*-(4-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide formic acid salt (12.2 mg, 23%, AUC HPLC 97.0%) as a yellow solid mp 130-132°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.29 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.38 (t, J = 1.1 Hz, 1H), 8.36 (d, J = 1.9 Hz, 1H), 8.30 (dd, J = 8.0, 1.9 Hz, 1H), 8.25 (s, 1H), 8.14 (d, J = 2.3 Hz, 1H), 8.09 (s, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 9.7 Hz, 1H), 7.48 (dd, J = 5.0, 1.5 Hz, 1H), 7.28 (dd, J = 9.7, 2.4 Hz, 1H), 3.94 (s, 3H), 3.69 (s, 2H), 2.86 (t, J = 4.9 Hz, 4H), 2.47–2.41 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.8, 164.0, 152.3, 149.9, 148.5, 142.7, 141.4, 139.8, 132.8, 132.0,

131.7, 130.6, 127.5, 127.3, 127.1, 126.9, 125.6, 125.0, 123.2, 121.6, 120.9, 117.9, 115.2, 107.8, 97.7, 81.5, 57.8, 56.4, 52.5, 44.6; MS (ESI) *m/z* 536 $[C_{28}H_{25}F_3N_6O_2 + H]^+$.

Example 261: 4-((dimethylamino)methyl)-N-(4-((3-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)et254hynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



Step 1: 1-(5-bromo-2-fluoropyridin-3-yl)-2-methylpropan-1-ol

[000657] To a solution of 5-bromo-2-fluoropyridine (2 g, 11.36 mmol) in THF (30 mL) under argon at -78 °C was added dropwise lithium diisopropylamide (6.1 mL, 12.15 mmol, 2M in THF). The mixture was stirred for 1 h at –78 °C prior to the addition of isobutyraldehyde (510 mg, 11.36 mmol). The reaction mixture was stirred for 1 h and the reaction was quenched by adding a saturated aqueous solution of NH_4Cl. The reaction mixture was diluted with diethyl ether and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 1-(5-bromo-2-fluoropyridin-3-yl)-2-methylpropan-1-ol (1.5 g, 30%) as yellow oil; MS (ESI) *m/z*: 247.95 $[C_9H_{11}BrFNO+H]^+$.

Step 2: 1-(5-bromo-2-fluoropyridin-3-yl)-2-methylpropan-1-one

[000658] To a ice cooled solution of 1-(5-bromo-2-fluoropyridin-3-yl)-2-methylpropan-1-ol (1.5g, 6.048 mmol) in 1,2-dichloroethane (20 mL) was added pyridinium chlorochromate (1.3 g, 9.07 mmol). The reaction mixture was heated at 40 °C for 3 h and was filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, eluent hexane/ethylacetate 90:10) to afford 1-(5-bromo-2-fluoropyridin-3-yl)-2-methylpropan-1-one (900 mg, 28%) as yellow oil. MS (ESI) *m/z*: 245.92 $[C_9H_9BrFNO+H]^+$.

Step 3: 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine

[000659] A solution of 1-(5-bromo-2-fluoropyridin-3-yl)-2-methylpropan-1-one (900 mg, 3.65 mmol) and hydrazine hydrate (548 mg, 10.97 mmol) in ethanol (10 mL) was heated at 90 °C for 15h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed in turn with water and brine. The organic phase

was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was diluted with a mixture of diethyl ether/n-hexane (10:90) and the precipitate was isolated by filtration and dried to afford 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine (300 mg, 34.1%, LC-MS 93.5%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.38 (s, 1H), 8.56 (d, *J* = 2.0 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 3.36–3.32 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 6H). (ESI) *m/z*: 239.87 (M+H) $[C_9H_{10}BrN_3+ H]^+$.

Step 4: *Tert*-butyl-5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate

[000660] To a solution of 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine (300 mg, 1.25 mmol) and DMAP (152 mg, 1.25 mmol) in THF (10 mL) was added $(Boc)_2O$ (545 mg, 2.5 mmol). The reaction mixture was stirred at room temperature for 1 h and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent hexane/ethyl acetate 90:10) to afford *tert*-butyl 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate (350 mg, 82%, LC-MS 86.4%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 3.37–3.34 (m, 1H), 1.71 (s, 9H), 1.46 (d, *J* = 7.2 Hz, 6H). (ESI) *m/z*: 339.84 $[C_{14}H_{18}BrN_3O_2+ H]^+$.

Step 5: *tert*-butyl 5-((2-aminopyridin-4-yl)ethynyl)-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate

[000661] To a solution of *tert*-butyl 5-bromo-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate (350 mg, 1.0 mmol) and *N,N*-diisopropylethylamine (0.55 mL, 3.0 mmol) in acetonitrile (25 mL) under argon were successively added $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), PPh_3 (13.1 mg, 0.05 mmol), CuI (28 mg, 0.15 mmol) and 4-ethynylpyridin-2-amine (118 mg, 1.0 mmol). The reaction mixture was heated at 80 °C for 5 h and was concentrated under reduced pressure. The residue was diluted with ethyl acetate and the organic phase thus obtained was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent dichloromethane/methanol 98:2) to afford *tert*-butyl 5-((2-aminopyridin-4-yl)ethynyl)-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate (200 mg, 51.5%) ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.83 (d, *J* = 1.6 Hz, 1H), 8.70 (d, *J* = 1.6 Hz, 1H), 7.97 (d, *J* = 5.6 Hz, 1H), 6.64 (d, *J* = 5.2 Hz, 1H), 6.60 (s, 1H), 6.16 (bs, 2H), 3.44–3.37 (m, 1H), 1.63 (s, 9H), 1.39 (d, *J* = 6.8 Hz, 6H). (ESI) *m/z*: 378.06 $[C_{21}H_{23}N_5O_2+ H]^+$.

Step 6: *Tert*-butyl 5-((2-(4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-3-isopropyl-1H-pyrazolo[3,4-b]pyridine-1-carboxylate

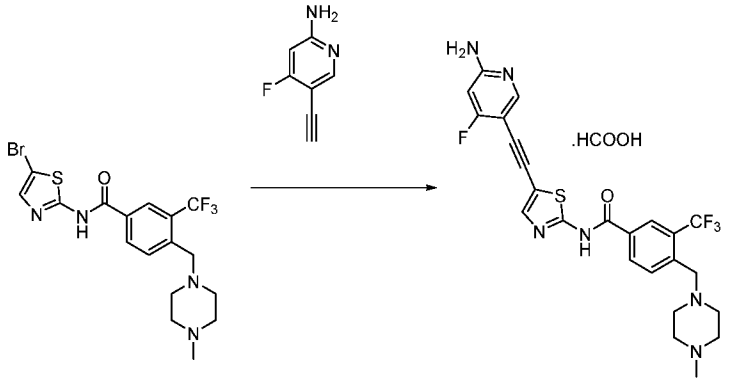
[000662] To an ice cooled solution of *tert*-butyl 5-((2-aminopyridin-4-yl)ethynyl)-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate (200 mg, 0.53 mmol) and 4-

((dimethylamino)methyl)-3-(trifluoromethyl)benzoic acid (240 mg, 0.79 mmol) in pyridine (2 mL) was added $POCl_3$ (238 mg, 1.59 mmol). The reaction mixture was stirred at room temperature for 2 h then poured into crushed ice and the resulting mixture was basified with a satured aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 5-((2-(4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate (250 mgas a solid. The crude product was carried forth to the next step without further purification. MS (ESI) *m/z*: 607.3 $[C_{32}H_{33}F_3N_6O_3+ H]^+$.

Step 7: 4-((dimethylamino)methyl)-*N*-(4-((3-isopropyl-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide

[000663] A solution of *tert*-butyl 5-((2-(4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamido)pyridin-4-yl)ethynyl)-3-isopropyl-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate (250 mg, 0.412 mmol) and TFA (2 mL) in dichloromethane (5 mL) was stirred at room temperature for 2 h and was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 4-((dimethylamino)methyl)-*N*-(4-((3-isopropyl-1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide (35 mg, AUC HPLC 98.1%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.50 (s, 1H), 11.26 (s, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.68 (d, J = 3.2 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.36–8.35 (m, 2H), 8.32 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.36 (dd, J = 5.2, 1.2 Hz, 1H), 3.61 (s, 2H), 3.42–3.37 (m, 1H), 2.22 (s, 6H), 1.39 (d, J = 6.8 Hz, 6H). (ESI) *m/z*: 506.9 (M+H) $[C_{27}H_{25}F_3N_6O+ H]^+$.

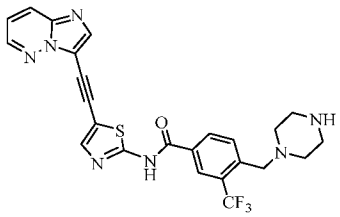
Example 262: N-(5-((6-amino-4-fluoropyridin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate



Preparation of *N*-(5-((6-amino-4-fluoropyridin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate

[000664] To a solution of 5-ethynyl-4-fluoropyridin-2-amine (22 mg, 0.16 mmol) in DMF (1 mL) under inert atmosphere were added *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (75 mg, 0.16 mmol), triphenylphophine (15 mg, 0.056 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol), copper iodide (3.0 mg, 0.016 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 8 h, then was diluted with water (10 mL) and extracted with EtOAc (3x15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(5-((6-amino-4-fluoropyridin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate (15 mg, 18%, AUC HPLC 98%) as yellow solid. m.p: 175.7-177.1 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.37 (s, 1H), 8.32-8.23 (m, 3H), 8.08 (d, *J* = 10.0 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.66 (s, 1H), 6.32 (d, *J* = 11.6 Hz, 1H), 3.86 (s, 2H), 3.40-3.20 (m, 4H), 2.87 (s, 3H), 2.78 (bs, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 170.25 (d, *J* = 260.9 Hz), 166.82, 166.01, 163.26(d, *J* = 12.1 Hz), 160.28, 154.30(d, *J* = 2.9 Hz), 143.05, 142.81, 133.10, 132.82, 132.43, 130.36 (q, *J* = 31.1 Hz), 127.05 (q, *J* = 5.7 Hz), 125.47 (q, *J* = 273.5 Hz), 114.14, 99.37(d, *J* = 14.3 Hz), 95.09(d, *J* = 20.3 Hz), 87.31, 84.48, 58.33, 54.95, 51.22, 43.60; MS (ESI) *m/z* 519.65[$C_{24}H_{22}F_4N_6OS$ + H]$^+$.

Example 263: N-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 4-(4-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate

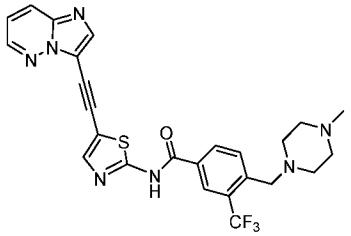
[000665] To a solution of Intermediate 29 (1 g, 1.766 mmol) in DMF (20 mL) under argon were successively added DIPEA (10.0 mL), $Pd(PPh_3)_4$ (98.0 mg, 0.088 mmol), PPh_3 (20.0 mg, 0.088 mmol), CuI (64.0 mg, 0.353 mmol), 3-ethynylimidazo[1,2-b]pyridazine (364 mg,

2.649 mmol). The reaction mixture was heated at 90 °C for 3 h and was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane:methanol 95:5) to afford *tert*-butyl 4-(4-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate: (450 mg, 29.2%, LCMS: 70%) as a yellow solid; MS (ESI) *m/z* :612 $[C_{29}H_{28}F_3N_7O_3S + H]^{+.}$

Step 2: Preparation of *N*-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide

[000666] To a solution of *tert*-butyl 4-(4-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (450 mg, 0.736 mmol) in dichloromethane (10 mL) was added TFA (2 mL) at room temperature. The reaction mixture was stirred for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford *N*-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide (120 mg, 29.70%, LC-MS 98.44%, AUC HPLC 98.8%) as a brown solid. mp: 252–256 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 8.67–8.65 (d, J = 3.6 Hz, 1H), 8.46 (s, 1H), 8.36–8.34 (d, J = 8.0 Hz, 1H), 8.22–8.20 (dd, J = 8.0 , 1.2 Hz, 1H), 8.13 (s, 1H), 7.85–7.83 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.36–7.32 (m, 1H), 3.71 (s, 2H), 3.09–3.01 (m, 4H), 2.51–2.31 (m, 4H); MS (ESI) m/z: 548.29 $[C_{24}H_{20}F_3N_7OS + H]^+$.

Example 264: N-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

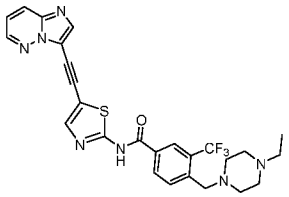


Preparation of *N*-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000667] To a solution of *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (500 mg, 1.082 mmol) in DMF (5.0 mL) under argon were successively added DIPEA (5.0 mL), $Pd(PPh_3)_4$ (62.49 mg, 0.054 mmol), PPh_3 (14.1 mg, 0.054 mmol), CuI (41.0 mg, 0.216 mmol) and 3-ethynylimidazo[1,2-b]pyridazine (232 mg,

1.62 mmol). The reaction mixture was heated at 80 °C for 15 h and was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane/methanol 95:5) and preparative HPLC to afford *N*-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (16 mg, AUC HPLC 98.2%) as a pale yellow solid. mp: 230–233 °C; ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 12.81 (bs, 1H), 8.70 (d, J = 3.2 Hz, 1H), 8.46 (s, 1H), 8.37–8.35 (d, J = 8.0 Hz, 1H), 8.25–8.20 (m, 2H), 7.97 (s, 1H), 7.94–7.92 (d, J = 8.0 Hz, 1H), 7.40–7.36 (d, J = 4.4 Hz, 1H), 3.70 (s, 2H), 2.50–2.32 (m, 8H), 2.25 (s, 3H); MS (ESI) *m/z* :525.9 $[C_{25}H_{22}F_3N_7OS + H]^+$.

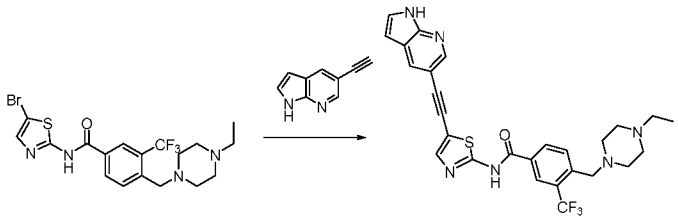
Example 265: 4-((4-ethylpiperazin-1-yl)methyl)-N-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide



Step1: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide

[000668] The title compound was synthesized following a method similar to general procedure C and starting from Intermediate 32. The reaction crude product was purified by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl) methyl)-*N*-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide (30 mg, AUC HPLC 98.8 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.70 (d, J = 3.2 Hz, 1H), 8.46 (s, 1H), 8.37(d, J = 8.0 Hz, 1H), 8.25–8.20 (m, 2H), 7.96–7.92 (m, 2H), 7.37 (dd, J = 9.2, 4.4 Hz, 1H), 3.70 (s, 2H), 2.44–2.32 (m, 10H), 1.02 (t, J = 6.8 Hz, 3H). MS (ESI) *m/z*:540.2 $[C_{26}H_{24}F_3N_7OS+ H]^+$.

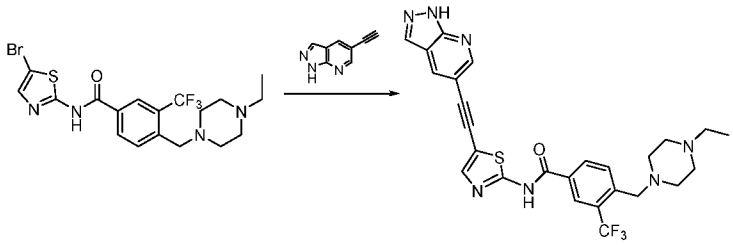
Example 266: N-(5-((1H-pyrrolo [2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-((1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000669] The title compound was synthesized following a method similar to general procedure C and starting from Intermediate 32 and 5-ethynyl-*1H*-pyrrolo[2,3-b]pyridine. The reaction crude product was purified by preparative HPLC to afford *N*-(5-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (27 mg, 12%, AUC HPLC 98.17 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.90 (s, 1H), 8.43 (s, 1H), 8.36–8.34 (m, 2H), 8.15 (s, 1H), 7.89–7.82 (m, 2H), 7.55 (s, 1H), 6.49 (s, 1H), 3.66 (s, 2H), 2.42–2.23 (m, 10H), 0.98–0.96 (m, 3H). MS (ESI) *m/z*:539.24 $[C_{27}H_{25}F_3N_6OS + H]^+$.

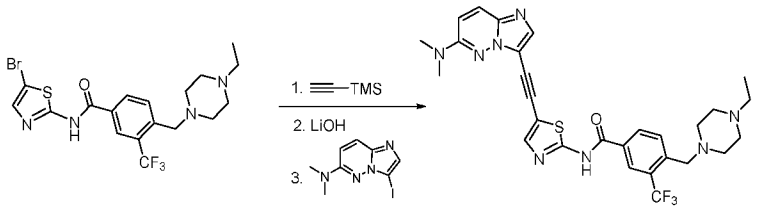
Example 267: N-(5-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-((1H-pyrazolo [3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000670] The title compound was synthesized following a method similar to general procedure C and starting from *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and 5-ethynyl-*1H*-pyrrolo[2,3-b]pyridine. The reaction crude product was purified by preparative HPLC to afford to afford *N*-(5-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (10 mg, 12%, AUC HPLC 92.0%) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.66 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 8.37 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H) 7.75 (s, 1H), 3.78 (s, 2H), 2.67–2.51 (m, 10H), 1.13 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z*: 540.0 $[C_{26}H_{24}F_3N_7OS+ H]^+$.

Example 268: N-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Step 1: preparation of 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide

[000671] The title compound was synthesized following a method similar to general procedure A and starting from *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide and ethynyltrimethylsilane. The reaction crude product was purified by column chromatography (neutral alumina, eluent: hexane/ethyl acetate 80:20) to afford 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide (400 mg) as pale yellow solid.^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H), 8.08–8.03 (m, 2H),7.46 (s, 1H), 3.74 (s, 2H), 2.56–2.41 (m, 10H), 1.09 (t, J = 6.8 Hz, 3H), 0.25 (s, 9H). MS (ESI) *m/z*: 494.9 $[C_{23}H_{29}F_3N_4OSSi + H]^+$.

[000672] Step 2: preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl)benzamide

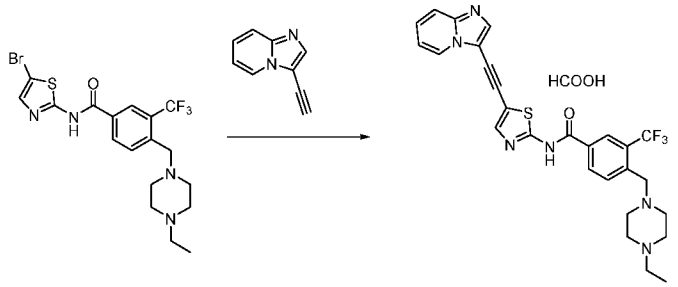
To a solution of $LiOH•H_2O$ (18 mg, 0.404 mmol) in water (2 mL) was added 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-*N*-(5-((trimethylsilyl)ethynyl)thiazol-2-yl)benzamide (200 mg, 0.404 mmol). Reaction mixture was stirred at room temperature for 2 h and was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl)benzamide (70 mg, 38.7%, LC-MS 95.9 %) as a yellow solid.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.42 (s, 1H), 8.32 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 4.35 (s, 1H), 3.65 (s, 2H), 2.41–2.30 (m, 10H), 0.98 (d, J = 7.2 Hz, 3H). MS (ESI) *m/z*: 423.26 $[C_{20}H_{21}F_3N_4OS + H]^+$.

Step 3: preparation of *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000673] The title compound was synthesized following a method similar to general procedure C and starting from 3-iodo-*N*,*N*-dimethylimidazo[1,2-b]pyridazin-6-amine and 4-

((4-ethylpiperazin-1-yl)methyl)-*N*-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl)benzamide. The reaction crude product was purified by flash column chromatography (silica gel eluent dichloromethwne/MeOH/NH_4OH 95:4:1) and preparative HPLC to afford *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (40 mg, 18.1%, AUC HPLC 94.11.%) as a yellow solid.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.9 (bs, 1H), 8.45 (s, 1H), 8.36 (d, J = 9.2 Hz, 1H), 7.90–7.86 (m, 3H), 7.83 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 10 Hz, 1H), 3.67 (s, 2H), 3.11 (s, 6H), 2.44–2.32 (m, 10H), 0.99 (d, J = 7.2 Hz, 3H). MS (ESI) *m/z*: 582.9 $[C_{28}H_{29}F_3N_8OS + H]^+$.

Example 269: 4-((4-ethylpiperazin-1-yl)methyl)-N-(5-(imidazo[1,2-a]pyridin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide formate

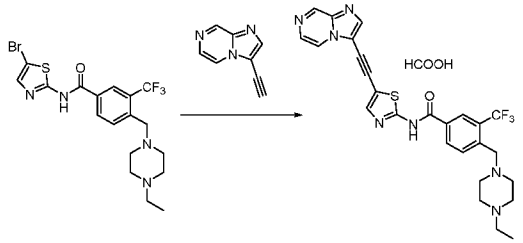


Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-(imidazo[1,2-*a*]pyridin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide formate

[000674] To a solution of 3-ethynylimidazo[1,2-*a*]pyridine (17 mg, 0.12 mmol) in DMF (1 mL) under inert atmosphere were added *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (57 mg, 0.12 mmol), triphenylphophine (11 mg, 0.042 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), copper iodide (2.3 mg, 0.012 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-(imidazo[1,2-*a*]pyridin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide formate (17 mg, 24%, AUC HPLC 99%) as yellow solid. m.p: 78.8–79.2 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.55-8.46 (m, 2H), 8.38 (s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.90 (s, 1H), 7.83 (s, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.52–7.43 (m, 1H), 7.19–7.11 (m, 1H), 3.85 (s, 2H), 3.19 (bs,

4H), 3.08 (q, *J* = 7.2 Hz, 2H), 2.76 (bs, 4H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-*d*$_4$) δ (ppm): 166.18, 161.20, 147.10, 144.41, 143.05, 138.64, 133.03, 132.81, 132.44, 130.35 (q, *J* = 30.9 Hz), 128.61, 127.04 (q, *J* = 6.0 Hz), 126.92, 125.49 (q, *J* = 273.6 Hz), 118.07, 115.44, 113.14, 110.00, 90.36, 82.22, 58.51, 53.10, 52.99, 51.66, 10.03; MS (ESI) *m/z* 539.95 $[C_{27}H_{25}F_3N_6OS+H]^+$.

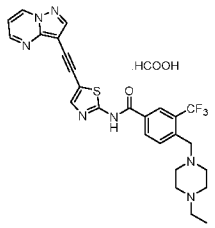
Example 270: N-(5-(imidazo[1,2-a]pyrazin-3-ylethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-(imidazo[1,2-*a*]pyrazin-3-ylethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000675] To a solution of 3-ethynylimidazo[1,2-*a*]pyrazine (58 mg, 0.12 mmol) in DMF (1 mL) under inert atmosphere was added *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)ethyl)-3-(trifluoromethyl)benzamide (21 mg, 0.12 mmol), triphenylphophine (11 mg, 0.042 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), copper iodide (2.3 mg, 0.012 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 8 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford *N*-(5-(imidazo[1,2-*a*]pyrazin-3-ylethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (55 mg, 42%, AUC HPLC 96%) as yellow solid. m.p: 168.6-169.7 °C; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ (ppm): 9.07 (d, *J* = 1.1Hz, 1H), 8.56 (dd, *J* = 4.5, 1.2 Hz, 1H), 8.38 (s, 1H), 8.28 (d, *J* = 8.2Hz, 1H), 8.13-8.07 (m, 2H), 8.02 (d, *J* = 8.2Hz, 1H), 7.89 (s, 1H), 3.83(s, 2H), 2.97 (bs, 4H), 2.87 (q, *J* = 7.3Hz, 2H), 2.70 (bs, 4H), 1.24 (t, *J* = 7.3Hz, 3H); ^{13}C NMR (100 MHz, MeOD-*d*$_4$) δ (ppm): 166.43, 162.00, 145.29, 144.03, 143.37, 141.92, 140.40, 133.04, 132.77, 132.42, 131.82, 130.31 (q, *J* = 30.9 Hz), 127.02 (q, *J* = 6.0 Hz), 125.52 (q, *J* = 273.6 Hz), 120.44, 112.28, 111.73, 91.89, 80.73, 58.72, 53.36, 53.24, 52.47, 10.69; MS (ESI) *m/z* 540.75$[C_{26}H_{24}F_3N_7OS + H]^+$.

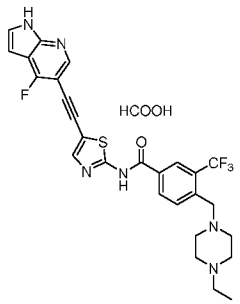
Example 271: 4-((4-ethylpiperazin-1-yl)methyl)-N-(5-(pyrazolo[1,5-a]pyrimidin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide formate salt



Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-(pyrazolo[1,5-a]pyrimidin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide formate

[000676] To a solution of 3-ethynylpyrazolo[1,5-*a*]pyrimidine (17 mg, 0.12 mmol) in DMF (1 mL) under inert atmosphere were added *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (58 mg, 0.12 mmol), triphenylphophine (11 mg, 0.042 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), copper iodide (2.3 mg, 0.012 mmol) and DIPEA (0.5 mL). The resulting mixture was heated to 90 °C for 8 h, then was diluted with water (10 mL) and extracted with EtOAc (3x15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-(pyrazolo[1,5-*a*]pyrimidin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide formate salt (3 mg, 4%, AUC HPLC 99%) as yellow solid. m.p: 104.6-105.3 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.99 (dd, *J* = 6.9, 1.2 Hz, 1H), 8.67-8.63 (m, 1H), 8.46 (s, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.72 (s, 1H), 7.13 (dd, *J* = 6.9, 4.1 Hz, 1H), 3.86 (s, 2H), 3.20 (bs, 4H), 3.09 (q, *J* = 7.3Hz, 2H), 2.76 (bs, 4H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 166.09, 160.25, 152.68, 149.67, 148.17, 142.94, 142.90, 138.08, 133.19, 132.81, 132.46, 130.36 (q, J = 31.2 Hz), 127.03 (q, *J* = 5.8 Hz), 125.51 (q, *J* = 273.5 Hz), 114.65, 110.91, 94.44, 86.08, 83.53, 58.48, 53.12, 53.01, 51.63, 10.00; MS (ESI) *m/z* 540.30$[C_{26}H_{24}F_3N_7OS + H]^+$.

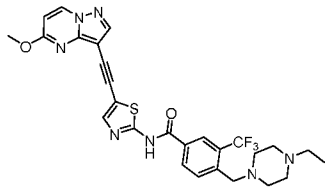
Example 272: 4-((4-ethylpiperazin-1-yl)methyl)-N-(5-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide



Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-((4-fluoro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide

[000677] To a solution of 5-ethynyl-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (19 mg, 0.12 mmol) in DMF (1 mL) under inert atmosphere were added *N*-(5-bromothiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (57 mg, 0.12 mmol), triphenylphophine (11 mg, 0.042 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), copper iodide (2.3 mg, 0.012 mmol) and DIPEA (0.5 mL). The resulting mixture was heated at 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-((4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide (9.4 mg, 14%, AUC HPLC 97%) as yellow solid. m.p: 220.5–221.4 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.52 (s, 1H), 8.40 (s, 1H), 8.36 (d, *J* = 9.0 Hz, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.77 (s, 1H), 7.47 (d, *J* = 3.5 Hz, 1H), 6.63 (d, *J* = 3.5 Hz, 1H), 3.86 (s, 2H), 3.07 (bs, 4H), 2.96 (q, *J* = 7.1 Hz, 2H), 2.73 (bs, 4H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, MeOD-*d*$_4$) δ (ppm): 166.19, 164.37, 161.71, 152.62 (d, *J* = 30.9 Hz), 148.26, 143.49, 143.19, 133.09, 132.78, 132.44, 130.34 (q, *J* = 31.1 Hz), 128.11, 127.01 (q, *J* = 5.8 Hz), 125.52 (q, *J* = 273.1 Hz), 113.89, 110.17 (d, *J* = 17.9 Hz), 100.71 (d, *J* = 10.9 Hz), 97.77, 87.67, 85.29, 58.64, 53.22, 53.19, 52.15, 10.42; MS (ESI) *m/z* 557.70[$C_{27}H_{24}F_4N_6OS$+ H]$^+$.

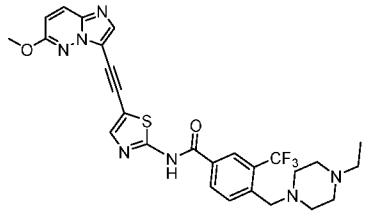
Example 273: 4-((4-ethylpiperazin-1-yl) methyl)-N-(5-((5- methoxypyrazolo [1, 5-a] pyrimidin-3-yl) ethynyl) thiazol-2-yl)-3-(trifluoromethyl) benzamide



Preparation of 4-((4-ethylpiperazin-1-yl) methyl)-*N*-(5-((5-methoxypyrazolo [1, 5-a] pyrimidin-3-yl) ethynyl) thiazol-2-yl)-3-(trifluoromethyl)benzamide

[000678] To a solution of 3-iodo-5-methoxypyrazolo [1, 5-a] pyramidine (245 mg, 0.890 mmol) in acetonitrile (6 mL) under argon successively were added $Pd(PPh_3)_4$ (35 mg, 0.02 mmol), PPh_3 (7.8 mg, 0.029 mmol), CuI (17mg, 0.089 mmol), 4-((4-ethylpiperazin-1-yl) methyl)-*N*-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl) benzamide (250 mg, 0.59 mmol) and DIPEA (216 mg, 1.78 mmol). The resulting mixture was heated at 80 °C for 4 h and was diluted with ethyl acetate (20 mL). The organic layer was washed in turn with water and brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent**:** dichloromethane/methanol 95:5) and by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide (18 mg, LC-MS 98%, AUC HPLC 95.9 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.91 (bs, 1H), 8.96 (d, *J* = 7.6 Hz, 1H), 8.45 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.32 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 6.67(d, *J* = 7.2 Hz, 1H), 4.01 (s, 3H), 3.69 (s, 2H), 2.32–2.50 (m, 10H), 1.00 (t, *J* = 7.2 Hz, 3H); MS (ESI) m/z: 570.2 $[C_{27}H_{26}F_3N_7O_2S+H]^+$.

Example 274: 4-((4-ethylpiperazin-1-yl)methyl)-N-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide

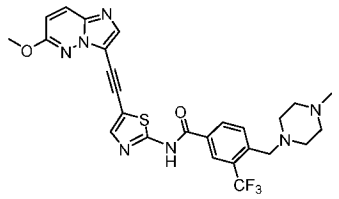


Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide

[000679] To a solution of 3-iodo-6-methoxyimidazo[1,2-b]pyridazine (245 mg, 0.89 mmol) in acetonitrile (6 mL) under argon were successively added Pd $(PPh_3)_4$ (35 mg, 0.02 mmol), PPh_3 (7.8 mg, 0.029 mmol), CuI (17 mg, 0.089 mmol), 4-((4-ethylpiperazin-1-yl) methyl)-*N*-

(5-ethynylthiazol-2-yl)-3-(trifluoromethyl) benzamide (250 mg, 0.59 mmol) and DIPEA (216 mg, 1.78 mmol) and the resulting mixture was heated at 80 °C for 4 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed in turn with water (20 mL) and brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent**:** dichloromethane/methanol 95:5) and by preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-((5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide (35 mg, AUC HPLC 99.7%) as an off white solid. mp:185–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.51 (bs, 1H), 8.46 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 9.6 Hz, 1H), 8.00 (s, 1H), 7.95–7.92 (m, 2H), 7.02 (d, J = 10.0 Hz, 1H), 4.02 (s, 3H), 3.70 (s, 2H), 2.50–2.43 (m, 10H), 1.02 (t, J = 6.8 Hz, 3H); MS (ESI) m/z: 570.2 [$C_{27}H_{26}F_3N_7O_2S$+ H]$^+$.

Example 275: N-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)

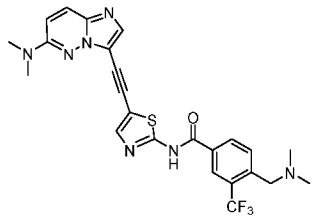


Preparation of *N*-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000680] To a solution of 3-iodo-6-methoxyimidazo[1,2-b]pyridazine (185 mg, 0.675 mmol) and diisopropylethylamine (237 mg, 1.84 mmol) in acetonitrile (10 mL) under argon were successively added $Pd(PPh_3)_4$ (35 mg, 0.0307 mmol), PPh_3 (8 mg, 0.0307 mmol), CuI (17.4 mg, 0.092 mmol), *N*-(5-ethynylthiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (250 mg, 0.614 mmol). The reaction mixture was heated at 80 °C for 3 h then was concentrated under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, dichlromethane/methanol/NH_4OH 97:2:1) to afford *N*-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (650 mg, 14.7%, AUC HPLC 99.2%) as a yellow solid, m.p. 125–129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.80 (bs, 1H), 8.46 (s, 1H), 8.36

(d, J = 9.2 Hz, 1H), 8.10 (d, J = 9.6 Hz, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 9.6 Hz, 1H), 4.02 (s, 3H), 3.69 (s, 2H), 2.46–2.43 (m, 8H), 2.24 (s, 3H). MS (ESI) *m/z*:555.9 $[C_{26}H_{24}F_3N_7O_2S + H]^+$.

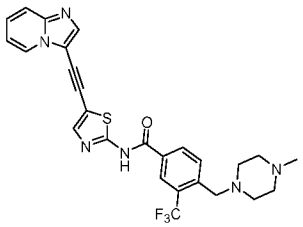
Example 276: N-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide

[000681] To a solution of *N*-(5-bromothiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (700 mg, 1.719 mmol) in DMF (7 mL) under argon, successively were added diisopropylethylamine (7 mL), $Pd(PPh_3)_4$ (99.0 mg, 0.085 mmol), PPh_3 (22.0 mg, 0.085 mmol), CuI (13.0 mg, 0.068 mmol), 3-ethynyl-*N,N*-dimethylimidazo[1,2-b]pyridazin-6-amine (402 mg, 2.58 mmol). The reaction mixture was heated at 80 °C for 2 h, was concentrated under reduced pressure and the residue was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel eluent, petroleum ether/EtOAc 60:40) and by preparative HPLC to afford *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (80 mg 9%, AUC HPLC 99.3%) as a yellow solid. m.p.: 208-212°C, ^{1}H NMR(400 MHz, (DMSO-d_6) δ (ppm): 13.20 (s, 1H), 8.46 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 7.96–7.84 (m, 4H), 7.15 (d, J = 10.0 Hz, 1H), 3.62 (s, 2H), 3.14 (s, 6H), 2.39(s, 6H); MS (ESI) *m/z*: 514.1 $[C_{24}H_{22}F_3N_7OS + H]^+$.

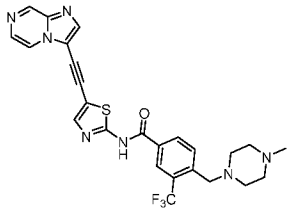
Example 277: N-(5-(imidazo[1,2-a]pyridin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Prparation of *of N-(5-(imidazo[1,2-a]pyridin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide*

[000682] To a solution of 3-ethynylimidazo[1,2-a]pyridine (21.5 mg, 0.151 mmol), *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (70 mg, 0.151 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.0196 mmol), CuI (3 mg, 0.0151 mmol), PPh_3 (14 mg, 0.0529 mmol) and DMF (1.0 mL) was added DIPEA (1.0 mL). After purging with Ar for 10 mins, the resulting mixture was stirred at 90°C for 3h in a microwave. Upon cooling to room temperature, DMF was then removed *in vacuo* and the resulting residue was purified by preparatory TLC (1:2:7 MeOH : diethyl ether : CH_2Cl_2)to afford *N*-(5-(imidazo[1,2-a]pyridin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (7.2 mg, 9%, AUC HPLC: 99.6%) as a yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.59 (dt, *J* = 6.8, 1.2 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 1H), 8.36 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.46 – 7.42 (m, 1H), 7.14 (td, *J* = 6.8, 1.2 Hz, 1H), 3.70 (s, 2H), 2.47 – 2.42 (m, 4H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.9, 145.3, 143.7, 141.7, 138.5, 132.1, 131.9, 130.7, 127.6, 127.4, 127.2, 126.9, 126.6, 125.8, 125.7, 125.0, 123.2, 117.4, 113.9, 109.7, 107.5, 90.0, 81.6, 57.4, 54.4, 52.3, 45.2; MS (ESI) *m/z* 525 $[C_{26}H_{23}F_3N_6OS + H]^+$

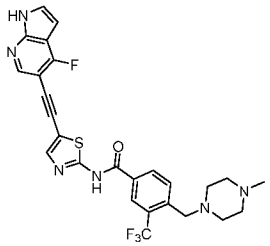
Example 278: N-(5-(imidazo[1,2-a]pyrazin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of N-(5-(imidazo[1,2-a]pyrazin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000683] To a solution of 3-ethynylimidazo[1,2-a]pyrazine (22 mg, 0.151 mmol), *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (70 mg, 0.151 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.0196 mmol), CuI (3 mg, 0.0151 mmol), PPh_3 (14 mg, 0.0529 mmol) and DMF (1.0 mL) was added DIPEA (1.0 mL). After purging with argon for 10 mins, the resulting mixture was stirred at 90°C for 3h in a microwave. Upon cooling to room temperature, DMF was then removed *in vacuo* and the resulting residue was purified by preparatory HPLC to afford *N*-(5-(imidazo[1,2-a]pyrazin-3-ylethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (20.5 mg, 26%, AUC HPLC: 98.7%) as a yellow solid; mp: 91.6–93.0 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.19 (d, J = 1.5 Hz, 1H), 8.68 (dd, J = 4.5, 1.5 Hz, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.37 (dd, J = 8.1, 1.8 Hz, 1H), 8.23 (s, 1H), 8.14 (s, 1H), 8.10 (d, J = 4.5 Hz, 1H), 8.03 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 3.70 (s, 2H), 2.48–2.43 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.0, 163.0, 144.5, 143.1, 141.7, 140.2, 139.5, 132.1, 130.6, 127.5, 127.3, 127.1, 126.9, 125.7, 125.0, 123.2, 119.1, 109.0, 91.2, 80.2, 57.3, 54.3, 52.2, 45.1; MS (ESI) *m/z* 527 $[C_{25}H_{22}F_3N_7OS + H]^+$

Example 279: N-(5-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

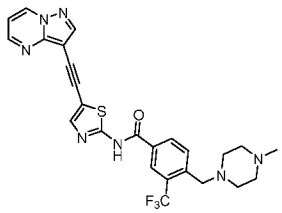


Preparation of *N*-(5-((4-fluoro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000684] To a solution of 5-ethynyl-4-fluoro-1*H*-pyrrolo[2,3-b]pyridine (24 mg, 0.151 mmol), *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (70 mg, 0.151 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.0196 mmol), CuI (3 mg, 0.0151 mmol), PPh_3 (14 mg, 0.0529 mmol) and DMF (1.0 mL) was added DIPEA (1.0 mL). After purging with argon for 10 mins, the resulting mixture was heated at 90°C for 3h in a microwave reactor. Upon cooling to room temperature, DMF was then removed *in vacuo* and the resulting residue was purified by preparative HPLC to afford *N*-(5-((4-fluoro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-

(trifluoromethyl)benzamide (10.3 mg, 13%, AUC HPLC: 99.3%) as a brown solid.; m.p. 238.1–239.3 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.30 (s, 1H), 8.46 (d, J = 1.8 Hz, 1H), 8.42 (d, J = 9.4 Hz, 1H), 8.36 (dd, J = 8.1, 1.8 Hz, 1H), 8.14 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.92 (s, 1H), 7.61 (dd, J = 3.5, 2.4 Hz, 1H), 6.62 (dd, J = 3.5, 1.9 Hz, 1H), 3.70 (s, 2H), 2.47–2.42 (m, 4H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.6, 163.1, 161.5, 159.7, 151.3, 151.3, 146.9, 143.1, 141.9, 132.1, 130.7, 127.7, 127.6, 127.4, 127.2, 127.0, 125.7, 125.0, 123.2, 110.2, 107.8, 107.7, 98.4, 98.4, 96.3, 86.6, 85.0, 57.4, 54.4, 52.4, 45.3; MS (ESI) *m/z* 544[$C_{26}H_{22}F_4N_6OS$ + H].

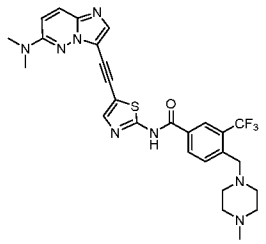
Example 280: Synthesis of 4-((4-methylpiperazin-1-yl)methyl)-N-(5-(pyrazolo[1,5-a]pyrimidin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide



Preparation of 4-((4-methylpiperazin-1-yl)methyl)-*N*-(5-(pyrazolo[1,5-a]pyrimidin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide

[000685] To a solution of 3-ethynylpyrazolo[1,5-a]pyrimidine (18 mg, 0.126 mmol), *N*-(5-bromothiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (58 mg, 0.126 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 0.0164 mmol), CuI (2.4 mg, 0.0164 mmol), PPh_3 (12 mg, 0.0441 mmol) and DMF (1.0 mL) was added DIPEA (1.0 mL). After purging with Ar for 10 mins, the resulting mixture was stirred at 90°C for 3h in a microwave. Upon cooling to room temperature, DMF was then removed *in vacuo* and the resulting residue was purified by preparative HPLC to afford 4-((4-methylpiperazin-1-yl)methyl)-*N*-(5-(pyrazolo[1,5-a]pyrimidin-3-ylethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide (10.2 mg, 15%, AUC HPLC 95.9%) as a yellow solid; m.p. 118.1-119.9 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.23 (dd, J = 7.0, 1.7 Hz, 1H), 8.70 (dd, J = 4.1, 1.7 Hz, 1H), 8.54 (s, 1H), 8.46 (d, J = 1.9 Hz, 1H), 8.36 (dd, J = 8.0, 1.8 Hz, 1H), 8.14 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.86 (s, 1H), 7.21 (dd, J = 7.0, 4.1 Hz, 1H), 3.69 (s, 2H), 2.47–2.41 (m, 4H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.5, 163.1, 159.5, 151.7, 148.1, 146.9, 142.3, 142.0, 137.0, 132.1, 131.5, 130.7, 127.6, 127.4, 127.2, 127.0, 125.8, 125.0, 123.2, 111.2, 110.0, 91.9, 85.7, 82.7, 57.4, 54.5, 52.4, 45.4; MS (ESI) *m/z* 527 $[C_{25}H_{22}F_3N_7OS + H]^+$

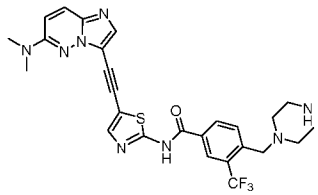
Example 281: N-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000686] To a solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzoic acid (320 mg, 1.05mmol) and 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (200 mg, 0.704 mmol) in pyridine (1.5 ml) was successively $POCl_3$ (0.2 ml) at 0 °C. The reaction mixture was stirred at room temperature for 4 h and was basified with aqueous $NaHCO_3$ then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to afford *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (40 mg, AUC HPLC 96.9%) as a yellow solid, mp:180-184 °C; ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 12.85 (s, 1H), 8.46 (s, 1H), 8.36 (d, J = 7.6 Hz, 1H), 7.94–7.87 (m, 3H), 7.83 (s, 1H), 7.15(d, J = 10 Hz, 1H), 3.69 (s, 2H), 3.11 (s, 6H), 2.50–2.46 (m, 8H), 2.24 (s, 3H); MS (ESI) *m/z*: 569 $[C_{27}H_{27}F_3N_8OS]^{+\cdot}$

Example 282: N-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 4-(4-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate:

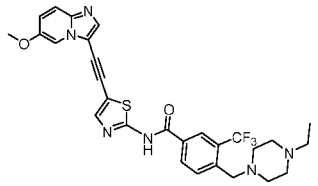
[000687] To a solution of 4-((4-(tert-butoxycarbonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)benzoic acid (320 mg, 1.06 mmol) in anhydrous pyridine (1.5 mL) at −10 °C

were successively added 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (200 mg, 0.704 mmol), Phosphorus oxychloride (0.2 mL) slowly under vigorous stirring. The reaction mixture was stirred at −10 °C for 30 min and stirred overnight while warming to room temperature. The reaction was quenched with crushed ice water (50 mL) and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (neutral alumina, eluent petroleum ether/ethyl acetate 80:20) to afford *tert*-butyl 4-(4-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as a semi solid (70 mgMS (ESI) *m/z*: 655 $[C_{31}H_{33}F_3N_8O_3S+H]^+$.

Step 2: Preparation of *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

[000688] A solution of *tert*-butyl 4-(4-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (70 mg, 0.107 mmol) and TFA (1.5 mL) in dichloromethane (10 mL) was stirred at room temperature for 2 h and was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford *N*-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (50 mg, AUC HPLC 97.8%) as a yellow solid. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 8.46 (s, 1H), 8.34 (d, J = 7.2 Hz, 1H), 7.87–7.83 (m, 2H), 7.76 (s, 1H), 7.71 (s, 1H), 7.12 (d, J = 10.0 Hz, 1H), 3.69 (s, 2H), 3.11 (s, 6H), 2.98–2.97 (m, 4H), 2.49 b(s, 4H); MS (ESI) *m/z*: 555 $[C_{26}H_{25}F_3N_8OS+H]^+$.

Example 283: 4-((4-ethylpiperazin-1-yl)methyl)-N-(5-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide

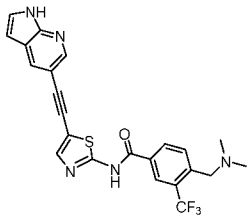


Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide

[000689] To a solution of 3-iodo-6-methoxyimidazo [1,2-a]pyridine (283 mg, 1.03 mmol) and TEA (0.36 mL) in acetonitrile (20 mL) under argon were successively added 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-ethynylthiazol-2-yl)-3-(trifluoromethyl)benzamide (290

mg, 0.68 mmol), $Pd(PPh_3)_4$ (39.7 mg, 0.034 mmol), PPh_3 (9.01 mg, 0.034 mmol) and CuI (19.6 mg, 0.103 mmol). The reaction mixture was heated at 80 °C for 6 h, was diluted with EtOAc and filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel eluent CH_2Cl_2/MeOH 10:90) and preparative HPLC to afford 4-((4-ethylpiperazin-1-yl)methyl)-*N*-(5-((6-methoxyimidazo[1,2-a]pyridin-3-yl)ethynyl)thiazol-2-yl)-3-(trifluoromethyl)benzamide (140 mg, AUC HPLC 99.4%) as a yellow solid. mp:178-181°C; ^{1}H NMR (400 MHz, (DMSO-D_6) δ (ppm): 12.55 (s, 1H), 8.47 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 2.4 Hz, 1H), 8.00 (s, 1H), 7.96-7.94 (m, 2H), 7.64 (d, *J* = 9.6 Hz, 1H), 7.21-7.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.90 (s, 3H), 3.71 (s, 2H), 2.60–2.54 (m, 10H), 1.03 (t, *J* = 7.2 Hz, 3H). MS (ESI) m/z:568.8 [$C_{28}H_{27}F_3N_6O_2S$+H].

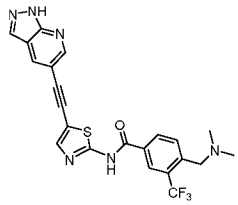
Example 284: N-(5-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-((1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (B1654 -37):

[000690] To a solution of *N*-(5-bromothiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (500 mg, 1.228 mmol) in DMF (5 mL) under argon, were successively added DIPEA (5.0 mL), $Pd(PPh_3)_4$ (70.0 mg, 0.061 mmol), PPh_3 (16.0 mg, 0.061 mmol), CuI (46.0 mg, 0.245 mmol), 5-ethynyl-1*H*-pyrrolo[2,3-b]pyridine (269 mg, 1.842 mmol) and the resulting mixture was heated at 80 °C for 2 h. The reaction mixture was diluted with water, the precipitate was isolated by filtration and purified by column chromatography (silica gel, eluent**:** dichloromethane/methanol 95:5) to afford *N*-(5-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (120 mg, 13.1%, AUC HPLC 98.09%) as a yellow solid. m.p: 258–261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.17 (s, 1H), 11.92 (s, 1H), 8.46 (s, 1H), 8.39–8.36 (m, 2H), 8.18 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.89 (s, 1H), 7.56 (s, 1H),6.50 (s, 1H), 3.62 (s, 2H), 2.22 (s, 6H). MS (ESI) *m/z*: 470.9 $[C_{23}H_{18}F_3N_5OS+H]^+$.

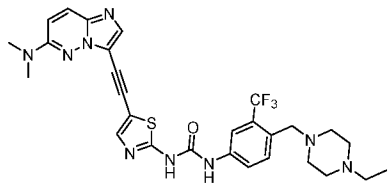
Example 285: N-(5-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide



Preparation of *N*-(5-((1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-(dimethylamino)methyl)-3-(trifluoromethyl)benzamide

[000691] To a solution of *N*-(5-bromothiazol-2-yl)-4-((dimethylamino) methyl)-3-(trifluoromethyl)benzamide (400 mg, 0.982 mmol) in DMF (2.5 mL) under argon, were successively added $Pd(PPh_3)_4$ (57 mg, 0.04 mmol), PPh_3 (13 mg, 0.04 mmol), CuI (38 mg, 0.196 mmol), 5-ethynyl-1*H*-pyrazolo [3,4-b] pyridine (217 mg, 1.47 mmol) and DIPEA (2.5 mL). The reaction mixture was heated at 80 °C for 10 h and was diluted with water. The precipitate was isolated by filtration and purified by preparative HPLC to afford *N*-(5-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-4-((dimethylamino)methyl)-3-(trifluoromethyl)benzamide (60 mg, 13.1%, AUC HPLC 97.1%) as a yellow solid; m.p: 259–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.91 (s, 1H), 13.23 (s, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.49 (d, J = 1.6 Hz, 1H), 8.46 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.20 (s, 1H), 7.96 (s, 1H), 7.94 (d, J = 4 Hz, 1H), 3.62 (s, 2H), 2.22 (s, 6H). MS (ESI) *m/z*:470.9 $[C_{22}H_{17}F_3N_6OS+ H]^+$.

Example 286: 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

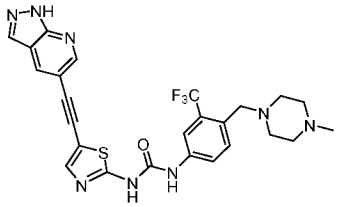


Preparation of 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000692] The title compound was synthesized following a method similar to general procedure B and starting from 1-(5-bromothiazol-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 3-ethynyl-*N*,*N*-dimethylimidazo[1,2-b]pyridazin-6-amine. The reaction crude product was purified by column chromatography (neutral alumina, eluent:

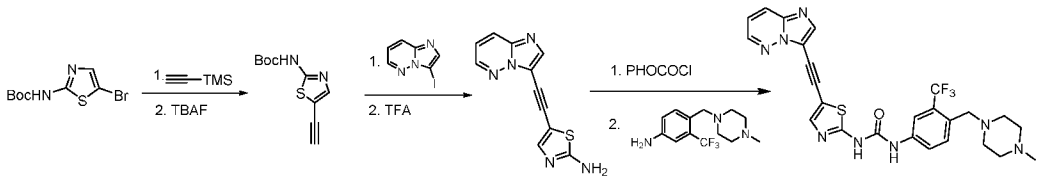
$CH_2Cl_2/CH_3OH/NH_3$ 87:10:3) and by preparative HPLC to afford 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-trifluoromethyl)phenyl)urea as a yellow solid (3 mg, AUC HPLC 95.85%). ^{1}H NMR(400 MHz, CD_3OD) δ (ppm): 7.89 (d, *J* = 2.0 Hz, 1H), 7.73–7.66 (m, 4H), 7.60 (s, 1H), 7.12 (d, *J* = 10.0 Hz, 1H), 3.64 (s, 2H), 3.17 (s, 6H), 2.54–2.48 (m, 10H), 1.11 (t, *J* = 7.2 Hz, 3H), MS (ESI) *m/z*: 598.30 $[C_{28}H_{30}F_3N_9OS+H]^+$.

Example 287: 1-(5-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



[000693] The title compound was synthesized following a method similar to general procedure B and starting from 1-(5-bromothiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea and 5-ethynyl-1H-pyrazolo [3,4-b]pyridine. The reaction crude product was purified by flash column chromatography and by preparative HPLC to afford 1-(5-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (30 mg, AUC HPLC 97%) as a yellow solid. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 13.95 (s, 1H), 11.10 (s, 1H), 9.35 (s, 1H), 8.66 (d, *J* = 1.7 Hz, 1H), 8.46 (d, *J* = 1.8 Hz, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 7.76 (s, 1H), 7.67 (s, 2H), 3.56 (s, 2H), 2.50–2.42 (m, 8H), 2.23 (s, 3H); MS (ESI) *m/z*: 541.15 $[C_{25}H_{23}F_3N_8OS+H]^+$.

Example 288: 1-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: preparation of *tert*-butyl 5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamate

[000694] To a solution of *tert*-butyl 5-bromothiazol-2-ylcarbamate (5 g, 17.92 mmol) in THF (30 mL) under argon were successively added $PdCl_2(PPh_3)_2$ (629 mg, 0.896 mmol),

PPh_3 (234 mg, 0.896 mmol), CuI (510 mg, 2.68 mmol), triethylamine (7.5 mL, 53.76 mmol) and ethynyl trimethylsilane (5.2 g, 53.76 mmol). The reaction mixture was heated at 80 °C for 3 h and was filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel eluent hexane/ethyl acetate 10:90) to afford *tert*-butyl 5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamate (5 g, 94.3 %, LC-MS 88%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.78 (s, 1H), 7.62 (s, 1H), 1.48 (s, 9H), 0.21 (s, 9H). MS (ESI) *m/z*: 240.9 $[C_{13}H_{20}N_2O_2SSi\text{-}55]^+$.

Step 2: preparation of *tert*-butyl 5-ethynylthiazol-2-ylcarbamate

[000695] To a solution of *tert*-butyl 5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamate (4 g, 13.51 mmol) in THF (20 mL) at 0 °C was added TBAF (20 mL, 1.0 M solution in THF, 20.27 mmol). The reaction mixture was stirred at room temperature for 2 h and was concentrated under reduced pressure. The residue was diluted with ice water and extracted with ethyl acetate. The organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluent hexane/ethyl acetate 10:90) to afford of *tert*-butyl 5-ethynylthiazol-2-ylcarbamate (2 g, 66%, AUC HPLC 90%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.78 (s, 1H), 7.63 (s, 1H), 4.54 (s, 1H), 1.48 (s, 9H). MS (ESI) *m/z*: 225.07 $[C_{10}H_{12}N_2O_2S + H]^+$.

Step 3: Preparation of phenyl tert-butyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate

[000696] To a solution of 3-iodoimidazo[1,2-b]pyridazine (2.38 g, 9.82 mmol) and *N,N*-diisopropylethylamine (4.8 mL, 26.78 mmol) in acetonitrile (20 mL) under argon were successively added Pd $(PPh_3)_4$ (515 mg, 0.446 mmol), PPh_3 (116 mg, 0.446 mmol), CuI (254 mg, 1.33 mmol) and *tert*-butyl 5-ethynylthiazol-2-ylcarbamate (2 g, 8.92 mmol). The reaction mixture was heated at 80 °C for 15 h. The reaction mixture was cooled to room temperature and the solid that has formed was isolated by filtration and purified by column chromatography (silica gel dichloromethane/MeOH 98:2) to afford *tert*-butyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate (2 g, 66.6%, LC-MS 90%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.89 (s, 1H), 8.66 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 8.19 (s, 1H), 7.79 (s, 1H), 7.45–7.36 (m, 1H), 1.50 (s, 9H). MS(ESI) *m/z*: 342.08 $[C_{16}H_{15}N_5O_2S + H]^+$.

Step 4: preparation of 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-amine

[000697] To a solution of *tert*-butyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate (2 g, 5.86 mmol) in dichloromethane (30 mL) was added TFA (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and was concentrated under reduced pressure. The residue was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel dichloromethane/methanol 98:2) to afford 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-amine (400 mg, 28.5% LC-MS 98.2%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.66 (dd, J = 4.4, 1.2 Hz, 1H), 8.22 (dd, J = 9.2, 1.6 Hz, 1H), 8.12 (s, 1H), 7.58 (bs, 2H), 7.39 (s, 1H), 7.36–7.33 (m, 1H). MS(ESI) *m/z*: 242.06 $[C_{11}H_7N_5S+ H]^+$.

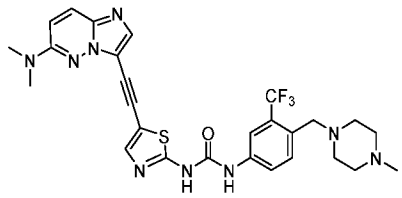
Step 5: Preparation of phenyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate

[000698] To a solution of 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-amine (400 mg, 1.65 mmol) and pyridine (262 mg, 3.31 mmol) in dichloromethane (10 mL) was added phenyl chloroformate (258 mg, 1.65 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and was concentrated under reduced pressure. The residue was diluted with water and n-hexane and the solid that has formed was isolated by filtration to afford phenyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate (480 mg, 12.6%, LC-MS 44%) as a solid. MS(ESI) *m/z*: 361.95 $[C_{18}H_{11}N_5O_2S+ H]^+$.

Step 6: Preparation of 1-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000699] A solution of phenyl 5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-ylcarbamate (400 mg, 1.10 mmol), 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (301 mg, 1.10 mmol) and triethylamine (0.3 mL, 2020 mmol) in 1,4 dioxane (10 mL) was heated at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed in turn with water and brine. The organic layer was dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 1-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (20 mg, AUC HPLC 94.11%) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.61 (d, J = 6.0 Hz, 1H), 8.09 (d, J = 13.6 Hz, 1H), 8.03 (s, 1H), 7.90 (s, 1H), 7.74–7.67 (m, 3H), 7.36–7.32 (m, 1H), 3.63 (s, 2H), 2.53–2.50 (m, 8H), 2.28 (s, 3H). MS (ESI) *m/z*:540.8 $[C_{25}H_{23}F_3N_8OS+ H]^+$.

Example 289: 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



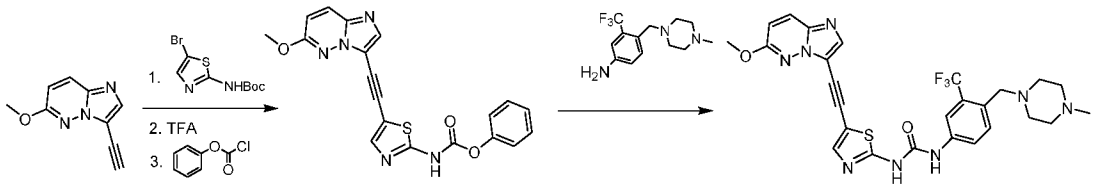
Step1: Preparation of phenyl 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate

[000700] To a solution of 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (800 mg, 2.81 mmol) in dichloromethane (30 ml) were successively added phenyl chloroformate (439 mg, 2.81mmol) and pyridine (216 mg, 2.81 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 h and was concentrated under reduced pressure. To the residue water was added and the precipitate that has formed was isolated by filtration and dried to afford phenyl 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate as an off white solid (1.1 g).

Step 2: Preparation of 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-trifluoromethyl)phenyl)urea

[000701] To a solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (270 mg, 0.989 mol) in 1,4-dioxane were successively added triethylamine (0.27ml, 1.97mol) and phenyl 5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (400 mg, 0.989 mol) and mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated and purified by preparative HPLC to afford 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3(trifluoromethyl)phenyl)urea (50 mg, AUC HPLC 98.7%) as a yellow solid. mp: 243–247 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.38 (s, 1H), 8.15 (s, 1H), 7.94 (s, 1H), 7.89 (d, J = 10.0 Hz, 2H), 7.82 (s, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.15 (d, J = 10.4 Hz, 1H), 3.55 (s, 2H), 3.10 (s, 6H), 2.49–2.32 (m, 8H), 2.19 (s, 3H); MS (ESI) m/z: 583.92 [$C_{27}H_{28}F_3N_9OS$+H].

Example 290: 1-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



Step 1: Preparation of *tert*-butyl 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate

[000702] To a solution of *N*-(5-bromothiazol-2-*tert*-butyl 5-bromothiazol-2-ylcarbamate (1.6 g, 5.78 mmol) in THF (30 mL) under argon were successively added $PdCl_2$(dppf)•DCM (235 mg, 0.289 mmol), dppf (160 mg, 0.289 mmol), CuI (164 mg, 0.867 mmol), triethyl amine (4 mL, 28.90 mmol) and 3-ethynyl-6-methoxyimidazo[1,2-b]pyridazine (1.0 g, 5.78 mmol). The reaction mixture was heated at 80 °C for 5 h, was filtered through a short pad of celite and the filtrate was concentrated under reduced pressure. The residue was diluted with methanol and the solid was isolated by filtration and dried to afford *tert*-butyl 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (800 mg, 38.09%, LC-MS 92%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.88 (s, 1H), 8.10 (d, J = 9.6 Hz, 1H), 8.00 (s, 1H), 7.78 (s, 1H), 7.02 (d, J = 9.8 Hz, 1H), 4.00 (s, 3H), 1.50 (s, 9H). MS (ESI) *m/z*: 372.16 $[C_{17}H_{17}N_5O_3S + H]^+$.

Step 2: preparation of 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine

[000703] An ice-cooled solution of *tert*-butyl 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (800 mg, 2.16 mmol) in dichloromethane (10 mL) and TFA (10 mL) was stirred at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure at 40 °C, the residue was diluted with EtOAc (100 mL) and basified with a saturated aqueous solution of $NaHCO_3$. The organic layer was washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford of 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (300 mg, 43%) as yellow solid.

Step 3: preparation of phenyl 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate

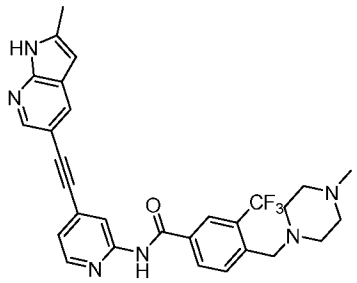
[000704] To an ice cooled solution of 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-amine (300 mg, 1.11 mmol) in dichloromethane (10 mL) was successfully added phenyl chloroformate (173 mg, 1.11 mmol) and pyridine (85 mg, 1.11 mmol). The reaction mixture was stirred at room temperature for 3 h and was concentrated under reduced pressure. The residue was diluted with water, the precipitate was isolated by

filtration, The cake was washed with n-hexane and dried to afford phenyl 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (300 mg, 41.6%) as a green solid. MS (ESI) *m/z*: 392.04 $[C_{19}H_{13}N_5O_3S + H]^+$.

Step 4: Preparation of 1-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

[000705] To a solution of phenyl 5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (300 mg, 0.767 mmol), in 1,4 dioxane (5 mL) were successively added 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (210 mg, 0.767 mmol) and tri ethyl amine (215 mg, 1.53 mmol). The reaction mixture was heread at 80 °C for 3h and was concentrated under reduced pressure. The residue was diluted with ethyl acetate and the organic layer was washed in turn with water and brine, dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 1-(5-((6-methoxyimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (20 mg, AUC HPLC 98.0%) as a yellow solid.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (s, 1H), 8.10 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 9.6 Hz, 1H), 7.85 (s,1H), 7.71 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 9.6 Hz, 1H), 4.01 (s, 3H), 3.47 (s, 2H), 2.35–2.32 (m, 8H), 2.14 (s, 3H); MS (ESI) *m/z*: 571 $[C_{26}H_{25}F_3N_8O_2S + H]^+$.

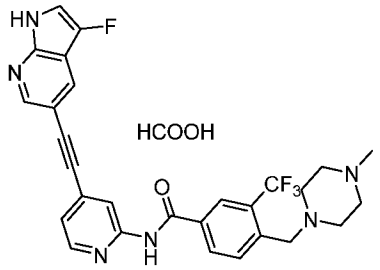
Example 291: Preparation of N-(4-((2-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



To a solution of *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (150 mg, 0.37 mmol) in anhydrous DMF (2 mL) was added 5-bromo-2-methyl-1*H*-pyrrolo[2,3-b]pyridine (118.22 mg, 0.56 mmol), PPh_3 (34 mg, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (33.76 mg, 0.048 mmol), CuI (7.05 mg, 0.037 mmol) and 1.5 mL of DIPEA. The reaction mixture was heated at 85 °C under nitrogen for 3 h., then was diluted with DCM (50 mL), filtered through celite and concentrated under reduced pressure. The

residue was purified by flash column chromatography (silica gel, 100% DCM to DCM/Methanol 90:10) to give *N*-(4-((2-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (82.14 mg, 0.15 mmol, 41.7 %, AUC HPLC 99.44 %); as white solid mp: 243.5-244.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.73 (s, 1H), 8.74 (s, 1H), 8.56 (s, 1H), 8.42 (s, 1H), 8.31 (d, J = 4.8 Hz, 1H), 8.23 (s, 1H), 8.10 (dd, J = 8.4, 1.8 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 4.8, 1.2 Hz, 1H), 6.24 (s, 1H), 3.77 (s, 2H), 2.80-2.58 (m, 7H), 2.55 (s, 4H), 2.38 (s, 3H); MS (ESI) *m/z* 533.20 $[C_{29}H_{27}F_3N_6O + H]^+$.

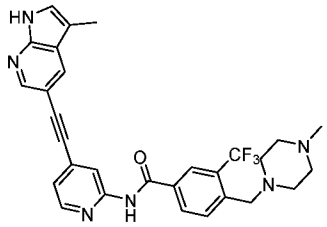
Example 292: Preparation of N-(4-((3-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate salt



To a solution of *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (150 mg, 0.37 mmol) in DMF (2 mL) under inert atmosphere was added 5-bromo-3-fluoro-1*H*-pyrrolo[2,3-b]pyridine (120 mg, 0.56 mmol), triphenylphophine (34 mg, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (34 mg, 0.048 mmol), copper iodide (7 mg, 0.037 mmol) and DIPEA (1 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((3-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate (51.5 mg, 22%, AUC HPLC 98%) as brown solid. m.p: 184.7-185.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.89 (s, 1H), 11.27 (s, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.48-8.45 (m, 1H), 8.37-8.34 (m, 3H), 8.31-8.28 (m, 1H), 8.16 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 2.3 Hz, 1H), 7.35 (dd, J = 5.0, 1.4 Hz, 1H), 3.69 (s, 2H), 2.44-2.31 (m, 8H), 2.20 (s, 3H);); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 165.36, 163.68, 152.85, 149.04, 147.17,

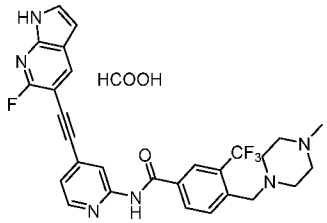
143.17 (d, *J* = 4.5 Hz), 142.20 (d, *J* = 243.3 Hz), 142.09, 133.34, 132.57, 132.45, 131.10, 128.94 (d, *J* = 3.2 Hz), 127.66 (q, *J* = 30.1 Hz), 126.13 (q, *J* = 5.4 Hz), 124.60 (q, *J* = 274.7 Hz), 121.92, 116.39, 110.87, 110.23, 108.49, 92.65, 88.13, 57.93, 55.04, 53.03, 45.96; MS (ESI) *m/z* 537 $[C_{28}H_{24}F_4N_6O + H]^+$.

Example 293: Preparation of N-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



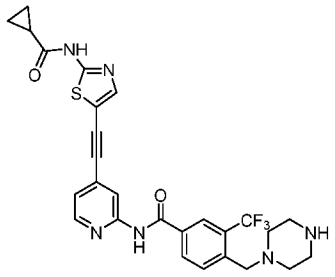
To a solution of *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (150 mg, 0.37 mmol) in DMF (2 mL) under inert atmosphere was added 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (118 mg, 0.56 mmol), triphenylphophine (34 mg, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (34 mg, 0.048 mmol), copper iodide (7 mg, 0.037 mmol) and DIPEA (1 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford *N*-(4-((3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (50.3 mg, 26%, AUC HPLC 96%) as brown solid. m.p: 249.7-251.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.83 (s, 1H), 11.25 (s, 1H), 8.46-8.43 (m, 1H), 8.36-8.34 (m, 2H), 8.32 (s, 1H), 8.29 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.10 (d, *J* = 1.9 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.32 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.23-6.21 (m, 1H), 3.68 (s, 2H), 2.45-2.25 (m, 11H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 165.34, 152.84, 148.98, 148.72, 144.74, 142.13, 139.22, 133.34, 132.86, 132.44, 131.07, 130.34, 127.65 (q, *J* = 30.0 Hz), 126.12 (q, *J* = 6.0 Hz), 124.61 (q, *J* = 274.4 Hz), 121.83, 120.88, 116.31, 109.57, 98.57, 93.72, 87.9, 57.99, 55.16, 53.22, 46.17, 14.05; MS (ESI) *m/z* 533 $[C_{29}H_{27}F_3N_6O + H]^+$.

Example 294: Preparation of N-(4-((6-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate



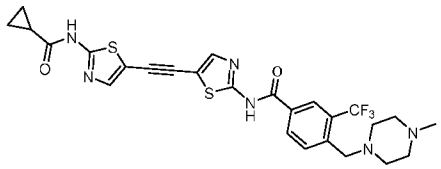
To a solution of *N*-(4-ethynylpyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (150 mg, 0.37 mmol) in DMF (2 mL) under inert atmosphere was added 5-bromo-6-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (120 mg, 0.56 mmol), triphenylphophine (34 mg, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (34 mg, 0.048 mmol), copper iodide (7 mg, 0.037 mmol) and DIPEA (1 mL). The resulting mixture was heated to 90 °C for 18 h, then was cooled, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed in turn with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) and by preparative HPLC (C18, eluent CH_3CN/H_2O/HCOOH 0.01%) to afford *N*-(4-((6-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide formate (42 mg, 21%, AUC HPLC 95%) as brown solid. m.p: 223.1-223.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.14 (s, 1H), 11.29 (s, 1H), 8.48-8.44 (m, 2H), 8.37-8.33 (m, 2H), 8.30 (dd, J = 8.1, 1.4 Hz, 1H), 8.17 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.55 (dd, J = 3.3, 2.5 Hz, 1H), 7.33 (dd, J = 5.0, 1.4 Hz, 1H), 6.57 (dd, J = 3.4, 1.8 Hz, 1H), 3.68 (s, 2H), 2.50-2.27 (m, 8H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 165.39, 163.77, 158.75 (d, J = 235.8 Hz), 152.88, 149.12, 144.97 (d, J = 18.4 Hz), 142.12, 136.85, 133.32, 132.44, 132.34, 131.09, 127.86, 127.67 (q, J = 30.8 Hz), 126.14 (q, J = 5.9 Hz), 124.61 (q, J = 274.3 Hz), 121.73, 118.30, 116.30, 101.51, 96.11 (d, J = 33.1 Hz), 90.63, 88.06 (d, J = 4.7 Hz), 57.95, 55.08, 53.10, 46.04; MS (ESI) *m/z* 537 $[C_{28}H_{24}F_4N_6O+H]^+$.

Example 295: Preparation of N-(4-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



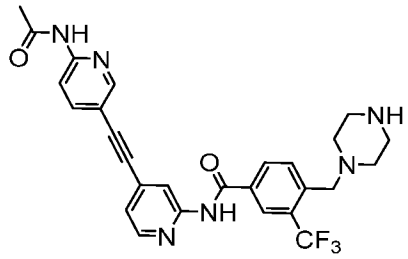
The title compound was prepared in 12.5% yield (100 mg, AUC HPLC 98.84%) as an off-white solid in a fashion similar to Example **227** synthesis starting from **Intermediate 12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.25 (bs, 1H), 8.44 (d, J = 4.8 Hz, 1H), 8.33–8.27 (m, 3H), 7.94–7.92 (m, 2H), 7.29 (dd, J = 4.8, 1.2 Hz, 1H), 3.54 (s, 2H), 2.74–2.71 (m, 4H), 2.35–2.33 (m, 4H), 1.99–1.93 (m, 1H), 0.95–0.93 (m, 4H). MS (ESI) m/z: 555.5 $[C_{27}H_{25}F_3N_6O_2S+H]^+$.

Example 296, Preparation of N-(5-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 22.14% yield (310 mg, AUC HPLC 96%) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** starting from **Intermediate 31.** ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.72 (s, 1H), 8.42 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.90–7.88 (m, 2H), 7.78 (s, 1H), 3.69 (s, 2H), 2.50–2.45 (m, 8H), 2.24 (s, 3H), 1.95–1.92 (m, 1H), 0.92–0.90 (m, 4H). MS (ESI) *m/z* 574.99 $[C_{26}H_{25}F_3N_6O_2S_2+H]^+$.

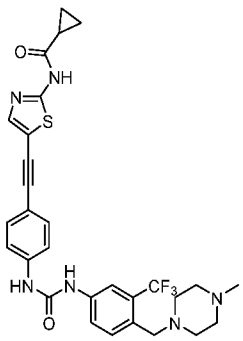
Example 297: Preparation of N-(4-((6-acetamidopyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: Preparation of *tert*-butyl 4-(4-(4-((6-acetamidopyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The title compound was prepared (600 mg, LC-MS 55%) from **Intermediate 12** using Sonogashira coupling conditions similar to **general procedure B**.

Step 2: Preparation of *tert*-butyl 4-(4-(4-((6-acetamidopyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. The title compound was prepared (110 mg, 19.09%m, AUC HPLC 97%) as a pale yellow solid from *tert*-butyl 4-(4-(4-((6-acetamidopyridin-3-yl)ethynyl)pyridin-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate using Boc removal conditions similar to **general procedure D**. mp: 225–230 °C. ^{1}H NMR (400 MHz, DMSO–d_6) δ (ppm): 11.27 (s, 1H), 10.78 (s, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 4.8 Hz, 1H), 8.34–8.27 (m, 3H), 8.16 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 5.2 Hz, 1H), 3.64 (s, 2H), 2.74–2.67 (m, 4H), 2.35–2.33 (s, 4H), 2.12 (s, 3H). MS (ESI) *m/z*: 523.08 $[C_{27}H_{25}F_3N_6O_2+H]^+$

Example 298: Preparation of N-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide



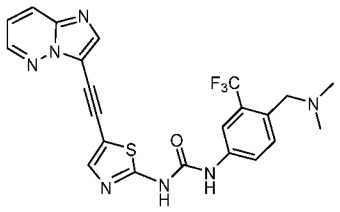
Step 1: Synthesis of *N*-(5-((4-aminophenyl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide. To a solution of *N*-(5-bromothiazol-2-yl)cyclopropanecarboxamide (4.6 g, 18.8 mmol) and DIPEA (9.1 mL, 51.26 mmol) in acetonitrile (50 mL) under argon were successively added

$Pd(PPh_3)_4$ (987 mg, 0.854 mmol), PPh_3 (223 mg, 0.854 mmol), CuI (487 mg, 2.56 mmol) and 4-ethynylaniline (2 g, 17.09 mmol), the reaction mixture was heated at 80 °C for 5 h and was concentrate under reduced pressure. The residue was diluted with water and extracted into ethyl acetate. The organic layer was washed in turn with water and brine, dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/CH_3OH 97:3) to afford *N*-(5-((4-aminophenyl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide (2 g, 41%, LC-MS 85%) as a brown solid. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 12.60 (bs, 1H), 7.62 (s, 1H), 7.18 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 5.60 (bs, 2H),1.98–1.92 (m, 1H), 0.96–0.88 (m, 4H). MS (ESI) m/z: 284.11 $[C_{15}H_{13}N_3OS+H]^+$.

Step 2: phenyl 4-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)phenylcarbamate. A solution of phenylchoroformate (275 mg, 1.76 mmol) in dichloromethane (5 mL) was added dropwise to a cooled solution of *N*-(5-((4-aminophenyl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide (500 mg, 1.76 mmol) and pyridine (139 mg, 1.76 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 3 h and was concentrated under reduced pressure. The residue was diluted with water and petroleum ether. The precipitate was isolated by filtration and dried to afford phenyl 4-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)phenylcarbamate (660 mg, LC-MS 85%) as an off-white solid. MS (ESI) m/z: 404.04 $[C_{22}H_{17}N_3O_3S+H]^+$.

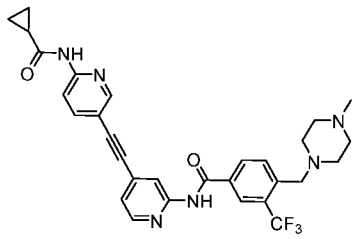
Step 3: Synthesis of *N*-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide. A mixture of phenyl 4-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)phenylcarbamate (600 mg, 1.488 mmol), 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (407 mg, 1.48 mmol) and triethyl amine (0.41 mL, 2.977 mmol) in 1,4-dioxane (15 mL) was heated at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure an the residue was purified by preparative HPLC to afford *N*-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)thiazol-2-yl)cyclopropanecarboxamide (82 mg, 9.4%, AUC HPLC 99%) as a pale yellow solid. mp: 239–248 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.68 (bs, 1H), 9.06 (s, 1H), 9.00 (s, 1H), 7.96 (s, 1H), 7.74 (s, 1H), 7.64–7.44 (m, 6H), 3.52 (s, 2H), 2.38–2.32 (m, 8H), 2.15 (s, 3H), 1.97–1.93 (m, 1H), 0.96–0.93 (m, 4H). MS (ESI) m/z: 583.01 $[C_{29}H_{29}F_3N_6O_2S+H]^+$.

Example 299: Preparation of 1-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)urea.



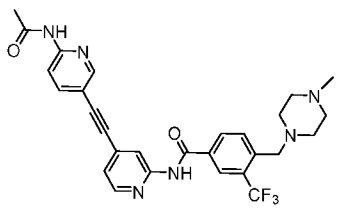
The title compound was prepared (10 mg, AUC HPLC 96.79%) as a pale orange solid in a fashion similar to Example 298 synthesis starting from **Intermediate 39**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.20 (bs, 1H), 9.35 (bs, 1H), 8.69–8.68 (m, 1H), 8.25 (d, J = 9.2 Hz, 1H), 8.18 (s, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 7.70–7.64 (m, 2H), 7.39–7.36 (m, 1H), 3.47 (s, 2H), 2.17 (s, 6H). MS (ESI) *m/z* 486.18 $[C_{22}H_{18}F_3N_7OS+H]^+$.

Example 300: Preparation of N-(4-((6-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



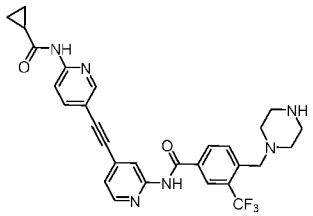
The title compound was prepared in 22.6% yield (140 mg, AUC HPLC 99%) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 14**. mp:119–123 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.27 (s, 1H), 11.08 (s, 1H), 8.61 (d, J = 1.6 Hz, 1H), 8.46 (d, J = 4.8 Hz, 1H), 8.34– 8.28 (m, 3H), 8.17 (d, J = 8.8 Hz, 1H), 8.04–8.01 (m, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.33–7.31 (m, 1H), 3.68 (s, 2H), 2.45–2.32 (m, 8H), 2.19 (s, 3H), 2.06–2.00 (m, 1H), 0.84 (d, J = 5.2 Hz, 4 H). MS (ESI) m/z: 563.11 $[C_{30}H_{29}F_3N_6O_2+H]^+$.

Example 301: Preparation of N-(4-((6-acetamidopyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



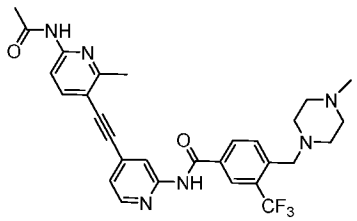
The title compound was prepared in 40.5% yield (190 mg, AUC HPLC 97%) as an orange solid using a Sonogashira coupling conditions similar to **general procedure B** starting from **Intermediate 14**. mp: 131–135 °C. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 11.27 (s, 1H), 10.78 (s, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 4.8 Hz, 1H), 8.34–8.28 (m, 3H), 8.16 (d, J = 8.8 Hz, 1H), 8.05–8.02 (dd, J = 2.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.33–7.31 (m, 1H), 3.68 (s, 2H), 2.50–2.32 (m, 8H), 2.18 (s, 3H), 2.12 (s, 3H). MS (ESI) m/z: 537.5 $[C_{28}H_{27}F_3N_6O_2+H]^+$.

Example 302: Preparation of N-(4-((6-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



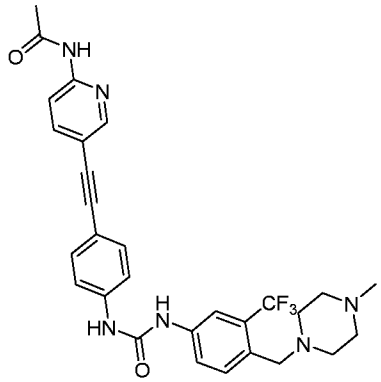
The title compound was prepared in 34.3% yield (110 mg, AUC HPLC 96%) as a pale yellow solid in a fashion similar to Example 297 symthesis starting from **Intermediate 12**. mp: 211–216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.27 (s, 1H), 11.18 (s, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.34–8.27 (m, 3H), 8.16 (d, J = 8.8 Hz, 1H), 8.04–8.01 (m, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.33–7.31 (m, 1H), 3.64 (s, 2H), 2.72–2.67 (m, 4H), 2.35–-2.32 (m, 4H), 2.06–2.00 (m, 1H), 0.85–0.86 (m, 4H). MS (ESI) *m/z*: 549.07 $[C_{29}H_{27}F_3N_6O_2+H]^+$.

Example 303: Preparation of N-(4-((6-acetamido-2-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



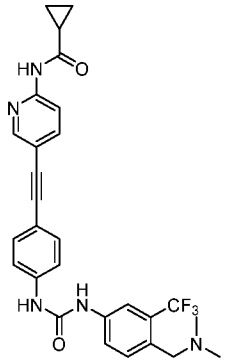
The title compound was prepared in 6.6% yield (40 mg, AUC HPLC 99.18 %) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** starting from **Intermediate 14**. mp: 137–141 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.27 (s, 1H), 10.72 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.34–8.28 (m, 3H), 8.01–7.90 (m, 3H), 7.34 (d, J = 4.8 Hz, 1H), 3.68 (s, 2H), 2.62 (s, 3H), 2.45–2.32 (m, 8H), 2.17 (s, 3H), 2.10 (s, 3H). MS (ESI) *m/z*: 551.12 $[C_{29}H_{29}F_3N_6O_2+H]^+$.

Example 304: Preparation of N-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)acetamide



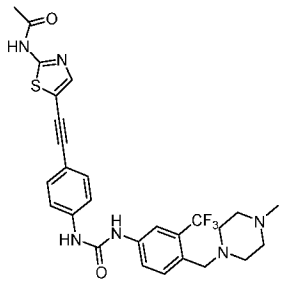
The title compound was prepared in 14.2% yield (110 mg, AUC HPLC 93.05%) as an off-white in a fashion similar to Example 298 synthesis. mp: 240–245 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.13 (bs, 2H), 8.47 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 8.4, 2.0, 2H), 7.63–7.53 (m, 4H), 7.48–7.46 (m, 2H), 3.52 (s, 2H), 2.40–2.32 (m, 8H), 2.15 (s, 3H), 2.11 (s, 3H). MS (ESI) *m/z*: 551.09 $[C_{29}H_{29}F_3N_6O_2+H]^+$.

Example 305: Preparation of N-(5-((4-(3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



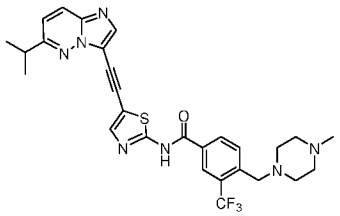
The title compound was prepared in (over 2 steps) 5.6% yield (35 mg, AUC HPLC 97.81%) as an off-White solid in a fashion similar to Example 298 synthesis. mp: 249–255 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.99 (bs, 1H), 9.40 (bs, 2H), 8.48 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.90 (dd, J = 8.8, 2.0 Hz, 1H), 7.61 (s, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 3.45 (s, 2H), 2.16 (s, 6H), 2.03–2.0 (m, 1H), 0.84–0.82 (m, 4H). MS (ESI) m/z: 522.34 $[C_{28}H_{26}F_3N_5O_2+H]^+$.

Example 306: Preparation of N-(5-((4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)ethynyl)thiazol-2-yl)acetamide



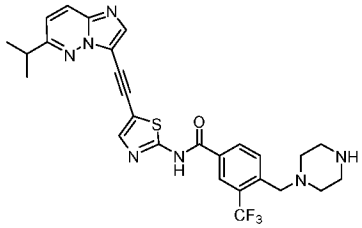
The title compound was prepared in 11.3% yield (100 mg, AUC HPLC 97%) as an off-white solid in a fashion similar to Example 298 synthesis. mp: 246–254 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.40 (bs, 1H), 9.08 (s, 1H), 9.01 (s, 1H), 7.96 (s, 1H), 7.73 (s, 1H), 7.64–7.44 (m, 6H), 3.52 (s, 2H), 2.38–2.32 (m, 8H), 2.16 (s, 3H), 2.15 (s, 3H). MS (ESI) m/z: 557.24 $[C_{27}H_{27}F_3N_6O_2S+H]^+$.

Example 307: Preparation of N-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 23.5% yield (80 mg, AUC HPLC 96%) as a yellow solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 31**. mp: 207–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.47 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.17–8.12 (m, 2H), 7.96–7.92 (m, 2H), 7.40 (d, J = 9.2 Hz, 1H, 3.70 (s, 2H), 3.23–3.16 (m, 2H), 2.50–2.47 (m, 8H), 2.25 (s, 3H), 1.33 (d, J = 6.8 Hz, 6H). MS (ESI) m/z: 568.14 $[C_{28}H_{28}F_3N_7OS+H]^+$.

Example 308: Preparation of N-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



Step 1: *tert*-butyl 4-(2-(trifluoromethyl)-4-(5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamoyl)benzyl)piperazine-1-carboxylate was prepared using a Sonogashira coupling conditions similar to **general procedure A** starting from **Intermediate 29**.

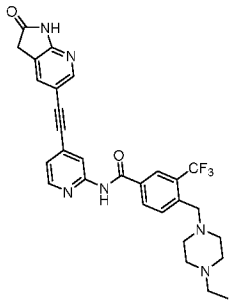
Step-2**:**Synthesis of *tert*-butyl 4-(4-(5-ethynylthiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate. To a sloution of *tert*-butyl 4-(2-(trifluoromethyl)-4-(5-((trimethylsilyl)ethynyl)thiazol-2-ylcarbamoyl)benzyl)piperazine-1-carboxylate (5 g, 9.12 mmol) in THF (30 mL) was added a solution of LiOH•H_2O (383 mg, 9.12 mmol) in water (15 mL). The reaction mixture was stirred at room temperatutre for 3 h then was diluted with water, extracted into EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 4-(4-(5-ethynylthiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (1.5 g) as a brown solid.

Step 3: Preparation of *tert*-butyl 4-(4-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate was prepared in the amount of 400 mg (LC-MS 50%) as a brown solid using a Sonogashira

coupling conditions similar to **general procedure B** and starting from the product of Step 2. MS (ESI) *m/z* 653.2 [$C_{32}H_{34}F_3N_7O_3S$ +1].

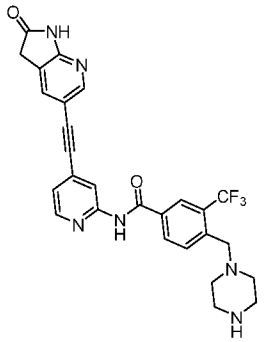
Step-4: Synthesis of *N*-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared in 10.3% yield (35 mg, AUC HPLC 96%) as a yellow solid using **general procedure D** and *tert*-butyl 4-(4-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamoyl)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate as tarting material. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.46 (s, 1H), 8.36–8.34 (m, 1H), 8.14 (d, *J* = 9.2 Hz, 1H), 8.05 (s, 1H), 7.85–7.77 (m, 2H), 7.36 (d, *J* = 9.2 Hz, 1H), 3.71 (s, 2H), 3.22–3.15 (m, 1H), 3.03-3.01 (m, 4H), 2.54–2.49 (m, 4H), 1.33 (d, *J* = 7.2 Hz, 6H). MS (ESI) m/z: 554.13 $[C_{27}H_{26}F_3N_7OS+H]^+$.

Example 309: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



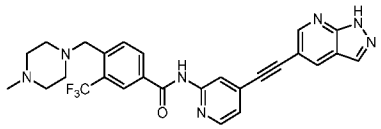
The title compound was prepared in 22.8% yield (60 mg, AUC HPLC 99.3%) as a pale Brown solid using a Sonogashira coupling conditions similar to **general procedure B** and with **Intermediate 17** as starting material. mp: 255–261 °C. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 11.31 (s, 1H), 11.26 (s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.37-8.27 (m, 4H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.31-7.30 (m, 1H), 3.68 (s, 2H), 3.61 (s, 2H), 2.43-2.2.31 (m, 10H), 0.99 (t, *J* = 6.8 Hz, 3H). MS (ESI) m/z: 549.6 $[C_{29}H_{27}F_3N_6O_2+H]^+$.

Example 310: Preparation of N-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



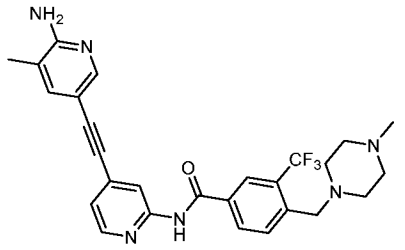
The title compound prepared in 85% yield (85 mg, AUC HPLC 97%) as an off-white solid in a fashion similar to Example 297 synthesis and starting from **intermediate 13**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 11.27 (bs, 2H), 8.45 (d, J = 4.8 Hz, 1H), 8.36 (d, J = 8.0 Hz, 2H), 8.30 (d, J = 11.2 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.30 (d, J = 5.2 Hz, 1H), 3.64 (s, 2H), 3.58 (s, 2H), 2.71 (t, J = 4.8 Hz, 4H), 2.39–2.32 (m, 4H). MS (ESI) m/z: 521.26 $[C_{27}H_{23}F_3N_6O_2+H]^+$.

Example 311: Preparation of N-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



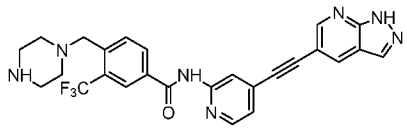
The title compound was prepared in 6.1% yield (40 mg, AUC HPLC 96%) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** and with **Intermediate 15** as starting material. mp: 193–197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):13.90 (s, 1H), 11.80 (s, 1H), 8.72 (s, 1H), 8.56 (s, 1H), 8.46 (d, J = 4.8 Hz, 1H), 8.35 (s, 2H), 8.29 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 4.8 Hz, 1H), 3.68 (s, 2H), 2.50–2.36 (m, 8H), 2.17 (s, 3H). MS (ESI) *m/z* 520.25 $[C_{27}H_{24}F_3N_7O+H]^+$.

Example 312: Preparation of N-(4-((6-amino-5-methylpyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



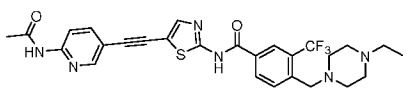
The title compound was prepared in 25% yield (65 mg, AUC HPLC 98%) as an off-white solid in a fashion similar to Example 297 starting from **Intermediate 15**. mp: 218–220 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.207 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H), 8.34 (s, 1H), 8.28 (d, J = 6.0 Hz, 1H), 8.22 (s, 1H), 8.09 (d, J = 1.2 Hz, 1H), 7.89 (d, J = 8.0 1H), 7.48 (s, 1H), 7.18 (d, J = 4.8, 1H), 6.36 (s, 2H), 3.67 (s, 2H), 2.49–2.33 (m, 8H) 2.16 (s, 3H), 2.05 (s, 3H). MS (ESI) *m/z* 509.48 $[C_{27}H_{27}F_3N_6O+H]^+$.

Example 313: Preparation of N-(4-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 30% yield (76 mg, AUC HPLC 96%) as an off-white solid in a fashion similar to Example 297 synthesis starting from **Intermediate 12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.26 (s, 1H), 8.72 (s, 1H), 8.56 (s, 1H), 8.47 (d, J = 4.8 Hz, 1H), 8.35 (s, 2H), 8.29 (d, J = 8.0 Hz, 1H), 8.22 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 4.4 Hz, 1H), 3.64 (s, 2H), 2.72 (t, J = 4.4 Hz, 4H), 2.33–2.27 (m, 4H). MS (ESI) *m/z*: 506.22 $[C_{26}H_{22}F_3N_7O+H]^+$.

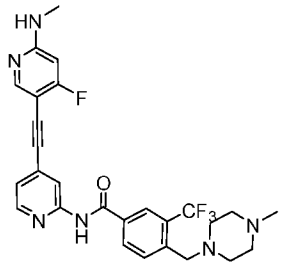
Example 314: Preparation of N-(5-((6-acetamidopyridin-3-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 20% yield (110 mg, AUC HPLC 96%) as a yellow solid using Sonogashira coupling conditions similar to **general procedure B** starting from **Intermediate 33**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 10.71 (s, 1H), 8.50 (d, J =

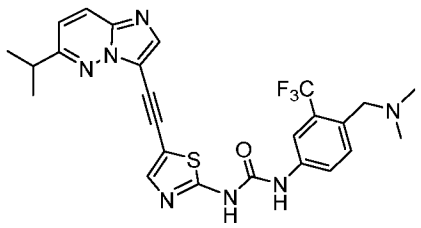
2.4 Hz, 1H), 8.45 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 6.0 Hz, 2H), 7.88 (s, 1H), 3.69 (s, 2H), 2.67–2.32 (m, 10H), 1.01 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J*= 7.2 Hz, 3H). MS (ESI) *m/z* 557.5 $[C_{27}H_{27}F_3N_6O_2S+H]^+$.

Example 315: Preparation of N-(4-((4-fluoro-6-(methylamino)pyridin-3-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 16% yield (14 mg, AUC HPLC 97%) as a pale orange solid in a fashion similar to **Example 297 synthesis** and starting from **Intermediate 15**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.24 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.34–8.25 (m, 4H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 4.4 Hz, 1H), 7.24 (d, *J* = 4.8 Hz, 1H), 6.36 (d, *J* = 11.6 Hz, 1H), 3.67 (s, 2H), 2.82 (d, *J* = 2.8 Hz, 3H), 2.50–2.33 (m, 8H), 2.17 (s, 3H). MS (ESI) m/z: 527.21 $[C_{27}H_{26}F_4N_6O+H]^+$.

Example 316: Preparation of 1-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)urea

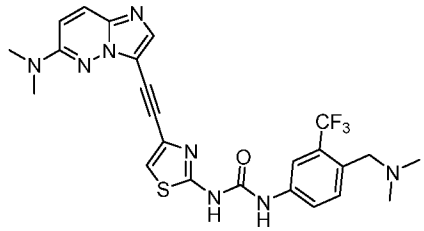


Step 1: Preparation of phenyl 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate. To an ice-cold solution of **Intermediate 37** (400 mg, 1.413 mmol) and pyridine (0.11 mL) in dichloromethane (10 mL) was added drop-wise a solution of phenylchloroformate (0.17 mL) in 5 mL of DCM. The reaction mixture was stirred at room temperature for 4 h and was concentrated under reduce pressure. The residue was diluted with water and the precipitate was isolated by filtration, washed with n-pentane abnd dried to

afford phenyl 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (600 mg, LC-MS 81%) as a yellow solid. MS (ESI) *m/z*: 403.46 [$C_{21}H_{17}N_5O_2S$+H]

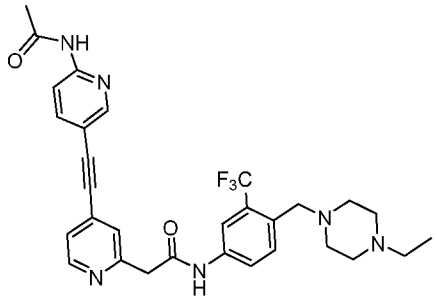
Step 2: Preparation of 1-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)urea. To a solution of phenyl 5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-ylcarbamate (600 mg, 1.48 mmol) in 1, 4- dioxane (15 mL) were added 4-((dimethylamino)methyl)-3-(trifluoromethyl)aniline (356 mg, 1.637 mmol), triethylamine (0.41 mL, 2.97). The resultant mixture was stirred at 80 °C for 5 h. Reaction mixture was diluted with water and extracted with ethyl acetate (50 mL). The organic layer was washed in turn with water and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 1-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)urea (23 mg, AUC HPLC 95%) as a red solid. mp: 127–133 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.19 (s, 1H), 9.31 (s, 1H), 8.17–8.11 (m, 2H), 7.93 (s, 1H), 7.83 (s, 1H), 7.67 (s, 2H), 7.39 (d, J = 9.6 Hz, 1H), 3.48 (s, 2H), 3.22–3.15 (m, 1H), 2.17 (s, 6H), 1.32 (d, J = 6.8 Hz, 6H). MS (ESI) m/z: 528.23 $[C_{25}H_{24}F_3N_7OS+H]^+$.

Example 317: Preparation of 1-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea



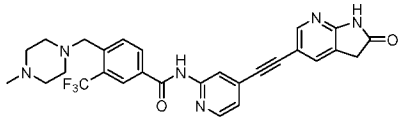
The title compound was prepared in 11.48% yield (75 mg, AUC HPLC 97%) as a yellow solid in a fashion similar to Example 316 synthesis. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 11.18 (bs, 1H), 9.38 (bs, 1H), 7.94 (s, 1H), 7.89 (d, J = 9.6 Hz, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.70 (s, 2H), 7.16 (d, J = 10.4 Hz, 1H), 3.60 (s, 2H), 3.10 (s, 6H), 2.22 (s, 6H). MS (ESI) m/z: 529.5 $[C_{24}H_{23}F_3N_8OS+H]^+$.

Example 318: Preparation of 2-(4-((6-acetamidopyridin-3-yl)ethynyl)pyridin-2-yl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



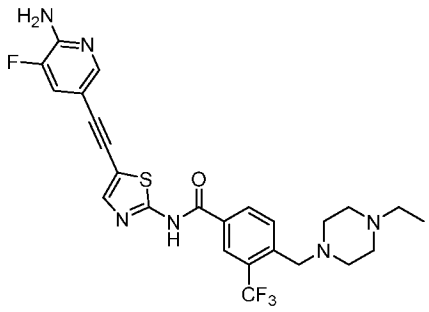
The title compound was prepared in 10% yield (60 mg, AUC HPLC 98%) as a pale yellow solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 26.** mp: 168–163 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 10.55 (s, 1H), 8.57 (d, J = 1.6 Hz, 1H), 8.55 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 8.01 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.43 (dd, J = 1.6, 4.8 Hz, 1H), 3.90 (s, 2H), 3.54 (s, 2H), 2.50–2.32 (m, 10H), 2.12 (s, 3H), 0.99–0.97 (m, 3H). MS (ESI) m/z: 565.25 $[C_{30}H_{31}F_3N_6O_2+H]^+$.

Example 319: Preparation of 4-((4-methylpiperazin-1-yl)methyl)-N-(4-((2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



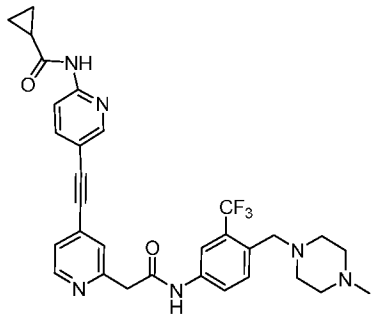
The title compound was prepared in 27% yield (180 mg, AUC HPLC 96%) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 15**. mp: 243–247 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.31 (s, 1H), 11.26 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.37 (d, J = 10.8 Hz, 2H), 8.30 (d, J = 12.0 Hz, 1H), 8.35 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 7.30 (dd, J = 4.8 Hz, J = 5.6 Hz, 1H), 3.69 (s, 2H), 3.61 (s, 2H), 2.50-2.32 (m, 8H) 2.23 (s, 3H). MS (ESI) *m/z* 535.21 $[C_{28}H_{25}F_3N_6O_2+H]^+$.

Example 320: Preparation of N-(5-((6-amino-5-fluoropyridin-3-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



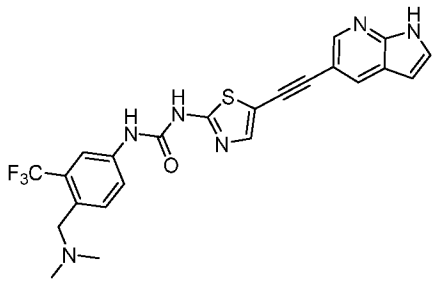
The title compound was prepared in 12% yield (20 mg, AUC HPLC 99%) as an off-white solid in a fashion similar to Example 297 starting from **Intermediate 15**. mp: 243–247 °C. ^{1}H NMR (400 MHz, (DMSO-d_6) δ (ppm): 12.9 (bs, 1H), 8.45 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.55 (d, J = 12.4 Hz, 1H), 6.75 (s, 2H), 3.69 (s, 2H), 1.01 (t, J = 6.8 Hz, 3H), 1.01 (t, 3H), 2.32-2.49 (m, 10H). MS (ESI) m/z: 533.17 $[C_{25}H_{24}F_4N_6O+H]^+$.

Example 321: Preparation of N-(5-((2-(2-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)pyridin-4-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



The title compound was prepared in 11% yield (35 mg, AUC HPLC 95%) as pale orange solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 25**. mp: 186–189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.18 (s, 1H), 10.55 (s, 1H), 8.58–8.55 (m, 2H), 8.15 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 8.8, 2.0 Hz, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.55 (s, 1H), 7.43–7.41 (m, 1H), 3.90 (s, 2H), 3.53 (s, 2H), 2.49–2.20 (m, 8H), 2.14 (s, 3H), 2.09–2.01 (m, 1H), 0.89–0.82 (m, 4H). MS (ESI) m/z: 577.05 $[C_{31}H_{31}F_3N_6O_2+H]^+$.

Example 322: Preparation of 1-(5-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea

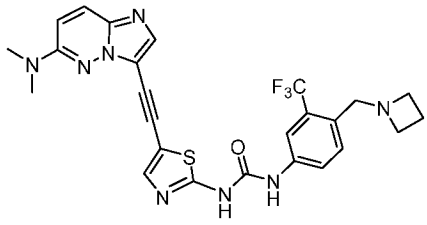


Step 1: Preparation of phenyl 4-((dimethylamino)methyl)-3-(trifluoromethyl)phenylcarbamate. To an ice-cold solution of 4-((dimethylamino)methyl)-3-(trifluoromethyl)aniline (3 g, 13.76 mmol) and pyridine (1g, 13.76 mmol) in dichloromethane (30 mL) was added dropwise a solution of phenylchloroformate (2.18 g, 13.76 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 3 h and a aqueous work-up gave phenyl 4-((dimethylamino)methyl)-3-(trifluoromethyl)phenylcarbamate (3.5 g, LC-MS 82%) as a brown oil.

Step 2: Preparation of 1-(5-bromothiazol-2-yl)-3-(4-(dimethylamino)-3-(trifluoromethyl) phenyl) urea. A mixture of phenyl 4-(dimethylamino)-3-(trifluoromethyl)phenylcarbamate (1 g, 2.958 mmol), 5-bromothiazol-2-amine (529 mg, 2.958 mmol) and Triethylamine (0.8 mL, 5.916 mmol) in 1,4-dioxane was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and submitted to an aqueous work-up to afford the reaction crude product. A purification by column chromatography (silica gel, eluent DCM/MeOH 92:8) gave 1-(5-bromothiazol-2-yl)-3-(4-(dimethylamino)-3-(trifluoromethyl)phenyl)urea (500 mg, LC-MS 81%) as a brown solid.

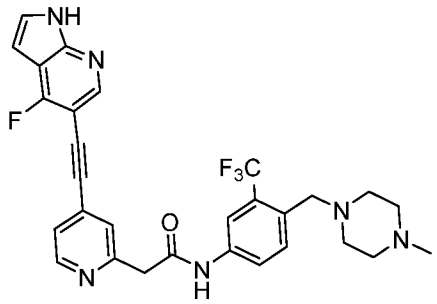
Step 3: The title compound was prepared in 5% yield (30 mg, AUC HPLC 95%) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** starting from 1-(5-bromothiazol-2-yl)-3-(4-(dimethylamino)-3-(trifluoromethyl)phenyl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.93 (s, 1H), 9.31 (s, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.93 (s, 1H), 7.73 (s, 2H), 7.68 (s, 1H), 7.56 (t, J = 3.2 Hz, 1H), 6.49 (q, J = 1.6 Hz, 3.2 Hz, 1H), 3.48 (s, 2H), 2.27–2.15 (m, 6H). MS (ESI) *m/z*: 485.25 $[C_{23}H_{19}F_3N_6OS+H]^+$.

Example 323: Preparation of 1-(4-(azetidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)-3-(5-((6-(dimethylamino)imidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)urea



The title compound was prepared in 3.6% yield (15 mg, AUC HPLC 94.03 %) as a yellow solid in a fashion similar to Example 316 synthesis starting from **Intermediate 11**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.00 (bs, 1H), 9.32 (s, 1H), 7.92–7.87 (m, 2H), 7.83–7.77 (m, 2H), 7.68–7.60 (m, 2H), 7.16 (d, J = 9.6 Hz, 1H), 3.68 (s, 2H), 3.24–3.17 (m, 4H), 3.10 (s, 6H), 2.05–2.01 (m, 2H). MS (ESI) *m/z*: 541.22 $[C_{25}H_{23}F_3N_8OS+H]^+$.

Example 324: Preparation of 2-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide



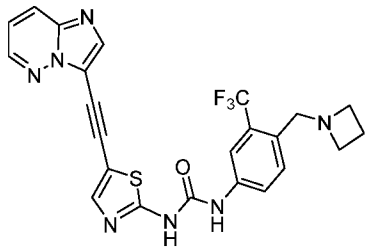
Step 1: Preparation of *N*-(3-bromo-4-((4-methylpiperazin-1-yl)methyl)phenyl)-2-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide: The title Compound was prepared in the amount of 320 mg as brown solid using a Sonogashira coupling conditions similar to **general procedure A** and starting from **Intermediate 25**. MS (ESI) m/z: 499.15 $[C_{24}H_{31}F_3N_4OSi+H]^+$.

Step 2: Synthesis of 2-(4-ethynylpyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide. A solution of *N*-(3-bromo-4-((4-methylpiperazin-1-yl)methyl)phenyl)-2-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (320 mg, 0.655 mmol) in THF (5 mL) was added LiOH (27 mg, 0.655 mmol) in water (5 mL) at room temperature and stirred for 2 h. The reaction mixture was concentrated and the redsidue was submitted to an aqueous work-up to afford 2-(4-ethynylpyridin-2-yl)-*N*-(4-((4-

methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (250 mg, LC-MS 77%) as brown solid. MS (ESI) m/z: 417.15 $[C_{22}H_{23}F_3N_4O+H]^+$.

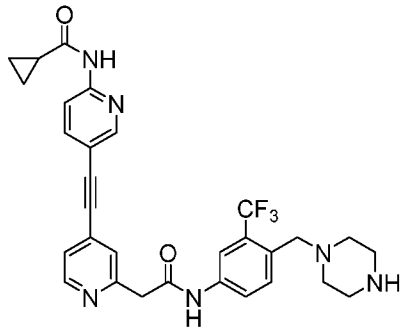
Step 3: Synthesis of 2-(4-((4-fluoro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide. The title compound was prepared in 4% yield (5 mg, AUC HPLC 96%) as a pale orange solid in a fashion similar to Example 297 using 2-(4-ethynylpyridin-2-yl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.54 (d, *J* = 4.8 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 4.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.60 (s, 1H), 7.45 (d, *J* = 3.2 Hz, 2H), 6.63 (d, *J* = 3.6 Hz, 1H), 3.96 (s, 2H), 3.63 (s, 2H), 2.76–2.38 (m, 8H), 2.32 (s, 3H). MS (ESI) m/z: 551.19 $[C_{29}H_{26}F_4N_6O+H]^+$.

Example 325: Preparation of 1-(4-(azetidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)-3-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)thiazol-2-yl)urea



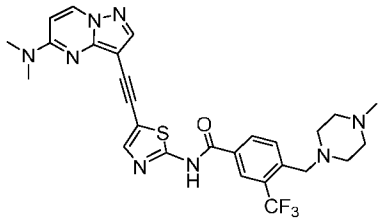
The title compound was prepared (15 mg, AUC HPLC 98%) as a pale yellow solid in a fashion similar to Example 316 using **Intermediate 39**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.31 (s, 1H), 8.68 (dd, *J* = 1.6 Hz, *J* = 2.8 Hz, 1H), 8.25 (d, *J* = 0.8 Hz, 1H), 8.23 (d, *J* = 1.2 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.82 (s, 1H), 7.61 (dd, *J* = 8.8 Hz, *J* = 14.0 Hz, 2H), 7.37 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1H), 3.63 (s, 2H), 3.17 (t, *J* = 6.8 Hz, 4H), 2.04 (m, 2H). MS (ESI) m/z: 498.16 $[C_{23}H_{18}F_3N_7OS+H]^+$.

Example 326: Preparation of N-(5-((2-(2-oxo-2-((4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)ethyl)pyridin-4-yl)ethynyl)pyridin-2-yl)cyclopropanecarboxamide



The title compound was prepared in 19% yield (25 mg, AUC HPLC 96%) as a pale yellow solid in a fashion similar to Example 297 using **Intermediate 24**. mp: 211–218 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.07 (s, 1H), 10.54 (s, 1H), 8.57–8.51 (m, 2H), 8.15 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 2.4, 2.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.42 (dd, J = 4.8, 1.2 Hz, 1H), 3.9 (s, 2H), 3.49 (s, 2H), 2.69–2.66 (m, 4H), 2.35–2.30 (m, 4H), 2.08–2.00 (m, 1H), 0.89–0.80 (m, 4H). MS (ESI) m/z: 563.0 $[C_{30}H_{29}F_3N_6O_2+H]^+$.

Example 327: Preparation of N-(5-((5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide

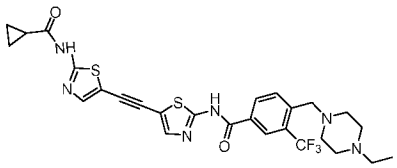


Step 1: Preparation of *N*-(5-((5-chloropyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. To a solution of 5-chloro-3-iodopyrazolo[1,5-a]pyrimidine (500 mg, 1.79 mmol) and DIPEA (0.66 mL, 3.59 mmol) in acetonitrile (60 mL) were successively added $Pd(PPh_3)_4$ (104 mg, 0.089 mmol), PPh_3 (23.3 mg, 0.089 mmol), CuI (51.2 mg, 0.269 mmol) and **Intermediate 31** (734 mg, 1.79 mmol) under argon. Reaction mixture was heated at 60 °C for 5 h. Reaction mixture was concentrated under reduced pressure, residue was diluted with water, solid separated was filtered and dried to afford *N*-(5-((5-chloropyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (240 mg, LC-MS 25%). MS (ESI) *m/z* 560.15 $[C_{25}H_{21}ClF_3N_7OS+H]^+$.

Step 2 Preparation of *N*-(5-((5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide. A

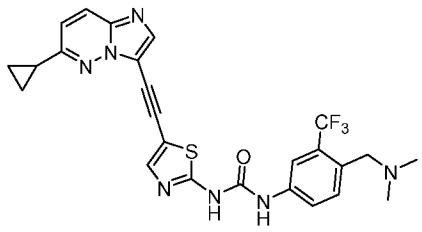
solution of *N*-(5-((5-chloropyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (240 mg, 0.429 mmol), K_2CO_3 (59 mg, 0.429 mmol) and dimethyl amine in THF (10 mL, 2M) was stirred at room temperature for 3 h. Insolubles were filtered off, filtrate was concentrated under reduced pressure. Residue was purified by preparative HPLC to afford of *N*-(5-((5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide (20 mg, 8.2%, AUC HPLC 98.0%) as a pale yellow solid. mp: 161–168 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.0 (s, 1H), 8.54 (d, J = 7.6 Hz, 1H), 8.43 (s, 1H), 8.33 (d, J = 7.6 Hz, 1H), 8.05 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 3.65 (s, 2H), 3.17 (s, 6H), 2.45–2.43 (m, 8H), 2.28 (s, 3H); MS (ESI) *m/z* 569.18 $[C_{27}H_{27}F_3N_8OS+H]^+$.

Example 328: Preparation of N-(5-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)thiazol-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 28% yield (20 mg, AUC HPLC 98%) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 33**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.75 (s, 1H), 8.45 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 3.70 (s, 2H), 2.67–2.52 (m, 6H), 2.50–2.38 (m, 4H), 1.97 (t, J = 4.8 Hz, 1H), 1.03 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.6 Hz, 4H). MS (ESI) *m/z* 589.19 $[C_{27}H_{27}F_3N_6O_2S_2+H]^+$.

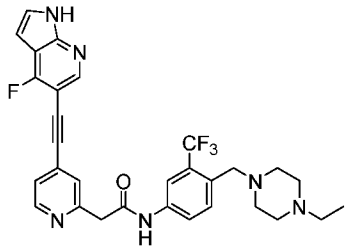
Example 329. Preparation of 1-(5-((6-cyclopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)-3-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)urea



The title compound was prepared (18 mg, AUC HPLC 98%) as a brown solid in a fashion similar to Example 316 starting from **Intermediate 38**. ^{1}H NMR (400 MHz, DMSO-d_6) δ

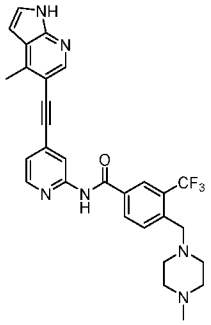
(ppm): 11.2 (bs, 1H), 9.31 (s, 1H), 8.09–8.07 (m, 2H), 7.93 (s, 1H), 7.82 (s, 1H), 7.67 (s, 2H), 7.19–7.16 (d, *J* = 9.2 Hz, 1H), 3.47 (s, 2H), 2.29–2.25 (m, 1H), 2.17 (s, 6H), 1.12–1.07 (m, 2H), 1.05–1.03 (m, 2H). MS (ESI) *m/z* 526.44 $[C_{25}H_{22}F_3N_7OS+H]^+$.

Example 330: Preparation of N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(4-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)acetamide



The title compound was prepared in 17.9 % yield (30 mg, AUC HPLC 96.21%) as a yellow solid using Sonogashira coupling conditions similar to **general procedure B** starting from **Intermediate 26** and **Intermediate 10**. mp: 101–105 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.36 (s, 1H), 10.54 (s, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 8.49 (d, *J* = 10.0 Hz, 1H), 8.07 (s, 1H), 7.77 (d, *J* = 6.8 Hz, 1H), 7.67–7.62 (m, 2H), 7.58 (s, 1H), 7.44 (dd, *J* = 5.6, 1.6 Hz, 1H), 6.64 (dd, *J* = 3.2, 2.0 Hz, 1H), 3.92 (s, 2H), 3.53 (s, 2H), 2.48–2.30 (m, 10H), 0.97 (t, *J* = 7.6 Hz, 3H). MS (ESI) *m/z* 565.34 $[C_{30}H_{28}F_4N_6O+H]^+$.

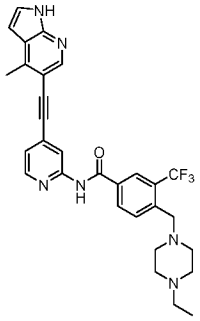
Example 331: Preparation of N-(4-((4-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared in 5.2% yield (21 mg, AUC HPLC 98.42%) as an off-white solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 15**. mp: 171–175 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.88 (s, 1H), 11.23 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.38 (s, 1H), 8.34 –8.27 (m, 3H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 2.8 Hz, 1H), 7.32 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.61 (dd, *J* = 3.6, 2.0 Hz,

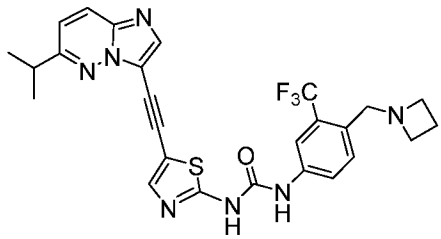
1H), 3.67 (s, 2H), 2.69 (s, 3H), 2.47–2.23 (m, 11H). MS (ESI) m/z: 533.34 $[C_{29}H_{27}F_3N_6O+H]^+$.

Example 332: Preparation of 4-((4-ethylpiperazin-1-yl)methyl)-N-(4-((4-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)pyridin-2-yl)-3-(trifluoromethyl)benzamide



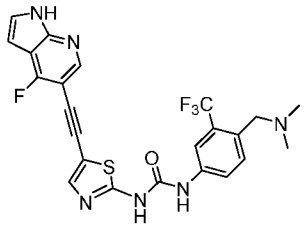
The title compound was prepared in 4% yield (16 mg, AUC HPLC 95.0%) as pale yellow solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 17**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.91 (s, 1H), 11.26 (s, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.41 (s, 1H), 8.36–8.30 (m, 3H), 7.92 (d, J = 8.0 Hz, 1H), 7.36 (dd, J = 5.2, 1.2 Hz, 1H), 6.63 (dd, J = 3.6 Hz, 2H), 3.70 (s, 2H), 2.70 (s, 3H), 2.50–2.23 (m, 10H), 1.02–0.99 (m, 3H); (ESI) m/z: 547.0 $[C_{30}H_{29}F_3N_6O+H]^+$.

Example 333: Preparation of 1-(4-(azetidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)-3-(5-((6-isopropylimidazo[1,2-b]pyridazin-3-yl)ethynyl)thiazol-2-yl)urea



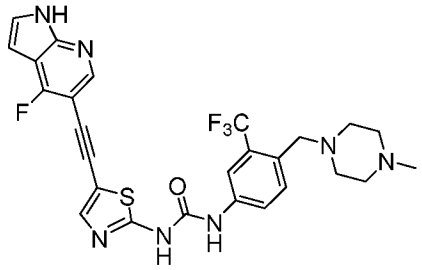
The title compound was prepared (16 mg, AUC HPLC 95.00 %) as a yellow solid in a fashion similar to Example 316 synthesis.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.2 (bs, 1H), 9.29 (s, 1H), 8.15 (d, J = 9.2 Hz, 1H), 8.11 (s, 1H), 7.92 (s, 1H), 7.83 (s, 1H), 7.67–7.61 (m, 2H), 7.40 (d, J = 9.6 Hz, 1H), 6.51 (s, 1H), 3.64 (s, 2H), 3.20–3.15 (m, 4H), 2.03–2.00 (m, 2H), 1.32 (d, J = 7.2 Hz, 6H); MS (ESI) *m/z*: 540.44 $[C_{26}H_{24}F_3N_7OS+H]^+$.

Example 334: Preparation of 1-(4-((dimethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(5-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)urea



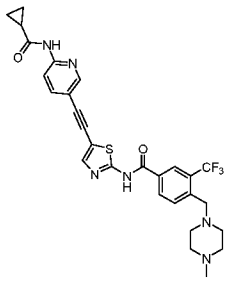
The title compound was prepared in 13.5% yield (40 mg, AUC HPLC 96%) as a yellow solid using **general procedure B** and **Intermediate 10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H), 11.30–10.8 (bs, 1H), 9.29 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 7.93 (s, 1H), 7.78 (s, 1H), 7.67–7.60 (m, 3H), 6.62–6.61 (d, J = 2.0 Hz, 1H), 3.48 (s, 2H), 2.17 (s, 6H); MS (ESI) *m/z*: 503.16 $[C_{23}H_{18}F_4N_6OS+H]^+$.

Example 335: Preparation of 1-(5-((4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)thiazol-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea



The title compound was prepared in 10.3% yield (40 mg, AUC HPLC 96%) as an off-white solid in a fashion similar to Example 217 synthesis starting from **Intermediate 10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H), 11.05 (bs, 1H), 9.31 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 7.95 (s, 1H), 7.75 (s, 1H), 7.66–7.60 (m, 3H), 6.62 (s, 1H), 3.54 (s, 2H), 2.50–2.20 (s, 8H), 2.17 (s, 3H). MS (ESI) *m/z*: 558.05 $[C_{26}H_{23}F_4N_7OS+H]^+$.

Example 336: Preparation of N-(5-((6-(cyclopropanecarboxamido)pyridin-3-yl)ethynyl)thiazol-2-yl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide



The title compound was prepared (45 mg, AUC HPLC 98%) as a yellow solid using a Sonogashira coupling conditions similar to **general procedure B** and starting from **Intermediate 30**. mp: 215–220 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.02 (s, 1H), 8.51 (s, 1H), 8.46 (s, 1H), 8.36 (d, J = 7.2 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.94–7.90 (m, 3H), 3.70 (s, 2 H), 2.50–2.32 (m, 8H), 2.32–2.17 (m, 3H), 2.04–2.01 (m, 1H), 0.84 (d, J = 5.6 Hz, 4H); MS (ESI) m/z: 569.25 $[C_{28}H_{27}F_3N_6O_2S+H]^+$

Biological assays

[000706] Compounds of formula (**I**) were synthesized and their ability to inhibit MNK1/2 kinase was evaluated both in enzymatic and in cell-based assays. In parallel, their ability to inhibit other kinases was also assessed. Enzymatic assays have shown that compounds of formula (**I**) are inhibitors of MNK1 and MNK2 with IC_{50} values in the range of >10 μM to lower than 1 nM. Enzymatic assays have shown that compounds of formula (**I**) are inhibitors of Abl-wild type and Abl-T315I with IC_{50} values in the range of >10 μM to lower than 1 nM. eIF4e phosphorylation inhibition in Hela cell line was found to have IC_{50s} vary from as low as single digit nanomolar.

[000707] Compounds of formula (**I**) were synthesized and their ability to inhibit MNK1/2 kinase was evaluated both in enzymatic and in cell-based assays. To further evaluate the therapeutic potential of these molecules, their ability to inhibit K562o/e eIF4E cell line growth was assessed. Below are the technical descriptions of these assays

Enzymatic and cell-based eIF4E phosphorylation assays

[000708] The compounds described in this invention bind to and inhibit the kinases MNK1 and MNK2. They were analyzed using both *in vitro* and *in vivo* assays that are known in the art.

[000709] *In Vitro* MNK Kinase Assay: MNK1 and MNK2 inhibitor activity was determined using recombinant kinase domains expressed in *E.coli*. MNK1 and MNK2 were expressed as GST fusion proteins and the GST tag was removed using PreScission protease. After concentration to 10-15 mg/ml the proteins were flash frozen in liquid nitrogen and stored at -80 °C. MNK1 and MNK2 were activated using recombinant ERK2 which was activated using a constitutively active mutant of MEK1, both ERK2 and MEK1 were expressed in

E.coli as N-terminally his tagged proteins. Recombinant ERK2 was activated by incubating 11.3 µM of the kinase with 1 µM MEK1 and 100 µM ATP. This reaction mixture was then used immediately for the activation of the MNKs. The activation of the MNK1 was performed by incubating 5.0 µM of MNK1 with 0.3 µM of activated ERK2 and 500 µM ATP at 30°C for 6 hours. The activation of MNK2 was performed by incubating 50 µM of MNK2 with 3.0 µM of activated ERK2 and 500 µM ATP at 30°C for 2 hours. The activated MNKs were stored at -20 °C until required for assay.

[000710] Kinase assays were performed on the Caliper Life Sciences (Mountain View, CA) Microfluidics LabChip® Platform. Enzyme activity was analyzed by 'sipping' reactions from a microtitre plate into LabChip. The data signature was generated by the shift in mobility of non-phosphorylated peptide substrates and phosphorylated products by electrophoresis in the chip and detected by LED induced fluorescence. The magnitude of the fluorescent signal revealed the extent of the reaction. The data was analyzed by calculating the relative heights of the substrate and product peaks and the product / (product+substrate) peak ratio was reported.

[000711] The following buffers were used to assay kinase activity:

Reconstitution buffer: 10mM HEPES/NaOH pH7.5, 0.003% Brij® L23, 0.004% TWEEN® 20.

Substrate buffer: 245mM HEPES/NaOH pH7.5, 0.003% Brij® L23, 0.004% TWEEN® 20, 26mM $MgCl_2$.

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

Separation buffer: 100mM HEPES/NaOH pH7.3, 0.02% Brij® L23, 5% DMSO, 0.1% CR3, 1mM EDTA pH8.0.

[000712] Peptide substrate (JH3): 5-FAM-TATKSGSTTKNRFVV-$CONH_2$.

[000713] The MNK1 assay was performed by adding 65nM of activated MNK1 and 1µl of test compound to a microtitre plate in a volume of 15µl of reconstitution buffer. The plate was incubated at 22°C for 15 minutes before the addition of 3.9 µM of JH3 and 3.12 mM ATP in 10 µl of substrate buffer and a further incubation period of 60 minutes at 28°C. The reaction was stopped by the addition of 45 µl of termination buffer. The final concentration of MNK1, JH3 peptide, ATP and compound in a 26 µl assay volume was 40 nM, 1.5 µM, 1.2 mM, and 1X respectively.

[000714] The MNK2 assay was performed by adding 32.5 nM of activated MNK1 and 1 µl of test compound to a microtitre plate in a volume of 15 µl of reconstitution buffer. The plate

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

[000715] Inhibition constants (IC_{50}) were determined by plotting kinase activity versus log compound concentration and fitting with a non-linear regression algorhithm using GraphPad Prism (GraphPad Software Inc.).

[000716] The ABL assay was performed by adding 2.44 nM of ABL (Carna biosciences, Full-length human ABL [2-1130(end) amino acids of accession number NP_005148.2] was expressed as N-terminal His-tagged protein (126 kDa) using baculovirus expression system. His-tagged ABL was purified by using Ni-NTA affinity chromatography and anion exchange chromatography) and 1 µl of test compound to a microtitre plate in a volume of 15 µl of reconstitution buffer. The plate was incubated at 22 °C for 15 minutes before the addition of 3.9 µM of FL-peptide2 (5-FAM-EAIYAAPFAKKK-CONH2) and 36.4 µM ATP in 10 µl of substrate buffer and a further incubation period of 150 minutes at 28 °C. The reaction was stopped by the addition of 45 µl of termination buffer. The final concentration of ABL, FL-peptide2, ATP and compound in a 26 µl assay volume was 1.5 nM, 1.5 µM, 14 µM, and 1X respectively.

[000717] The ABL(T315I) assay was performed by adding 3.25 nM of ABL(T315I) (Carna biosciences, Full-length human ABL [2-1130(end) amino acids and T315I of accession number NP_005148.2] was expressed as N-terminal His-tagged protein (126 kDa) using baculovirus expression system. His-tagged ABL[T315I] was purified by using Ni-NTA affinity chromatography) and 1µl of test compound to a microtitre plate in a volume of 15 µl of reconstitution buffer. The plate was incubated at 22°C for 15 minutes before the addition of 3.9 µM of FL-peptide2 (5-FAM-EAIYAAPFAKKK-CONH2) and 31.2 µM ATP in 10µl of substrate buffer and a further incubation period of 150 minutes at 28°C. The reaction was stopped by the addition of 45 µl of termination buffer. The final concentration of ABL(T315I), FL-peptide2, ATP and compound in a 26 µl assay volume was 2 nM, 1.5 µM, 12 µM, and 1X respectively.

[000718] Inhibition constants (IC50) were determined by plotting kinase activity versus log compound concentration and fitting with a non-linear regression algorhithm using GraphPad Prism (GraphPad Software Inc.).

MNK Cell-Based Assay

[000719] It has been reported that Ser209 of eIF4E is solely phosphorylated by the MNK enzymes. The ability of compounds to inhibit this process in Hela cells was investigated using the AlphaScreen *SureFire*® assay platform from Perkin Elmer (Waltham, MA). eIF4E phosphorylated on Ser209 is recognized by two antibodies, the first which is fused to a streptavidin coated donor bead binds to an epitope away from Ser209, the second which is fused to a protein A conjugated acceptor bead binds to phosphorylated Ser209. The phosphorylation of eIF4E on Ser209 brings the two antibodies into close proximity and when excited by a laser singlet oxygen is released by the donor bead which excites the acceptor bead resulting in the emission of light. This enables the monitoring of eIF4E Ser209 phosphorylation and its inhibition in a cellular context.

[000720] HeLa cells were seeded into microtitre plates (30,000 cells per well) in 100 µl of culture medium and incubated at 37 °C for 24 hours. The media was then removed by aspiration and the cells resuspended in 50µl of serum free medium containing the test compound and incubated at 37 °C for 2 hours. The culture medium was again removed by aspiration and the cells resuspended in lysis buffer (provided in Perkin Elmer SureFire® Assay Kit). After agitation at 350 rpm for 20 minutes at 22 °C, 4 µl was transferred to a 384 well OptiPlate™ (Perkin Elmer, Waltham, MA). To each well was added 5 µl of acceptor mix; the plate was sealed and agitated gently at 22 °C for 2 hours. Then, in subdued light, 2 µl of donor mix was added to each well, the plate was sealed, wrapped in aluminum foil and agitated gently at 22 °C for 2 hours. Emission was measured using the EnVision® plate reader (Perkin Elmer, Waltham, MA).

[000721] Inhibition constants (IC_{50}) were determined by plotting AlphaScreen signal versus log compound concentration and fitting with a non-linear regression algorhithm using GraphPad Prism (GraphPad Software Inc.).

[000722] K562 cells (myelogenous leukemia) over-expressing eIF4E, were also used for the cytotoxicity assay. For cells treated for 48 hours, 5000 cells were seeded in 70 µl of growth medium in black, flat-bottom 96-well plate. The cells were treated with compound doses ranging from 0.003 µM to 50 µM. 50 µl of the diluted compounds was added to the cells and incubated at 37 °C in 5% CO_2. After 48 hours treatment, cell viability was determined by CellTiter-Glo Luminescent Cell Viability Assay (Promega, Madison, WI). 120 µl of the reagent was added to the cells and luminescence was measured using Tecan Safire Reader. Data was analyzed with Graphpad Prism software.

[000723] Table 2 shows the IC_{50} values for selected compounds in the inhibition of MNK1 and MNK2, ABL (wt), ABL (T315I), the inhibition of phosphorylation of eIF4E in HeLa cells as well as the growth inhibition of K562 o/e eIF4E cell line.

Table 2. Biological Data of Exemplary Compounds

Example	IC50 (μM)					GI50 K562 o/e eIF4E (μM)
	Mnk1	Mnk2	Abl (wt)	Abl (T315I)	Hela	
49	<1	<1	<1	<1	<1	<1
48	<1	<1	<1	<1	<1	<1
44	<1	<1	<1	<1	<1	<1
46	<1	<1	<1	<1	<1	<1
52	<1	<1	<1	<1	<1	<1
51	<1	<1	<1	<1	<1	<1
60	<1	<1	<1	<1	<1	<1
43	<1	<1	<1	<1	<1	<1
204	<1	<1	<1	<1	<1	<1
195	<1	<1	<1	<1	<1	<1
61	<1	<1	<1	<1	<1	<1
21	<1	<1	<1	<1	<1	<1
162	<1	<1	<1	<1	<1	<1
187	<1	<1	<1	<1	<1	<1
72	<1	<1	<1	<1	<1	<1
99	<1	<1	<1	<1	<1	<1
124	<1	<1	<1	<1	<1	<1
167	<1	<1	<1	<1	<1	<1
186	<1	<1	<1	<1	<1	<1
125	<1	<1	<1	<1	<1	<1
14	<1	<1	<1	<1	<1	<1
82	<1	<1	<1	<1	<1	<1
123	<1	<1	<1	<1	<1	<1
128	<1	<1	<1	<1	<1	<1
172	<1	<1	<1	<1	<1	<1
70	<1	<1	<1	<1	<1	<1
171	<1	<1	<1	<1	<1	<1
176	<1	<1	<1	<1	<1	<1
129	<1	<1	<1	<1	<1	<1
201	<1	<1	<1	<1	<1	<1
135	<1	<1	<1	<1	<1	<1
189	<1	<1	<1	<1	<1	<1

Example	IC50 (μM)					GI50 K562 o/e eIF4E (μM)
	Mnk1	Mnk2	Abl (wt)	Abl (T315I)	Hela	
127	<1	<1	<1	<1	<1	<1
133	<1	<1	<1	<1	<1	<1
168	<1	<1	<1	<1	<1	<1
155	<1	<1	<1	<1	<1	<1
142	<1	<1	<1	<1	<1	<1
188	<1	<1	<1	<1	<1	<1
198	<1	<1	<1	<1	<1	<1
174	<1	<1	<1	<1	<1	<1
130	<1	<1	<1	<1	<1	<1
179	<1	<1	<1	<1	<1	<1
286	<1	<1	<1	<1	<1	<1
203	<1	<1	<1	<1	<1	<1
206	<1	<1	<1	<1	<1	<1
131	<1	<1	<1	<1	<1	<1
154	<1	<1	<1	<1	<1	<1
114	<1	<1	<1	<1	<1	<1
191	<1	<1	<1	<1	<1	<1
194	<1	<1	<1	<1	<1	<1
178	<1	<1	<1	<1	<1	<1
190	<1	<1	<1	<1	<1	<1
287	<1	<1	<1	<1	<1	<1
140	<1	<1	<1	<1	<1	<1
192	<1	<1	<1	<1	<1	<1
193	<1	<1	<1	<1	<1	<1
226	<1	<1	<1	<1	<1	<1
281	<1	<1	<1	<1	<1	<1
227	<1	<1	<1	<1	<1	<1
228	<1	<1	<1	<1	<1	<1
229	<1	<1	<1	<1	<1	<1
232	<1	<1	<1	<1	<1	<1
233	<1	<1	<1	<1	<1	<1
234	<1	<1	<1	<1	<1	<1
235	<1	<1	<1	<1	<1	<1
289	<1	<1	<1	<1	<1	<1
288	<1	<1	<1	<1	<1	<1
290	<1	<1	<1	<1	<1	<1
244	<1	<1	<1	<1	<1	<1
263	<1	<1	<1	<1	<1	<1
251	<1	<1	<1	<1	<1	<1
275	<1	<1	<1	<1	<1	<1

Example	IC50 (μM)					GI50 K562 o/e eIF4E (μM)
	Mnk1	Mnk2	Abl (wt)	Abl (T315I)	Hela	
299	<1	<1	<1	<1	<1	<1
298	<1	<1	<1	<1	<1	<1
306	<1	<1	<1	<1	<1	<1
308	<1	<1	<1	<1	<1	<1
317	<1	<1	<1	<1	<1	<1
316	<1	<1	<1	<1	<1	<1
321	<1	<1	<1	<1	<1	<1
322	<1	<1	<1	<1	<1	<1
323	<1	<1	<1	<1	<1	<1
325	<1	<1	<1	<1	<1	<1

Equivalents and Scope

[000724] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[000725] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore,

unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[000726] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[000727] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

Reference List

1. Berkel, H. J.; Turbat-Herrera, E. A.; Shi, R.; De Benedetti, A. Expression of the translation initiation factor eIF4E in the polyp-cancer sequence in the colon
1. *Cancer Epidemiol. Biomarkers Prev.* **2001,** *10* (6), 663-666.

2. Wendel, H. G.; De Stanchina, E.; Fridman, J. S.; Malina, A.; Ray, S.; Kogan, S.; Cordon-Cardo, C.; Pelletier, J.; Lowe, S. W. Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy. *Nature* **2004,** *428* (6980), 332-337.

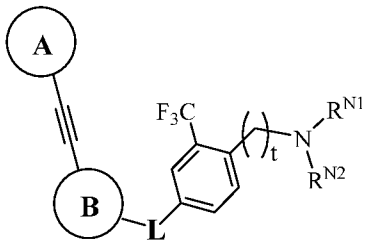
3. Wendel, H. G.; De Stanchina, E.; Fridman, J. S.; Malina, A.; Ray, S.; Kogan, S.; Cordon-Cardo, C.; Pelletier, J.; Lowe, S. W. Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy. *Nature* **2004,** *428* (6980), 332-337.

4. De Benedetti, A.; Graff, J. R. eIF4E expression and its role in malignancies and metastases, *Oncogene* **2004,** *23* (18), 3189-3199.

CLAIMS

What is claimed is:

1. A compound of Formula (**I**):



(**I**)

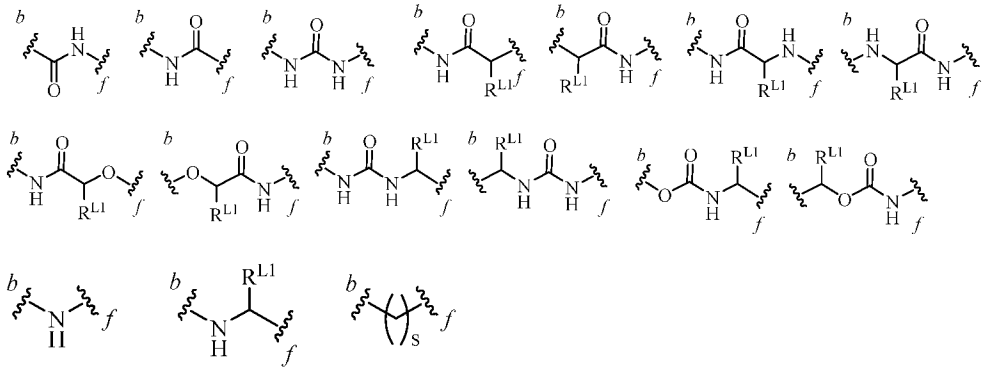
or a pharmaceutically acceptable salt thereof,

wherein

Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, optionally substituted 5,6- or 6,6-bicyclic heteroaryl, or optionally substituted 5,6- or 6,6-bicyclic heterocycle;

Ring B is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl;

L is one of the following formulae:



b indicates the point of attachment to Ring B;

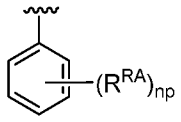
f indicates the point of attachment to *m*-CF_3-Ph;

R^{L1} is hydrogen or optionally substituted C_{1-6} alkyl;

each of R^{N1} and R^{N2} is independently hydrogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} carbocyclyl, or R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted heterocyclic moiety;

t is 1, 2, or 3; and

s is 1, 2, or 3.

2. The compound of claim 1, wherein Ring A is optionally substituted phenyl of the formula  ,

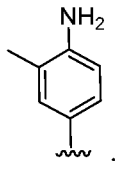
wherein

each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

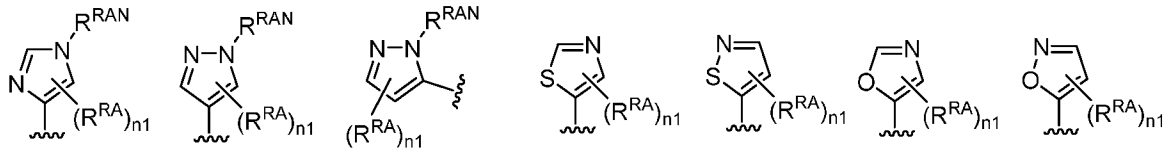
each instance of R^{RAN} and R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{RAN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl, or two R^{AN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl; and

np is 0, 1, 2, 3, 4, or 5.

3. The compound of claim 2, wherein Ring A is of one the formula  .

4. The compound of claim 1, wherein Ring A is optionally substituted five-membered heteroaryl.

5. The compound of claim 4, wherein Ring A is one of the following formulae:



wherein

each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

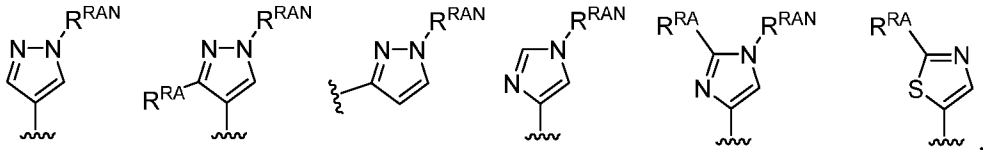
each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^{RAN} and R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{RAN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl, or two R^{AN} are taken with the intervening nitrogen to form an optionally substituted heterocyclyl; and

n1 is 0, 1 or 2.

6. The compound of claim 5, wherein n1 is 1 or 2.

7. The compound of claim 5, wherein Ring A is one of the following formulae:



8. The compound of any one of claims 5-7, wherein

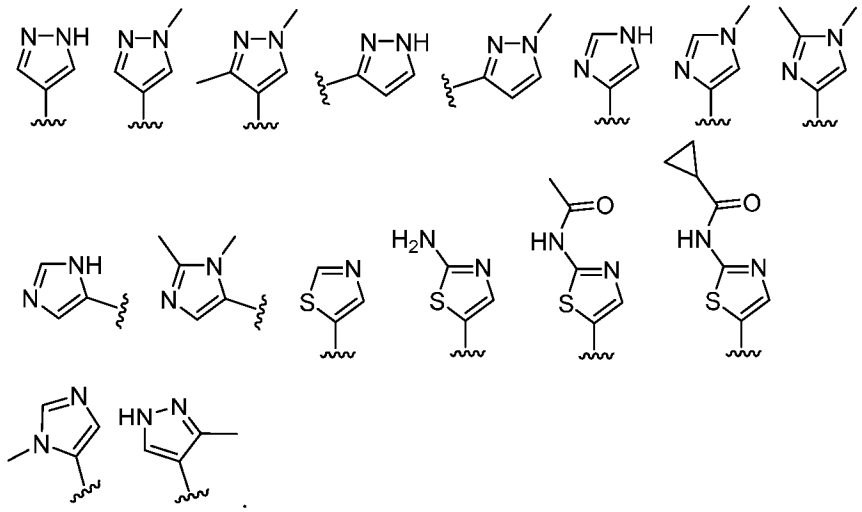
R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-NHC(=O)R^{AN1}$; and

each instance of R^{AN1} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

9. The compound of claim 8, wherein R^{RA} is $-NH_2$, -NHAc, or -NHC(=O)-cyclopropyl.

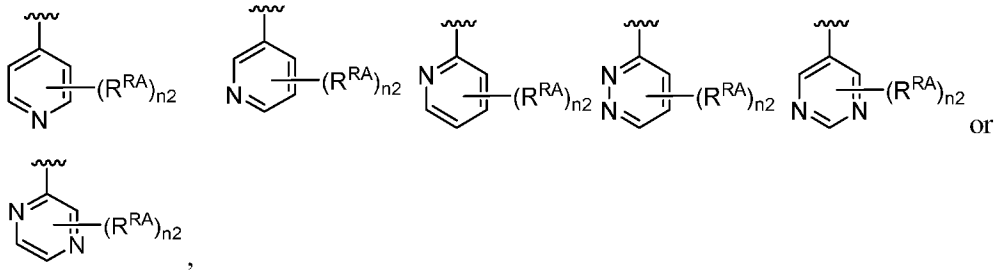
10. The compound of any one of claims 5-7, wherein R^{RA} is $-CH_3$.

11. The compound of any one of claims 5-10, wherein Ring A is one of the following formulae:



12. The compound of claim 1, wherein Ring A is optionally substituted six-membered heteroaryl.

13. The compound of claim 12, wherein Ring A is one of the following formulae:



or

,

wherein

each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{AN} are taken with the intervening atoms to form an optionally substituted heterocyclyl; and

n2 is 0 or an integer between 1 and 4, inclusive.

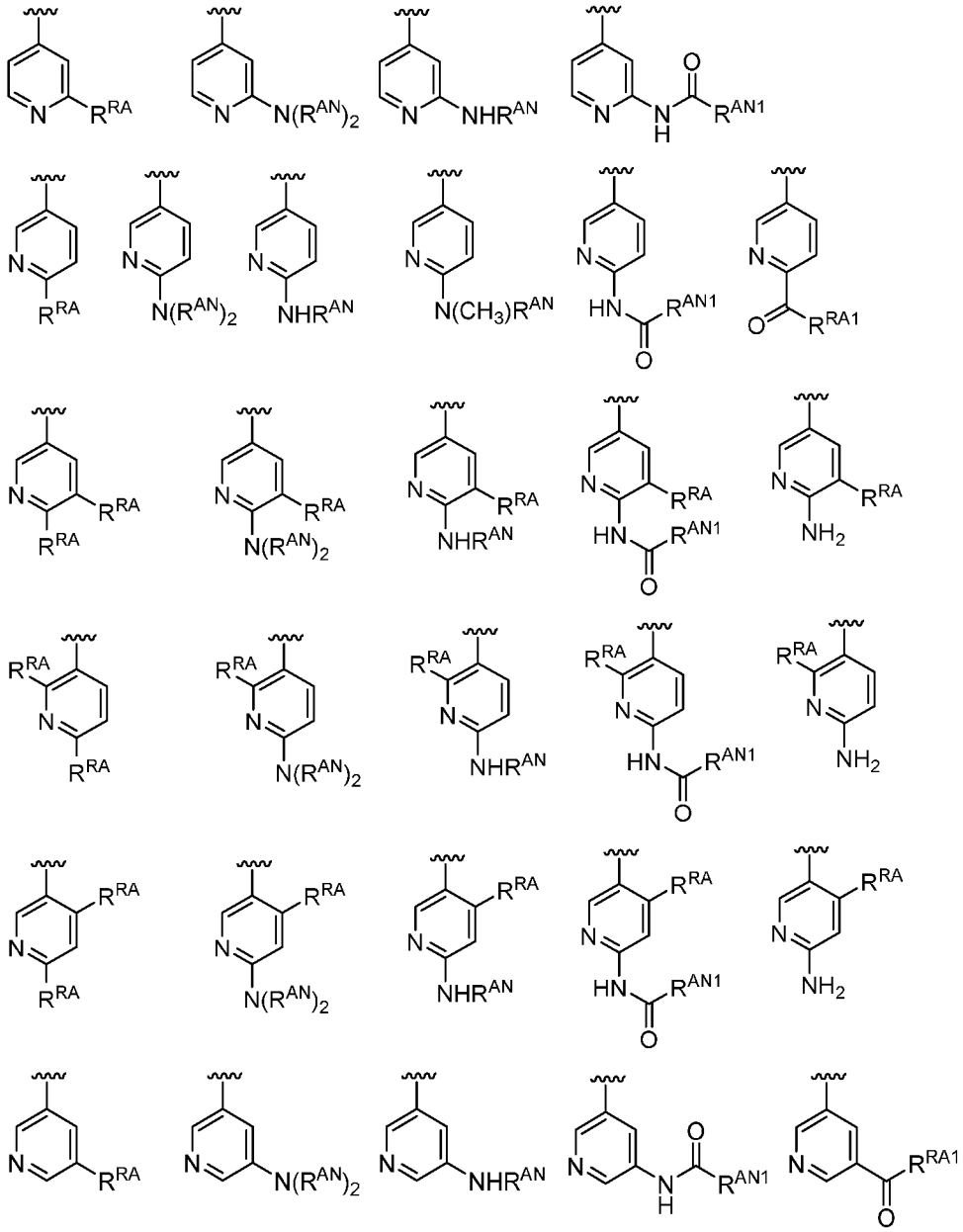
14. The compound of claim 13, wherein n2 is 1 or 2.

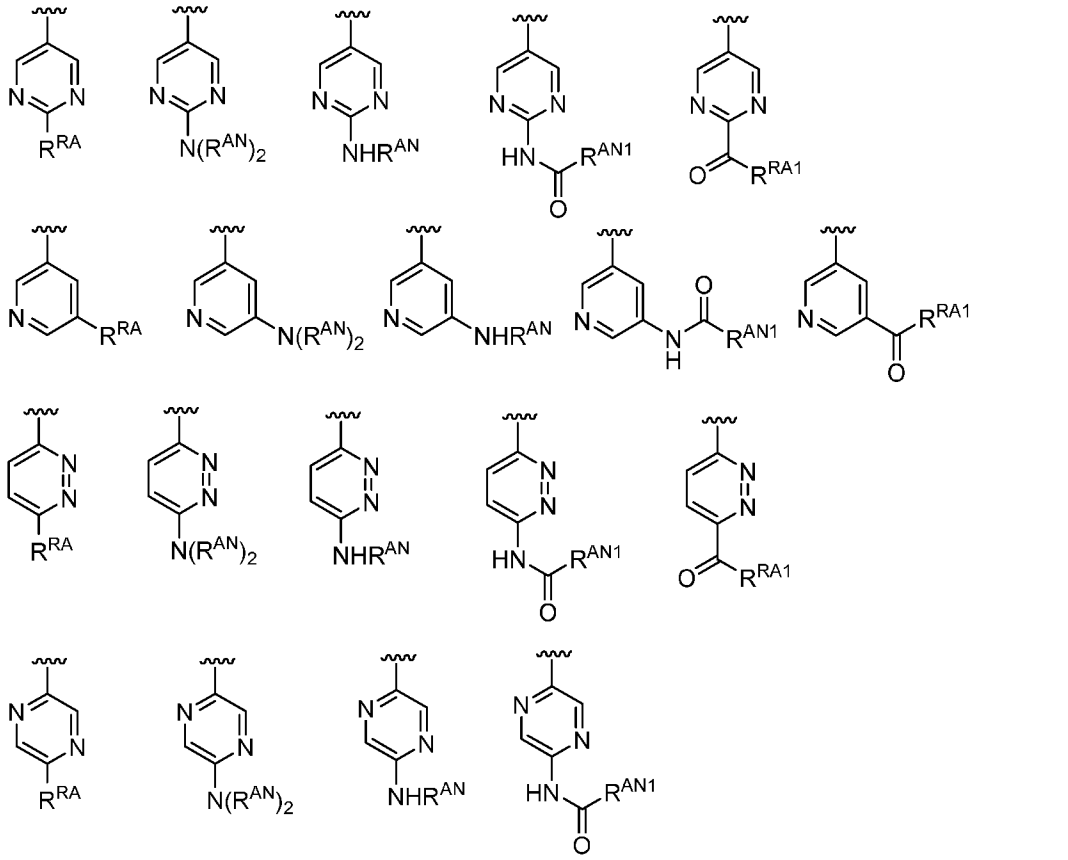
15. The compound of claim 13 or 14, wherein

R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-NHC(=O)R^{AN1}$; and

each instance of R^{AN1} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

16. The compound of any one of claims 13-15, wherein Ring A is one of the following formulae:



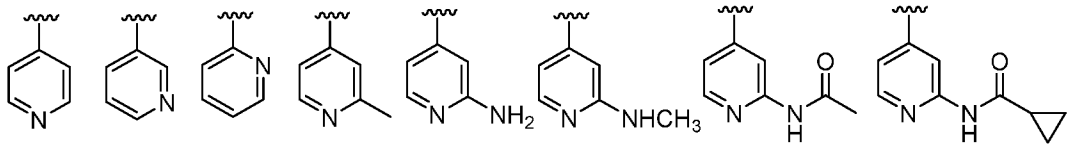


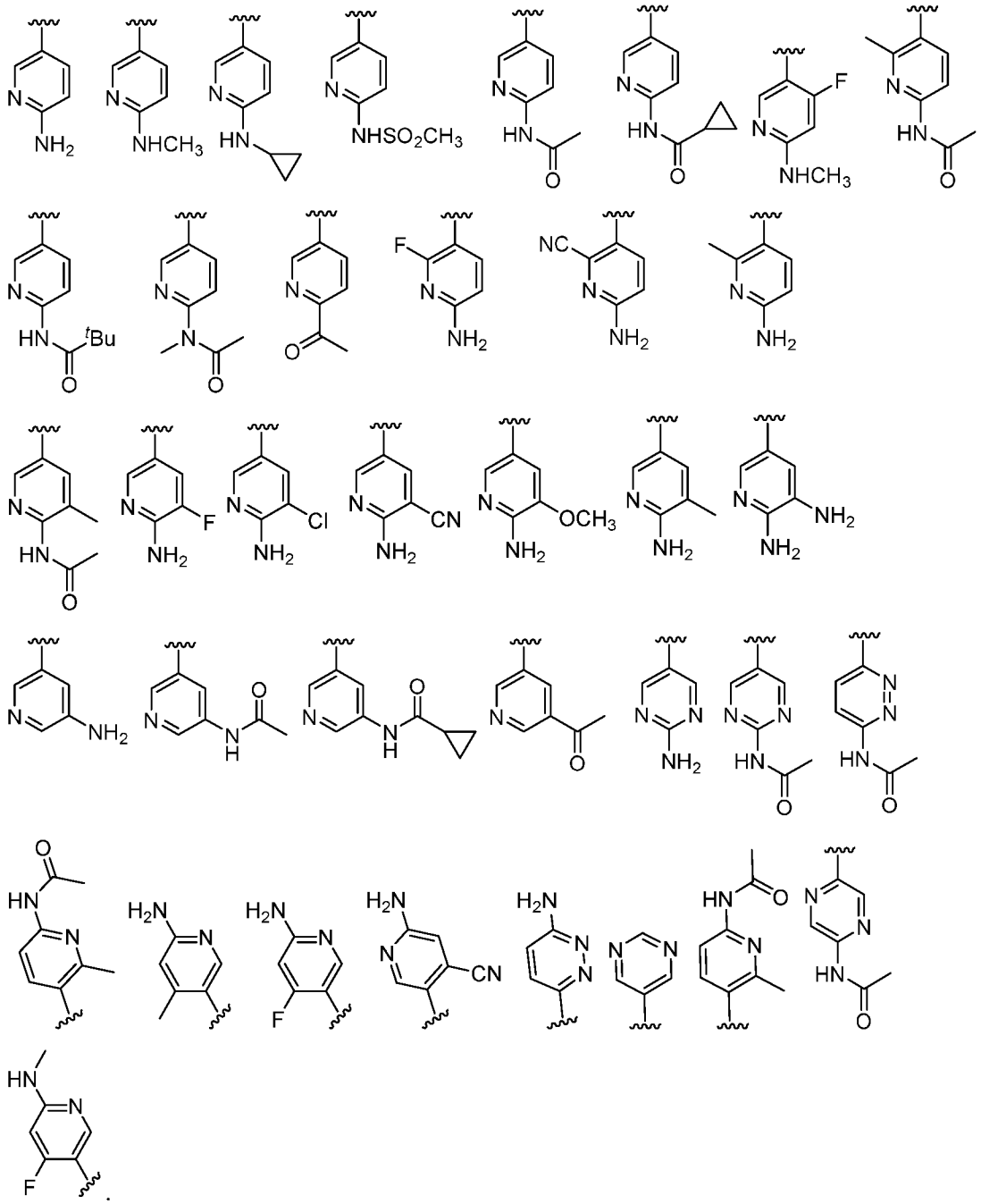
wherein

each instance of R^{RA1} and R^{AN1} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

17. The compound of any one of claims 13-16, wherein R^{RA} is of one of the following formulae: -CN, -F, -Cl, $-CH_3$, $-NH_2$, $-NHCH_3$, $-N(C_2H_5)_2$, -NHAc, $-N(CH_3)Ac$, -NHC(=O)-cyclopropyl, or $-C(=O)CH_3$.

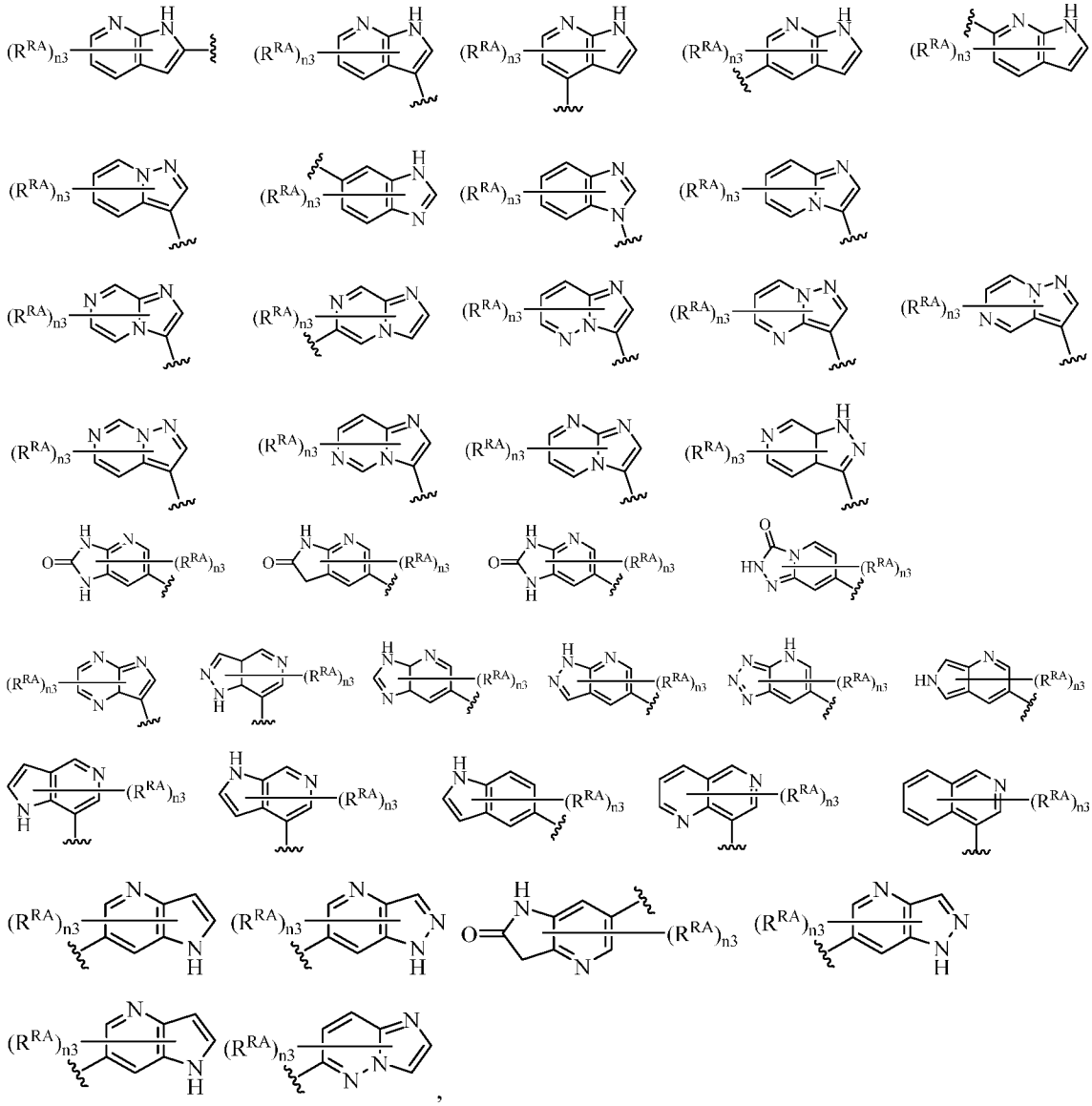
18. The compound of any one of claims 13-17, wherein Ring A is one of the following formulae:





19. The compound of claim 1, wherein Ring A is optionally substituted 5,6- or 6,6-bicyclic heterocycle or optionally substituted 5,6- or 6,6-bicyclic heteroaryl.

20. The compound of claim 19, wherein Ring A is one of the following formulae:



wherein

each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

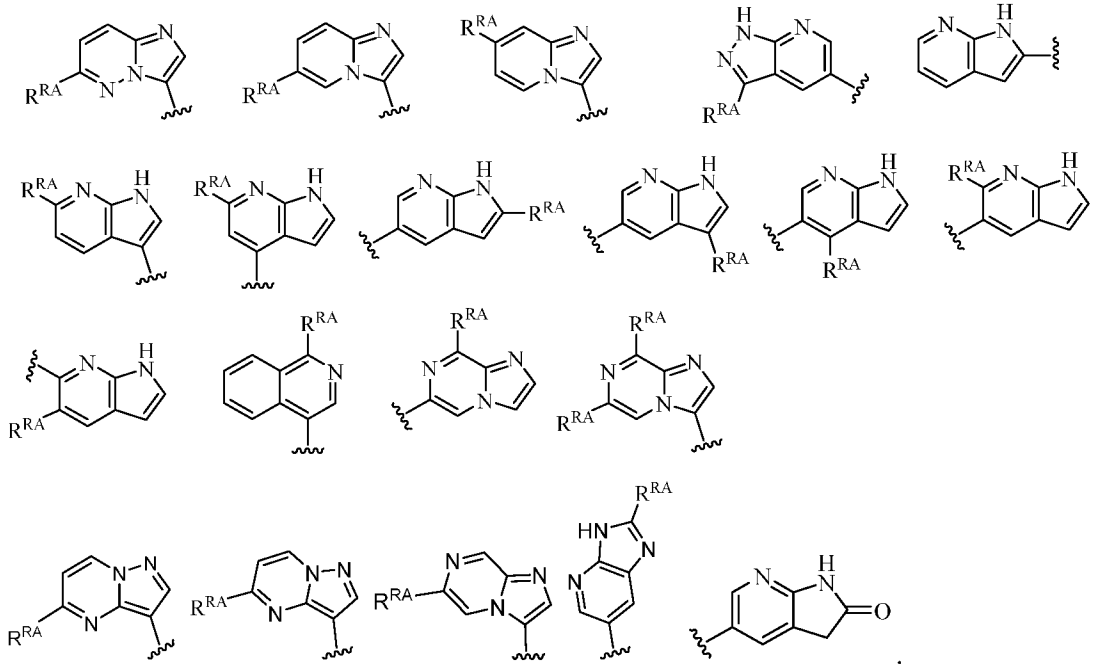
each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{AN} are taken with the intervening atoms to form an optionally substituted heterocyclyl; and

n3 is 0 or an integer between 1 and 6, inclusive, as valency permits.

21. The compound of claim 20, wherein n3 is 1 or 2.

22. The compound of claim 21, wherein Ring A is one of the following formulae:



23. The compound of any one of claims 20-22, wherein R^{RA} is hydrogen, halogen, or optionally substituted C_{1-6} alkyl.

24. The compound of any one of claims 20-22, wherein

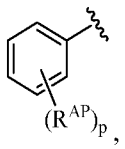
R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-NHC(=O)R^{AN1}$; and

each instance of R^{AN1} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

25. The compound of any one of claims 20-22, wherein R^{RA} is $-OR^{AO}$.

26. The compound of any one of claims 20-22, wherein R^{RA} is optionally substituted carbocyclyl.

27. The compound of any one of claims 20-22, wherein R^{RA} is optionally substituted phenyl of the formula:

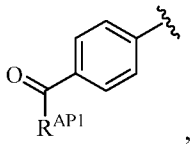


wherein

each instance of R^{AP} is independently hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or optionally substituted acyl; and

p is an integer of 1 to 5, inclusive.

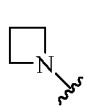
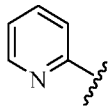
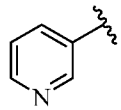
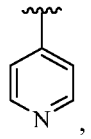
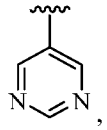
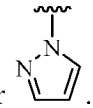
28. The compound of claim 27, wherein R^{RA} is of the formula:



wherein

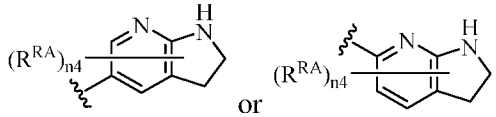
R^{AP1} is independently optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

29. The compound of any one of claims 20-28, wherein R^{RA} is one of the following formulae:

-CN, -F, -Cl, $-CH_3$, $-C_2H_5$, $-^iPr$, -Ph, , $-O^iPr$, $-OCH_3$, $-OC_2H_5$, $-NH_2$, $-NHCH_2{}^iPr$, $-N(CH_3)_2$, $-NHCH_3$, $-N(C_2H_5)_2$, $-NH-(CH_2)_3-OH$, $-N(CH_3)-(CH_2)_2-OCH_3$, $-NHC(=O)^iPr$, -NHAc,  ,  ,  ,  ,  , or  .

30. The compound of claim 1, wherein Ring A is optionally substituted 5,6- or 6,6-bicyclic heterocycle.

31. The compound of claim 30, wherein Ring A is of the formula:



wherein

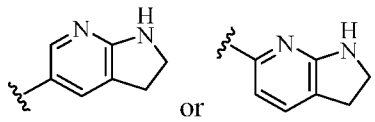
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

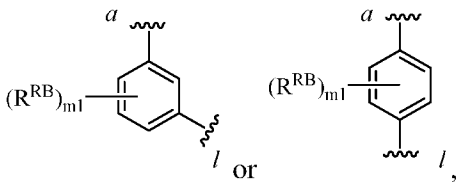
each instance of R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{AN} are taken with the intervening atoms to form an optionally substituted heterocyclyl; and

n4 is 0 or an integer between 1 and 6, inclusive, as valency permits.

32. The compound of claim 31, wherein Ring A is of the formula:



33. The compound of any one of preceding claims, wherein Ring B is optionally substituted phenyl of the formula:



wherein

each instance of R^{RB} is independently hydrogen, halogen, or optionally substituted C_{1-6} alkyl;

a indicates the point of attachment to alkynyl;

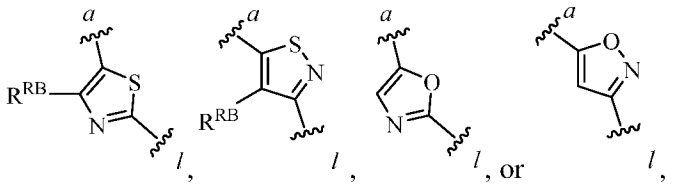
l indicates the point of attachment to L; and

m1 is 1, 2, 3, or 4.

34. The compound of claim 33, wherein m1 is 1.

35. The compound of any one of claims 1-32, wherein Ring B is optionally substituted five-membered heteroaryl.

36. The compound of claim 35, wherein Ring B is of the formula:



wherein

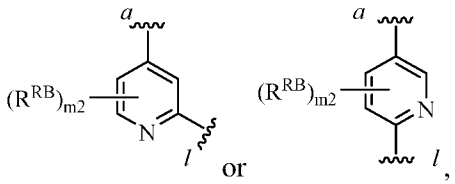
each instance of R^{RB} is independently hydrogen, halogen, or optionally substituted C_{1-6} alkyl;

a indicates the point of attachment to alkynyl; and

l indicates the point of attachment to L.

37. The compound of any one of claims 1-32, wherein Ring B is optionally substituted six-membered heteroaryl.

38. The compound of claim 37, wherein Ring B is of the formula:



wherein

each instance of R^{RB} is independently hydrogen, halogen, or optionally substituted C_{1-6} alkyl;

a indicates the point of attachment to alkynyl;

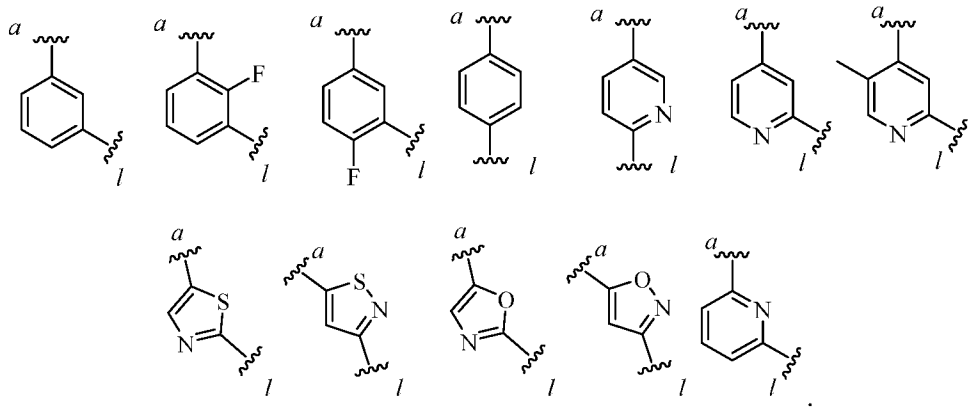
l indicates the point of attachment to L; and

m2 is 1, 2, or 3.

39. The compound of claim 38, wherein m2 is 1.

40. The compound of any one of claims 38-39, wherein R^{RB} is $-CH_3$ or F.

41. The compound of any one of claims 1-32, wherein Ring B is one of the following formulae:



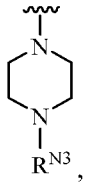
42. The compound of any one of preceding claims, wherein each of R^{N1} and R^{N2} is independently hydrogen or optionally substituted C_{1-6} alkyl.

43. The compound of claim 42, wherein each of R^{N1} and R^{N2} is independently hydrogen, or unsubstituted C_{1-6} alkyl.

44. The compound of any one of preceding claims, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted heterocyclic moiety.

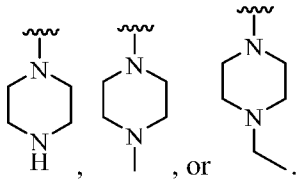
45. The compound of claim 44, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted three-, four-, five-, or six-membered heterocyclic moiety.

46. The compound of claim 45, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted six-membered heterocyclic moiety of the formula:

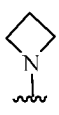


, wherein R^{N3} is independently hydrogen, optionally substituted C_{1-6} alkyl, or a nitrogen protecting group.

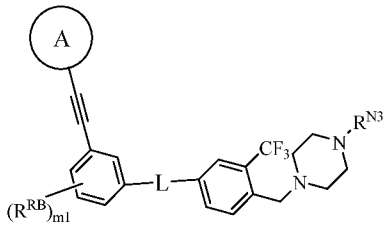
47. The compound of claim 46, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted six-membered heterocyclic moiety of the formula:

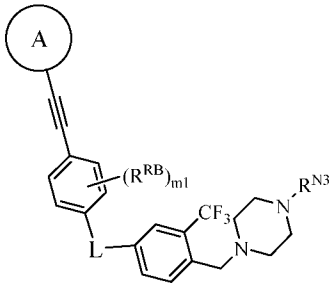


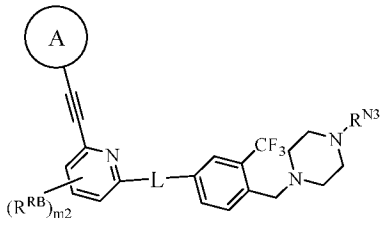
48. The compound of claim 45, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted azetidinyl moiety.

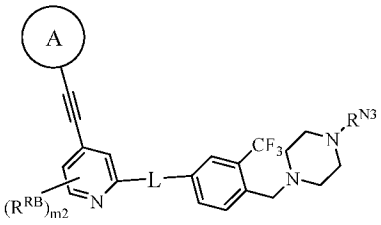
49. The compound of claim 48, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted azetidinyl moiety of the formula  .

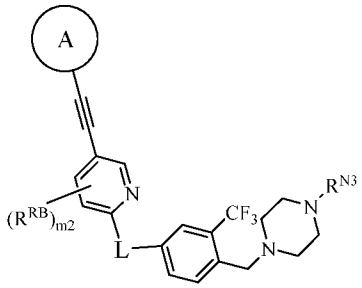
50. The compound of claim 1 having one of the following formulae:

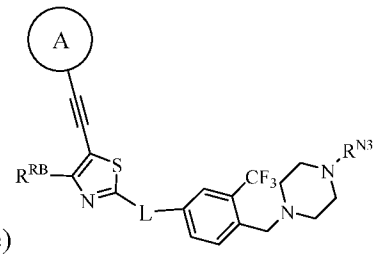

(I-a),


(I-b),


(I-c),


(I-d),


(I-e)


(I-f),

or a pharmaceutically acceptable salt thereof,

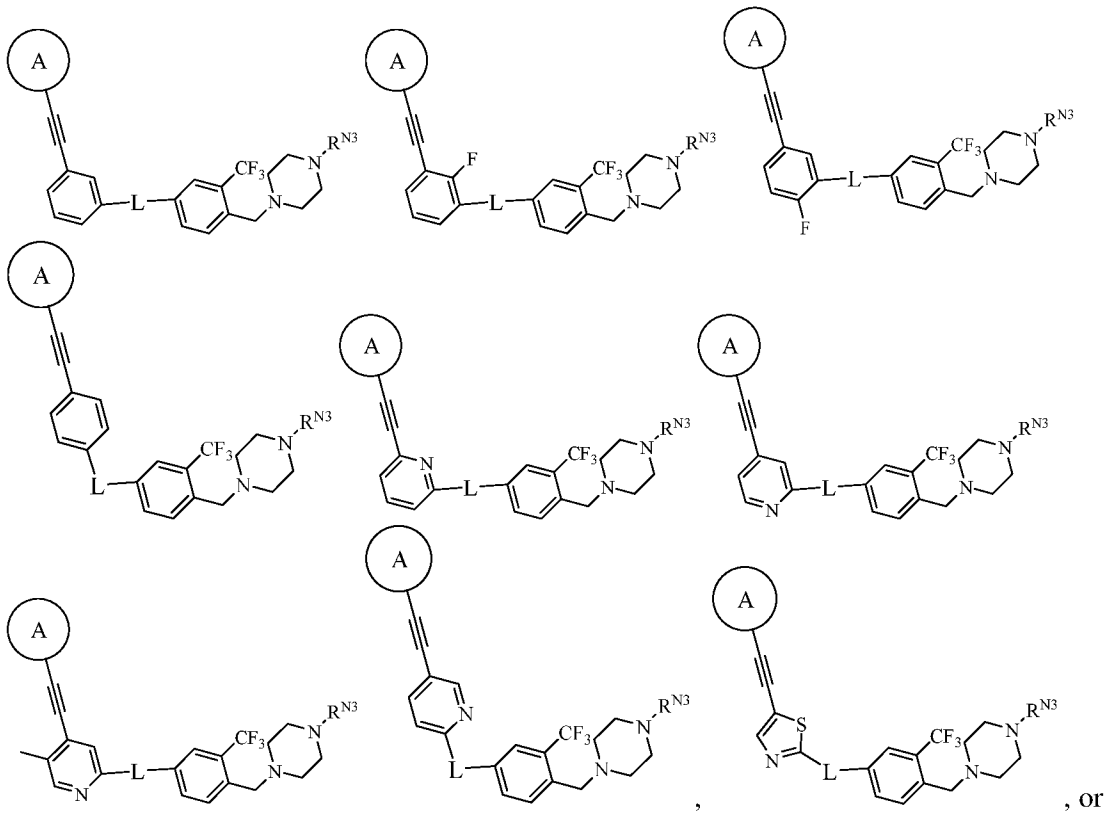
wherein

each instance of R^{RB} is independently hydrogen, halogen, or optionally substituted C_{1-6} alkyl;

each instance of R^{N3} is independently hydrogen, optionally substituted C_{1-6} alkyl, or a nitrogen protecting group; and

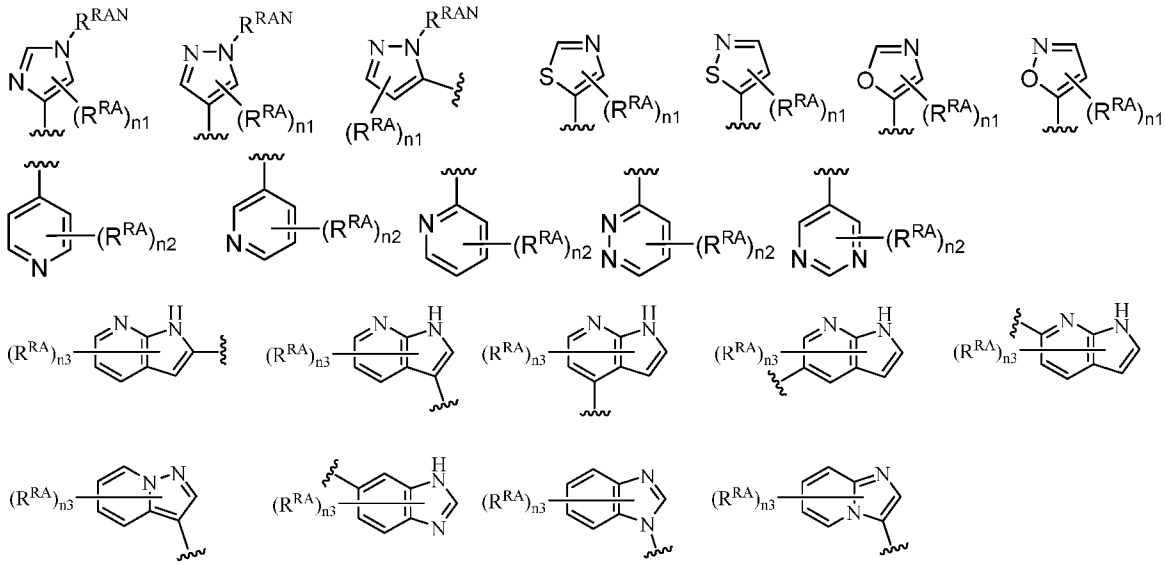
each of m1, m2, and m3 is independently 1, 2, or 3.

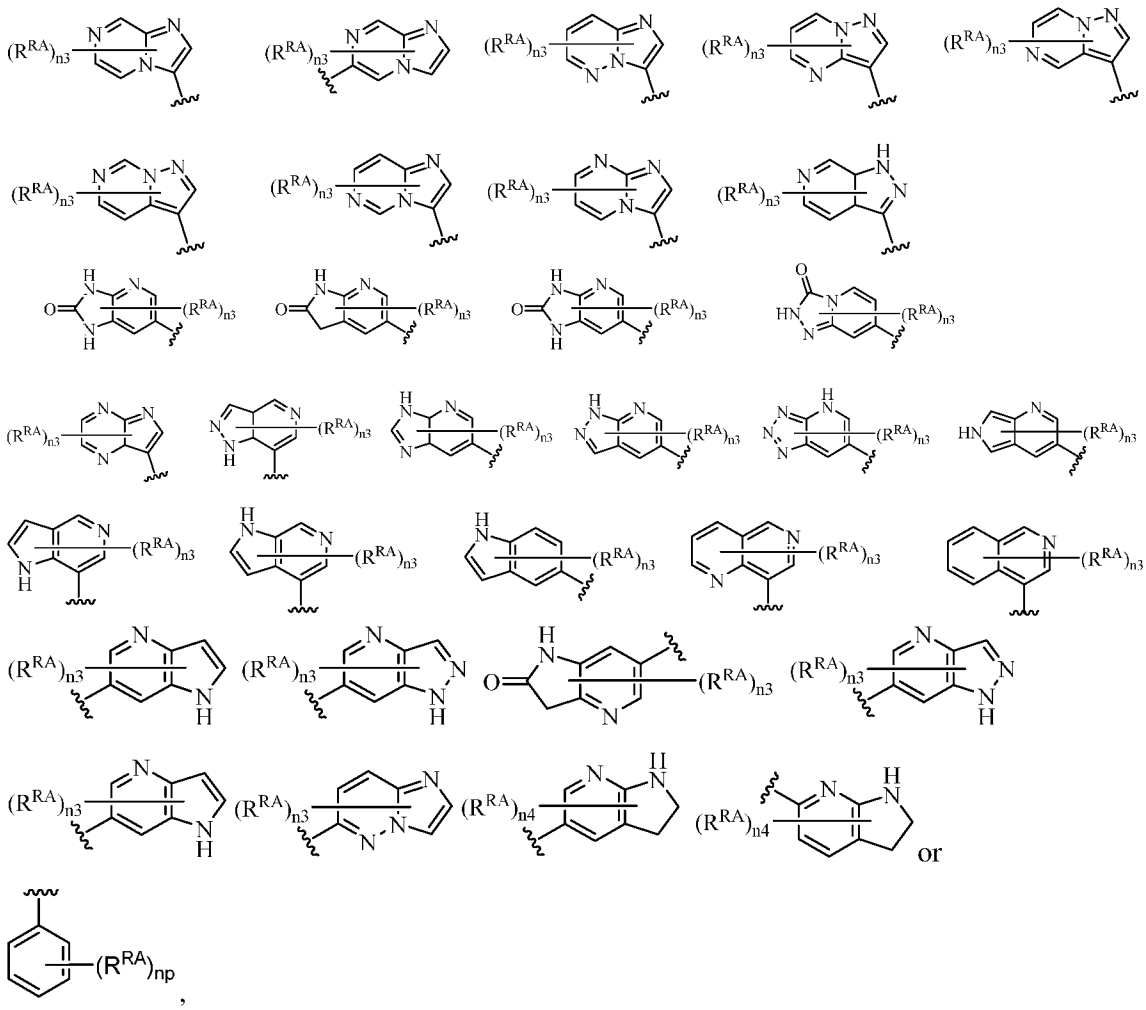
51. The compound of claim 50 having one of the following formulae:



a pharmaceutically acceptable salt thereof.

52. The compound of claim 50 or 51, wherein Ring A is of any one of the following formulae:





wherein

each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted four-, five-, or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, optionally substituted acyl, -CN, $-OR^{AO}$, or $-N(R^{AN})_2$;

each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group;

each instance of R^{RAN} and R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group, or two R^{RAN} are taken with the intervening atoms to form an optionally

substituted heterocyclyl, or two R^{AN} are taken with the intervening atoms to form an optionally substituted heterocyclyl;

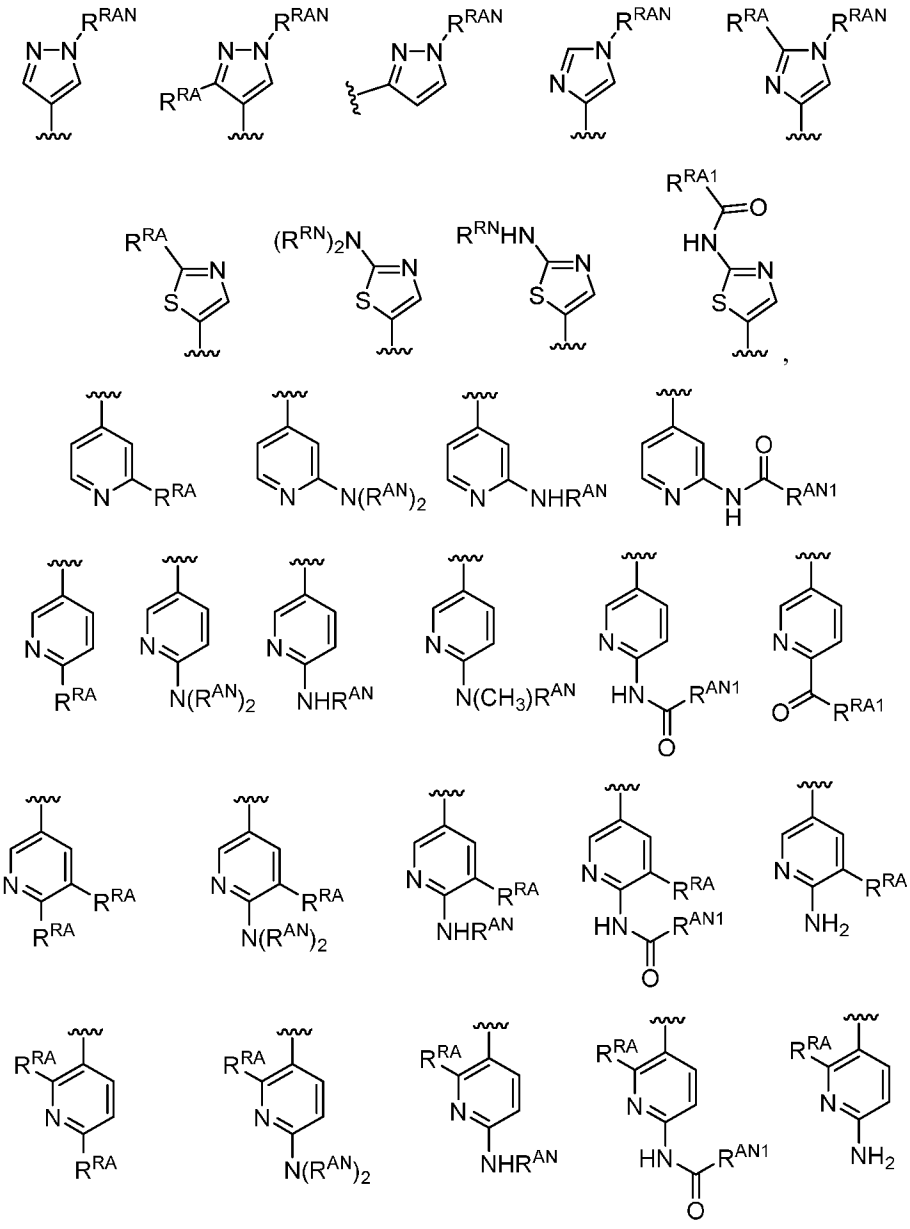
np is 0, 1, 2, 3, 4, or 5;

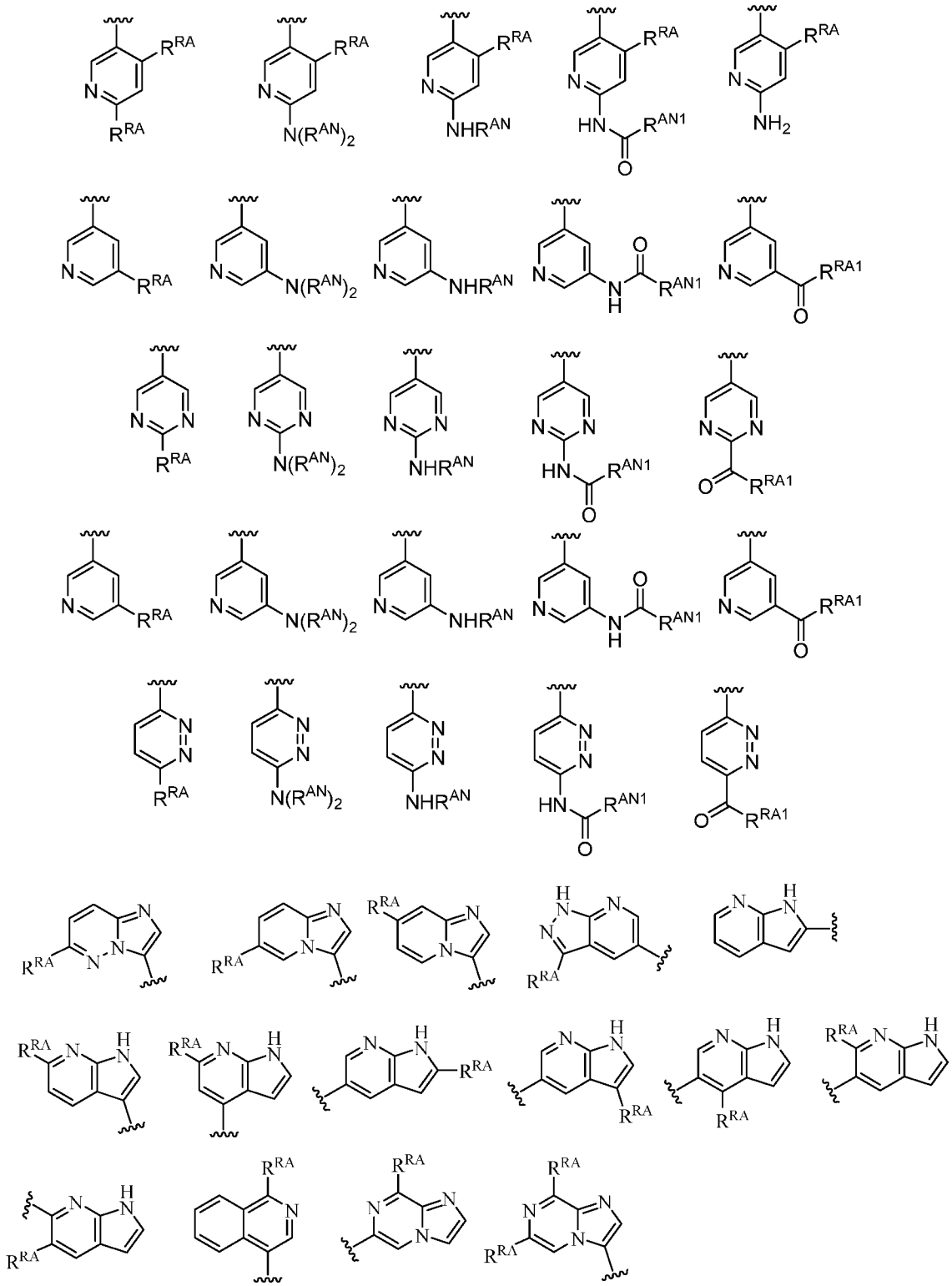
n1 is 0, 1, or 2;

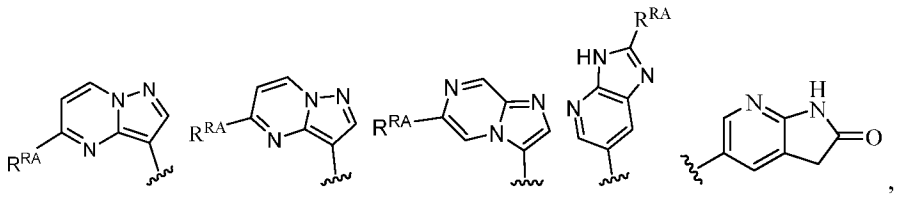
n2 is 0 or an integer between 1 and 4, inclusive; and

n3 is 0 or an integer between 1 and 6, inclusive, as valency permits.

53. The compound of claim 52, wherein Ring A is of any one of the following formulae:



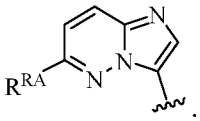




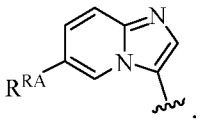
wherein

each instance of R^{AN1} is independently hydrogen, o optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

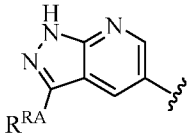
54. The compound of claim 52, wherein Ring A is of the formula:



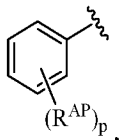
55. The compound of claim 52, wherein Ring A is of the formula:



56. The compound of claim 52, wherein Ring A is of the formula:

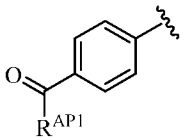


57. The compound of any one of claims 52-56, wherein R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-NHC(=O)R^{AN1}$, wherein each instance of R^{AN1} is independently hydrogen, o optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

58. The compound of any one of claims 52-56, wherein R^{RA} is optionally substituted phenyl of the formula:  , wherein

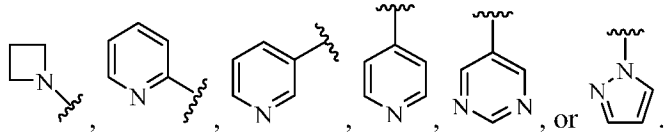
each instance of R^{AP} is independently hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or optionally substituted acyl; and

p is an integer of 1 to 5, inclusive.

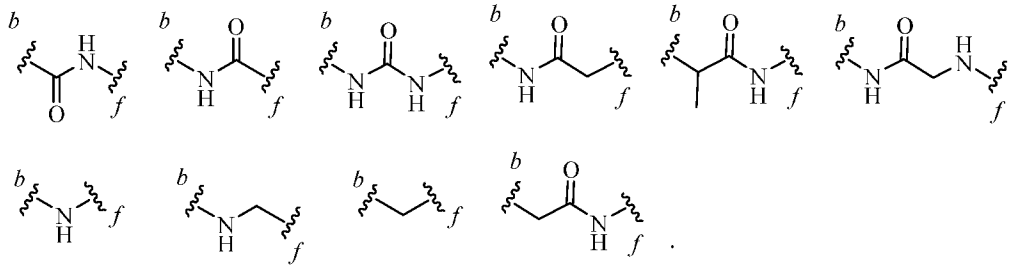
59. The compound of claim 58, wherein R^{RA} is of the formula:  , wherein

R^{AP1} is independently optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

60. The compound of any one of claims 52-59, wherein R^{RA} is one of the following formulae:

-CN, -F, -Cl, -CH_3, -C_2H_5, -^{i}Pr, -Ph, , -O^{i}Pr, -OCH_3, -OC_2H_5, -NH_2, -$NHCH_2{}^i$Pr, -$N(CH_3)_2$, -$NHCH_3$, -$N(C_2H_5)_2$, -NH-$(CH_2)_3$-OH, -N(CH_3)-$(CH_2)_2$-OCH_3, -NHC(=O)^{i}Pr, -NHAc,  .

61. The compound of any one of preceding claims, wherein L is one of the following formulae:

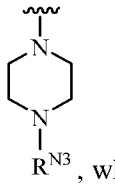


62. The compound of any one of claims 52-61, wherein each of R^{N1} and R^{N2} is independently hydrogen or optionally substituted C_{1-6} alkyl.

63. The compound of any one of claims 52-61, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted heterocyclic moiety.

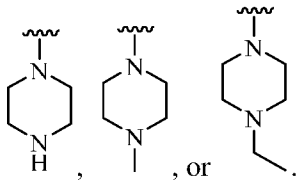
64. The compound of claim 63, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted three-, four-, five-, or six-membered heterocyclic moiety.

65. The compound of claim 64, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted six-membered heterocyclic moiety of the formula:

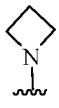


, wherein R^{N3} is independently hydrogen, optionally substituted C_{1-6} alkyl, or a nitrogen protecting group.

66. The compound of claim 65, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted six-membered heterocyclic moiety of the formula:



67. The compound of claim 64, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted azetidinyl moiety.

68. The compound of claim 67, wherein R^{N1} and R^{N2} are taken with the intervening nitrogen to form an optionally substituted azetidinyl moiety of the formula 

:

69. The compound of claim 1, wherein the compound is one of the formulae in Table 1, or a pharmaceutically acceptable salt thereof.

70. A pharmaceutical composition comprising a compound of any one of claims 1-67 and a pharmaceutically acceptable excipient.

71. Use of a compound of any one of claims 1-69, or a pharmaceutical composition of claim 70, for treatment of a Mnk-related disorder.

72. Use of the compound or pharmaceutical composition of claim 71, wherein the Mnk-related disorder is a Mnk1-related disorder.

73. Use of the compound or pharmaceutical composition of claim 71, wherein the Mnk-related disorder is a Mnk2-related disorder.

74. Use of a compound of any one of claims 1-69, or a pharmaceutical composition of claim 70 for inhibiting Abelson (Abl) tyrosine kinase.

75. Use of the compound or pharmaceutical composition of claim 74, wherein the Abl tyrosine kinase is wild type Abl tyrosine kinase.

76. Use of the compound or pharmaceutical composition of claim 75, wherein the Abl tyrosine kinase is a mutant Abl tyrosine kinase.

77. Use of the compound or pharmaceutical composition of claim 75, wherein the Abl tyrosine kinase has a T315I mutation.

78. Use of the compound or pharmaceutical composition of claim 75, wherein the Abl tyrosine kinase has a E255K mutation.

79. Use of the compound or pharmaceutical composition of any one of claims 71-78, wherein the compound is used in combination with another agent.

80. Use of the compound or pharmaceutical composition of any one of claim 79, wherein the agent is a small molecule or biologic.

81. Use of the compound or pharmaceutical composition of any one of claim 79, wherein the agent is a kinase inhibitor.

82. Use of the compound or pharmaceutical composition of any one of claim 79, wherein the agent is a monoclonal antibody.

83. Use of the compound or pharmaceutical composition of any one of claim 79, wherein the agent is an siRNA.

84. Use of the compound or pharmaceutical composition of any one of claims 71-78, wherein the disorder is cancer, an inflammatory disease, neurodegenerative disease, neurodevelopmental disorder, or a metabolic disorder.

85. Use of the compound or pharmaceutical composition of claim 84, wherein the disorder is cancer.

86. Use of the compound or pharmaceutical composition of claim 84, wherein the disorder is solid tumor.

87. Use of the compound or pharmaceutical composition of claim 84, wherein the disorder is hematological tumor.

88. Use of the compound or pharmaceutical composition of claim 84, wherein the disorder is a metabolic disorder.

89. Use of the compound or pharmaceutical composition of claim 88, wherein the disorder is obesity.

90. Use of the compound or pharmaceutical composition of claim 88, wherein the disorder is diabetes.

91. Use of the compound or pharmaceutical composition of claim 84, wherein the disorder is a neurodegenerative disease.

92. Use of the compound or pharmaceutical composition of claim 91, wherein the disorder is Alzheimer's disease.

93. Use of the compound or pharmaceutical composition of claim 84, wherein the disorder is a neurodevelopmental disorder.

94. Use of the compound or pharmaceutical composition of claim 93, wherein the neurodevelopmental disorder is autism.

95. Use of the compound or pharmaceutical composition of any one of claims 71-94, wherein the compound or pharmaceutical composition is administered at a dosage level sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg to a subject in need thereof.

96. A method of treating a Mnk-related disorder in a subject comprising administering an effective amount of a compound of any one of claims 1-69, or a pharmaceutical composition of claim 70, to the subject.

97. A kit comprising a compound of any one of claims 1-69 or a pharmaceutical composition of claim 70; and instructions for administering the compound or the composition to a subject.