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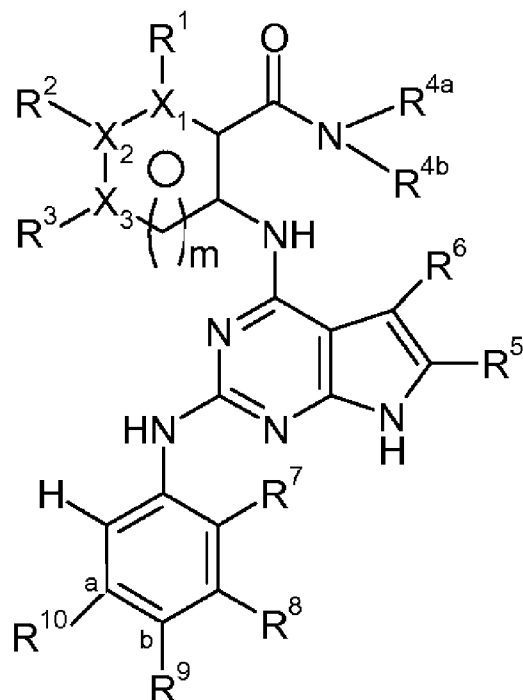
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(54) Title: PYRROLOPYRIMIDINE COMPOUNDS



(I)

(57) Abstract: Novel pyrrolopyrimidines as shown in formula (I); and pharmaceutically acceptable derivatives thereof. The compounds are useful in the inhibition of IGF-1R.



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PYRROLOPYRIMIDINE COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to pyrrolopyrimidine derivatives, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, compositions and medicaments. Such pyrrolopyrimidine derivatives are useful in the treatment of diseases associated with inappropriate IGF-1R and IR activity.

BACKGROUND OF THE INVENTION

Receptor tyrosine kinases (RTKs) have been implicated in cellular signaling pathways that control various cellular functions, including cell division, growth, metabolism, differentiation, and survival, through reversible phosphorylation of the hydroxyl groups of tyrosine residues in proteins. Extracellular signals are transduced via activation of the cell surface receptors, with amplification and propagation using a complex choreography of cascades of protein phosphorylation, and protein dephosphorylation events to avoid uncontrolled signaling. These signaling pathways are highly regulated, often by complex and intermeshed kinase pathways where each kinase may itself be regulated by one or more other kinases and protein phosphatases. The biological importance of these finely tuned systems is such that a variety of cell proliferative disorders have been linked to defects in one or more of the various cell signaling pathways mediated by tyrosine or serine/threonine kinases.

Receptor tyrosine kinases (RTKs) catalyse phosphorylation of certain tyrosyl amino acid residues in various proteins, including themselves, which govern cell growth, proliferation and differentiation. Insulin-like growth factor-1 receptor (IGF-1R) is a transmembrane tyrosine kinase ubiquitous among fetal and post-natal cell types.

The IGF signaling axis is made up of multiple ligands (IGF-1, IGF-2 and Insulin), at least six high affinity ligand binding proteins and proteases, multiple receptors (IGF-1R & IGF-2R, IR and IRR), and many other down stream signaling proteins (Pollak, MN et al., Nature Reviews Cancer (2004) 4(7):505-518). The structure and function of the IGF-1R has been reviewed by Adams et al., Cell. Mol. Life Sci. (2000) 57:1050-1093 and Benito, M et al., Int J Biochem Cell Biol (1996) 28(5):499-510. The receptor is activated

by the ligands IGF-1 and IGF-2, which are mitogenic proteins that signal through the IGF-1R and IR in an endocrine, paracrine or autocrine manner. Activation of the IGF-1 receptor elicits cellular responses which include cellular proliferation and protection of cells from apoptosis. (Id.) Overexpression of IGF-1R leads to malignant transformation of cultured cells, while downregulation can reverse the transformed phenotype of tumor cells and potentially render them susceptible to apoptosis. (Id.)

There are two splice variants of the IR gene, the IR-B isoform which regulates glucose uptake and is expressed in liver, muscle and adipose tissue, and the exon 11 variant human insulin receptor isoform A (IR-A) binds IGF-2 with high affinity and promotes proliferation and protection from apoptosis (Sciacca L. *Oncogene* (2002) 21(54):8240-8250). IR-A is predominantly expressed in fetal tissue and malignancies and at this receptor, IGF-2 is more potent than insulin in stimulating cancer cell migration. (Sciacca, *Oncogene* (2002) supra). Insulin receptor-related receptor (IRR) has 79% homology with the kinase domain of IR and is expressed only in a few limited cell types (Dandekar, AA et al., *Endocrinology* (1998) 139(8):3578-3584).

IGF-1R is a hetero-tetrameric, transmembrane, cell surface receptor. (Benito, *Int J Biochem Cell Biol* (1996)) An IGF-1 binding domain is part of the extracellular alpha-chain of IGF-1R, whereas the intracellular beta-chain contains the tyrosine kinase domain. Three tyrosine residues represent autophosphorylation sites, specifically Tyr1131, Tyr1135, and Tyr1136, within the activation loop of the IGF-1R beta catalytic domain (Li, W et al., *J. Biol. Chem.* (2006) 281(33):23785-23791). Phosphorylation of all three is required for full receptor activation, and preceeds phosphorylation of juxtamembrane tyrosines and carboxy terminus serines. The insulin receptor has three similar autophosphorylation sites on the activation loop and juxtamembrane region.

Activation and autophosphorylation results in the recruitment of multiple docking proteins and the generation of intracellular signaling (Benito, *Int J Biochem Cell Biol* (1996)). Once activated, IGF-1R and IR can phosphorylate or interact directly with a number of intracellular protein substrates, including IRS-1, IRS-2, Grb2, Grb10, Grb14, Shc, SOC, 14.3.3, FAK, or indirectly with other proteins like PI3K and MAPK (Benito, M et al. *Int J Biochem Cell Biol* (1996) 28(5):499-510) (Brown, GC et al., *Biochem. J* (1992) 284:1-13; Bruning, JC et al., *Mol. Cell* (1998) 2(5):559-569). Focal adhesion kinase (FAK) is of particular interest because of its role as a regulator of cell survival, proliferation, migration and invasion. FAK is activated by growth factor receptors such as IGF-1R, by

binding through its N-terminal domain and autophosphorylation at TyR³⁹⁷. Activated or over expressed FAK is common in a wide variety of cancers, and may play a role in human carcinogenesis (van Nimwegen, MJ et al., *Biochem. Pharmacol.* (2007) 73(5):597-609).

5 In addition to its role in cancers, the insulin-like growth factor receptor plays important and diverse roles in growth and development (Benito, M et al. *Int J Biochem Cell Biol* (1996) 28(5):499–510). It IGF-1R has been implicated in several metabolic, and immunological diseases (Walenkamp, MJ et al., *Horm. Res.* (2006) 66(5):221–230; Kurmasheva, R. T et al., *Biochim. Biophys. Acta –Rev on Cancer* (2006) 1766(1):1–22; Bateman, JM et al., *Cell. Mol. Life Sci.* (2006) 63(15):1701–1705, LeRoith, D, et al., *Can.Lett.* (2003) 195:127-137 and Samani A, et al., *Endocrine Reviews* 28(1):20-47.)

The role of the IGF/IGF-1R signaling system in cancer has been thoroughly examined over the last 15 years. In particular, the implication of IGF-1R in human cancer stems from its roles in stimulating mitogenesis, mobility and metastasis and in protecting against apoptosis. (Kurmasheva, *Biochim. Biophys. Acta* (2006).) Interest has grown with the understanding that in addition to its antiapoptotic and mitogenic roles, IGF/IGF-1R signaling seems to be necessary for the establishment and continuation of a transformed phenotype. It has been well established that constitutive activation or over expression, often results in non-adherent cell growth, even under serum depleted conditions in vitro, and is associated with the formation of tumors in nude mice. (Kaleko M et al, *Mol Cell Biol.* (1990) 10(2): 464-473). Perhaps even more importantly, it has been firmly established that cells, in which the gene encoding for IGF-1R has been deactivated, are totally resistant to transformation by agents which are normally capable of immortalizing normal cells, such as over expression of PDGFR or EGFR, the T antigen of the SV40 virus, the E5 protein of bovine papilloma virus, and activated ras. (DeAngelis T et al., *Cell. Physiol.* (1995) 164() :214-221; Coppola D et al., *Mol. Cell. Biol.* (1994) 14(7) :4588-4595 ; Morrione AJ, *Viol.* 1995 695300-5303; Sell C et al., *Mol. Cell. Biol.* (1994) 14(6):3604-3612; Sell C et al., *Proc. Natl. Acad. Sci. USA* (1993) 90(23):11217-11221). Thus, IGF-1R has been identified as the major survival factor that protects from oncogene induced cell death (Harrington et al., *EMBO J.* (1994) 13():3286-3295). IGF-1R is expressed in a large number and variety of tumors and the IGFs amplify the tumor growth through their interaction with the receptor. Evidence supporting the role of IGF-1R in carcinogenesis can be found in studies using

monoclonal antibodies directed towards the receptor which inhibit the proliferation of numerous cell lines in culture and in vivo (Arteaga C et al., Cancer Res. (1989) 49(22):6237-6241; Li et al., Biochem. Biophys. Res. Com. (1993) 196(1):92-98; Scotlandi K et al., Cancer Res. (1998) 58(18):4127-4131). Dominant negative IGF-1R is capable of inhibiting tumor proliferation (Jiang et al., Oncogene (1999) 18(44):6071-6077).

The IGF signaling axis is implicated in various tumor types including: breast cancer (Surmacz, J. Mammary Gland Bio. Neoplasia (2000) 5(1):95-105, LeRoith, Can.Lett. (2003) and Arteaga, Cancer Res. (1989)), bone and bone marrow cancers including Ewing's sarcoma, osteosarcoma, giant cell tumor of bone (Scotlandi, Cancer Res. (1998) lung cancer, including non-small cell and small cell lung carcinomas and mesotheliomas (Jiang, Y et al., Oncogene (1999) 18:6071-6077 and LeRoith, Can.Lett. (2003), prostate cancer (Djavan et al., World J Urol. (2001) 19(4):225-233; O'Brien et al., Urology (2001) 58(1):1-7 and LeRoith, Can.Lett. (2003)), colorectal cancer (Guo et al., Gastroenterology, 1992, 102, 1101-1108; Durai, R et al., Int. J Colorectal Dis. (2005) 20(3):203-220 and LeRoith, Can.Lett. (2003)), renal cancer (Kellerer M. et al., Int. J. Cancer (1995) 62(5):501-507), pancreatic cancer (Bergmann, U et al., Cancer Res. (1995) 55(10):2007-2011), hematopoietic cancers, including lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, mantle cell leukemia, multiple myeloma, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, myelodysplastic syndromes, (Zumkeller W et al., Leuk. Lymph (2002) 43(3):487-491; and Qi, Ann Hematol. (2006) 85:95-101.), neuroblastomas (Zumkeller, W et al., Horm. Metab. Res. 1999, 31, 138-141), gliomas, meningiomas, medulloblastomas, astrocytomas, and glioblastoma (Zumkeller, W et al., Mol. Pathol. (2001) 54(4):227-229, Del Valle L, et al., Clin.Cancer Res. (2002) 8:1822-1830 and Trojan et al., Proc. Natl. Acad. Sci. USA (1992) 89:4874-4878.), thyroid cancer (Vella V et al., J. Clin. Endocrinol. Metab. (2002) 87:245-254; Vella V et al., Mol. Pathol. (2001) 54(3):121-124), and hepatocarcinoma (Alexia, C et al., Biochem. Pharmacol. (2004) 68(1):1003-1015).

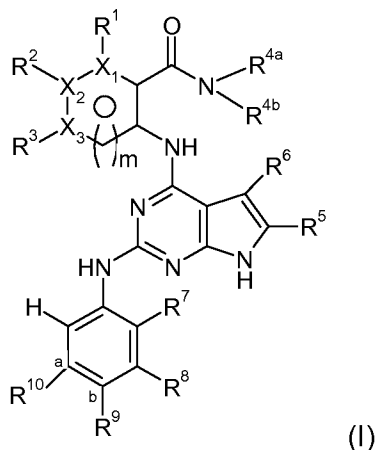
ovarian cancer, testicular cancer, vulval cancer, cervical cancer, endometrial cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor), skin cancer including melanoma, and soft-tissue sarcoma.

Thus, in virtually all types of human cancers there is a strong association between dysregulation of IGF signaling and carcinogenesis (Bohula EA et al., *Anticancer Drugs* (2003) 14(9):669-682). Inhibition of IGF-1R expression or function has been shown to block tumor growth and metastasis and also enhance sensitivity to other anti-neoplastic therapies, including cytotoxic drugs and radiation. (Bohula, *Anticancer Drugs* (2003).

SUMMARY OF THE INVENTION

We have now found a group of novel pyrrolopyrimidines that are inhibitors of IGF-1R.

The present invention provides a compound of formula (I):



or a pharmaceutically acceptable salt or solvate thereof wherein:

R^{4a} and R^{4b} are each independently selected from H, alkyl_{C1-C6}, -OH, -alkylene_{C1-C6}-OH, -alkylene_{C1-C6}-phenyl (optionally substituted with a halo), and -alkylene_{C1-C6}-C(O)NH₂;

one or two of X^1 , X^2 , and X^3 are independently selected from N, O, and S, while the remaining one or two of X^1 , X^2 , and X^3 are C;

m is 0 or 1;

R^1 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^1 is C, otherwise R^1 is absent;

R^2 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^2 is C, otherwise R^2 is absent;

R^3 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^3 is C, otherwise R^3 is absent;

5 R^5 and R^6 are independently selected from H and alkyl_{C1-C3};

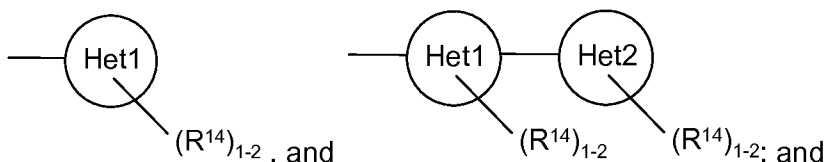
R^7 is selected from alkyl_{C1-C6}, -O-alkyl_{C1-C6}, halo, -NR²²R²³, and -O-alkylene_{C1-C6}-halo₁₋₃;

R^8 is selected from H, halo, and alkyl_{C1-C6};

one of R^9 and R^{10} is selected from -alkylene_{C1-C6}-SO₂-alkyl_{C1-C6},

-N-alkylene_{C0-C6}-C(O)-alkylene_{C0-C6}-NR²²R²³,

10 -O-alkylene_{C0-C6}(optionally substituted with -OH)-NR²²R²³,



the other of R^9 and R^{10} is selected from H, alkyl_{C1-C6}, -O-alkyl_{C1-C6}, and halo;

wherein Het1 and Het2 are each independently a five or six membered heterocyclic ring

15 having an N atom and optionally one or two additional heteroatoms selected from N and O, and

each R^{14} is independently selected from H, OH, halo, alkyl_{C1-C6}, -O-alkyl_{C1-C6},

-cyclopropyl, -C(O)-alkyl_{C1-C6}, SO₂-alkyl_{C1-C6}, -(CH₂)₁₋₄-halo, and

-(CH₂)₁₋₄-SO₂-alkyl_{C1-C6}; -C(O)-alkylene_{C0-C6}-NR²²R²³, -NR²²R²³;

20 or

R^9 and R^{10} , together with the atoms to which they are attached form a five, six, or seven-membered heterocyclic ring containing one or two N atom and the remainder C atoms, wherein at least one N atom is substituted with R^{15} , and the C atoms of the heterocyclic ring are optionally substituted with $(R^{19})_{1-2}$;

25

wherein R^{15} is selected from H, -alkyl_{C1-C4}, -alkylene_{C1-C4}-halo,

-C(O)-alkylene_{C0-C6}-NR²²R²³, -C(O)-alkyl_{C1-C6}, -alkylene_{C1-C4}-NR²²R²³,

-alkylene_{C1-C4}-C(O)-NR²²R²³, -C(O)-alkylene_{C1-C4}-O-alkyl_{C1-C6}, -C(O)-pyrrolidine,

and -C(O)-pyrrolidine-alkyl_{C1-C6}; and,

30 each R^{19} is independently selected from H and alkyl_{C1-C6};

each R²² is selected from H, alkyl_{C1-C6}, -O-alkyl_{C1-C6}, -alkylene_{C1-C6}-O-alkyl_{C1-C6}; and,

each R²³ is selected from H and alkyl_{C1-C6}; or

- 5 R²² and R²³ combine to form a four, five, or six membered, heterocyclic ring containing the N atom to which they are attached and optionally an additional heteroatom selected from N and O, wherein the ring is optionally substituted with -OH or -alkyl_{C1-C6}.

- 10 According to another embodiment, a compound of formula I is provided as described in any one of the examples. According to another embodiment, a pharmaceutically acceptable derivative of the compound of formula I described in any one of the examples is provided.

- According to another embodiment, the invention provides a pharmaceutical
15 composition comprising compound of Formula I, or pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carrier, diluent, or excipient.

- According to another embodiment, the invention provides a method of treatment of a condition mediated by inappropriate activity of at least one IGF-1R
20 family receptor in a mammal in need thereof, with a compound of Formula I, or pharmaceutically acceptable derivative thereof.

- According to another embodiment, the invention provides a method for treating a susceptible neoplasm in a mammal in need thereof, comprising: administering to the mammal, a therapeutically effective amount of a compound of formula (I) or a
25 pharmaceutically acceptable derivative thereof.

- According to another embodiment, the invention provides a method for treating a condition selected from breast cancer, sarcomas, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers (including multiple myeloma), neuroblastomas, gliomas, head and
30 neck cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer, testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor and skin cancer (including melanoma) in a mammal in

need thereof, comprising: administering to the mammal, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another embodiment, the invention provides a method for treating a condition selected from breast cancer, sarcoma, lung cancer, non-small cell lung carcinoma, prostate cancer, colorectal cancer, pancreatic cancer, hematologic cancers, multiple myeloma, head and neck cancer or ovarian cancer in a mammal in need thereof, comprising: administering to the mammal, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another embodiment, the invention provides a compound of Formula I, or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition mediated by inappropriate activity of at least one IGF-1R family receptor.

According to another embodiment, the invention provides a compound of Formula I, or a pharmaceutically acceptable derivative thereof for use in the treatment of a susceptible neoplasm in a mammal in need thereof.

According to another embodiment, the invention provides a compound of Formula I, or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition selected from breast cancer, sarcomas, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers (including multiple myeloma), neuroblastomas, gliomas, head and neck cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer, testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor and skin cancer (including melanoma) in a mammal in need thereof.

According to another embodiment, the invention provides a compound of Formula I, or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition selected from breast cancer, sarcoma, lung cancer, non-small cell lung carcinoma, prostate cancer, colorectal cancer, pancreatic cancer, hematologic cancers, multiple myeloma, head and neck cancer or ovarian cancer in a mammal in need thereof.

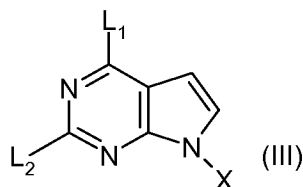
According to another embodiment, the invention provides the use of a compound of formula I, or pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of a condition mediated by inappropriate activity of at least one IGF-1R family receptor.

5 According to another embodiment, the invention provides the use of a compound of formula I, or pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of a susceptible neoplasm in a mammal in need thereof.

10 According to another embodiment, the invention provides the use of a compound of formula I, or pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of a condition selected from breast cancer, sarcomas, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers (including multiple myeloma), neuroblastomas, gliomas, head and neck
15 cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer, testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor and skin cancer (including melanoma) in a mammal in need thereof.

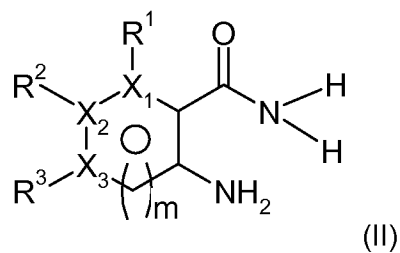
20 According to another embodiment, the invention provides the use of a compound of formula I, or pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of a condition selected from breast cancer, sarcoma, lung cancer, non-small cell lung carcinoma, prostate cancer, colorectal cancer, pancreatic cancer, hematologic cancers, multiple
25 myeloma, head and neck cancer or ovarian cancer in a mammal in need thereof.

According to another embodiment, the invention provides for a process for preparing a compound of formula I, comprising the steps of reacting a compound of formula (III),

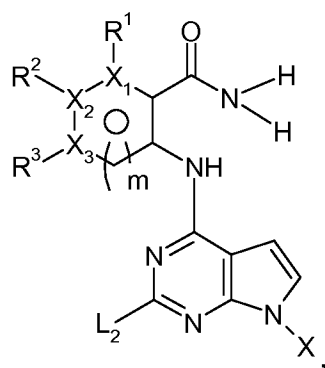


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with a compound of formula (II),



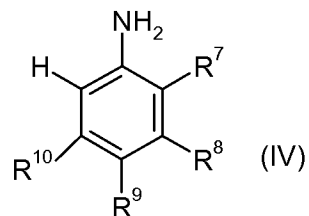
in the presence of a tertiary amine to form intermediate (V)



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wherein L_1 and L_2 are leaving groups, X is a protecting group, and R^1 , R^2 , and R^3 are as described above;

then reacting intermediate (V) with a compound of formula (IV)



10

in the presence of an acid, a catalyst, and a polar protic solvent having low nucleophilicity, under heat, wherein R^7 , R^8 , R^9 , and R^{10} are as described above;

then reacting the product of the preceding step with an amine-containing heteroatom nucleophile in solvent; and

15

then removing the protecting group X with a base in solvent.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms "alkyl" (and "alkylene") refer to straight or branched hydrocarbon chains containing from 1 to 6 carbon atoms, unless a different number of atoms is specified. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, and tert-butyl. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylene, and isobutylene. "Alkyl" also includes substituted alkyl. The alkyl (and alkylene) groups may be optionally substituted one or more times with a halogen or hydroxyl. Thus, the term "alkyl" may include for example, trifluoromethyl and trifluoroethyl, among other halogenated alkyls, and hydroxymethyl and other hydroxylated alkyls when specified.

As used herein, the term "alkenyl" (and "alkylene") refers to straight or branched hydrocarbon chains containing from 2 to 6 carbon atoms, unless a different number of atoms is specified, and at least one and up to three carbon-carbon double bonds.

Examples of "alkenyl" as used herein include, but are not limited to ethenyl and propenyl. Examples of "alkenylene" as used herein include, but are not limited to, ethenylene, propenylene and butenylene. "Alkenyl" (and "alkenylene") also may include substituted alkenyl. The alkenyl groups may optionally be substituted one or more times with a halogen or hydroxyl, as specified.

As used herein, the term "alkynyl" refers to straight or branched hydrocarbon chains containing from 2 to 6 carbon atoms, unless a different number of atoms is specified, and at least one and up to three carbon-carbon triple bonds. Examples of "alkynyl" as used herein include, but are not limited to ethynyl and propynyl. "Alkynyl" may also include substituted alkynyl. The alkynyl groups may optionally be substituted one or more times with a halogen or hydroxyl, as specified.

As used herein, the term "cycloalkyl" refers to a saturated monocyclic carbocyclic ring having from 3 to 6 carbon atoms, unless a different number of atoms is specified. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. "Cycloalkyl" also includes substituted cycloalkyl. The cycloalkyl may optionally be substituted on any available carbon with one or more substituents selected from the group consisting of alkoxy, halo, and haloalkyl, e.g., perfluoroalkyl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

As used herein, the term "alkoxy" refers to the group -O-alkyl, where alkyl is as defined above. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and t-butoxy. "Alkoxy" also includes substituted alkoxy. The alkoxy groups may be optionally substituted one or more times with a halogen.

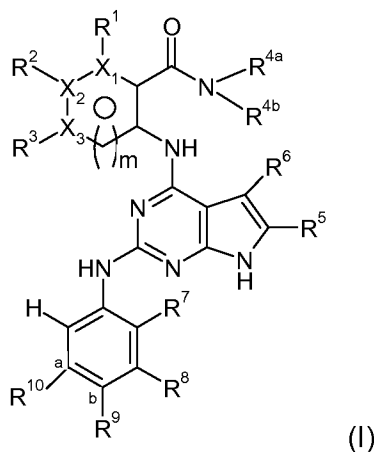
The term "aryl" refers to monocyclic carbocyclic groups and fused bicyclic carbocyclic groups having from 6 to 10 carbon atoms, unless a different number of atoms is specified, and having at least one aromatic ring. Examples of particular aryl groups include but are not limited to phenyl and naphthyl. One particular aryl group according to the invention is phenyl.

The term "heterocycle", "heterocyclic ring", or "heterocyclyl" refers to a mono- or poly-cyclic ring system containing optionally one or more degrees of unsaturation and also containing one or more heteroatoms. Heteroatoms may include N, O, and/or S. Preferred heteroatoms are N and O, particularly N. The heterocycle is three to ten-membered and is either saturated or has one or more degrees of unsaturation. Heterocycles may be optionally fused to one or more of another heterocyclic ring, heteroaryl ring, aryl ring, or cycloalkyl ring. Examples of heterocyclic groups include, e.g. indole, indoline, isoquinoline.

The term "pharmaceutically acceptable derivative" refers to salts and solvates of the selected compound.

The term "solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

As stated above, according to the main embodiment, the present invention provides a compound of formula (I):



5 or a pharmaceutically acceptable salt or solvate thereof wherein:

R^{4a} and R^{4b} are each independently selected from H, alkyl_{C1-C6}, -OH, -alkylene_{C1-C6}-OH, -alkylene_{C1-C6}-phenyl (optionally substituted with a halo), and -alkylene_{C1-C6}-C(O)NH₂;

one or two of X^1 , X^2 , and X^3 are independently selected from N, O, and S, while the remaining one or two of X^1 , X^2 , and X^3 are C;

m is 0 or 1;

R^1 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^1 is C, otherwise R^1 is absent;

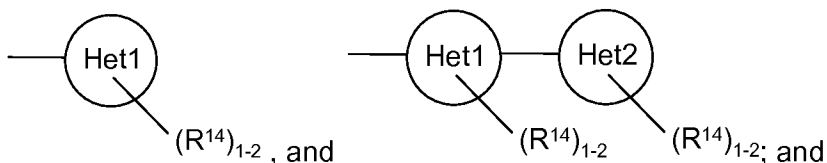
R^2 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^2 is C, otherwise R^2 is absent;

R^3 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^3 is C, otherwise R^3 is absent;

R^7 is selected from alkyl_{C1-C6}, -O-alkyl_{C1-C6}, halo, -NR²²R²³, and -O-alkylene_{C1-C6}-halo₁₋₃;

R^8 is selected from H, halo, and alkyl_{C1-C6};

one of R^9 and R^{10} is selected from -alkylene_{C1-C6}-SO₂-alkyl_{C1-C6}, -N-alkylene_{C0-C6}-C(O)-alkylene_{C0-C6}-NR²²R²³, -O-alkylene_{C0-C6}(optionally substituted with -OH)-NR²²R²³,



the other of R^9 and R^{10} is selected from H, alkyl_{C1-C6}, -O-alkyl_{C1-C6}, and halo;

wherein Het1 and Het2 are each independently a five or six membered heterocyclic ring
having an N atom and optionally one or two additional heteroatoms selected from
5 N and O, and

each R^{14} is independently selected from H, OH, halo, alkyl_{C1-C6}, -O-alkyl_{C1-C6},
-cyclopropyl, -C(O)-alkyl_{C1-C6}, SO₂-alkyl_{C1-C6}, -(CH₂)₁₋₄-halo, and
-(CH₂)₁₋₄-SO₂-alkyl_{C1-C6}; -C(O)-alkylene_{C0-C6}-NR²²R²³, -NR²²R²³;

or

10 R^9 and R^{10} , together with the atoms to which they are attached form a five, six, or seven-membered heterocyclic ring containing one or two N atom and the remainder C atoms, wherein at least one N atom is substituted with R^{15} , and the C atoms of the heterocyclic ring are optionally substituted with (R¹⁹)₁₋₂;

15 wherein R^{15} is selected from H, -alkyl_{C1-C4}, -alkylene_{C1-C4}-halo,
-C(O)-alkylene_{C0-C6}-NR²²R²³, -C(O)-alkyl_{C1-C6}, -alkylene_{C1-C4}-NR²²R²³,
-alkylene_{C1-C4}-C(O)-NR²²R²³, -C(O)-alkylene_{C1-C4}-O-alkyl_{C1-C6}, -C(O)-pyrrolidine,
and -C(O)-pyrrolidine-alkyl_{C1-C6}; and,

each R^{19} is independently selected from H and alkyl_{C1-C6};

20 each R^{22} is selected from H, alkyl_{C1-C6}, -O-alkyl_{C1-C6}, -alkylene_{C1-C6}-O-alkyl_{C1-C6}; and,

each R^{23} is selected from H and alkyl_{C1-C6}; or

R^{22} and R^{23} combine to form a four, five, or six membered, heterocyclic ring containing
25 the N atom to which they are attached and optionally an additional heteroatom selected from N and O, wherein the ring is optionally substituted with -OH or -alkyl_{C1-C6}.

According to an alternative embodiment of the invention, R^7 is -O-alkyl_{C1-C6} and
30 the remaining substituents are as described above in the main embodiment.

According to another embodiment, R^7 is -O-alkyl_{C1-C6}, R^{10} is H, and the remaining substituents are as described above in the main embodiment.

According to another embodiment, R^7 is $-O\text{-alkyl}_{C1-C6}$, m is 0, $X1$ is S, $X2$ and $X3$ are C, and the remaining substituents are as described above in the main embodiment.

According to another embodiment, R^7 is $-O\text{-alkyl}_{C1-C6}$; m is 0, $X1$ is O, $X2$ and $X3$ are C, and the remaining substituents are as described above in the main embodiment.

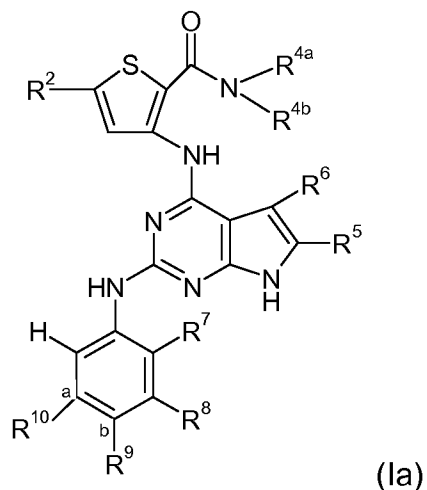
According to another embodiment, R^7 is $-O\text{-alkyl}_{C1-C6}$; m is 0, $X1$ is C, $X2$ is S, $X3$ is C, and the remaining substituents are as described above in the main embodiment.

According to another embodiment, R^7 is $-O\text{-alkyl}_{C1-C6}$; m is 1, $X1$ is N, $X2$ and $X3$ are C, and the remaining substituents are as described above in the main embodiment.

According to another embodiment, the substituents are as described in the above embodiments, respectively, wherein R^7 is $-O\text{-methyl}$.

According to another embodiment, R^5 and R^6 are H, and the remaining substituents are as described above in the main embodiment.

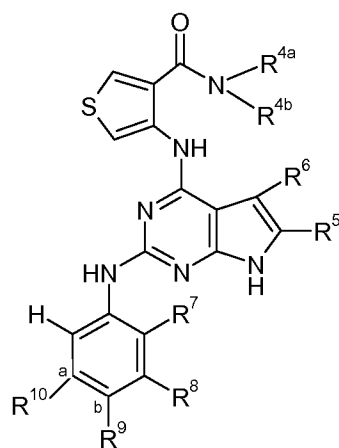
According to another embodiment, the compound is of formula (Ia):



wherein the substituents are as described above in the main embodiment.

According to another embodiment, the compound is of formula (Ib):

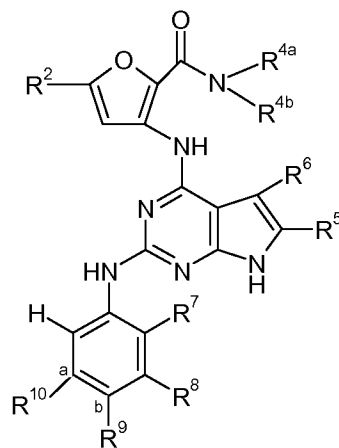
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(Ib)

wherein the substituents are as described above in the main embodiment.

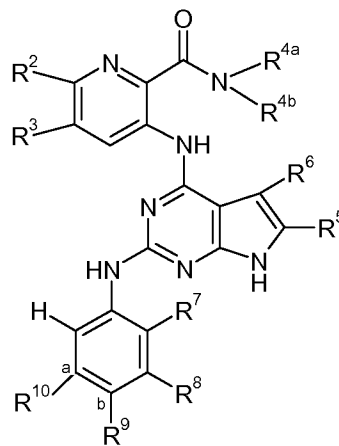
According to another embodiment, the compound is of formula (Ic):



(Ic)

5 wherein the substituents are as described above in the main embodiment.

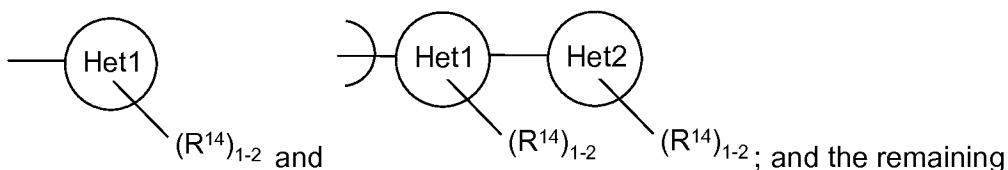
According to another embodiment, the compound is of formula (Id):



(Id)

wherein the substituents are as described above in the main embodiment.

According to another embodiment, R^{10} is H and R^9 is selected from

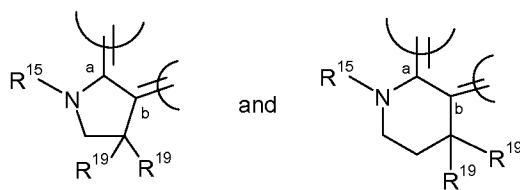


5 substituents are as described above in the main embodiment.

According to another embodiment of the invention, R^9 and R^{10} , together with the atoms to which they are attached form a five, six, or seven-membered heterocyclic ring containing one or two N atom and the remainder C atoms, wherein at least one N atom is substituted with R^{15} , and the C atoms of the heterocyclic ring are optionally substituted with one or more groups selected from $(R^{19})_{1-2}$, and the remaining substituents are as described above in the main embodiment.

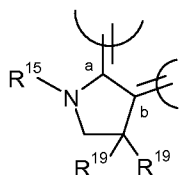
According to another embodiment, R^9 and R^{10} , together with the atoms to which they are attached form a five, six, or seven-membered heterocyclic ring containing one or two N atom and the remainder C atoms, wherein at least one N atom is substituted with R^{15} , and the C atoms of the heterocyclic ring are optionally substituted with one or more groups selected from $(R^{19})_{1-2}$, R^7 is $-O\text{-alkyl}_{C1-C6}$, and the remaining substituents are as described above in the main embodiment.

20 According to an alternative embodiment of the invention, R^9 and R^{10} , together with the atoms to which they are attached form a five or six-membered heterocyclic ring selected from

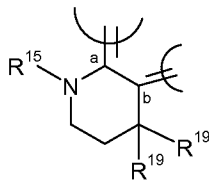


25 According to another embodiment, R^9 and R^{10} , together with the atoms to which they are attached form a five or six-membered heterocyclic ring selected from

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and

, R^7 is $-O\text{-alkyl}_{C1-C6}$, and the

remaining substituents are as described above in the main embodiment.

With regard to each of the invented compounds, substitution at the R^7 position is favorable and has generally been found to boost IGF1R potency in comparison to otherwise similar compounds that are unsubstituted at the R^7 position. Further, substitution at the R^7 position has been found to increase selectivity over other kinases, for instance the Aurora A and Aurora B kinase, which is often desirable.

It is to be understood that the present invention includes all combinations and subsets of the particular groups defined herein, including the substituents as defined in the Summary defined hereinabove, as illustrated in the various examples throughout the specification, and as recited in the attached claims.

Specific examples of compounds of the present invention include those recited in the Examples which follow, and pharmaceutically acceptable salts or solvates thereof.

It will be appreciated by those skilled in the art that the compounds of the present invention may be utilized in the form of a pharmaceutically acceptable salt or solvate.

The pharmaceutically acceptable salts of the compounds of formula (I) include conventional salts formed from pharmaceutically acceptable (i.e., non-toxic) inorganic or organic acids or bases as well as quaternary ammonium salts. Representative salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. Other salts, such as oxalic, which are not themselves pharmaceutically acceptable, may be

useful in the preparation of salts useful as intermediates in obtaining compounds of this invention and these form a further aspect of the invention.

Processes for preparing pharmaceutically acceptable salts and solvates of compounds such as the compounds of formula (I) are conventional in the art. See, e.g.,
5 Burger's Medicinal Chemistry And Drug Discovery 5th Edition, Vol 1: Principles And Practice.

As will be apparent to those skilled in the art, in the processes described below for the preparation of compounds of formula (I) certain intermediates may be in the form of pharmaceutically acceptable salts or solvates of the compound. Those terms as
10 applied to any intermediate employed in the process of preparing compounds of formula (I) have the same meanings as noted above with respect to compounds of formula (I). Processes for preparing pharmaceutically acceptable salts and solvates of intermediates are known in the art and are analogous to the process for preparing pharmaceutically acceptable salts and solvates of compounds such as the compounds of formula (I).

15 The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they
20 may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. It is understood
25 that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure
30 and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

The compounds of the present invention are inhibitors of one or more IGFR family receptors. By "IGFR inhibitor" is meant a compound which exhibits a pIC_{50} of greater than 5.5 against at least one IGFR family receptor in the IGFR inhibition enzyme assay described below (TR-FRET) and/or an IC_{50} of below about 1.0 μM potency against IGFR cellular autophosphorylation and/or in cell proliferation of a cell line that is dependent upon IGF signaling (e.g. Colo205, NCI-H929) in at least one of the cellular assay described below. In a more particular embodiment "IGFR inhibitor" refers to a compound which exhibits a pIC_{50} of greater than 7.6 against at least one IGFR family receptor in the IGFR inhibition enzyme assay described below. In an alternative particular embodiment "IGFR inhibitor" refers to a compound which exhibits an IC_{50} of below about 250 nM potency against IGFR cellular autophosphorylation and/or in cell proliferation of a cell line that is dependent upon IGF signaling (e.g. Colo205, NCI-H929) in at least one of the cellular assay described below.

The present invention is not limited to compounds of formula (I) which are selective for IGFR family receptor kinases; rather, the present invention expressly contemplates compounds of formula (I) which may also possess activity against receptors in addition to the IGFR family receptors. For instance, the compounds of formula (I) are selective for insulin receptor (IR) family kinases. Several compounds of the present invention also possess activity against, for instance, one or more of the Jnk1, Jnk2, and Jnk3, anaplastic lymphoma kinase (ALK), and insulin related receptor (IRR).

The present invention further provides compounds of formula (I) for use in medical therapy in a mammal, e.g. a human. In particular, the present invention provides compounds of formula (I) for use in the treatment of a condition mediated by at least one IGFR family receptor in a mammal, and, advantageously, conditions mediated by inappropriate activity of one or more IGFR family receptor in a mammal.

The inappropriate IGFR family receptor activity referred to herein is any IGFR receptor activity that deviates from the normal IGFR family receptor activity expected in a particular mammalian subject. Inappropriate IGFR family receptor activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and/or control of IGFR family receptor activity. Such inappropriate activity may result then, for example, from overexpression or mutation of the protein kinase or ligand leading to inappropriate or uncontrolled activation of the receptor. Furthermore, it is also

understood that unwanted IGFR family receptor activity may reside in an abnormal source, such as a malignancy. That is, the level of IGFR family activity does not have to be abnormal to be considered inappropriate, rather the activity derives from an abnormal source.

5 The compounds of formula (I) and salts and solvates thereof, are believed to have anticancer and antitumor activity as a result of inhibition of one or more IGFR family receptor and its effect on selected cell lines whose growth is dependent on IGFR family activity.

10 The present invention provides compounds of formula (I) for use in the treatment of a susceptible neoplasm. "Susceptible neoplasm" as used herein refers to neoplasms which are susceptible to treatment with a IGFR inhibitor. Neoplasms which have been associated with inappropriate activity of one or more IGFR family receptors and are therefor susceptible to treatment with a IGFR inhibitor are known in the art, and include both primary and metastatic tumors and cancers. For example, susceptible neoplasms
15 within the scope of the present invention include but are not limited to breast cancer, sarcomas, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers (including multiple myeloma), neuroblastomas, gliomas, head and neck cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer,
20 testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor, and skin cancer (including melanoma). More particularly, susceptible neoplasms may be selected from breast cancer, sarcoma, lung cancer, non-small cell lung carcinoma, prostate cancer, colorectal cancer, pancreatic cancer, hematologic cancers, multiple
25 myeloma, head and neck cancer, and ovarian cancer.

 The present invention provides methods for the treatment of several conditions in a mammal in need thereof, all of which comprise the step of administering a therapeutically effective amount of a compound of formula (I). The mammal in need of treatment with a compound of the present invention is advantageously a human.

30 As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression of the condition and preventing or delaying the reoccurrence of the condition in a previously afflicted subject.

As used herein, the term “therapeutically effective amount” means an amount of a compound of formula (I) which is sufficient, in the subject to which it is administered, to elicit the biological or medical response of a cell culture, tissue, system, mammal (including human) that is being sought, for instance, by a researcher or clinician. The term also includes within its scope amounts effective to enhance normal physiological function. For example, a therapeutically effective amount of a compound of formula (I) for the treatment of a condition mediated by at least one IGFR family receptor is an amount sufficient to treat the condition in the subject. Similarly, a therapeutically effective amount of a compound of formula (I) for the treatment of a susceptible neoplasm is an amount sufficient to treat the susceptible neoplasm in the subject. In one embodiment of the present invention, a therapeutically effective amount of a compound of formula (I) is an amount sufficient to regulate, modulate, bind or inhibit at least one IGFR family receptor.

The precise therapeutically effective amount of the compounds of formula (I) will depend on a number of factors including, but not limited to, the age and weight of the subject being treated, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. Typically, the compound of formula (I) will be given for treatment in the range of 0.1 to 200 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 100 mg/kg body weight per day. Acceptable daily dosages, may be from about 0.1 to about 2000 mg/day, and preferably from about 0.1 to about 100 mg/day. Thus, for a 70kg adult human being treated for a condition mediated by at least one IGFR family receptor, the actual amount per day would usually be from 5 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day or, alternatively, on an alternative dosing schedule such as weekly or monthly, such that the total daily dose is the same. A therapeutically effective amount of a salt or solvate, may be determined as a proportion of the therapeutically effective amount of the compound of formula (I) *per se*. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

The present invention also provides the use of a compound of formula (I) for the preparation of a medicament for the treatment of condition mediated by at least one IGFR family receptor in a mammal (e.g., a human) in need thereof. The present

invention further provides the use of a compound of formula (I) for the preparation of a medicament for the treatment of a susceptible neoplasm in a mammal.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of formula (I) may be administered as the raw chemical, it is typically

presented as the active ingredient of a pharmaceutical composition or formulation.

Accordingly, the invention further provides a pharmaceutical composition comprising a compound of the formula (I). The pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers, diluents, and/or excipients. The carrier(s), diluent(s) and/or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I) with one or more pharmaceutically acceptable carriers, diluents and/or excipients.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc,

magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous

solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural
5 sweeteners or saccharin or other artificial sweeteners, and the like can also be added. Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

10 The compounds of formula (I) may be administered by inhalation, such as by metered dose pressurised aerosols, metered dose inhalers, dry powder inhalers, nebulizers or insufflators.

According to one embodiment, the compound is provided in the form of a dry powder composition. As such, the composition is suitable for inhaled administration and
15 may be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of the dry powder composition may be administered by inhalation via a device such as the DISKUSTM device, marketed by GlaxoSmithKline. The DISKUSTM inhalation device is, for example,
20 described in GB2242134A.

According to another embodiment, the compounds of formula (I) may be formulated into spray compositions for inhalation which may, for example, be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler (MDI), with the use of a suitable liquefied propellant.
25 Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. The
30 aerosol composition may optionally contain additional formulation excipients well known in the art such as surfactants e.g. oleic acid, lecithin or an oligolactic acid derivative e.g. as described in WO94/21229 and WO98/34596 and cosolvents e.g. ethanol.

The compounds of formula (I) can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

5 The compounds of formula (I) may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide -phenol, polyhydroxyethylaspartamidephenol, or
10 polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

15 Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

20 Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated
25 in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable
30 carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations. Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation near isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

In the above-described methods of treatment and uses, a compound of the invention may be employed alone, in combination with one or more other compounds of the invention, or in combination with other therapeutic methods or agents. In particular, in methods of treating a condition improved by inhibition of IGF-1R and in methods of treating susceptible neoplasms, the compound of the invention may be used alone or in

combination with one or more of a chemotherapeutic, a hormonal and/or antibody agent, surgical therapy, and radiotherapy.

The term "chemotherapeutic" as used herein refers to any chemical agent having a therapeutic effect on the subject to which it is administered. "Chemotherapeutic" agents include but are not limited to anti-neoplastic agents, analgesics and anti-emetics. As used herein, "anti-neoplastic agents" include both cytostatic and cytotoxic agents. Anti-emetics include but are not limited to 5HT₃ antagonists such as ondansetron, granisetron, and the like; metaclopramide; dexamethasone and neurokinin-1 antagonists.

As an additional aspect, the present invention provides the methods of treatment and uses as described above, which comprise administering a compound of the invention together with at least one chemotherapeutic agent. In one particular embodiment, the chemotherapeutic agent is an anti-neoplastic agent. In another embodiment, the present invention provides a pharmaceutical composition as described above further comprising at least one other chemotherapeutic agent, more particularly, the chemotherapeutic agent is an anti-neoplastic agent.

The compounds of the invention and at least one additional anti-neoplastic therapy may be employed in combination concomitantly or sequentially in any therapeutically appropriate combination. The administration of a compound of the invention with one or more other anti-neoplastic agents may be in combination in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including both or all compounds or (2) separate pharmaceutical compositions each including one of the compounds. The combination may be administered separately in a sequential manner wherein one anti-neoplastic agent is administered first and the other(s) second or vice versa. Such sequential administration may be close in time or remote in time.

When a compound of the invention is used in combination with a chemotherapeutic agent, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. The appropriate dose of the compound(s) of the invention and the other therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect, and are within the expertise and discretion of the attendant clinician.

Among the many chemotherapeutic agents, which may be used in combination with a compound of the present invention, are anti-proliferative/anti-neoplastic agents. Anti-neoplastic agents may induce anti-neoplastic effects in a cell-cycle specific manner, i.e., are phase specific and act at a specific phase of the cell cycle, or bind DNA and act in a non cell-cycle specific manner, i.e., are non-cell cycle specific and operate by other mechanisms. Both types of anti-neoplastic agents may be employed in combination with the compounds of the present invention.

Typically, any chemotherapeutic agent that has activity against a susceptible neoplasm being treated may be utilized in combination with the compounds the invention, provided that the particular agent is clinically compatible with therapy employing a compound of the invention. Typical anti-neoplastic agents useful in the present invention include, but are not limited to: alkylating agents, anti-metabolites, antitumor antibiotics, antimitotic agents, topoisomerase I and II inhibitors, hormones and hormonal analogues, matrix metalloprotease inhibitors; signal transduction pathway inhibitors including inhibitors of cell growth or growth factor function, angiogenesis inhibitors, and serine/threonine inhibitors; cyclin dependent kinase inhibitors; antisense therapies and immunotherapeutic agents.

Examples of alkylating agents include but are not limited to: nitrogen mustards such as cyclophosphamides, temozolamide, melphalan, and chlorambucil; oxazaphosphor-ines; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; triazenes such as dacarbazine; and platinum coordination complexes such as cisplatin, oxaplatin and carboplatin.

Examples of antimetabolite anti-neoplastic agents include purine and pyrimidine analogues and anti-folate compounds, and more specifically, hydroxyurea, cytosine, arabinoside, raltitrexed, tegafur, fluorouracil (e.g., 5FU), methotrexate, cytarabine, mecapurine and thioguanine.

Examples of antitumor antibiotic agents include, but are not limited to, actinomycins such as dactinomycin, mitomycin-C, anthracyclins such as daunorubicin, doxorubicin, idarubicin, epirubicin; daunomycin, adriamycin and bleomycins.

Examples of antimitotic agents include, but are not limited to, diterpenoids, vinca alkaloids, polo-like kinase (PLK) inhibitors and CenpE inhibitors. Examples of diterpenoids include, but are not limited to, taxol, taxotere, paclitaxel and its analog

docetaxel. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, vindesine and vinorelbine. PLK inhibitors are discussed further below.

Examples of topoisomerase I inhibitors include camptothecins, such as amsacrine, irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-
5 methylene)-10,11-ethylenedioxy-20-camptothecin. Examples of topoisomerase II inhibitors include epipodophyllotoxins, such as etoposide and teniposide.

Examples of hormones and hormonal analogues believed to be useful in the treatment of neoplasms include, but are not limited to: antiestrogens, such as tamoxifen, toremifene, raloxifene, fulvestrant, idoxifene and droloxifene;

10 anti-androgens; such as flutamide, nilutamide, bicalutamide and cyproterone acetate; adrenocorticosteroids such as prednisone and prednisolone; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrozole, vorazole, and exemestane; progestrins such as megestrol acetate; 5 α -reductase inhibitors such as finasteride and dutasteride; and gonadotropin-releasing hormones (GnRH) and analogues thereof, such
15 as Leutinizing Hormone-releasing Hormone (LHRH) agonists and antagagonists such as goserelin luprolide, leuporelin and buserelin.

An example of a matrix metalloproteinases (MMP) inhibitor is marimastat.

Signal transduction pathway inhibitors useful in the present invention include, but are not limited to, inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases,
20 SH2/SH3 domain blockers, serine/threonine kinases, phosphatidyl inositol-3-OH kinases, myo-inositol signaling, and Ras oncogenes (e.g. farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy).

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl
25 residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Examples of receptor tyrosine kinases, also known as "growth factor receptor inhibitors", in addition to IGF-1R inhibitors, include but are not limited to inhibitors of: epidermal growth factor family receptors (EGFR, ErbB2, and ErbB4); platelet derived
30 growth factor receptors (PDGFRs), vascular endothelial growth factor receptors (VEGFRs), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), macrophage colony stimulating factor (c-fms), c-kit, c-met, fibroblast growth factor receptors (FGFRs), hepatocyte growth factor receptors (HGFRs),

Trk receptors (TrkA, TrkB, and TrkC), ephrin (Eph) receptors, the RET protooncogene, and Akt kinases.

Several inhibitors of growth factor receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors, anti-sense oligonucleotides and aptamers. Any of these growth factor receptor inhibitors may be employed in combination with the compounds of the present invention in any of the compositions and methods/uses described herein. Trastuzumab (Herceptin®) is an example of an anti-erbB2 antibody inhibitor of growth factor function. One example of an anti-erbB1 antibody inhibitor of growth factor function is cetuximab (ErbixTM, C225). Examples of small molecule inhibitors of epidermal growth factor receptors include but are not limited to lapatinib (TykerbTM), erlotinib (TARCEVA®), gefitinib (IRESSA®), canetinib or CI1033. Imitanib is one example of a PDGFR inhibitor. Examples of VEGFR inhibitors include pazopanib, ZD6474, AZD2171, PTK787, SU11248 and sunitinib.

Tyrosine kinases that are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Inhibitors of non-receptor tyrosine kinases are sometimes referred to as “anti-metastatic agents” and are useful in the present invention. Targets or potential targets of anti-metastatic agents, include, but are not limited to, c-Src, Lck, Fyn, Yes, Jak, abl kinase (c-Abl and Bcr-Abl), FAK (focal adhesion kinase) and Bruton's tyrosine kinase (BTK). Non-receptor kinases and agents, which inhibit non-receptor tyrosine kinase function, are described in Sinha, S. and Corey, S.J., (1999) J. Hematother. Stem Cell Res. 8:465–80; and Bolen, J.B. and Brugge, J.S., (1997) Annu. Rev. of Immunol. 15:371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, but not limited to, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. Examples of Src inhibitors include but are not limited to dasatinib and BMS-354825 (J.Med.Chem (2004) 47:6658-6661).

Examples of serine/threonine kinase inhibitors include, but are not limited to polo-like kinase inhibitors (Plk family e.g., Plk1, Plk2, and Plk3), such as 5-{6-[(4-Methylpiperazin-1-yl)methyl]-1H-benzimidazol-1-yl}-3-[(1R)-1-[2-(trifluoromethyl)phenyl]ethoxy]thiophene-2-carboxamide; MAP kinase cascade blockers, which include Ras/Raf kinase inhibitors, mitogen or extracellular regulated kinases (MEKs), and extracellular regulated kinases (ERKs); Aurora kinase inhibitors (including

inhibitors of Aurora A and Aurora B); protein kinase C (PKC) family member blockers; inhibitors of kappa-B (IkB) kinase family (IKK-alpha, IKK-beta); PKB/Akt kinase family inhibitors; and inhibitors of TGF-beta receptor kinases. Examples of Plk inhibitors are described in PCT Publication No. WO04/014899 to GlaxoSmithKline.

5 Inhibitors of urokinase, also referred to as urokinase-type Plasminogen Activator (uPA), expression may be used in combination with the compounds of the present invention in the compositions and methods described above.

 Inhibitors of kinases involved in the IGF signalling axis may also be useful in combination with the compounds of the present invention. Such inhibitors include but
10 are not limited to inhibitors of JNK1/2/3, PI3K, AKT and MEK, and 14.3.3 signalling inhibitors.

 Cell cycle signaling inhibitors, including inhibitors of cyclin dependent kinases (CDKs) are also useful in combination with the compounds of the invention in the compositions and methods described above. Examples of cyclin dependent kinases,
15 including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania G. R., et al., Exp. Opin. Ther. Patents (2000) 10:215-230.

 Receptor kinase angiogenesis inhibitors may also find use in the present invention. Inhibitors of angiogenesis related to VEGFR and TIE-2 are discussed above in regard to signal transduction inhibitors (both are receptor tyrosine kinases). Other
20 inhibitors may be used in combination with the compounds of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin ($\alpha_v\beta_3$) that inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the compounds of the invention. One example of a VEGFR antibody is
25 bevacizumab (AvastinTM).

 Inhibitors of phosphatidylinositol-3-OH kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku may also be useful in combination with the present invention.

 Also of potential use in combination with the compounds of the invention are
30 myo-inositol signaling inhibitors such as phospholipase C blockers and myoinositol analogues.

Examples of antisense therapies include those directed towards the targets described above such as ISIS 2503 and gene therapy approaches such as those using thymidine kinase or cytosine deaminase.

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of the invention. Immunotherapeutic regimens include ex-vivo and in-vivo approaches to increasing immunogenicity of patient tumor cells such as transfection with cytokines (IL-2, IL-4, GM-CSF and M-CSF), approaches to increase T-cell activity, approaches with transfected immune cells and approaches with anti-idiotypic antibodies.

Agents used in proapoptotic regimens (e.g., Bcl-2 antisense oligonucleotides) may also be used in combination with the compounds of the invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of Bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the Bcl-2 family (i.e., bcl-1). Therefore, strategies designed to downregulate the expression of Bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for Bcl-2 are discussed in Water, J.S., et al., J. Clin. Oncol. (2000) 18:1812-1823; and Kitada, S., et al., Antisense Res. Dev. (1994) 4:71-79.

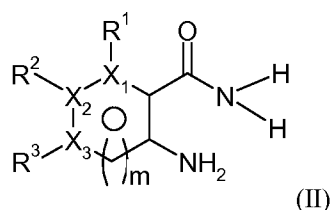
Compounds of formula (I) may be prepared using the processes described below. In all of the schemes described below, it is understood that protecting groups may be employed where necessary in accordance with general principles known to those of skill in the art, for example, see T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons. These groups may be removed at a convenient stage of the compound synthesis using methods known to those of skill in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I).

The invention also provides a process for preparing the compound of formula (I) and pharmaceutically acceptable derivatives thereof. Specifically, compounds of formula (I) are prepared by reacting the three main components of the compounds, referred to herein as the head, core, and tail of the compounds.

Synthesis and Schemes

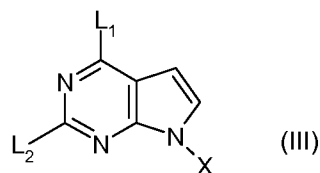
Each compound of formula (I) may be conveniently prepared by separately preparing three constituents of the compound and subsequently combining those constituents to form the compound (I). For convenience, the three constituents are referred to herein as the head (II), the core (III), and the tail (IV). For convenience, the head, core, and tail nomenclature is used throughout to refer to each constituent when referred to individually, and also to refer to the corresponding moiety when described in the context of head/core, tail/core, and/or head/core/tail combinations.

The head component of the invented compounds is an o-amino carboxamide represented by formula (II):



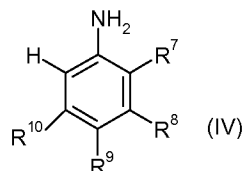
wherein substituents R¹, R², and R³ are as defined above.

The core component of the invented compounds is pyrrolopyrimidine represented by formula (III):



wherein each of substituents L₁ and L₂ represent a leaving group, e.g. a halogen, preferably chlorine, or OTF, and X represents a protecting group, e.g. sulfonamide or alcoholated alkyl, e.g. allyl, benzyl, or SEM.

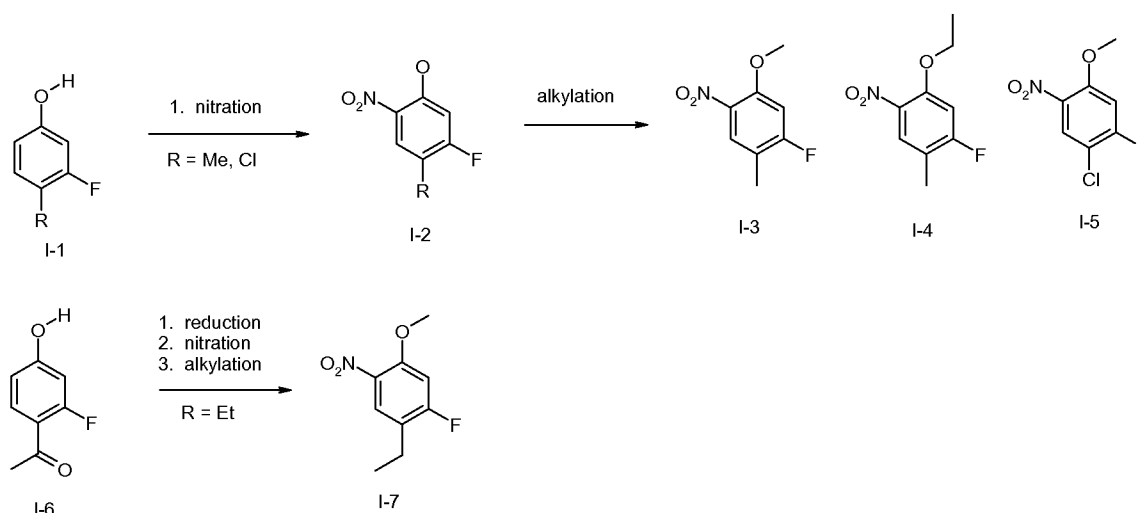
The tail component of the invented compounds is a substituted aniline represented by formula (IV):



wherein substituents R⁷, R⁸, R⁹, and R¹⁰ are as defined above.

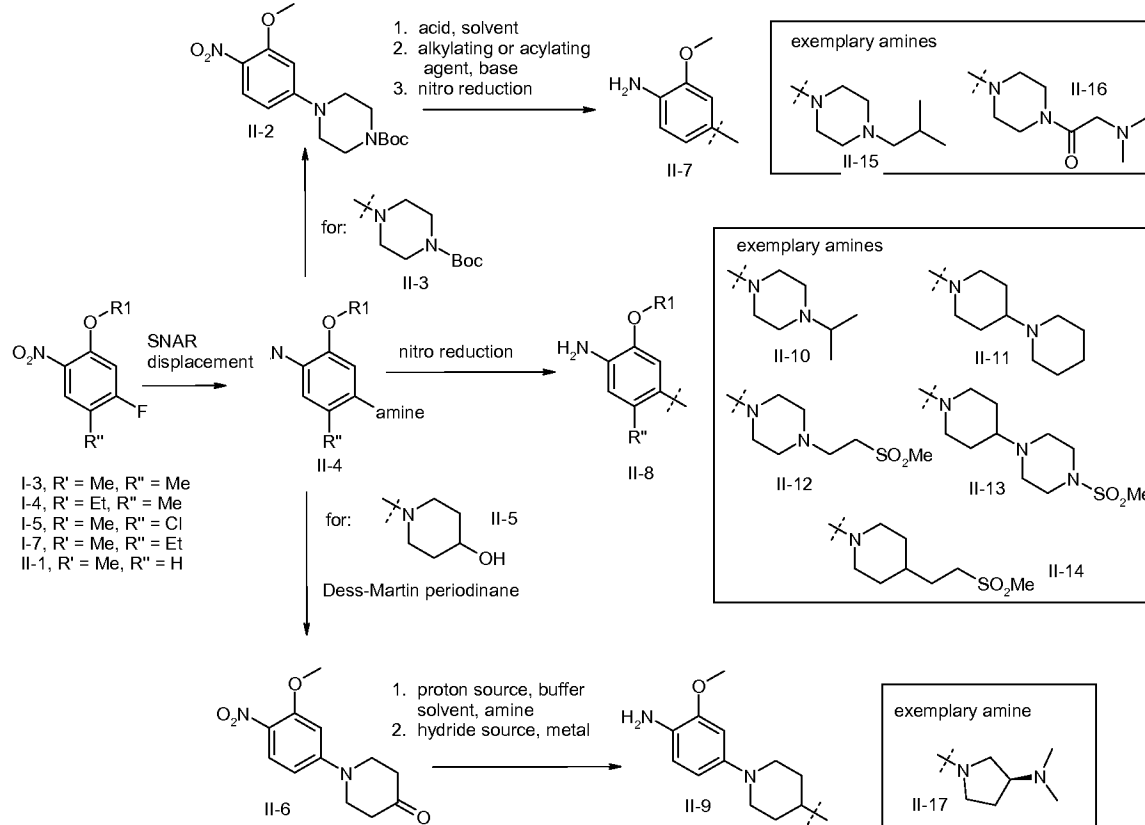
The head (II), core (III), and tail (IV) of the compounds may be synthesized and combined, for instance, with the synthetic routes shown below:

Scheme 1: Preparation of Aryl Precursors



As shown in Scheme 1, some requisite aniline precursors can be prepared from commercially available phenols such as I-1 (R = Me & Cl from 3B Scientific Corporation) and I-6 (VWR International). Nitration of phenol I-1 in a solvent (i.e. dichloromethane or dichloroethane), with a nitrating agent (i.e. nitric acid) and phase-transfer catalyst (tetrabutylammonium bromide) affords the corresponding nitro-benzene I-2. Alkylation with an alkyl halide (i.e. methyl iodide, ethyl iodide), base (potassium carbonate) and solvent (typically DMF) affords precursors I-3, I-4, and I-5. Alternatively, acetophenone I-6 can be preferentially reduced at the carbonyl carbon (preferably zinc dust/HCl), and subsequently nitrated and alkylated using analogous conditions described for I-1, to afford I-7.

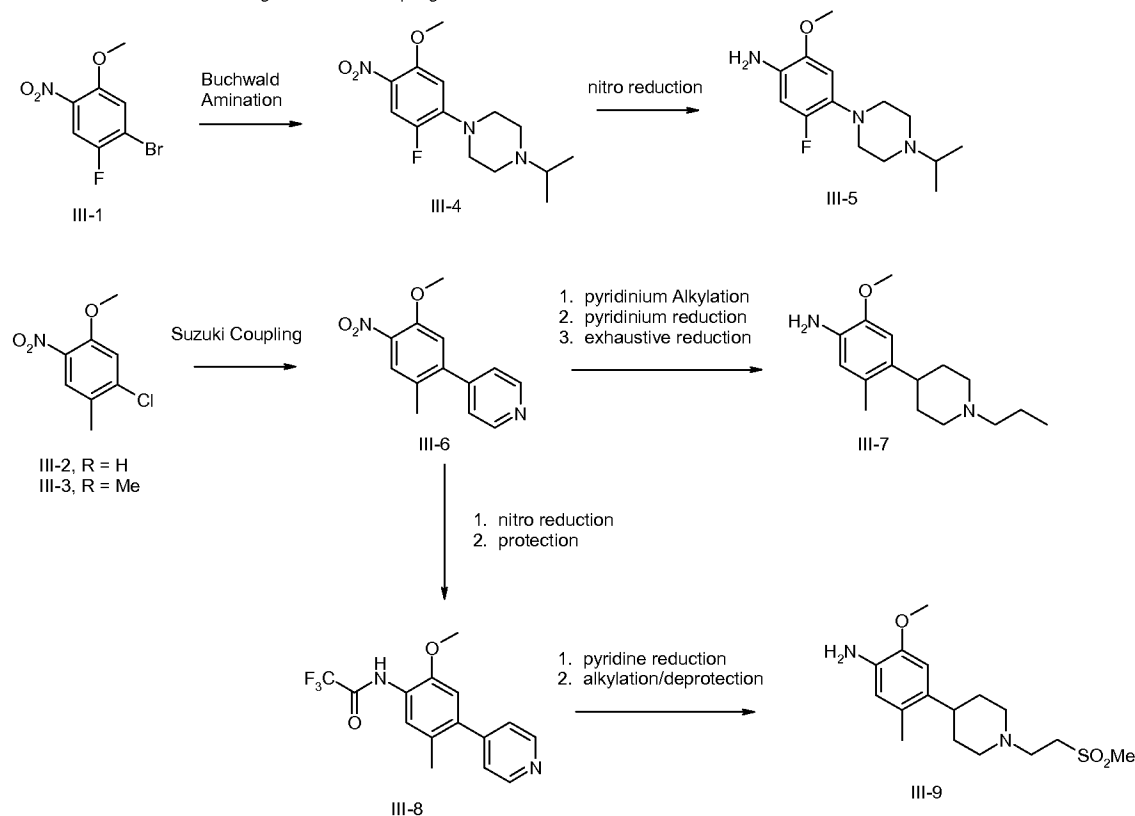
Scheme 2: Tails derived via SNAR Displacements



As shown in Scheme 2, a variety of substituted anilines can be prepared via direct SNAR displacement of 4-fluoro nitrobenzenes I-3, I-4, I-5, I-7, and II-1 (commercially available through Oakwood Products) by addition of base (for example potassium carbonate), solvent (DMF), and a primary or secondary amine (including exemplary amines II-10 through II-14.) Subsequent selective nitro reduction using a catalyst (iron (III) chloride or palladium on carbon), additive (activated carbon), alcoholic or ethereal solvent (MeOH, EtOH, or THF), and reducing agent (hydrogen gas or hydrazine) affords the desired anilines II-8. Alternatively SNAR displacement with a versatile multifunctional amine (including N-Boc piperazine II-3) affords Boc protected nitrobenzene II-2. Boc deprotection with acid (i.e. hydrochloric or trifluoroacetic acid), followed by alkylation at nitrogen with base and an electrophile (potassium carbonate, iso-butyl iodide) or acylation at nitrogen with a base and an electrophile followed by displacement with an amine (triethyl amine, α -Cl acetyl bromide, then dimethyl amine) gives the corresponding nitro-benzenes which may be reduced as described for II-8 to afford the corresponding functionalized anilines II-15 and II-16. Alternatively SNAR

displacement with amino-alcohol II-5 followed by alcohol oxidation using an oxidant (for example Dess-Martin periodinane or the Swern reagent) affords ketone II-6. Reductive amination with a buffered proton source (for example acetic acid with triethyl amine), solvent (dichloroethane), and amine (for example exemplary amine II-17) followed by
5 nitro reduction as described above for intermediate II-8 or with a hydride source (for example sodium borohydride) with added metal (for example NiCl_2) in alcoholic solvent (MeOH) affords the corresponding functionalized aniline II-9.

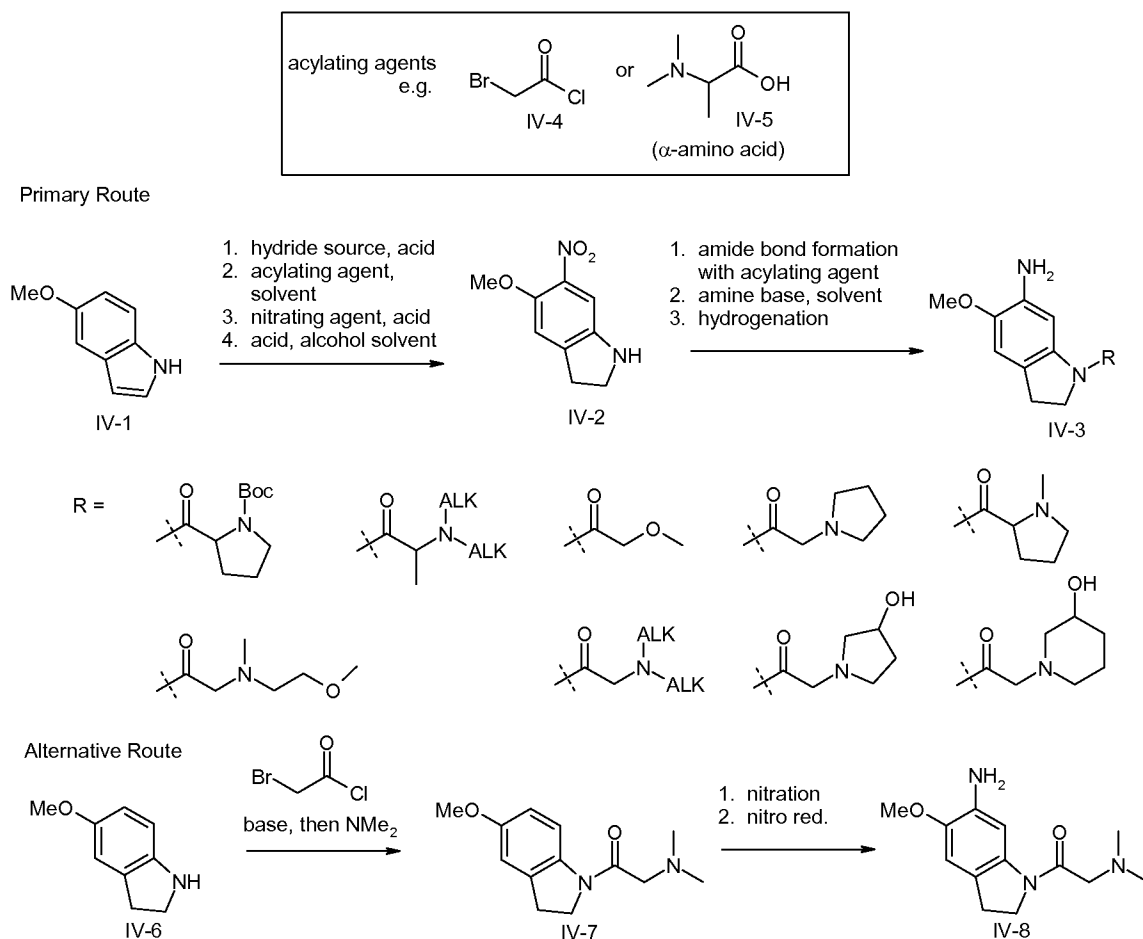
Scheme 3: Tails Derived from Organometallic Coupling Reactions



- 5 Alternatively similarly functionalized anilines may be generated from organometallic coupling reactions as illustrated in Scheme 3. Nitro-benzenze III-1 (see Hirst, Gavin C.; Calderwood, David; Wishart, Neil; Rafferty, Paul; Ritter, Kurt; Arnold, Lee D.; Friedman, Michael M. Preparation of pyrazolopyrimidines as protein kinase inhibitors. PCT Int. Appl.(2001), 527 pp.) can be subjected to Buchwald-Hartwig
- 10 amination conditions including typically a palladium catalyst (i.e. $\text{Pd}_2(\text{dba})_3$), trialkyl amine or inorganic base (i.e. triethyl amine, potassium carbonate, cesium carbonate), a phosphine catalyst (i.e. xantphos), solvent (tertiary butanol, dimethyl formamide, dioxane) and an amine (for example isopropyl piperazine as above) to afford the nitrogen coupled product III-4. Nitro reduction utilizing a metal catalyst (i.e. iron (III)
- 15 chloride), additive (activated carbon), alcoholic solvent (i.e. methanol) and reducing agent (hydrazine) affords functionalized aniline III-5. Alternatively Suzuki coupling protocols involving addition of a palladium catalyst (i.e. $\text{Pd}(\text{PPh}_3)_4$), a boronic acid or

ester (for example piperidyl 4-boronic acid as used in Scheme 3), a solvent mixture (often dioxane or THF in water) with an inorganic base (for example potassium carbonate) affords functional nitrobenzene III-6. Alkylation of III-6 with an electrophile (for example propyl iodide) in high-boiling polar solvent (for example pinacolone) affords the corresponding pyridinium salt. Reduction of this intermediate typically is carried out in two steps, first via reduction of pyridinium by addition of a hydride source (sodium borohydride or sodium cyanoborohydride) in solvent and second via reduction of the in-situ generated olefin and nitro-group using catalyst (palladium on carbon) in an alcoholic or ethereal solvent (THF, MeOH, EtOH) under pressurized hydrogen gas (typically 30-50 psi) affords piperidine analog III-7. Alternatively, selective nitro reduction of III-6 can be carried out with a poisoned hydrogenation catalyst (for example Pt-C with sulphide) under a pressure of hydrogen gas (30-50 psi) to afford the corresponding aniline. Protection of this aniline with a suitable protecting group (i.e. trifluoroacetic anhydride, triethyl amine) affords acetamide III-8. One-step exhaustive pyridine reduction can be effected with a catalyst (Pt-carbon) under hydrogen gas (30-50 psi) with alcoholic or ethereal solvent (typically MeOH, EtOH, THF) to give the corresponding piperidine. Subsequent alkylation with an electrophile (i.e. methyl-vinyl sulfone) in the presence of base (triethyl amine) including in situ aniline deprotection affords the desired aniline III-9.

Scheme 4: indoline-derived Anilines

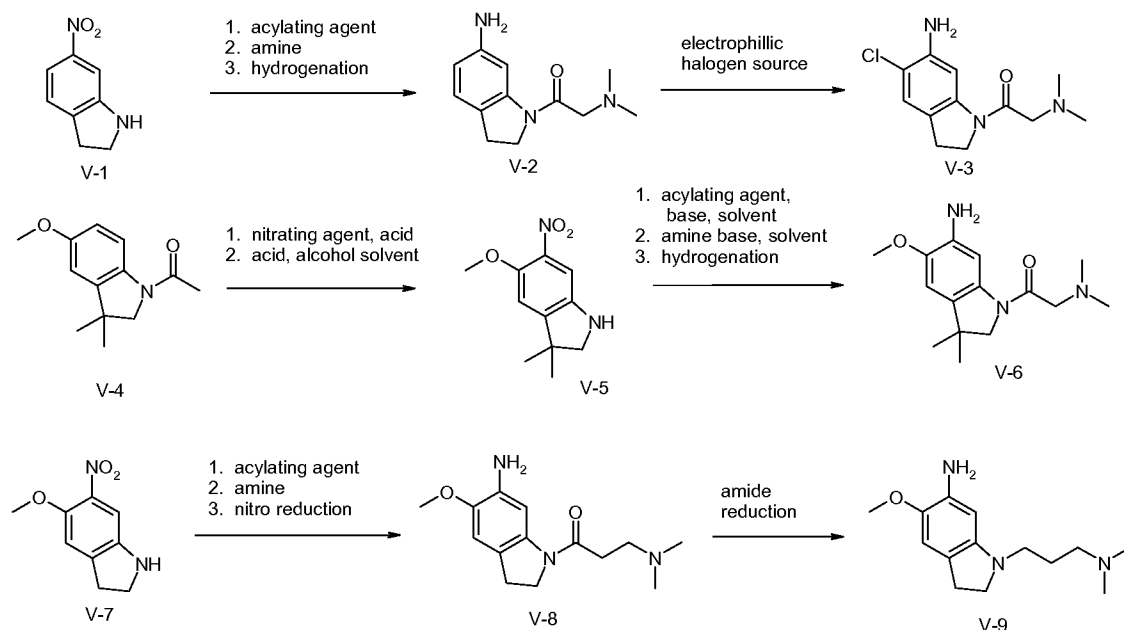


As shown in scheme 4, bicyclic indoline tails may be prepared using 5-methoxy indole (Aldrich) as a starting material. The 5-methoxy indole is first reduced using a hydride source, e.g. Na(CN)BH₃, and acid, e.g. AcOH, then protected with an acylating agent, e.g. Ac₂O, in solvent, e.g. AcOH, optionally with a base. The protection provides for subsequent selective nitration with nitrating agent, e.g. HNO₃/Ac₂O, followed by deacylation with acid, e.g. HCl in solvent, e.g. MeOH to provide intermediate IV-2

Intermediate IV-2 is subjected to subsequent acylation with an acylating agent, e.g. α -bromoacetyl chloride or an amino acid, with coupling reagents, e.g. HATU, DMAP, and base, e.g. PS-DIPEA, and solvent, e.g. THF. The α -bromoacetyl product may be reacted with an appropriate amine base, e.g. Me₂NH (with solvent, e.g. THF), and the product then reduced (see reduction of II-4, Scheme 2) to provide anilino indoline tails IV-3.

Alternatively, the set of reaction described above for Scheme 4 can be reordered to allow for the elimination of the acylation/deacylation sequence. For example direct acylation of indoline IV-6 (commercially available as the HCl salt from ChemPacific) with an acylating agent (α -bromo-acetyl chloride) and base (optionally a trialkyl amine base such as triethyl amine or an inorganic base such as potassium carbonate) followed by treatment with a nucleophile (for example dimethyl amine) affords IV-7. Direct nitration of IV-7 using an acid (i.e. trifluoroacetic acid) and one equivalent of a nitrating agent (for example potassium or sodium nitrate) affords the corresponding nitro-indoline which may be reduced in analogy to the reduction of II-4 (Scheme 2) to afford functionalized aniline indoline IV-8.

Scheme 5: Additional indoline-derived tails



As shown in scheme 5, additional indoline tails may be prepared by alternative schemes. Chloro aniline V-3 is readily prepared via acylation of 6-nitro indoline with an acylating agent, e.g. α -bromoacetyl chloride, subsequent displacement with an amine base, and nitro-reduction (hydrogenation). Subsequent reaction with an electrophilic halogen source, e.g. NCS, affords V-3.

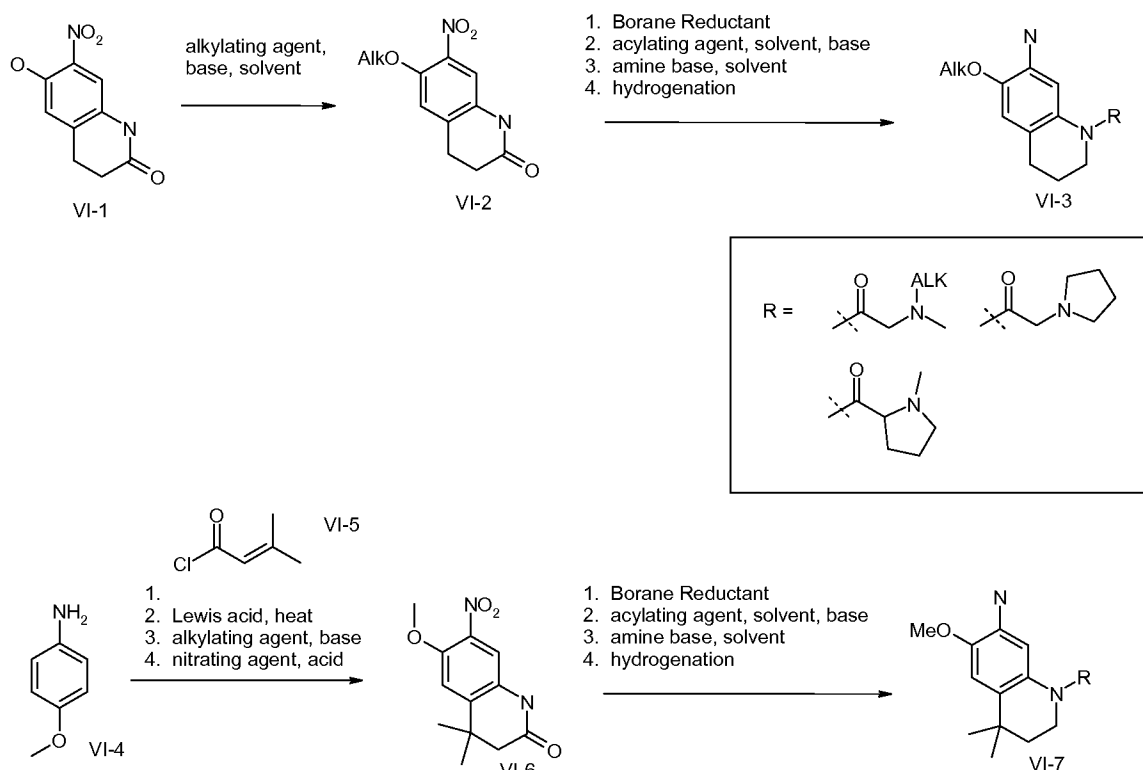
Similarly, aniline V-5 is produced via nitration and deprotection of amide V-4 (see International Patent Publication WO 2001023374), acylation, e.g. α -bromoacetyl chloride and a suitable base (i.e. K_2CO_3), subsequent displacement with an amine base (for example dimethyl amine or pyrrolidine), and nitro-reduction via hydrogenation (with a palladium source, i.e. Pd/C, and hydrogen gas).

Aniline V-9 is prepared starting with nitro-indoline V-7 according to Scheme 5. Acylation with an acylating agent (for example here acryloyl chloride) in the presence of a trialkylamine base (i.e. Hunig's base) and solvent (dichloromethane) followed by 1,4-conjugate addition of a nucleophile (for example dimethyl amine) to the corresponding α,β -unsaturated amide and then nitro reduction as described for Intermediate II-4 (Scheme 2) affords functionalized aniline V-8. Further reduction of the amide can be

effected via treatment of V-8 with a hydride reducing agent (lithium aluminum hydride) in ethereal solvent (for example tetrahydrofuran or diethyl ether) to afford V-9.

5

Scheme 6: Tetrahydroisoquinoline-derived tails



As shown in Scheme 6, tetrahydroquinoline tails may be prepared as follows.

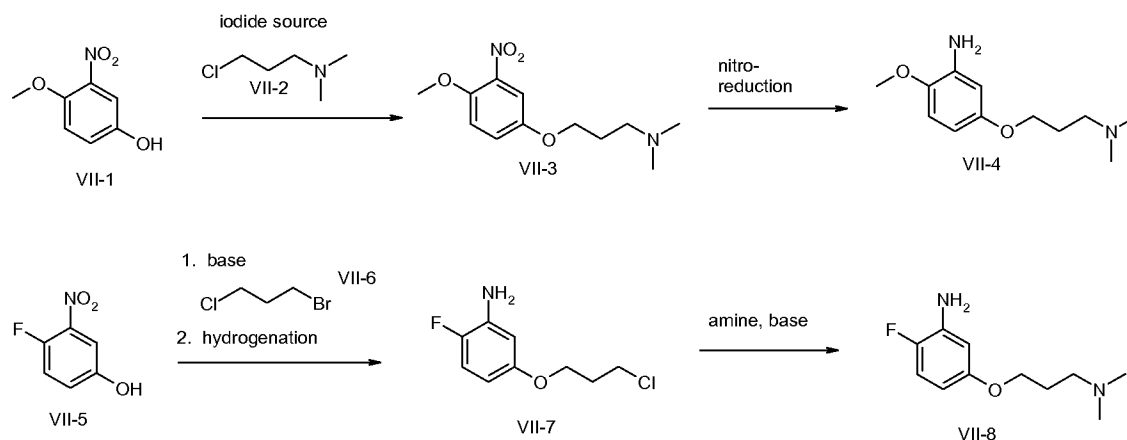
Intermediate (VI-1), prepared according to Chem. Pharm. Bull. (2001) p.822, may be alkylated with an alkylating agent and base, e.g. MeI and K_2CO_3 , to provide VI-2, then amide reduced, e.g. borane, treated with an acylating agent, e.g. α -chloro acetyl chloride, an amine base, e.g. dimethyl amine or other exemplary amines, and nitro-reduced (as with Intermediate II-4, Scheme 2) to provide (VI-3).

Intermediate (VI-4), readily available 4-anisidine, may be acylated with 3,3-dimethylacryloyl chloride and base, e.g. K_2CO_3 , heated with a Lewis acid, e.g. $AlCl_3$, and solvent, e.g. methylene chloride, followed by nitration with an oxidative reagent, e.g.

NaNO₂, in acid, e.g. TFA, to provide VI-6. Subsequent amide reduction, e.g. borane, followed by treatment with an acylating agent, e.g. α-bromoacetyl chloride, displacement with an amine base, e.g. dimethyl amine, and nitro reduction provides (VI-7).

5

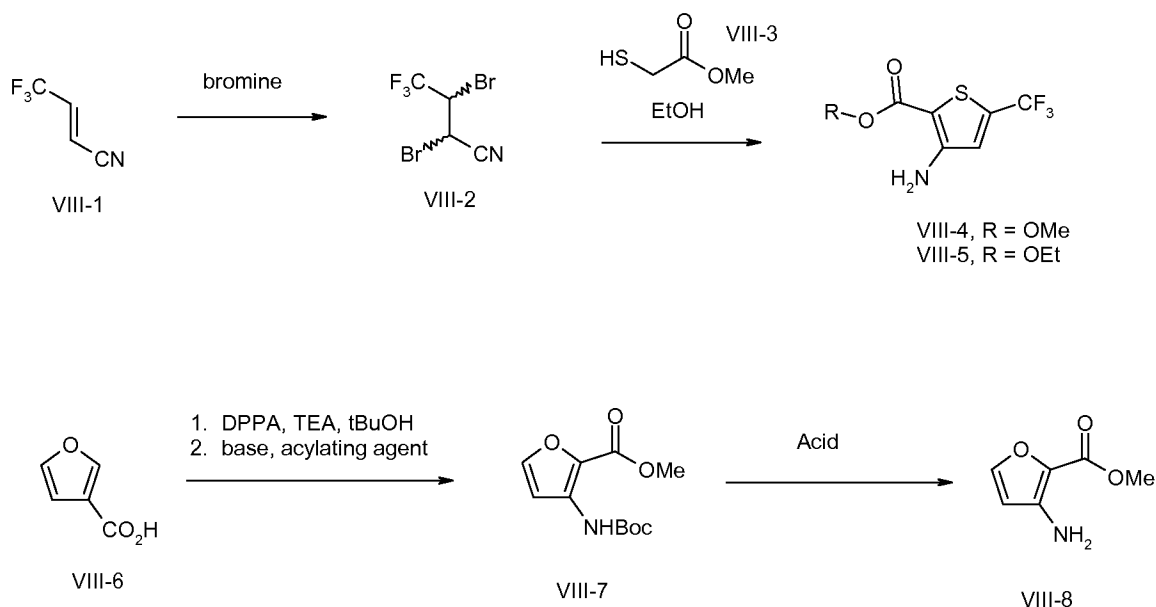
Scheme 7: Oxygen-linked Anilines



Further functionalized anilines may be accessed from nitrophenols including VII-I (commercially available through CiventChem) and VII-5 (Meurs, Jan H. H.; Eilenberg, Wolf. *Oxidative fluorination in amine-hydrogen fluoride mixtures*. Tetrahedron (1991), 47(4-5), 707-14.). Alkylation of VII-1 with an alkylating agent (i.e. VII-2), iodide source (i.e. tetrabutylammonium iodide or KI) and base (i.e. potassium carbonate) affords O-alkylated nitrobenzene VII-3. Subsequent nitro reduction (see Intermediate II-4, Scheme 2) affords aniline VII-4. Similarly, alkylation of VII-5 with a bifunctional electrophile (for example VII-6) and base (potassium carbonate) followed by nitro reduction in the presence of a catalyst (Pd/C), solvent (MeOH) and reducing agent (hydrogen gas, typically 30-50 psi) affords aniline VII-7. Direct chloride displacement can be effected via exposure of VII-7 to an amine nucleophile (for example dimethylamine) and base (potassium carbonate) to afford VII-8.

20

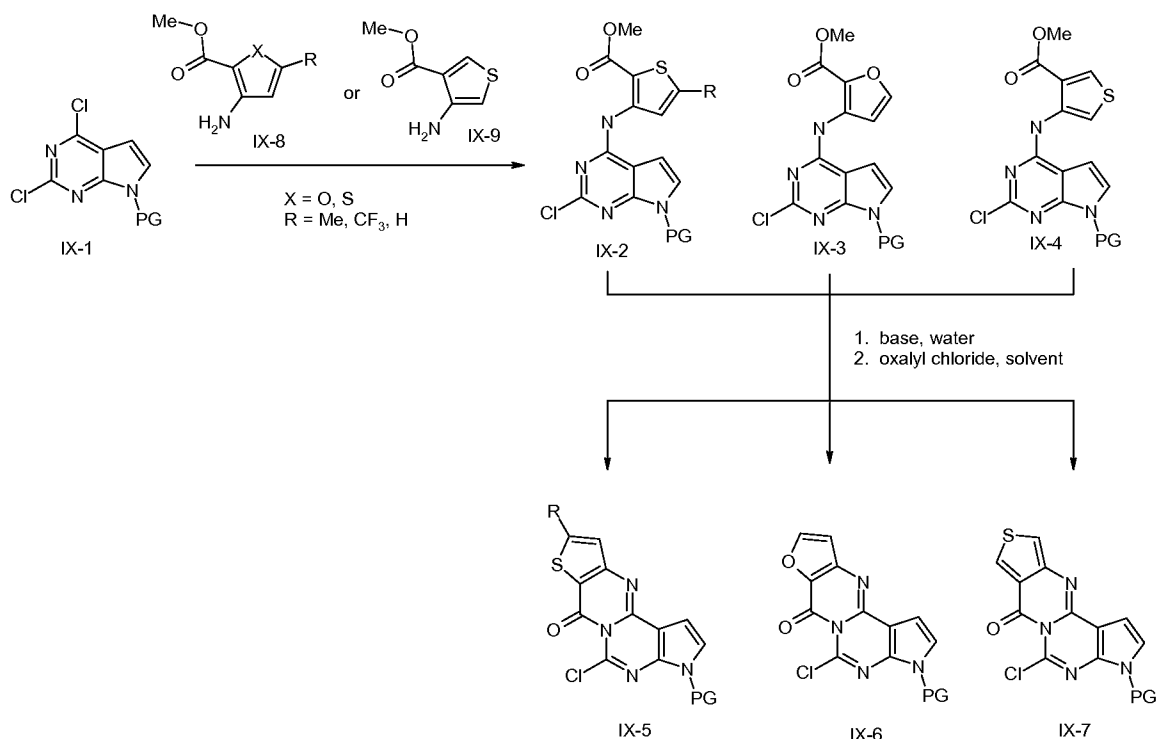
Scheme 8: Synthesis of Carboxamide-Containing Amines



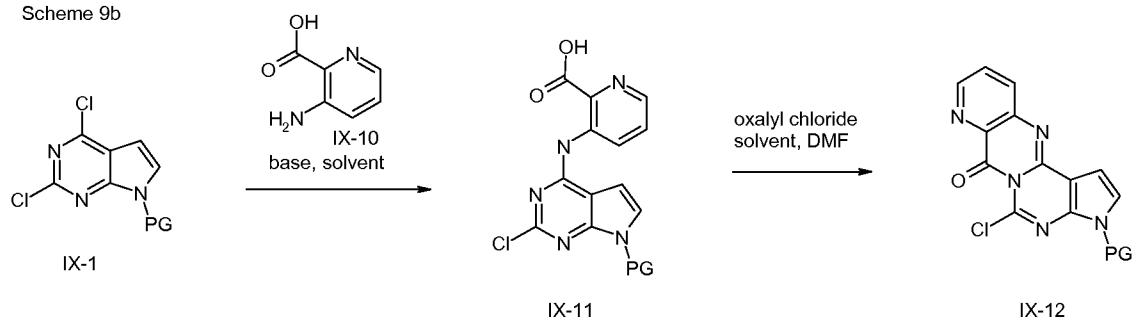
Several heterocyclic carboxamide-containing amines can be prepared as illustrated in Scheme 8. Bromination of vinyl-nitrile VIII-1 can be effected via direct treatment with bromine. Subsequent thiophene formation occurs when VIII-2 is treated with a 2-mercapto ester (for example VIII-3) in alcoholic solvent (EtOH).

Furan-containing carboxamide VIII-8 can be generated from 3-furanoic acid VIII-6. A Curtius rearrangement may be effected via activation of VIII-6 (oxalyl chloride or DPPA) and an azide source (sodium azide or DPPA) which when carried out in the presence of base (triethyl amine) in t-BuOH solvent affords the corresponding 3-N-boc furan. Subsequent exposure to 2 equivalents of a strong base (for example tertiary butyl lithium) and then an electrophile (using methylchloroformate above) affords functionalized furan VIII-7. Boc-deprotection of VIII-7 can be carried out via direct treatment with acid (TFA or HCl) to afford free aniline VIII-8.

Scheme 9a: Pyrrolopyrimidine Intermediates



Scheme 9b



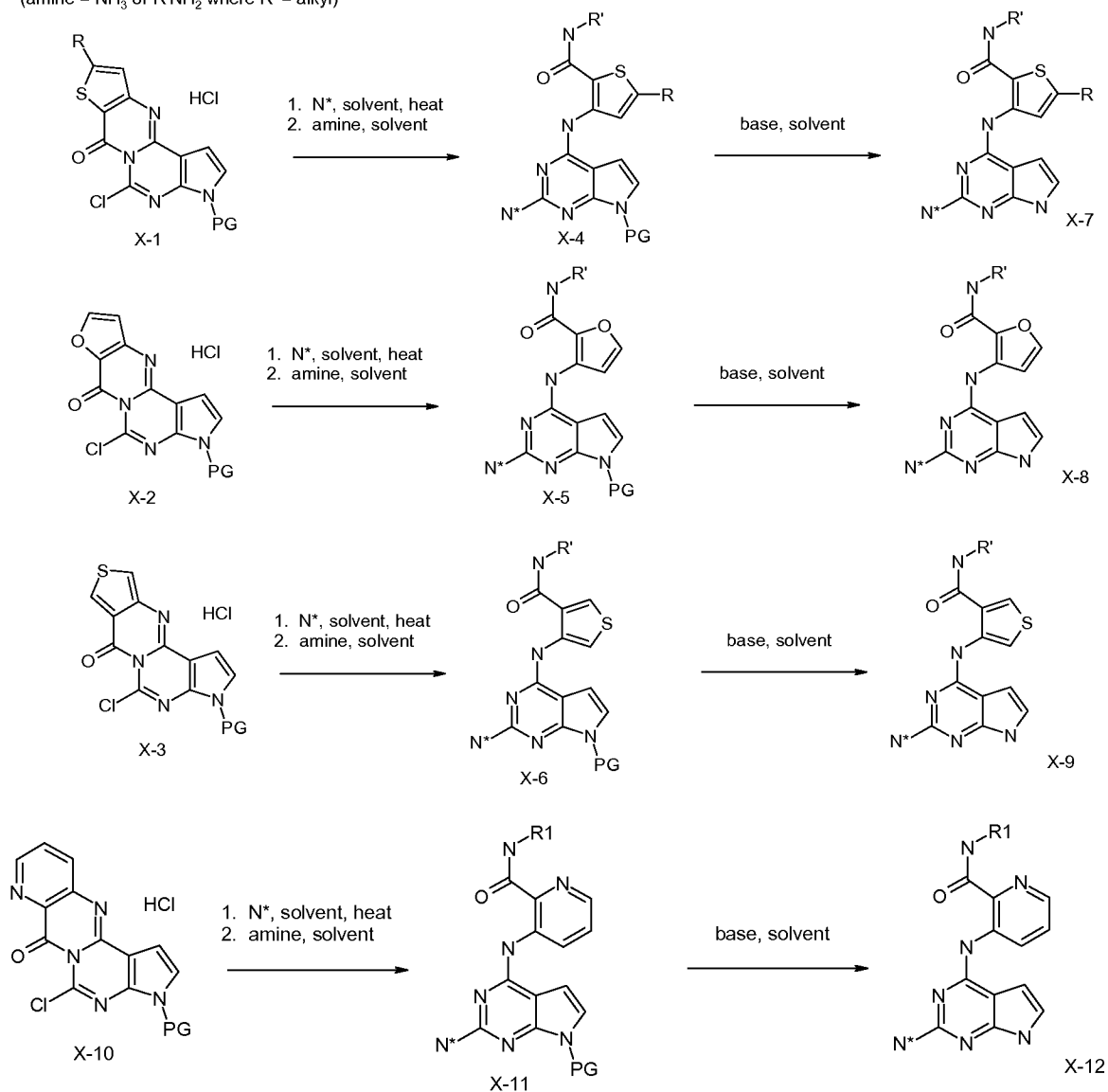
- 5 The head (IX-8 & IX-9, IX-10) and core (IX-1) can be combined as illustrated in Scheme 9a-b. 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine is combined with an appropriate amine or aniline (for example IX-8 or IX-9) and a suitable solvent (for example trifluoroethanol) with acid (TFA) to give the corresponding 4-substituted pyrrolo[2,3-d] pyrimidines (IX-2 through IX-4) or with a suitable amine (i.e. IX-
- 10 10) in solvent (iPrOH) with base (Hunig's base). The carboxylate esters present on IX-2 through IX-4 may be hydrolyzed under standard aqueous basic conditions (LiOH, water, tetrahydrofuran) and the derived acids (including IX-11 obtained directly) may be

activated by conversion to the corresponding acid chlorides by treatment with a chloride source/activating agent (oxalyl chloride) and catalyst (DMF). The in situ generated acid chlorides react intramolecularly with the 5-nitrogen group to give the corresponding tetracyclic species IX-5 through IX-7 and IX-12. Tetracyclic species IX-5 through IX-7

5 activate the C(7) chloride toward further displacement (see Scheme 10).

Scheme 10: Elaboration of Activated Intermediates

(N* = Functionalized Aniline--See Schemes 1-7)

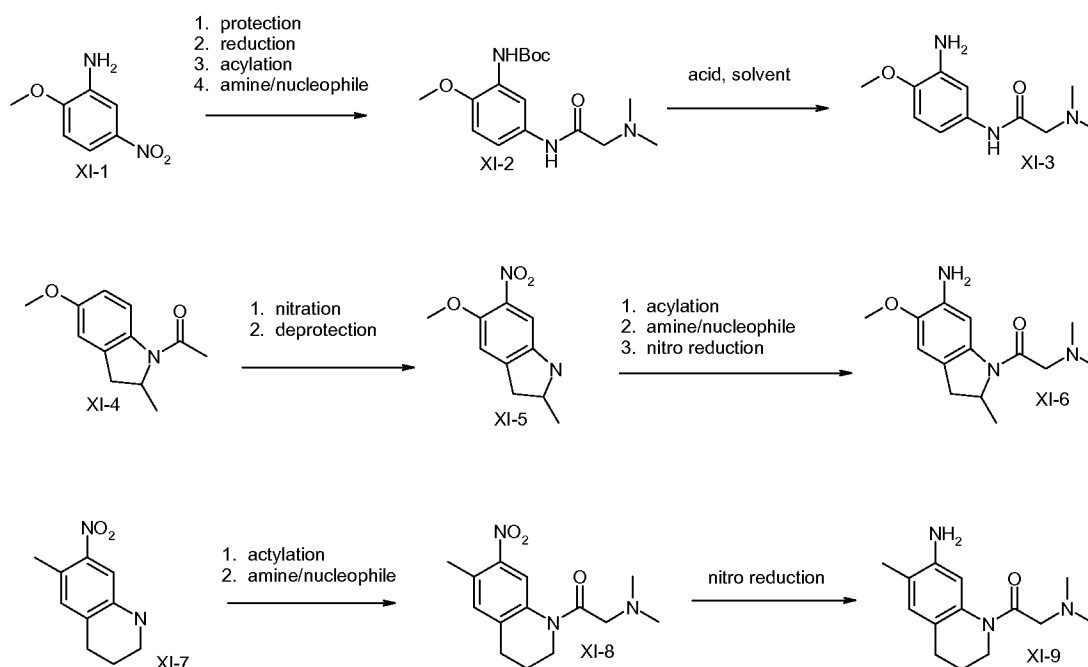
(amine = NH₃ or R'NH₂ where R' = alkyl)

5

Treatment of chlorides X-1 through X-3 and X-10 with a functionalized aniline (see Schemes 1-7) in solvent (tetrahydrofuran, trifluoroethanol, dioxane) with acid catalysis (hydrochloric acid) gives C(7)-Cl displacement. Subsequent exposure to a nucleophile (typically a primary or secondary amine, for example ammonium, methyl amine, propyl amine) gives reaction at the carbonyl and affords X-4, X-5, X-6, and X-11. Removal of the tosyl protection group proceeds upon treatment with base (KOH, NaOH, NaOMe) in a polar protic solvent (H₂O, MeOH) with optional cosolvent (dioxane,

tetrahydrofuran) and heating (optionally in a microwave reactor) to afford X-7, X-8, X-9, and X-12.

Scheme 11



5

Exposure of commercially available XI-1 to aniline protection conditions (i.e. BOC₂O, DIPEA), nitro reduction conditions (i.e. Pd/C, hydrogen gas), acylation conditions (i.e. α -bromo acetyl chloride, DIPEA), and then introduction of a nucleophile (i.e. dimethyl amine) affords XI-2. Deprotection of XI-2 with acid (i.e. HCl, or TFA) affords XI-3.

Exposure of XI-4 (see Arp, Forrest O.; Fu, Gregory C. *Kinetic Resolutions of Indolines by a Nonenzymatic Acylation Catalyst*. Journal of the American Chemical Society (2006), 128(44), 14264-14265.) to nitration conditions (i.e. sodium nitrate and TFA) followed by deprotection of the acyl group with acid (i.e. HCl) affords XI-5. Advancement of XI-5 or XI-7 (see: Achvlediani, R.; Natsvlishvili, M.; Baberkina, E.; Khachidze, M.; Abesadze, I.; Suvorov, N. *Synthesis of 1H-pyrrolo[3,2- γ]- and 1H-pyrrolo[2,3- γ]quinoline*. Izvestiya Akademii Nauk Gruzii, Seriya Khimicheskaya (1996), 22(1-4), 43-47.) through a reaction sequence similar to that described above (i.e. acylation with α -bromo acetyl chloride, displacement with an amine or other nucleophile, and nitro reduction) affords anilines XI-6 and XI-9.

EXAMPLES

The following specific examples are included as illustrations and are not to be construed as limiting the scope of the present invention.

As used herein, the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples, schemes, biological writeups, and throughout the specification:

APC (Allophycocyanin)	M (molar);
ATP (adenosine triphosphate)	MeOH (methanol);
Ac (acetyl)	mg (milligrams)
atm (atmosphere)	MgCl ₂ , magnesium chloride
BSA (bovine serum albumin)	MHz (megahertz)
CHAPS (3-[3-Cholamidopropyl)Dimethylammonio] -1-Propanesulfonate)	min (minutes)
DIPEA(diisopropylethylamine)	mL (milliliters)
DMSO (dimethyl sulfoxide)	mM (millimolar)
DTT (Dithiothreitol)	mmol (millimoles)
EDTA (ethylenediaminetetraacetic acid)	mol (moles);
Eu (Europium)	mp (melting point);
G (grams)	NaCl, Sodium chloride
GST (Glutathione S-transferase)	NCBI, National Center for Biotechnology Information
h (hours);	nM, nanomolar
HEPES (N-(2-Hydroxyethyl)piperazine-N'-2-ethanesulfonic acid)	OTF (trifluoromethane sulfonate)
hIGF1R or IGF-1R (human Insulin-like growth factor 1 receptor kinase)	psi (pounds per square inch);
hIR (human insulin receptor kinase)	RP (reverse phase);
HPLC (high performance/pressure liquid chromatography)	rt (room temperature);
Hz (Hertz);	SEM (2-trimethylsilyl(ethoxymethyl)
<i>i</i> -PrOH (isopropanol);	TBAI (tetrabutylammonium iodide);
i. v. (intravenous);	TFA (trifluoroacetic acid);
L (liters);	TFE (trifluoroethanol)
	THF (tetrahydrofuran);
	TLC (thin layer chromatography);
	T _r (retention time);
	μL (microliters);
	μM, micromolar

Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification. Unless otherwise indicated, all reactions were conducted at room temperature and all temperatures are expressed in °C (degrees Centigrade).

Throughout the specification, multi-step syntheses are described with respect to various intermediate and exemplary compounds. In general, all but the first step of each multi-step synthesis refer to a product compound of a preceding step. Unless otherwise noted, such reference is understood as reference to the compound in general, though not necessarily to the actual sample of product that was produced in carrying out the preceding step.

Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ precoated plates. Detection was effected by exposure to UV light (254 nm). Flash and flush column chromatography was performed using Silica Gel 60. Reverse phase preparative and analytical HPLC were performed using C18 columns and acetonitrile:water gradients with 0.05% TFA as a modifier.

Compound purity and characterization were determined by ¹H-NMR, liquid chromatography-mass spectrometry (LCMS), high resolution mass spectrometry (HRMS), combustion (elemental) analysis, HPLC, and melting point. Compounds of general formula I were typically found to have purities of > 90%.

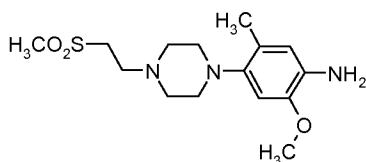
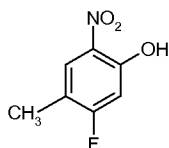
¹H NMR spectra were recorded on Varian INOVA-300 and Varian INOVA-400 instruments. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

Low resolution mass spectra were obtained on Micromass ZQ, Micromass ZMD, Micromass QuattroMicro, and Micromass GCT instruments from Micromass Ltd., Altricham, UK, using either Atmospheric Pressure Chemical Ionization (APCI) or ESI Ionization (ESI).

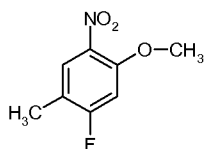
High resolution mass spectral data (HRMS) were recorded with Micromass LCT and Micromass GCT instruments.

Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, Georgia).

Melting points were recorded in open capillary tubes and are uncorrected.

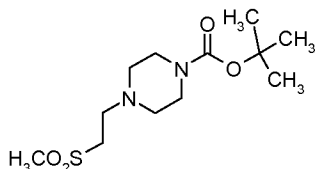
Section A: Functionalized Anilines**5 Intermediate A1: 5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline****10 Step A/Intermediate A2: 5-fluoro-4-methyl-2-nitrophenol**

3-fluoro-4-methylphenol (3.66 g, 29.0 mmol) was dissolved in DCE (32 mL) and tetrabutylammonium bromide (0.935 g, 2.90 mmol) was added. 70% aqueous HNO₃ (3.7 mL, 58 mmol) was diluted with H₂O (33 mL) to make a 7% HNO₃ solution. This solution was added to the reaction mixture, which was then stirred at rt for 4h at which time the reaction was judged complete by TLC. The reaction was poured into H₂O and extracted with DCM (3x). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was adsorbed onto silica gel and flash chromatographed to give 5-fluoro-4-methyl-2-nitrophenol (2.83 g, 57%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.10 (s, 1 H), 7.89 (d, *J*=8.1 Hz, 1 H), 6.85 (d, *J*=11.0 Hz, 1 H), 2.13 (s, 3 H).

Step B/Intermediate A3: 1-fluoro-2-methyl-5-(methyloxy)-4-nitrobenzene

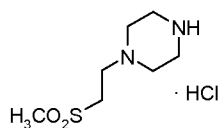
5-Fluoro-4-methyl-2-nitrophenol (2.83 g, 16.5 mmol) was dissolved in *N,N*-dimethylformamide (25 mL). K_2CO_3 (3.4 g, 25 mmol) and iodomethane (1.2 mL, 20 mmol) were added and the mixture was stirred at rt overnight. The mixture was then
5 poured into H_2O and stirred until solids crashed out. The solids were filtered and air dried to give the 1-fluoro-2-methyl-5-(methoxy)-4-nitrobenzene (2.76 g, 90 %). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.92 (d, $J=8.1$ Hz, 1 H), 7.25 (d, $J=11.7$ Hz, 1 H), 3.89 (s, 3 H), 2.19 (d, $J=1.5$ Hz, 3 H).

- 10 Step C/Intermediate A4: 1,1-dimethylethyl 4-[2-(methylsulfonyl)ethyl]-1-piperazinecarboxylate



- To a solution of 1,1-dimethylethyl 1-piperazinecarboxylate (72.8 g, 390 mmol) in acetonitrile (1.4 L) was added methyl vinyl sulfone (50 g, 470 mmol) and Na_2CO_3 (124 g,
15 1170 mmol) and the mixture was refluxed overnight. Then the mixture was cooled to rt, and poured into H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give 1,1-dimethylethyl 4-[2-(methylsulfonyl)ethyl]-1-piperazinecarboxylate (106 g, 93% yield). 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.41-1.57 (m, 9H), 2.39-2.51(m, 4H), 2.88 (t, $J=8.4$ Hz, 2H), 3.02 (s,
20 3H), 3.14 (t, $J=8.4$ Hz, 2H), 3.35-3.50 (m, 4H).

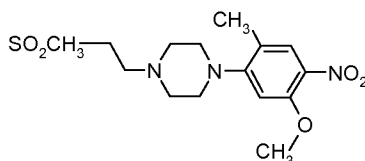
Step D/Intermediate A5: 1-[2-(methylsulfonyl)ethyl]piperazine hydrochloride



- To the solution of 1,1-dimethylethyl 4-[2-(methylsulfonyl)ethyl]-1-piperazinecarboxylate
25 (106 g, 360 mmol) in MeOH (500 mL) was added HCl/MeOH (5M, 1000 mL, 5000 mmol), and the mixture was heated at 50 °C for 1 h before evaporating most of the solvent. The residue was filtered and washed with MeOH to give 1-[2-

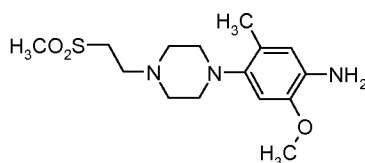
(methylsulfonyl)ethyl]piperazine hydrochloride (90.3 g, 95% yield). ^1H NMR (400 MHz, D_2O) δ ppm 3.30-3.72 (m, 12H), 3.09 (s, 3H).

Step E/Intermediate A6: 1-[2-methyl-5-(methoxy)-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperazine



1-fluoro-2-methyl-5-(methoxy)-4-nitrobenzene (5.0 g, 27 mmol), K_2CO_3 (11.2 g, 81 mmol), and 1-[2-(methylsulfonyl)ethyl]piperazine hydrochloride (8.0 g, 35 mmol) were weighed into a 150 mL sealed tube, taken up in 85 mL of DMSO and heated to 100°C for 24 h. The mixture was poured into 500 mL of H_2O , filtered, washed with H_2O , air dried for 15 min, washed with hexanes (200 mL), washed with 20% ether/ hexanes (200 mL), and air dried for 2 h to give 1-[2-methyl-5-(methoxy)-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperazine (6.6 g, 18.5 mmol, 68%). An additional (540 mg, 5.5%) of product was obtained by extraction of the H_2O layer, followed by flash chromatography. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.75 (s, 1 H), 6.70 (s, 1 H), 3.90 (s, 3 H), 3.31 - 3.35 (m, 2 H), 3.04 (s, 3 H), 2.99 - 3.03 (m, 4 H), 2.77 (t, $J=6.60$ Hz, 2 H), 2.56 - 2.63 (m, 4 H), 2.19 (s, 3 H).

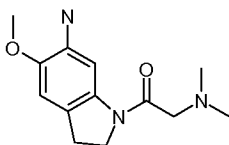
Step F/Intermediate A1: 5-methyl-2-(methoxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline



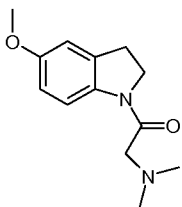
1-[2-methyl-5-(methoxy)-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperazine from a separate batch (0.257 g, 0.72 mmol) was placed in a 40 mL high vial and dissolved in 10 mL of 1 to 1 EtOAc/MeOH. 5 wt% Platinum(sulfided)/carbon (0.165 g, 0.043 mmol) was added and the vial was quickly sealed by a screw cap septum. The vial was evacuated and filled with N_2 six times to remove any oxygen. The vial was then pressurized with H_2 (balloon). The solution stirred overnight. The next morning the vessel was evacuated

and filled with N₂ six times to remove any H₂. The solution was filtered through celite and evaporated to afford 5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline (0.194 g, 0.59 mmol, 82%). ¹H NMR (400 MHz, CDCl₃) δ ppm 6.54 (s, 2 H), 3.80 (s, 3 H), 3.30 - 3.37 (m, 2 H), 3.07 (s, 3 H), 2.91 - 2.98 (m, 6 H), 2.82 - 2.90 (m, 4 H), 2.15 (s, 3 H).

Intermediate A7: 1-[(dimethylamino)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine



Step A/Intermediate A8: *N,N*-dimethyl-2-[5-(methyloxy)-2,3-dihydro-1H-indol-1-yl]-2-oxoethanamine

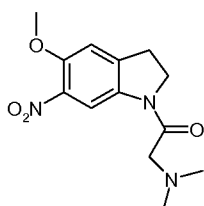


A suspension of 5-(methyloxy)-2,3-dihydro-1H-indole hydrogen chloride (94.5g, 509 mmol) in CH₂Cl₂ (250mL) was added dropwise to a mixture of α-bromoacetylchloride (120g, 764 mmol) and K₂CO₃ (78g, 560mmol) in CH₂Cl₂ (750 mL) at 0 °C. After the addition, the suspension was stirred at 0 °C for 1.5 hours. The reaction was washed with water and filtered. The residue (presumed to be K₂CO₃) was rinsed with DCM (2x100ml). The organic layers were separated, combined, dried over Na₂SO₄, filtered, and concentrated to provide a brown solid (135g, 98%).

The brown solid (135g, 499 mmol) was dissolved in DCM (500ml), cooled to 0 °C, then treated with K₂CO₃ (139g, 999 mmol), and 650ml of 2 M dimethyl amine in THF. The reaction was stirred at 0 °C for 1 hour and filtered. The resulting solid was washed with DCM. The combined filtrates were washed with water, dried over Na₂SO₄, filtered,

and concentrated to provide *N,N*-dimethyl-2-[5-(methoxy)-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine as a grey solid (111g, 95%).

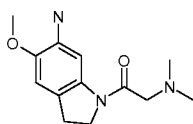
Step B/Intermediate A9: *N,N*-dimethyl-2-[5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine



To a solution of NaNO₃ (43.9g, 516 mmol) in TFA (250 mL) was added *N,N*-dimethyl-2-[5-(methoxy)-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine (110.0 g, 469 mmol) in TFA (50 mL) at 0°C and the mixture was stirred at 0°C for 1.5h. The reaction mixture was poured into ice-water (1000mL), the TFA and some water was removed by reduced pressure (the volume was reduced to 400 mL), the reaction mixture was adjusted to pH = 11 by addition of 2N NaOH (the mixture became cloudy), and the aqueous layer was extracted with CHCl₃ (2x300mL), and washed with water. The organic layer was separated, dried over with Na₂SO₄, and the solvents were removed under reduced pressure to yield *N,N*-dimethyl-2-[5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine (130g, 99%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.24 (s, 6 H), 3.15 - 3.24 (m, 4 H), 3.86 (s, 3 H), 4.18 (t, *J*=8.5 Hz, 2 H), 7.31 (s, 1 H), 8.45 (s, 1 H).

This protocol could be repeated to generate larger quantities of *N,N*-dimethyl-2-[5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine which could be carried forward in the synthetic sequence as blended batches.

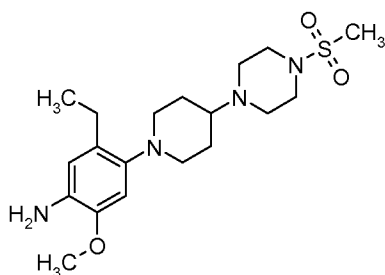
Step C/Intermediate A7: 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



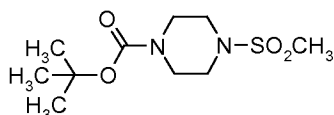
A suspension of *N,N*-dimethyl-2-[5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine (26.6 g, 95 mmol), iron(III)chloride (3.09 g, 19.05 mmol), activated

carbon (25 g, 95 mmol), and hydrazine hydrate (37.4 mL, 762 mmol) in methanol (500 mL) was warmed to 65°C and maintained overnight. The reaction was filtered through celite while still warm and all methanol was removed under reduced pressure. The solids were partitioned between ethyl acetate (ca 1 L) and saturated sodium chloride (ca 1 L) and the aqueous layer was washed twice with ethyl acetate (ca 500 mL). The combined organic layers were dried over sodium sulfate, taken to a residue under reduced pressure, and the derived solids triturated with hexanes/diethyl ether and filtered to afford 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (16.46 g, 69.3 % yield) as an off-white solid: NMR: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.23 (s, 6 H), 2.95 (t, *J*=8.25 Hz, 2 H), 3.11 (s, 2 H), 3.69 (s, 3 H), 4.07 (s, 2 H), 4.61 (s, 2 H), 6.68 (s, 1 H), 7.53 (s, 1 H).

Intermediate A10: 5-ethyl-2-(methoxy)-4-{4-[4-(methanesulfonyl)-1-piperazinyl]-1-piperidinyl}aniline

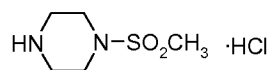


Step A/Intermediate A11: 1,1-dimethylethyl 4-(methanesulfonyl)-1-piperazinecarboxylate



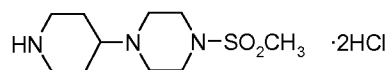
To 1,1-dimethylethyl 1-piperazinecarboxylate (568 g, 3.05 mol) in DCM (4 L) was added Et₃N (617 g, 6.10 mol). After stirring for 10 min at 0 °C, MsCl (384 g, 3.35 mol) was added via addition funnel. The mixture was stirred at rt overnight. The mixture was poured into H₂O (1 L) and extracted with DCM (1 L). The organic layer was separated, washed with H₂O (1 L), dried (Na₂SO₄), and concentrated to provide 1,1-dimethylethyl 4-(methanesulfonyl)-1-piperazinecarboxylate (720 g, 2.72 mol, 90 %) which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9 H), 2.76 (s, 3 H), 3.11 - 3.17 (m, 4 H), 3.50 - 3.53 (m, 4 H).

Step B/Intermediate A12: 1-(methylsulfonyl)piperazine hydrochloride



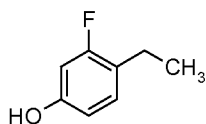
To 1,1-dimethylethyl 4-(methylsulfonyl)-1-piperazinecarboxylate (360 g, 1.36 mol) in MeOH (1 L) was added HCl (6 M in MeOH, 2 L) dropwise. The mixture was stirred at rt for 1 h. About 1 L of MeOH was rotovapped off. The resultant precipitate was filtered, washed with MeOH, and dried on high vacuum to provide 1-(methylsulfonyl)piperazine hydrochloride (A combination of 2 batches, 570 g) which was used without further purification. ¹H NMR (400 MHz, D₂O) δ 2.95 (s, 3 H), 3.27 - 3.29 (m, 4 H), 3.42 - 3.46 (m, 4 H).

Step C/Intermediate A13: 1-(methylsulfonyl)-4-(4-piperidinyl)piperazine dihydrochloride



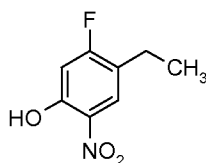
To 1-(methylsulfonyl)piperazine hydrochloride (150 g, 632 mmol) in DCE (3.5 L) was added Et₃N (192 g, 1.90 mol). The mixture was stirred at rt for 1 h and then acetic acid (94.8 g, 1.58 mol) and 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (251 g, 1.26 mol) was added. After stirring another hour, the reaction was cooled with an ice water bath and NaBH(OAc)₃ (294 g, 1.39mol) was added in four portions. The mixture was stirred overnight at rt. The reaction mixture was neutralized with saturated Na₂CO₃ to pH 8-9. The organic phase was washed with brine and H₂O, dried (Na₂SO₄), and concentrated to provide the crude Boc-protected amine (A combination of 3 batches, 720 g). This amount was split into 2 batches and used without further purification. To 1,1-dimethylethyl 4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinecarboxylate (360 g, 1.04 mol) in MeOH (1 L) was added HCl (6 M in MeOH, 2 L). The mixture was stirred at rt for 30 min. About 1 L of MeOH was rotovapped off. The resultant precipitate was filtered, washed with MeOH, and dried on high vacuum to provide 1-(methylsulfonyl)-4-(4-piperidinyl)piperazine dihydrochloride (A combination of 2 batches, 600 g, 1.87 mol, 89 % over 2 steps). ¹H NMR (400 MHz, D₂O) δ 1.87 - 1.91 (m, 2 H), 2.33 - 2.36 (m, 2 H), 2.97 (s, 3 H), 2.99 - 3.05 (m, 2 H), 3.45 - 3.59 (m, 11 H).

Step D/Intermediate A14: 4-ethyl-3-fluorophenol



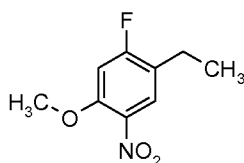
2-Fluoro-4-hydroxyacetophenone (15.14 g, 100 mmol) and zinc dust (19.61 g, 300 mmol) was suspended in 50 mL of H₂O with stirring. Concentrated HCl (37%, 50 mL, 610 mmol) were added and the mixture was heated to reflux for six hours. The reaction
5 was cooled to rt, and diethyl ether was added. The mixture was saturated with NaCl, and filtered through celite washing with diethyl ether. The filtrate was poured into brine, and the layers were separated. The aqueous layer was extracted with diethyl ether. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford 7.24 g (52%) of 4-ethyl-3-fluorophenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.53 (s, 1H), 7.00 (t, *J* = 8.8 Hz, 1H), 6.52 - 6.40 (m, 2H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.06 (t, *J* = 7.5 Hz, 3H).
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Step E/Intermediate A15: 4-ethyl-5-fluoro-2-nitrophenol



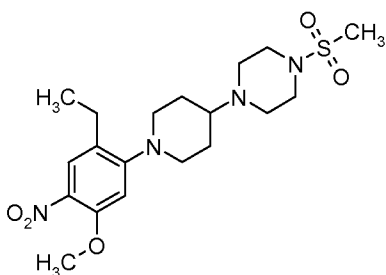
4-Ethyl-3-fluorophenol (7.24 g, 51.6 mmol) was dissolved in 100 mL of DCM with stirring. Tetrabutylammonium bromide (1.66 g, 5.15 mmol) was added. A seven percent aqueous solution of HNO₃ (66 mL) was prepared and added to the reaction. The biphasic mixture was stirred vigorously overnight. The reaction was poured into DCM and H₂O, and the layers were separated. The aqueous layer was washed with DCM
20 (2X). The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford 5.72 g (60%) of 4-ethyl-5-fluoro-2-nitrophenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 11.2 Hz, 1H), 2.56 (q, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H).

Step F/Intermediate A16: 1-ethyl-2-fluoro-4-(methoxy)-5-nitrobenzene



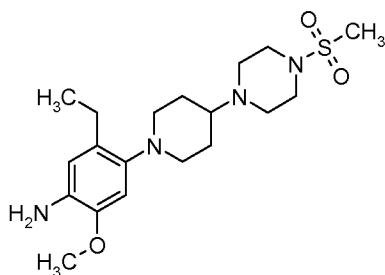
4-Ethyl-5-fluoro-2-nitrophenol (5.72 g, 30.9 mmol) was dissolved in 60 mL of DMSO with stirring. K_2CO_3 (6.41 g, 46.4 mmol) was added. Methyl iodide (2.5 mL, 40 mmol) was added via syringe. The reaction was stirred overnight and poured into H_2O and diethyl ether. The layers were separated, and the organic layer was washed with brine. The combined aqueous layers were extracted with EtOAc (2X). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford 5.13 g (83%) of 1-ethyl-2-fluoro-4-(methoxy)-5-nitrobenzene. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.88 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 12.1 Hz, 1H), 3.86 (s, 3H), 2.56 (q, J = 7.6 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H).

Step G/Intermediate A17: 1-{1-[2-ethyl-5-(methoxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)piperazine



A mixture of 1-ethyl-2-fluoro-4-(methoxy)-5-nitrobenzene (0.93 g, 4.67 mmol), 1-(methylsulfonyl)-4-(4-piperidinyl)piperazine (1.155 g, 4.67 mmol) and K_2CO_3 (0.774 g, 5.60 mmol) in DMSO (20 mL) was heated at 90 °C for 48 h. The reaction had not progressed sufficiently so the reaction was then heated at 120 °C for an additional 4 h. The reaction was cooled to rt, poured into H_2O and extracted exhaustively with DCM. The combined organics were washed with H_2O then dried over $MgSO_4$. The resultant solution was concentrated onto silica and purified by flash chromatography to afford 1-{1-[2-ethyl-5-(methoxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)piperazine (1.12 g, 56%). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.73 - 7.80 (m, 1 H), 6.75 (s, 1 H), 3.91 (s, 3 H), 3.23 - 3.30 (m, 1 H), 3.05 - 3.19 (m, 3 H), 2.87 (s, 2 H), 2.70 - 2.84 (m, 2 H), 2.53 - 2.67 (m, 5 H), 1.77 - 1.94 (m, 2 H), 1.48 - 1.67 (m, 2 H), 1.19 (t, J =7.42 Hz, 3 H). (some protons obstructed by solvent).

Step H/Intermediate A10: 5-ethyl-2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}aniline

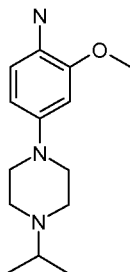


A mixture of 1-{1-[2-ethyl-5-(methoxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)piperazine (1.12 g, 2.63 mmol) and sulfided platinum on carbon (0.410 g, 0.105 mmol) in EtOAc (40 mL) was sealed in a round bottom flask with a rubber septum.

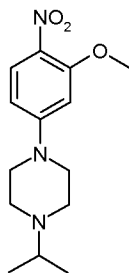
- 5 The reaction mixture was purged with N₂ gas and then a balloon of H₂ gas was connected and the vessel was flushed with the H₂ gas. The reaction was stirred at rt for 48 h. TLC analysis showed the complete consumption of the starting nitro compound so the reaction vessel was purged with N₂ and the reaction mixture was filtered through celite to remove the catalyst. The filtrate was concentrated onto silica gel and purified by
- 10 flash chromatography to afford 5-ethyl-2-(methoxy)-4-{4-[4-(1-methylsulfonyl)-1-piperazinyl]-1-piperidinyl}aniline (0.479 g, 46%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.60 (s, 1 H), 6.46 (s, 1 H), 4.35 (br. s., 2 H), 3.71 (s, 3 H), 3.03 - 3.16 (m, 4 H), 2.81 - 2.93 (m, 5 H), 2.56 - 2.68 (m, 6 H), 2.29 - 2.42 (m, 1 H), 1.72 - 1.89 (m, 2 H), 1.44 - 1.62 (m, 2 H), 1.09 (t, *J*=7.51 Hz, 3 H). (some protons obstructed by solvent).

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Intermediate A18: 4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)aniline

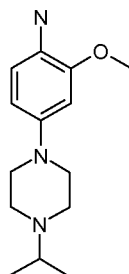


- 20 Step A/Intermediate A19: 1-(1-methylethyl)-4-[3-(methoxy)-4-nitrophenyl]piperazine



To 4-chloro-2-(methyloxy)-1-nitrobenzene (3.0 g, 16.0 mmol) in dioxane (75 mL) was added 1-(1-methylethyl)piperazine (4.1 g, 32.0 mmol), XANTPHOS (1.4 g, 2.4 mmol),
5 and Cs_2CO_3 (10.4 g, 32.0 mmol). The mixture was bubbled with N_2 for 15 min prior to the addition of $\text{Pd}_2(\text{dba})_3$ (1.5 g, 1.6 mmol). The reaction was stirred at 100 °C for 5 h. Following cooling to room temperature, the reaction mixture was diluted with ethyl acetate (150 mL) and water (100 mL). The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by silica gel
10 chromatography to afford 1-(1-methylethyl)-4-[3-(methyloxy)-4-nitrophenyl]piperazine (4.0 g, 90% yield). ESIMS ($\text{M}+\text{H}$)⁺ = 280.

Step B/Intermediate A18: 4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)aniline



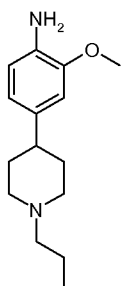
15

In a pressure vessel was placed a solution of 1-(1-methylethyl)-4-[3-(methyloxy)-4-nitrophenyl]piperazine (4.0 g, 14.3 mmol) in EtOH (100 mL). The solution was purged with N_2 for 15 min before the addition of 10% Pd/C (0.5 g). The reaction was stirred at
20 RT for 5 h under 60 psi H_2 . After releasing H_2 pressure, filtration removed the solid resin, and the filtrate was concentrated and purified with silica gel chromatography (0-5% 2 M NH_3 in MeOH/DCM) to furnish 4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)aniline (3.6 g, 99% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.09 (d, J = 6.6

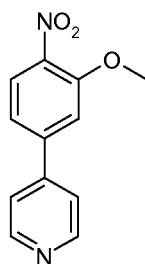
Hz, 6 H), 2.66 - 2.75 (m, 5 H), 3.05 - 3.10 (m, 4 H), 3.47 (s, 3 H), 3.83 (s, 2 H), 6.42 (dd, $J = 8.2, 2.4$ Hz, 1 H), 6.52 (d, $J = 2.2$ Hz, 1 H), 6.64 (d, $J = 8.4$ Hz, 1 H).

Intermediate A20: 2-(methyloxy)-4-(1-propyl-4-piperidiny)aniline

5



Step A/Intermediate A21: 4-[3-(methyloxy)-4-nitrophenyl]pyridine



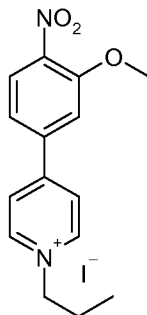
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Nitrogen was bubbled through dioxane (800 mL) for 1 h followed by the addition of 4-chloro-2-(methyloxy)-1-nitrobenzene (61 g, 0.33 mol), 3-pyridinylboronic acid (Boron Molecular, 40 g, 0.33 mmol), dichloro(triphenylphosphine)palladium (10 g, 14 mmol), and degassed aqueous 3 M Na₂CO₃ (325 mL, 975 mmol). The reaction mixture was stirred with a mechanical stirrer and heated at 90 °C for 3 h. The reaction was cooled and most of the dioxane was removed in vacuo. It was diluted with water and then extracted with ethyl acetate. Combined organic phases were dried (Mg₂SO₄), filtered and concentrated. The resultant solid was washed with diethyl ether to afford 4-(3-methoxy-4-nitrophenyl)pyridine (50 g, 66% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.05 (s, 3 H), 7.53 (dd, $J=8.4, 1.8$ Hz, 1 H), 7.69 (d, $J=1.8$ Hz, 1 H), 7.84 (d, $J=6.2$ Hz, 2 H), 8.02 (d, $J=8.4$ Hz, 1 H), 8.72 (d, $J=6.2$ Hz, 2 H). ESIMS (M+H)⁺ = 231.

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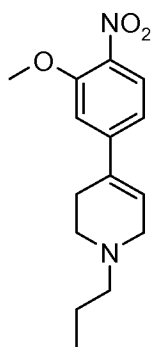
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Step B/Intermediate A22: 4-[3-(methoxy)-4-nitrophenyl]-1-propylpyridinium iodide



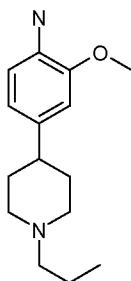
- 5 n-Propyliodide (200 mL, 2.05 mol) was added to a solution of 4-(3-methoxy-4-nitrophenyl)pyridine (25.0 g, 109 mmol) in pinacolone (500 mL). The reaction was fitted with a reflux condenser, stirred, and heated at 100 °C for 12 h. A light brown suspension was observed. An aliquot (~2.0 mL) was taken out from the reaction mixture, concentrated, and analyzed by ¹H NMR which revealed the formation of the alkylated
- 10 product and the absence of starting material. The reaction was cooled; the solids were filtered off and rinsed once with cold (0 °C) acetone to afford 4-(3-methoxy-4-nitrophenyl)-1-propylpyridinium iodide as a light brown residue (29.0 g, 67% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.92 (t, *J*=7.3 Hz, 3 H), 1.99 (dt, *J*=7.3, 7.3 Hz, 2 H), 4.08 (s, 3 H), 4.59 (t, *J*=7.1 Hz, 2 H), 7.78 (dd, *J*=1.5, 8.4 Hz, 1 H), 7.92 (d, *J*=1.5 Hz, 1
- 15 H), 8.13 (d, *J*=8.4 Hz, 1 H), 8.65 (d, *J*=7.0 Hz, 2 H), 9.22 (d, *J*=6.6 Hz, 2 H).

Step C/Intermediate A23: 4-(3-methoxy-4-nitrophenyl)-1-propyl-1,2,3,6-tetrahydropyridine



4-(3-methoxy-4-nitrophenyl)-1-propylpyridinium iodide (10 g, 25 mmol) was dissolved in methanol (200 mL). As the mixture was cooled to -10 °C the starting material started to precipitated out of the solution. Sodium borohydride (4.61 g, 11.3 mmol) was added in ~500 mg portions. Effervescence was observed during the addition as dissolution of the solids in the reaction was observed. The reaction was stirred for 2 h at -10 °C when analysis by TLC revealed completion of the reaction. Saturated aqueous ammonium chloride was added and the reaction warmed to room temperature. The mixture was extracted with ethyl acetate, the organic layers were dried (Mg₂SO₄), filtered, and concentrated in vacuo to provide 4-(3-methoxy-4-nitrophenyl)-1-propyl-1,2,3,6-tetrahydropyridine (6.7 g, 97% yield). This protocol could be reproduced to generate additional product which could be carried forward as blended batches. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.4 Hz, 3 H), 1.50 (dt, *J*=7.3, 7.3 Hz, 2 H), 2.37 (t, *J*=7.2 Hz, 2 H), 2.53 (m, 2 H), 2.63 (m, 2 H), 3.11 (br s, 2 H), 3.96 (s, 3 H), 6.43 (t, *J*=3.5 Hz, 1 H), 7.16 (dd, *J*=8.4, 1.5 Hz, 1 H), 7.29 (d, *J*=1.3 Hz, 1 H), 7.86 (d, *J*=8.6 Hz, 1 H). ESIMS (M+H)⁺ = 277.

Step D/Intermediate A20: 2-(methoxy)-4-(1-propyl-4-piperidinyl)aniline

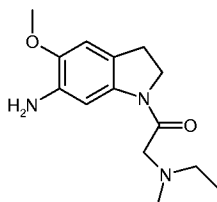


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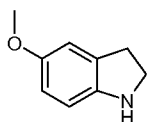
Palladium on carbon (10% by weight, 2.5 g) was added to a nitrogen-flushed Fischer-Porter vessel. A solution of the 4-(3-methoxy-4-nitrophenyl)-1-propyl-1,2,3,6-tetrahydropyridine (9.20 g, 33.3 mmol) in ethyl acetate (150 mL) followed by methanol (50 mL) were added to the vessel. The reaction was purged and then kept under a hydrogen pressure of 60 psi for 2 d. The pressure was released and the reaction was purged with nitrogen. The reaction was filtered through celite and concentrated to afford 2-methoxy-4-(1-propylpiperidin-4-yl)aniline as a white solid (7.0 g, 85% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.86 (t, *J*=7.5 Hz, 3 H), 1.44 (dt, *J*=7.4, 7.4 Hz, 2 H), 1.52 -

1.63 (m, 2 H), 1.63 - 1.70 (m, 2 H), 1.90 (td, $J=11.6$, 2.4 Hz, 2 H), 2.20 - 2.25 (m, 2 H), 2.30 (tt, $J=11.9$, 4.0 Hz, 1 H), 2.89 - 2.94 (m, 2 H), 3.74 (s, 3 H), 4.45 (s, 2 H), 6.53 (s, 2 H), 6.65 (s, 1 H). ESIMS (M+H)⁺ = 249.

5 **Intermediate A14: 1-[ethyl(methyl)amino]acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine**



Step A/Intermediate A25: 5-(methyloxy)-2,3-dihydro-1H-indole

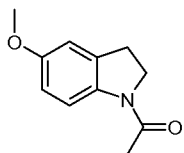


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At room temperature, to a solution of 5-(methyloxy)-1H-indole (12 g, 81.5 mmol, 1.0 eq) in acetic acid (150 mL) was added sodium cyanoborohydride (10.25 g, 163 mmol, 2.0eq) in small portions, and the mixture was stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and brine, and dried over Na₂SO₄. The solvent was removed under reduced pressure to give 5-(methyloxy)-2,3-dihydro-1H-indole (8.91 g, 45% yield) ¹H NMR (CDCl₃, 300 MHz) δ 6.76 (s, 1H), 6.60 (s, 2H), 3.54 (t, 2H), 3.01 (t, 2H).

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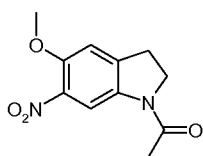
Step B/Intermediate A26: 1-acetyl-5-(methyloxy)-2,3-dihydro-1H-indole



To a solution 5-(methyloxy)-2,3-dihydro-1*H*-indole (8.9 g, 59.8 mmol, 1.0 eq) in acetic acid (120 mL) was added dropwise acetic anhydride (6.1 g, 59.8 mmol, 1.0 eq). The mixture was heated at 60 °C for 15 minutes. The reaction was quenched by pouring into water (100 mL). After cooling, a grey precipitate was formed. The precipitate was
5 filtered by a Buchner funnel and rinsed with water to afford 1-acetyl-5-(methyloxy)-2,3-dihydro-1*H*-indole (10.5 g, 91% yield). ¹H-NMR (CDCl₃, 300 MHz) δ 8.13 (d, *J* = 6.3 Hz, 1H), 6.74-6.71 (m, 2 H), 4.05 (t, 2 H), 3.78 (s, 3 H), 3.17 (t, 2 H), 2.21 (s, 3 H).

Step C/Intermediate A27: 1-acetyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole

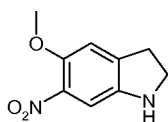
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To a solution of 5-(methyloxy)-2,3-dihydro-1*H*-indole (10.4 g, 54.4 mmol, 1.0 eq) in acetic anhydride (150 mL) was added dropwise fuming nitric acid (3.43 g, 54.4 mmol, 1.0 eq) at 0°C, then the mixture was stirred for 1 hour at room temperature. After stirring
15 for 1 hour the yellow precipitate which formed was filtered via Buchner funnel and washed with water and dried in vacuo to give 1-acetyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole as a yellow solid (8.0 g, 62% yield). ¹H-NMR (CDCl₃, 300 MHz) δ 8.43 (s, 1H), 7.31 (s, 1H), 4.13 (t, 2H), 3.87 (s, 3H), 3.22 (t, 2H), 2.14 (s, 3H).

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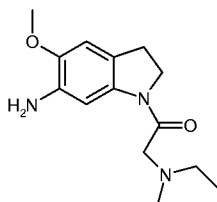
Step D/Intermediate A28: 5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole



25 To the solution of conc. HCl (20 mL) in methanol (40 mL) was added 1-acetyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole (7.8 g, 33 mmol) and the resulting mixture was refluxed for 4 hours. After cooling, the solvent was removed in vacuo, the residue was neutralized with saturated aqueous sodium hydrogencarbonate solution, and a brown precipitate formed. The precipitate was filtered via Buchner funnel, washed with water,

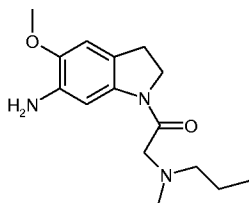
and dried under reduced pressure to give 5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole as a brown solid (6.1 g, 94% yield). ¹H-NMR (DMSO, 300 MHz) δ 7.11 (s, 1H), 6.87 (s, 1H), 5.59 (brs, 1H), 3.78 (s, 3H), 3.43 (t, 2H), 2.97 (t, 2H).

5 Step E/Intermediate A24 : 1-[[ethyl(methyl)amino]acetyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



A solution of 5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole (33.6g, 173 mmol) in CH₂Cl₂ (150mL) was added dropwise to a mixture of bromoacetylchloride (54.5g, 346 mmol) and K₂CO₃ (53.0g, 381 mmol) in CH₂Cl₂ (150 mL). The resulting solution was stirred at 0°C for 1 hour, then warmed up RT for 4 hours. Water (150 mL) was added and the mixture was extracted with CH₂Cl₂ (2x100mL). The organic phase was dried over Na₂SO₄, the solvent was removed to yield the 1-(bromoacetyl)-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole (54.2g, 99%). ¹HNMR (400 MHz, DMSO) δ ppm 2.47(s, 2H), 3.25 (m, 2 H), 3.87 (s, 3 H), 4.21 (m, 2 H), 7.34 (s, 1 H), 8.42 (s, 1 H). The 1-(bromoacetyl)-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole (4.0g, 12.7 mmol) was dissolved in 50 mL of dichloromethane, then K₂CO₃ (4.4g, 31.7 mmol) and N-methylethanamine(1.5g, 25.4 mmol) in 10 mL dichloromethane were added and the reaction was stirred at RT for 3 hours. After filtration, the organic layers were washed with water (2x100mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the derived residue (3.4 g, 11.59mmol) was dissolved in 10 mL of EA, 25 mL of MeOH and 15 mL of THF, then 0.8 g 10% Pd/C was added, the reaction was stirred at RT overnight under H₂ pressure (65 psi). The catalyst was removed via filtration, and the solvent was evaporated under reduced pressure to afford 1-[[ethyl(methyl)amino]acetyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine as a yellow solid, 3.0g (97%). ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm: 0.97 (t, J=7.14 Hz, 3 H), 2.20 (s, 3H), 2.46 (m, 2H), 2.94 (t, 2 H), 3.16 (s, 2H), 3.68 (s, 3H), 4.06 (t, J=8.42 Hz, 2 H), 4.60 (s, 2H), 6.67 (s, 1 H), 7.52 (s, 1 H).

Intermediate A29: 5-(methoxy)-1-[[methyl(propyl)amino]acetyl]-2,3-dihydro-1H-indol-6-amine



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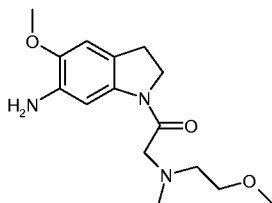
1-(bromoacetyl)-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (4.0g, 12.7 mmol) was dissolved in 50 mL of dichloromethane, then K_2CO_3 (4.4g, 31.7 mmol) and *N*-methyl-1-propanamine (1.9g, 25.4 mmol) in 10 mL dichloromethane were added, the reaction was stirred at RT for 3 hours. After filtration, the organic layers were washed with water (2x100mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the resulting residue was dissolved in 10 mL of EA, 25 mL of MeOH and 15 mL of THF, then 0.8 g 10% Pd/C was added and the reaction was stirred at RT overnight under H_2 pressure (65 psi). The catalyst was removed via filtration and the solvent was removed under reduced pressure to afford 5-(methoxy)-1-

10

15 {[[methyl(propyl)amino]acetyl]-2,3-dihydro-1H-indol-6-amine as a yellow solid, 3.0g (96%). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm: 0.81 (t, $J=7.14$ Hz, 3 H), 1.40 (m, 2H), 2.21 (s, 3H), 2.35(m, 2H), 2.94 (t, $J=8.24$ Hz, 2 H), 3.17(s, 2H), 3.70 (s, 3H), 4.07 (t, $J=8.33$ Hz, 2 H), 4.60 (s, 2H), 6.67 (s, 1 H), 7.52 (s, 1 H).

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Intermediate A30: 1-({methyl[2-(methoxy)ethyl]amino}acetyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-amine

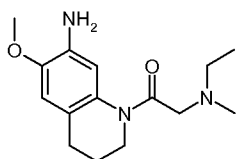


The 1-(bromoacetyl)-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (4.0g, 12.7 mmol) was dissolved in 50 mL of dichloromethane, then K_2CO_3 (4.4g, 31.7 mmol) and *N*-methyl-2-(methoxy)ethanamine (1.4g, 15.2 mmol) in 10 mL dichloromethane were added, the

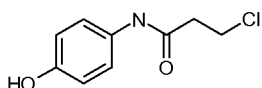
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reaction was stirred at RT overnight. The reaction mixture was diluted with 100 mL of water, the organic solvents were washed with water (2x100mL), and dried over Na₂SO₄. The solvent was removed under reduced pressure and the resulting residue was dissolved in 10 mL of EA, 25 mL of MeOH and 15 mL of THF, then 0.8 g 10% Pd/C was added, and the reaction was stirred at RT overnight under a balloon of H₂ pressure. The catalyst was removed via filtration and the solvent was evaporated under reduced pressure to yield the 1-({methyl[2-(methyloxy)ethyl]amino}acetyl)-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-amine as a white solid (3.1g, 89%). ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm: 2.28(s, 3H), 2.62 (t, *J*=5.77 Hz, 2 H), 2.94 (t, *J*=8.24Hz, 2H), 3.19 (s, 3H), 3.25(s, 2H), 3.41 (t, *J*=5.77 Hz, 2 H), 3.68 (s, 3H), 4.04 (t, *J*=8.33Hz, 2 H), 4.61 (s, 2H), 6.67 (s, 1 H), 7.52 (s, 1 H).

Intermediate A31: 1-{{ethyl(methyl)amino}acetyl}-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinamine

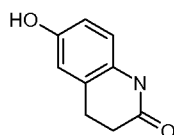


Step A/Intermediate A32: 3-chloro-*N*-(4-hydroxyphenyl)propanamide



A solution of 4-aminophenol (250 g, 2.29 mol, 1 equiv) in CH₂Cl₂ (2L) and saturated NaHCO₃ (2L) was stirred for 5 min at 25°C, then 3-chloropropanoyl chloride (314 g, 2.52 mol 1.1equiv) was added dropwise and the reaction was stirred for an additional 3h at 25°C. The solids were filtered and dried under high vacuum to afford 3-chloro-*N*-(4-hydroxyphenyl)propanamide suitable for direct use in the next step. (250g, crude). ¹H NMR (400 MHz, DMSO) δ, 2.96-2.99 (m, 2 H), 4.06-4.10 (m, 2 H), 6.88-6.92 (m 2 H), 7.57-7.60 (m, 2 H), 9.38-9.39 (br s, 1 H), 10.1 (br s, 1 H).

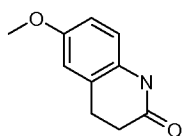
Step B/Intermediate A33: 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone



A mixture of 3-chloro-*N*-(4-hydroxyphenyl)propanamide (122 g, 0.61 mol) and AlCl_3 (327 g, 2.45 mol) were slowly heated with vigorous stirring at 180°C (a thick melt formed) and
5 after 5 hours the liquid was poured over ice. The solids were collected by filtration, washed with water, and recrystallized from MeOH to afford 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (80g, 40% yield). ^1H NMR (400 MHz, DMSO) δ , 2.32-2.36 (m, 2 H), 2.74 (t, 2 H, $J=7.2$ Hz), 6.50 (m, 1 H), 6.54 (d, 1 H, $J=2.8$ Hz), 6.62(d, 1 H, $J=8.4$ Hz), 9.00 (br, 1 H), 9.78 (br, 1 H).

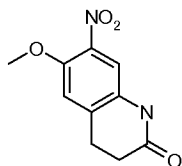
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Step C/Intermediate A34: 6-(methyloxy)-3,4-dihydro-2(1*H*)-quinolinone



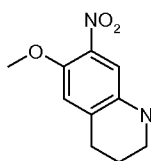
15 To 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (90.8 g, 0.56 mol, 1 equiv) in CH_3CN (2L) was added potassium carbonate (230.67 g, 1.67 mol, 3 equiv). The mixture was stirred for 1h at 25°C , then MeI (75 g, 0.53 mol, 0.95 equiv) was added and the mixture was maintained at 60°C for 12 hours. The mixture was filtered and the filtrate was taken to a residue under reduce pressure. The crude 6-(methyloxy)-3,4-dihydro-2(1*H*)-quinolinone
20 was directly used in the next step. (128g, crude) ^1H NMR (400 MHz, DMSO) δ , 2.34-2.38 (m, 2 H), 2.79 (t, 2 H, $J=7.2$ Hz), 3.65 (s, 3 H), 6.67 (m, 1 H), 6.72-6.75 (m, 2 H), 9.86 (br s, 1 H). This procedure was reproduced multiple times to prepare >300g quantities of 6-(methyloxy)-3,4-dihydro-2(1*H*)-quinolinone.

25 Step D/Intermediate A35: 6-(methyloxy)-7-nitro-3,4-dihydro-2(1*H*)-quinolinone



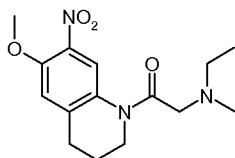
To a solution of 6-(methoxy)-3,4-dihydro-2(1H)-quinolinone (209 g, 1.18 mol) in TFA (1500 mL) was added NaNO₂ (96 g, 1.41 mol, 1.2 equiv) at 0°C, then the temperature
5 was raised to 25 °C and the mixture was stirred for 4 hours. The mixture was poured into ice and the yellow precipitate was collected via filtration and dried under high vacuum at 50 °C. The crude product was recrystallized from ethyl acetate to afford 6-(methoxy)-7-nitro-3,4-dihydro-2(1H)-quinolinone (75.6g, 29%). ¹H NMR (400 MHz, DMSO) δ 2.39-2.43 (m, 2 H), 2.92(t, 2 H, J=7.2 Hz), 3.82 (s, 3 H), 7.22 (s, 1 H), 7.32 (s,
10 1 H), 10.11(br s, 1 H).

Step E/Intermediate A36: 6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline



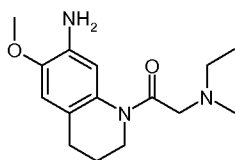
To a stirred solution of 6-(methoxy)-7-nitro-3,4-dihydro-2(1H)-quinolinone (75 g of, 0.34 mol, 1 equiv) in THF (1L) was added BH₃.DMS (10 M, 150 mL, 1.5 mol, 4.4equiv) dropwise at 25 °C. After the addition, the mixture was stirred for 6 h at 60 °C. The reaction was cooled and quenched with excess MeOH, concentrated under reduced
20 pressure and purified via chromatography on SiO₂ to afford 6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (51.5 g, 73% yield). ¹H NMR (400 MHz, DMSO) δ 1.73-1.80 (m, 2 H), 2.71 (t, 2 H, J=6.4 Hz), 3.13-3.16 (m, 2 H), 3.75 (s, 3 H), 5.83(br s, 1 H), 6.88(s, 1 H), 6.95(s, 1 H).

Step F/Intermediate A37: *N*-ethyl-*N*-methyl-2-[6-(methoxy)-7-nitro-3,4-dihydro-1(2H)-quinolinyl]-2-oxoethanamine



A solution of 6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (3.00 g, 14.41 mmol), Hunig's Base (12.55 mL, 72.0 mmol), and bromo-acetylchloride (1.500 mL, 18.01 mmol) was stirred at room temperature for 2 hours, at which time quinoline was observed to still remain. Additional bromo-acetylchloride (1.500 mL, 18.01 mmol) was added, the reaction was stirred an additional 5 hours, N-ethylmethylamine (12.38 mL, 144 mmol) was added, and the reaction was maintained for 16 hours at room temperature. The reaction was poured into saturated aqueous sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over sodium sulfate, taken to a residue under reduced pressure, and the residue was purified by silica gel chromatography to afford N-ethyl-N-methyl-2-[6-(methoxy)-7-nitro-3,4-dihydro-1(2H)-quinolinyl]-2-oxoethanamine (2.02 g, 45.6 % yield) as a dark red solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.35 (s, 1 H), 7.18 (s, 1 H), 3.89 (s, 3 H), 3.75 (s, 2 H), 3.30 (s, 2 H), 2.81 (t, *J*=6.12 Hz, 2 H), 2.36 - 2.47 (m, 2 H), 2.19 (s, 3 H), 1.80 - 1.97 (m, 2 H), 0.86 - 1.02 (m, 3 H).

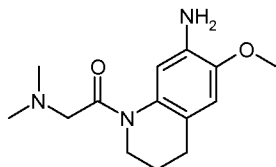
Step G/Intermediate A31: 1-[[ethyl(methyl)amino]acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine



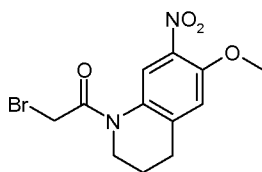
A solution of N-ethyl-N-methyl-2-[6-(methoxy)-7-nitro-3,4-dihydro-1(2H)-quinolinyl]-2-oxoethanamine (2.02 g, 6.57 mmol) and 10% palladium on carbon (1.05 g) in methanol (55 mL) was maintained under 40 psi of H₂ gas in a pressure flask for 24 hours. The solution was purged with nitrogen, filtered through celite, taken to a residue under reduced pressure, and purified by column chromatography to afford 1-[[ethyl(methyl)amino]acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (1.16 g, 64 % yield) as a dark orange oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.82 (s, 1 H),

6.56 (s, 1 H), 4.54 (s, 2 H), 3.72 (s, 3 H), 3.61 (t, $J=5.82$ Hz, 2 H), 3.25 (s, 2 H), 2.57 (t, $J=6.22$ Hz, 2 H), 2.43 (q, $J=7.02$ Hz, 2 H), 2.20 (s, 3 H), 1.70 - 1.89 (m, 2 H), 0.84 - 1.03 (m, 3 H).

5 **Intermediate A38: 1-[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine**

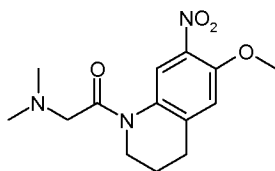


10 **Step A/Intermediate A39: 1-(bromoacetyl)-6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline**



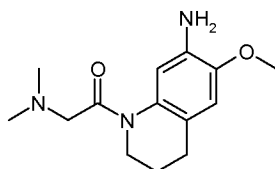
15 A mixture of 6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (0.19 g, 0.91 mmol) and triethylamine (0.5 mL, 3.7 mmol, Aldrich) in dichloromethane was treated with dropwise addition of bromoacetyl chloride (0.33 mL, 4.0 mmol, Fluka). A catalytic amount of 4-dimethylaminopyridine was added and the reaction stirred overnight. The mixture was diluted with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give
20 1-(bromoacetyl)-6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline which was taken directly to the next step without determination of yield. RF = 0.3 (50% EtOAc/hexanes).

Step B/Intermediate A40: N,N-dimethyl-2-[6-(methoxy)-7-nitro-3,4-dihydro-1(2H)-quinolinyl]-2-oxoethanamine



1-(bromoacetyl)-6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (crude from previous reaction, assumed 0.91 mmol) was treated with excess dimethyl amine (4.5 mL, 9.0 mmol, 2 M in THF, Aldrich), and the reaction stirred for 16 h. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give *N,N*-dimethyl-2-[6-(methoxy)-7-nitro-3,4-dihydro-1(2*H*)-quinoliny]-2-oxoethanamine which was taken directly to the next step without determination of yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.85 - 1.95 (m, 2 H), 2.22 (s, 6 H), 2.82 (t, *J*=6.6 Hz, 2 H), 3.22 (bs, 2 H), 3.72 - 3.79 (m, 2 H), 3.89 (s, 3 H), 7.19 (s, 1 H), 8.37 (bs, 1 H); ESIMS (M+H)⁺ = 294.

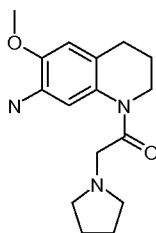
Step C/Intermediate A38: 1-[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine



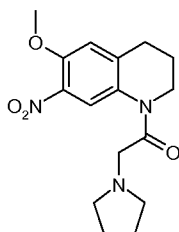
N,N-dimethyl-2-[6-(methoxy)-7-nitro-3,4-dihydro-1(2*H*)-quinoliny]-2-oxoethanamine (crude from previous reaction, assumed 0.91 mmol) was dissolved in methanol (5 mL), treated with 10% palladium on carbon (40 mg, Aldrich), and stirred under 60 psi of hydrogen pressure for 16 h in a Fischer-Porter apparatus. The pressure was released, the reaction vessel evacuated, and back-filled with nitrogen twice. The mixture was filtered through celite, the filtrate was concentrated and purified by chromatography on SiO₂ (0 to 20% methanol/dichloromethane) to provide 1-[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (0.18 g, 0.68 mmol, 75% over three steps). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.88 - 1.97 (m, *J*=6.5, 6.5, 6.5, 6.5 Hz, 2 H), 2.35 (s, 6 H), 2.65 (m, 2 H), 3.24 (s, 2 H), 3.74 - 3.80 (m, 2 H), 3.84 (s, 3 H), 6.55 (s, 1

H), 6.76 (very broad singlet due to amide rotomers, 1H), aniline NH₂ not visible probably due to fast exchange.

Intermediate A41: 6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine



Step A : Intermediate A42: 6-(methyloxy)-7-nitro-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydroquinoline

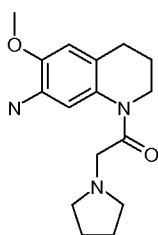


A solution of 6-(methyloxy)-7-nitro-1,2,3,4-tetrahydroquinoline (4.5g, 21.6 mmol) in CH₂Cl₂ (40mL) was added dropwise to a mixture of bromoacetylchloride (6.8g, 43.2 mmol) and K₂CO₃ (6.6g, 47.5 mmol) in CH₂Cl₂ (40 mL). The resulting solution was

stirred at 0°C for 1 hour, then warmed up to RT for 4 hours. Water (50 mL) was added and extracted with CH₂Cl₂ (2x50mL). The organic phase was dried over Na₂SO₄, the solvent was removed under reduced pressure, and the resulting residue was dissolved in 50 mL of dicholomethane. Potassium carbonate (6.2g, 44.4 mmol) and pyrrolidine (4.0g, 55.4 mmol) in 10 mL dicholomethane were added and the reaction was stirred at RT for 3 hours. After filtration, the organic layers were washed with water (2x100mL), and dried over Na₂SO₄. The solvent was removed to yield the 6-(methyloxy)-7-nitro-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydroquinoline as a yellow solid (6.8g, 97%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.66 (br. s., 4 H), 1.85 (app d, *J*=6.04 Hz, 2 H), 2.49 (br. s.,

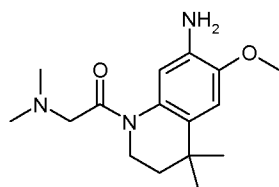
4 H), 2.79 (t, $J=6.00$ Hz, 2 H), 3.35 (br. s., 2 H), 3.71 (br. s., 2 H), 3.86 (s, 3 H), 7.16 (s, 1 H), 8.39 (s, 1 H)

Step B/Intermediate A41: 6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine

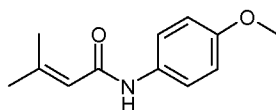


The 6-(methyloxy)-7-nitro-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydroquinoline (6.9 g, 21.6 mmol) was dissolved in 10 mL of EA, 25 mL of MeOH and 15 mL of THF, then 1.0 g 10% Pd/C was added, the reaction was stirred at RT overnight under a balloon of H_2 pressure. The catalyst was removed via filtration and the solvent was evaporated under reduced pressure to yield 6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine as a white solid, 6.0g (95%). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 1.09 (m, 1 H), 1.44 (m, 1 H), 1.62 (m, 1 H), 1.74 (m, 1 H), 2.14 (br, 1H), 2.47(s, 1H), 2.74(br s, 2H), 2.95 (m, 4 H), 3.50 (s, 2H), 3.68 (s, 3H), 4.04 (t, $J=6.13$ Hz, 2 H), 4.71 (s, 2H), 6.68 (s, 1 H), 7.51 (s, 1 H).

Intermediate A43: 1-[(dimethylamino)acetyl]-4,4-dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinamine

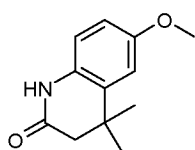


Step A/Intermediate A44: 3-methyl-N-[4-(methyloxy)phenyl]-2-butenamide



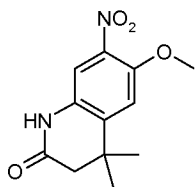
A mixture of *p*-anisidine (10 g, 81 mmol, Aldrich) and potassium carbonate (13.5 g, 97.5 mmol, Aldrich) in acetone (125 mL) was cooled to 0 °C and treated with dimethyl acryloyl chloride (10.2 mL, 89.3 mmol). The mixture was allowed to warm to room temperature overnight. The reaction was diluted with water and extracted with dichloromethane. The organic layer was separated, dried over magnesium sulfate, filtered, concentrated, and purified by chromatography on SiO₂ (0 to 100% ethyl acetate/dichloromethane) to give 3-methyl-*N*-[4-(methoxy)phenyl]-2-butenamide (12.4 g, 67%) as a light violet solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.84 (s, 3 H), 2.13 (s, 3 H), 3.71 (s, 3 H), 5.82 (s, 1 H), 6.85 (d, *J*=9.0 Hz, 2 H), 7.52 (d, *J*=9.0 Hz, 2 H), 9.67 (s, 1 H); ESIMS (*M*+*H*)⁺ = 206.

Step B/Intermediate A45: 4,4-dimethyl-6-(methoxy)-3,4-dihydro-2(1*H*)-quinolinone



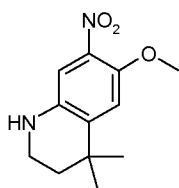
A solution of 3-methyl-*N*-[4-(methoxy)phenyl]-2-butenamide (5.8 g, 28 mmol) in dichloromethane (250 mL) was treated with aluminum trichloride (13 g, 97 mmol, Aldrich). The mixture was refluxed for 7 h, cooled, and then poured over ice. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to give 4,4-dimethyl-6-(methoxy)-3,4-dihydro-2(1*H*)-quinolinone (4.5 g, 77%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.20 (s, 6 H), 2.29 (s, 2 H), 3.71 (s, 3 H), 6.72 - 6.81 (m, 2 H), 6.83 (d, *J*=2.6 Hz, 1 H), 9.97 (s, 1 H).

Step C/Intermediate A46: 4,4-dimethyl-6-(methoxy)-7-nitro-3,4-dihydro-2(1*H*)-quinolinone



A solution of 4,4-dimethyl-6-(methoxy)-3,4-dihydro-2(1*H*)-quinolinone (4.45 g, 21.7 mmol) in trifluoroacetic acid (110 mL) was treated at 0 °C with sodium nitrite (1.9 g, 28 mmol, Aldrich). The dark brown mixture was allowed to warm to room temperature overnight. Analysis of an aliquot of the reaction mixture by ¹H NMR revealed that starting material still remained. Another 1.15 g (16.7 mmol) of sodium nitrite was added in three installments of 300/500/350 mg at room temperature and the reaction stirred for 3/3/20 h respectively. The reaction mixture was concentrated, dissolved in dichloromethane, and washed with saturated aqueous sodium bicarbonate. The organic layer was separated, the aqueous layer was filtered (due to emulsions) and back- extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, concentrated, and triturated with dichloromethane/diethyl ether/hexanes. The mixture was filtered to obtain pure product (3.6 g) and the filtrate was purified by column chromatography on SiO₂ (0 to 100% ethyl acetate/ dichloromethane) to obtain another 350 mg of 4,4-dimethyl-6-(methoxy)-7-nitro-3,4-dihydro-2(1*H*)-quinolinone (a total of 3.97 g, 15.8 mmol, 73%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.28 (s, 6 H), 2.39 (s, 2 H), 3.92 (s, 3 H), 7.21 (s, 1 H), 7.40 (s, 1 H), 10.25 (s, 1 H).

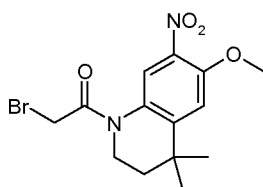
Step D/Intermediate A47: 4,4-dimethyl-6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline



A solution of 4,4-dimethyl-6-(methoxy)-7-nitro-3,4-dihydro-2(1*H*)-quinolinone (2.5 g, 10 mmol) in tetrahydrofuran (45 mL) was treated with borane-dimethylsulfide complex (20.5 mL, 41 mmol, 2 M in THF, Acros Organics). The mixture was heated at reflux for 16 h, cooled, quenched carefully via dropwise of excess methanol,

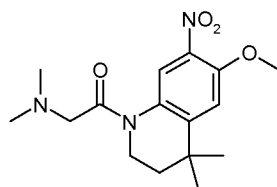
concentrated, and purified by column chromatography on SiO₂ (0 to 100% ethyl acetate/dichloromethane) to obtain 4,4-dimethyl-6-(methyloxy)-7-nitro-1,2,3,4-tetrahydroquinoline (1.33 g, 5.63 mmol, 56%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.26 (s, 6 H), 1.58 - 1.65 (m, 2 H), 3.13 - 3.21 (m, 2 H), 3.79 (s, 3 H), 5.95 (bs, 1 H), 6.96 (s, 1 H), 7.06 (s, 1 H).

Step E/Intermediate A48: 1-(bromoacetyl)-4,4-dimethyl-6-(methyloxy)-7-nitro-1,2,3,4-tetrahydroquinoline



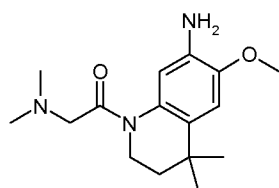
4,4-dimethyl-6-(methyloxy)-7-nitro-1,2,3,4-tetrahydroquinoline (1.32 g, 5.59 mmol) was dissolved in tetrahydrofuran (50 mL). This solution was treated with potassium carbonate (1.54 g, 11.2 mmol, Aldrich) and cooled to 0 °C. Bromoacetyl chloride (0.93 mL, 11 mmol, Fluka) was added (white precipitation observed) and the reaction stirred for 15 min. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 1-(bromoacetyl)-4,4-dimethyl-6-(methyloxy)-7-nitro-1,2,3,4-tetrahydroquinoline (assumed 5.59 mmol, 100%). This material was analyzed by ¹H NMR (amide rotomers were observed) and taken to bromide displacement reactions directly without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.33 (s, 6 H), 1.75 - 1.86 (m, 2 H), 3.72 - 3.82 (m, 2 H), 3.95 (s, 3 H), 4.31 - 4.69 (two singlets at 4.37 and 4.63, 2 H), 7.27 (s, 1 H), 8.28 (very broad singlet, 1H).

Step F/Intermediate A49: {2-[4,4-dimethyl-6-(methyloxy)-7-nitro-3,4-dihydro-1(2H)-quinoliny]-2-oxoethyl}dimethylamine



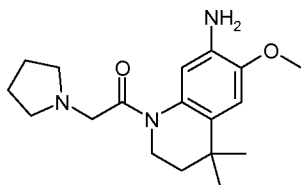
A solution of 1-(bromoacetyl)-4,4-dimethyl-6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (1.0 g, 2.8 mmol) in tetrahydrofuran (35 mL) was treated with potassium carbonate (1.3 g, 9.4 mmol) and dimethyl amine (10 mL, 20 mmol, 2 M in THF, Aldrich). The mixture was heated in sealed tube at 55 °C for 1h, cooled, diluted with water, and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to give {2-[4,4-dimethyl-6-(methoxy)-7-nitro-3,4-dihydro-1(2H)-quinoliny]-2-oxoethyl}dimethylamine which was taken directly to the next step. ESIMS (M+H)⁺ = 322.

Step G/Intermediate A43: 1-[(dimethylamino)acetyl]-4,4-dimethyl-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine

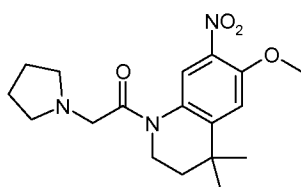


{2-[4,4-dimethyl-6-(methoxy)-7-nitro-3,4-dihydro-1(2H)-quinoliny]-2-oxoethyl}dimethylamine (assumed 2.8 mmol) was dissolved in a mixture of ethyl acetate (50 mL) and water (5 mL) and transferred to a Fischer Porter apparatus. 10% Palladium on carbon (500 mg, Aldrich) was added followed by methanol (5 mL) and the mixture stirred under 60 psi hydrogen pressure for 2 h. The pressure was released, the reaction vessel evacuated, and back-filled with nitrogen twice. The mixture was filtered through celite and the filtrate was concentrated to provide 1-[(dimethylamino)acetyl]-4,4-dimethyl-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (724 mg, 2.49 mmol, 89% over three steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.20 (s, 6 H), 1.62 - 1.68 (m, 2 H), 2.20 (s, 6 H), 3.17 (s, 2 H), 3.62 - 3.69 (m, 2 H), 3.75 (s, 3 H), 4.58 (bs, 2 H), 6.56 - 6.94 (s at 6.71 on top of a very broad singlet caused by amide rotomers, 2 H); ESIMS (M+H)⁺ = 292.

Intermediate A50: 4,4-dimethyl-6-(methoxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine

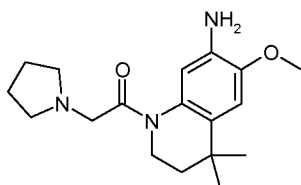


- 5 Step A/Intermediate A51: 4,4-dimethyl-6-(methoxy)-7-nitro-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydroquinoline



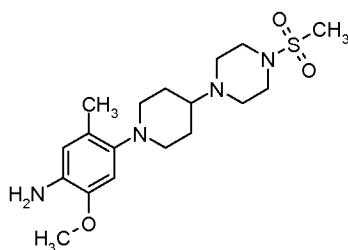
- 10 A solution of 1-(bromoacetyl)-4,4-dimethyl-6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (1.0 g, 2.8 mmol) in tetrahydrofuran (35 mL) was treated with potassium carbonate (1.3 g, 9.4 mmol) and pyrrolidine (1.5 mL, 18 mmol, Aldrich). The mixture was heated in sealed tube at 55 °C for 1h, cooled, diluted with water, and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to give 4,4-dimethyl-6-(methoxy)-7-nitro-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydroquinoline which was taken directly to the next step. ESIMS (M+H)⁺ = 348.

- Step B/Intermediate A50: 4,4-dimethyl-6-(methoxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine

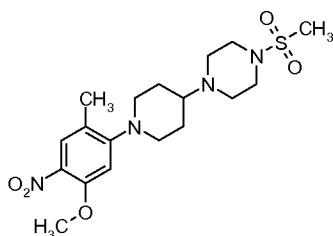


4,4-dimethyl-6-(methyloxy)-7-nitro-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydroquinoline (assumed 2.8 mmol) was dissolved in a mixture of ethyl acetate (50 mL) and water (5 mL) and transferred to a Fischer Porter apparatus. 10% Palladium on carbon (500 mg, Aldrich) was added followed by methanol (5 mL) and the mixture stirred under 60 psi hydrogen pressure for 2 h. The pressure was released, the reaction vessel evacuated, and back-filled with nitrogen twice. The mixture was filtered through celite and the filtrate was concentrated to provide 4,4-dimethyl-6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine (790 mg, 89% over three steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.19 (s, 6 H), 1.61 - 1.71 (m, 6 H), 2.50 - 2.54 (m, signal underneath DMSO, 4 H), 3.32 - 3.35 (m, signal underneath H₂O, 2 H), 3.62 - 3.69 (m, 2 H), 3.75 (s, 3 H), 4.58 (bs, 2 H), 6.62 - 7.00 (s at 6.71 on top of a very broad singlet caused by amide rotomers, 2 H).

Intermediate A52: 5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}-aniline



Step A/Intermediate A53: 1-{1-[2-methyl-5-(methyloxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)-piperazine

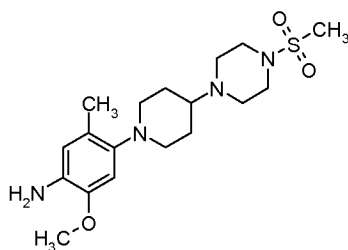


A mixture of 1-fluoro-2-methyl-5-(methyloxy)-4-nitrobenzene (0.90 g, 4.9 mmol), 1-(methylsulfonyl)-4-(4-piperidinyl)piperazine (1.20 g, 4.9 mmol) and K₂CO₃ (0.81 g, 5.8 mmol) in DMSO (15 mL) was heated at 100 °C for 48 h. The reaction was cooled to rt, poured into H₂O and extracted exhaustively with DCM. The combined organics were washed with H₂O then dried over MgSO₄. The resultant solution was concentrated onto silica and purified by flash chromatography to afford 1-{1-[2-methyl-5-(methyloxy)-4-

nitrophenyl]-4-piperidinyl]-4-(methylsulfonyl)piperazine (1.09 g, 55%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.77 (s, 1 H), 6.69 (s, 1 H), 3.90 (s, 3 H), 3.29 - 3.38 (m, 2 H), 3.06 - 3.15 (m, 4 H), 2.87 (s, 3 H), 2.68 - 2.79 (m, 2 H), 2.59 - 2.66 (m, 4 H), 2.40 - 2.48 (m, 1 H), 2.20 (s, 3 H), 1.80 - 1.92 (m, 2 H), 1.49 - 1.67 (m, 2 H).

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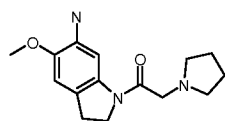
Step B/Intermediate A52: 5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}-aniline



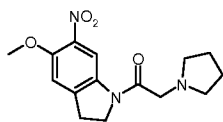
Sodium borohydride (0.30 g, 7.93 mmol) was added in portions to a stirring suspension of 1-{1-[2-methyl-5-(methyloxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)piperazine (1.09 g, 2.64 mmol) and NiCl₂·6H₂O (0.19 g, 0.8 mmol) in THF (10 mL) and MeOH (20 mL) at rt. The reaction mixture was allowed to stir at rt for 2 h and then it was concentrated *in vacuo*. The residue was taken up in DCM and passed through a bed of celite. The resultant filtrate was then concentrated onto silica gel and purified by flash chromatography to afford 5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}aniline (0.58 g, 57%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.55 (s, 1 H), 6.43 (s, 1 H), 4.30 (s, 2 H), 3.70 (s, 3 H), 3.05 - 3.15 (m, 4 H), 2.89 - 2.96 (m, 2 H), 2.86 (s, 3 H), 2.52 - 2.65 (m, 6 H), 2.26 - 2.41 (m, 1 H), 2.06 (s, 3 H), 1.74 - 1.85 (m, 2 H), 1.43 - 1.63 (m, 2 H).

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Intermediate A54: 5-(methyloxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indol-6-amine

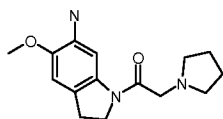


25 Step A/Intermediate A55: 5-(methyloxy)-6-nitro-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indole

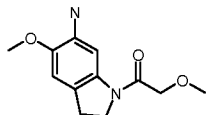
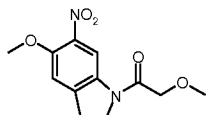


To a 0 °C slurry of 5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole hydrogen chloride (743 mg, 3.22 mmol) and DIPEA (2.8 mL, 16.11 mmol) was added bromoacetyl chloride (0.3 mL, 3.54 mmol) dropwise. After stirring at rt for 40 min pyrrolidine (1 mL, 12.89 mmol) was added and the reaction mixture was stirred overnight. The resulting mixture was concentrated and the residue was partitioned between EtOAc (200 mL) and water (200 mL). The organic layer was washed with a saturated NaCl solution (100 mL). The aqueous layers were back-extracted with EtOAc (100 mL). The organic layers were combined, dried (Na₂SO₄) and concentrated to obtain 5-(methoxy)-6-nitro-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indole as a brown solid (754 mg, 77%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.71 (br s, 4H), 2.58 (br s, 4H), 3.23 (t, *J*=8.42 Hz, 2H), 3.40 (s, 2H), 3.89 (s, 3H), 4.20 (t, *J*=8.42 Hz, 2H), 7.34 (s, 1H), 8.38 (s, 1H); ESIMS (M+H)⁺ = 305.97.

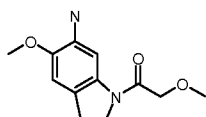
Step B/Intermediate A54: 5-(methoxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indol-6-amine



To a solution of 5-(methoxy)-6-nitro-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indole (750 mg, 2.46 mmol) in THF (20 mL) and MeOH (40 mL) was added NiCl₂·6H₂O (source: Riedel De Halën) (175 mg, 0.74 mmol), followed by addition of NaBH₄ (280 mg, 7.4 mmol) in small portions. After stirring overnight the reaction mixture was concentrated onto Celite and purified by silica gel chromatography using 0-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 5-(methoxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indol-6-amine as a brown solid (364 mg, 54%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.70 (br s, 4H), 2.56 (br s, 4H), 2.97 (t, *J*=8.24 Hz, 2H), 3.71 (s, 3H), 4.06 (t, *J*=8.33 Hz, 2H), 4.63 (s, 2H), 6.70 (s, 1H), 7.54 (s, 1H) a CH₂ signal with 2 protons is missing, may overlap with water peak in sample; ESIMS (M+H)⁺ = 276.11.

Intermediate A56: 5-(methoxy)-1-[(methoxy)acetyl]-2,3-dihydro-1H-indol-6-amine**5 Step A/Intermediate A57: 5-(methoxy)-1-[(methoxy)acetyl]-6-nitro-2,3-dihydro-1H-indole**

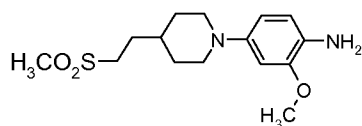
A slurry of 5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (3.2 g, 13.87 mmol) in THF (100 mL) was treated with diisopropylethylamine (4.83 mL, 27.7 mmol), followed by (methoxy)acetyl chloride (1.903 mL, 20.81 mmol). The resulting yellow slurry was stirred at rt for 3 days, then diluted with CH₂Cl₂ (300 mL), washed with water (150 mL), a saturated NaCl solution (150 mL), dried (Na₂SO₄) and concentrated to obtain 5-(methoxy)-1-[(methoxy)acetyl]-6-nitro-2,3-dihydro-1H-indole as an orange solid (3.96 g). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.24 (t, J=8.42 Hz, 2H), 3.36 (s, 3H), 3.89 (s, 3H), 4.07 (t, J=8.42 Hz, 2H), 4.19 (s, 2H), 7.35 (s, 1H), 8.47 (s, 1H); ESIMS (M+H)⁺ = 266.87.

Step B/Intermediate A56: 5-(methoxy)-1-[(methoxy)acetyl]-2,3-dihydro-1H-indol-6-amine

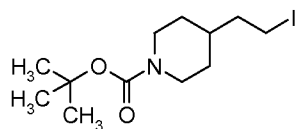
A slurry of 5-(methoxy)-1-[(methoxy)acetyl]-6-nitro-2,3-dihydro-1H-indole (3.96 g, 14.87 mmol) and NiCl₂ 6H₂O (1.061 g, 4.46 mmol) in THF (50 mL) and MeOH (100 mL) was treated with NaBH₄ (1.69 g, 44.6 mmol) in small portions. After 5 minutes the reaction mixture was concentrated onto Celite and purified by silica gel chromatography using THF. The crude product was triturated using CH₂Cl₂ and Et₂O to obtain 5-(methoxy)-1-[(methoxy)acetyl]-2,3-dihydro-1H-indol-6-amine as a white solid (884 mg, 25%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.98 (t, J=8.24Hz, 2H), 3.34 (s, 3H),

3.71 (s, 3H), 3.93 (t, $J=8.33$ Hz, 2H), 4.12 (s, 2H), 4.67 (s, 2H), 6.71 (s, 1H), 7.54 (s, 1H); ESIMS ($M+H$)⁺ = 237.4.

Intermediate A58: 2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}aniline

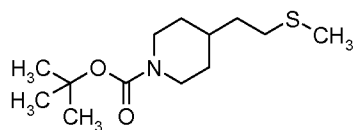


Step A/Intermediate A59: 1,1-dimethylethyl 4-(2-iodoethyl)-1-piperidinecarboxylate



To *N*-Boc-4-piperidone-ethanol (5.00 g, 21.8 mmol) in THF (100 mL) was added triphenylphosphine (6.29 g, 24.0 mmol), imidazole (1.64 g, 24.1 mmol) and iodine (6.09 g, 24.0 mmol). The reaction was stirred at rt for 2 h. The mixture was filtered through Celite® purified by flash chromatography to provide 1,1-dimethylethyl 4-(2-iodoethyl)-1-piperidinecarboxylate (6.31 g, 18.6 mmol, 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (dq, $J=12.2$, 4.3 Hz, 2 H), 1.42 (s, 9 H), 1.49 - 1.58 (m, 1 H), 1.62 (d, $J=13.2$ Hz, 2 H), 1.75 (q, $J=7.1$ Hz, 2 H), 2.67 (td, $J=12.9$, 2.5 Hz, 2 H), 3.18 (t, $J=7.1$ Hz, 2 H), 4.06 (d, $J=13.0$ Hz, 2 H).

Step B /Intermediate A60: 1,1-dimethylethyl 4-[2-(methylthio)ethyl]-1-piperidinecarboxylate

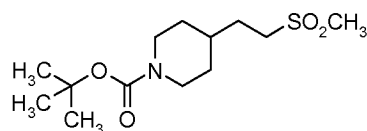


To 1,1-dimethylethyl 4-(2-iodoethyl)-1-piperidinecarboxylate (3.13 g, 9.23 mmol) in DMF (50 mL) was added sodium thiomethoxide (0.661 g, 10.4 mmol) in one portion. The reaction was stirred for 3 days. Upon completion by TLC, the reaction was diluted with EtOAc (250 mL), washed with H₂O (4 times), dried (MgSO₄) and concentrated to provide 1,1-dimethylethyl 4-[2-(methylthio)ethyl]-1-piperidinecarboxylate (2.37 g, 9.20

mmol, 99%, approximately 93% pure, used without further purification). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.02 - 1.13 (m, 2 H), 1.42 (s, 9 H), 1.48 - 1.55 (m, 3 H), 1.63 (d, $J=12.5$ Hz, 2 H), 2.07 (s, 3 H), 2.45 - 2.53 (m, 2 H), 2.65 (td, $J=12.8$, 2.6 Hz, 2 H), 4.02 - 4.09 (m, 2 H).

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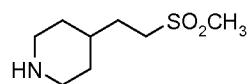
Step C/Intermediate A61: 1,1-dimethylethyl 4-[2-(methylsulfonyl)ethyl]-1-piperidinecarboxylate



To 1,1-dimethylethyl 4-[2-(methylthio)ethyl]-1-piperidinecarboxylate (2.37 g, 9.20 mmol) in DCM (20 mL) at 0°C was added *meta*-chloroperoxybenzoic acid (5.29 g, 77% by weight, 23.0 mmol) in portions. The reaction was stirred overnight. Additional *meta*-chloroperoxybenzoic acid (2.50 g, 77% by weight, 14.5 mmol) was added and the reaction was stirred for 2 days. The mixture was washed with saturated NaHCO_3 , brine and H_2O . The organic layer was dried (MgSO_4) and concentrated. Purification by flash chromatography provided 1,1-dimethylethyl 4-[2-(methylsulfonyl)ethyl]-1-piperidinecarboxylate (1.44 g, 4.90 mmol, 54%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.09 - 1.20 (m, 2 H), 1.45 (s, 9 H), 1.51 - 1.62 (m, 1 H), 1.67 (dd, $J=13.4$, 2.0 Hz, 2 H), 1.77 - 1.85 (m, 2 H), 2.63 - 2.73 (m, 2 H), 2.91 (s, 3 H), 2.99 - 3.05 (m, 2 H), 4.08 - 4.15 (m, 2 H).

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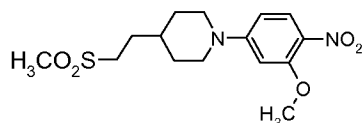
Step D/Intermediate A62: 4-[2-(methylsulfonyl)ethyl]piperidine



A solution of 1,1-dimethylethyl 4-[2-(methylsulfonyl)ethyl]-1-piperidinecarboxylate (1.4 g, 4.9 mmol) and DCM (110 mL) was cooled with an ice/ H_2O bath. TFA (10 mL, 130 mmol) was added in one portion. Upon completion the reaction mixture was quenched at 0°C with 6N NaOH (30 mL), extracted with DCM, EA, dried (MgSO_4) and concentrated to provide 4-[2-(methylsulfonyl)ethyl]piperidine (0.81 g, 4.3 mmol, 87%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.14 - 1.26 (m, 2 H), 1.49 - 1.59 (m, 1 H), 1.70 (d, $J=13.6$ Hz, 2 H), 1.76 - 1.84 (m, 2 H), 2.27 (br. s., 1 H), 2.61 (td, $J=12.3$, 2.6 Hz, 2 H), 2.90 (s, 3 H), 2.99 - 3.05 (m, 2 H), 3.11 (ddd, $J=12.4$, 3.3, 3.0 Hz, 2 H).

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Step E/Intermediate A63: 1-[3-(methyloxy)-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperidine

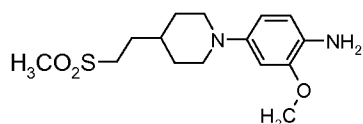


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To 5-fluoro-2-nitrophenyl methyl ether (0.41 g, 2.1 mmol), 4-[2-(methylsulfonyl)ethyl]piperidine (0.74 g, 4.3 mmol) and K_2CO_3 (1.0 g, 7.5 mmol) was added DMSO. The mixture was stirred at room temperature overnight and allowed to stand for 25 days. The mixture was diluted with EA and washed with water (6 times). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography provided 1-[3-(methyloxy)-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperidine (0.43 g, 1.3 mmol, 58%). 1H NMR (400 MHz, $CDCl_3$) δ 1.38 - 1.57 (m, 3 H), 1.72 - 1.80 (m, 1 H), 1.83 - 1.89 (m, 4 H), 2.90 (s, 3 H), 2.93 - 2.98 (m, 1 H), 3.00 - 3.07 (m, 2 H), 3.87 (d, $J=12.8$ Hz, 2 H), 3.93 (s, 3 H), 6.48 (d, $J=9.2$ Hz, 1 H), 6.55 (br. s., 1 H), 7.97 (d, $J=9.3$ Hz, 1 H).

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Step F/Intermediate A58: 2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}aniline



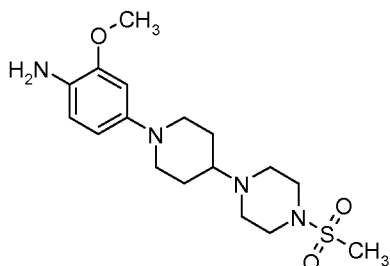
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To 1-[3-(methyloxy)-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperidine (0.42 g, 1.3 mmol) in THF (60 mL) cooled to 0 °C was added $SnCl_2$ (1.0 g, 5.4 mmol) dissolved in conc. HCl dropwise. The solution was stirred overnight at room temperature (TLC confirms consumption of starting material). The mixture was cooled to 0 °C and quenched with 6 N NaOH (25 mL). The solution was poured into EtOAc and H_2O was washed with brine, back extracted with EtOAc, dried ($MgSO_4$), filtered, and rotovaped down to give 2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}aniline (0.39 g, 1.3 mmol, 96%). 1H NMR (400 MHz, $CDCl_3$) δ 1.18 - 1.29 (m, 2 H), 1.31 - 1.43 (m, 1 H), 1.57 - 1.65 (m, 2 H), 1.70 (d, $J=12.5$ Hz, 2 H), 2.37 - 2.43 (m, 2 H), 2.92 (s, 3

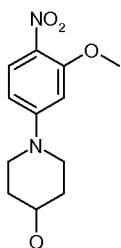
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H), 3.07 - 3.14 (m, 2 H), 3.34 (d, $J=11.5$ Hz, 2 H), 3.69 (s, 3 H), 4.16 (br. s., 2 H), 6.25 (d, $J=7.7$ Hz, 1 H), 6.40 - 6.48 (m, 2 H).

Intermediate A64: 2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}aniline

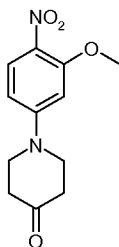


Step A/Intermediate A65: 1-[3-(methyloxy)-4-nitrophenyl]-4-piperidinol



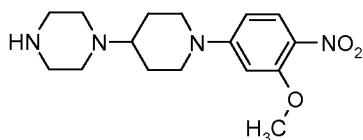
A mixture of 4-fluoro-2-(methyloxy)-1-nitrobenzene (7.52 g, 44 mmol), 4-hydroxypiperidine (4.45 g, 44 mmol) and potassium carbonate (8.0g, 88 mmol) in 100 mL DMSO was stirred for 72h. The reaction was diluted with water and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated to give 1-[3-(methyloxy)-4-nitrophenyl]-4-piperidinol (10.9 g, 99% yield). ¹H NMR (400 MHz, d₆-DMSO) δ 7.84 (d, $J = 9.2$ Hz, 1H), 6.54 (d, $J = 9.6$ Hz, 1H), 6.46 (s, 1H), 4.73 (d, $J = 4.4$ Hz, 1H), 3.86 (s, 3H), 3.80-3.69 (m, 3H), 3.18-3.12 (m, 2H), 1.79-1.76 (m, 2H), 1.42-1.34 (m, 2H).

Step B/Intermediate A66: 1-[3-(methyloxy)-4-nitrophenyl]-4-piperidinone



To a solution of (10 g, 40 mmol) in 400 mL DCM was added sodium bicarbonate (16.8 g, 200 mmol), water (0.72 mL, 40 mmol) and 1,1,1-tri(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinone, 20.4 g, 48 mmol, Aldrich). After 1.5 h, the reaction still contained starting material and was not progressing. The reaction was quenched with equal parts sat'd NaHCO₃ and sat'd Na₂S₂O₃. After stirring for 1 hour, the layers were separated. The aqueous phase was extracted with DCM. The combined organics were washed with water and brine, dried over MgSO₄, concentrated onto silica gel and purified by flash column chromatography. Fractions containing product were concentrated to give 1.8 g of desired product. Fractions containing starting material were concentrated and resubjected to the above conditions. After workup and purification, a further 6.1 g of product was collected to give 7.9 g (79%) of 1-[3-(methoxy)-4-nitrophenyl]-4-piperidinone. ¹H NMR (400 MHz, d₆-DMSO) δ 7.89 (d, J = 9.2 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 6.50 (d, J = 1.2 Hz, 1H), 3.90 (s, 3H), 3.82-3.78 (m, 4 H), 2.49-2.46 (m, 4H).

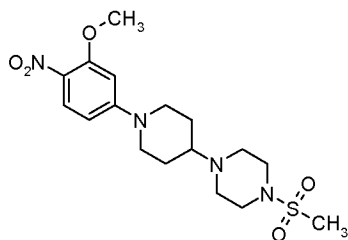
Step C/Intermediate A67: 1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidinyl}piperazine



To a solution of 1-[4-amino-3-(methoxy)phenyl]-4-piperidinone (combined batches) (17.35 g, 69.3 mmol) in toluene (600 mL) was added sequentially, TEA (25 mL, 179.4 mmol), 1-Boc-piperazine (25.36 g, 136.2 mmol), and HOAc (6.0 mL, 105.9 mmol). The solution was stirred at rt for 30 min. Sodium triacetoxyborohydride (12.2 g, 57.6 mmol) was added in one portion and stirred for 30 min. A second portion of sodium triacetoxyborohydride (12.2 g, 57.6 mmol) was added and stirring continued for 30 min. A third portion of sodium triacetoxyborohydride (12.2 g, 57.6 mmol) was added. The reaction was stirred (3 hours) until ketone was consumed as indicated by TLC. The

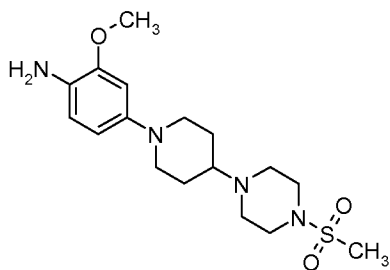
reaction was quenched with a saturated solution of NaHCO_3 (600 mL) and stirred 2 days. The solution was separated and extracted with DCM (x3), dried with MgSO_4 , filtered and concentrated. The resultant solid was dissolved in DCM (600 mL) and cooled to 0 °C. TFA (110 mL) was added; the reaction was warmed to rt and stirred overnight. The reaction was cooled to 0 °C and quenched with 6N NaOH (320 mL) dropwise. The solution was separated and extracted with DCM (x3), dried with MgSO_4 , filtered and concentrated. Purification by flash chromatography provided 1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidinyl}piperazine (18.03 g, 56.10 mmol, 81%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.41 (qd, $J=12.0, 3.7$ Hz, 2 H) 1.77 - 1.84 (m, 2 H) 2.38 - 2.47 (m, 5 H) 2.67 - 2.73 (m, 4 H) 2.88 - 2.98 (m, 2 H) 3.32 (br. s., 1 H) 3.88 (s, 3 H) 4.03 (d, $J=12.8$ Hz, 2 H) 6.48 (d, $J=2.6$ Hz, 1 H) 6.56 (dd, $J=9.5, 2.6$ Hz, 1 H) 7.85 (d, $J=9.2$ Hz, 1 H).

Step D/Intermediate A68: 1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)piperazine



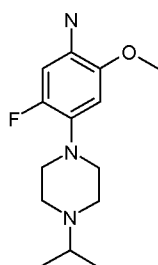
To a suspension of 1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidinyl}piperazine (5.0g, 11.6mmol), methane sulfonyl chloride (1.4mL, 17.5mmol) and DCM (200mL) was added TEA (8.1mL, 58.2mmol). The reaction was stirred at rt and monitored by TLC. After complete consumption of the starting material the clear yellow solution was concentrated onto silica gel and purified by chromatography to afford 1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)piperazine as a yellow solid (3.54g, 76%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.85 (d, $J = 9.5$ Hz, 1H), 6.57 (dd, $J = 9.2, 2.6$ Hz, 1H), 6.48 (d, $J = 2.6$ Hz, 1H), 4.09 – 4.00 (m, 2H), 3.89 (s, 3H), 3.10 – 3.03 (m, 4H), 2.99 – 2.90 (m, 2H), 2.84 (s, 3H), 2.61 – 2.52 (m, 5H), 1.85 – 1.77 (m, 2H), 1.50 – 1.37 (m, 2H).

Step E/Intermediate A64: 2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}aniline

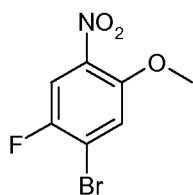


NaBH₄ (1.18g, 31.1mmol) was added carefully in portions (exothermic) to a suspension of 1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidinyl}-4-(methylsulfonyl)-piperazine (3.54g, 8.9mmol), nickel(II)chloride hexahydrate (1.06g, 4.4mmol), MeOH (100mL) and THF
 5 (50mL) at 0 °C. The ice bath was removed and the reaction mixture was warmed to rt. TLC analysis indicated the complete consumption of the starting material. The reaction mixture was concentrated onto silica gel and purified by flash chromatography to afford 2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}aniline (2.93g, 90%) as a colorless solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.49 – 6.46 (m, 2H), 6.27 (dd, *J* = 8.5,
 10 2.6 Hz, 1H), 4.18 (bs, 2H), 3.71 (s, 3H), 3.44 – 3.38 (m, 2H), 3.11 – 3.04 (m, 4H), 2.84 (s, 3H), 2.61 – 2.54 (m, 4H), 2.35 – 2.26 (m, 1H), 1.80- 1.77 (m, 2H), 1.56 – 1.46 (m, 2H).

Intermediate A69: 5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)aniline

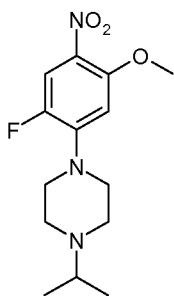


Step A/Intermediate A70: 5-bromo-4-fluoro-2-nitrophenyl methyl ether



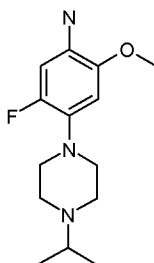
1-Bromo-2,5-difluoro-4-nitrobenzene (15.0 g, 63.0 mmol) was added to a solution of sodium methoxide in methanol (164 mL, 0.5 M, Aldrich). The reaction was heated to 60 °C for 1 h. After cooling to room temperature, the solution was concentrated, and the residue was diluted with water (100 mL) followed by extraction with ethyl acetate (2 × 80 mL). The organic phase was dried (Na₂SO₄) and concentrated to afford 5-bromo-4-fluoro-2-nitrophenyl methyl ether as an orange solid (15.2 g, 95% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.93 (s, 3 H), 7.76 (d, *J*=5.5 Hz, 1 H), 8.08 (d, *J*=8.4 Hz, 1 H).

Step B/Intermediate A71: 1-[2-fluoro-5-(methoxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine



To 5-bromo-4-fluoro-2-nitrophenyl methyl ether (4.0 g, 16.0 mmol) in dioxane (150 mL) was added 1-(1-methylethyl)piperazine (4.1 g, 32.0 mmol), XANTPHOS (0.9 g, 1.6 mmol), and Cs₂CO₃ (10.4 g, 32.0 mmol). The mixture was bubbled with N₂ for 15 min prior to the addition of Pd₂(dba)₃ (0.7 g, 0.8 mmol). The reaction was stirred at 100 °C for 18 h. Ethyl acetate (100 mL) was used to dilute the reaction mixture, followed by the addition of water (80 mL). After partitioning, extraction with ethyl acetate (2 × 75 mL), drying (Na₂SO₄), filtration and concentration, silica gel chromatography afforded 1-[2-fluoro-5-(methoxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine as a yellow solid (3.3 g, 70% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.98 (d, *J*=6.6 Hz, 6 H), 2.54 - 2.61 (m, 4 H), 2.68 (sept, *J* = 6.6 Hz, 1 H), 3.24 - 3.31 (m, 4 H), 3.91 (s, 3 H), 6.64 (d, *J*=7.7 Hz, 1 H), 7.82 (d, *J*=13.6 Hz, 1 H).

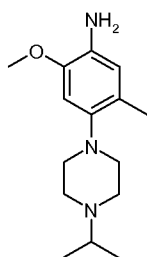
Step Cintermediate A69: 5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)aniline



To 1-[2-fluoro-5-(methyloxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine (2.0 g, 6.7 mmol) in MeOH (100 mL) was added iron (III) chloride (0.3 g, 2.0 mmol) and activated carbon

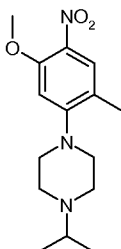
- 5 (2.0 g). The reaction mixture was stirred at 64 °C for 20 min before the dropwise addition of hydrazine hydrate (4.0 mL, 80.7 mmol) over 5 min. The reaction was kept stirring at 64 °C for additional 4 h. Filtration, concentration of the residue, and purification via column chromatography on SiO₂ (0-10% 2 M NH₃ in MeOH/DCM) afforded 5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)aniline as a dark
- 10 brown solid (1.7 g, 95% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.96 (d, *J*=6.6 Hz, 6 H), 2.45 - 2.54 (m, 4 H), 2.62 (sept, *J* = 6.6 Hz, 1 H), 2.79 - 2.86 (m, 4 H), 3.69 (s, 3 H), 4.55 (s, 2 H), 6.38 (d, *J*=13.6 Hz, 1 H), 6.49 (d, *J*=8.2 Hz, 1 H).

Intermediate A72: 5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)aniline



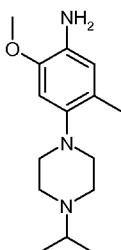
Step A/Intermediate A73: 1-(1-methylethyl)-4-[2-methyl-5-(methyloxy)-4-nitrophenyl]piperazine

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To a solution of 1-fluoro-2-methyl-5-(methyloxy)-4-nitrobenzene (1.3g, 7.03 mmol) in dimethylsulfoxide was added potassium carbonate (1.9g, 14.0 mmol) and isopropylpiperazine (2.0 mL, 14 mmol). The resulting suspension was warmed at 70°C for 12 hours, poured into water, and extracted with diethyl ether. The ether layers were washed with aqueous saturated sodium chloride, dried over sodium sulfate, taken to a residue under reduced pressure, and purified by chromatography on SiO₂ to afford 1-(1-methylethyl)-4-[2-methyl-5-(methyloxy)-4-nitrophenyl]piperazine (1.78g, 86% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.11 (d, *J*=6.60 Hz, 6 H), 2.24 (s, 3 H), 2.72 (s, 4 H), 2.79 (app s, 1 H), 3.06 (s, 4 H), 3.93 (s, 3 H), 6.57 (s, 1 H), 7.81 (s, 1 H).

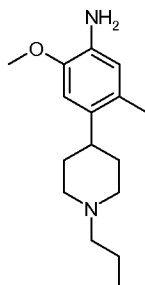
Step B/Intermediate A72: 5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)aniline



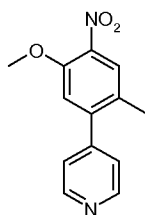
To a solution of 1-(1-methylethyl)-4-[2-methyl-5-(methoxy)-4-nitrophenyl]piperazine (1.78g, 6.08 mmol) in methanol (75 mL) was added hydrazine (1.33 mL, 7.0 mmol), iron (III) chloride (0.200 g, 1.22 mmol) and activated charcoal (2g). The resulting slurry was warmed to 60°C and maintained overnight. The next morning the slurry was filtered and concentrated to a residue. The residue was partitioned between ethyl acetate and sat. NaCl(aq). The organic layer was washed twice with saturated brine, dried over sodium

sulfate, and taken to a residue under reduced pressure to afford 5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)aniline (1.50g, 94% yield) of sufficient purity for use directly in the next step. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.98 (d, $J=6.60$ Hz, 6 H), 2.04 (s, 3 H), 2.52 (s, 4 H), 2.64 (sept, $J = 6.6$ Hz, 1 H), 2.68 - 2.72 (m, 4 H), 3.69 (s, 3 H), 4.28 (s, 2 H), 6.41 (s, 1 H), 6.55 (s, 1 H).

Intermedaite A74: 5-methyl-2-(methyloxy)-4-(1-propyl-4-piperidiny)aniline



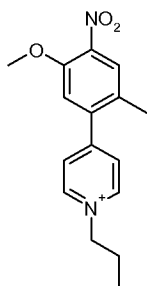
Step A/Intermediate A75: 4-[2-methyl-5-(methyloxy)-4-nitrophenyl]pyridine



To a nitrogen purged solution of 1-chloro-2-methyl-5-(methyloxy)-4-nitrobenzene (8 g, 39.7 mmol, see Canadian Journal of Chemistry (1987), 65(6), 1233-40.) and 4-pyridinylboronic acid (6.34 g, 51.6 mmol) in 1,4 dioxane (250 mL) was added dichlorobis(triphenylphosphine)palladium(II) (2.79 g, 3.97 mmol) and degassed 3.0M aqueous sodium carbonate (39.7 ml, 119 mmol). The resulting suspension was maintained at 90 °C overnight. The reaction was subsequently cooled to room temperature, filtered through celite, and partitioned between saturated sodium bicarbonate and ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The resulting residue was purified by chromatography on SiO_2 (0 to 30% EtOAc in CH_2Cl_2) to afford 4-[2-methyl-5-(methyloxy)-4-nitrophenyl]pyridine (6.2 g, 25.4 mmol, 64.0 % yield) as a pale yellow solid. ^1H NMR

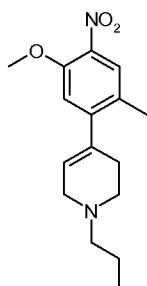
(400 MHz, CDCl_3 -d) δ ppm 8.64 - 8.78 (m, 2 H), 7.79 (s, 1 H), 7.15 - 7.31 (m, 2 H), 6.90 (s, 1 H), 3.95 (s, 3 H), 2.22 (s, 3 H)

- 5 Step B/Intermediate A76: 4-[2-methyl-5-(methoxy)-4-nitrophenyl]-1-propylpyridinium iodide



- To a solution of 4-[2-methyl-5-(methoxy)-4-nitrophenyl]pyridine (6.2 g, 25.4 mmol) in pinacolone (150 ml) at 100 °C was added 1-iodopropane (17.36 ml, 178 mmol) and the resulting solution was stirred rapidly for 24 hr., during which time a thick yellow precipitate forms. The reaction was cooled to 0°C, filtered, and the solids washed with diethyl ether to give analytically pure 4-[2-methyl-5-(methoxy)-4-nitrophenyl]-1-propylpyridinium iodide (8.74 g, 21.10 mmol, 83 % yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.21 (d, $J=6.97$ Hz, 2 H), 8.31 (d, $J=6.60$ Hz, 2 H), 7.95 (s, 1 H), 7.39 (s, 1 H), 4.62 (t, $J=7.15$ Hz, 2 H), 3.94 (s, 3 H), 2.27 (s, 3 H), 1.85 - 2.09 (m, 2 H), 0.78 - 1.08 (m, 3 H)

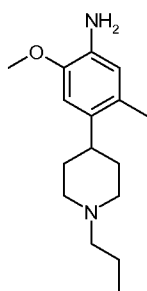
Step C/Intermediate A77: 4-[2-methyl-5-(methoxy)-4-nitrophenyl]-1-propyl-1,2,3,6-tetrahydropyridine



To a suspension of 4-[2-methyl-5-(methoxy)-4-nitrophenyl]-1-propylpyridinium (8.74 g, 30.4 mmol) in methanol (100 ml) at 0 °C was added portionwise sodium borohydride

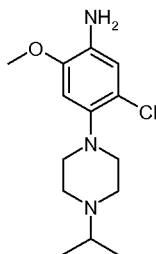
(3.45 g, 91 mmol). The resulting solution was stirred for four hours and poured into ethyl acetate/saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford 4-[2-methyl-5-(methoxy)-4-nitrophenyl]-1-propyl-1,2,3,6-tetrahydropyridine (6.08 g, 20.94 mmol, 68.8 % yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.71 (s, 1 H), 7.00 (s, 1 H), 5.54 - 5.68 (m, 1 H), 3.87 (s, 3 H), 3.02 (q, *J*=2.81 Hz, 2 H), 2.59 (t, *J*=5.68 Hz, 2 H), 2.48 (m, 2 H), 2.27 - 2.38 (m, 2 H), 2.20 (s, 3 H), 1.40 - 1.59 (m, 2 H), 0.87 (t, *J*=7.52 Hz, 3 H).

10 Step D/Intermediate A74: 5-methyl-2-(methoxy)-4-(1-propyl-4-piperidiny)aniline

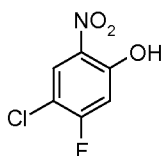


A suspension of 4-[2-methyl-5-(methoxy)-4-nitrophenyl]-1-propyl-1,2,3,6-tetrahydropyridine (8.74 g, 30.1 mmol) and 10% palladium on carbon (3.20 g, 3.01 mmol) in ethanol (100 ml) was maintained under 60 psi of hydrogen in a Parr hydrogenator for 16 hours. Following purging with nitrogen, the mixture was filtered and solvents removed under reduced pressure to afford analytically pure [5-methyl-2-(methoxy)-4-(1-propyl-4-piperidiny)phenyl]amine (5.01 g, 19.09 mmol, 63.4 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.56 (s, 1 H), 6.35 (s, 1 H), 4.34 (s, 2 H), 3.67 (s, 3 H), 2.89 (d, *J*=11.35 Hz, 2 H), 2.39 - 2.44 (m, 1 H), 2.14 - 2.24 (m, 2 H), 2.04 (s, 3 H), 1.81 - 1.95 (m, 2 H), 1.49 - 1.64 (m, 4 H), 1.32 - 1.48 (m, 2 H), 0.82 (t, *J*=7.33 Hz, 3 H).

Intermediate A78: 5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)aniline



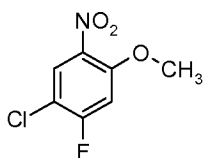
Step A/Intermediate A79: 4-chloro-5-fluoro-2-nitrophenol



- 5 4-chloro-3-fluorophenol (2.38 g, 16.2 mmol) was dissolved in DCE (32 mL) and tetrabutylammonium bromide (0.524 g, 1.62 mmol) was added. Aqueous 70% HNO₃ (2.1 mL, 32 mmol) was diluted with H₂O (18.9 mL) to make a 7% HNO₃ solution. This solution was added to the reaction mixture which was then stirred at rt for 4h at which time the reaction was judged complete by TLC. The reaction was poured into H₂O and
10 extracted with DCM (3x). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was adsorbed onto silica gel and flash chromatographed to give 4-chloro-5-fluoro-2-nitrophenol (2.29 g, 74%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.76 (br. s., 1 H), 8.18 (d, *J*=8.1 Hz, 1 H), 7.10 (d, *J*=10.6 Hz, 1 H).

15

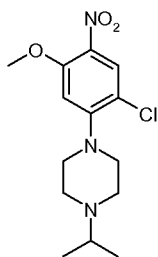
Step B/Intermediate A80: 4-chloro-5-fluoro-2-nitrophenyl methyl ether



- 4-Chloro-5-fluoro-2-nitrophenol (2.29 g, 12.0 mmol) was dissolved in DMF (25 mL). K₂CO₃ (2.5 g, 18 mmol) and iodomethane (0.893 mL, 14.3 mmol) were added and the
20 mixture was stirred at rt overnight. The mixture was then poured into H₂O and extracted with EtOAc (2x) and then the combined organics were extracted with H₂O (5x). The organic layer was dried with MgSO₄, filtered, and concentrated *in vacuo* to give 4-chloro-5-fluoro-2-nitrophenyl methyl ether without further purification (2.19 g, 89 %). ¹H NMR

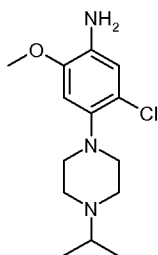
(400 MHz, DMSO-*d*₆) δ ppm 8.22 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.54 (d, *J*=11.4 Hz, 1 H), 3.90 (d, *J*=1.1 Hz, 3 H).

Step C/Intermediate A81: 1-[2-chloro-5-(methyloxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine



A suspension of 1-chloro-2-fluoro-4-(methyloxy)-5-nitrobenzene (0.650 g, 3.17 mmol), isopropylpiperazine (1.0 mL, 6.34 mmol), and potassium carbonate (0.900g, 6.50 mmol) in dimethylsulfoxide (10 mL) was maintained at 70°C for 24 hours. The solution was diluted with diethyl ether, washed with saturated sodium chloride (aq), and purified by silica gel chromatography to afford 1-[2-chloro-5-(methyloxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine (1.0g, quant. yield). ¹H NMR (400 MHz, CDCl₃-*d*) δ ppm 8.03 (s, 1 H), 6.57 (s, 1 H), 3.95 (s, 3 H), 3.14 - 3.32 (m, 4 H), 2.76 - 2.82 (m, 1 H), 2.66 - 2.76 (m, 4 H), 1.11 (d, *J*=6.23 Hz, 6 H)

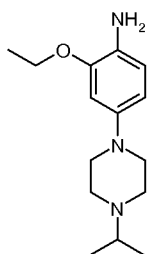
Step D/ Intermediate A78: 5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)aniline



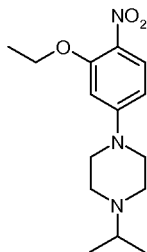
A suspension of 1-[2-chloro-5-(methyloxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine (1.0 g, 3.2 mmol), hydrazine hydrate (0.700 mL, 22.4 mmol), iron (III) chloride (0.100 g, 0.64 mmol), and activated carbon (1g) in methanol (40 ml) was warmed at 60°C for 16 hours. The solution was filtered through celite while still warm and concentrated to an

oily residue. The residue was partitioned between ethyl acetate and saturated sodium chloride and the organic layer was washed three times with saturated NaCl (aq), dried over sodium sulfate, filtered, and taken to an oil under reduced pressure to afford analytically pure 5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)aniline (0.550 g, 61% yield) as a pale yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.64 (s, 1 H), 6.63 (s, 1 H), 4.62 (s, 2 H), 3.74 (s, 3 H), 2.75 - 2.88 (m, 4 H), 2.59 - 2.70 (m, 1 H), 2.50 - 2.59 (m, 4 H), 0.98 (d, *J*=6.60 Hz, 6 H).

Intermediate A82: 2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]aniline



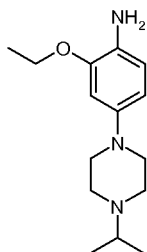
Step A/ Intermediate A83: 1-[3-(ethyloxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine



A solution of 2-(ethyloxy)-4-fluoro-1-nitrobenzene (7.11 g, 38.4 mmol, Combi-Blocks Catalog), potassium carbonate (15.92 g, 115 mmol), and 1-(1-methylethyl)piperazine (8.24 ml, 57.6 mmol) in dimethyl sulfoxide (DMSO) (75 ml) was stirred at 80°C for 16 hours. The resulting slurry was poured into diethyl ether/water and washed three times with saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford 1-[3-(ethyloxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine (7.09 g, 24.17 mmol, 62.9 % yield) as a bright yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.84 (d, *J*=9.53 Hz, 1 H), 6.55 (dd, *J*=9.53, 2.57 Hz, 1 H), 6.49 (d, *J*=2.20 Hz, 1 H),

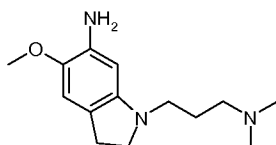
4.16 (q, $J=7.09$ Hz, 2 H), 3.34 - 3.42 (m, 4 H), 2.58 - 2.74 (m, 1 H), 2.48 - 2.55 (m, 4 H), 1.33 (t, $J=6.97$ Hz, 3 H), 0.97 (d, $J=6.60$ Hz, 6 H).

5 Step B/ Intermediate A82: 2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]aniline

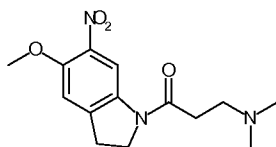


A suspension of 1-[3-(ethyloxy)-4-nitrophenyl]-4-(1-methylethyl)piperazine (7.09 g, 24.17 mmol), hydrazine hydrate (9.49 ml, 193 mmol), iron (III) chloride (0.587 g, 3.63 mmol), and activated carbon (8 g, 24.17 mmol) in methanol (500 ml) was warmed at 60°C for 16 hours. The solution was filtered through celite while still warm and concentrated to an oily residue. The residue was partitioned between ethyl acetate and saturated sodium chloride and the organic layer was washed three times with saturated NaCl (aq), dried over sodium sulfate, filtered, and taken to an oil under reduced pressure to afford analytically pure {2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]phenyl}amine (5.007 g, 19.01 mmol, 79 % yield) as a pale yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 6.49 (d, $J=8.43$ Hz, 1 H), 6.43 (d, $J=2.57$ Hz, 1 H), 6.25 (dd, $J=8.43, 2.57$ Hz, 1 H), 4.15 (s, 2 H), 3.94 (q, $J=6.97$ Hz, 2 H), 2.82 - 2.91 (m, 4 H), 2.57 - 2.68 (m, 1 H), 2.49 - 2.55 (m, 4 H), 1.29 (t, $J=6.97$ Hz, 3 H), 0.97 (d, $J=6.60$ Hz, 6 H).

20 **Intermediate A84: 1-[3-(dimethylamino)propyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine**

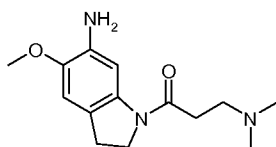


25 Step A/Intermediate A85: *N,N*-dimethyl-3-[5-(methyloxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-3-oxo-1-propanamine



A suspension of 5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole (1.50g, 7.73 mmol) and polymer supported diisopropylethylamine (4.1g, 16 mmol) in dichloromethane (100 mL) was cooled to 0°C and 2-propenoyl chloride (0.750 mL, 9.3 mmol) was added dropwise. The solution was warmed slowly to room temperature and all solids were observed to dissolve. The mixture was filtered through celite, the celite washed twice with dichloromethane, and the combined filtrates were concentrated under reduced pressure to give a crude residue which was dissolved directly in a 1.0M dimethyl amine solution in tetrahydrofuran (40 mL). The solution was maintained at 60°C for 12 hours, cooled, taken to a residue under reduced pressure, and purified by chromatography on SiO₂ to afford *N,N*-dimethyl-3-[5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-3-oxo-1-propanamine (1.52g, 67% Yield). This protocol could be reproduced on similar scale to generate larger quantities of product which would be carried forward as blended batches. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.68 (s, 1 H), 6.91 (s, 1 H), 4.15 (t, *J*=8.43 Hz, 2 H), 3.91 (s, 3 H), 3.26 (t, *J*=8.43 Hz, 2 H), 2.81 (t, *J*=7.33 Hz, 2 H), 2.66 (t, *J*=7.15 Hz, 2 H), 2.27 - 2.41 (m, 6 H).

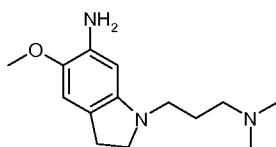
Step B/Intermediate A86: 1-[3-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



To *N,N*-dimethyl-3-[5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-3-oxo-1-propanamine (4.8g, 51.6 mmol) in degassed tetrahydrofuran (50 mL) was added activated palladium on carbone (10%, 3.0g). The reaction mixture was maintained under 40 psi hydrogen gas for 16 hours, purged with nitrogen and filtered through celite. The filtrates were concentrated to afford 1-[3-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (4.15g, 96% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.72

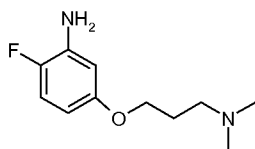
(s, 1 H), 6.63 (s, 1 H), 3.95 - 4.15 (m, 2 H), 3.81 (s, 3 H), 3.76 (s, 2 H), 3.10 (t, $J=8.43$ Hz, 2 H), 2.83 - 2.96 (m, 2 H), 2.70 (t, $J=7.15$ Hz, 2 H), 2.41 (s, 6 H).

Step C/Intermediate A84: 1-[3-(dimethylamino)propyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine

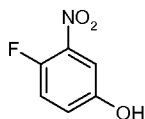


A solution of 1-[3-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (1.35 g, 5.13 mmol) in tetrahydrofuran (50 ml) was treated with lithium aluminum hydride (1.0M soln. in THF, 25.6 ml, 25.6 mmol) at 0°C and allowed to warm to room temperature overnight. The solution was poured cautiously into a saturated ammonium chloride (aq)/ice mixture and extracted three times with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford 1-[3-(dimethylamino)propyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (0.410 g, 1.644 mmol, 32.1 % yield) as a dark brown oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.65 (s, 1 H), 6.01 (s, 1 H), 3.76 (s, 3 H), 3.65 (s, 2 H), 3.22 (t, $J=8.13$ Hz, 2 H), 2.90 - 3.00 (m, 2 H), 2.77 - 2.88 (m, 2 H), 2.31 - 2.39 (m, 2 H), 2.24 (s, 6 H), 1.67 - 1.83 (m, 2 H).

Intermediate A87: 5-{[3-(dimethylamino)propyl]oxy}-2-fluoroaniline

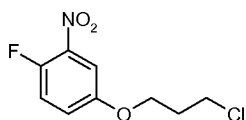


Step A/ Intermediate A88: 4-fluoro-3-nitrophenol



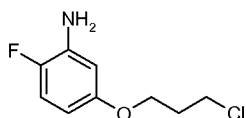
To a solution of 1-(4-fluoro-3-nitrophenyl)ethanone (12 g, 65.6 mmol, 1 eq) in H_2SO_4 (160 mL) and AcOH (96 mL) was added MeCO_3H (50 mL, 285.7 mmol, 4.3 eq) dropwise at 0°C . The mixture was stirred at room temperature overnight. The mixture was added to ice-water and extracted with EtOAc, the organic layer was washed with sat NaHCO_3 , dried over Na_2SO_4 , and concentrated and purified by column chromatography to afford 4-fluoro-3-nitrophenol. (4.0 g). ^1H NMR (400 MHz, DMSO) δ ppm 7.43-7.51 (m, 1H), 8.17-8.27 (m, 1H), 8.47-8.55 (m, 1H). Exchangeable protons are absent likely due to rapid exchange.

10 Step B/ Intermediate A89: 3-chloropropyl 4-fluoro-3-nitrophenyl ether



To a solution of 4-fluoro-3-nitrophenol (4 g, 25.4 mmol, 1 eq) in DMF (50 mL) was added NaH (60%, 1.5 g, 37 mmol, 1.4 eq) at 0°C , the mixture was stirred for 30 min. 1-Bromo-3-chloropropane (4.5 g, 29 mmol, 1.1 eq) was added to the mixture at 0°C dropwise. The mixture was stirred for 4h, poured into water, and extracted with EtOAc. The organic layer was washed with sat NaHCO_3 , dried over Na_2SO_4 , concentrated and purified by column chromatography to afford 3-chloropropyl 4-fluoro-3-nitrophenyl ether. (3.6 g, 62% yield)(2 batches). ^1H NMR (400 MHz, CDCl_3) δ ppm 2.17-2.25 (m, 2H), 3.65-3.70 (m, 2H), 4.07-4.13 (m, 2H), 7.05-7.20 (m, 2H), 7.47-7.51 (m, 1H)

Step C/ Intermediate A90: {5-[(3-chloropropyl)oxy]-2-fluorophenyl}amine

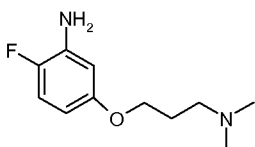


25 To a solution of 3-chloropropyl 4-fluoro-3-nitrophenyl ether (2 g, 8.5 mmol) in ethanol (40 mL) was added Pd/C (0.6 g) under N_2 and the mixture was stirred under H_2 for 2h at room temperature. The mixture was filtered and filtrates concentrated under reduced pressure to afford {5-[(3-chloropropyl)oxy]-2-fluorophenyl}amine (1.8 g, 100% yield—performed twice and batches blended). ^1H NMR (400 MHz, MeOD) δ ppm 2.10-2.21 (m,

2H), 3.68-3.78 (m, 2H), 3.97-4.07 (m, 2H), 6.12-6.20 (m, 1H), 6.37-6.47 (m, 1H), 6.75-6.85 (m, 1H). Exchangeable protons are absent likely due to rapid exchange.

Step D/ Intermediate A87: 5-[[3-(dimethylamino)propyl]oxy]-2-fluoroaniline

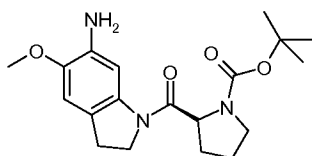
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To a solution of {5-[(3-chloropropyl)oxy]-2-fluorophenyl}amine (2.8 g, 13.8 mmol, 1 eq) in MeCN (25 mL) was added K₂CO₃ (7.6 g, 55 mmol, 4 eq) and dimethylamine HCl salt (1.34 g, 13.8 mmol, 1 eq) and the mixture was heated to 80°C overnight. The solvent was removed under reduced pressure. The crude product was poured into water and extracted with EtOAc. The organic layer was dried over Na₂SO₄, and concentrated (2 batches). To the solution of crude product (3.6 g) in MeOH (10 mL) was added sat HCl/MeOH (20 mL) at 0°C, the mixture was stirred for 1h. The solvent was removed under reduced pressure. The solid was washed with Et₂O and filtered to give 5-[[3-(dimethylamino)propyl]oxy]-2-fluoroaniline. (3.85 g, 95%). ¹H NMR (400 MHz, MeOD): δ ppm 2.05-2.15 (m, 2 H), 2.78 (s, 6 H), 3.19-3.23 (m, 2 H), 3.98-4.01 (m, 2 H), 6.82-6.85 (m, 2 H), 7.09-7.15 (m, 1 H)

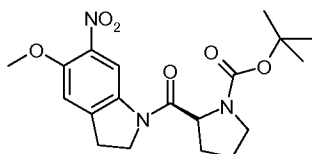
Intermediate A91: 1,1-dimethylethyl (2S)-2-[[6-amino-5-(methoxy)-2,3-dihydro-1H-indol-1-yl]carbonyl]-1-pyrrolidinecarboxylate

20



Step A/ Intermediate A92: 1,1-dimethylethyl (2S)-2-[[5-(methoxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]carbonyl]-1-pyrrolidinecarboxylate

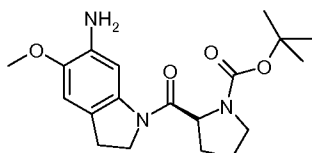
25



A solution of 5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole (3 g, 13.01 mmol), 1-[[[(1,1-dimethylethyl)oxy]carbonyl]-L-proline (3.22 g, 14.96 mmol), HATU (6.43 g, 16.91 mmol), and DIPEA (6.82 ml, 39.0 mmol) in N,N-Dimethylformamide (80 ml) was stirred at room temperature overnight. The solution was poured into ethyl acetate and washed

successively with 0.5% lithium chloride (aq) and saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by chromatography on SiO₂ to afford 1,1-dimethylethyl (2*S*)-2-[[5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]carbonyl]-1-pyrrolidinecarboxylate (4.75 g, 12.14 mmol, 93 % yield) as a pale yellow solid. Distinct Rotameric Forms Present at Room Temperature. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.73 (s, 1 H), 8.72 (s, 1 H), 6.94 (s, 1 H), 6.90 (s, 1 H), 4.53 - 4.61 (m, 1 H), 4.46 - 4.53 (m, 1 H), 4.38 - 4.47 (m, 1 H), 4.20 - 4.32 (m, 1 H), 4.03 - 4.19 (m, 2 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.59 - 3.74 (m, 2 H), 3.48 - 3.57 (m, 1 H), 3.38 - 3.49 (m, 1 H), 3.15 - 3.36 (m, 4 H), 2.06 - 2.33 (m, 4 H), 1.78 - 2.07 (m, 4 H), 1.45 (s, 9 H), 1.34 (s, 9 H).

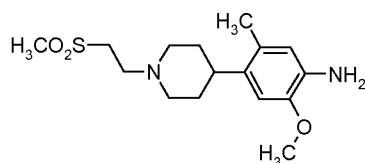
Step B/ Intermediate A91: 1,1-dimethylethyl (2*S*)-2-[[6-amino-5-(methyloxy)-2,3-dihydro-1*H*-indol-1-yl]carbonyl]-1-pyrrolidinecarboxylate



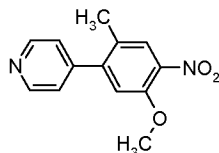
A suspension of 1,1-dimethylethyl (2*S*)-2-[[5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]carbonyl]-1-pyrrolidinecarboxylate (4.75 g, 12.14 mmol) in methanol (100 ml)/tetrahydrofuran (100 ml) was warmed to 55°C until all solids had dissolved and then cooled to room temperature. Nitrogen was bubbled through the solution for 25 minutes, and then the 10% palladium on carbon (1.1 g, 12.14 mmol) was added (as a slurry in degassed methanol) and the suspension was maintained under 50 psi of H₂ gas for 16 hours with rapid stirring. The solution was again purged with nitrogen, filtered through celite, and all volatiles removed to afford 1,1-dimethylethyl (2*S*)-2-[[6-amino-5-(methyloxy)-2,3-dihydro-1*H*-indol-1-yl]carbonyl]-1-pyrrolidinecarboxylate (3.9 g, 10.79 mmol, 89 % yield) as a white foam. Distinct rotamers are present at room temperature by ¹H NMR. ¹H NMR (400 MHz) δ ppm 7.54 (s, 1 H), 7.51 (s, 1 H), 6.69 (s, 2 H), 4.62

(s, 4 H), 4.36 - 4.50 (m, 1 H), 4.08 - 4.17 (m, 1 H), 3.95 - 4.07 (m, 4 H), 3.69 (s, 6 H), 3.24 - 3.48 (m, 4 H), 2.86 - 3.12 (m, 4 H), 2.08 - 2.31 (m, 2 H), 1.66 - 2.01 (m, 6 H), 1.37 (s, 9 H), 1.22 (s, 9 H).

5 **Intermediate A93: 5-methyl-2-(methyloxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidiny}aniline**



Step A/ Intermediate A94: 4-[2-methyl-5-(methyloxy)-4-nitrophenyl]pyridine

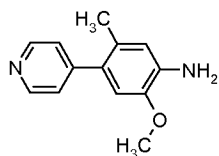


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A solution of 5-bromo-4-methyl-2-nitrophenyl methyl ether (6.0g, 24.38 mmol), PdCl₂(dppf)*DCM adduct (1.43 g, 1.95 mmol) and 4-pyridylboronic acid (20.4 g, 165.8 mmol) in dioxane was deoxygenated by bubbling with N₂(g) for ca 15 min. To this solution was added degassed 2.0 N Na₂CO₃(aq) (170 mL, 14.0 equiv.) and the resulting slurry was stirred at 80°C for 24 h. The dioxane was removed under reduced pressure and the solids were dissolved in EtOAc and washed with H₂O, dried (Na₂SO₄), and purified by flash chromatography to give 4-[2-methyl-5-(methyloxy)-4-nitrophenyl]pyridine (2.81g, 11.5 mmol, 57%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.72 (d, J=4.77 Hz, 2 H), 7.79 (s, 1 H), 7.22 - 7.31 (m, 2 H), 6.90 (s, 1 H), 3.95 (s, 3 H), 2.22 (s, 3 H).

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Step B/ Intermediate A95: 5-methyl-2-(methyloxy)-4-(4-pyridinyl)aniline

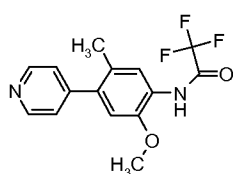


4-[2-methyl-5-(methyloxy)-4-nitrophenyl]pyridine (2.44 g, 9.99 mmol) was placed in a 250 mL high pressure vessel and dissolved in 60 mL of 1 to 1 EtOAc/MeOH. 5 wt% Platinum(sulfided)/carbon (1.17 g, 0.3 mmol) was added and the vessel quickly sealed

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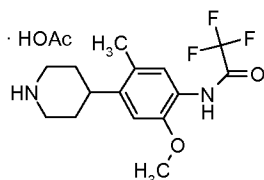
by a rubber septum. The flask was evacuated and filled with N₂ six times to remove any oxygen. The vessel was then pressurized with H₂ (60 psi). The solution was stirred for 72 h. The vessel was evacuated and filled with N₂ six times to remove any H₂. The solution was filtered through celite and evaporated to give 5-methyl-2-(methoxy)-4-(4-pyridinyl)aniline (2.28 g, 10.6 mmol, quantitative yield). ¹H NMR (400 MHz, DMSO-*d*₆) ppm 8.50 - 8.53 (m, 2 H), 7.30 - 7.33 (m, 2 H), 6.68 (s, 1 H), 6.54 (s, 1 H), 4.88 (bs, 2 H), 3.75 (s, 3 H), 2.12 (s, 3 H).

Step C/ Intermediate A96: 2,2,2-trifluoro-N-[5-methyl-2-(methoxy)-4-(4-pyridinyl)phenyl]acetamide



To 5-methyl-2-(methoxy)-4-(4-pyridinyl)aniline (2.28 g, 10.6 mmol) in THF was added triethylamine (3.23 g, 32 mmol), and trifluoroacetic anhydride (4.5 g, 21.3 mmol). The mixture was heated to 40 °C overnight. The solvent was concentrated and the residue purified by chromatography on SiO₂ to give 2,2,2-trifluoro-N-[5-methyl-2-(methoxy)-4-(4-pyridinyl)phenyl]acetamide (2.37 g, 7.64 mmol, 71%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.76 (s, 1 H), 8.62 - 8.65 (m, 2 H), 7.42 - 7.44 (m, 2 H), 7.35 (s, 1 H), 6.98 (s, 1 H), 3.81 (s, 3 H), 2.16 (s, 3 H).

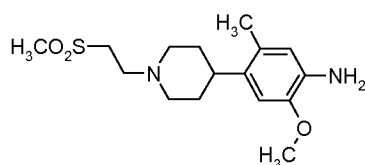
Step D/ Intermediate A97: 2,2,2-trifluoro-N-[5-methyl-2-(methoxy)-4-(4-piperidinyl)phenyl]acetamide acetate



2,2,2-Trifluoro-N-[5-methyl-2-(methoxy)-4-(4-pyridinyl)phenyl]acetamide (2.37 g, 7.64 mmol) was placed in a 250 mL high pressure vessel and dissolved in 70 mL of HOAc. Platinum oxide (0.173 g, 0.76 mmol) was added and the vessel sealed quickly by a rubber septum. The flask was evacuated and filled with N₂ six times to remove any oxygen. The vessel was then pressurized with H₂ (60 psi). The solution was stirred for

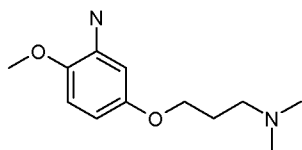
24 h. The vessel was evacuated and filled with N₂ six times to remove any H₂. The solution was filtered through celite and evaporated to give 2,2,2-trifluoro-*N*-[5-methyl-2-(methoxy)-4-(4-piperidinyl)phenyl]acetamide acetate (2.83 g, 7.46 mmol, 98%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.11 (s, 1 H), 6.86 (s, 1 H), 3.76 (s, 3 H), 3.14 (d, *J*=12.27 Hz, 2 H), 2.82 - 2.91 (m, 1 H), 2.72 - 2.81 (m, 2 H), 2.20 (s, 3 H), 1.81 (s, 3 H), 1.64 - 1.75 (m, 4 H).

Step E Intermediate A93: 5-methyl-2-(methoxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidinyl}aniline



To 2,2,2-trifluoro-*N*-[5-methyl-2-(methoxy)-4-(4-piperidinyl)phenyl]acetamide acetate (1.5 g, 4.0 mmol) in 30 mL of dioxane was added TEA (2 g, 20 mmol) and methyl vinyl sulfone (1.06 g, 10 mmol). The mixture was heated to 90 °C for 72 h. The solvent was concentrated and the crude product was purified by flash chromatography to give 480 mg of 2,2,2-trifluoro-*N*-(5-methyl-2-(methoxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidinyl}phenyl)acetamide and 5-methyl-2-(methoxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidinyl}aniline (0.40 g, 1.2 mmol, 31%). ¹H NMR (400 MHz, CDCl₃) δ ppm 6.62 (s, 1 H), 6.51 (s, 1 H), 5.22 (s, 2 H), 3.80 (bs, 3 H), 3.29 (t, *J*=6.87 Hz, 2 H), 3.13 (d, *J*=11.17 Hz, 2 H), 3.04 (s, 3 H), 2.98 (t, *J*=6.96 Hz, 2 H), 2.61 - 2.70 (m, 1 H), 2.24 - 2.31 (m, 2 H), 2.17 (s, 3 H), 1.73 - 1.81 (m, 4 H).

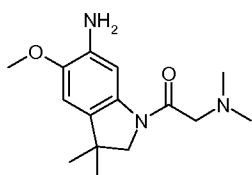
Intermediate A98: 5-{[3-(dimethylamino)propyl]oxy}-2-(methoxy)aniline



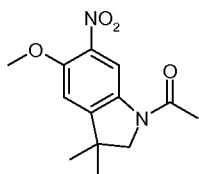
In 2-butanone (200 mL) were added 4-(methoxy)-3-nitrophenol (6.0 g, 26.7 mmol), 3-dimethylaminopropylchloridehydrochloride (12.6 g, 80.0 mmol), potassium carbonate (16.6 g, 120.2 mmol), and TBAI (0.5 g). The reaction was kept stirring at 80 °C for 48 h.

After concentration the residue was partitioned between ethyl acetate and water and the aqueous layer was washed three times with ethyl acetate. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. Silica gel column chromatography afforded the purified dimethyl(3-{[4-(methoxy)-3-nitrophenyl]oxy}propyl)amine, and the product was dissolved in ethanol (100 mL) with the addition of 10% palladium on carbon (0.5 g). The reaction was kept stirring under H₂ at 60 psi over the weekend. After releasing the H₂ pressure, filtration removed the catalyst and the filtrate was concentrated. The crude product was purified by silica gel column chromatography to afford 5-{[3-(dimethylamino)propyl]oxy}-2-(methoxy)aniline (5.3 g, 90% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.71 - 1.81 (m, 2 H), 2.11 (s, 6 H), 2.29 (t, *J*=7.1 Hz, 2 H), 3.66 (s, 3 H), 3.81 (t, *J*=6.4 Hz, 2 H), 4.63 - 4.73 (m, 2 H), 6.02 (dd, *J*=8.4, 2.9 Hz, 1 H), 6.22 (d, *J*=2.9 Hz, 1 H), 6.62 (d, *J*=8.8 Hz, 1 H).

Intermediate A99: 1-[(dimethylamino)acetyl]-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



Step A/Intermediate A100: 1-acetyl-3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole

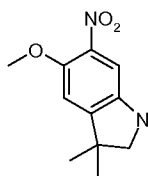


A solution of 1-acetyl-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1*H*-indole (2.44 g, 11.13 mmol, see PCT Int. Appl. (2001), WO 2001023374 A1 20010405) in trifluoroacetic acid (50 mL) was stirred at 0°C and potassium nitrate (1.181 g, 11.68 mmol) was added in one portion. The reaction was maintained at 0°C for 3 hours and poured into water.

The solids were collected via filtration to afford 1-acetyl-3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (2.545 g, 87 % yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.41 (s, 1 H), 7.34 (s, 1 H), 3.91 (s, 3 H), 2.15 (s, 2 H), 1.36 (s, 6 H).

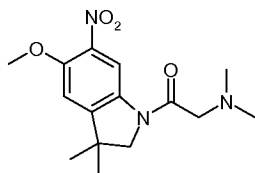
Note: proton resonance corresponding to acetyl was extremely broad and/or not evident for a variety of lots.

Step B/Intermediate A101: 3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole



A solution of 1-acetyl-3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (2.55 g, 9.65 mmol) in methanol (75 mL) was treated with 4.0N HCl in dioxane (19.30 mL, 77 mmol) and maintained at 70°C for 16 hours. The solution was concentrated under reduced pressure, solids were triturated with diethyl ether and the slurry was filtered to afford 3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (2.340 g, 94 % yield) as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.68 (s, 1 H), 7.36 (s, 1 H), 3.89 (s, 3 H), 3.41 (s, 2 H), 1.33 (s, 6 H).

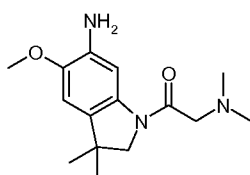
Step C/Intermediate A102: {2-[3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}dimethylamine



A solution of 3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (2.38 g, 10.71 mmol), Hunig's base (9.33 mL, 53.5 mmol) and bromo-acetylchloride (1.159 mL, 13.92 mmol) in tetrahydrofuran (100 mL) was maintained at 0°C for 2 hours. Dimethylamine (2.0M in THF, 42.8 mL, 86 mmol) was added to the solution and the reaction was

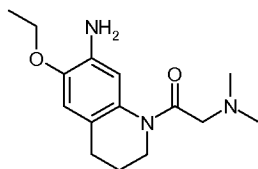
warmed to room temperature and maintained for 5 hours. The reaction was poured into saturated sodium bicarbonate, the organic layer was dried over sodium sulfate, filtered, and purified by column chromatography to afford {2-[3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}dimethylamine (2.14 g, 65.0 % yield) as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.44 (s, 1 H), 7.35 (s, 1 H), 3.97 (s, 2 H), 3.92 (s, 3 H), 3.21 (s, 2 H), 2.26 (s, 6 H), 1.34 (s, 6 H).

StepD/Intermediate A99: 1-[(dimethylamino)acetyl]-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1H-indol-6-amine

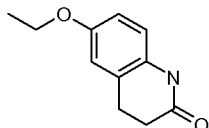


A suspension of {2-[3,3-dimethyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}dimethylamine (2.20 g, 7.16 mmol), hydrazine hydrate (2.81 mL, 57.3 mmol), iron(III)chloride (0.232 g, 1.432 mmol), and activated carbon (2 g, 7.16 mmol) was warmed at 65°C for 16 hours. The solution was filtered while still warm through celite, taken to a residue under reduced pressure, and partitioned between chloroform and saturated sodium bicarbonate. The organic layer was washed with saturated sodium chloride (aq), dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford 1-[(dimethylamino)acetyl]-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (1.41 g, 71 % yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.49 (s, 1 H), 6.69 (s, 1 H), 4.62 (s, 2 H), 3.82 (s, 2 H), 3.73 (s, 3 H), 3.12 (s, 2 H), 2.23 (s, 6 H), 1.22 (s, 6 H).

Intermediate A103: 1-[(dimethylamino)acetyl]-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinamine

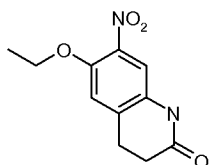


Step A/Intermediate A104: 6-(ethyloxy)-3,4-dihydro-2(1H)-quinolinone



- 5 To 6-hydroxy-3,4-dihydro-2(1H)-quinolinone (90.2 g, 0.55 mol, 1 equiv) in DMF (1.8L) was added potassium carbonate (228 g, 1.65 mol, 3 equiv). The slurry was stirred for 45 min. at 25°C, then iodoethane (114 g, 0.73 mol, 1.33 equiv) was added and stirring was continued for 12 hours. The mixture was filtered, the filtrate was poured into water, and the white precipitate was collected via filtration, washed with water (500mL), and dried
10 under high vacuum to provide 6-(ethyloxy)-3,4-dihydro-2(1H)-quinolinone (72.3g, 69%).
¹H NMR (400 MHz, DMSO) δ , 1.25 (t, $J=7.2$ Hz, 3H), 2.35 (m, 2 H), 2.78 (m, 2H), 3.90 (m, 2H), 6.70-6.73 (m, 3H), 9.83 (br, 1H).

StepB/Intermediate A105: 6-(ethyloxy)-7-nitro-3,4-dihydro-2(1H)-quinolinone

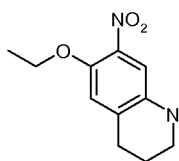


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- To the solution of 6-ethoxy-3,4-dihydroquinolin-2(1H)-one (72.3 g, 0.38 mol, 1 equiv) in TFA (800 mL) was added NaNO₂ (33.7 g, 0.496 mol, 1.3 equiv) at 0°C. The solution was allowed to warm to room temperature and stirring was continued for 4 hours. The
20 mixture was poured into ice and the yellow precipitate was isolated via filtration and dried under high vacuum at 50 °C. The crude product was recrystallized from ethyl acetate to afford 6-(ethyloxy)-7-nitro-3,4-dihydro-2(1H)-quinolinone (69.2 g, 77% yield).
¹H NMR (400 MHz, DMSO) δ 1.31 (t, $J=6.8$ Hz, 3H), 2.45-2.49 (m, 2 H), 2.95 (t, 2 H, $J=6.4$ Hz), 4.13-4.15 (m, 2 H), 7.25 (s, 1 H), 7.34 (s, 1 H), 10.16 (bs, 1 H).

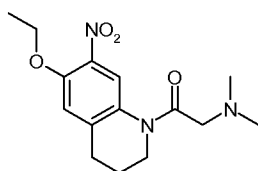
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Step C/Intermediate A106: 6-(ethyloxy)-7-nitro-1,2,3,4-tetrahydroquinoline



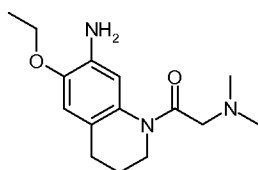
To a stirred solution of 6-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (69 g of, 0.29 mol, 1 equiv) in THF (1L) was added BH₃.DMS (10 M, 120 mL, 1.2 mol, 4equiv) dropwise at 25 °C. The mixture was stirred for 4 h at 60 °C. The reaction was cooled and quenched carefully with excess MeOH, then the mixture was concentrated under reduced pressure and the resultant solid suspended in a mixture of Et₂O and EtOAc and filtered to afford 6-(ethoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (26.7 g, 42% yield) as an orange solid. ¹H NMR (400 MHz, DMSO) δ 1.24 (t, *J* = 6.8 Hz, 3 H), 1.73-1.77 (m, 2 H), 2.68 (m, 2 H), 3.95-4.01 (m, 2 H), 5.81 (s, 1 H), 6.85 (s, 1 H), 6.89 (s, 1 H). Several protons obstructed by solvent.

Step D/Intermediate A107: {2-[6-(ethoxy)-7-nitro-3,4-dihydro-1(2*H*)-quinolinyl]-2-oxoethyl}dimethylamine



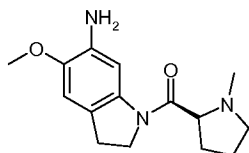
A suspension of 6-(ethoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (5.0 g, 22.50 mmol) and potassium carbonate (6.22 g, 45.0 mmol) in dichloromethane (100 mL) was treated with bromoacetylchloride (2.336 mL, 28.1 mmol) and stirred for 25 minutes. Water was added and the organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, redissolved in THF, and 2.0M dimethyl amine in THF (67.5 mL, 135 mmol) was added. The solution was stirred overnight, diluted with saturated sodium bicarbonate, and the organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford {2-[6-(ethoxy)-7-nitro-3,4-dihydro-1(2*H*)-quinolinyl]-2-oxoethyl}dimethylamine (5.8 g, 84 % yield) as a pale yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.34 (s, 1 H), 7.16 (s, 1 H), 4.17 (q, *J*=6.96 Hz, 2 H), 3.74 (t, *J*=5.62 Hz, 2 H), 3.21 (s, 2 H), 2.80 (t, *J*=6.32 Hz, 2 H), 2.21 (s, 6 H), 1.76 - 2.01 (m, 2 H), 1.33 (t, *J*=6.92 Hz, 3 H).

Step E/Intermediate A103: 1-[(dimethylamino)acetyl]-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinamine

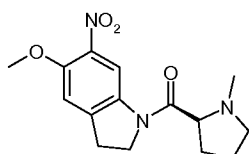


- 5 A solution of {2-[6-(ethoxy)-7-nitro-3,4-dihydro-1(2H)-quinolinyl]-2-oxoethyl}dimethylamine (5.8 g, 18.87 mmol) in degassed methanol (50.0 mL) was added to a suspension of 10% Pd/C (3.0 g, 16.36 mmol) in degassed methanol (5 mL) and maintained under a 50 psi hydrogen gas with rapid stirring for 16 hours. The suspension was purged with nitrogen, filtered through celite, all volatiles removed, and the resulting
- 10 residue was purified by flash column chromatography to afford 1-[(dimethylamino)acetyl]-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinamine (2.85 g, 63 %) as a viscous yellow liquid which solidified upon standing for 10 hours. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.80 (s, 1 H), 6.55 (s, 1 H), 4.52 (s, 2 H), 3.95 (q, *J*=6.89 Hz, 2 H), 3.61 (t, *J*=6.02 Hz, 2 H), 3.15 (s, 2 H), 2.55 (t, *J*=6.52 Hz, 2 H), 2.20 (s, 6 H), 1.73 -
- 15 1.86 (m, 2 H), 1.32 (t, *J*=7.02 Hz, 3 H).

Intermediate A108: 5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1H-indol-6-amine



- 20 Step A/Intermediate A109: 5-(methoxy)-1-(1-methyl-L-prolyl)-6-nitro-2,3-dihydro-1H-indole indole

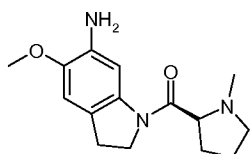


- A solution of 5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (2.7 g, 11.71 mmol), 1-methyl-L-proline (Acros, 1.739 g, 13.46 mmol), HATU (5.79 g, 15.22 mmol), and DIPEA (6.13
- 25

mL, 35.1 mmol) in N,N-dimethylformamide (25 mL) was stirred at room temperature overnight. The next morning the solution had completely solidified. The solids were diluted with ethyl acetate/THF and washed with saturated sodium bicarbonate until all solids had dissolved. The organic layer was dried over sodium sulfate, filtered,

5 concentrated onto celite, and purified by column chromatography to afford 5-(methoxy)-1-(1-methyl-L-prolyl)-6-nitro-2,3-dihydro-1*H*-indole (3.4 g, 95 % yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.51 (s, 1 H), 7.35 (s, 1 H), 4.20 - 4.31 (m, 1 H), 4.10 - 4.20 (m, 1 H), 3.88 (s, 3 H), 3.56 - 3.70 (m, 1 H), 3.25 (t, *J*=8.43 Hz, 2 H), 3.15 - 3.21 (m, 1 H), 2.52 - 2.64 (m, 1 H), 2.45 (s, 3 H), 2.21 - 2.35 (m, 1 H), 1.75 - 1.93 (m, 3 H).

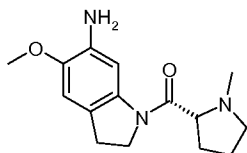
Step B/Intermediate A108: 5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1*H*-indol-6-amine



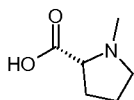
15 A suspension of 5-(methoxy)-1-(1-methyl-L-prolyl)-6-nitro-2,3-dihydro-1*H*-indole (2.50 g, 8.19 mmol) in methanol (100 mL)/tetrahydrofuran (100 mL) was warmed to 65°C and maintained until all solids had dissolved. The solution was cooled, purged with nitrogen for 40 minutes, and 10% palladium on carbon (1.1 g, 8.19 mmol) was added and the suspension was maintained under 40 psi of H₂ gas with rapid stirring for 24 hours. The solution was carefully purged with nitrogen, filtered through a pad of celite, and all solvents removed under reduced pressure to afford 5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1*H*-indol-6-amine (2.23 g, 99% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.57 (s, 1 H), 6.70 (s, 1 H), 4.76 (s, 2 H), 4.06 - 4.17 (m, 1 H), 3.93 - 4.06 (m, 1 H), 3.70 (s, 3 H), 3.46 (s, 1 H), 3.06 - 3.18 (m, 1 H), 2.98 (t, *J*=8.25 Hz, 2 H), 2.41 - 2.47 (m, 1 H), 2.37 (s, 3 H), 2.12 - 2.29 (m, 1 H), 1.66 - 1.92 (m, 3 H).

Intermediate A110: 5-(methoxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1*H*-indol-6-amine

120



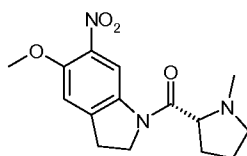
Step A/Intermediate A111: 1-methyl-D-proline



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To a solution of D-proline (30 g, 260.7mmol, 1eq) and 37% aqueous formaldehyde (80.5mL, 782mmol, 3eq) in H₂O (900 mL) was added 10% Pd/C (30 g) under N₂. The mixture was stirred at 50°C under H₂ (30psi) overnight. The mixture was heated to boiling and filtered to remove the catalyst. The solution was concentrated under reduced pressure, and then water (150 mL) was added to the mixture and concentrated, the procedure was repeated three times so as to remove unreacted formaldehyde. The crude product was resuspended in MeCN/H₂O (1:1, v/v) and lyophilized. The solid product was recrystallized from EtOH/acetone, filtered, liberally washed with acetone, and dried under reduced pressure to give 1-methyl-D-proline (12.3g, 40%) as white solid. ¹H NMR (400 MHz, MeOD) δ ppm 1.95-1.99 (s, 1H), 2.1-2.2 (s, 2H), 2.4-2.5 (m, 1H), 3.05-3.15 (m, 1H), 3.3-3.35 (s, 1H), 3.65-3.75 (m, 1H), 3.75-3.85 (m, 1H). Several protons obstructed by residual solvent.

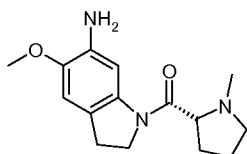
Step B/Intermediate A112: 5-(methoxy)-1-(1-methyl-D-prolyl)-6-nitro-2,3-dihydro-1H-indole



A solution of 5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (4.35 g, 18.86 mmol), 1-methyl-D-proline (2.436 g, 18.86 mmol), HATU (9.32 g, 24.52 mmol), and DIPEA (9.88 mL, 56.6 mmol) in N,N-dimethylformamide (25 mL) was stirred at room temperature overnight. The solution was poured into ethyl acetate/saturated sodium bicarbonate and the

organic layer was washed three times with saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford 5-(methoxy)-1-(1-methyl-D-prolyl)-6-nitro-2,3-dihydro-1H-indole (3.62 g, 11.86 mmol, 62.9 % yield) as a pale brown oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.52 (s, 1 H), 7.37 (s, 1 H), 4.21 - 4.34 (m, 1 H), 4.05 - 4.21 (m, 1 H), 3.90 (s, 3 H), 3.78 - 3.88 (m, 1 H), 3.22 - 3.31 (m, 2 H), 3.16 (d, *J*=3.01 Hz, 1 H), 2.64 - 2.81 (m, 1 H), 2.54 (s, 3 H), 2.30 - 2.44 (m, 1 H), 1.67 - 2.09 (m, 3 H).

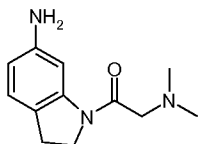
Step C/Intermediate A110: 5-(methoxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1H-indol-6-amine



A suspension of 5-(methoxy)-1-(1-methyl-D-prolyl)-6-nitro-2,3-dihydro-1H-indole (3.62 g, 11.86 mmol) in tetrahydrofuran (50.0 mL)/methanol (50 mL) was warmed to 60°C and maintained until all solids dissolved. The solution was cooled, degassed by bubbling with N₂ gas for 20 minutes, added to a pressure flask containing 10% palladium on carbon (1.1 g, 8.19 mmol), and maintained under 60 psi H₂ gas for 24 hours. The solution was purged with nitrogen, filtered through celite, the celite washed with methanol, and all volatiles removed under reduced pressure to afford 5-(methoxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1H-indol-6-amine (2.35 g, quantitative yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.57 (s, 1 H), 6.72 (s, 1 H), 4.69 (s, 2 H), 4.06 - 4.17 (m, 1 H), 3.93 - 4.06 (m, 1 H), 3.71 (s, 3 H), 3.64 (s, 1 H), 3.32 (s, 1 H), 3.21 (d, *J*=10.83 Hz, 1 H), 3.00 (t, *J*=8.03 Hz, 2 H), 2.49 (t, 3 H), 2.30 (d, *J*=8.23 Hz, 1 H), 1.65 - 1.96 (m, 3 H).

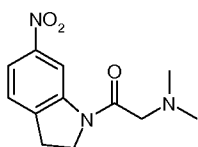
Intermediate A113: 1-[(dimethylamino)acetyl]-2,3-dihydro-1H-indol-6-amine

122



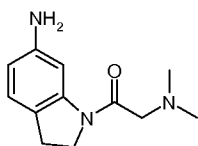
Step A/Intermediate A114: *N,N*-dimethyl-2-(6-nitro-2,3-dihydro-1*H*-indol-1-yl)-2-oxoethanamine

5



A suspension of 6-nitro-2,3-dihydro-1*H*-indole (10 g, 60.9 mmol) and potassium carbonate (16.84 g, 122 mmol) in dichloromethane (250 mL) was treated with bromoacetylchloride (6.33 mL, 76 mmol) and stirred for 25 minutes. Water was added and the organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure. The residue was redissolved in THF and 2.0M dimethyl amine in THF (Aldrich, 152 mL, 305 mmol) was added. The solution was stirred overnight, diluted with saturated sodium bicarbonate, and the organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford *N,N*-dimethyl-2-(6-nitro-2,3-dihydro-1*H*-indol-1-yl)-2-oxoethanamine (13.6 g, 54.6 mmol, 90 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.80 (d, *J*=2.01 Hz, 1 H), 7.90 (dd, *J*=8.23, 2.21 Hz, 1 H), 7.48 (d, *J*=8.23 Hz, 1 H), 4.26 (t, *J*=8.53 Hz, 2 H), 3.18 - 3.31 (m, 4 H), 2.28 (s, 6 H).

Step B/Intermediate A113: 1-[(dimethylamino)acetyl]-2,3-dihydro-1*H*-indol-6-amine



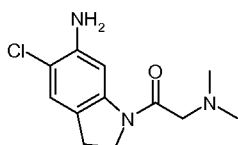
25

A suspension of *N,N*-dimethyl-2-(6-nitro-2,3-dihydro-1*H*-indol-1-yl)-2-oxoethanamine (13.6 g, 54.6 mmol), hydrazine hydrate (21.42 mL, 436 mmol), iron (III) chloride (1.768 g, 10.91 mmol), activated carbon (15 g), and methanol (100 mL) was maintained at 65°C for 12 hours, cooled, and filtered through celite (rinsed with additional methanol).

- 5 Filtrates were concentrated, redissolved in ethyl acetate, and washed twice with saturated aqueous sodium chloride and sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated to afford 1-[(dimethylamino)acetyl]-2,3-dihydro-1*H*-indol-6-amine (9.6 g, 80 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.44 (d, *J*=1.40 Hz, 1 H), 6.83 (d, *J*=8.03 Hz, 1 H), 6.20 (dd, *J*=7.93, 2.11 Hz, 1 H), 4.94 (s, 2 H), 4.06 (t, *J*=8.43 Hz, 2 H), 3.14 (s, 2 H), 2.91 (t, *J*=8.33 Hz, 2 H), 2.25 (s, 6 H).

Intermediate A115: 5-chloro-1-[(dimethylamino)acetyl]-2,3-dihydro-1*H*-indol-6-amine

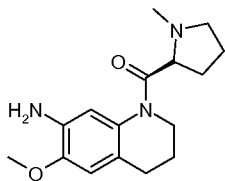
15



- A solution of 1-[(dimethylamino)acetyl]-2,3-dihydro-1*H*-indol-6-amine (3.0 g, 13.68 mmol) in acetonitrile (150 mL) was treated with *N*-chlorosuccinimide (2.010 g, 15.05 mmol) and stirred at room temperature for 15 minutes. The solution was poured into chloroform/saturated sodium bicarbonate (aq.) and the organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford 5-chloro-1-[(dimethylamino)acetyl]-2,3-dihydro-1*H*-indol-6-amine (0.510 g, 15 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.66 (s, 1 H), 7.01 (s, 1 H), 5.21 (s, 2 H), 4.08 (t, *J*=8.33 Hz, 2 H), 3.16 (s, 2 H), 2.95 (t, *J*=8.33 Hz, 2 H), 2.25 (s, 6 H).

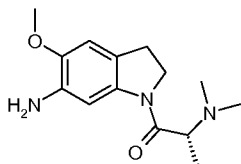
Intermediate A116: 6-(methoxy)-1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinolinamine

30

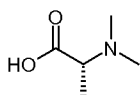


A solution of 6-(methoxy)-7-nitro-1,2,3,4-tetrahydroquinoline (3.0 g, 14.41 mmol), 1-methyl-L-proline (2.140 g, 16.57 mmol), HATU (7.12 g, 18.73 mmol), and DIPEA (6.29 mL, 36.0 mmol) in *N,N*-dimethylformamide (25 mL) was stirred for 2.5 days at room temperature. Reaction was poured into ethyl acetate and washed successively with 5% lithium chloride (aq) and saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, and purified by column chromatography (10% MeOH/CH₂Cl₂) to afford 6-(methoxy)-1-(1-methyl-L-prolyl)-7-nitro-1,2,3,4-tetrahydroquinoline (2.09 g, 6.54 mmol, 45.4 % yield). The residue was suspended in ethanol (300 mL) and *N,N*-dimethylacetamide (50 mL) was added followed by tin(II)chloride dihydrate (6.78 g, 30.1 mmol) and 1.0M HCl (2.505 mL, 2.505 mmol). After overnight stirring the reaction was quenched with excess saturated NaHCO₃ (300 mL) and allowed to stir at rt for 30 min. The solids were removed through a celite pad, rinsed with MeOH, and evaporated. The aqueous layer was extracted with DCM (2x100 mL). The combined organic layers were filtered through a cotton plug, and concentrated by rotary evaporation to provide 6-(methoxy)-1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinolinamine (1.1 g, 26% over two steps). ESIMS (M+H)⁺ = 290.

Intermediate A117: 1-[(2R)-2-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine

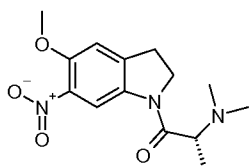


Step A/Intermediate A118: *N,N*-dimethyl-D-alanine



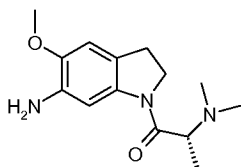
To a solution of D-alanine (30 g, 336mmol) and 37% aqueous formaldehyde (90.5mL, 930mmol) in H₂O (900 mL) was added 10% Pd/C (30 g) under N₂, the mixture was stirred at 50°C under H₂ (30psi) overnight. The mixture was heated to boiling and filtered to remove the catalyst. The solution was concentrated under reduced pressure, and then water (150 mL) was added to the mixture and concentrated, the procedure was repeated 3 times in order to remove any unreacted formaldehyde. The crude product was resuspended in ACN/H₂O (1:1, v/v) and lyophilized. The solid product was recrystallized from EtOH/acetone, filtered, liberally washed with acetone, and dried under reduced pressure to give N,N-dimethyl-D-alanine (30.4g, 77.07%) as white, very hygroscopic solid. ¹H NMR (400 MHz, MeOD) δ ppm 1.41-1.49 (m, 3H), 2.8-2.85 (s, 6H), 3.6-3.65 (m, 1H), 4.9-4.95 (s, 1H)

Step B/Intermediate A119: 1-[(2*R*)-*N,N*-dimethyl-1-[5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-1-oxo-2-propanamine



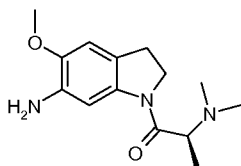
To a solution of 5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole hydrogen chloride (2 g, 8.67 mmol) in *N,N*-dimethylformamide (100 mL) was added *N,N*-dimethyl-D-alanine (1.524 g, 13.01 mmol), PyBOP (13.54 g, 26.0 mmol), and DIPEA (15.14 mL, 87 mmol). After stirring overnight at rt, the solvent was removed and the residue was suspended in dichloromethane (150 mL), washed with water (100 mL), concentrated on the rotovap, and purified by column chromatography (DCM to 5% MeOH/DCM) to provide 1-[(2*R*)-*N,N*-dimethyl-1-[5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-1-oxo-2-propanamine (2.2 g, 86%). ESIMS (M+H)⁺ = 294.

Step C/Intermediate A117: 1-[(2*R*)-2-(dimethylamino)propanoyl]-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-amine

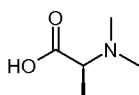


To a solution of (2*R*)-*N,N*-dimethyl-1-[5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-1-oxo-2-propanamine (2.2 g, 7.50 mmol) in ethyl acetate (250 mL) was added Pd/C (0.798 g, 0.750 mmol) and the reaction maintained under 50 psi of H₂(g) overnight in a Fisher-Porter apparatus. The crude material was filtered through a celite pad, washed with ethyl acetate, concentrated, and placed under high vacuum overnight to afford 1-[(2*R*)-2-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (1.4 g, 71%). ESIMS (M+H)⁺ = 264.

Intermediate A120: 1-[(2*S*)-2-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



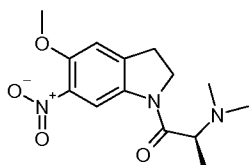
Step A/Intermediate A121: *N,N*-dimethyl-L-alanine



To a solution of L-alanine (30 g, 360mmol) and 37% aqueous formaldehyde (90 mL, 930 mmol) in H₂O (900 mL) was added 10% Pd/C (30 g) under N₂, the mixture was stirred at 50°C under H₂ (30psi) overnight. The mixture was heated to boiling and filtered to remove the catalyst. The solution was concentrated under reduced pressure, and then water (150 mL) was added to the mixture and concentrated, the procedure was repeated for 3 times in order to remove any unreacted formaldehyde. The crude product was resuspended in ACN/H₂O (1:1, v/v) and lyophilized. The solid product was recrystallized from EtOH/acetone, filtered, liberally washed with acetone, and dried under reduced pressure to give *N,N*-dimethyl-L-alanine (30.4g, 77.07%) as white, very hygroscopic

solid. ^1H NMR (400 MHz, MeOD) δ ppm 1.41-1.49 (d, $J=7.2\text{Hz}$, 3H), 2.8-2.85 (s, 6H), 3.6-3.65 (q, $J=7.2\text{Hz}$, 1H), 4.7-4.95 (br, 1H).

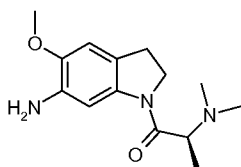
Step B/Intermediate A122: (2S)-N,N-dimethyl-1-[5-(methyloxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-1-oxo-2-propanamine



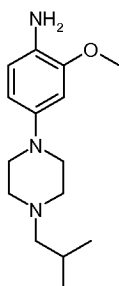
To a solution of 5-(methyloxy)-6-nitro-2,3-dihydro-1H-indole hydrogen chloride (2 g, 8.67 mmol) in N,N-dimethylformamide (100 mL) was added N,N-dimethyl-L-alanine (1.524 g, 13.01 mmol), PyBOP (13.54 g, 26.0 mmol), and DIPEA (15.14 mL, 87 mmol). After stirring overnight at rt, the solvent was removed, the residue was suspended in dichloromethane (150 mL), washed with water (100 mL), concentrated, and purified by column chromatography (DCM to 5% MeOH/DCM) to give (2S)-N,N-dimethyl-1-[5-(methyloxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-1-oxo-2-propanamine (2.2 g, 86%).

ESIMS (M+H) $^+$ = 294.

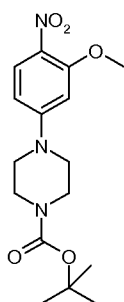
Step C/Intermediate A120: 1-[(2S)-2-(dimethylamino)propanoyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine



To a solution of (2S)-N,N-dimethyl-1-[5-(methyloxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-1-oxo-2-propanamine (2.2 g, 7.50 mmol) in ethyl acetate (250 mL) was added 10% Pd/C (0.798 g, 0.750 mmol) and the reaction was maintained under 50 psi of $\text{H}_2(\text{g})$ overnight on the Fisher-Porter apparatus. The reaction was filtered through a celite pad which was washed with ethyl acetate, concentrated by rotary evaporation, and maintained under high vacuum for 12 hours to afford 1-[(2S)-2-(dimethylamino)propanoyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine (1.5 g, 76%). ESIMS (M+H) $^+$ = 264.

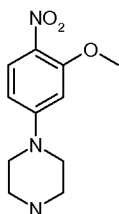
Intermediate A123: 2-(methoxy)-4-[4-(2-methylpropyl)-1-piperazinyl]aniline

- 5 Step A/Intermediate A123: 1,1-dimethylethyl 4-[3-(methoxy)-4-nitrophenyl]-1-piperazinecarboxylate



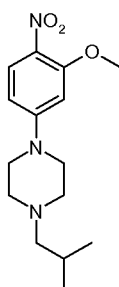
- 10 4-chloro-2-(methoxy)-1-nitrobenzene (10g, 53.2 mmol, Aldrich), 1,1-dimethylethyl 1-piperazinecarboxylate (20g, 107.5 mmol), cesium carbonate (35.0g, 107.5 mmol), Pd₂dba₃ (5g, 5.5 mmol), and XANTPHOS (4.62g, 8.0 mmol) were added to degassed dioxane (100 mL) and heated to 100°C under a water cooled reflux condenser for 12 hours. The dioxane was removed under reduced pressure and the solids were
- 15 partitioned between methylene chloride (500 mL) and water (500 mL). The organic layer was dried over sodium sulfate, taken to a residue under reduced pressure, and triturated with a methylene chloride/hexanes mixture (15:85) to precipitate out analytically pure 1-dimethylethyl 4-[3-(methoxy)-4-nitrophenyl]-1-piperazinecarboxylate as a yellow solid (13.2g, 39.2 mmol, 73% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.49 (s, 9 H), 3.33 -
- 20 3.42 (m, 4 H), 3.62-3.64 (m, 4 H), 3.96 (s, 3 H), 6.39 (s, 1 H), 6.44 (dd, J=9.16, 2.56 Hz, 1 H), 8.01 (d, J=9.16 Hz, 1 H).

Step B/Intermediate A125: 1-[3-(methoxy)-4-nitrophenyl]piperazine



1-dimethylethyl 4-[3-(methoxy)-4-nitrophenyl]-1-piperazinecarboxylate (2.25g, 6.67 mmol) was dissolved in methylene chloride (50 mL) and trifluoroacetic acid (10 mL). The resulting solution turned dark immediately and was stirred overnight. The solution was concentrated and partitioned between methylene chloride and 2.0N sodium hydroxide. The organic layer was collected and the aqueous layer was saturated by addition of sodium chloride and subsequently backextracted with additional methylene chloride. The combined organic layers were dried over sodium sulfate, filtered, and taken to a residue under reduced pressure to afford analytically pure 1-[3-(methoxy)-4-nitrophenyl]piperazine as a yellow solid (1.7g, 7.2 mmol, quant. yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.28 - 2.37 (m, 1 H), 2.76 (q, *J*=4.64 Hz, 4 H), 3.29 - 3.34 (m, 4 H), 3.86 (s, 3 H), 6.46 (d, *J*=2.38 Hz, 1 H), 6.54 (dd, *J*=9.43, 2.47 Hz, 1 H), 7.84 (d, *J*=9.34 Hz, 1 H).

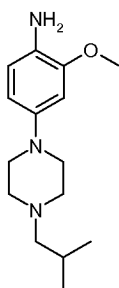
Step C/Intermediate A126: 1-[3-(methoxy)-4-nitrophenyl]-4-(2-methylpropyl)piperazine



A solution of 1-[3-(methoxy)-4-nitrophenyl]piperazine (2.09g, 8.44 mmol), 2-methyl-iodopropane (2.1g, 11.39 mmol), and potassium carbonate (4.7g, 34 mmol) in acetonitrile (80 mL) was heated in a pressure vessel at 80°C for 24 hours. The reaction was cooled and the acetonitrile was removed under reduced pressure. The solids were

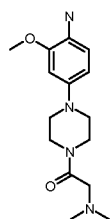
dissolved in methylene chloride/water. The organic layer was dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. The resultant residue was purified by chromatography on SiO₂ (10% MeOH/CH₂Cl₂ with 0.2% NH₃) to give 1-[3-(methoxy)-4-nitrophenyl]-4-(2-methylpropyl)piperazine as a pale yellow solid (1.70g, 5.8 mmol, 69% yield). ¹H NMR (400 MHz, CDCl₃) ppm 0.91 (d, *J*=6.59 Hz, 6 H), 1.80 (sept t, *J* = 7.05, 6.91, 1 H), 2.13 (d, *J*=6.04 Hz, 2 H), 2.52 (s, 4 H), 3.38 (s, 4 H), 3.93 (s, 3 H), 6.29 (d, *J*=2.38 Hz, 1 H), 6.40 (dd, *J*=9.43, 2.47 Hz, 1 H), 7.98 (d, *J*=9.52 Hz, 1 H).

Step D/Intermediate A123: 2-(methoxy)-4-[4-(2-methylpropyl)-1-piperazinyl]aniline

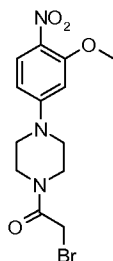


A solution of 1-[3-(methoxy)-4-nitrophenyl]-4-(2-methylpropyl)piperazine (1.7g, 5.82 mmol), FeCl₃ (0.280 g, 1.75 mmol), activated carbon (2.0g), and hydrazine hydrate (2.23 mL, 70 mmol) was heated in methanol (50 mL) for 3 hours. The mixture was filtered over celite and concentrated to give 2-(methoxy)-4-[4-(2-methylpropyl)-1-piperazinyl]aniline as a white solid (1.24g, 4.80 mmol, 83% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.94 (d, *J*=6.22 Hz, 6 H), 1.85 (s, 1 H), 2.20 (s, 2 H), 2.61 (s, 4 H), 3.10 (s, 4 H), 3.54 (s, 2 H), 3.83 (s, 3 H), 6.43 (m, 1 H), 6.52 (d, *J*=1.83 Hz, 1 H), 6.64 (d, *J*=8.42 Hz, 1 H).

Intermediate A127: 4-[4-[(dimethylamino)acetyl]-1-piperazinyl]-2-(methoxy)aniline

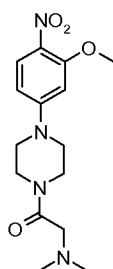


Step A/Intermediate A128: 1-(bromoacetyl)-4-[3-(methoxy)-4-nitrophenyl]piperazine



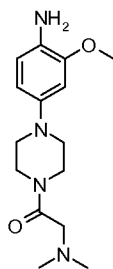
A solution of bromoacetyl chloride (0.404 mL, 4.85 mmol) was stirred in dichloromethane (8 mL) at 0 °C. Potassium carbonate (0.436 g, 3.16 mmol) was added. In a separate vial, the 1-[3-(methoxy)-4-nitrophenyl]piperazine (1.0 g, 4.21 mmol) was mixed with
5 dichloromethane (8 mL), then added dropwise to the reaction. Upon complete addition the reaction became a slurry, so additional dichloromethane was added to facilitate stirring (approximately 8 mL). This mixture was stirred at 0 °C for about 1 hr. TLC indicated incomplete reaction so additional bromoacetyl chloride (0.100 mL) was added. The reaction mixture was stirred for 1 h at rt. The reaction was then diluted with water
10 and extracted with dichloromethane. The water layer's pH was checked and it was acidic, so aqueous (saturated) Na₂CO₃ was added until the pH was basic. The aqueous layer was extracted with dichloromethane and EtOAc. The combined organic layers were dried over MgSO₄ and concentrated under vacuum to give 1-(bromoacetyl)-4-[3-(methoxy)-4-nitrophenyl]piperazine as a bright yellow solid (1.49 g, 99%). ¹H NMR
15 (400 MHz, CDCl₃) δ ppm 3.42-3.48 (m, 2 H), 3.49-3.58 (m, 2H), 3.71-3.79 (m, 2H), 3.79-3.87 (m, 2H), 3.92 (s, 2H), 3.98 (s, 3H), 6.35 (d, J=1.8 Hz, 1H), 6.45 (dd, J=9.2 Hz, 2.2 Hz, 1H), 8.03 (d, J=9.3 Hz, 1H).

Step B/Intermediate A129: N,N-dimethyl-2-{4-[3-(methoxy)-4-nitrophenyl]-1-piperazinyl}-2-oxoethanamine
20



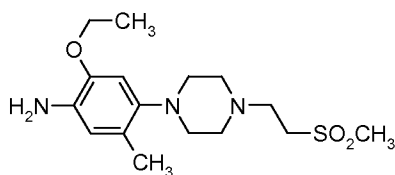
To a 0 °C slurry of 1-(bromoacetyl)-4-[3-(methoxy)-4-nitrophenyl]piperazine (1.49 g, 4.16 mmol) in dichloromethane (8 mL) under nitrogen was added dimethylamine (2M in THF, 8.32 mL, 16.64 mmol). The resulting slurry was stirred for 30 minutes at 0 °C, then was allowed to warm to rt and stirred for about 1 hour. The resulting mixture was concentrated under vacuum. The residue was dissolved in EtOAc and water. The aqueous layer was extracted with EtOAc (with 5% IPA) and dichloromethane (with 5% IPA). The combined organic layers were dried over MgSO₄ and concentrated under vacuum to give *N,N*-dimethyl-2-{4-[3-(methoxy)-4-nitrophenyl]-1-piperazinyl}-2-oxoethanamine as a yellow solid (1.01 g, 75%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.46 (s, 6H), 3.38 (s, 2H), 3.40-3.52 (m, 4H), 3.75-3.87 (m, 4H), 3.97 (s, 3 H), 6.34 (d, *J*=1.6 Hz, 1H), 6.43 (dd, *J*=9.3, 2.2 Hz, 1H), 8.02 (d, *J*=9.3 Hz, 1H); ESIMS (*M*+H)⁺ = 323.

Step C/Intermediate A127: 4-{4-[(dimethylamino)acetyl]-1-piperazinyl}-2-(methoxy)aniline



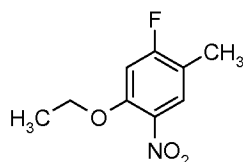
N,N-dimethyl-2-{4-[3-(methoxy)-4-nitrophenyl]-1-piperazinyl}-2-oxoethanamine (1.00 g, 3.10 mmol) was added to a thick-walled hydrogenation flask. To the flask were added ethanol (15 mL), ethyl acetate (15 mL), and methanol (15 mL). Under nitrogen, 10% palladium on carbon (0.330 g, 0.310 mmol) was added. The flask was purged with vacuum and nitrogen (3x). The flask was purged with vacuum and hydrogen (3x). The flask was then maintained under H₂ atm (50 psi) for approximately 24 hours. The resulting mixture was diluted with methanol and dichloromethane, and filtered through a Celite pad using methanol and dichloromethane. The filtrate was concentrated under vacuum and the residue was purified by silica gel chromatography to give 4-{4-[(dimethylamino)acetyl]-1-piperazinyl}-2-(methoxy)aniline as a light grey solid (617 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 6H), 2.97-3.07 (m, 4H), 3.16 (s, 2H), 3.73-3.81 (m, 4H), 3.85 (s, 3H), 6.37-6.45 (m, 1H), 6.52 (s, 1H), 6.66 (d, *J*=8.2 Hz, 1H).

Intermediate A130: 2-(ethoxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline



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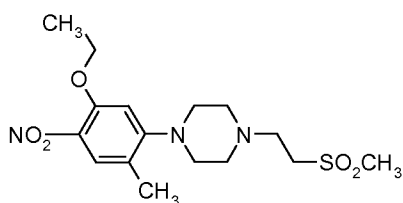
Step A/Intermediate A131: 1-(ethoxy)-5-fluoro-4-methyl-2-nitrobenzene



- 10 5-fluoro-4-methyl-2-nitrophenol (11.1 g, 65.0 mmol) and iodoethane (12.2 g, 78.0 mmol) were dissolved in 100 mL of DMSO with stirring. K_2CO_3 (13.5 g, 97.5 mmol) was added. The reaction was stirred for 3 h and then diluted with DCM and filtered. The filtrate was poured into H_2O and extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 1-(ethoxy)-5-fluoro-4-methyl-2-
- 15 nitrobenzene (8.00 g, 39.4 mmol) as a pale yellow crystalline solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 11.0 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 2.22 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H).

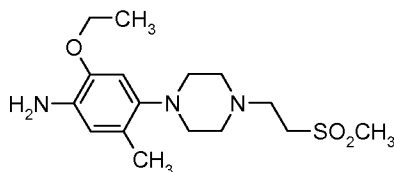
Step B/Intermediate A132: 1-[5-(ethoxy)-2-methyl-4-nitrophenyl]-4-[2-

- 20 (methylsulfonyl)ethyl]piperazine



1-(ethyloxy)-5-fluoro-4-methyl-2-nitrobenzene (5.74 g, 28.8 mmol) was dissolved in DMSO (60 mL). K_2CO_3 (11.9 g, 86.4 mmol) and 1-[2-(methylsulfonyl)ethyl]piperazine hydrochloride (9.85 g, 43.2 mmol) were added and the reaction mixture was heated to 100 °C and allowed to stir overnight. The mixture was cooled to rt then diluted with DCM and filtered. The filtrate was poured into H_2O and extracted with DCM. The combined organics were dried with $MgSO_4$, filtered, and concentrated in vacuo to give 1-[5-(ethyloxy)-2-methyl-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperazine (9.70 g, 26.1 mmol, 90%) as an orange solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 6.51 (s, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.16 (t, J = 6.5 Hz, 2H), 3.03 (s, 3H), 3.00-2.91 (m, 6H), 2.72-2.62 (m, 4H), 2.21 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H).

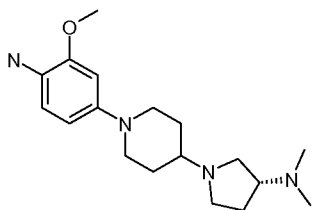
Step C/Intermediate A130: 2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline



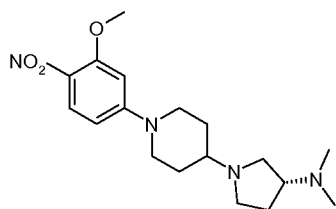
1-[5-(ethyloxy)-2-methyl-4-nitrophenyl]-4-[2-(methylsulfonyl)ethyl]piperazine (9.7 g, 26 mmol) was taken up in EtOH (100 mL). The catalyst, 5% sulfided platinum on carbon (1.0 g) was added. The reaction was placed under 1 atm of H_2 gas and was allowed to stir at rt overnight. The catalyst was filtered off and the filtrate was concentrated onto silica in vacuo. The product was purified on a 120 g ISCO column (DCM to 2% (2N NH_3 in MeOH) to give 2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline (1.9 g, 5.7 mmol, 22 %) as a pale orange oil. The mixed fractions (product and starting material) were resubmitted to the above conditions to provide additional product (5.2 g, 15 mmol, 58%). 1H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.52 (s, 1H), 3.99 (q, J = 7.0 Hz, 2H), 3.56 (s, 2H), 3.15 (t, J = 6.3 Hz, 2H), 3.05 (s, 3H), 2.91 (t, J = 6.4 Hz, 2H), 2.84-2.78 (m, 4H), 2.67-2.54 (m, 4H), 2.13 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H).

Intermediate A133: (3R)-1-{1-[4-amino-3-(methyloxy)phenyl]-4-piperidinyl}-N,N-dimethyl-3-pyrrolidinamine

135



Step A/Intermediate A134: (3R)-N,N-dimethyl-1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidiny]-3-pyrrolidinamine



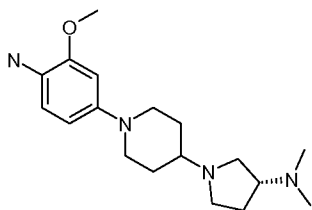
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A mixture of 1-[3-(methoxy)-4-nitrophenyl]-4-piperidinone (1.0 g, 4.0 mmol), commercially available (3R)-(+)-3-dimethylaminopyrrolidine (1.0 g, 8.0 mmol), acetic acid (0.34 ml, 6 mmol) and triethylamine (0.56 ml, 4.0 mmol) in 1,2-dichloroethane (40 mL) was stirred for 30 minutes. Sodium triacetoxymethylborohydride (1.3 g, 6.0 mmol) was added. When tlc indicated the absence of starting material, the reaction was quenched by addition of sat'd NaHCO₃. The reaction was diluted with DCM and the layers were separated. The aqueous phase was extracted with DCM. The combined organic layers were washed with water, dried over MgSO₄ and concentrated to give a quantitative yield of (3R)-N,N-dimethyl-1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidiny]-3-pyrrolidinamine as a yellow oil. ¹H NMR (400 MHz, d₆-DMSO) δ 7.84 (d, J = 9.2 Hz, 1H), 6.55 (dd, J = 9.6 and 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 3.87-3.84 (m, 5H), 3.05-2.99 (m, 2H), 2.73 (t, J = 7.8 Hz, 1H), 2.62-2.55 (m, 2H), 2.47-2.43 (m under DMSO peak, 1H), 2.28-2.20 (m, 2H), 2.05 (s, 6H), 1.86-1.74 (m, 3H), 1.57-1.50 (m, 1H), 1.44-1.34 (m, 2H).

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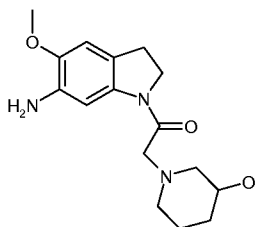
Step B/Intermediate A133: (3R)-1-{1-[4-amino-3-(methoxy)phenyl]-4-piperidiny]-N,N-dimethyl-3-pyrrolidinamine

25



(3*R*)-*N,N*-dimethyl-1-{1-[3-(methoxy)-4-nitrophenyl]-4-piperidiny]-3-pyrrolidinamine (1.4g, 4.0 mmol) (crude from previous step) and 5% sulfided platinum on carbon (50 mg, catalytic amount) in EtOAc was stirred under 60 psi hydrogen pressure in a Fisher-Porter vessel. After 16 h, the reaction was filtered through a pad of celite, rinsing well with EtOAc. The filtrate was concentrated to give (3*R*)-1-{1-[4-amino-3-(methoxy)phenyl]-4-piperidiny]-*N,N*-dimethyl-3-pyrrolidinamine as a grey solid (1.09g, 3.4 mmol). ¹H NMR (400 MHz, CDCl₃) δ 6.61 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.4 and 2.4 Hz, 1H), 3.82 (s, 3H), 3.49-3.42 (m, 4H), 3.00 (t, *J* = 8.0 Hz, 1H), 2.89-2.84 (m, 1H), 2.75-2.61 (m, 3H), 2.53-2.47 (m, 1H), 2.28 (t, *J* = 8.2 Hz, 1H), 2.20 (s, 6H), 2.17-2.08 (m, 1H), 2.04-1.92 (m, 3H), 1.73-1.60 (m, 3H).

Intermediate A135: 1-{2-[6-amino-5-(methoxy)-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethyl}-3-piperidinol

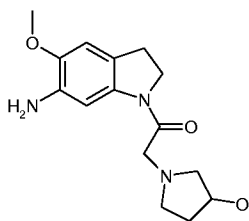


The 1-(bromoacetyl)-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole (4.0g, 12.7 mmol) was dissolved in 50 mL of dichloromethane, then K₂CO₃ (4.4g, 31.7 mmol) and 3-piperidinol (1.54g, 15.2 mmol) in 10 mL dichloromethane were added, the reaction was stirred at RT overnight. The reaction mixture was diluted with 100 mL of water, the organic solvents were washed with water (2x100mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure. The resulting residue was dissolved in 10 mL of EA, 25 mL of MeOH and 15 mL of THF, then 0.8 g 10% Pd/C was added, the reaction was stirred at RT overnight under balloon H₂ pressure. The catalyst was removed via filtration and the solvent was removed under reduced pressure to yield 1-{2-[6-amino-5-

(methyloxy)-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethyl]-3-piperidinol as a white solid (3.0g, 92%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 1.09 (m, 1H), 1.44 (m, 1H), 1.62 (m, 1H), 1.74 (m, 1H), 2.14(br s, 1H), 2.47(s, 1H), 2.74(br, 2H), 2.95 (m, 4 H), 3.50 (s, 2H), 3.68 (s, 3H), 4.04 (t, J=6.13Hz, 2 H), 4.71 (s, 2H), 6.68 (s, 1 H), 7.51 (s, 1 H).

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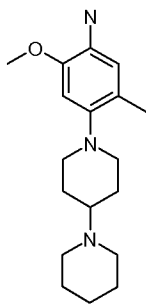
Intermediate A136 : 1-{2-[6-amino-5-(methyloxy)-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethyl}-3-pyrrolidinol



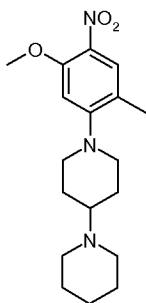
- 10 The 1-(bromoacetyl)-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole (4.0g, 12.7 mmol) was dissolved in 50 mL of dichloromethane, then K₂CO₃ (4.4g, 31.7 mmol) and 3-pyrrolidinol (1.33g, 15.2 mmol) in 10 mL dichloromethane were added, and the reaction was stirred at RT overnight. The reaction mixture was diluted with 100 mL of water, the organic solvents were washed with water (2x100mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The resulting residue was dissolved in 10 mL of EA , 25 mL of MeOH and 15 mL of THF, then 0.8 g 10% Pd/C was added, and the reaction was stirred at RT overnight under a balloon of H₂ pressure. The catalyst was removed via filtration and the solvent was evaporated under reduced pressure to yield 1-{2-[6-amino-5-(methyloxy)-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethyl}-3-pyrrolidinol as a white solid
- 15
- 20 (3.0g, 92%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 1.60 (m, 1 H), 1.97 (m, 1 H), 2.47 (s, 1H), 2.59 (m, 1H), 2.72 (m, 1H), 2.85 (m, 1H), 2.96 (m, 4H), 3.50(s, 2H), 3.68 (s, 3H), 4.00 (t, J=8.33Hz, 2 H), 4.86 (s, 2H), 6.68 (s, 1 H), 7.51 (s, 1 H).

Intermediate A137: 4-(1,4'-bipiperidin-1'-yl)-5-methyl-2-(methyloxy)aniline

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Step A/Intermediate A138: 1'-[2-methyl-5-(methoxy)-4-nitrophenyl]-1,4'-bipiperidine

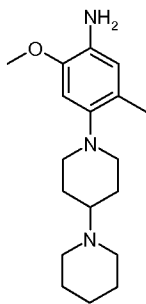


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A yellow slurry of 1-fluoro-2-methyl-5-(methoxy)-4-nitrobenzene (10 g, 54.0 mmol), 1,4'-bipiperidine (10.91 g, 64.8 mmol) and K_2CO_3 (18.66 g, 135 mmol) in dimethyl sulfoxide (200 ml) was heated at 130 °C for 2h, then was allowed to cool to 60 °C. The resulting slurry was filtered, the solids were washed with DMSO (50 mL). The filtrate was concentrated and the solids were washed with CH_2Cl_2 (200 mL). The filtrate was washed with water (200 mL). The aqueous layer was back extracted with EtOAc (100 mL). The organic layers were combined, concentrated onto Celite and purified by silica gel chromatography using 0-20% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to obtain 1'-[2-methyl-5-(methoxy)-4-nitrophenyl]-1,4'-bipiperidine (11.0 g, 61%) as an orange solid.

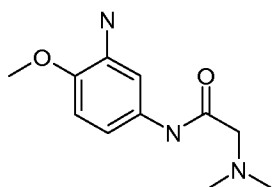
1H NMR (400 MHz, $DMSO-d_8$) δ ppm 1.25-1.70 (m, 8H), 1.82 (d, $J=11.72$ Hz, 2H), 2.19 (s, 3H), 2.28-2.43 (m, 1H), 2.70 (t, $J=11.81$ Hz, 2H), 3.32 (d, $J=11.35$ Hz, 3H), 3.90 (s, 3H), 6.68 (s, 1H), 7.76 (s, 1H), 3 protons are missing, they presumably overlap with DMSO peak; ESIMS ($M+H$) $^+$ = 334.

Step B/Intermediate A137: 4-(1,4'-bipiperidin-1'-yl)-5-methyl-2-(methoxy)aniline

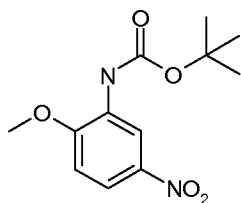


The 1'-[2-methyl-5-(methoxy)-4-nitrophenyl]-1,4'-bipiperidine (1.5g, 4.5 mmol) was dissolved in 30 ml of THF, then 0.3 g 10% Pd/C was added, the reaction was stirred at
 5 RT overnight under H₂ pressure (60 psi). The catalyst was filtered out, the solvent was removed to yield the 4-(3'-methyl-1,4'-bipiperidin-1'-yl)-2-(methoxy)aniline as a yellow solid, 1.3g (95%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.33 (br. s., 2 H), 1.47 (br. s., 6 H), 1.73 (dd, J=6.97, 3.21 Hz, 2 H), 2.03 (s, 3 H), 2.48 (dt, J=3.57, 1.79 Hz, 6H), 2.90 (d, J=11.55 Hz, 2H), 3.31 (s., 1H), 3.68 (s, 3H), 4.27 (s., 2H), 6.40 (s, 1H), 6.52 (s, 1H).

10

Intermediate A139**N¹-[3-amino-4-(methoxy)phenyl]-N²,N²-dimethylglycinamide hydrogen chloride**

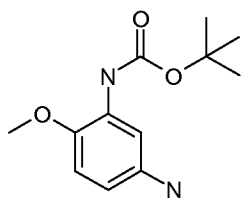
15 Step A/Intermediate A140: 1,1-dimethylethyl [2-(methoxy)-5-nitrophenyl]carbamate



To a solution of 2-(methoxy)-5-nitroaniline (10 g, 59.5 mmol) in anhydrous THF (100 mL) was added triethylamine (9.95 mL, 71.4 mmol), followed by DMAP (0.727 g, 5.95 mmol) and BOC-anhydride (14.50 mL, 62.4 mmol). The reaction mixture was stirred at rt
 20 for 19 h. The resulting slurry was diluted with EtOAc (300 mL), washed with a 10% aqueous citric acid solution and a saturated NaCl solution. The organic layer was filtered

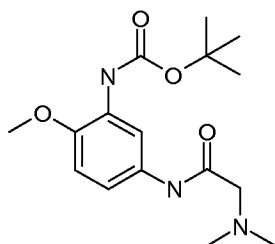
through a pad of Celite. The filtrate was concentrated to afford a yellow foamy solid, which was then triturated using CH_2Cl_2 . The reaction was repeated on the same scale. The two crops of crude material were combined, dissolved in THF, concentrated onto Celite and purified by silica gel chromatography using 20-100% CH_2Cl_2 /hexanes to afford 1,1-dimethylethyl [2-(methyloxy)-5-nitrophenyl]carbamate (4.66 g 14% for 2 batches). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.48 (s, 9H), 3.94 (s, 3H), 7.21 (d, $J=9.16$ Hz, 1H), 7.97 (dd, $J=9.06$, 2.84 Hz, 1H), 8.48 (s, 1H), 8.68 (d, $J=2.75$ Hz, 1H).

Step B/Intermediate A141: 1,1-dimethylethyl [5-amino-2-(methyloxy)phenyl]carbamate



10% Pd on carbon (0.5 g, 17.37 mmol) was placed under N_2 atm. EtOH (20 mL) was added, followed by a slurry of 1,1-dimethylethyl [2-(methyloxy)-5-nitrophenyl]carbamate (4.66 g, 17.37 mmol) in EtOH (230 mL). The reaction mixture was placed under H_2 atm via a balloon and stirred at rt. After 3 days the resulting mixture was filtered through a pad of Celite using EtOH. The filtrate was concentrated. The residue was taken up into Et_2O and concentrated again to afford 1,1-dimethylethyl [5-amino-2-(methyloxy)phenyl]carbamate (4.15 g, 100%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.45 (s, 9H), 3.66 (s, 3H), 4.65 (br s, 2H), 6.20 (dd, $J=8.61$, 2.75 Hz, 1H), 6.68 (d, $J=8.61$ Hz, 1H), 7.10 (d, $J=2.01$ Hz, 1H), 7.56 (s, 1H).

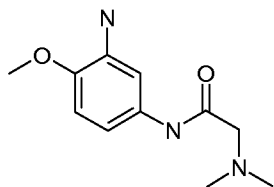
Step C/Intermediate A142: 1,1-dimethylethyl [5-[(*N,N*-dimethylglycyl)amino]-2-(methyloxy)phenyl]carbamate



A solution of 1,1-dimethylethyl [5-amino-2-(methyloxy)phenyl]carbamate (1.5 g, 6.30 mmol) in THF (50 mL) was cooled to 0 °C. K_2CO_3 (2.61 g, 18.89 mmol) was added,

followed by dropwise addition of bromoacetyl chloride (0.685 mL, 8.18 mmol). After 10 min the reaction mixture was allowed to warm to rt and treated with a Me₂NH solution (2M in THF, 9.45 mL, 18.90 mmol). After 4 h more Me₂NH solution (2M in THF, 9.45 mL, 18.90 mmol) was added and the mixture was stirred at rt. After 3 days the resulting mixture was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 1,1-dimethylethyl [5-[(N,N-dimethylglycyl)amino]-2-(methyloxy)phenyl]carbamate as a white foamy semi-solid (1.7 g, 83%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.46 (s, 9H), 2.26 (s, 6H), 3.21 (s, 2H), 3.76 (s, 3H), 6.91 (d, *J*=8.79 Hz, 1H), 7.37 (dd, *J*=8.79, 2.38 Hz, 1H), 7.86 (s, 1H), 7.96 (d, *J*=2.38 Hz, 1H), 9.56 (s, 1H); ESIMS (M+H)⁺ = 323.

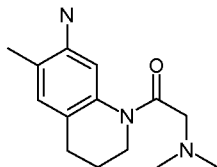
Step D/Intermediate A139: *N*¹-[3-amino-4-(methyloxy)phenyl]-*N*²,*N*²-dimethylglycinamide hydrogen chloride



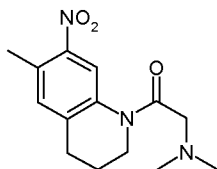
A solution of 1,1-dimethylethyl [5-[(N,N-dimethylglycyl)amino]-2-(methyloxy)phenyl]carbamate (1.7 g, 5.26 mmol) in dioxane (10 mL) was treated with a 4N HCl solution in dioxane (19.71 mL, 79 mmol). The resulting white slurry was maintained at rt. After 3 h the slurry was filtered, the solids were washed with Et₂O to obtain *N*¹-[3-amino-4-(methyloxy)phenyl]-*N*²,*N*²-dimethylglycinamide hydrogen chloride as a white solid (1.28 g, 94%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.87 (s, 6H), 3.56 (s, 3H), 4.17 (s, 2H), 7.18 (d, *J*=9.16 Hz, 1H), 7.50-7.67 (m, 1H), 7.73-7.89 (m, 1H), 10.14 (br s, 3H), 11.07-11.35 (m, 1H).

Intermediate A143

1-[(dimethylamino)acetyl]-6-methyl-1,2,3,4-tetrahydro-7-quinolinamine



Step A/Intermediate A144: N,N-dimethyl-2-(6-methyl-7-nitro-3,4-dihydro-1(2H)-quinolinyl)-2-oxoethanamine

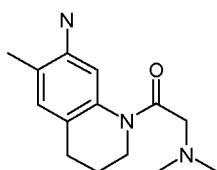


To a bright orange solution of 6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (2 g, 10.41 mmol)—(see Achvlediani, R.; Natsvlishvili, M.; Baberkina, E.; Khachidze, M.; Abesadze, I.; Suvorov, N. **Synthesis of 1H-pyrrolo[3,2-γ]- and 1H-pyrrolo[2,3-γ]quinoline.**

Izvestiya Akademii Nauk Gruzii, Seriya Khimicheskaya (1996), 22(1-4), 43-47.)—in THF (50 mL) was added K₂CO₃ (4.31 g, 31.2 mmol). The resulting mixture was cooled to 0 °C and was treated with bromoacetyl chloride (1.040 mL, 12.49 mmol) dropwise.

The reaction mixture was stirred for 20 min. EtOAc (100 mL) and water (100 mL) were then added. The organic layer was dried (Na₂SO₄) and concentrated. The crude 1-(bromoacetyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (3.26 g, 10.41 mmol) was dissolved in THF (50 mL). A 2M Me₂NH solution in THF (50 mL) was added. The resulting slurry was filtered, the solids were rinsed with THF. The filtrate was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford as a yellow solid (2.09 g, 72%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.81-1.97 (m, 2H), 2.24 (s, 6H), 2.47 (s, 3H), 2.80 (t, J=6.89 Hz, 2H), 3.25 (s, 2H), 3.68-6.85 (m, 2H), 7.29 (s, 1H), 8.54 (br s, 1H); ESIMS (M+H)⁺ = 278.40.

Step B/Intermediate A143: 1-[(dimethylamino)acetyl]-6-methyl-1,2,3,4-tetrahydro-7-quinolinamine

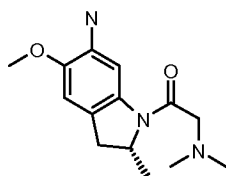


10% Pd on carbon (0.5 g, 17.37 mmol) was placed under N₂ atm. MeOH (20 mL) was added, followed by a solution of N,N-dimethyl-2-(6-methyl-7-nitro-3,4-dihydro-1(2H)-quinolinyl)-2-oxoethanamine (2.07 g, 7.46 mmol) in MeOH (80 mL). The mixture was placed under H₂ atm via balloon and maintained for 1 day. The resulting mixture was filtered through a pad of Celite using MeOH. The filtrate was concentrated, the residue

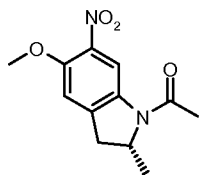
was taken up into Et₂O and concentrated again to afford 1-[(dimethylamino)acetyl]-6-methyl-1,2,3,4-tetrahydro-7-quinolinamine as a grey solid (1.55 g, 84%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.71-1.87 (m, 2H), 1.99 (s, 3H), 2.20 (s, 6H), 2.45-2.58 (m, 2H), 3.18 (s, 2H), 3.61 (t, *J*=6.13 Hz, 2H), 4.66 (br s, 2H), 6.69 (s, 1H), 6.78 (br s, 1H); ESIMS (M+H)⁺ = 248.17.

Intermediate A145

(2*R*)-1-[(dimethylamino)acetyl]-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



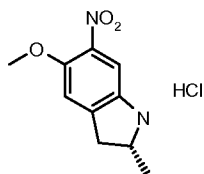
Step A/Intermediate A146: (2*R*)-1-acetyl-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole



A solution of (2*R*)-1-acetyl-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indole (100 mg, 0.487 mmol)—see (Arp, Forrest O.; Fu, Gregory C. **Kinetic Resolutions of Indolines by a Nonenzymatic Acylation Catalyst.** Journal of the American Chemical Society (2006), 128(44), 14264-14265.)—in TFA (2 mL) at 0°C was treated with sodium nitrite (33.6 mg, 0.487 mmol). The resulting red solution was stirred at 0 °C for 1 h. H₂O (20 mL) was added and the resulting slurry was filtered and the solids were washed with water to afford (2*R*)-1-acetyl-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole as a yellow solid (85 mg, 70%). ¹H NMR (400 MHz, DMSO-*d*₈) δ ppm 1.22 (d, *J*=6.41 Hz, 3H), 2.22 (s, 3H), 2.76 (d, *J*=17.21 Hz, 1H), 3.45 (dd, *J*=17.12, 8.88 Hz, 1H), 3.89 (s, 3H), 4.59-4.74 (m, 1H), 7.35 (s, 1H), 8.40 (s, 1H); ESIMS (M+H)⁺ = 251.00.

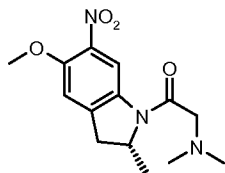
This procedure was repeated on 5 g of (2*R*)-1-acetyl-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indole to obtain 5.8 g of (2*R*)-1-acetyl-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole.

Step B/Intermediate A147: (2*R*)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole hydrogen chloride



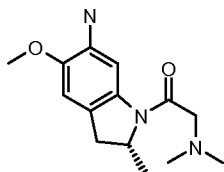
A slurry of (2*R*)-1-acetyl-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole (5.78 g, 23.10 mmol) in MeOH (50 mL) and a 4*N* HCl solution in dioxane (57.7 mL, 231 mmol) was heated at 70 °C for 8 h. The resulting mixture was allowed to cool to rt and concentrated to afford (2*R*)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole hydrogen chloride as a brown sticky solid (5.47 g, 97%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.38 (d, *J*=6.59 Hz, 3H), 2.82 (dd, *J*=16.85, 7.69 Hz, 1H), 3.32 (dd, *J*=16.85, 8.06 Hz, 1H), 3.90 (s, 3H), 4.09-4.26 (m, 1H), 7.39 (s, 1H), 7.60 (s, 1H); ESIMS (M+H)⁺ = 209.00.

Step C/Intermediate A148: N,N-dimethyl-2-[(2*R*)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine



A 0 °C slurry of (2*R*)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indole hydrogen chloride (4.55 g, 18.60 mmol) and K₂CO₃ (10.28 g, 74.4 mmol) in THF (200 mL) was treated with bromoacetyl chloride (3.10 mL, 37.2 mmol). After 2 h the reaction mixture was allowed to warm to rt. A 2*M* Me₂NH solution in THF (55.8 mL, 112 mmol) was added and the reaction mixture was stirred at rt for 18 h. The resulting thick slurry was filtered and the solids were rinsed with EtOAc. The filtrate was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain N,N-dimethyl-2-[(2*R*)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine as an orange solid (2.92 g, 54%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.23 (d, *J*=6.04 Hz, 3H), 2.28 (s, 6H), 2.75 (d, *J*=17.03 Hz, 1H), 3.14 (d, *J*=14.83 Hz, 1H), 3.44 (d, *J*=14.65 Hz, 2H), 3.90 (s, 3H), 4.77-4.92 (m, 1H), 7.36 (s, 1H), 8.43 (s, 1H); ESIMS (M+H)⁺ = 294.01.

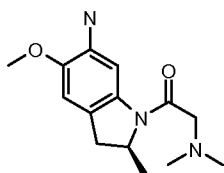
Step D/Intermediate A145: (2*R*)-1-[(dimethylamino)acetyl]-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



- 5 10% palladium on carbon (0.25 g, 8.52 mmol) was placed under N₂ atm. MeOH (10 mL) was added, followed by a solution of N,N-dimethyl-2-[(2*R*)-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indol-1-yl]-2-oxoethanamine (2.92 g, 9.96 mmol) in MeOH (190 mL). The slurry was purged with N₂, then was placed under H₂ atm via a rubber balloon and maintained at rt for 2 days. The resulting mixture was filtered through a pad of Celite
- 10 and the filtrate was concentrated. The oily residue was taken up into Et₂O and concentrated again to obtain (2*R*)-1-[(dimethylamino)acetyl]-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine as a beige solid (2.43 g, 93%). ¹H NMR (400 MHz, DMSO-*d*₈) δ ppm 1.17 (d, *J*=5.86 Hz, 3H), 2.26 (s, 6H), 2.44 (d, *J*=14.83 Hz, 1H), 3.02 (d, *J*=14.28 Hz, 1H), 3.10-3.27 (m, 1H), 3.36 (d, *J*=14.28 Hz, 1H), 3.72 (s, 3H), 4.52-4.77 (m, 3H),
- 15 6.72 (s, 1H), 7.48 (s, 1H); ESIMS (M+H)⁺ = 264.23.

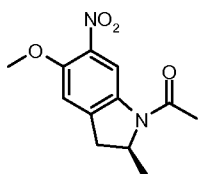
Intermediate A149

(2*S*)-1-[(dimethylamino)acetyl]-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine



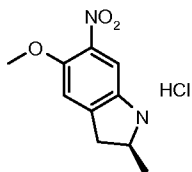
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Step A/Intermediate A150: (2*S*)-1-acetyl-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1*H*-indole



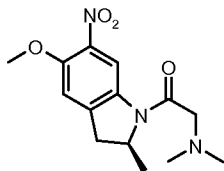
A 0 °C orange solution of (2S)-1-acetyl-2-methyl-5-(methoxy)-2,3-dihydro-1H-indole (5.19 g, 25.3 mmol) in TFA (30 mL) was treated with NaNO₂ (1.745 g, 25.3 mmol) portion wise. After 2 h more NaNO₂ (800 mg, 11.6 mmol) was added. After 1 h the resulting mixture was poured into water (450 mL). The resulting slurry was filtered and the solids were washed with water. The solids were dissolved in CH₂Cl₂. The layers were separated, the organic layer was dried (Na₂SO₄) and concentrated to afford (2S)-1-acetyl-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole as a green solid (5.73 g, 91%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.23 (d, *J*=6.23 Hz, 3H), 2.22 (s, 3H), 2.76 (d, *J*=17.21 Hz, 1H), 3.45 (dd, *J*=17.03, 8.97 Hz, 1H), 3.89 (s, 3H), 4.58-4.78 (m, 1H), 7.35 (s, 1H), 8.41 (s, 1H); ESIMS (M+H)⁺ = 251.02.

Step B/Intermediate A151: (2S)-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole hydrogen chloride



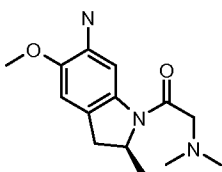
A slurry of (2S)-1-acetyl-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole (5.7 g, 22.78 mmol) in MeOH (50 mL) and a 4N HCl solution in dioxane (56.9 mL, 228 mmol) was heated at 70 °C for 10 h. The resulting mixture was allowed to cool to rt and concentrated to afford (2S)-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indole hydrogen chloride as a beige solid (5.55 g, 100%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.39 (d, *J*=6.41 Hz, 3H), 2.84 (dd, *J*=16.94, 7.60 Hz, 1H), 3.34 (dd, *J*=16.85, 8.06 Hz, 1H), 3.90 (s, 3H), 4.12-4.27 (m, 1H), 7.41 (s, 1H), 7.66 (s, 1H); ESIMS (M+H)⁺ = 209.00.

Step C/Intermediate A152: N,N-dimethyl-2-[(2S)-2-methyl-5-(methoxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-2-oxoethanamine



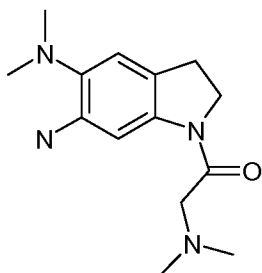
A slurry of (2S)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1H-indole hydrogen chloride (4.43 g, 18.11 mmol) and K₂CO₃ (10.01 g, 72.4 mmol) in THF (200 mL) at 0°C was treated with bromoacetyl chloride (3.02 mL, 36.2 mmol). After 2 h the resulting mixture was allowed to warm to rt. A 2M Me₂NH solution in THF (54.3 mL, 109 mmol) was added. After 18 h the resulting thick slurry was filtered and the solids were washed with EtOAc. The filtrate was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂. The foamy oily product was chased using CH₂Cl₂ and hexanes, CH₂Cl₂ and Et₂O, then Et₂O to obtain N,N-dimethyl-2-[(2S)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-2-oxoethanamine as an orange solid (2.50 g, 47%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.23 (d, *J*=6.04 Hz, 3H), 2.28 (s, 6H), 2.75 (d, *J*=17.21 Hz, 1H), 3.14 (d, *J*=14.65 Hz, 1H), 3.44 (d, *J*=14.65 Hz, 2H), 3.90 (s, 3H), 4.75-4.92 (m, 1H), 7.37 (s, 1H), 8.43 (s, 1H); ESIMS (M+H)⁺ = 293.88.

Step D/Intermediate A149: (2S)-1-[(dimethylamino)acetyl]-2-methyl-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine

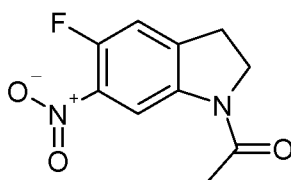


10% palladium on carbon (0.25 g, 8.52 mmol) was placed under N₂ atm. MeOH (10 mL) was added, followed by a solution of N,N-dimethyl-2-[(2S)-2-methyl-5-(methyloxy)-6-nitro-2,3-dihydro-1H-indol-1-yl]-2-oxoethanamine (2.50 g, 8.52 mmol) in MeOH (190 mL). The slurry was purged with N₂, then was placed under H₂ atm via a rubber balloon and maintained at rt for 2 days. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The oily residue was taken up into Et₂O and concentrated again to obtain (2S)-1-[(dimethylamino)acetyl]-2-methyl-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine as a beige solid (2.10 g, 94%). ¹H NMR (400 MHz, DMSO-*d*₈) δ ppm 1.17 (d, *J*=5.68 Hz, 3H), 2.26 (s, 6H), 2.44 (d, *J*=15.02 Hz, 1H), 3.03 (d, *J*=14.28 Hz, 1H), 3.10-3.25 (m, 1H), 3.36 (d, *J*=14.28 Hz, 1H), 3.72 (s, 3H), 4.54-4.76 (m, 3H), 6.72 (s, 1H), 7.48 (s, 1H); ESIMS (M+H)⁺ = 264.20.

Intermediate A153

1-[(dimethylamino)acetyl]-*N*⁵,*N*⁵-dimethyl-2,3-dihydro-1*H*-indole-5,6-diamine

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Step A/Intermediate A154: 1-acetyl-5-fluoro-6-nitro-2,3-dihydro-1*H*-indole

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To a solution of 5-fluoro-1*H*-indole (5.0 g, 37 mmols) in acetic acid (300 ml) was added sodium cyanoborohydride (2.79 g, 44 mmols). After stirring overnight at rt, the reaction was concentrated under reduced pressure, redissolved in ethyl acetate (300 ml) and the pH was adjusted to 8 with saturated sodium bicarbonate. The organic layer was separated, filtered through a cotton plug, evaporated, and placed on the high vacuum for one hour prior to the next synthetic step. The crude material was then dissolved in acetic acid (100 ml), followed by the addition of acetic anhydride (3.5 ml, 37 mmols). After heating at 60C for one hour, the reaction was poured into ice, stirred for one hour, solid was removed by vacuum filtration, rinsed with water and allowed to dry overnight under house vacuum. Next, to a solution of the 1-acetyl-5-fluoro-2,3-dihydro-1*H*-indole (500 mg, 2.79 mmol) in sulfuric acid (10 ml) at OC was added nitric acid (0.196 ml, 3.07 mmols) by a slow dropwise addition. After stirring 30 min at OC, the reaction was quenched by pouring into ice water. The solids were removed by vacuum filtration, redissolved in dichloromethane (50 ml), adsorbed to silica gel, and purified by LC(25% to 75% ethyl acetate/hexanes). The lower *R_f* spot was isolated and the structure was determined to be the desired regioisomer by IR profiling. ¹H NMR (400 MHz, DMSO-

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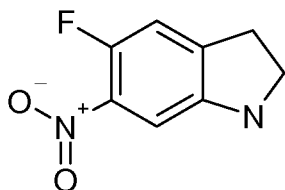
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d_6) δ ppm 2.18 (s, 3 H) 3.25 (t, $J=8.63$ Hz, 2 H) 4.18 (t, $J=8.53$ Hz, 2 H) 7.50 (d, $J=11.24$ Hz, 1 H) 8.64 (d, $J=7.22$ Hz, 1 H).

Step B/Intermediate A155: 5-fluoro-6-nitro-2,3-dihydro-1H-indole

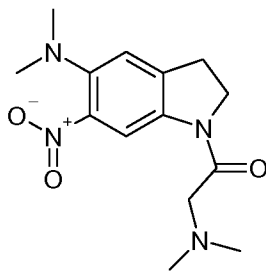
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A solution of 1-acetyl-5-fluoro-6-nitro-2,3-dihydro-1H-indole (1.22 g, 5.44 mmol) and 4.0 M HCl/dioxane (6.80 ml, 27.2 mmol) in tetrahydrofuran (50 ml) and methanol (100 ml) was heated overnight at 50°C. The reaction was quenched with saturated NaHCO₃ (200 ml), solvent removed, aqueous layer extracted with dichloromethane (250 ml), organic layer adsorbed to silica gel and purified by LC (20-75% ethyl acetate/hexanes) to afford the indoline (0.9 g, 91%). ESIMS (M+H)⁺ = 183.

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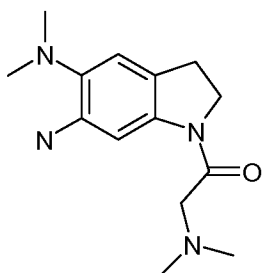
Step C/Intermediate A156: 1-[(dimethylamino)acetyl]-N,N-dimethyl-6-nitro-2,3-dihydro-1H-indol-5-amine



To a solution of 5-fluoro-6-nitro-2,3-dihydro-1H-indole (0.9 g, 4.94 mmol) and potassium carbonate (2.049 g, 14.82 mmol) in tetrahydrofuran (300 ml) was added bromoacetyl chloride (0.414 ml, 4.94 mmol) and the reaction was stirred at rt for 30 min. To this reaction was added 2.0M dimethylamine in THF (7.41 ml, 14.82 mmol) and the mixture was stirred overnight at rt. The solvent removed, water added (200 ml), aqueous layer extracted with dichloromethane (2 x 250 ml), organic layers adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to give the title compound (1g, 69%). ESIMS (M+H)⁺ = 293.

Step D/Intermediate A153: 1-[(dimethylamino)acetyl]-*N*⁶,*N*⁵-dimethyl-2,3-dihydro-1*H*-indole-5,6-diamine

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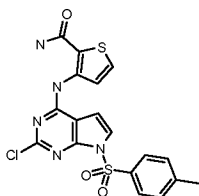


To an N₂ degassed solution of 1-[(dimethylamino)acetyl]-*N*,*N*-dimethyl-6-nitro-2,3-dihydro-1*H*-indol-5-amine (1.00 g, 3.42 mmol) and 10% Pd/C (3.64 g, 3.42 mmol) in ethanol (100 ml) was added H₂ and the reaction was stirred at rt overnight on the Fisher Porter at 50 psi. The reaction was filtered through celite, rinsed with methanol (100 ml), concentrated by rotary evaporation, and high vacced prior to the next reaction to give the title compound (0.9g, 100%). ESIMS (M+H)⁺ = 263.

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Section B: Pyrrolopyrimidine Intermediates

Intermediate B1: 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



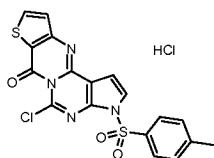
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A mixture of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (6.22 g, 18.2 mmol), 3-amino-2-thiophenecarboxamide (2.35 g, 16.5 mmol) and TFA (6.4 mL, 82.6 mmol) in 2,2,2-trifluoroethanol (100 mL) was heated at 80 °C for 3 days. The resulting mixture was allowed to cool to rt and filtered. The solids were washed with Et₂O to obtain 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide as a yellow solid (4.0 g, 49%). ¹H NMR (400 MHz,

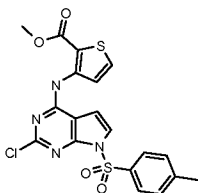
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THF- d_8) δ ppm 2.37 (s, 3H), 6.69 (d, $J=4.03$ Hz, 1H), 7.48 (d, 8.42 Hz, 2H), 7.55-7.95 (m, 4H), 8.00 (d, $J=8.24$ Hz, 2H), 8.05 (d, $J=5.49$ Hz, 1H); ESIMS ($M+H$)⁺ = 447.98.

Intermediate B2: 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride

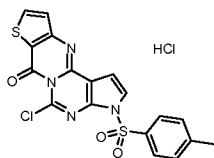


Step A/Intermediate B3: methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxylate



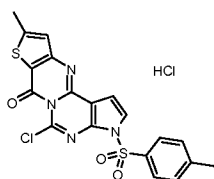
A solution of trifluoroacetic acid (63.0 ml, 818 mmol), 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (40 g, 117 mmol), and methyl 3-amino-2-thiophenecarboxylate (27.6 g, 175 mmol) in 2,2,2-trifluoroethanol (450 ml) was maintained at 90°C for 16 hours, at which time a thick white precipitate formed. The slurry was filtered while warm and solids collected to afford methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxylate (35.6 g, 77 mmol, 65.8 % yield). ¹H NMR (400 MHz, DMSO- d_6) δ ppm 10.28 (s, 1 H), 7.96 (d, $J=8.24$ Hz, 2 H), 7.91 - 7.94 (m, 1 H), 7.86 - 7.89 (m, 1 H), 7.74 (dd, $J=4.03$, 0.92 Hz, 1 H), 7.44 (d, $J=8.61$ Hz, 2 H), 6.85 (d, $J=4.03$ Hz, 1 H), 3.78 (s, 3 H), 2.33 (s, 3 H).

Step B/Intermediate B2: 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride



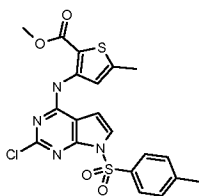
A mixture of methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxylate (20.1 g, 43.4 mmol) and THF (1400 mL) was treated with a solution of LiOH (10.40 g, 434 mmol) in water (200 mL). The reaction mixture
 5 was maintained at rt for 7 h. The layers were separated, the organic layer was washed with a saturated NaCl solution (2x200 mL), concentrated down to a thick slurry. The slurry was filtered and the solids were washed with Et₂O. The filtrate was concentrated and diluted with Et₂O. The resulting slurry was filtered and the solids were washed with Et₂O. The filtrates were combined, concentrated onto Celite and purified by silica gel
 10 chromatography using 5-20% MeOH/THF. The second batch of solids and the product from chromatography were dissolved in warm THF (500 mL) and filtered through pad of silica gel using 20% MeOH/THF. The filtrate was concentrated, the residue was dissolved in THF (400 mL) and CH₂Cl₂ (250 mL). DMF (0.507 mL, 6.55 mmol) was added, followed by slow addition of a solution of oxalyl chloride (2M in CH₂Cl₂, 13.64 mL,
 15 27.3 mmol). The reaction mixture was stirred for 17 h, then was cooled to 0 °C and filtered. The filtrate was treated with additional oxalyl chloride solution (2M in CH₂Cl₂, 20 mL, 40 mmol). After 1 h the reaction mixture was cooled to 0 °C and filtered. The two batches of solids were combined to obtain 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one
 20 hydrogen chloride as a white solid (6.65 g, 36%). ESIMS (M+H)⁺ = 431.08.

Intermediate B4: 5-chloro-9-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride



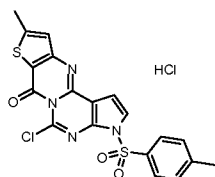
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Step A/Intermediate B5: methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-5-methyl-2-thiophenecarboxylate



A mixture of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (33.0 g, 96 mmol) and methyl 3-amino-5-methyl-2-thiophenecarboxylate (15 g, 88 mmol) in 2,2,2-trifluoroethanol (500 mL) was treated with TFA (33.7 mL, 438 mmol), then heated at 80 °C. Some of the volatiles were distilled off (300 mL total over 3 h). The resulting thick slurry was filtered hot and the solids were washed with warm TFE to obtain methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-5-methyl-2-thiophenecarboxylate (16.2 g, 39%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.38 (s, 3H), 3.80 (s, 3H), 6.83 (br s, 1H), 7.49 (d, *J*=7.87 Hz, 2H), 7.70 (s, 1H), 7.78 (d, *J*=3.48 Hz, 1H), 8.01 (d, *J*=7.87 Hz, 2H), 10.33 (s, 1H), a CH₃ signal in missing, may overlap with DMSO-*d*₆; ESIMS (M+H)⁺ = 477.12.

Step B/Intermediate B4: 5-chloro-9-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride

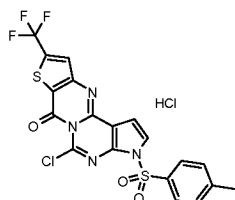


A mixture of methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-5-methyl-2-thiophenecarboxylate (16.2 g, 34.0 mmol) and THF (1400 mL) was treated with a solution of LiOH (8.13 g, 340 mmol) in water (200 mL). The resulting mixture was stirred at rt for 34 h. The layers were separated, the organic layer was washed with a saturated NaCl solution (2 x 200 mL), dried (Na₂SO₄) and concentrated to about 300 mL. The resulting slurry was filtered, the filtrate concentrated onto Celite and purified by silica gel chromatography using 0-30% MeOH/THF. The derived solids (4.22 g, 9.12 mmol) and DMF (5 drops) in tetrahydrofuran (100 mL) were stirred while 2.0M oxalyl chloride in dichloromethane (5.70 mL, 11.39 mmol) was added dropwise over five minutes. Stirring was continued until bubbling ceased, then the reaction was cooled to 0°C and stirring stopped. The solids which precipitated were collected by vacuum filtration and washed with diethyl ether to afford 5-chloro-9-methyl-3-[(4-

methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride (3.42 g, 7.10 mmol, 78 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.02 (d, *J*=8.43 Hz, 2 H), 7.77 (d, *J*=3.67 Hz, 1 H), 7.50 (d, *J*=8.07 Hz, 2 H), 7.14 (s, 1 H), 7.03 (d, *J*=3.67 Hz, 1 H), 6.66 (s, 1 H), 2.60 (s, 3 H), 2.37 (s, 3 H).

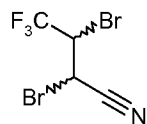
5

Intermediate B6: 5-chloro-3-[(4-methylphenyl)sulfonyl]-9-(trifluoromethyl)pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride



10

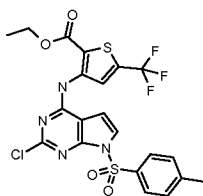
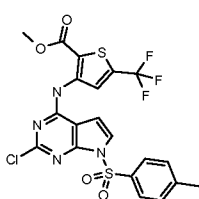
Step A/Intermediate B7: *rac syn*-2,3-dibromo-4,4,4-trifluorobutanenitrile and *rac anti*-2,3-dibromo-4,4,4-trifluorobutanenitrile



- 15 An orange solution of (2*E*)-4,4,4-trifluoro-2-butenenitrile (5 g, 41.3 mmol) and Br₂ (2.128 mL, 41.3 mmol) in CCl₄ (120 mL) was heated at the reflux temperature for 3 h. The resulting mixture was diluted with H₂O (5 mL) and washed with a 5% aqueous sodium thiosulfate solution (50 mL) and a saturated NaCl solution (50 mL). The organic layer was dried (Na₂SO₄) and concentrated to obtain a mixture of *rac syn*-2,3-dibromo-4,4,4-trifluorobutanenitrile and *rac anti*-2,3-dibromo-4,4,4-trifluorobutanenitrile as a yellow oil (10.4 g, 90%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.72-5.83 (m, 0.6H), 5.94-6.06 (m, 0.4H), 6.13-6.24 (m, 1H).
- 20

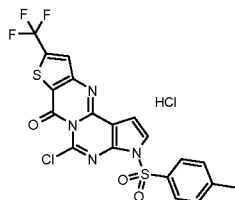
Step B/Intermediate B8: methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-5-(trifluoromethyl)-2-thiophenecarboxylate and ethyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-5-(trifluoromethyl)-2-thiophenecarboxylate

25



A solution of a mixture of *rac syn*-2,3-dibromo-4,4,4-trifluorobutanenitrile and *rac anti*-2,3-dibromo-4,4,4-trifluorobutanenitrile (10.4 g, 37.0 mmol) in EtOH (150 mL) was treated with methyl mercaptoacetate (3.31 mL, 37.0 mmol), followed by dropwise addition of Et₃N (5.16 mL, 37.0 mmol). The reaction mixture was maintained at rt for 17. Additional Et₃N (10 mL, 63 mmol) was added and the reaction mixture was maintained at rt for 3 days. The resulting slurry was filtered, the filtrate was diluted with EtOAc (200 mL) and washed with a saturated NaCl solution (2x100 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 50-100% CH₂Cl₂/hexanes. The mixture of the crude products and 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (5.24 g, 15.31 mmol) in a 4N HCl solution in dioxane (100 mL) was heated at 80 °C for 21 h. The resulting mixture was allowed to cool to rt and filtered. The solids were washed with Et₂O to obtain a 2:1 mixture of methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-5-(trifluoromethyl)-2-thiophenecarboxylate and ethyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-5-(trifluoromethyl)-2-thiophenecarboxylate as a white solid (1.65 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.19 (t, *J*=7.14 Hz, 1H), 2.38 (s, 3H), 3.86 (s, 2H), 4.29 (q, *J*=4.28 Hz, 0.65H), 6.93-7.02 (m, 1H), 7.49 (d, *J*=8.24 Hz, 2H), 7.76-7.85 (m, 1H), 7.96-8.05 (m, 2H), 8.31 (d, *J*=0.73 Hz, 0.33H) 8.34 (d, *J*=0.73 Hz, 0.67H) 1.032-10.41 (m, 1H); ESIMS (M+H)⁺ = 531.01 and 545.04.

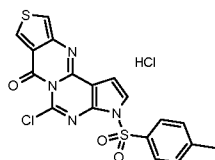
Step C/Intermediate B6: 5-chloro-3-[(4-methylphenyl)sulfonyl]-9-(trifluoromethyl)pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride



A solution of methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-5-(trifluoromethyl)-2-thiophenecarboxylate (1.65 g, 3.11 mmol) in THF (130 mL) was treated with a solution of LiOH (0.744 g, 31.1 mmol) in water (40 mL). The resulting mixture was stirred vigorously at rt for 3.5 h, then diluted with EtOAc (100 mL).

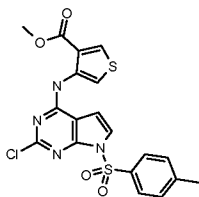
- 5 The organic layer was washed with a saturated NaCl solution (2x50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-20% MeOH (containing 2% AcOH)/THF. The crude product was taken up into benzene and concentrated. The residue was dissolved in THF (50 mL) and treated with a drop of DMF, followed by oxalyl chloride (0.450 mL, 5.15 mmol). After 30 minutes at rt the reaction mixture was
- 10 concentrated, taken up into benzene and concentrated again. The residue was triturated using Et₂O to obtain 5-chloro-3-[(4-methylphenyl)sulfonyl]-9-(trifluoromethyl)pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride as a yellow solid (1.05 g). ¹H NMR (400 MHz, THF-*d*₈) δ ppm 2.40 (s, 3H), 2.84 (br s, 2H), 7.01 (d, *J*=3.66 Hz, 1H), 7.44 (d, *J*=8.24 Hz, 2H), 7.72 (d, 3.85 Hz, 1H), 7.82 (s, 1H), 8.12 (d, 8.42 Hz,
- 15 2H); ESIMS (M+H)⁺ = 498.86

Intermediate B9: 5-chloro-3-[(4-methylphenyl)sulfonyl]-3*H*,7*H*-pyrrolo[3,2-e]thieno[3',4':4,5]pyrimido[1,2-c]pyrimidin-7-one hydrogen chloride



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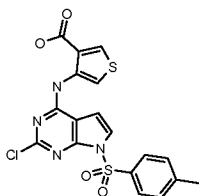
Step A/Intermediate B10: methyl 4-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-3-thiophenecarboxylate



- 25 A brown slurry of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (26.1 g, 72.5 mmol) and methyl 4-amino-3-thiophenecarboxylate (Maybridge, 11.4 g, 72.5 mmol) in 2,2,2-trifluoroethanol (400 mL) and TFA (27.9 mL, 363 mmol) was heated

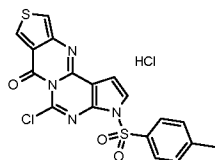
at the reflux temperature. After 40 min half of the solvent was removed via distillation and the remaining mixture was heated at 80 °C overnight. The resulting slurry was allowed to cool somewhat and was filtered warm. The solid was washed with 2,2,2-trifluoroethanol to obtain methyl 4-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-3-thiophenecarboxylate as a beige solid (14.0 g, 42%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.37 (s, 3H), 3.76 (s, 3H), 6.76 (br s, 1H), 7.48 (d, *J*=8.24 Hz, 2H), 7.73 (d, *J*=4.03 Hz, 1H), 7.85 (d, *J*=3.3 Hz, 1H), 7.99 (d, *J*=8.24 Hz, 2H), 8.39 (d, *J*=3.48 Hz, 1H), 10.20 (s, 1H); ESIMS (M+H)⁺ = 463.02.

- 10 Step B/Intermediate B11: 4-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-3-thiophenecarboxylic acid



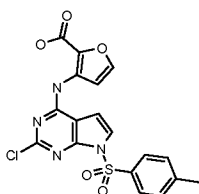
- A slurry of methyl 4-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-3-thiophenecarboxylate (14.0 g, 27.2 mmol) in THF (1000 mL) was treated with a solution of LiOH (6.52 g, 272 mmol) in water (200 mL). The reaction mixture was stirred for 3 h. EtOAc (1000 mL) was added and the organic layer was washed with a saturated NaCl solution (2x300 mL), dried (Na₂SO₄) and concentrated. The residue was diluted with benzene and concentrated to obtain 4-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-3-thiophenecarboxylic acid as a pale yellow solid (13.32 g, quantitative yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.36 (s, 3H), 6.62 (d, *J*=3.85 Hz, 1H), 7.47 (d, *J*=8.06 Hz, 2H), 7.73 (dd, *J*=7.51 Hz, 3.66 Hz, 2H), 7.79 (d, *J*=3.48 Hz, 1H), 7.98 (d, *J*=8.42 Hz, 2H); ESIMS (M+H)⁺ = 448.94.

- 25 Step C/Intermediate B9: 5-chloro-3-[(4-methylphenyl)sulfonyl]-3*H*,7*H*-pyrrolo[3,2-*e*]thieno[3',4':4,5]pyrimido[1,2-*c*]pyrimidin-7-one hydrogen chloride

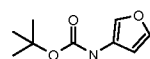


To a yellow slurry of 4-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-3-thiophenecarboxylic acid (13.32 g, 29.7 mmol) in THF (250 mL) were added two drops of DMF, followed by a solution of oxalyl chloride (2M in CH₂Cl₂, 37.1 mL, 74.2 mmol). The reaction mixture was stirred at rt and cooled to 0 °C. The resulting
 5 slurry was filtered and the solids were washed with Et₂O to obtain 5-chloro-3-[(4-methylphenyl)sulfonyl]-3*H*,7*H*-pyrrolo[3,2-*e*]thieno[3',4':4,5]pyrimido[1,2-*c*]pyrimidin-7-one hydrogen chloride as a yellow solid (12.15 g, 88%). ESIMS (M+H)⁺ = 430.99.

**Intermediate B12: 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-
 10 *d*]pyrimidin-4-yl}amino)-2-furancarboxylic acid**

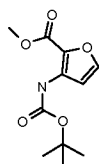


Step A/Intermediate B13: 1,1-dimethylethyl 3-furanylcarbamate



A mixture of 3-furancarboxylic acid (17.5 g, 156 mmol), DPPA (47.3 g, 172 mmol), tBuOH (22.40 mL, 234 mmol), TEA (26.1 mL, 187 mmol) and toluene (500 mL) was heated at the reflux temperature under N₂ atm. After 5 h the resulting mixture was allowed to cool to rt and filtered through pad of silica gel using toluene. The filtrate was
 20 concentrated to a slurry and filtered. The solids were washed with hexanes. The filtrate was further concentrated, the resulting slurry was filtered. The solids were washed with hexanes. The two batches were combined to afford 1,1-dimethylethyl 3-furanylcarbamate as a white solid (11.71 g, 41%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.44 (s, 9H), 6.33 (s, 1H), 7.46 (d, *J*=1.47 Hz, 1H), 7.64 (br s, 1H), 9.24 (br s, 1H).

Step B/Intermediate B14: methyl 3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-furancarboxylate



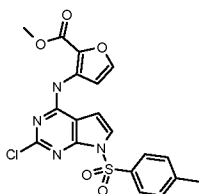
A solution of 1,1-dimethylethyl 3-furanylcabamate (11 g, 60.0 mmol) and N,N,N',N'-tetramethylethylenediamine (22.47 ml, 150 mmol) in tetrahydrofuran (350 ml) was cooled to -78°C and t-butyllithium in hexanes (88 ml, 150 mmol) was added dropwise over 10 minutes. The solution was allowed to warm to -40°C (monitored by internal temperature sensor) for 2 hours and then methylchloroformate (5.75 ml, 74.5 mmol) was added. The reaction was warmed to 0°C and maintained for 45 minutes. The reaction was diluted with saturated ammonium chloride, the organic layer washed with brine, dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by column chromatography to afford methyl 3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-furancarboxylate (7.91 g, 32.8 mmol, 54.6 % yield) as a pale yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.31 (s, 1 H), 7.83 (d, *J*=1.81 Hz, 1 H), 7.08 (s, 1 H), 3.81 (s, 3 H), 1.47 (s, 9 H)

Step C/Intermediate B15: methyl 3-amino-2-furancarboxylate



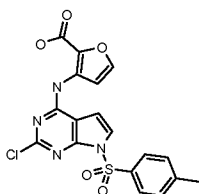
A yellow solution of methyl 3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-furancarboxylate (7.92 g, 32.8 mmol) in CH₂Cl₂ (100 mL) was treated with TFA (10 mL). The resulting deep orange solution was stirred at rt. After 5 h the reaction mixture was poured into a saturated NaHCO₃ solution (400 mL). Solid K₂CO₃ was added until the aqueous layer turned basic. The organic layer was washed with a saturated NaCl solution (100 mL), concentrated onto Celite and purified by silica gel chromatography using 10-100% EtOAc/hexanes as a light brown oil (2.14 g, 46%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.70 (s, 3H), 5.67 (br s, 2H), 6.18 (d, 1.83 Hz, 1H), 7.52 (d, *J*=1.83 Hz, 1H); ESIMS (M+H)⁺ = 142.11.

Step D/Intermediate B16: methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-furancarboxylate



A slurry of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (5.19 g, 15.16 mmol) and methyl 3-amino-2-furancarboxylate (2.14 g, 15.16 mmol) in a 4N solution of HCl in dioxane (100 mL) was heated at 80 °C for 42 h and was allowed to cool to rt. EtOAc (200 mL) and a saturated NaHCO₃ solution (300 mL) were added, followed by solid K₂CO₃ to obtain neutral pH. The organic layer was washed with a saturated NaCl solution (100 mL), dried (Na₂SO₄), concentrated onto Celite and purified by silica gel chromatography using 20-100% CH₂Cl₂/hexanes to afford methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-furancarboxylate as a pale yellow solid (3.1 g, 46%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.37 (s, 3H), 3.81 (s, 3H), 7.02 (d, *J*=4.03 Hz, 1H), 7.23 (d, *J*=1.83 Hz, 1H), 7.48 (d, 8.06 Hz, 2H), 7.76 (d, 3.85 Hz, 1H), 7.93 (d, *J*=1.83 Hz, 1H), 7.98 (s, 1H), 8.00 (s, 1H), 9.75 (s, 1H); ESIMS (M+H)⁺ = 447.03.

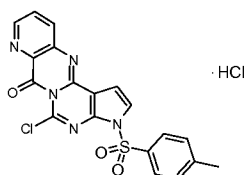
Step E/Intermediate B12: 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-furancarboxylic acid



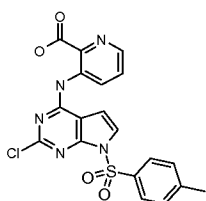
To a solution of methyl 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-furancarboxylate (3.41 g, 7.63 mmol) in THF (200 mL) was added a solution of LiOH (1.827 g, 76 mmol) in water (50 mL). The resulting mixture was stirred vigorously at rt. After 10 h EtOAc (200 mL) was added. The organic layer was washed with a saturated NaCl solution (2x100 mL), concentrated onto Celite and purified by silica gel chromatography using 50-100% THF/CH₂Cl₂, then 0-30% MeOH/THF to obtain 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-furancarboxylic acid as a pale yellow solid (0.66 g, 20%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.37 (s, 3H), 6.76 (d, *J*=3.85 Hz, 1H), 7.25 (d, *J*=1.83 Hz, 1H), 7.47 (d, *J*=8.06 Hz,

2H), 7.63 (d, $J=1.83$ Hz, 1H), 7.72 (d, $J=4.03$ Hz, 1H), 7.98 (d, $J=8.42$ Hz, 2H), 11.14 (br s, 1H); ESIMS (M+H)⁺ = 432.97.

Intermediate B17: 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrido[3,2-d]pyrrolo[2',3':4,5]pyrimido[1,6-a]pyrimidin-7(3H)-one hydrogen chloride

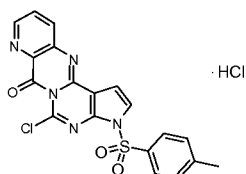


Step A/Intermediate B18: 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-pyridinecarboxylic acid



A slurry of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (4.41 g, 12.89 mmol), 3-amino-2-pyridinecarboxylic acid (1.78 g, 12.89 mmol) and DIPEA (11.25 mL, 64.4 mmol) in iPrOH (100 mL) was heated at 90 °C for 5 days. The resulting mixture was allowed to cool to rt, diluted with EtOAc (200 mL) and a 1N aqueous HCl solution. The resulting slurry was filtered, the solids were washed with Et₂O and dried in vacuum at 60 °C overnight to obtain 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-pyridinecarboxylic acid as a light green solid (3.08 g, 54%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.38 (s, 3H), 6.83 (d, $J=4.03$ Hz, 1H), 7.49 (d, $J=8.06$ Hz, 2H), 7.72-7.88 (m, 2H), 8.00 (d, $J=8.24$ Hz, 2H), 8.42 (dd, $J=4.58$, 1.10 Hz, 1H), 8.74-8.82 (m, 1H), 11.83 (s, 1H); ESIMS (M+H)⁺ = 444.11.

Step B/Intermediate B17: 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrido[3,2-d]pyrrolo[2',3':4,5]pyrimido[1,6-a]pyrimidin-7(3H)-one hydrogen chloride

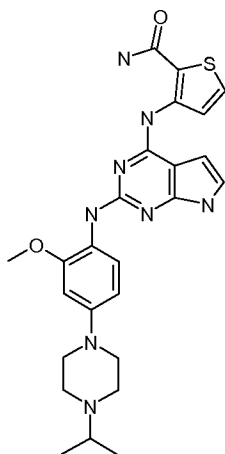


A solution of 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-pyridinecarboxylic acid (107 mg, 0.241 mmol) in THF (50 mL) was treated with a drop of DMF followed by oxalyl chloride (0.2 mL, 2.29 mmol). The reaction mixture was stirred at rt for 3 days. The resulting slurry was filtered, the solids were washed with Et₂O to afford 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrido[3,2-d]pyrrolo[2',3':4,5]pyrimido[1,6-a]pyrimidin-7(3H)-one hydrogen chloride as a yellow solid (93 mg, 83%). ¹H NMR (400 MHz, THF-*d*₈) δ ppm 2.40 (s, 3H), 4.78 (br s, 1H), 7.16 (dd, *J*=3.75, 0.82 Hz, 1H), 7.45 (d, *J*=8.24 Hz, 2H), 7.65-7.70 (m, 1H), 8.04-8.16 (m, 3H), 8.72 (d, *J*=4.21 Hz, 1H), 7.73 (dd, *J*=8.33, 4.12 Hz, 1H); ESIMS (M+H)⁺ = 426.00.

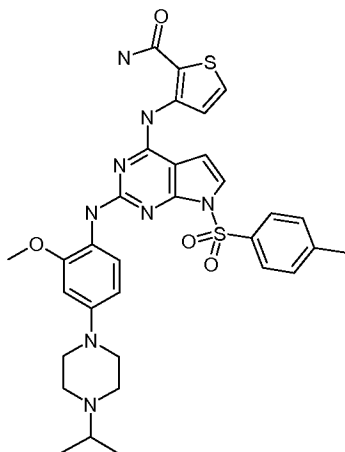
Section C: Examples

Example 1

3-[(2-{[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



Step A/Intermediate C1: 3-({2-([4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino)-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



A mixture of 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (400 mg, 0.89 mmol) and 4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)aniline (223 mg, 0.89 mmol), a 4*N* HCl solution in dioxane (0.9 mL, 3.56 mmol) and 2,2,2-trifluoroethanol (7 mL) was heated at 80°C for 7 days. Additional 4*N* HCl solution in dioxane (3 mL, 12 mmol) was added and the reaction mixture was heated at 80°C for 7 days. THF (20 mL) and a 27% aqueous NH₄OH solution (100 mL) were added, and the reaction mixture was maintained at rt for 2 days. The resulting mixture was diluted with EtOAc (100 mL) and a saturated NaCl solution (100 mL). The aqueous layer was back extracted with EtOAc (100 mL). The organic layers were combined, dried (Na₂SO₄), concentrated onto Celite and purified by silica gel chromatography using 0-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-({2-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide as an orange solid (130 mg, 22%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.03 (d, *J*=6.04 Hz, 6H), 2.35 (s, 3H), 2.53-2.80 (m, 5H), 3.18 (br s, 4H), 3.81 (s, 3H), 5.76 (s, 1H), 6.47 (d, *J*=3.66 Hz, 1H), 6.60 (d, *J*=8.79 Hz, 1H), 6.68 (s, 1H), 7.28-7.42 (m, 3H), 7.46-7.82 (m, 4H), 7.92 (d, *J*=7.69 Hz, 2H), 8.10 (s, 1H) 11.49 (s, 1H); ESIMS (M+H)⁺ = 661.19.

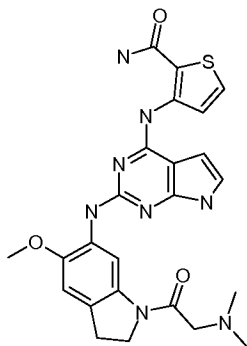
Step B/Example 1: 3-[(2-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide

A mixture of 3-({2-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide

(112 mg, 0.17 mmol) and NaOMe (92 mg, 1.7 mmol), THF (20 mL) and MeOH (20 mL) was maintained at rt for 2 days. Additional NaOMe (108 mg, 3.4 mmol) was added and the reaction mixture was stirred for 2 days, then was heated at 60 °C for 5 h. The resulting mixture was diluted with EtOAc (50 mL), washed with a saturated NaHCO₃ solution (25 mL) and a saturated NaCl solution (25 mL). The aqueous layers were back extracted with EtOAc (50 mL). The organic layers were combined, concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-{[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide as a yellow solid (60 mg, 70%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.02 (d, *J*=6.23 Hz, 6H), 2.53-2.77 (m, 5H), 3.11 (s, 4H), 3.81 (s, 3H), 6.22 (s, 1H), 6.49 (d, *J*=8.61, 1H), 6.63 (s, 1H), 6.95 (s, 1H), 7.36-7.74 (m, 4H), 7.83 (d, *J*=8.42 Hz, 1H), 8.42 (d, *J*=4.76 Hz, 1H), 11.31 (s, 1H), 11.36 (s, 1H); ESIMS (M+H)⁺ = 507.02.

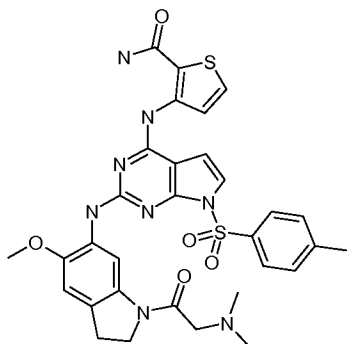
Example 2

3-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



Step A/Intermediate C2: 3-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

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A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (400 mg, 0.928 mmol) and 1-
 5 [(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (289 mg, 1.160
 mmol) in 2,2,2-trifluoroethanol was heated to 90°C in a sealed tube for 45 minutes. The
 reaction was cooled, poured into DCM/saturated sodium bicarbonate and the organic
 layer taken to a residue under reduced pressure. Trituration from diethyl ether afforded
 5-{{1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl}amino}-3-[(4-
 10 methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one
 which was dissolved in 27% aqueous NH₄OH solution (50 mL) in THF (50 mL) was
 heated at 80 °C for 17 h. The resulting mixture was diluted with EtOAc (50 mL) and a
 saturated NaCl solution (100 mL). The organic layer was washed with a saturated NaCl
 solution (100 mL), dried (Na₂SO₄), concentrated onto Celite and purified by silica gel
 15 chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-({2-{{1-
 (*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl}amino)-7-[(4-
 methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide
 (235 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.24 (s, 6H), 2.34 (s, 3H), 3.06-3.28 (m,
 4H), 3.74 (s, 3H), 4.24 (t, *J*=7.87 Hz, 2H), 6.39-6.49 (m, 1H), 7.07 (s, 1H), 7.19-7.41 (m,
 20 3H), 7.42-7.75 (m, 3H), 7.94 (d, *J*=7.87 Hz, 2H), 8.04-8.26 (m, 2H), 8.44 (s, 1H), 11.49
 (s, 1H); ESIMS (*M*+*H*)⁺ = 661.29.

Step B/Example 2: 3-({2-{{1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-
 yl}amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide

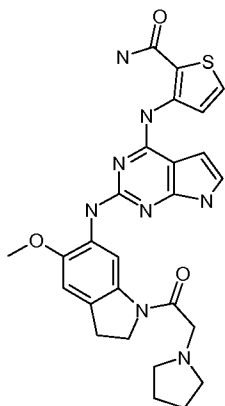
25

A mixture of 3-({2-{{1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-
 yl}amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-

thiophenecarboxamide (235 mg, 0.356 mmol), NaOMe (192 mg, 3.56 mmol), THF (20 mL) and methanol (40 mL) was heated at 80 °C for 4 h. The resulting mixture was diluted with EtOAc (100 mL), washed with a saturated NaHCO₃ solution (100 mL) and a saturated NaCl solution (100 mL). The aqueous layers were back extracted with EtOAc (50 mL). The organic layers were dried (Na₂SO₄), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide as a yellow solid (92 mg, 51%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.25 (s, 6H), 3.05-3.25 (m, 4 H), 3.78 (s, 3H), 4.19 (t, *J*=8.06 Hz, 2H), 6.23 (s, 1H), 6.97 (s, 2H), 7.37-7.84 (m, 4H), 8.41 (d, *J*=4.94 Hz, 1H), 8.59 (s, 1H), 11.30 (s, 1H), 11.41 (s, 1H); ESIMS (M+H)⁺ = 507.27.

Example 3

3-[(2-[[5-(methyloxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

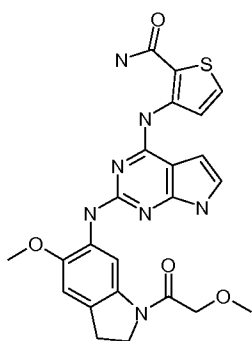


A mixture of 5-(methyloxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indol-6-amine (256 mg, 0.928 mmol) and 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride (400 mg, 0.928 mmol) in 2,2,2-trifluoroethanol (10 mL) was heated at 80 °C for 3 h. The resulting mixture was allowed to cool to rt, diluted with CH₂Cl₂ (100 mL), and a NaHCO₃ solution (100 mL). The organic layer was washed with a saturated NaHCO₃ solution (100 mL) and a saturated NaCl solution (100 mL), dried (Na₂SO₄) and concentrated. The residue was triturated with Et₂O to afford crude 5-[[5-(methyloxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indol-6-yl]amino]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one. The solids were taken up into THF (50 mL) and a 27% aqueous NH₄OH solution (200

mL). The reaction mixture was heated at 80 °C for 28 h. The resulting mixture was allowed to cool to rt and diluted with EtOAc (200 mL) and a saturated NaCl solution (100 mL). The aqueous layer was back extracted with EtOAc (200 mL). The organic layers were combined, washed with a saturated NaCl solution (2 x 100 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂. The isolated intermediate product was dissolved in THF (10 mL) and MeOH (10 mL), and was treated with NaOMe (192 mg, 3.55 mmol). The reaction mixture was heated at 70 °C for 3 h. The resulting mixture was allowed to cool to rt, diluted with EtOAc (100 mL), washed with a saturated NaHCO₃ solution (50 mL) and a saturated NaCl solution (50 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-[[5-(methoxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide as a light brown solid (55 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.7 (br s, 4H), 2.56 (br s, 4H), 3.14 (t, *J*=7.87 Hz, 2H), 3.37 (s, 2H), 3.78 (s, 3H), 4.18 (t, *J*=8.06 Hz, 2H), 6.23 (s, 1H), 6.97 (s, 2H), 7.33-7.79 (m, 4H), 8.41 (d, *J*=4.94 Hz, 1H), 8.58 (s, 1H), 11.30 (s, 1H), 11.41 (s, 1H); ESIMS (M+H)⁺ = 533.30.

Example 4

3-[[2-([5-(methoxy)-1-[(methoxy)acetyl]-2,3-dihydro-1H-indol-6-yl]amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-2-thiophenecarboxamide

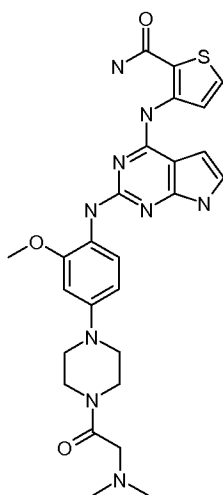


A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride (400 mg, 0.856 mmol) and 5-(methoxy)-1-[(methoxy)acetyl]-2,3-dihydro-1H-indol-6-amine (201 mg, 0.851 mmol) in THF (15 mL) was heated at 80 °C for 17 h. The resulting mixture was

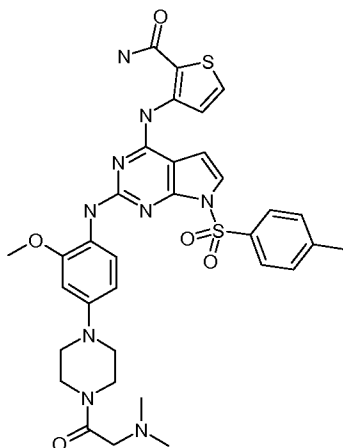
diluted with THF (30 mL) and a 27% aqueous NH_4OH solution (200 mL). The reaction mixture was heated at 80 °C. After 17 h the mixture was allowed to cool to rt and diluted with EtOAc (50 mL) and a saturated NaCl solution (50 mL). The organic layer was washed with a saturated NaCl solution (2x50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 . The isolated intermediate product was dissolved in THF (6 mL) and MeOH (6 mL) and was treated with NaOMe (198 mg, 3.67 mmol). The reaction mixture was heated at 80 °C for 3 h. The resulting mixture was allowed to cool to rt and diluted with EtOAc (50 mL) and a saturated NaHCO_3 solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to obtain 3-[(2-[(5-(methoxy)-1-[(methoxy)acetyl]-2,3-dihydro-1*H*-indol-6-yl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (53 mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.14 (t, $J=8.06$ Hz, 2H), 3.79 (s, 3H), 4.05 (t, $J=8.33$ Hz, 2H), 4.18 (s, 2H), 6.18-6.29 (m, 1H), 6.90-7.06 (m, 2H), 7.33-7.82 (m, 4H), 8.12 (d, $J=5.31$ Hz, 1H), 8.62 (s, 1H), 11.32 (s, 1H), 11.42 (s, 1H) a CH_3O signal is missing, may overlap with water peak; ESIMS $(\text{M}+\text{H})^+ = 494.13$.

Example 5

3-[(2-[(4-[4-(*N,N*-dimethylglycyl)-1-piperazinyl]-2-(methoxy)phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



Step A/Intermediate C3: 3-({2-([4-[4-(*N,N*-dimethylglycyl)-1-piperazinyl]-2-(methoxy)phenyl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



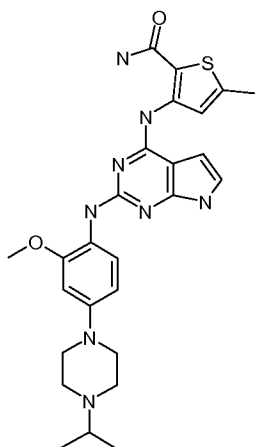
- 5 A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one hydrogen chloride (400 mg, 0.855
mmol) and 4-{4-[(dimethylamino)acetyl]-1-piperazinyl}-2-(methoxy)aniline (250 mg,
0.855 mmol) in THF (50 mL) was stirred at rt for 20 h. A 27% aqueous NH_4OH solution
10 mixture was allowed to cool to rt, and diluted with EtOAc (100 mL) and a saturated NaCl
solution (100 mL). The organic layer was washed with a saturated NaCl solution (2x100
mL), concentrated onto Celite and purified by silica gel chromatography using 1-10%
MeOH (containing 0.2% NH_3)/ CH_2Cl_2 , followed by trituration using a mixture of CH_2Cl_2
and Et_2O to obtain 3-({2-([4-[4-(*N,N*-dimethylglycyl)-1-piperazinyl]-2-
15 (methoxy)phenyl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-
yl}amino)-2-thiophenecarboxamide as a yellow solid (104 mg, 17%). ^1H NMR (400 MHz,
DMSO- d_6) δ ppm 2.20 (s, 6H), 2.35 (s, 3H), 3.04-3.28 (m, 6H), 3.64 (br s, 2H), 3.73 (br s,
2H), 3.82 (s, 3H), 6.47 (d, $J=3.85$ Hz, 1H), 6.64 (d, $J=8.42$ Hz, 1H), 6.73 (s, 1H), 7.29-
7.44 (m, 3H), 7.44-7.85 (m, 5H), 7.92 (d, $J=7.51$ Hz, 1H), 8.11 (s, 1H), 8.27 (br s, 1H),
20 11.49 (s, 1H); ESIMS ($\text{M}+\text{H}$) $^+$ = 704.27.

Step B/Example 5: 3-[(2-([4-[4-(*N,N*-dimethylglycyl)-1-piperazinyl]-2-(methoxy)phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

A mixture of 3-({2-[4-[4-(*N,N*-dimethylglycyl)-1-piperazinyl]-2-(methoxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (104 mg, 0.148 mmol), dioxane (10 mL) and a 1N aqueous KOH solution (2.60 mL, 2.60 mmol) was heated at 80 °C for 16.5 h. The resulting mixture was allowed to cool to rt and diluted with EtOAc (100 mL). The organic layer was washed with a saturated NaHCO₃ solution (50 mL), a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-[4-[4-(*N,N*-dimethylglycyl)-1-piperazinyl]-2-(methoxy)phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide as a light brown solid (38.7 mg, 48%). ¹H NMR (400 MHz, CDCl₃+CD₃OD) δ ppm 2.18 (s, 6H), 2.98 br s, 4H), 3.06 (s, 2H), 3.52-3.68 (m, 4H), 3.74 (s, 3H), 6.29 (d, *J*=3.11 Hz, 1H), 6.34-6.53 (m, 2H), 6.71 (d, *J*=3.30 Hz, 1H), 7.22 (d, *J*=5.49 Hz, 1H), 7.96 (d, *J*=8.42 Hz, 1H), 8.29 (d, *J*=5.49 Hz, 1H); ESIMS (M+H)⁺ = 550.28.

Example 6

5-methyl-3-[(2-[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

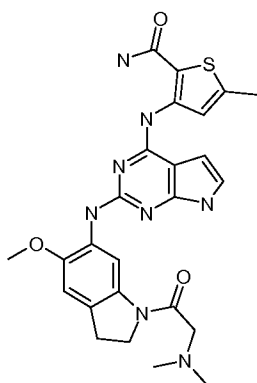


A suspension of 5-chloro-9-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one (450 mg, 1.011 mmol) and [4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amine (315 mg, 1.264 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed to 90°C in a sealed pressure vessel for 16 hours. The solution was cooled, poured into dichloromethane/saturated sodium bicarbonate, and the organic layer was taken to a residue under reduced pressure and triturated with

diethyl ether. The derived solids were mixed with a 27% aqueous NH_4OH solution (190 mL) in THF (60 mL) and heated at 80 °C for 17 h. The resulting mixture was diluted with EtOAc (100 mL) and the layers were separated. The aqueous layer was back extracted with EtOAc (100 mL). The organic layers were combined, washed with a saturated NaCl solution (2 x 100 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 . The isolated intermediate product was taken up into THF (5 mL) and MeOH (5 mL), and was treated with NaOMe (115 mg, 2.134 mmol). The reaction mixture was heated at 80 °C for 1.5 h, then was diluted with EtOAc (100 mL), washed with a saturated NaHCO_3 solution (50 mL) and a saturated NaCl solution (75 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to obtain 5-methyl-3-[(2-[[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-2-thiophenecarboxamide as a yellow solid (90 mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.01 (d, $J=6.41$ Hz, 6H), 2.44 (s, 3H), 2.52-2.75 m, 5H), 3.12 (br s, 4H), 3.79 (s, 3H), 6.19 (s, 1H), 6.50 (d, $J=8.79$ Hz, 1H), 6.63 (s, 1H), 6.94 (s, 1H), 7.38 (br s, 2H), 7.51 (s, 1H), 7.65 (d, $J=8.42$ Hz, 1H), 8.09 (s, 1H), 11.25 (s, 1H), 11.39 (s, 1H); ESIMS ($\text{M}+\text{H}$) $^+$ = 521.33.

Example 7

3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-5-methyl-2-thiophenecarboxamide

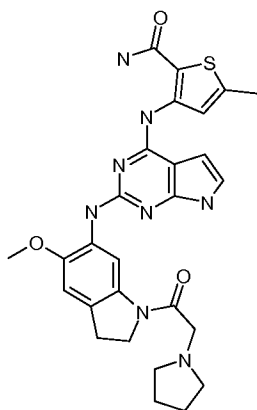


A suspension of 5-chloro-9-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (450 mg, 1.011 mmol) and 1-[(dimethylamino)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine (303 mg, 1.214 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed to 90°C in a sealed pressure vessel.

After 1 hour all solids had dissolved, and the reaction was cooled to room temperature and poured into dichloromethane/saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure and the oil was triturated with diethyl ether. The derived solids were taken up into THF (60 mL) and a 27% aqueous NH_4OH solution (190 mL), and was heated at 80 °C for 24 h. The resulting mixture was allowed to cool to rt and diluted with EtOAc (100 mL). The aqueous layer was back extracted with EtOAc (50 mL). The organic layers were combined, washed with a saturated NaCl solution (2 x 100 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 . The isolated intermediate product was dissolved in THF (5 mL) and MeOH (5 mL), and was treated with NaOMe (96 mg, 1.778 mmol). The reaction mixture was heated at 80 °C until all starting material was consumed as evident by LCMS. The resulting mixture was diluted with EtOAc (100 mL), washed with a saturated NaHCO_3 solution (50 mL) and a saturated NaCl solution (75 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to obtain 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-5-methyl-2-thiophenecarboxamide as an off-white solid (62 mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.24 (s, 6H), 2.37 (s, 3H), 3.06-3.22 (m, 4H), 3.76 (s, 3H), 4.17 (t, $J=8.24$ Hz, 2H), 6.16-6.27 (m, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.38 (br s, 2H), 7.74 (s, 1H), 8.05 (s, 1H), 8.46 (s, 1H), 11.25 (s, 1H), 11.43 (s, 1H); ESIMS ($\text{M}+\text{H}$) $^+$ = 521.26.

Example 8

5-methyl-3-[(2-[[5-(methoxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

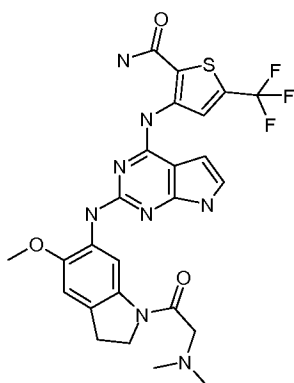


A mixture of 5-(methoxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1H-indol-6-amine (265 mg, 0.962 mmol) and 5-chloro-9-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride (428 mg, 0.962 mmol) in 2,2,2-trifluoroethanol (10 mL) was heated at 80 °C for 3 h. The resulting mixture was allowed to cool to rt, diluted with CH₂Cl₂ (100 mL) and a saturated NaHCO₃ solution (100 mL). The organic layer was washed with a saturated NaCl solution (100 mL), dried (Na₂SO₄) and concentrated. The residue was triturated with Et₂O. The crude product was taken up into in THF (50 mL) and a 27% aqueous NH₄OH solution (200 mL). The reaction mixture was heated at 80 °C for 28 h. The resulting mixture was allowed to cool to rt, diluted with EtOAc (200 mL) and a saturated NaCl solution (100 mL). The aqueous layer was back extracted with EtOAc (200 mL). The organic layers were combined, washed with a saturated NaCl solution (2 x 100 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂. The isolated intermediate product was dissolved in in THF (10 mL) and MeOH (10 mL) and treated with NaOMe (202 mg, 3.73 mmol). The reaction mixture was heated at 70 °C for 3 h. The resulting mixture was allowed to cool to rt, diluted with EtOAc (100 mL) and washed with a saturated NaHCO₃ solution (50 mL). The organic layer was diluted with a saturated NaCl solution (50 mL). The resulting slurry was filtered and the solids were washed with Et₂O to obtain 5-methyl-3-[(2-[[5-(methoxy)-1-(1-pyrrolidinylacetyl)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide as a white solid (122 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.69 (br s, 4H), 2.37 (s, 3H), 2.53 (br s, 4H), 3.15 (t, *J*=8.42 Hz, 2H), 3.76 (s, 3H), 4.17 (t, *J*=8.06 Hz, 2H), 6.20 (s, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.38 (s, 2H), 7.73 (s, 1H), 8.05 (s, 1H), 8.45 (s, 1H), 11.26 (s, 1H), 11.44 (s, 1H), a CH₂ signal is missing, may overlap with water peak; ESIMS (M+H)⁺ = 547.29.

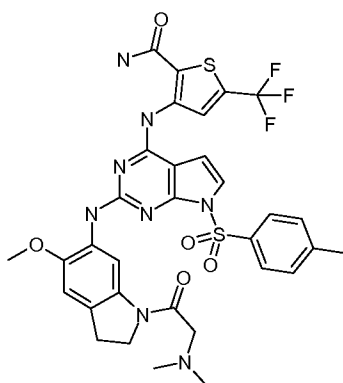
Example 9

3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-5-(trifluoromethyl)-2-thiophenecarboxamide

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Step A/Intermediate C4: 3-({2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-5-(trifluoromethyl)-2-thiophenecarboxamide



A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]-9-(trifluoromethyl)pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride (358 mg, 0.602 mmol) and 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (150 mg, 0.602 mmol) in THF (50 mL) was heated at 80 °C for 17 h. The resulting mixture was allowed to cool to rt and diluted with a 27% aqueous NH_4OH solution (200 mL). The reaction mixture was stirred at rt for 1 h, and diluted with EtOAc (100 mL) and a saturated NaCl solution (50 mL). The organic layer was washed with a saturated NaCl solution (2x100 mL), dried (Na_2SO_4), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to obtain as a yellow solid (270 mg, 62%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.22 (s, 6H), 2.35 (s, 3H), 3.05-3.27 (m, 4H), 3.72 (s, 3H), 4.19 (t, 8.15 Hz, 2H), 6.47 (d, 3.85 Hz, 1H), 7.05 (s, 1H), 7.24-7.45 (m, 3H), 7.71-8.11 (m, 4H), 8.14 (s, 1H), 8.48 (br s, 1H), 8.62 (s, 1H), 11.41 (s, 1H); ESIMS ($\text{M}+\text{H}$) $^+$ = 729.36.

Step B/Example 9: 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-5-(trifluoromethyl)-2-thiophenecarboxamide

5

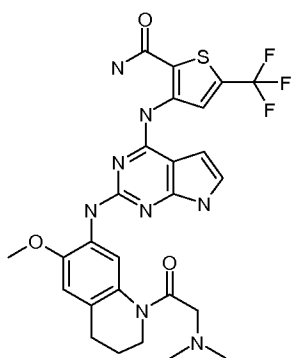
A mixture of 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-5-(trifluoromethyl)-2-thiophenecarboxamide (270 mg, 0.370 mmol), a 1N aqueous KOH solution (3.70 mL, 3.70 mmol) and dioxane (20 mL) was heated at 80 °C for 9 h. The resulting mixture was diluted with EtOAc (100 mL), washed with a saturated NaHCO₃ solution (100 mL) and a saturated NaCl solution (50 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-5-(trifluoromethyl)-2-thiophenecarboxamide as a yellow solid (63 mg, 30%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.21 (s, 6H), 3.03-3.23 (m, 4H), 3.74 (s, 3H), 4.15 (t, *J*=8.33 Hz, 2H), 6.23 (d, *J*=1.47 Hz, 1H), 6.90-7.04 (m, 2H), 7.69-8.18 (m, 3H), 8.40 (s, 1H), 8.76 (s, 1H), 11.24-11.47 (m, 2H); ESIMS (M+H)⁺ = 575.11.

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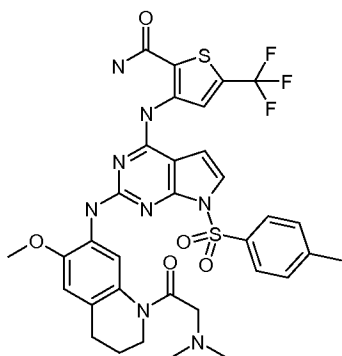
20 Example 10

3-[(2-[[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-5-(trifluoromethyl)-2-thiophenecarboxamide



25

Step A/Intermediate C5: 3-(2-([1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-(trifluoromethyl)-2-thiophenecarboxamide



- 5 A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]-9-(trifluoromethyl)pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one hydrogen chloride (390 mg, 0.656
mmol) and 1-[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine
(173 mg, 0.656 mmol) in THF (15 mL) was heated at 80 °C for 17 hours. Additional 1-
[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (27 mg, 0.102
10 mmol) was added and the reaction mixture was heated at 80 °C for 17 hours. THF (40
mL) was added, followed by a 27% aqueous NH₄OH solution (200 mL). The reaction
mixture was heated at 80 °C for 30 min and then allowed to cool to rt. EtOAc (100 mL)
and a saturated NaCl solution (50 mL) were added. The organic layer was washed with
a saturated NaCl solution (2 x 100 mL), concentrated onto Celite and purified by silica
15 gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-(2-
{[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-
methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-(trifluoromethyl)-2-
thiophenecarboxamide as a yellow solid (193 mg, 40%). ESIMS (M+H)⁺ = 743.38.

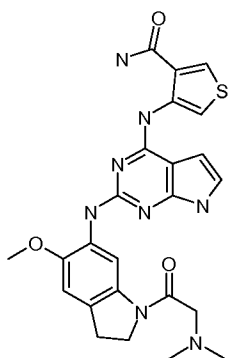
- 20 Step B/Example 10: 3-[(2-([1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-
quinolinyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-5-(trifluoromethyl)-2-
thiophenecarboxamide

- A mixture of 3-(2-([1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-
25 quinolinyl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-
(trifluoromethyl)-2-thiophenecarboxamide (193 mg, 0.260 mmol) and a 1*N* aqueous KOH
solution (2.60 mL, 2.60 mmol) in dioxane (10 mL) was heated at 80 °C for 17 h. The

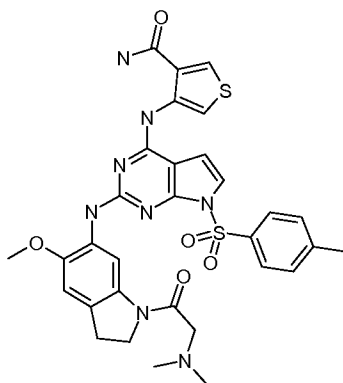
resulting mixture was allowed to cool to rt and diluted with EtOAc (100 mL) and a saturated NaHCO₃ solution (100 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-[[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinoliny]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-5-(trifluoromethyl)-2-thiophenecarboxamide as a beige solid (25 mg, 16%). ¹H NMR (400 MHz, THF-*d*₈) δ ppm 1.23-1.79 (m, 8H) 2.71 (br s, 2H), 3.71 (s, 2H), 3.58-3.95 (m, 5H), 6.25 (s, 1H), 6.84 (s, 1H), 7.02 (s, 1H), 7.64-8.28 (m, 4H), 8.79 (s, 1H), 11.30 (s, 1H), 11.41 (br s, 1H); ESIMS (M+H)⁺ = 589.20.

Example 11

4-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-3-thiophenecarboxamide



Step A/Intermediate C6: 4-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-3-thiophenecarboxamide



A yellow slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]-3H,7H-pyrrolo[3,2-e]thieno[3',4':4,5]pyrimido[1,2-c]pyrimidin-7-one hydrogen chloride (1.2 g, 2.57 mmol) was heated in THF (500 mL) at the reflux temperature. 1-[(Dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (0.640 g, 2.57 mmol) was added and the reaction mixture was heated at the reflux temperature for 2 h 20 min. The resulting mixture was allowed to cool to rt and concentrated. EtOAc (200 mL), a few mL THF and a saturated NaHCO₃ solution (100 mL) were added. The organic layer was washed with a saturated NaCl solution (100 mL). The aqueous layers were back extracted with a mixture of THF (20 mL) and EtOAc (100 mL). The organic layers were combined, dried (Na₂SO₄) and concentrated and twice triturated using Et₂O to obtain the crude product (1195 mg). 319 mg of this crude mixture was taken up into a 27% aqueous NH₄OH solution (50 mL) and THF (50 mL) and was maintained at rt for 18 h. EtOAc (100 mL) and a saturated NaCl solution (50 mL) were added. The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ followed by trituration using Et₂O to obtain 4-({2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-3-thiophenecarboxamide as a white solid (75 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.26 (s, 6H), 2.34 (s, 3H), 3.10-3.28 (m, 4H), 3.75 (s, 3H), 4.24 (d, *J*=8.42 Hz, 2H), 6.41 (d, *J*=3.66 Hz, 1H), 7.08 (s, 1H), 7.25-7.39 (m, 3H), 7.66 (br s, 1H), 7.88-8.10 (m, 3H), 8.20 (br s, 1H), 8.25 (s, 1H), 8.31 (d, *J*=3.11 Hz, 1H), 8.39 (s, 1H), 11.31 (s, 1H); ESIMS (M+H)⁺ = 661.28.

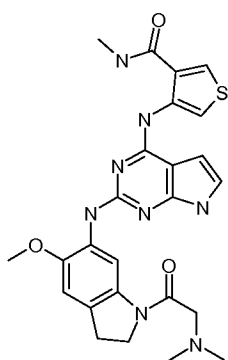
Step B/Example 11: 4-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-3-thiophenecarboxamide

A mixture of 4-({2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-3-thiophenecarboxamide (49 mg, 0.074 mmol), dioxane (5 mL) and a 1 M aqueous KOH solution (0.7 mL) was heated at 80 °C for 8 h and was allowed to cool to rt. EtOAc (100 mL) was added, followed by a saturated NaHCO₃ solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 4-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-3-thiophenecarboxamide as a white solid (75 mg).

1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-3-thiophenecarboxamide as a beige solid (15.1 mg, 40%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.26 (s, 6H), 3.04-3.26 (m, 4H), 3.79 (s, 3H), 4.19 (t, *J*=8.15 Hz, 2H), 6.20 (br s, 1H), 6.39 (br s, 1H), 6.97 (s, 1H), 7.63 (br s, 1H), 7.71 (s, 1H), 8.11-8.27 (m, 2H), 8.32 (d, *J*=3.11, 1H), 8.62 (s, 1H), 11.16 (s, 1H), 11.24 (s, 1H); ESIMS (M+H)⁺ = 507.18.

Example 12

4-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-3-thiophenecarboxamide

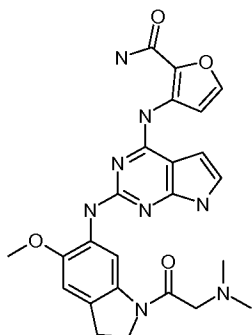


131 mg of the crude intermediate from the synthesis of 4-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-3-thiophenecarboxamide was dissolved in a solution of methylamine (2N in THF, 10 mL) and stirred at rt. After 20 h the resulting mixture was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂. The crude product was dissolved in dioxane (10 mL) and a 1N aqueous KOH solution (0.845 mL, 0.845 mmol) and was heated at 80 °C. After 2.5 h the resulting mixture was allowed to cool to rt. EtOAc (100 mL) and a saturated NaHCO₃ solution (50 mL) was added. The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 4-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-3-thiophenecarboxamide as a brown solid (36.1 mg, 82%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.27 (s, 6H), 2.83 (d, *J*=4.4 Hz, 3H), 3.05-3.27 (m, 4H), 3.79 (s, 3H), 4.18 (t, *J*=8.24 Hz, 2H), 6.23 (s, 1H), 6.85-7.05 (m, 2H), 7.71

(s, 1H), 8.23 (s, 2H), 8.57-8.78 (m, 2H), 11.09 (s, 1H), 11.25 (s, 1H); ESIMS (M+H)⁺ = 521.21.

Example 13

5 3-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-furancarboxamide



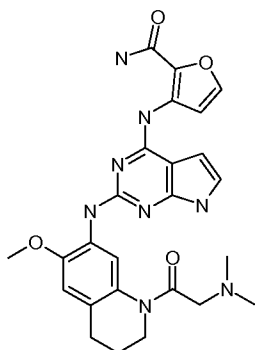
A solution of 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-furancarboxylic acid (0.66 g, 1.525 mmol) in THF (50 mL) was treated with 2
 10 drops of DMF followed by an oxalyl chloride solution (2N in CH₂Cl₂, 4.5 mL, 9 mmol). After 30 min the reaction mixture was concentrated. The residue was dissolved in THF and concentrated again to obtain a beige solid (650 mg). 500 mg of the crude intermediate was taken up into THF (50 mL) and treated with 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (0.404 g, 1.620 mmol). The reaction mixture
 15 was heated at 70 °C for 17 h and was allowed to cool to rt. EtOAc (200 mL) was added, followed by a saturated NaHCO₃ solution (100 mL). The organic layer was washed with a saturated NaCl solution (100 mL), dried (Na₂SO₄) and concentrated. The resulting brown oily residue was triturated with Et₂O. The crude intermediate was taken up into 2,2,2-trifluoroethanol (50 mL) and was treated with K₂CO₃ (550 mg, 3.98 mmol). After 24
 20 h a 27% aqueous NH₄OH solution (50 mL) was added, followed by addition of 2,2,2-trifluoroethanol (20 mL). The reaction mixture was stirred at rt for 20 h. The resulting slurry was filtered. The crude intermediate was dissolved in dioxane (10 mL) and a 1N aqueous KOH solution (2.414 mL, 2.414 mmol) and was heated at 90 °C. After 5.5 h the resulting mixture was allowed to cool to rt. EtOAc (100 mL) and a saturated NaHCO₃
 25 solution (50 mL) were added. The organic layer was washed with a saturated NaCl solution (100 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-{[1-(*N,N*-

dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-2-furancarboxamide (39 mg, 33%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.25 (s, 6H), 3.02-3.25 (m, 4H), 3.78 (s, 3H), 4.18 (t, *J*=8.15Hz, 2H), 6.13-6.28 (m, 1H), 6.86-7.05 (m, 2H), 7.33-7.87 (m, 5H), 8.57 (s, 1H), 9.69 (s, 1H), 11.29 (s, 1H);

5 ESIMS (M+H)⁺ = 491.16.

Example 14

3-[(2-{[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-2-furancarboxamide



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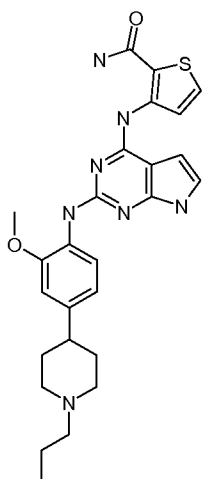
A suspension of 3-[(2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-2-furancarboxylic acid (1.15 g, 2.66 mmol) in THF (100 mL) was treated with a drop of DMF and oxalyl chloride (2.66 mL, 5.31 mmol). The resulting yellow opaque
 15 mixture was stirred at rt for 3 days and concentrated. The residue was taken up into benzene and concentrated again. The derived residue was taken up into THF (50 mL) and treated with 1-[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (447 mg, 1.698 mmol). The reaction mixture was heated at 80 °C for 3 h. The resulting orange slurry was allowed to cool to rt and treated with a 27% aqueous
 20 NH₄OH solution (200 mL). The reaction mixture was heated in a sealed vessel at 80 °C for 22 h. The resulting mixture was allowed to cool to rt and diluted with EtOAc (100 mL). The organic layer was washed with a saturated NaCl solution (3x100 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂, followed by trituration using a mixture of THF and Et₂O. The derived
 25 solids were taken up into dioxane (10 mL) and a 1N aqueous KOH solution (3.02 mL, 3.02 mmol) and was heated at 80 °C for 11 h. The resulting mixture was allowed to cool to rt. EtOAc (50 mL) was then added. The organic layer was washed with a saturated

NaCl solution (2x50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂, followed by trituration using Et₂O to obtain 3-[(2-{[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-

- 5 furancarboxamide as a pale yellow solid (120 mg). ¹H NMR (400 MHz, THF-*d*₈) δ ppm 1.77-1.98 (m, 2H), 2.12 (br s, 6H), 2.70 (br s, 2H), 3.26 (s, 2H), 3.62-3.78 (s, 2H), 3.85 (s, 3H), 6.24 (br s, 1H), 6.84 (br s, 1H), 7.00 (br s, 1H), 7.38-7.90 (s, 5H), 8.36 (br s, 1H), 9.71 (s, 1H), 11.41 (br s, 1H); ESIMS (M+H)⁺ = 505.21.

10 Example 15

3-[(2-{[2-(methoxy)-4-(1-propyl-4-piperidiny)]phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



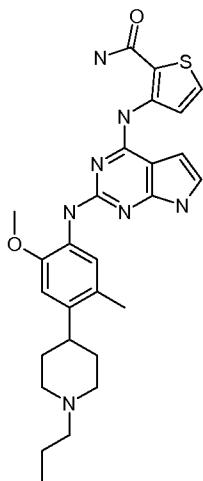
15

A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (400 mg, 0.928 mmol) and [2-
(methoxy)-4-(1-propyl-4-piperidiny)]phenylamine (277 mg, 1.114 mmol) in 2,2,2-
trifluoroethanol is heated to 90°C in a sealed pressure tube for 45 minutes. The reaction
20 was cooled and poured into DCM/saturated sodium bicarbonate and the organic layer
was taken to dark residue under reduced pressure. Trituration of the residue with diethyl
ether affords 5-{[2-(methoxy)-4-(1-propyl-4-piperidiny)]phenylamino}-3-[(4-
methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one
(245 mg, 0.381 mmol, 41.1 % yield) as a pale yellow solid. A solution of 5-{[2-

(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (245 mg, 0.381 mmol) in THF and 27% ammonium hydroxide (80mL total) was stirred at room temperature for 72 hrs. Essentially no reaction was observed by LCMS after this time. The reaction was poured into a pressure vessel and heated at 80°C overnight. The reaction was cooled, poured into ethyl acetate/brine, and the organic layer was dried over sodium sulfate, filtered and taken to a residue under reduced pressure to afford 3-({2-[[2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl]amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (215 mg, 0.244 mmol, 64.1 % yield) as a pale yellow solid (approximately 70% purity.) A solution of crude 3-({2-[[2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl]amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (215 mg, 0.244 mmol) and sodium methoxide (132 mg, 2.444 mmol) in THF/MeOH was warmed to 80°C and maintained for three hours. The reaction was poured into ethyl acetate/2.0N sodium hydroxide and the organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-[[2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (77 mg, 0.152 mmol, 62.3 % yield) as a pale white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.40 (s, 1 H), 11.38 (s, 1 H), 8.41 (d, *J*=5.50 Hz, 1 H), 8.12 (d, *J*=8.07 Hz, 1 H), 7.70 (d, *J*=5.50 Hz, 1 H), 7.58 (s, 1 H), 7.57 (bs, 2 H), 6.98 (dd, *J*=3.67, 2.20 Hz, 1 H), 6.89 (d, *J*=1.83 Hz, 1 H), 6.79 (dd, *J*=8.07, 1.83 Hz, 1 H), 6.23 (dd, *J*=3.67, 1.83 Hz, 1 H), 3.85 (s, 3 H), 2.95 (d, *J*=11.00 Hz, 2 H), 2.38 - 2.46 (m, 1 H), 2.18 - 2.31 (m, 2 H), 1.85 - 2.02 (m, 2 H), 1.60 - 1.79 (m, 4 H), 1.36 - 1.51 (m, 2 H), 0.86 (t, *J*=7.33 Hz, 3 H). ESIMS (M+H)⁺ = 506.

Example 16

3-[(2-[[5-methyl-2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

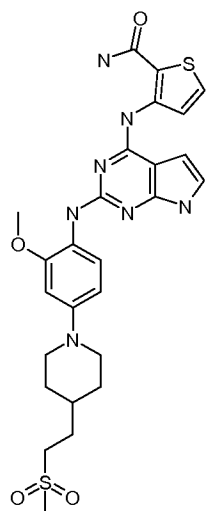


A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (400 mg, 0.928 mmol) and [5-methyl-2-(methoxy)-4-(1-propyl-4-piperidiny)phenyl]amine (292 mg, 1.114 mmol) in 2,2,2-trifluoroethanol was heated to 90°C in a sealed pressure tube. After 45 minutes, the reaction was cooled and poured into dichloromethane/saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure and triturated with diethyl ether to afford 5-{[5-methyl-2-(methoxy)-4-(1-propyl-4-piperidiny)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (375 mg, 0.571 mmol, 61.5 % yield) as a pale yellow solid. A solution of 5-{[5-methyl-2-(methoxy)-4-(1-propyl-4-piperidiny)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (275 mg, 0.419 mmol) in THF/27% ammonium hydroxide was stirred at room temperature over the weekend (ca 72 hours). Essentially no reaction observed by TLC or LCMS. The reaction was poured into a pressure flask and warmed to 80°C for 2 hrs. TLC/LCMS retaken and indicates partial consumption of starting material (ca 50% completion). Flask was re-sealed and heated an additional 4 hours. The flask was cooled and the reaction poured into ethylacetate/saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and taken to a residue under reduced pressure to afford 3-({2-{[5-methyl-2-(methoxy)-4-(1-propyl-4-piperidiny)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (250 mg, 0.186 mmol, 44.3 % yield) as a pale yellow solid with roughly 50% purity. This residue and sodium methoxide (220 mg, 4.08 mmol) in THF/MeOH is warmed to 80°C for three hours, cooled, and poured into

EtOAc/saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by chromatography on silica gel to afford 3-[(2-
 5 {5-methyl-2-(methoxy)-4-(1-propyl-4-piperidiny)phenyl]amino}-1H-pyrrolo[2,3-
 d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (90 mg, 0.173 mmol, 85 % yield) as a
 pale grey solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.38 (s, 1 H), 11.34 (s, 1 H), 8.39
 (d, *J*=5.13 Hz, 1 H), 7.91 (s, 1 H), 7.69 (d, *J*=5.13 Hz, 1 H), 7.56 (s, 2 H), 7.49 (s, 1 H),
 6.93 - 7.03 (m, 1 H), 6.83 (s, 1 H), 6.23 (dd, *J*=3.48, 2.02 Hz, 1 H), 3.82 (s, 3 H), 2.97 (d,
 10 *J*=10.63 Hz, 2 H), 2.57 - 2.69 (m, 1 H), 2.24 - 2.28 (m, 2 H), 2.22 - 2.25 (m, 3 H), 1.91 -
 2.04 (m, 2 H), 1.62 - 1.77 (m, 4 H), 1.39 - 1.53 (m, 2 H), 0.86 (t, *J*=7.33 Hz, 3 H). ESIMS
 (M+H)⁺ = 520.

Example 17

**3-({2-[(2-(methoxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidiny}phenyl)amino]-1H-
 15 pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide**

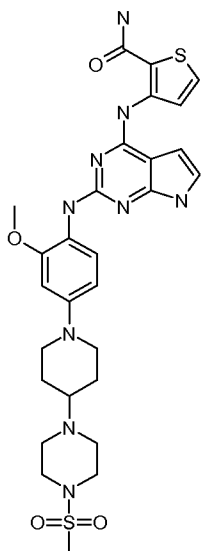


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (400 mg, 0.928 mmol) and (2-
 20 (methoxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidiny}phenyl)amine
 2-(methoxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidiny}aniline (334 mg, 1.068 mmol) in
 2,2,2-trifluoroethanol was warmed to 80°C and maintained for 45 minutes. The reaction
 was cooled, poured into methylene chloride/saturated sodium bicarbonate, and the
 organic layer was taken to a residue under reduced pressure and solids triturated with

diethylether to afford 5-[(2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (515 mg, 0.729 mmol, 78 % yield) as a yellow solid. A suspension of 5-[(2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (515 mg, 0.729 mmol) in THF/27% ammonium hydroxide (50mL each) was warmed at 80°C for 5.5 hours. The reaction was diluted further with THF/27% ammonium hydroxide (75mL more of each) and heated for an additional 16 hours at 90°C in a pressure vessel. The reaction was cooled and layers separated. The organic layer was taken to a residue under reduced pressure and 3-[(2-[(2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (400 mg, 0.359 mmol, 49.3 % yield) was isolated as a yellow solid of sufficient purity for direct use in the next step. A solution of 3-[(2-[(2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (400 mg, 0.553 mmol) in dioxane/2.0N NaOH was heated in a uW vial at 120°C for 12 minutes. The solution was poured into THF/2.0N sodium hydroxide and the organic layer was washed with brine, dried over sodium sulfate, filtered, and stripped onto celite. Purification by chromatography on SiO₂ afforded a number of mixed fractions, however upon sitting at 0°C a thick white precipitate formed in 6 column fractions. Filtration of these fractions and drying afforded 3-[(2-[(2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperidinyl}phenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (85 mg, 0.149 mmol, 27.0 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.34 (s, 1 H), 11.24 - 11.31 (m, 1 H), 8.40 (d, *J*=5.50 Hz, 1 H), 7.82 (d, *J*=8.43 Hz, 1 H), 7.66 (d, *J*=5.50 Hz, 1 H), 7.54 (s, 2 H), 7.48 (s, 1 H), 6.88 - 6.98 (m, 1 H), 6.62 (d, *J*=2.57 Hz, 1 H), 6.49 (dd, *J*=8.98, 2.38 Hz, 1 H), 6.20 (dd, *J*=3.67, 1.83 Hz, 1 H), 3.80 (s, 3 H), 3.64 (d, *J*=12.46 Hz, 2 H), 3.11 - 3.20 (m, 2 H), 2.96 (s, 3 H), 2.54 - 2.65 (m, 1 H), 1.78 (d, *J*=12.46 Hz, 2 H), 1.61 - 1.71 (m, 2 H), 1.41 - 1.56 (m, 2 H), 1.20 - 1.36 (m, 2 H). ESIMS (M+H)⁺ = 570.

Example 18

3-({2-[(2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidiny}]phenyl}amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



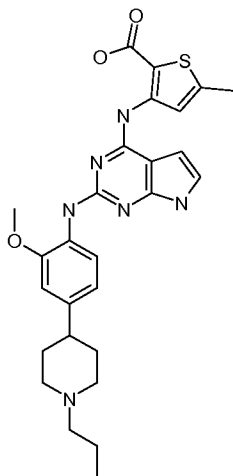
5

A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (300 mg, 0.696 mmol) and (2-
(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidiny}]phenyl)amine (257 mg,
10 0.696 mmol) in 2,2,2-trifluoroethanol was heated at 90°C for 72 hours. Many solids were
observed in solution, but when poured into methylenechloride (ca 50 mL) and washed
with saturated sodium bicarbonate all solids dissolved. The organic layer was taken to a
residue under reduced pressure and triturated with diethyl ether to afford 5-[(2-
(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidiny}]phenyl)amino]-3-[(4-
15 methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one
(307 mg, 0.402 mmol, 57.8 % yield) as a bright yellow solid. This procedure was
reproduced to generate additional quantities of this material. 5-[(2-(methyloxy)-4-{4-[4-
(methylsulfonyl)-1-piperazinyl]-1-piperidiny}]phenyl)amino]-3-[(4-
methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one
20 (400 mg, 0.524 mmol) was suspended between THF (150 mL) and 27% ammonium
hydroxide (150 mL) and heated in a pressure vial for 16 hours. The reaction was
cooled, and the organic layer was washed with brine, dried over sodium sulfate, filtered,
and taken to a residue under reduced pressure. The residue was suspended in dioxane

(7 mL) and 2.0N NaOH solution (aqueous, 7 mL) was added. The resulting mixture was warmed to 120°C for 12 minutes under microwave irradiation. The solution was cooled, poured into ethyl acetate/brine, and the organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-({2-[(2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (145 mg, 0.232 mmol, 44.2 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.34 (s, 1 H), 11.28 (s, 1 H), 8.39 (d, *J*=5.50 Hz, 1 H), 7.81 (d, *J*=8.80 Hz, 1 H), 7.66 (d, *J*=5.13 Hz, 1 H), 7.54 (s, 2 H), 7.48 (s, 1 H), 6.89 - 6.98 (m, 1 H), 6.62 (d, *J*=2.20 Hz, 1 H), 6.49 (dd, *J*=8.80, 2.57 Hz, 1 H), 6.20 (dd, *J*=3.48, 2.02 Hz, 1 H), 3.79 (s, 3 H), 3.68 (d, *J*=12.10 Hz, 2 H), 3.01 - 3.14 (m, 4 H), 2.85 (s, 3 H), 2.55 - 2.72 (m, 6 H), 2.34 - 2.45 (m, 1 H), 1.84 (d, *J*=11.36 Hz, 2 H), 1.44 - 1.65 (m, 2 H). ESIMS (M+H)⁺ = 626.

Example 19

5-methyl-3-[(2-{[2-(methoxy)-4-(1-propyl-4-piperidinyl)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxylic acid

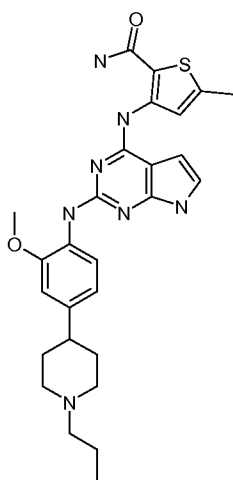


A suspension of 5-chloro-9-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (450 mg, 1.011 mmol) and [2-(methoxy)-4-(1-propyl-4-piperidinyl)phenyl]amine (301 mg, 1.214 mmol) in 2,2,2-trifluoroethanol was heated at 90°C in a sealed pressure tube for 50 minutes. The reaction was cooled, and poured into CH₂Cl₂/saturated sodium bicarbonate. The

organic layer was taken to a residue under reduced pressure and triturated with diethyl ether to afford 9-methyl-5-{{2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl}amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (356 mg, 0.542 mmol, 53.6 % yield) as a bright yellow solid. This protocol has been repeated and allowed generation of larger quantities of 9-methyl-5-{{2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl}amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one. A solution of 9-methyl-5-{{2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl}amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (305 mg, 0.464 mmol) and sodium amide (181 mg, 4.64 mmol) in tetrahydrofuran (25 ml) was stirred for 4 hours at room temperature. The reaction was diluted with saturated sodium bicarbonate and ethyl acetate, and the organic layer was dried over sodium sulfate and taken to a residue under reduced pressure. The residue was dissolved in 1,4-dioxane/2.0N sodium hydroxide and heated at 120°C in a microwave reactor for 12 minutes. The reaction was cooled and poured into ethyl acetate/saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography (required addition of AcOH to mobile phase for product to elute) to afford 5-methyl-3-[(2-{{2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl}amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxylic acid (32 mg, 0.061 mmol, 13.24 % yield) as a white solid. Many exchangeable protons absent/obstructed by water/DMSO: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.25 (s, 1 H), 8.05 (d, *J*=8.07 Hz, 1 H), 7.99 (s, 1 H), 7.44 (s, 1 H), 6.90 - 6.99 (m, 1 H), 6.87 (d, *J*=1.47 Hz, 1 H), 6.79 (d, *J*=9.90 Hz, 1 H), 6.23 (dd, *J*=3.48, 2.02 Hz, 1 H), 3.82 (s, 3 H), 2.58 - 2.74 (m, 2 H), 2.36 (s, 2 H), 1.86 (s, 2 H), 1.54 - 1.71 (m, 2 H), 0.90 (t, *J*=7.33 Hz, 3 H). ESIMS (M+H)⁺ = 521.

Example 20

5-methyl-3-[(2-{{2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl}amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



A suspension of 9-methyl-5-[(2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (305 mg, 0.464 mmol) in THF (100 mL)/27% ammonium hydroxide (100 mL) was heated in a sealed pressure vial at 90°C for 16 hours. Analysis by LCMS indicates only ca 10% conversion to the desired product, so the reaction was heated an additional 24 hours, at which time LCMS indicates ca 50% conversion to the desired product. The reaction was poured into THF/brine, and the organic layer was concentrated to a residue under reduced pressure, redissolved in THF (ca 20 mL) and added to a pressure vessel with fresh 27% ammonium hydroxide (200 mL) and heated for 24 hours at 90°C. Following cooling, LCMS analysis indicated >90% consumption of starting material. The reaction was poured into ethyl acetate/ saturated sodium chloride and the organic phase was dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The residue was dissolved in dioxane (8 mL) and added to a uW vial along with 2.0N NaOH (aq, 8mL). The mixture was heated at 120°C for 12 minutes, cooled, and poured into ethyl acetate/2.0N sodium hydroxide. The organic layer was washed with saturated aq. brine, dried over sodium sulfate, stripped onto celite, and purified by flash column chromatography to afford 5-methyl-3-[(2-{[2-(methyloxy)-4-(1-propyl-4-piperidinyl)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (92 mg, 0.177 mmol, 38% yield) as a pale yellow solid. Several protons obstructed by DMSO: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.43 (s, 1 H), 11.35 (s, 1 H), 8.16 (s, 1 H), 8.00 (d, *J*=8.43 Hz, 1 H), 7.57 (s, 1 H), 7.41 (s, 2 H), 6.94 - 7.00 (m, 1 H), 6.90 (d, *J*=1.83 Hz, 1 H), 6.81 (dd, *J*=8.25, 1.65 Hz, 1 H), 6.21 (dd,

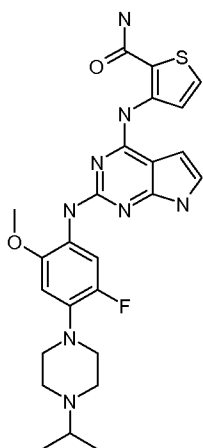
$J=3.48$, 2.02 Hz, 1 H), 3.84 (s, 3 H), 2.95 (d, $J=11.00$ Hz, 2 H), 2.16 - 2.29 (m, 2 H), 1.87 - 2.01 (m, 2 H), 1.57 - 1.82 (m, 4 H), 1.34 - 1.51 (m, 2 H), 0.85 (t, $J=7.33$ Hz, 3 H).

ESIMS (M+H)⁺ = 520.

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Example 21

3-[(2-{[5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



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A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (500 mg, 1.160 mmol) and [5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amine (310 mg, 1.160 mmol) in 2,2,2-trifluoroethanol (8 ml) was stirred at 90°C in a pressure tube until all solids had dissolved (45 minutes). The vial was cooled, and the mixture poured into dichloromethane/saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure. Trituration with diethyl ether affords 5-{[5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (535 mg, 0.808 mmol, 69.7 % yield) as a pale yellow solid. A suspension of 5-{[5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (535 mg, 0.808 mmol) in THF/27% ammonium hydroxide was stirred at 90°C in a pressure vessel for 16 hours. The reaction was cooled, diluted with ethyl

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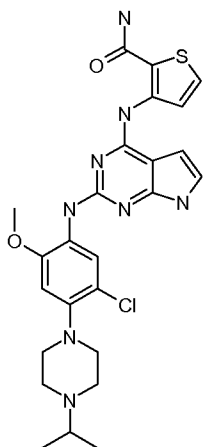
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acetate/THF/brine, and the organic layer was washed with additional brine, dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The resulting solids are suspended in 1,4-dioxane/2.0N sodium hydroxide, added to a uW vial, and warmed at 120°C for 12 minutes. The resulting biphasic solution was poured into ethyl acetate/THF/brine, and the organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by chromatography on SiO₂ to afford 3-[(2-{[5-fluoro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (97 mg, 0.185 mmol, 22.87 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.46 (s, 1 H), 11.40 (s, 1 H), 8.43 (d, *J*=5.50 Hz, 1 H), 8.18 (d, *J*=14.66 Hz, 1 H), 7.71 (d, *J*=5.50 Hz, 1 H), 7.60 (s, 1 H), 7.56 (s, 2 H), 6.95 - 7.05 (m, 1 H), 6.68 (d, *J*=8.07 Hz, 1 H), 6.25 (dd, *J*=3.67, 1.83 Hz, 1 H), 3.85 (s, 3 H), 2.92 - 3.04 (m, 4 H), 2.62 - 2.75 (m, 1 H), 2.54 - 2.61 (m, 4 H), 1.00 (d, *J*=6.60 Hz, 6 H). ESIMS (M+H)⁺ = 525.

Example 22

3-[(2-{[5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



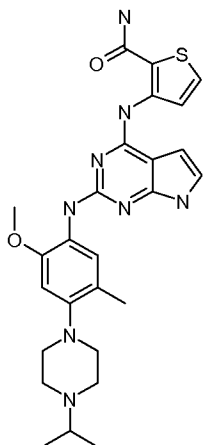
A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (381 mg, 0.884 mmol) and [5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amine (228 mg, 0.803 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed in a sealed tube for 55 minutes at 90°C. The solution was cooled and poured into dichloromethane/saturated sodium

bicarbonate. The organic layer was taken to a residue under reduced pressure and the solids triturated with diethyl ether to afford 5-[[5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (418 mg, 0.616 mmol, 77 % yield).

- 5 A suspension of 5-[[5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (418 mg, 0.616 mmol) in THF/27% ammonium hydroxide was warmed to 90°C in a sealed pressure tube for 16 hours. The reaction was subsequently cooled and poured into EtOAc/THF/Brine. The organic layer
- 10 was dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The solids were suspended in 1,4-dioxane/2.0N NaOH, added to a uW vial, and warmed at 120°C for 12 minutes. The reaction was cooled, poured into EtOAc/THF/brine, and the organic layer was washed with additional 2.0N sodium hydroxide, dried over sodium sulfate, filtered, stripped directly onto celite, and purified by column chromatography to
- 15 afford 3-[(2-[[5-chloro-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (102 mg, 0.189 mmol, 30.6 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.45 (s, 1 H), 11.42 (s, 1 H), 8.40 (d, *J*=5.13 Hz, 1 H), 8.28 (s, 1 H), 7.70 (d, *J*=5.50 Hz, 1 H), 7.61 (s, 1 H), 7.57 (s, 2 H), 6.98 - 7.03 (m, 1 H), 6.82 (s, 1 H), 6.25 (dd, *J*=3.48, 2.02 Hz, 1 H),
- 20 3.87 (s, 3 H), 2.97 (s, 4 H), 2.63 - 2.74 (m, 1 H), 2.60 (s, 4 H), 1.00 (d, *J*=6.60 Hz, 6 H). ESIMS (M+H)⁺ = 541.

Example 23

- 3-[(2-[[5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide
- 25

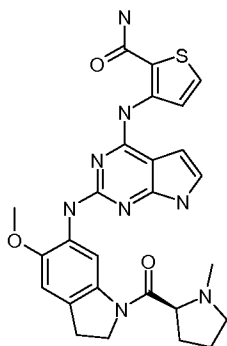


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (500 mg, 1.070 mmol) and [5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amine (423 mg, 1.605 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed at 80°C for 45 minutes in a sealed pressure tube. The reaction was cooled and poured into methylene chloride/saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure and the solids triturated with diethyl ether to afford 5-[[5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (478 mg, 0.727 mmol, 67.9 % yield) as a bright yellow solid. A suspension of 5-[[5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (478 mg, 0.727 mmol) in THF/27% ammonium hydroxide was warmed to 80°C in a sealed pressure vessel for 14 hours. The reaction was cooled and poured into ethyl acetate/saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, dissolved in 1,4-dioxane (8 mL) and added to a microwave vessel with 2.0N sodium hydroxide (8 mL). The resulting mixture was heated at 120°C for 12 minutes, cooled, and poured into ethyl acetate/THF/saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-[[5-methyl-4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (75 mg, 0.144 mmol, 20 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.37 (s, 1 H), 11.31 (s, 1 H), 8.37 (d, *J*=5.50 Hz, 1 H), 7.84 (s, 1

H), 7.67 (d, $J=5.50$ Hz, 1 H), 7.56 (s, 2 H), 7.47 (s, 1 H), 6.91 - 7.01 (m, 1 H), 6.72 (s, 1 H), 6.21 (dd, $J=3.48, 2.02$ Hz, 1 H), 3.79 (s, 3 H), 2.78 - 2.88 (m, 4 H), 2.63 - 2.72 (m, 1 H), 2.53 - 2.63 (m, 4 H), 2.19 (s, 3 H), 1.00 (d, $J=6.60$ Hz, 6 H). ESIMS ($M+H$)⁺ = 521.

5 Example 24

3-[(2-{[5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



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A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (500 mg, 1.070 mmol) and 5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1H-indol-6-amine (368 mg, 1.337 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed at 90°C in a sealed pressure vessel for 3 hours.

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The reaction was cooled and poured into saturated sodium bicarbonate/methylene chloride. The organic layer was taken to a residue under reduced pressure and triturated with diethyl ether, but the remaining 5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1H-indol-6-amine (368 mg, 1.337 mmol) could not be removed in this manner following repeated attempts. The crude solids were stripped onto celite (from methylene chloride) and purified by chromatography on silica gel to afford 5-{[5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (530 mg, 0.791 mmol, 74.0 % yield) as a pale yellow solid. A solution of 5-{[5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-

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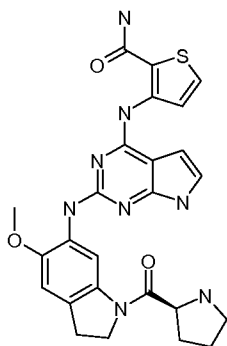
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e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (530 mg, 0.791 mmol) in 27% ammonium hydroxide (aq) (100 ml)/Tetrahydrofuran (THF) (50 ml) was stirred at 90°C in a sealed pressure flask for 14 hours. The flask was cooled, and its contents poured into

ethyl acetate/saturated sodium chloride. The organic layer was dried over sodium sulfate, taken to a residue under reduced pressure, and redissolved in tetrahydrofuran (15 mL) and methanol (5 mL). Sodium methoxide (427 mg, 7.91 mmol) was added and the resulting solution was stirred for 6 hours at 60°C. The reaction was cooled and poured into ethyl acetate, and washed successively with 2.0N sodium hydroxide and saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-{[5-(methoxy)-1-(1-methyl-L-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (125 mg, 0.235 mmol, 29.7 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.39 (s, 1 H), 11.28 (s, 1 H), 8.62 (s, 1 H), 8.38 (d, *J*=5.13 Hz, 1 H), 7.68 (s, 1 H), 7.59 (d, *J*=5.50 Hz, 1 H), 7.52 (s, 2 H), 6.89 - 6.99 (m, 2 H), 6.21 (dd, *J*=3.30, 1.83 Hz, 1 H), 4.04 - 4.30 (m, 2 H), 3.76 (s, 3 H), 3.08 - 3.24 (m, 3 H), 2.88 - 3.03 (m, 1 H), 2.24 (s, 3 H), 2.08 - 2.21 (m, 1 H), 1.67 - 1.83 (m, 4 H). ESIMS (M+H)⁺ = 533.

Example 25

3-[(2-{[5-(methoxy)-1-L-prolyl-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

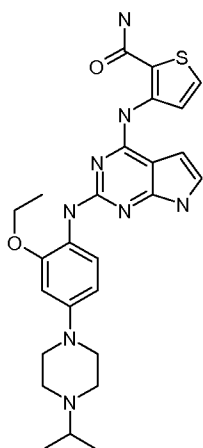


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrido[1,2-c]pyrimidin-7(3H)-one HCl (550 mg, 1.279 mmol) and 1,1-dimethylethyl (2S)-2-[[6-amino-5-(methoxy)-2,3-dihydro-1H-indol-1-yl]carbonyl]-1-pyrrolidinecarboxylate (532 mg, 1.471 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed at 90°C for 25 minutes. The solution was cooled, poured into DCM/saturated sodium bicarbonate and the organic layer dried over sodium sulfate, filtered, and taken

to a residue under reduced pressure. The solids were dissolved in DCM (ca 25 mL) and trifluoroacetic acid (0.986 ml, 12.79 mmol) was added. The solution was stirred for 3 hours and poured into saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, taken to a residue under reduced pressure, and purified by chromatography to afford 5-[[5-(methyloxy)-1-L-prolyl-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrido[1,2-c]pyrimidin-7(3H)-one (520 mg, 0.794 mmol, 62.1 % yield) as a bright yellow solid. A solution of 5-[[5-(methyloxy)-1-L-prolyl-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (518 mg, 0.790 mmol) in tetrahydrofuran (50 ml)/27% ammonium hydroxide (aq) (100 ml) was maintained at 80°C in a sealed pressure flask for 16 hours. The reaction was cooled, poured into ethyl acetate/saturated sodium chloride, and the organic layer was dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The solids were dissolved in 1,4-Dioxane (8 ml) and added to a microwave vial containing 2.0N sodium hydroxide (aq) (8 ml). The mixture was heated in a microwave reactor at 120°C for 12 minutes, cooled, and poured into THF/EtOAc/2.0N sodium hydroxide. The organic layer was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-[[5-(methyloxy)-1-L-prolyl-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (110 mg, 0.212 mmol, 26.9 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.39 (s, 1 H), 11.30 (s, 1 H), 8.60 (s, 1 H), 8.39 (d, *J*=5.50 Hz, 1 H), 7.67 (s, 1 H), 7.59 (d, *J*=5.50 Hz, 1 H), 7.53 (s, 2 H), 6.90 - 6.98 (m, 2 H), 6.21 (dd, *J*=3.30, 1.83 Hz, 1 H), 4.17 - 4.32 (m, 1 H), 4.00 - 4.14 (m, 1 H), 3.83 (dd, *J*=8.07, 5.87 Hz, 1 H), 3.77 (s, 3 H), 3.06 - 3.20 (m, 2 H), 2.87 - 3.01 (m, 1 H), 2.60 - 2.73 (m, 1 H), 1.94 - 2.12 (m, 1 H), 1.54 - 1.76 (m, 4 H). ESIMS (M+H)⁺ = 519.

Example 26

3-[[2-({2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]phenyl}amino)-1H-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-2-thiophenecarboxamide

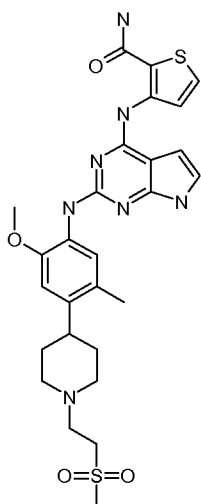


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (550 mg, 1.177 mmol) and {2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]phenyl}amine (372 mg, 1.412 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed to 80°C in a pressure tube for 1.5 hr. The solution was cooled and poured into dichloromethane/saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure and triturated with diethyl ether to afford 5-({2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]phenyl}amino)-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (556 mg, 0.845 mmol, 71.8 % yield) as a yellow solid. A suspension of 5-({2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]phenyl}amino)-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (0.556 g, 0.845 mmol) in tetrahydrofuran (50 ml)/27% ammonium hydroxide (aq) (100 ml) was maintained at 80°C in a sealed pressure vessel for 16 hours. The solution was cooled, diluted with ethyl acetate, and the organic layer was washed with saturated sodium chloride, dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The residue was redissolved in 1,4-dioxane (8 ml) and added to a microwave vial along with 2.0N NaOH (aq) (8 ml). The resulting mixture was heated at 120°C for 12 minutes in a microwave reactor with rapid stirring, cooled, and poured into ethylacetate/2.0N sodium hydroxide. The organic layer was washed with saturated sodium chloride, dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-{[2-({2-(ethyloxy)-4-[4-(1-methylethyl)-1-piperazinyl]phenyl}amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-2-thiophenecarboxamide (115 mg, 0.221 mmol, 26.1 % yield) as a pale yellow solid. ¹H

NMR (400 MHz, DMSO- d_6) δ ppm 11.31 (s, 1 H), 11.26 (s, 1 H), 8.33 (d, $J=5.31$ Hz, 1 H), 7.83 (d, $J=8.79$ Hz, 1 H), 7.64 (d, $J=5.49$ Hz, 1 H), 7.52 (s, 2 H), 7.39 (s, 1 H), 6.85 - 6.95 (m, 1 H), 6.58 (d, $J=2.56$ Hz, 1 H), 6.44 (dd, $J=8.88, 2.29$ Hz, 1 H), 6.18 (dd, $J=3.30, 1.83$ Hz, 1 H), 4.04 (q, $J=6.96$ Hz, 2 H), 2.97 - 3.08 (m, 4 H), 2.58 - 2.70 (m, 1 H), 2.48 - 2.58 (m, 4 H), 1.28 (t, $J=6.96$ Hz, 3 H), 0.97 (d, $J=6.41$ Hz, 6 H). ESIMS (M+H)⁺ = 521.

Example 27

3-({2-[(5-methyl-2-(methyloxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



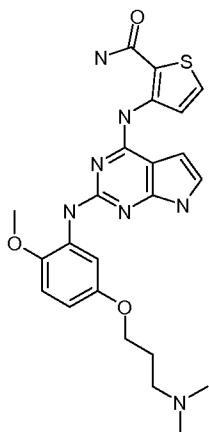
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A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one HCl (515 mg, 1.102 mmol) and (5-methyl-2-(methyloxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidinyl}phenyl)amine (414 mg, 1.267 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed in a sealed pressure tube at 90°C for 55 minutes. The solution was cooled and poured into CH₂Cl₂/saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure, triturated with diethyl ether, and the solids collected by vacuum filtration to afford 5-[(5-methyl-2-(methyloxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one

(565 mg, 0.784 mmol, 71.1 % yield) as a bright yellow solid. A solution of 5-[(5-methyl-2-(methyloxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidiny}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (565 mg, 0.784 mmol) in tetrahydrofuran (50 ml)/27% ammonium hydroxide (aq) (100 ml) was warmed to 90°C in a sealed pressure tube for 16 hours. The tube was cooled, and the reaction poured into ethyl acetate/saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The residue was suspended in 1,4-dioxane (8 ml) and added to a microwave-safe vial along with 2.0N NaOH (aq) (8 ml). The mixture was warmed in a microwave reactor at 120°C for 12 minutes, cooled, and poured into ethyl acetate/THF/2.0N sodium hydroxide. The organic layer was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-({2-[(5-methyl-2-(methyloxy)-4-{1-[2-(methylsulfonyl)ethyl]-4-piperidiny}phenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (85 mg, 0.146 mmol, 18.58 % yield) as a yellow solid. Several Protons obstructed by H₂O or DMSO: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.35 (s, 1 H), 11.29 - 11.33 (m, 1 H), 8.35 (d, *J*=5.31 Hz, 1 H), 7.89 (s, 1 H), 7.66 (d, *J*=5.31 Hz, 1 H), 7.53 (s, 2 H), 7.47 (s, 1 H), 6.91 - 6.97 (m, 1 H), 6.78 (s, 1 H), 6.15 - 6.25 (m, 1 H), 3.78 (s, 3 H), 3.02 (s, 3 H), 2.99 (d, *J*=10.44 Hz, 2 H), 2.71 (t, *J*=6.87 Hz, 2 H), 2.55 - 2.66 (m, 1 H), 2.22 (s, 3 H), 1.98 - 2.15 (m, 2 H), 1.58 - 1.70 (m, 4 H). ESIMS (M+H)⁺ = 584.

Example 28

3-[(2-{[5-{[3-(dimethylamino)propyl]oxy}-2-(methyloxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

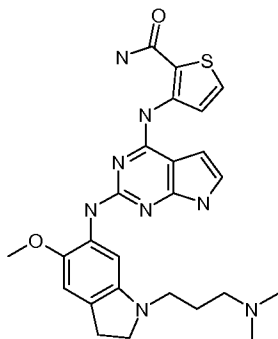


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (600 mg, 1.284 mmol) and (3-
 5 {[(3-amino-4-(methoxy)phenyl]oxy}propyl)dimethylamine (432 mg, 1.926 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed to 80°C for 3 hours, cooled, and poured into saturated sodium bicarbonate/dichloromethane. The organic layer was taken to a residue under reduced pressure and triturated with diethyl ether to afford 5-{[5-{[3-(dimethylamino)propyl]oxy}-2-(methoxy)phenyl]amino}-3-[(4-
 10 methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (465 mg, 0.752 mmol, 58.5 % yield) with roughly 70% purity, sufficient for use in the next step. A solution of 5-{[5-{[3-(dimethylamino)propyl]oxy}-2-(methoxy)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (465 mg, 0.752 mmol) in tetrahydrofuran (75 ml)/27% ammonium hydroxide (200
 15 ml) was maintained at 80°C in a sealed pressure vial for 16 hours. The reaction was allowed to cool, diluted with ethyl acetate, and washed twice with saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-({2-([5-([3-(dimethylamino)propyl]oxy)-2-(methoxy)phenyl]amino)-7-[(4-methylphenyl)sulfonyl]-7H-
 20 pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (114 mg, 0.179 mmol, 23.86 % yield) as a pale yellow solid with >90% purity. A solution of 3-({2-([5-([3-(dimethylamino)propyl]oxy)-2-(methoxy)phenyl]amino)-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (110 mg, 0.173 mmol) in 1,4-dioxane (8 ml) was treated with 2.0N sodium hydroxide (aq) (8.00 ml) and warmed
 25 under microwave heating at 120°C for 12 minutes. LCMS at this stage indicates

additional starting material remains, so the vial was resubjected to 120°C in a microwave reactor for an additional 10 minutes. The solution was cooled and poured into ethyl acetate/THF/2.0N sodium hydroxide. The organic layer was washed with saturated sodium chloride, dried over sodium sulfate, filtered, stripped onto celite, and the residue purified by column chromatography to afford 3-[(2-[[5-[[3-(dimethylamino)propyl]oxy]-2-(methoxy)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (57 mg, 0.118 mmol, 68.4 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.49 (s, 1 H), 11.40 (s, 1 H), 8.39 (d, *J*=5.49 Hz, 1 H), 8.06 (d, *J*=2.93 Hz, 1 H), 7.69 (d, *J*=5.49 Hz, 1 H), 7.57 (s, 1 H), 7.54 (s, 2 H), 6.97 - 7.05 (m, 1 H), 6.86 (d, *J*=8.79 Hz, 1 H), 6.42 (dd, *J*=8.88, 3.02 Hz, 1 H), 6.24 (dd, *J*=3.11, 1.65 Hz, 1 H), 3.89 (t, *J*=6.41 Hz, 2 H), 3.79 (s, 3 H), 2.30 (t, *J*=7.14 Hz, 2 H), 2.09 (s, 6 H), 1.69 - 1.87 (m, 2 H). ESIMS (M+H)⁺ = 482.

Example 29

3-[(2-[[1-[3-(dimethylamino)propyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

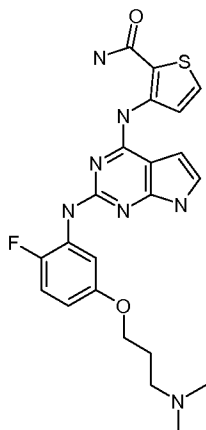


A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (600 mg, 1.284 mmol) and 1-[3-(dimethylamino)propyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (320 mg, 1.284 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed to 80°C in a sealed pressure tube for 3 hours. The solution was cooled and poured into saturated sodium bicarbonate/methylene chloride. The organic layer was taken to a residue under reduced pressure and triturated with diethyl ether but the solids remain impure. All solids and filtrates were combined, dissolved in methylene chloride, stripped onto celite,

and purified by column chromatography to afford 5-([1-[3-(dimethylamino)propyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino)-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (560 mg, 0.870 mmol, 67.8 % yield) with >95% purity as a bright yellow solid. A solution of 5-([1-[3-(dimethylamino)propyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino)-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (560 mg, 0.870 mmol) in tetrahydrofuran (THF) (75 ml)/27% ammonium hydroxide (200 ml) was warmed in a sealed pressure tube for 16 hrs. at 80°C. The reaction was cooled and poured into ethyl acetate/brine. The organic layer was washed with brine, dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The solids were dissolved in 1,4-dioxane (8 ml) and placed in a uW vial along with 2.0N sodium hydroxide (aq) (8 ml). The suspension was warmed at 120°C for 12 minutes in a microwave reactor with rapid stirring, cooled, and poured into THF/EtOAc/2.0N sodium hydroxide. The organic layer was washed with brine, dried over sodium sulfate, filtered, stripped onto celite, and purified by flash column chromatography to afford 3-([2-([1-[3-(dimethylamino)propyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl]amino)-2-thiophenecarboxamide (41 mg, 0.081 mmol, 9.30 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.42 (s, 1 H), 11.33 - 11.39 (m, 1 H), 8.41 (d, *J*=5.42 Hz, 1 H), 7.69 (d, *J*=5.42 Hz, 1 H), 7.57 (s, 2 H), 7.50 (s, 2 H), 6.99 - 7.04 (m, 1 H), 6.84 (s, 1 H), 6.25 (s, 1 H), 3.75 (s, 3 H), 3.22 (t, *J*=8.13 Hz, 2 H), 2.91 - 2.99 (m, 2 H), 2.84 (t, *J*=7.12 Hz, 2 H), 2.25 (t, *J*=7.02 Hz, 2 H), 2.10 (s, 6 H), 1.56 - 1.75 (m, 2 H). ESIMS (M+H)⁺ = 507.

Example 30

3-([2-([5-([3-(dimethylamino)propyl]oxy)-2-fluorophenyl]amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl]amino)-2-thiophenecarboxamide



A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (600 mg, 1.284 mmol) and {3-[(3-amino-4-fluorophenyl)oxy]propyl}dimethylamine (409 mg, 1.926 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed at 80°C for 3 hours, cooled, and poured into saturated sodium bicarbonate/methylene chloride. The organic layer was taken to a residue under reduced pressure and the solids were triturated with diethyl ether to afford 5-[(5-{[3-(dimethylamino)propyl]oxy}-2-fluorophenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (565 mg, 0.931 mmol, 72.5 % yield) as a yellow solid. A solution of 5-[(5-{[3-(dimethylamino)propyl]oxy}-2-fluorophenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (565 mg, 0.931 mmol) in tetrahydrofuran (75 ml)/27% Ammonium Hydroxide (200 ml) was warmed in a sealed pressure tube for 16 hrs. at 80°C. The reaction was cooled and poured into ethyl acetate/brine. The organic layer was washed with brine, dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The solids were dissolved in 1,4-dioxane (8 ml) and placed in a microwave-safe vial along with 2.0N sodium hydroxide (aq) (8 ml). The suspension was warmed at 120°C for 12 minutes in a microwave reactor with rapid stirring, cooled, and poured into THF/EtOAc/2.0N sodium hydroxide. The organic layer was washed with brine, dried over sodium sulfate, filtered, stripped onto celite, and purified by flash column chromatography to afford 3-({2-[(5-{[3-(dimethylamino)propyl]oxy}-2-fluorophenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (165 mg, 0.351 mmol, 37.7 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.44 (s, 2 H), 8.51 (d, *J*=5.49 Hz, 1 H),

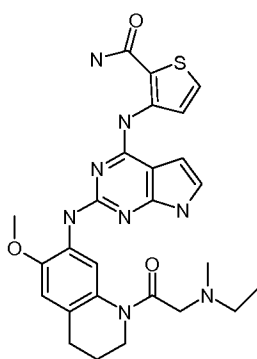
8.40 (s, 1 H), 7.69 (dd, $J=6.87$, 3.02 Hz, 1 H), 7.62 (d, $J=5.49$ Hz, 1 H), 7.55 (s, 2 H), 7.07 (dd, $J=10.71$, 9.06 Hz, 1 H), 6.96 - 7.01 (m, 1 H), 6.46 - 6.55 (m, 1 H), 6.22 (dd, $J=3.30$, 1.65 Hz, 1 H), 3.91 (t, $J=6.41$ Hz, 2 H), 2.30 (t, $J=7.23$ Hz, 2 H), 2.09 (s, 6 H), 1.72 - 1.87 (m, 2 H). ESIMS (M+H)⁺ = 470.

5

Example 31

3-[(2-{[1-(*N*-ethyl-*N*-methylglycyl)-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

10



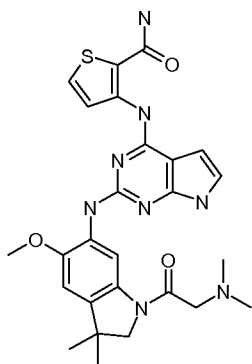
A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-

15 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (600 mg, 1.284 mmol) and 1-
{[ethyl(methyl)amino]acetyl}-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinamine (356 mg,
1.284 mmol) in 2,2,2-trifluoroethanol (8 ml) was warmed to 80°C in a sealed pressure
tube for 3 hours. The solution was cooled, poured into saturated sodium bicarbonate,
and diluted with methylene chloride. The organic layer was dried over sodium sulfate,
20 filtered, taken to a residue under reduced pressure, and the resulting solids triturated
with diethyl ether to afford 5-{[1-(*N*-ethyl-*N*-methylglycyl)-6-(methyloxy)-1,2,3,4-
tetrahydro-7-quinolinyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (605 mg, 0.901 mmol, 70% yield) as
a pale yellow solid. A suspension of 5-{[1-(*N*-ethyl-*N*-methylglycyl)-6-(methyloxy)-
25 1,2,3,4-tetrahydro-7-quinolinyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (605 mg, 0.901 mmol) in
tetrahydrofuran (50 ml)/27% ammonium hydroxide (150 ml) was warmed to 90°C in a

sealed pressure tube for 16 hours. The solution was cooled and poured into ethyl acetate/saturated sodium chloride. The organic layer was dried over sodium sulfate, taken to a residue under reduced pressure, dissolved in 1,4-dioxane (8 ml), and added to a microwave-safe vial with 2.0N NaOH (aq) (8 ml). The vial was warmed in a microwave reactor for 12 minutes at 120°C, cooled, and poured into saturated sodium bicarbonate/ethyl acetate/THF. The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-[[1-(N-ethyl-N-methylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (125 mg, 0.234 mmol, 26% yield) as a pale yellow solid. Several protons obstructed by DMSO/H₂O: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.37 (s, 2 H), 8.35 (s, 1 H), 8.34 (s, 1 H), 7.63 (d, *J*=5.49 Hz, 1 H), 7.59 (s, 1 H), 7.53 (s, 2 H), 6.97 (s, 1 H), 6.80 (s, 1 H), 6.18 - 6.22 (m, 1 H), 3.80 (s, 3 H), 3.67 (t, *J*=5.22 Hz, 2 H), 2.65 (s, 2 H), 2.28 (s, 2 H), 2.07 (s, 3 H), 1.76 - 1.91 (m, 2 H), 0.75 (s, 3 H). ESIMS (M+H)⁺ = 535.

Example 32

3-[(2-[[1-(*N,N*-dimethylglycyl)-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

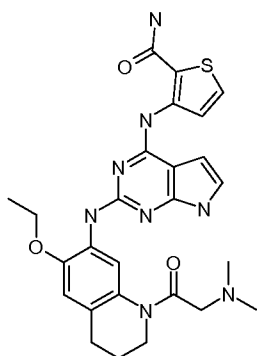


A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one HCl (550 mg, 1.177 mmol) and 1-[(dimethylamino)acetyl]-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (375 mg, 1.353 mmol) in THF (8 ml) was warmed in a sealed pressure tube for 16 hours. The reaction was cooled, concentrated, suspended in dichloromethane (ca 25 mL) and

washed with saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure and triturated with diethyl ether to afford 5-[[1-(N,N-dimethylglycyl)-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (0.627 g, 0.933 mmol, 79 % yield) as a light yellow solid. A solution of 5-[[1-(N,N-dimethylglycyl)-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (0.620 g, 0.923 mmol) in THF (40 ml) and 27% ammonium hydroxide (100 ml) was warmed at 80°C in a pressure tube for 16 hours. The reaction was cooled and poured into ethyl acetate/saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The residue was dissolved in 1,4-dioxane (8 ml) and added to a microwave-safe vial along with 2.0N NaOH (aq) (40.0 ml). The contents were warmed at 120°C for 12 minutes in a microwave reactor, cooled, and poured into ethyl acetate/THF/saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography. The solids collected after concentration of the column fractions contained 1-[(dimethylamino)acetyl]-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1H-indol-6-amine. All solids were triturated with methylenechloride/diethyl ether to afford pure 3-[(2-[[1-(N,N-dimethylglycyl)-3,3-dimethyl-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.096 g, 0.180 mmol, 19% yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.39 (s, 1 H), 11.28 (s, 1 H), 8.51 (s, 1 H), 8.37 (d, *J*=5.82 Hz, 1 H), 7.70 (s, 1 H), 7.57 (d, *J*=5.02 Hz, 1 H), 7.52 (s, 2 H), 6.97 (s, 1 H), 6.93 - 6.97 (m, 1 H), 6.22 (dd, *J*=3.51, 1.50 Hz, 1 H), 3.94 (s, 2 H), 3.80 (s, 3 H), 3.17 (s, 2 H), 2.24 (s, 6 H), 1.33 (s, 6 H). ESIMS (M+H)⁺ = 535.

Example 33

3-[(2-[[1-(N,N-dimethylglycyl)-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

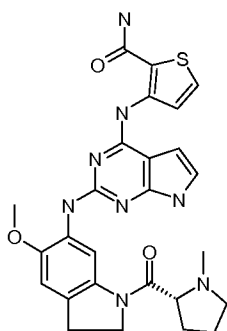


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (550 mg, 1.177 mmol) and 1-[(dimethylamino)acetyl]-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinamine (326 mg, 1.177 mmol) in THF (8 ml) was warmed in a pressure vessel at 75°C for 16 hours. The volatiles were removed and the solids partitioned between dichloromethane and saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure and solids triturated with diethyl ether to afford 5-[[1-(N,N-dimethylglycyl)-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (0.640 g, 0.953 mmol, 81 % yield) as a yellow solid. A solution of 5-[[1-(N,N-dimethylglycyl)-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (640 mg, 0.953 mmol) in THF (50 ml)/27% ammonium hydroxide (100 ml) was maintained at 80°C in a sealed pressure flask for 16 hours. The reaction was cooled, diluted with ethyl acetate/THF/saturated sodium chloride (aq) and the organic layer was dried over sodium sulfate and taken to a residue under reduced pressure. The residue was dissolved in 1,4-dioxane (8 ml), 2.0N NaOH (aq) (8 ml) was added, and the mixture was stirred rapidly under microwave heating at 120°C for 12 minutes. The reaction was cooled and poured into ethyl acetate/saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-[[1-(N,N-dimethylglycyl)-6-(ethoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.075 g, 0.140 mmol, 14.73 % yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.41 (s, 2 H), 8.39 (s, 1 H), 8.34 (d, *J*=5.42 Hz, 1 H), 7.67 (d, *J*=5.42 Hz, 1 H), 7.54 - 7.56 (m, 1 H), 7.55 (s, 2 H), 6.95 - 7.06 (m, 1 H), 6.83 (s, 1 H), 6.26 (s, 1 H), 4.10 (q, *J*=7.02 Hz, 2 H), 3.64 - 3.77 (m,

2 H), 3.23 (s, 2 H), 2.62 - 2.73 (m, 2 H), 2.54 (s, 6 H), 1.79 - 1.94 (m, 2 H), 1.37 (t, $J=6.82$ Hz, 3 H). ESIMS (M+H)⁺ = 535.

Example 34

5 3-[(2-{[5-(methyloxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

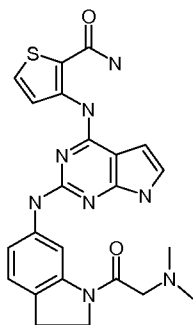


10 A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (600 mg, 1.284 mmol) and 5-(methyloxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1H-indol-6-amine (353 mg, 1.284 mmol) in 2,2,2-trifluoroethanol (50 ml) was warmed to 80°C and maintained for 2 hours. The solution was cooled, poured into dichloromethane, and washed with saturated sodium bicarbonate. The organic layer was taken to a residue under reduced pressure and
15 purified via trituration with diethyl ether to afford 5-{[5-(methyloxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (0.410 g, 0.612 mmol, 48% yield) as a dark yellow solid. A solution of 5-{[5-(methyloxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (410 mg, 0.612 mmol) in tetrahydrofuran (50 ml)/27% ammonium hydroxide (50.0 ml) was maintained at 80°C in a pressure vessel for 16 hours. The vessel was cooled, diluted with tetrahydrofuran/ethyl acetate/saturated sodium chloride, and the organic layer was washed with additional water. The organic layer was dried
20 over sodium sulfate, filtered, taken to a residue under reduced pressure, and resuspended in 1,4-dioxane (8 ml)/2.0N NaOH (aq) (8 ml). The suspension was warmed at 120°C for 12 minutes in a microwave reactor, cooled, and poured into ethyl

acetate/tetrahydrofuran, saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-{[5-(methoxy)-1-(1-methyl-D-prolyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.090 g, 0.169 mmol, 28% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.40 (s, 1 H), 11.29 (s, 1 H), 8.63 (s, 1 H), 8.39 (d, *J*=5.42 Hz, 1 H), 7.68 (s, 1 H), 7.60 (d, *J*=5.22 Hz, 1 H), 7.54 (s, 2 H), 6.93 - 6.99 (m, 2 H), 6.23 (s, 1 H), 4.09 - 4.26 (m, 2 H), 3.78 (s, 3 H), 3.18 - 3.24 (m, 1 H), 3.09 - 3.17 (m, 2 H), 2.93 - 3.02 (m, 1 H), 2.25 (s, 3 H), 2.11 - 2.21 (m, 1 H), 1.66 - 1.85 (m, 4 H). ESIMS (M+H)⁺ = 533.

Example 35

3-[(2-{[1-(*N,N*-dimethylglycyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

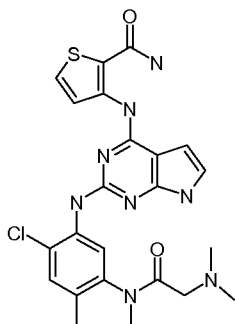


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (600 mg, 1.284 mmol) and 1-[(dimethylamino)acetyl]-2,3-dihydro-1H-indol-6-amine (282 mg, 1.284 mmol) was maintained at 70°C in tetrahydrofuran (20 ml) in a pressure tube for 16 hours. The reaction was cooled, opened, concentrated under reduced pressure, and redissolved in methylene chloride/2,2,2-trifluoroethanol (ca 15 mL). Saturated sodium bicarbonate was added and all solids dissolve. The organic layer was dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and triturated with diethyl ether to afford 5-[(1-(*N,N*-dimethylglycyl)-2,3-dihydro-1H-indol-6-yl]amino)-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one

(0.600 g, 0.978 mmol, 76 % yield) as a yellow solid. A solution of 5-{{1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl}amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one (0.600 g, 0.978 mmol) in tetrahydrofuran (40 ml)/27% ammonium hydroxide (aq) (150 ml) was maintained at 80°C in a sealed pressure tube for 12 hours. The solution was cooled and poured into ethyl acetate/saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-{{2-{{1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl}amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide of sufficient purity for use in the next transformation. The solid was dissolved in 1,4-dioxane (8 ml)/2.0*N* NaOH (aq) (40.0 ml) and maintained at 120°C for 12 minutes under microwave heating. The solution was cooled, poured into ethyl acetate/THF/saturated sodium chloride (aq) and the organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-{{1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl}amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.075 g, 0.157 mmol, 16% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.46 (s, 1 H), 11.34 - 11.39 (m, 1 H), 9.09 (s, 1 H), 8.74 (d, *J*=5.02 Hz, 1 H), 8.22 (s, 1 H), 7.88 (d, *J*=7.83 Hz, 1 H), 7.69 (d, *J*=5.42 Hz, 1 H), 7.55 (s, 2 H), 7.12 (d, *J*=8.23 Hz, 1 H), 6.99 (dd, *J*=3.31, 2.51 Hz, 1 H), 6.24 (dd, *J*=3.51, 1.91 Hz, 1 H), 4.16 (t, *J*=8.13 Hz, 2 H), 3.23 (s, 2 H), 3.07 (t, *J*=9.13 Hz, 2 H), 2.29 (s, 6 H). ESIMS (*M*+*H*)⁺ = 477.

Example 36

3-[(2-{{5-chloro-1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl}amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

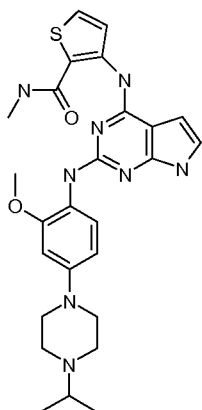


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl (800 mg, 1.712 mmol) and 5-chloro-1-[(dimethylamino)acetyl]-2,3-dihydro-1H-indol-6-amine (499 mg, 1.969 mmol) in tetrahydrofuran (20 ml) was maintained at 80°C for 24 hours. The solution was cooled, all solvents evaporated, and the solids were partitioned between methylene chloride/trifluoroethanol/saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, taken to a solid under reduced pressure, and the solids were triturated with diethyl ether to afford 5-[[5-chloro-1-(N,N-dimethylglycyl)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (0.920 g, 1.419 mmol, 83 % yield) as a green-yellow solid. A solution of 5-[[5-chloro-1-(N,N-dimethylglycyl)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (770 mg, 1.188 mmol) in tetrahydrofuran (40 ml)/27% ammonium hydroxide (aq) (150 ml) was maintained in a pressure tube at 80°C for 12 hours. The solution was cooled, opened cautiously, and poured into ethyl acetate/saturated sodium chloride (aq). The organic layer was dried over sodium sulfate, taken to a residue under reduced pressure, dissolved in 1,4-dioxane (8 ml), and added to a microwave vial with 2.0N NaOH (aq) (40.0 ml). The vial was maintained under microwave heating at 120°C for 12 minutes, cooled, poured into ethyl acetate/tetrahydrofuran/saturated sodium bicarbonate, and the organic layer was dried over sodium sulfate, filtered, stripped onto celite, and purified by column chromatography to afford 3-[(2-[[5-chloro-1-(N,N-dimethylglycyl)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.040 g, 0.078 mmol, 7% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.42 (s, 1 H), 11.28 - 11.35 (m, 1 H), 8.37 (s, 1 H), 8.28 - 8.35 (m, 2 H), 7.56 - 7.60 (m, 1 H), 7.55 (s, 2 H), 7.35 (s, 1 H), 6.97 (s, 1 H), 6.23 (s, 1 H), 4.21 (t, *J*=8.63 Hz, 2 H), 3.29 (s, 2 H), 3.08 - 3.20 (m, 2 H), 2.28 (s, 6 H). ESIMS (M+H)⁺ = 511.

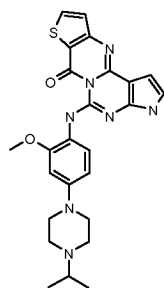
Example 37:

***N*-methyl-3-[(2-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-1H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**

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Step A/Intermediate C7: 5-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one



A slurry of 4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)aniline (3.18 g, 12.76 mmol) and 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (5.5 g, 12.76 mmol) in 2,2,2-trifluoroethanol (200 mL) was heated at 80 °C for 1.5 h, then was allowed to cool to rt. The resulting mixture was diluted with EtOAc (200 mL), washed with a saturated NaHCO₃ solution (100 mL) and a saturated NaCl solution (100 mL). The aqueous layers were back extracted with EtOAc (200 mL). The organic layers were combined and concentrated. The residue was triturated using Et₂O to give 5-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one as a yellow solid. ESIMS (M+H)⁺ = 644.32.

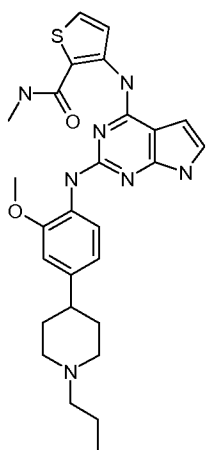
Step B/Example 37: *N*-methyl-3-[(2-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-

thiophenecarboxamide

A mixture of 5-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one (150 mg, 0.23mmol) and methylamine 2.0M/THF (11.65ml, 23.30 mmol)) in tetrahydrofuran (THF) (20ml) was stirred at rt for three days.. Next, the crude reaction was adsorbed on silica gel and purified by LC (DCM to 10% MeOH/DCM). ESIMS (M+H)⁺ = 675. The isolated amide was redissolved in 1,4-dioxane (10 ml), potassium hydroxide (8.72 ml, 8.72 mmol) was added and the reaction was heated in the microwave at 120°C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford *N*-methyl-3-[(2-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methyloxy)phenyl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.035g, 30% over two steps). ESIMS (M+H)⁺ = 521. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.00 (d, *J*=6.23 Hz, 6 H) 2.54 - 2.60 (m, 4 H) 2.64 - 2.72 (m, 1 H) 2.77 (d, *J*=4.77 Hz, 3 H) 3.05 - 3.13 (m, 4 H) 3.79 (s, 3 H) 6.23 (dd, *J*=3.48, 2.02 Hz, 1 H) 6.46 (dd, *J*=8.80, 2.57 Hz, 1 H) 6.61 (d, *J*=2.57 Hz, 1 H) 6.88 - 6.97 (m, 1 H) 7.49 (s, 1 H) 7.63 (d, *J*=5.50 Hz, 1 H) 7.81 (d, *J*=8.80 Hz, 1 H) 8.06 - 8.14 (m, 1 H) 8.40 (d, *J*=5.13 Hz, 1 H) 11.26 (s, 1 H) 11.28 - 11.30 (m, 1 H).

Example 38:

***N*-methyl-3-[(2-[[2-(methyloxy)-4-(1-propyl-4-piperidiny]phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**



A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one hydrochloride (109 mg, 0.23 mmol) and [2-(methyloxy)-4-(1-propyl-4-piperidiny)phenyl]amine

(64 mg, 0.26 mmol) in trifluoroethanol (22 ml) was heated at 90°C for 3 hrs. The

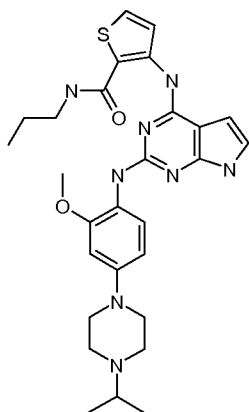
5 reaction was concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum prior to next step. ESIMS (M+H)⁺ = 643. The solids were then added to tetrahydrofuran (50 ml) followed by methylamine 2.0M/THF (11.67 mL, 23.34 mmol) and the resulting mixture was stirred at rt for 72 hrs. Next, the crude reaction was adsorbed to silica gel and purified by LC (DCM to 5%

10 MeOH/DCM over 30 min). ESIMS (M+H)⁺ = 674. The isolated amide was dissolved in 1,4-dioxane (10 ml), potassium hydroxide (1.039 mL, 1.039 mmol) was added and the reaction was heated in the microwave at 120°C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford the *N*-methyl-3-[(2-{[2-(methyloxy)-4-(1-propyl-4-piperidiny)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.018 g, 15% over three steps).

15 ESIMS (M+H)⁺ = 520. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.86 (t, J=7.33 Hz, 3 H) 1.49-1.93 (s, 6 H) 2.74 (d, J=4.40 Hz, 4 H) 3.82 (s, 3 H) 6.22-6.25 (m, 1 H) 6.76 (d, J=8.24 Hz, 1 H) 6.85 (s, 1 H) 6.93 - 6.99 (m, 1 H) 7.58 (s, 1 H) 7.65 (d, J=5.49 Hz, 1 H) 8.06 - 8.14 (m, 2 H) 8.37 (d, J=5.31 Hz, 1 H) 11.27 (s, 1 H) 11.35 (s, 1 H)

20 **Example 39:**

3-[(2-{[4-[4-(1-methylethyl)-1-piperaziny]l]-2-(methyloxy)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-propyl-2-thiophenecarboxamide

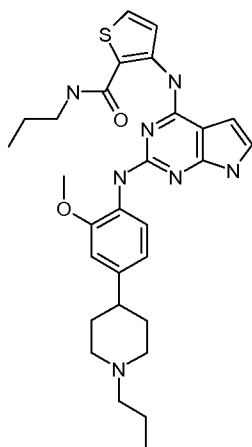


A mixture of 5-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-(methoxy)phenyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one (200 mg, 0.311 mmol) and propylamine (2.55 mL, 31.1 mmol) in tetrahydrofuran (THF) (20ml) was stirred at rt for 36 hrs. Next, the crude reaction was adsorbed to silica gel and purified by LC (DCM to 5% MeOH/DCM). ESIMS (M+H)⁺ = 703. The isolated pure amide was redissolved in 1,4-dioxane (10 ml), potassium hydroxide (2.276 mL, 2.276 mmol) was added and the reaction was heated in the microwave at 120C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[4-[4-(1-methylethyl)-1-piperazinyl]-2-

(methoxy)phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-propyl-2-thiophenecarboxamide (0.035g, 22% over two steps). ESIMS (M+H)⁺ = 549. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.84 (t, *J*=7.42 Hz, 3 H) 0.97 (d, *J*=6.59 Hz, 6 H) 1.45 - 1.54 (m, 2 H) 2.51 - 2.57 (m, 4 H) 2.59 - 2.67 (m, 1 H) 3.03 - 3.09 (m, 4 H) 3.13 - 3.21 (m, 2 H) 3.76 (s, 3 H) 6.18-6.21 (m, 1 H) 6.44 (dd, *J*=8.79, 2.20 Hz, 1 H) 6.57-6.60 (m, 1 H) 6.88-6.91 (m, 1 H) 7.45 (s, 1 H) 7.61 (d, *J*=5.49 Hz, 1 H) 7.79 (d, *J*=8.79 Hz, 1 H) 8.13 (t, *J*=5.77 Hz, 1 H) 8.37 (d, *J*=5.49 Hz, 1 H) 11.22 (s, 1 H) 11.25 (s, 1 H).

Example 40:

3-[(2-[[2-(methoxy)-4-(1-propyl-4-piperidiny]phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-propyl-2-thiophenecarboxamide



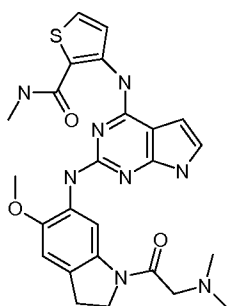
A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one hydrochloride (137 mg, 0.29 mmol) and [2-(methoxy)-4-(1-propyl-4-piperidiny]phenyl]amine

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(80 mg, 0.32 mmol) in 2,2,2-trifluoroethanol (27 ml) was heated at 90°C for 3 hrs. The reaction was concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum prior to next step. ESIMS (M+H)⁺ = 643. The solids were then added to tetrahydrofuran (50 ml) followed by propylamine (2.56 mL, 31.1 mmol) and the resulting mixture was stirred at rt for 36 hrs. Next, the crude reaction was adsorbed to silica gel and purified by LC (DCM to 5% MeOH/DCM). ESIMS (M+H)⁺ = 702. The isolated amide was redissolved in 1,4-Dioxane (10 ml), potassium hydroxide (1.995 mL, 1.995 mmol) was added and the reaction was heated in the microwave at 120°C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[2-(methoxy)-4-(1-propyl-4-piperidinyl)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-propyl-2-thiophenecarboxamide (0.035 g, 22% over three steps). ESIMS (M+H)⁺ = 548. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.81 - 0.91 (m, 6 H) 1.47 - 2.03 (m, 9 H) 2.90-3.05 (m, 2H) 3.13 - 3.22 (m, 2 H) 3.82 (s, 3 H) 6.21 - 6.27 (m, 1 H) 6.77 (d, *J*=8.06 Hz, 1 H) 6.85 (s, 1 H) 6.94 - 6.98 (m, 1 H) 7.58 (s, 1 H) 7.65 (d, *J*=5.49 Hz, 1 H) 8.10 - 8.21 (m, 2 H) 8.36 (d, *J*=5.31 Hz, 1 H) 11.26 (s, 1 H) 11.35 (s, 1 H).

Example 41:

3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide

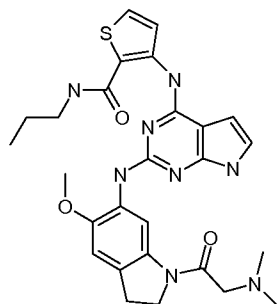


A mixture of 5-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one (300 mg, 0.44mmol, generated as in Example 2) and methylamine 2.0M/THF (11.65 mL, 23.30 mmol) in tetrahydrofuran (THF) (20ml) was stirred at rt for three days.. Next, the crude reaction was adsorbed to silica gel and purified by LC (DCM to 5%

MeOH/DCM). ESIMS (M+H)⁺ = 675. The isolated pure amide was redissolved in 1,4-dioxane (10 ml), potassium hydroxide (4.08 mL, 4.08 mmol) was added and the reaction was heated in the microwave at 120°C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-
 5 d]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (0.055g, 24% over two steps). ESIMS (M+H)⁺ = 521. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.23 (s, 6 H) 2.76 (d, *J*=4.77 Hz, 3 H) 3.11 (t, *J*=8.07 Hz, 2 H) 3.16 (s, 2 H) 3.76 (s, 3 H) 4.16 (t, *J*=8.43 Hz, 2 H) 6.23-6.26 (m, 1 H) 6.91 - 6.96 (m, 2 H) 7.57 (d, *J*=5.50 Hz, 1 H) 7.68 (s, 1 H) 8.08-
 10 8.11 (m, 1 H) 8.38 (d, *J*=5.50 Hz, 1 H) 8.56 (s, 1 H) 11.27 (s, 1 H) 11.30 (s, 1 H).

Example 42:

3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-propyl-2-thiophenecarboxamide



A mixture of 5-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-
 20 one (300 mg, 0.44mmol, generated as in Example 2) and propylamine (1.916 mL, 23.30 mmol) in tetrahydrofuran (THF) (20ml) was stirred at rt for two days. Next, the crude reaction was adsorbed to silica gel and purified by LC (DCM to 5% MeOH/DCM). ESIMS (M+H)⁺ = 703. The isolated amide was redissolved in 1,4-dioxane (10 ml), potassium hydroxide (7.68 mL, 7.68 mmol) was added and the reaction was heated in
 25 the microwave at 120°C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-propyl-2-thiophenecarboxamide (0.080g, 33% over two steps). ESIMS (M+H)⁺ = 549.

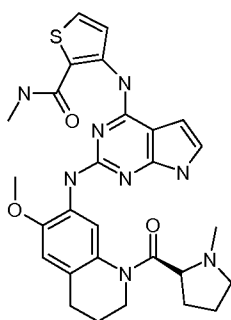
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.84 (t, *J*=7.42 Hz, 3 H) 1.44 - 1.55 (m, 2 H) 2.20 (s, 6 H) 3.03 - 3.23 (m, 6 H) 3.73 (s, 3 H) 4.14 (t, *J*=8.15 Hz, 2 H) 6.19 - 6.24 (m, 1 H) 6.88 - 6.99 (m, 2 H) 7.54 (d, *J*=6.04 Hz, 1 H) 7.64 (s, 1 H) 8.09 - 8.17 (m, 1 H) 8.35 (d, *J*=5.68 Hz, 1 H) 8.54 (s, 1 H) 11.21 - 11.32 (m, 2 H).

5

Example 43:

***N*-methyl-3-[(2-[[6-(methyloxy)-1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**

10



A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (300 mg, 0.64 mmol) and 6-(methyloxy)-1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinolinamine (223 mg, 0.77 mmol) in THF (20 ml) was heated at 65°C for 4 hrs. The reaction was diluted with ethyl acetate (200 ml) and washed with saturated NaHCO₃ (300 ml). Organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum prior to next step. ESIMS (M+H)⁺ = 684. The solids were then added to tetrahydrofuran (THF) (100 ml) followed by methylamine 2.0M/THF (25.6 mL, 51.2 mmol) and the resulting mixture was stirred at rt overnight. The crude reaction was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM). ESIMS (M+H)⁺ = 715. The isolated amide was redissolved in 1,4-Dioxane (6 ml), potassium hydroxide (6.29 mL, 6.29 mmol) added and the reaction was heated in the microwave at 120°C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford *N*-methyl-3-[(2-[[6-(methyloxy)-1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-

15

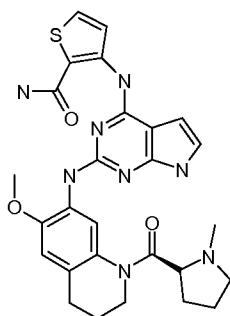
20

25

d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.05 g, 14% over three steps). ESIMS (M+H)⁺ = 561. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.48 - 1.98 (m, 8 H) 2.06 (s, 3 H) 2.10 - 2.21 (m, 1 H) 2.57 - 2.74 (m, 2 H) 2.78 (d, *J*=4.01 Hz, 2 H) 2.86 - 2.95 (m, 1 H) 3.42 - 3.54 (m, 1 H) 3.87 (s, 3 H) 3.93 - 4.02 (m, 1 H) 6.30 (s, 1 H) 6.88 (s, 1 H) 7.01-7.04 (m, 1 H) 7.62 - 7.71 (m, 2 H) 8.14-8.18 (m, 1 H) 8.30 - 8.41 (m, 2 H) 11.32-11.35 (m, 2 H).

Example 44:

3-[(2-[[6-(methoxy)-1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

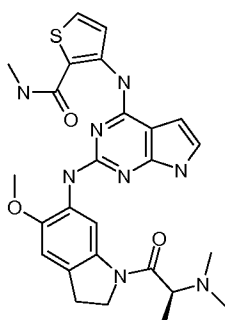


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (300 mg, 0.64 mmol) and 6-(methoxy)-1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinolinamine (223 mg, 0.77 mmol) in THF (20 ml) was heated at 65°C for 4 hrs. The reaction was diluted with ethyl acetate (200 ml) and washed with saturated NaHCO₃ (300 ml). Organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum prior to next step. ESIMS (M+H)⁺ = 684. The solids were then added to tetrahydrofuran (THF) (50 ml) followed by ammonium hydroxide (199 mL, 5118 mmol) and the resulting mixture was stirred at rt for three days. The crude reaction was adsorbed to silica gel and purified by LC (DCM to 5% MeOH/DCM). ESIMS (M+H)⁺ = 701. To the isolated amide in tetrahydrofuran (10 ml) and methanol (2 ml) was added sodium methoxide (46.3 mg, 0.856 mmol) and the reaction was heated at 60°C for 2 hrs. The reaction was adsorbed to silica gel and purified by LC (DCM to 5% MeOH/DCM + 0.1% NH₄OH) to afford 3-[(2-[[6-(methoxy)-

1-(1-methyl-L-prolyl)-1,2,3,4-tetrahydro-7-quinoliny]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.013 g, 3.7% over three steps). ESIMS (M+H)⁺ = 547. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.47 - 1.92 (m, 5 H) 2.07 (s, 3 H) 2.15 - 2.20 (m, 1 H) 2.55 - 2.91 (m, 4 H) 3.39-3.55 (m, 2 H) 3.88 (2, 3 H) 3.94-4.02 (m, 1 H) 6.27 (dd, *J*=3.21, 1.81 Hz, 1 H) 6.89 (s, 1 H) 7.02-7.44 (m, 1 H) 7.51-7.63 (m, 2H) 7.66 (s, 1 H) 7.69 (d, *J*=5.42 Hz, 1 H) 8.33 - 8.37 (m, 1 H) 8.39 (d, *J*=5.42 Hz, 1 H) 11.34 (s, 1 H) 11.43 (s, 1 H)

Example 45:

10 **3-[(2-{[1-(*N,N*-dimethyl-L-alanyl)-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide**



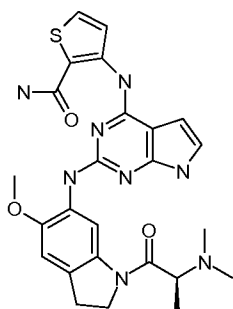
15 A mixture 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (500 mg, 1.07 mmols) and 1-[(2*S*)-2-(dimethylamino)propanoyl]-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-amine (336 mg, 1.276 mmol) in tetrahydrofuran (50 ml) was heated at 65°C for 4 hrs. The reaction was diluted with ethyl acetate (200 ml) and washed with saturated NaHCO₃ (300 ml). The organic
20 layer was removed, concentrated, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. ESIMS (M+H)⁺ = 658. A solution of 5-{[1-(*N,N*-dimethyl-L-alanyl)-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one (450 mg, 0.672 mmol) and methylamine 2.0M/THF (16.80 ml, 33.6 mmol) in tetrahydrofuran (50 ml) was stirred at
25 rt overnight. The crude reaction was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM). ESIMS (M+H)⁺ = 701. The isolated amide was dissolved in 1,4-dioxane (10 ml), potassium hydroxide (2.497 ml, 12.49 mmol) was added and the

reaction was heated in the microwave at 120°C for 20 min. The resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-
 {[1-(*N,N*-dimethyl-L-alanyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-
 pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (0.100g, 18%
 5 over three steps). ESIMS (M+H)⁺ = 521. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.04 (d,
J=6.62 Hz, 3 H) 2.20 (s, 6 H) 2.76 - 2.80 (m, 3 H) 3.09 - 3.17 (m, 2 H) 3.55 - 3.63 (m, 1
 H) 3.77 (s, 3 H) 4.11 - 4.21 (m, 1 H) 4.36 - 4.43 (m, 1 H) 6.26 (dd, *J*=3.61, 1.81 Hz, 1 H)
 6.94 - 7.00 (m, 2 H) 7.57 (d, *J*=5.62 Hz, 1 H) 7.69 (s, 1 H) 8.09 - 8.16 (m, 1 H) 8.39 (d,
J=5.42 Hz, 1 H) 8.57 (s, 1 H) 11.28 (s, 1 H) 11.32 (s, 1 H).

10

Example 46:

**3-[(2-{[1-(*N,N*-dimethyl-L-alanyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-
 1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**



15

A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (222 mg, 0.48 mmol)
 and 1-[(2*S*)-2-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine
 (149 mg, 0.57 mmol) in THF (50 ml) was heated at 65°C for 4 hrs. The reaction was
 20 diluted with ethyl acetate (200 ml) and washed with saturated NaHCO₃ (300 ml). Organic
 layer was removed, concentrated by rotary evaporation, solids triturated from ethyl
 acetate/hexanes, and dried under house vacuum prior to next step. ESIMS (M+H)⁺ =
 658. A solution of 5-[[1-(*N,N*-dimethyl-L-alanyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-
 yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-
 25 *c*]pyrimidin-7(3*H*)-one (200 mg, 0.304 mmol) and potassium carbonate (840 mg, 6.08
 mmol) in 2,2,2-trifluoroethanol (100 ml) was stirred at rt overnight. The crude reaction
 was concentrated, diluted with ethyl acetate (200 ml) and washed with water (300 ml).
 The organic layer was removed, concentrated, and maintained under vacuum overnight.

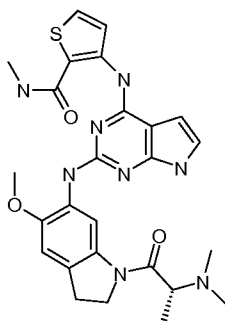
ESIMS (M+H)⁺ = 758. The solids were then added to tetrahydrofuran (50 ml) and trifluoroethanol (25 ml) followed by 27% ammonium hydroxide (103 ml, 2639 mmol) and the resulting mixture was stirred overnight at rt. The crude reaction was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM). ESIMS (M+H)⁺ = 675. To the

isolated amide in tetrahydrofuran (25 ml) and methanol (5 ml) was added sodium methoxide (46.3 mg, 0.856 mmol) and the reaction was heated at 60°C for 2 hrs. The reaction was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-{[1-(*N,N*-dimethyl-L-alanyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.076 g, 31% over four

steps). ESIMS (M+H)⁺ = 521. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.04 (d, *J*=6.62 Hz, 3 H) 2.20 (s, 6 H) 3.08 - 3.18 (m, 2 H) 3.55 - 3.64 (m, 1 H) 3.77 (s, 3 H) 4.11 - 4.22 (m, 1 H) 4.36 - 4.46 (m, 1 H) 6.22 (dd, *J*=3.51, 1.91 Hz, 1 H) 6.94 - 7.00 (m, 2 H) 7.50-7.62 (m, 3 H) 7.70 (s, 1 H) 8.39 (d, *J*=5.42 Hz, 1 H) 8.57 (s, 1 H) 11.28 (s, 1 H) 11.40 (s, 1 H)

Example 47:

3-[(2-{[1-(*N,N*-dimethyl-D-alanyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide

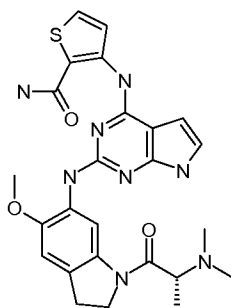


A mixture 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (250 mg, 0.54 mmols) and 1-[(2*R*)-2-(dimethylamino)propanoyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (153 mg, 0.58 mmol) in tetrahydrofuran (50 ml) was heated at 65°C for 4 hrs. The reaction was diluted with ethyl acetate (200 ml) and washed with saturated NaHCO₃ (300 ml). The organic layer was removed, concentrated, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. ESIMS (M+H)⁺ = 658. A solution of 5-{[1-(*N,N*-dimethyl-D-

alanyl)-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (200 mg, 0.304 mmol) and methylamine 2.0M/THF (15.20 ml, 30.4 mmol) in tetrahydrofuran (50 ml) was stirred at rt overnight. The crude reaction was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM). ESIMS (M+H)⁺ = 689. The isolated amide was redissolved in tetrahydrofuran (20 ml) and methanol (5 ml), followed by the addition of sodium methoxide (157 mg, 2.90 mmol). After heating at 60°C for 3 hrs, the resulting solution was adsorbed onto silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[1-(*N,N*-dimethyl-D-alanyl)-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (0.100g, 35% over three steps). ESIMS (M+H)⁺ = 535. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.04 (d, *J*=6.62 Hz, 3 H) 2.20 (s, 6 H) 2.77 - 2.80 (m, 3 H) 3.08 - 3.18 (m, 2 H) 3.55 - 3.64 (m, 1 H) 3.77 (s, 3 H) 4.09 - 4.21 (m, 1 H) 4.36 - 4.48 (m, 1 H) 6.26 (d, *J*=3.41 Hz, 1 H) 6.93 - 7.00 (m, 2 H) 7.57 (d, *J*=5.62 Hz, 1 H) 7.69 (s, 1 H) 8.06 - 8.17 (m, 1 H) 8.39 (d, *J*=5.42 Hz, 1 H) 8.57 (s, 1 H) 11.32 (s, 2 H).

Example 48:

3-[(2-[[1-(*N,N*-dimethyl-D-alanyl)-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (250 mg, 0.54 mmol) and 1-[(2*R*)-2-(dimethylamino)propanoyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine (153 mg, 0.58 mmol) in THF (50 ml) was heated at 65°C for 4 hrs. The reaction was diluted with ethyl acetate (200 ml) and washed with saturated NaHCO₃ (300 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from

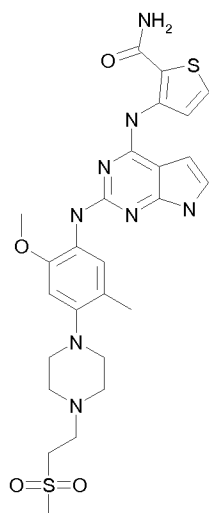
ethyl acetate/hexanes, and dried under house vacuum prior to next step. ESIMS (M+H)⁺ = 658. A solution of 5-[[1-(N,N-dimethyl-D-alanyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (200 mg, 0.304 mmol) and potassium carbonate (840 mg, 6.08 mmol) in 2,2,2-trifluoroethanol (100 ml) was stirred at rt overnight. The crude reaction was concentrated, diluted with ethyl acetate (200 ml) and washed with water (300 ml). The organic layer was removed, concentrated, and dried under high vacuum overnight. ESIMS (M+H)⁺ = 758. The solids were then added to tetrahydrofuran (50 ml) and trifluoroethanol (25 ml) followed by 27% ammonium hydroxide (103 ml, 2639 mmol) and the resulting mixture was stirred overnight at 50°C. The organic layer was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[1-(N,N-dimethyl-D-alanyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.130 g, 47% over three steps). ESIMS (M+H)⁺ = 521. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.04 (d, *J*=6.42 Hz, 3 H) 2.20 (s, 6 H) 3.08 - 3.18 (m, 2 H) 3.56 - 3.64 (m, 1 H) 3.77 (s, 3 H) 4.11 - 4.22 (m, 1 H) 4.36 - 4.46 (m, 1 H) 6.22 (dd, *J*=3.41, 1.81 Hz, 1 H) 6.92 - 7.00 (m, 2 H) 7.51 - 7.61 (m, 3 H) 7.70 (s, 1 H) 8.39 (d, *J*=5.42 Hz, 1 H) 8.57 (s, 1 H) 11.28 (s, 1 H) 11.40 (s, 1 H).

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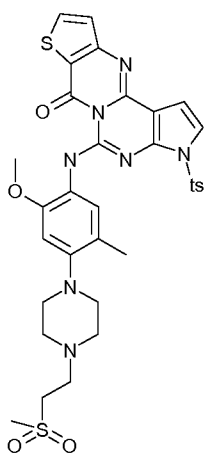
Example 49

3-({2-[(5-methyl-2-(methoxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide

226



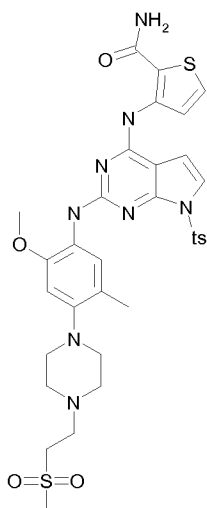
Step A\ Intermediate C28: 5-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 5 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one



To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 10 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl salt (0.5 g, 1.07 mmol) in 2,2,2-trifluoroethanol (15 mL) was added 5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline (0.419 g, 1.28 mmol). The resulting slurry was stirred at rt for 4 h. The reaction mixture was diluted with dichloromethane and saturated sodium bicarbonate as to adjust the aqueous layer to pH >10. The organic layer was
 15 washed with water and saturated brine solution and dried over sodium sulfate. Solvents

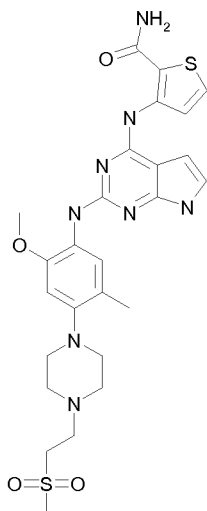
were removed under reduced pressure to afford a green solid that was purified via trituration from diethyl ether to afford 5-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (760 mg, 1.05 mmol) as a green solid (90% clean) (ESIMS (M+H)⁺ = 722)

Step B\ Intermediate C9: 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



To a solution of : 5-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (760 mg, 1.05 mmol) in THF (50 mL) was added ammonium hydroxide (27 % aqueous) (>100 mL) The resulting mixture was let stir at 90°C in a pressure vessel for 8 h at which time it was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure. Purification via column chromatography afforded a yellow solid, 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (291 mg, 0.0395 mmol)). ESIMS(M+H)⁺ = 739

Step C\ Example 49: 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



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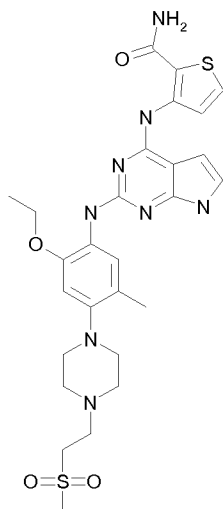
3-({2-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (291 mg, 0.0395 mmol) was dissolved in 1,4-dioxane (10 mL) and transferred to a 20 ml microwave vessel. A solution of 6M NaOH (3 ml) and water (3 ml) was added and reaction heated in microwave at 120°C for 25 minutes. Resulting brown solution was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure to afford a yellow solid which was purified via chromatography on SiO₂ to afford 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (105 mg, 0.108 mmol) as a yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.22 (s, 3 H) 2.56 - 2.68 (m, 4 H) 2.75 - 2.82 (m, 2 H) 2.83 - 2.91 (m, 4 H) 3.08 (s, 3 H) 3.33 - 3.37 (m, 2 H) 3.82 (s, 3 H) 6.20 - 6.27 (m, 1 H) 6.73 (s, 1 H) 6.95 - 7.02 (m, 1 H) 7.49 (s, 1 H) 7.52 - 7.67 (m, 2 H) 7.69 (d, *J*=5.40 Hz, 1 H) 7.89 (s, 1 H) 8.35 - 8.42 (m, 1 H) 11.29 - 11.36 (m, 1 H) 11.39 (s, 1 H)

ESIMS(M+H)⁺ = 585

Example 50

3-({2-[(2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide

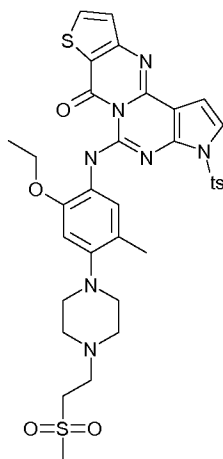


5

N2679-66-1

Step A\Intermediate C10: 5-[(2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one

10



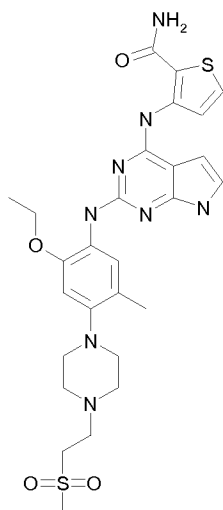
To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-

15

e]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one HCl salt (0.5 g, 1.07 mmol) in 2,2,2-

trifluoroethanol (15 mL) was added 2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}aniline (0.435 g, 1.28 mmol). The resulting slurry was stirred at rt in a pressure vial for 16 h. The reaction mixture was diluted with dichloromethane and saturated sodium bicarbonate as to adjust the aqueous layer to pH >10. The organic layer was washed with water and saturated brine solution and dried over sodium sulfate. Solvents were removed under reduced pressure to afford a yellow solid that was purified via trituration from diethyl ether to afford 5-[(2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (700 mg, 0.951 mmol) as a green solid. (ESIMS (M+H)⁺ =736)

Step B\ Example 50: 3-({2-[(2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



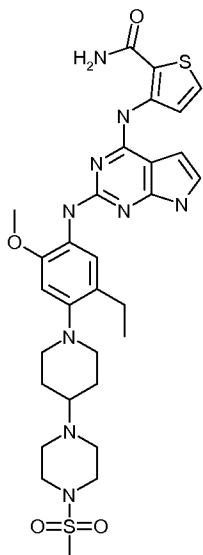
To a solution of 5-[(2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (700 mg, 0.951 mmol) in THF (50 mL) was added ammonium hydroxide (27 % aqueous) (>100 mL). The resulting mixture was let stir at 90°C in a pressure vessel for ~24 h at which time it was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure. Purification via column chromatography afforded a yellow solid

containing 3-({2-[(2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (70% pure, 312 mg, 0.414 mmol) This material was dissolved in 1,4-dioxane (10 mL) and transferred to a 20 ml microwave vessel. A solution of 6M NaOH (3 ml) and water (3 ml) was added and the reaction was heated in a microwave at 120°C for 20 minutes. Resulting brown solution was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure to afford a yellow solid which was purified via chromatography on SiO₂ to afford 3-({2-[(2-(ethyloxy)-5-methyl-4-{4-[2-(methylsulfonyl)ethyl]-1-piperazinyl}phenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (185 mg, 0.309 mmol) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.34 (t, *J*=6.97 Hz, 3 H) 2.21 (s, 3 H) 2.54 - 2.68 (m, 4 H) 2.78 (t, *J*=6.62 Hz, 2 H) 2.82 - 2.90 (m, 4 H) 3.08 (s, 3 H) 3.34 - 3.39 (m, 2 H) (partly under water peak) 4.08 (q, *J*=6.86 Hz, 2 H) 6.25 (dd, *J*=3.36, 1.76 Hz, 1 H) 6.72 (s, 1 H) 7.00 (dd, *J*=3.26, 2.26 Hz, 1 H) 7.42 (s, 1 H) 7.47 - 7.67 (m, 2 H) 7.71 (d, *J*=5.32 Hz, 1 H) 7.93 (s, 1 H) 8.36 (d, *J*=5.42 Hz, 1 H) 11.34 (s, 1 H) 11.40 (s, 1 H)
ESIMS(M+H)⁺ = 599

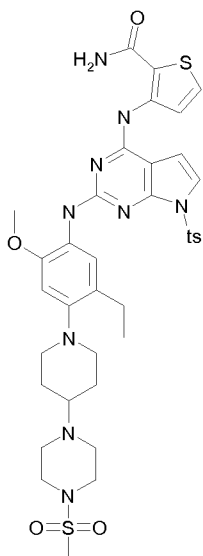
Example 51

3-({2-[(5-ethyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide

232



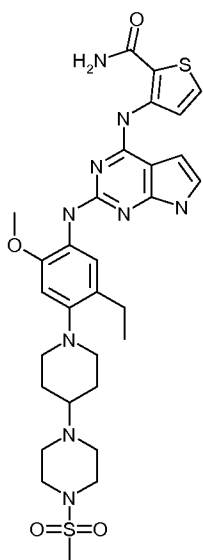
Step A\ Intermediate C11: 3-({2-[(5-ethyl-2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidiny]phenyl}amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-
5 *d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one HCl salt (0.5 g, 1.07 mmol) in
10 tetrahydrofuran (50 mL) was added 5-ethyl-2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidiny]aniline (0.508 g, 1.28 mmol). The resulting slurry was stirred at
rt in a pressure vial for 16 h. Analysis by LCMS indicated all starting material had been

consumed so ammonium hydroxide (27 % in water) (100 ml) was added and the reaction was heated to 80°C in a pressure vessel for 16 hours. The resulting solution was cooled to room temperature and diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, water and saturated brine solution and dried over sodium sulfate. Solvents were removed under reduced pressure to afford a yellow solid that was purified via column chromatography to afford 3-({2-[(5-ethyl-2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (0.575 g, 0.712 mmol) as a yellow solid. (90% clean) (ESIMS (M+H)⁺ =809)

Step B\ Example 51: 3-({2-[(5-ethyl-2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide:



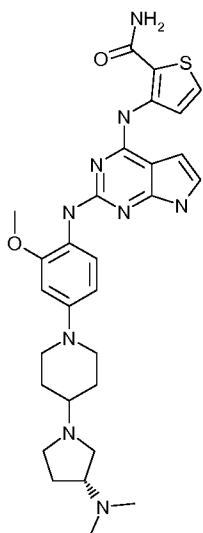
A solution of 3-({2-[(5-ethyl-2-(methoxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (0.575 g, 0.712 mmol) in 1,4-dioxane (10 mL) was transferred to a 20 ml microwave vessel. A solution of 6M NaOH (3 ml) and water (3 mL) was added and reaction heated in microwave at 120°C for 10 minutes. Microwave heating in 10 min intervals was continued until LCMS analysis indicated starting material consumed (~40 min). Resulting brown solution was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine

solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure to afford an off white solid. Attempts to redissolve the compound in organic solvents were not successful so the solid was filtered. This material was then dissolved in a DMSO-MeOH solution and purified by HPLC (acetonitrile/ water with TFA).

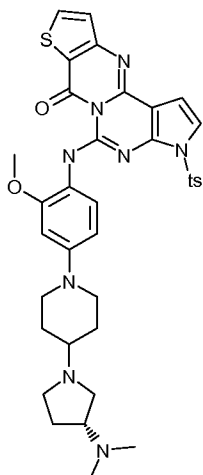
- 5 Fractions containing clean product were combined and neutralized with potassium carbonate. The resulting solution was diluted with EtOAc and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure to afford 3-({2-[(5-ethyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (88 mg, 0.135 mmol) as
 10 an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.17 (t, *J*=7.46 Hz, 3 H) 1.53 - 1.67 (m, 2 H) 1.79 - 1.90 (m, 2 H) 2.35 - 2.47 (m, 1 H) 2.58 - 2.76 (m, 8 H) 2.88 (s, 3 H) 3.03 (d, *J*=11.35 Hz, 2 H) 3.08 - 3.16 (m, 4 H) 3.81 (s, 3 H) 6.24 (d, *J*=3.39 Hz, 1 H) 6.77 (s, 1 H) 6.99 (d, *J*=3.30 Hz, 1 H) 7.44 - 7.63 (m, 3 H) 7.67 (d, *J*=5.31 Hz, 1 H) 7.93 (s, 1 H) 8.37 (d, *J*=5.31 Hz, 1 H) 11.25 - 11.36 (m, 1 H) 11.39 (s, 1 H)
 15 ESIMS(*M*+*H*)⁺ = 654

Example 52

- 3-[(2-{[4-{4-[(3*R*)-3-(dimethylamino)-1-pyrrolidinyl]-1-piperidinyl]-2-(methyloxy)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide

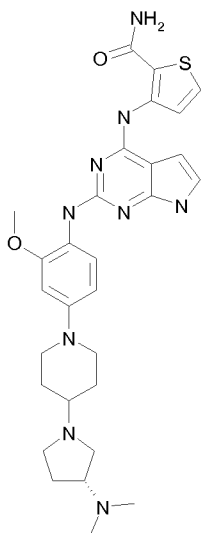


Step A\ Intermediate C12: 5-[[4-{4-[(3R)-3-(dimethylamino)-1-pyrrolidinyl]-1-piperidinyl]-2-(methoxy)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 5 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one



To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 10 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl salt (0.5 g, 1.07 mmol) in 2,2,2-trifluoroethanol (15 mL) was added (3R)-1-{1-[4-amino-3-(methoxy)phenyl]-4-piperidinyl}-N,N-dimethyl-3-pyrrolidinamine (0.406 g, 1.27 mmol). The resulting slurry was stirred at rt for 3 h. Reaction mixture was diluted with dichloromethane and saturated sodium bicarbonate as to adjust the aqueous layer to pH >10. The organic
 15 layer was washed with water and saturated brine solution and dried over sodium sulfate. Solvents were removed under reduced pressure to afford a yellow solid that was purified via trituration from diethyl ether to afford 5-[[4-{4-[(3R)-3-(dimethylamino)-1-pyrrolidinyl]-1-piperidinyl]-2-(methoxy)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 20 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (680 mg, 0.954 mmol) as a green yellow solid. (ESIMS (M+H)⁺ = 713

Step B\ Example 52: 3-[(2-{4-[(3R)-3-(dimethylamino)-1-pyrrolidinyl]-1-piperidinyl}-2-(methoxy)phenyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



To a solution of 5-[[4-{4-[(3R)-3-(dimethylamino)-1-pyrrolidinyl]-1-piperidinyl]-2-(methoxy)phenyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (680 mg, 0.954 mmol) in THF (50 mL) was added ammonium hydroxide (27 % aqueous) (>100 mL). The resulting mixture was let stir at 80°C in a pressure vessel for 16 h at which time it was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure. Purification via column chromatography afforded a yellow solid containing 3-[(2-{[4-{4-[(3R)-3-(dimethylamino)-1-pyrrolidinyl]-1-piperidinyl]-2-(methoxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (90% pure, 123 mg, 0.169 mmol). This material was dissolved in 1,4-dioxane (5 mL) and transferred to a 20 mL microwave vessel. A solution of 6M NaOH (1.5 mL) and water (1.5 mL) was added and reaction heated in microwave at 120°C for 16 minutes. Resulting brown solution was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure to afford a yellow solid which was purified via chromatography on SiO₂ to afford 3-[(2-{[4-{4-[(3R)-3-(dimethylamino)-1-pyrrolidinyl]-1-piperidinyl]-2-(methoxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (52 mg, 0.090 mmol) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.43 - 1.64 (m, 3 H) 1.78 - 1.96 (m, 3 H) 2.10 (s, 6 H) 2.31 (d, *J*=7.93

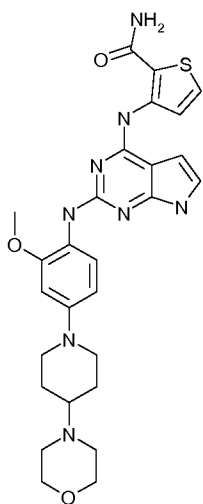
237

Hz, 1 H) 2.44 - 2.49 (m, 1 H)(hidden by DMSO peak) 2.59 - 2.77 (m, 4 H) 2.81 (t, $J=7.88$ Hz, 1 H) 3.17 (d, $J=5.02$ Hz, 1 H) 3.58 (d, $J=12.34$ Hz, 2 H) 3.80 (s, 3 H) 6.21 (dd, $J=3.26, 1.86$ Hz, 1 H) 6.50 (dd, $J=8.68, 2.26$ Hz, 1 H) 6.63 (d, $J=2.31$ Hz, 1 H) 6.95 (dd, $J=3.26, 2.36$ Hz, 1 H) 7.46 - 7.63 (m, 3 H) 7.68 (d, $J=5.42$ Hz, 1 H) 7.80 (d, $J=8.63$ Hz, 1 H) 8.39 (d, $J=5.32$ Hz, 1 H) 11.30 (s, 1 H) 11.36 (s, 1 H)

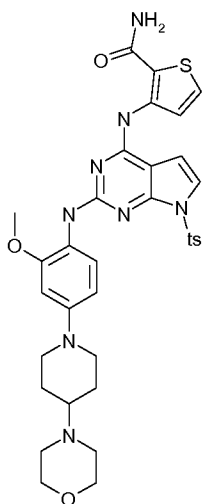
ESIMS(M+H)⁺ = 576

Example 53

3-[[2-({2-(methyloxy)-4-[4-(4-morpholinyl)-1-piperidinyl]phenyl}amino)-1H-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-2-thiophenecarboxamide

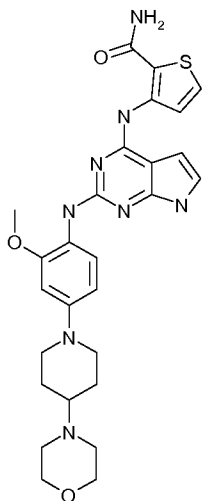


Step A\ Intermediate C13: 3-({2-({2-(methyloxy)-4-[4-(4-morpholinyl)-1-piperidinyl]phenyl}amino)-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one HCl salt (0.5 g, 1.07 mmol) in
5 tetrahydrofuran (50 mL) was added 2-(methoxy)-4-[4-(4-morpholinyl)-1-
piperidinyl]aniline (0.342 g, 1.17 mmol)—for synthesis see: Garcia-Echeverria, Carlos;
Kanazawa, Takanori; Kawahara, Eiji; Masuya, Keiichi; Matsuura, Naoko; Miyake,
Takahiro; Ohmori, Osamu; Umemura, Ichiro. Preparation of novel 2,4-
di(phenylamino)pyrimidines useful in the treatment of neoplastic diseases, inflammatory
10 and immune system disorders. PCT Int. Appl. (2004), 185 pp. CODEN: PIXXD2
WO 2004080980 A1 20040923 CAN 141:296041 AN 2004:780679 CAPLUS. The
resulting slurry was stirred at rt for 4 h. Ammonium hydroxide (27 % aqueous) (>100
mL) was added and the resulting mixture was let stir at 80°C in a pressure vessel for 2
days at which time it was diluted with ethyl acetate and washed with a saturated sodium
15 bicarbonate solution, water and a saturated brine solution. Organics were dried over
sodium sulfate and solvents removed under reduced pressure. Purification via column
chromatography afforded a yellow solid containing 3-({2-({2-(methoxy)-4-[4-(4-
morpholinyl)-1-piperidinyl]phenyl}amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-
d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (283 mg, 0.403 mmol) as a yellow
20 solid. (ESIMS (M+H)⁺ = 703

Step B\ Example 53: 3-[[2-({2-(methoxy)-4-[4-(4-morpholinyl)-1-
piperidinyl]phenyl}amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-2-
thiophenecarboxamide

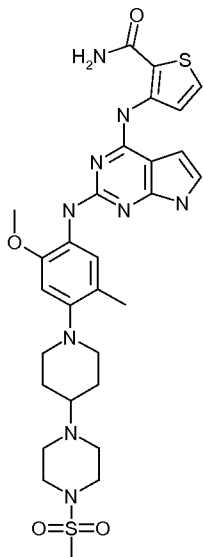


- 5 3-({2-({2-(methyloxy)-4-[4-(4-morpholinyl)-1-piperidinyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (283 mg, 0.403 mmol) was dissolved in 1,4-dioxane (10 mL) and transferred to a 20 ml microwave vessel. A solution of 6M NaOH (3 ml) and water (3 ml) was added and the reaction heated in microwave at 120°C for 15 minutes. Resulting brown solution was
- 10 diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure to afford a yellow solid which was purified via chromatography on SiO₂ to afford 3-{{2-({2-(methyloxy)-4-[4-(4-morpholinyl)-1-piperidinyl]phenyl}amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl}amino}-2-
- 15 thiophenecarboxamide (88 mg, 0.160 mmol) as a tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.52 (dd, *J*=11.67, 3.07 Hz, 2 H) 1.88 (d, *J*=11.54 Hz, 2 H) 2.21 - 2.31 (m, 1 H) 2.65 (t, *J*=11.35 Hz, 3 H) 3.17 - 3.19 (m, 2 H) 3.54 - 3.63 (m, 5 H) 3.69 (d, *J*=12.27 Hz, 2 H) 3.81 (s, 3 H) 6.18 - 6.25 (m, 1 H) 6.50 (dd, *J*=8.70, 2.29 Hz, 1 H) 6.64 (d, *J*=2.20 Hz, 1 H) 6.91 - 6.99 (m, 1 H) 7.45 - 7.64 (m, 3 H) 7.68 (d, *J*=5.40 Hz, 1 H) 7.81 (d, *J*=8.70
- 20 Hz, 1 H) 8.39 (d, *J*=5.40 Hz, 1 H) 11.30 (s, 1 H) 11.36 (s, 1 H)
ESIMS(M+H)⁺ = 549

Example 54

240

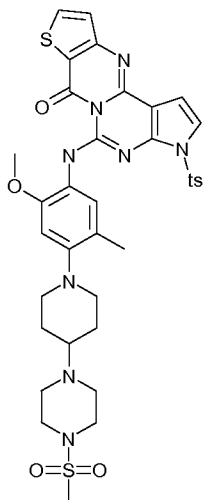
3-({2-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



5

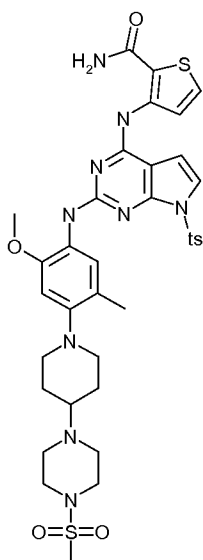
Step A\ Intermediate C14: 5-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one

10



To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one HCl salt (0.450 g, 1.07 mmol) in
2,2,2-trifluoroethanol (50 mL) was added 5-methyl-2-(methyloxy)-4-{4-[4-
(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}aniline (0.384 g, 1.00 mmol). The resulting
5 slurry was stirred at rt for 3 h. The reaction mixture was diluted with dichloromethane
and saturated sodium bicarbonate as to adjust the aqueous layer to pH >10. The
organic layer was washed with water and saturated brine solution and dried over sodium
sulfate. Solvents were removed under reduced pressure to afford a yellow solid that
was purified via trituration from diethyl ether to afford 5-[(5-methyl-2-(methyloxy)-4-{4-[4-
10 (methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-3-[(4-
methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one
(618 mg, 0.79 mmol) as a yellow solid. (ESIMS (M+H)⁺ = 713

Step B\ Example C15: 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-
15 piperazinyl]-1-piperidinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-
d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide



To a solution of 5-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-
piperidinyl}phenyl)amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
20 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one (618 mg, 0.79 mmol) in THF (50
mL) was added ammonium hydroxide (27 % aqueous) (>150 mL). The resulting mixture
was let stir at 90°C in a pressure vessel for 16 h at which time it was diluted with ethyl
acetate and washed with a saturated sodium bicarbonate solution, water and a saturated

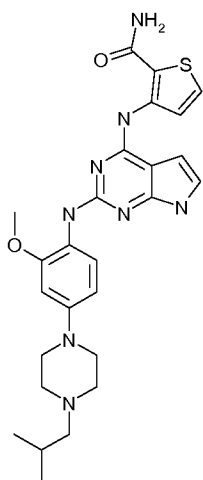
brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure. Purification via column chromatography afforded a yellow solid, 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (384 mg, 0.961 mmol). (ESIMS (M+H)⁺ = 777

Step C\ Example 54: 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide

3-({2-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (384 mg, 0.961 mmol) was dissolved in 1,4-dioxane (6 mL) and transferred to a 20 ml microwave vessel. A solution of 6M NaOH (2 ml) and water (2 ml) was added and the reaction heated in microwave at 120°C for 35 minutes. Resulting brown solution was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics were dried over sodium sulfate and solvents removed under reduced pressure to afford a yellow solid which was purified via chromatography on SiO₂ to afford 3-({2-[(5-methyl-2-(methyloxy)-4-{4-[4-(methylsulfonyl)-1-piperazinyl]-1-piperidinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxamide (159 mg, 0.249 mmol) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.54 - 1.68 (m, 2 H) 1.86 (d, *J*=10.99 Hz, 2 H) 2.21 (s, 3 H) 2.37 - 2.47 (m, 1 H) 2.59 - 2.72 (m, 6 H) 2.88 (s, 3 H) 3.06 - 3.16 (m, 6 H) 3.81 (s, 3 H) 6.24 (dd, *J*=3.16, 1.79 Hz, 1 H) 6.72 (s, 1 H) 6.95 - 7.02 (m, 1 H) 7.44 - 7.66 (m, 3 H) 7.69 (d, *J*=5.40 Hz, 1 H) 7.87 (s, 1 H) 8.38 (d, *J*=5.40 Hz, 1 H) 11.32 (s, 1 H) 11.39 (s, 1 H). ESIMS(M+H)⁺ = 640

Example 55

3-{{2-[(5-methyl-2-(methyloxy)-4-{4-(2-methylpropyl)-1-piperazinyl}phenyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino}-2-thiophenecarboxamide



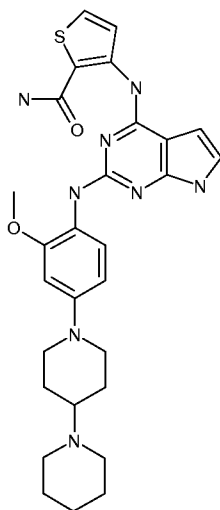
To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one HCl salt (0.5 g, 1.07 mmol) in
 5 tetrahydrofuran (50 mL) was added 2-(methyloxy)-4-[4-(2-methylpropyl)-1-
 piperazinyl]aniline (0.295 g, 1.12 mmol). The resulting slurry was stirred at rt for 4 h.
 Ammonium hydroxide (27 % aqueous) (>100 mL) was added and the resulting mixture
 was let stir at 80°C in a pressure vessel for 8 h at which time it was diluted with ethyl
 acetate and washed with a saturated sodium bicarbonate solution, water and a saturated
 10 brine solution. Organics were dried over sodium sulfate and solvents removed under
 reduced pressure. Purification via column chromatography afforded a yellow solid
 containing ~50% 3-{[2-({2-(methyloxy)-4-[4-(2-methylpropyl)-1-
 piperazinyl]phenyl}amino)-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-
 yl]amino)-2-thiophenecarboxamide (323 mg, 0.239 mmol). This material was dissolved
 15 in 1,4-dioxane (10 mL) and transferred to a 20 ml microwave vessel. A solution of 6M
 NaOH (3 ml) and water (3 ml) was added and the reaction heated in microwave at 120°C
 for 15 minutes. Resulting brown solution was diluted with ethyl acetate and washed with
 a saturated sodium bicarbonate solution, water and a saturated brine solution. Organics
 were dried over sodium sulfate and solvents removed under reduced pressure to afford
 20 a yellow solid which was purified via chromatography on SiO₂ to afford 3-{[2-({2-
 (methyloxy)-4-[4-(2-methylpropyl)-1-piperazinyl]phenyl}amino)-1*H*-pyrrolo[2,3-
 d]pyrimidin-4-yl]amino}-2-thiophenecarboxamide (114 mg, 0.219 mmol) as a tan solid.
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.89 (d, *J*=6.50 Hz, 6 H) 1.75 - 1.87 (m, 1 H) 2.10
 (d, *J*=7.32 Hz, 2 H) 3.08 - 3.15 (m, 4 H) 3.82 (s, 3 H) 6.22 (dd, *J*=3.16, 1.79 Hz, 1 H)

6.45 - 6.53 (m, 1 H) 6.64 (d, $J=2.29$ Hz, 1 H) 6.92 - 6.99 (m, 1 H) 7.46 - 7.64 (m, 3 H) 7.68 (d, $J=5.40$ Hz, 1 H) 7.85 (d, $J=8.70$ Hz, 1 H) 8.42 (d, $J=5.40$ Hz, 1 H) 11.27 - 11.40 (m, 2 H) **4H missing, assumed to be hidden under DMSO peak @2.5. ESIMS(M+H)⁺ = 521

5

Example 56

3-[(2-{[4-(1,4'-bipiperidin-1'-yl)-2-(methoxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



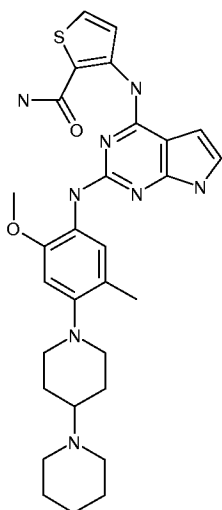
- 10 A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (600 mg, 1.39 mmol) and [4-(1,4'-bipiperidin-1'-yl)-2-(methoxy)phenyl]amine (484 mg, 1.70 mmol) in THF (50 ml) was heated at 85°C for 2 hrs. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed,
- 15 concentrated by rotary evaporation, solids were triturated from ethyl acetate/hexanes, and dried under house vacuum. A solution of 5-{[4-(1,4'-bipiperidin-1'-yl)-2-(methoxy)phenyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (50 ml), and ammonium hydroxide (28% in water, 50 mL) was stirred at 85°C overnight, the solvent
- 20 was removed and dried under house vacuum. A solution of 3-[(2-{[4-(1,4'-bipiperidin-1'-yl)-2-(methoxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide in THF (25 mL)/MeOH (25 mL) was treated with NaOMe (0.23 g) and the resulting mixture was stirred at 70°C for 4 hours, the solvent was removed to yield the crude product which was adsorbed to silica gel and purified by

245

LC (DCM to 10% MeOH/DCM) to afford 3-[(2-{[4-(1,4'-bipiperidin-1'-yl)-2-(methoxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.078 g, 33%). ESIMS (M+H)⁺ = 547. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.68 (br. s., 7 H), 1.99 (br. s., 2 H), 2.24 (br. s., 3 H), 2.63 (br. s., 2 H),
 5 2.93 (br. s., 2 H), 3.78 (br. s., 6 H), 6.18 (br. s., 1 H), 6.49 (br. s., 1 H), 6.61 (br. s., 1 H),
 6.92 (br. s., 1 H), 7.08 (br. s., 1 H), 7.45 (d, J=19.04 Hz, 2 H), 7.64 (s., 1 H), 7.82 (s., 1 H), 8.37 (s., 1 H), 11.32 (s., 2 H).

Example 57:

10 **3-[(2-{[4-(1,4'-bipiperidin-1'-yl)-5-methyl-2-(methoxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**

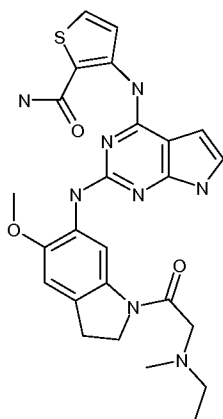


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 15 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (600 mg, 1.39 mmol)
 and [4-(1,4'-bipiperidin-1'-yl)-5-methyl-2-(methoxy)phenyl]amine (507 mg, 1.70 mmol)
 in THF (50 ml) was heated at 85°C for 0.5 hrs. The reaction was diluted with ethyl
 acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was
 removed, concentrated by rotary evaporation, solids triturated from ethyl
 20 acetate/hexanes, and dried under house vacuum prior to next step. A solution of 5-[(4-
 (1,4'-bipiperidin-1'-yl)-5-methyl-2-(methoxy)phenyl]amino}-3-[(4-
 methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in
 tetrahydrofuran (50 ml) and 27% ammonium hydroxide (50 mL) was stirred at 85°C
 overnight. The solvent was removed and dried under house vacuum. A solution of 3-[(2-

{[4-(1,4'-bipiperidin-1'-yl)-5-methyl-2-(methyloxy)phenyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino)-2-thiophenecarboxamide in THF (25 mL)/MeOH (25 mL) was treated with NaOMe (0.82g) and the resulting mixture was stirred at 70°C for 4 hours. The solvent was removed to yield the crude product which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-{[4-(1,4'-bipiperidin-1'-yl)-5-methyl-2-(methyloxy)phenyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.12 g, 42%). ESIMS (M+H)⁺ = 561. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.58 (br. s., 8 H), 1.91 (br. s., 3 H), 2.21 (s, 3 H), 2.29 (s, 3 H), 2.65 (br. s., 4 H), 3.10 (br. s., 2 H), 3.81 (s, 2 H), 6.24 (dd, J=3.44, 1.88 Hz, 1 H), 6.71 (s, 1 H), 6.99 (dd, J=3.30, 2.29 Hz, 1 H), 7.11 (d, J=7.88 Hz, 1 H), 7.49 (d, J=3.48 Hz, 2 H), 7.69 (d, J=5.50 Hz, 1 H), 7.88 (s, 1 H), 8.38 (d, J=5.32 Hz, 1 H), 11.39 (s, 2 H).

Example 58

3-[(2-{[1-(N-ethyl-N-methylglycyl)-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

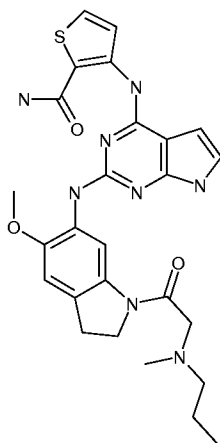


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (400 mg, 0.95 mmol) and 1-{[ethyl(methyl)amino]acetyl}-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine (300 mg, 1.1 mmol) in THF (30 ml) was heated at 65°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. A solution of

5-{{1-(N-ethyl-N-methylglycyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-yl}amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one was dissolved in tetrahydrofuran (50 ml) and 27% ammonium hydroxide (50 mL) and the resulting mixture was stirred at 85°C overnight. The solvent was removed and dried under house vacuum prior to next step. A solution of 3-({2-{{1-(N-ethyl-N-methylglycyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-yl}amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide in THF (25 mL) and MeOH (5 mL) was treated with NaOMe (0.12g) and the resulting mixture was stirred at 70°C for 2 hours. The solvent was removed to yield the crude product. Next, the crude product was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-{{1-(N-ethyl-N-methylglycyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-yl}amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.030 g, 49%). ESIMS (M+H)⁺ = 521. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.01 (t, 3 H), 2.24 (s, 3 H), 2.43 - 2.49 (m, 2 H), 3.13 (t, J=8.06 Hz, 2 H), 3.25 (s, 2 H), 3.78 (s, 3 H), 4.21 (t, J=8.19 Hz, 2 H), 6.23 (s, 1 H), 6.97 (s, 2 H), 7.61 (d, J=5.31 Hz, 3 H), 7.71 (s, 1 H), 8.40 (d, J=5.31 Hz, 1 H), 8.58 (s, 1 H), 11.30 (s, 1 H), 11.41 (s, 1 H).

Example 59

3-[(2-{{5-(methoxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl}amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



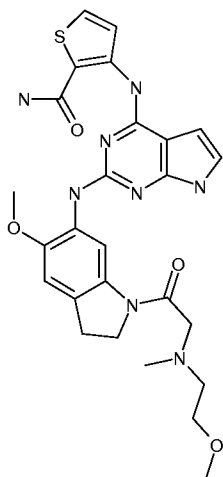
A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (0.5 mg, 1.20 mmol) and 5-(methoxy)-1-[[methyl(propyl)amino]acetyl]-2,3-dihydro-1H-indol-6-amine (350

mg, 1.4 mmol) in THF (30 ml) was heated at 65°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). Organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. A solution of

5 5-[[5-(methyloxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (35 ml) and 27% ammonium hydroxide (40 mL) and the resulting mixture was stirred at 85°C overnight. The solvent was removed and dried under house vacuum. A solution of 3-({2-[[5-(methyloxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl]amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-thiophenecarboxamide in THF (25 mL) and MeOH (5 mL) was treated with NaOMe (0.12g) and the resulting mixture was stirred at 70°C for 2 hours. The solvent was removed to yield the crude product which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[5-(methyloxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.11 g, 43%). ESIMS (M+H)⁺ = 535. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.81 - 0.91 (m, 3 H), 1.52 (d, J=6.50 Hz, 2 H), 2.38 - 2.47 (m, 3 H), 2.56 - 2.67 (m, 2 H), 3.16 (s., 2 H), 3.60 (br. s., 2 H), 3.78 (s, 3 H), 4.18 (t, J=7.78 Hz, 2 H), 6.23 (br. s., 1 H), 6.98 (d, J=7.33 Hz, 2 H), 7.62 (d, J=5.04 Hz, 3 H), 7.73 (s, 1 H), 8.40 (d, J=5.13 Hz, 1 H), 8.57 (s, 1 H), 11.29 (s., 1 H), 11.42 (s., 1 H).

Example 60

3-[(2-[[1-{N-methyl-N-[2-(methyloxy)ethyl]glycyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

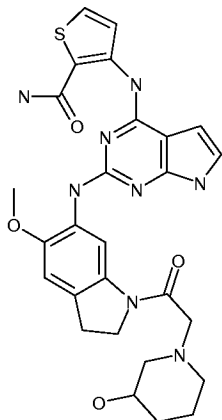


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (0.45 mg, 1.0 mmol) and 1-({methyl[2-(methyloxy)ethyl]amino}acetyl)-5-(methyloxy)-2,3-dihydro-1H-indol-6-amine (350 mg, 1.2 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. A solution of 5-[[1-{N-methyl-N-[2-(methyloxy)ethyl]glycyl}-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (35 ml) and 27% ammonium hydroxide (40 mL) was stirred at 85°C overnight. The solvent was removed and dried under house vacuum. A solution of 3-[(2-{[1-{N-methyl-N-[2-(methyloxy)ethyl]glycyl}-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide in THF (25 mL) and MeOH (5 mL) was treated with NaOMe (0.30g) and the resulting mixture was stirred at 70°C for 2 hours. The solvent was removed to yield the crude product which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-{[1-{N-methyl-N-[2-(methyloxy)ethyl]glycyl}-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.16 g, 51%). ESIMS (M+H)⁺ = 551. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.30 (s, 3 H), 2.65 (s, 2 H), 3.07 - 3.17 (m, 2 H), 3.22 (s, 3 H), 3.32 (br. s., 2 H), 3.43 (br. s., 2 H), 3.78 (s, 3 H), 4.18 (s, 2 H), 6.24 (s, 1 H), 6.96 (s, 2 H), 7.52 -

7.65 (m, 3 H), 7.70 (s, 1 H), 8.41 (s, 1 H), 8.59 (s, 1 H), 11.31 (s, 1 H), 11.42 (s, 1 H).

Example 61

5 **3-[(2-{[1-[(3-hydroxy-1-piperidiny)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**



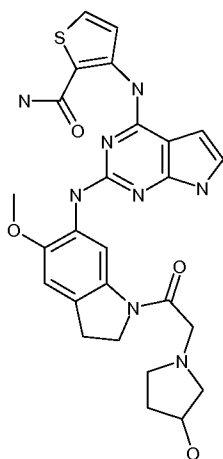
A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 10 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (0.45 mg, 1.0 mmol) and 1-{2-[6-amino-5-(methyloxy)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-3-piperidinol (350 mg, 1.1 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from
 15 ethyl acetate/hexanes, and dried under house vacuum. A solution of 5-[[1-[(3-hydroxy-1-piperidiny)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (35 ml) and 27% ammonium hydroxide (40 mL) was stirred at 85°C overnight. The solvent was removed and the residue was dried under house
 20 vacuum. A solution of 3-[(2-{[1-[(3-hydroxy-1-piperidiny)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide in THF (2mL), water (2mL) and MeOH (5 mL) was treated with K₂CO₃ (0.80g) and the resulting mixture was stirred at 80°C for 3 hours. The K₂CO₃ was filtered out and the solvent was removed to yield the crude product
 25 which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford

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3-[(2-{[1-[(3-hydroxy-1-piperidiny]acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.10 g, 61%). ESIMS (M+H)⁺ = 563. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.06 (d, 1 H), 1.42 (d, J=11.90 Hz, 1 H), 1.61 (d, J=13.19 Hz, 1 H), 1.78 (d, J=8.79 Hz, 1 H), 1.91 (t, J=9.71 Hz, 1 H), 2.02 (t, J=10.26 Hz, 1 H), 2.69 (d, J=10.62 Hz, 1 H), 2.89 (d, J=7.05 Hz, 1 H), 3.12 (t, J=8.19 Hz, 2 H), 3.23 (d, J=5.77 Hz, 2 H), 3.48 (dd, J=8.84, 4.44 Hz, 1 H), 3.78 (s, 3 H), 4.20 (t, J=6.78 Hz, 2 H), 4.63 (d, J=4.76 Hz, 1 H), 6.24 (s, 1 H), 6.96 (s, 2 H), 7.62 (d, J=5.40 Hz, 3 H), 7.70 (s, 1 H), 8.42 (d, J=5.31 Hz, 1 H), 8.60 (s, 1 H), 11.31 (s, 1 H), 11.42 (s, 1 H).

Example 62

3-[(2-{[1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

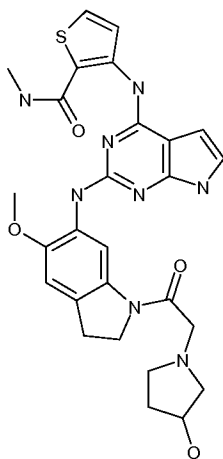


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (0.45 mg, 1.0 mmol) and 1-{2-[6-amino-5-(methoxy)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-3-pyrrolidinol (330 mg, 1.1 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum prior to next step. Next, a solution of 5-{[1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (35 ml), followed by ammonium hydroxide

(28% in water), and the resulting mixture was stirred at 85°C overnight, the solvent was removed and dried under house vacuum. A solution of 3-({2-[[1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-thiophenecarboxamide in THF (2 mL), water (2 mL), and MeOH (5 mL) was treated with K₂CO₃ (0.80g) and the resulting mixture was stirred at 80°C for 3 hours. The K₂CO₃ was filtered out, and the solvent was removed to yield the crude product which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-[[1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.09 g, 57%). ESIMS (M+H)⁺ = 549. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.55 (dd, 1 H), 1.98 (dd, J=13.05, 6.91 Hz, 1 H), 2.45 (dd, J=9.52, 3.20 Hz, 1 H), 2.53 - 2.61 (m, 1 H), 2.71 (q, J=7.60 Hz, 1 H), 2.83 (dd, J=9.39, 6.18 Hz, 1 H), 3.14 (q, J=8.12 Hz, 2 H), 3.37 (br. s., 3 H), 3.78 (s, 3 H), 4.17 (t, J=8.38 Hz, 2 H), 4.73 (d, J=4.21 Hz, 1 H), 6.24 (br. s., 1 H), 6.96 (s, 2 H), 7.51 - 7.65 (m, 3 H), 7.70 (s, 1 H), 8.41 (d, J=5.40 Hz, 1 H), 8.59 (s, 1 H), 11.31 (s., 1 H), 11.41 (s, 1 H).

Example 63

3-[(2-[[1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-methyl-2-thiophenecarboxamide

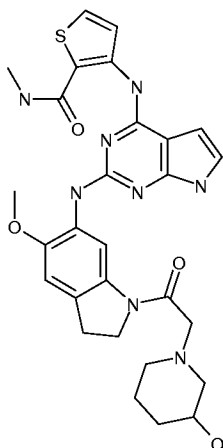


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (0.45 mg, 1.0 mmol) and 1-{2-[6-amino-5-(methoxy)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-3-pyrrolidinol

(330 mg, 1.1 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. Next, a solution of 5-
5 {1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (35 ml) and methyl amine (2M in THF, 30 mL) was stirred at room temperature overnight. The solvent was removed and the resulting residue was dried under house vacuum. A solution of 3-
10 {2-{1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methyl-2-thiophenecarboxamide in THF (20 mL) was treated with NaOMe (0.40g) and stirred at 70°C for 2 hours. The solvent was removed and the residue was redissolved in 50 ml of DCM and washed with 50 ml of sat.NH₄Cl. The organic solvent was removed under reduced pressure to yield the crude
15 product which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3-[(2-{1-[(3-hydroxy-1-pyrrolidinyl)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-methyl-2-thiophenecarboxamide (0.056 g, 21%). ESIMS (M+H)⁺ = 563. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.56 (dd, 1 H), 1.98 (dd, J=12.82, 7.05 Hz, 1 H), 2.46 (dd, J=9.61, 3.20 Hz, 1 H), 2.54 - 2.63 (m, 1
20 H), 2.68 - 2.75 (m, 1 H), 2.79 (d, J=4.39 Hz, 3 H), 2.85 (d, J=4.21 Hz, 1 H), 3.13 (t, J=8.06 Hz, 2 H), 3.38 (d, J=6.59 Hz, 3 H), 3.78 (s, 3 H), 4.16 (t, J=8.38 Hz, 2 H), 4.74 (br. s., 1 H), 6.27 (br. s., 1 H), 6.96 (s, 2 H), 7.60 (d, J=5.40 Hz, 1 H), 7.70 (s, 1 H), 8.13 (d, J=4.49 Hz, 1 H), 8.42 (d, J=5.31 Hz, 1 H), 8.59 (s, 1 H), 11.32 (d, J=9.71 Hz, 2 H).

25 Example 64

3-[(2-{1-[(3-hydroxy-1-piperidinyl)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-methyl-2-thiophenecarboxamide

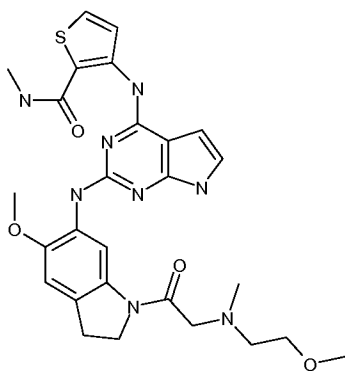


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (0.45 mg, 1.0 mmol)
5 and 1-{2-[6-amino-5-(methyloxy)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-3-piperidinol
(350 mg, 1.1 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was
diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The
organic layer was removed, concentrated by rotary evaporation, solids triturated from
ethyl acetate/hexanes, and dried under house vacuum. A solution of 5-[[1-[(3-hydroxy-1-
10 piperidiny)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-
methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in
tetrahydrofuran (35 ml) and methyl amine (2M in THF, 30 mL) was stirred at room
temperature overnight. The solvent was removed and dried under house vacuum. A
solution of 3-({2-[1-[(3-hydroxy-1-piperidiny)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-
15 6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-
methyl-2 thiophenecarboxamide in THF (2 mL), water (2 mL), and MeOH (5 mL) was
treated with K₂CO₃ (0.60g) and the resulting mixture was stirred at 80°C for 3 hours.
The K₂CO₃ was filtered off and the solvent was removed to yield the crude product.
which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford
20 3-[(2-{[1-[(3-hydroxy-1-piperidiny)acetyl]-5-(methyloxy)-2,3-dihydro-1H-indol-6-yl]amino}-
1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-methyl-2-thiophenecarboxamide (0.16 g, 61%).
ESIMS (M+H)⁺ = 577. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.08 (s., 1 H), 1.42 (d,
J=11.72 Hz, 1 H), 1.61 (d, J=12.91 Hz, 1 H), 1.77 (br. s., 1 H), 1.91 (t, J=9.57 Hz, 1 H),
2.02 (t, J=10.30 Hz, 1 H), 2.69 (d, J=10.71 Hz, 1 H), 2.79 (d, J=4.30 Hz, 3 H), 2.90 (br.
25 s., 1 H), 3.12 (t, J=8.10 Hz, 2 H), 3.23 (d, J=5.13 Hz, 2 H), 3.48 (d, J=4.67 Hz, 1 H), 3.78

(s, 3 H), 4.14 - 4.27 (m, 2 H), 4.62 (d, J=4.67 Hz, 1 H), 6.27 (s, 1 H), 6.96 (s, 2 H), 7.60 (d, J=5.31 Hz, 1 H), 7.70 (s, 1 H), 8.12 (d, J=4.30 Hz, 1 H), 8.42 (d, J=5.31 Hz, 1 H), 8.58 (s, 1 H), 11.31 (d, J=10.44 Hz, 2 H).

5 Example 65

N-methyl-3-[(2-{[1-{N-methyl-N-[2-(methoxy)ethyl]glycyl}-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-2-thiophenecarboxamide

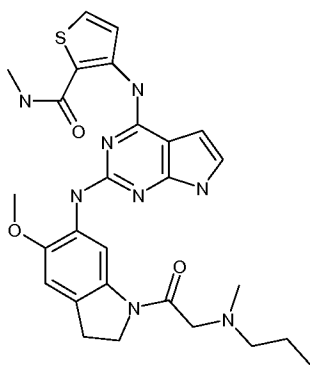


- 10 A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (450 mg, 1.0 mmol) and 1-({methyl[2-(methoxy)ethyl]amino}acetyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (350 mg, 1.2 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml).
- 15 The organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. A solution of 5-[(1-{N-methyl-N-[2-(methoxy)ethyl]glycyl}-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (35 ml) and methyl amine (2M in THF, 30 mL) was stirred at room
- 20 temperature overnight. The solvent was removed and dried under house vacuum prior. A solution of N-methyl-3-[(2-{[1-{N-methyl-N-[2-(methoxy)ethyl]glycyl}-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino)-2-thiophenecarboxamide THF (20 mL) and MeOH (20 mL) was treated with NaOMe (0.4g) and stirred at 70°C for 2 hours. The solvent was removed, the residue
- 25 was redissolved in 50 ml of DCM, washed with 50 ml of sat.NH₄Cl, and the organic solvent was removed to yield the crude product which was adsorbed to silica gel and

purified by LC (DCM to 10% MeOH/DCM) to afford N-methyl-3-[(2-{[1-{N-methyl-N-[2-(methoxy)ethyl]glycyl}-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.15 g, 38%). ESIMS (M+H)⁺ = 565. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.30 (s, 3 H), 2.65 (t, J=5.59 Hz, 2 H), 2.79 (d, J=4.21 Hz, 2 H), 2.93 - 3.00 (m, 1 H), 3.12 (t, J=7.97 Hz, 1 H), 3.22 (d, J=3.57 Hz, 3 H), 3.27 (s, 1 H), 3.32 (s, 1 H), 3.36 (br. s., 1 H), 3.43 (d, J=2.66 Hz, 2 H), 3.71 (s, 1 H), 3.78 (s, 2 H), 4.02 - 4.09 (m, 1 H), 4.18 (t, J=8.06 Hz, 1 H), 6.28 (s., 1 H), 6.96 (br. s., 2 H), 7.56 (s, 1 H), 7.60 (d, J=5.31 Hz, 1 H), 7.70 (s, 1 H), 8.42 (d, J=5.40 Hz, 1 H), 8.60 (s, 1 H), 11.31 (s., 1 H), 11.34 (s, 1 H)

Example 66

N-methyl-3-[(2-{[5-(methoxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

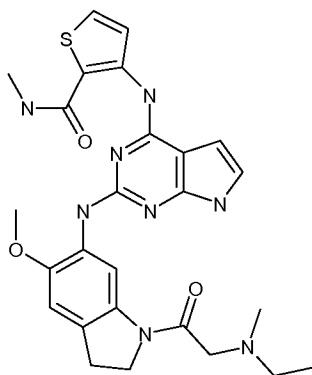


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (500mg, 1.2 mmol) and 5-(methoxy)-1-[[methyl(propyl)amino]acetyl]-2,3-dihydro-1H-indol-6-amine (380 mg, 1.4 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was diluted with ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. A solution of 5-[[5-(methoxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one in tetrahydrofuran (35 ml) and methyl amine (2M in THF, 30 mL) was stirred at room temperature overnight. The solvent was removed and the resulting residue was dried

under house vacuum. Next, a solution of N-methyl-3-({2-([5-(methoxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl]amino)-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino)-2-thiophenecarboxamide in THF (20 mL) and MeOH (20 mL) was treated with sodium methoxide (0.30g) stirred at 70°C for 2 hours. The solvent was removed, the residue was redissolved in 50 ml of DCM, washed with 50 ml of sat.NH₄Cl, and the organic solvent was removed to yield the crude product which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford N-methyl-3-[(2-([5-(methoxy)-1-(N-methyl-N-propylglycyl)-2,3-dihydro-1H-indol-6-yl]amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (0.22 g, 81%). ESIMS (M+H)⁺ = 549. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.84 (t, J=7.23 Hz, 3 H), 1.38 - 1.49 (m, 2 H), 2.23 (s, 3 H), 2.38 (t, J=7.10 Hz, 2 H), 2.79 (d, J=4.21 Hz, 3 H), 3.13 (t, J=8.10 Hz, 1 H), 3.19 (s, 1 H), 3.24 (s, 1 H), 3.35 (s, 2 H), 3.71 (s, 1 H), 3.78 (s, 2 H), 4.21 (t, J=8.19 Hz, 1 H), 6.27 (br. s., 1 H), 6.96 (s, 2 H), 7.59 (d, J=5.31 Hz, 1 H), 7.70 (s, 1 H), 8.12 (d, J=4.30 Hz, 1 H), 8.41 (d, J=5.31 Hz, 1 H), 8.58 (s, 1 H), 11.32 (d, J=13.09 Hz, 2 H).

Example 67

3-[(2-([1-(N-ethyl-N-methylglycyl)-5-(methoxy)-2,3-dihydro-1H-indol-6-yl]amino)-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-methyl-2-thiophenecarboxamide

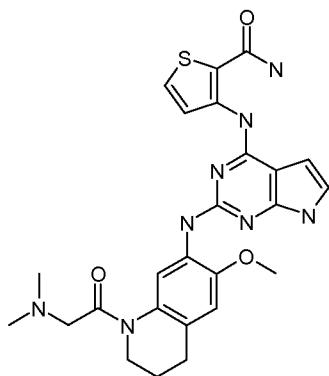


A suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrochloride (400 mg, 0.9 mmol) and 1-[[ethyl(methyl)amino]acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (300 mg, 1.1 mmol) in THF (30 ml) was heated at 70°C overnight. The reaction was diluted with

ethyl acetate (100 ml) and washed with saturated NaHCO₃ (100 ml). The organic layer was removed, concentrated by rotary evaporation, solids triturated from ethyl acetate/hexanes, and dried under house vacuum. A solution of 5- $\{[1-(N\text{-ethyl-}N\text{-methylglycyl})\text{-}5\text{-(methyloxy)}\text{-}2,3\text{-dihydro-}1H\text{-indol-}6\text{-yl)]\text{amino}\}$ -3- $\{[4\text{-methylphenyl)sulfonyl]pyrrolo}[3,2\text{-e}]\text{thieno}[3',2':4,5]\text{pyrimido}[1,2\text{-c}]\text{pyrimidin-}7(3H)\text{-one}$ in tetrahydrofuran (35 ml) and methyl amine (2M in THF, 50 mL) was stirred at room temperature overnight. The solvent was removed and dried under house vacuum. A solution of 3- $\{[2\text{-}\{[1-(N\text{-ethyl-}N\text{-methylglycyl})\text{-}5\text{-(methyloxy)}\text{-}2,3\text{-dihydro-}1H\text{-indol-}6\text{-yl)]\text{amino}\}$ -7- $\{[4\text{-methylphenyl)sulfonyl}\}$ -7H-pyrrolo $[2,3\text{-d}]\text{pyrimidin-}4\text{-yl}\}$ amino)-N-methyl-2-thiophenecarboxamide in THF (20 mL) and MeOH (20 mL) was treated with sodium methoxide (0.35g) and stirred at 70°C for 2 hours. The solvent was removed, the residue was redissolved in 50 ml of DCM, washed with 50 ml of sat.NH₄Cl, and the organic solvent was removed to yield the crude product which was adsorbed to silica gel and purified by LC (DCM to 10% MeOH/DCM) to afford 3- $\{[2\text{-}\{[1-(N\text{-ethyl-}N\text{-methylglycyl})\text{-}5\text{-(methyloxy)}\text{-}2,3\text{-dihydro-}1H\text{-indol-}6\text{-yl)]\text{amino}\}$ -1H-pyrrolo $[2,3\text{-d}]\text{pyrimidin-}4\text{-yl}\}$ amino]-N-methyl-2-thiophenecarboxamide (0.20 g, 57%). ESIMS (M+H)⁺ = 535. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.98 (t, J=7.00 Hz, 3 H), 2.20 (s, 3 H), 2.47 (dd, J=4.17, 2.06 Hz, 2 H), 2.76 (d, J=4.40 Hz, 3 H), 3.10 (t, J=8.15 Hz, 2 H), 3.21 (s, 2 H), 3.75 (s, 3 H), 4.18 (t, J=8.19 Hz, 2 H), 6.25 (br. s., 1 H), 6.93 (s, 2 H), 7.56 (d, J=5.40 Hz, 1 H), 7.67 (s, 1 H), 8.09 (d, J=4.30 Hz, 1 H), 8.39 (d, J=5.40 Hz, 1 H), 8.57 (s, 1 H), 11.29 (d, J=13.09 Hz, 2 H)

Example 68

3- $\{[2\text{-}\{[1-(N,N\text{-dimethylglycyl})\text{-}6\text{-(methyloxy)}\text{-}1,2,3,4\text{-tetrahydro-}7\text{-quinolinyl)]\text{amino}\}$ -1H-pyrrolo $[2,3\text{-d}]\text{pyrimidin-}4\text{-yl}\}$ amino]-2-thiophenecarboxamide

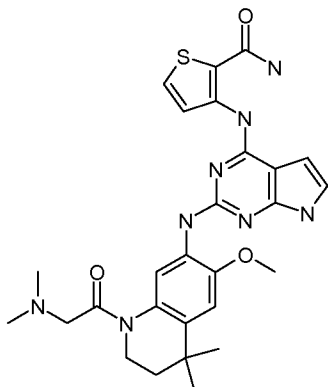


A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido [1,2-c]pyrimidin-7(3*H*)-one hydrochloride (1.00 g, 2.14 mmol) and 1-[(dimethylamino) acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (700 mg, 2.66 mmol) was
 5 dissolved in 2,2,2-trifluoroethanol (30 mL) and heated in a sealed tube overnight. The reaction was concentrated, added to a sealed tube, diluted with tetrahydrofuran (20 mL), treated with excess 28% aqueous ammonia (25 mL), and stirred overnight at 90 °C. The reaction was cooled, the organic layer was separated, dried over sodium sulfate, filtered,
 10 concentrated, and subjected to purification via flash silica gel chromatography (0 to 20% methanol/dichloromethane, with ~1% ammonium hydroxide). The product obtained, 3-({2-[[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide, (ESIMS (*M*+*H*)⁺ = 675), was dissolved in THF (10 mL), 1,4-dioxane (30 mL), and treated
 15 with excess potassium hydroxide (3.0 g dissolved in 5 mL of water), and stirred at 100 °C for 6 h. The reaction was cooled, diluted with water and EtOAc, and transferred to a separatory funnel and shaken. Brine was added to assist in the separation of layers. The organic layer was separated, dried over sodium sulfate, filtered, and subjected to purification via flash silica gel column chromatography (0 to 20%
 20 methanol/dichloromethane, spiked with ~1% ammonium hydroxide). Relevant fractions were combined, concentrated, and suspended in diethyl ether/ethyl acetate. The solids obtained were filtered to obtain 3-[(2-[[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (259 mg, 0.47 mmol, 21% over 3 steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.83 - 1.94 (m, 2 H), 2.12 (s, 6 H), 2.64 - 2.75 (m, 2 H), 3.25 (s, 2 H),
 25

3.67 - 3.77 (m, 2 H), 3.84 (s, 3 H), 6.21 - 6.28 (m, 1 H), 6.84 (s, 1 H), 7.01 (s, 1 H), 7.51 - 7.70 (m, 4 H), 8.33 - 8.44 (m, 2 H), 11.36 - 11.46 (m, 2 H); ESIMS (M+H)⁺ = 521.

Example 69

5 **3-[(2-{[1-(*N,N*-dimethylglycyl)-4,4-dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**



A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido
 10 [1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (90% pure, 603 mg, 1.16 mmol) and 1-[(dimethylamino) acetyl]-4,4-dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinamine (367 mg, 1.26 mmol) was dissolved in 2,2,2-trifluoroethanol (25 mL) and refluxed for 3 h. The reaction was cooled, diluted with excess saturated aqueous sodium bicarbonate, and then extracted with dichloromethane. The organic layer was separated, dried over
 15 magnesium sulfate, filtered, and concentrated. The crude material 5-[(1-(*N,N*-dimethylglycyl)-4,4-dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo [3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one was divided approximately into two equal parts.

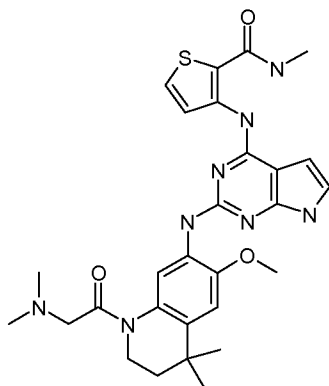
One part (assumed ~0.58 mmol) was taken in a sealed tube, diluted with tetrahydrofuran
 20 (10 mL), treated with excess 28% aqueous ammonia (10 mL), and stirred overnight at 50 °C. The reaction was cooled, the organic layer was separated, dried over magnesium sulfate, filtered, concentrated, and subjected to purification via flash silica gel chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol:2*M* ammonia in methanol). The product obtained, 3-[(2-{[1-(*N,N*-dimethylglycyl)-4,4-
 25 dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide,

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was dissolved in THF (10 mL), MeOH (10 mL), treated with excess sodium methoxide (200 mg, 3.70 mmol), and stirred at 70 °C for 2 h. The reaction was cooled, diluted with water and EtOAc, and transferred to a separatory funnel and shaken. Brine was added to assist in the separation of layers. The organic layer was separated, dried over sodium sulfate, filtered, and subjected to purification via flash silica gel column chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol :2M ammonia in methanol). Relevant fractions were combined, concentrated, suspended in diethyl ether/ethyl acetate. The solids were filtered to obtain 3-[(2-{[1-(*N,N*-dimethylglycyl)-4,4-dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (110 mg, 0.200 mmol, ~34% over three steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (s, 6 H), 1.69 - 1.77 (m, 2 H), 2.11 (s, 6 H), 3.27 (s, 2 H), 3.73 - 3.80 (m, 2 H), 3.88 (s, 3 H), 6.25 (s, 1 H), 6.96 (s, 1 H), 7.02 (s, 1 H), 7.51 - 7.72 (m, 4 H), 8.34 (s, 1 H), 8.39 (d, *J*=5.3 Hz, 1 H), 11.42 (s, 2 H); ESIMS (*M*+*H*)⁺ = 549.

Example 70

3-[(2-{[1-(*N,N*-dimethylglycyl)-4,4-dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide

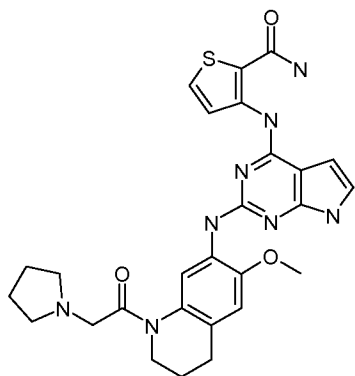


A part of the crude material 5-{[1-(*N,N*-dimethylglycyl)-4,4-dimethyl-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-3-[(4-methylphenyl)sulfonyl]pyrrolo [3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one (assumed ~0.58 mmol) obtained from Example 69 was taken in a sealed tube, diluted with tetrahydrofuran (10 mL), treated with excess methyl amine (10 mL, 20 mmol, 2M in THF), and stirred overnight at

50 °C. The reaction was cooled, concentrated, and subjected to purification via flash silica gel chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol:2M ammonia in methanol). The product obtained, 3-({2-([1-(*N,N*-dimethylglycyl)-4,4-dimethyl-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-*N*-methyl-2-thiophenecarboxamide, was characterized by LC (ESIMS (M+H)⁺ = 717), dissolved in THF (3 mL), MeOH (6 mL), treated with excess sodium methoxide (200 mg, 3.70 mmol), and stirred at 70 °C for 2 h. The reaction was cooled, diluted with water, EtOAc, and transferred to a separatory funnel and shaken. Brine was added to assist in the separation of layers. The organic layer was separated, dried over sodium sulfate, filtered, and subjected to purification via flash silica gel column chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol:2M ammonia in methanol). Relevant fractions were combined, concentrated, and subjected to further purification under reverse phase HPLC (10 to 70% acetonitrile/water with 0.05% trifluoroacetic acid). Relevant fractions were collected and treated with excess saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, concentrated, suspended in diethyl ether/ethyl acetate. The solids obtained were filtered to obtain 3-[(2-([1-(*N,N*-dimethylglycyl)-4,4-dimethyl-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (29 mg, 0.05 mmol, ~9% over three steps) ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (s, 6 H), 1.68 - 1.78 (m, 2 H), 2.11 (s, 6 H), 2.79 (d, *J*=4.6 Hz, 3 H), 3.28 (s, 2 H), 3.73 - 3.80 (m, 2 H), 3.88 (s, 3 H), 6.29 (s, 1 H), 6.96 (s, 1 H), 7.02 (s, 1 H), 7.63 - 7.68 (m, 2 H), 8.13 - 8.19 (m, 1 H), 8.32 - 8.35 (m, 1 H), 8.39 (d, *J*=5.3 Hz, 1 H), 11.33 (s, 1 H), 11.42 (br. s., 1 H); ESIMS (M+H)⁺ = 563.

Example 71

3-[(2-([6-(methoxy)-1-(1-pyrrolidinyl)acetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

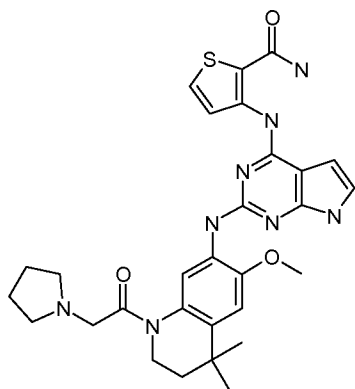


A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido [1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (730 mg, 2.08 mmol) and 6-(methoxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine (730 mg, 2.52 mmol) were mixed
 5 in tetrahydrofuran (~25 mL) and heated at 90 °C in a sealed tube overnight. The reaction was concentrated, the crude material was diluted with tetrahydrofuran (~20 mL), treated with excess 28% aqueous ammonia (~25 mL), and heated in a sealed tube overnight at 80 °C. The mixture was cooled; the organic layer was separated, dried over sodium
 10 sulfate, and subjected to purification by flash silica gel chromatography (0 to 20% methanol/dichloromethane, spiked with ~1% ammonium hydroxide). Relevant fractions were mixed and concentrated; the solids obtained were triturated with dichloromethane/hexanes/diethylether. The mixture was filtered and the residue, 3-({2-[[6-(methoxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-7-[(4-methylphenyl)sulfonyl]-
 15 7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-2-thiophenecarboxamide (ESIMS ($M+H$)⁺ = 701, 95% pure). The residue was diluted with tetrahydrofuran (15 mL), methanol (20 mL), treated with excess sodium methoxide (1.4 g, 26 mmol) and stirred at 80 °C for 2 h. The reaction was cooled, diluted with water and EtOAc. Brine was added to assist in the separation of layers. The organic layer was separated, dried over sodium sulfate,
 20 filtered, adsorbed on silica gel and purified by flash silica gel chromatography (0 to 20% methanol/dichloromethane, with ~1% ammonium hydroxide). Fractions, which seemed clean were concentrated, triturated with dichloromethane/hexanes, and filtered. ¹H NMR of the solids obtained revealed the presence of an impurity (~35%) which was presumed to be *p*-toluenesulfonic acid. The solids were taken up in dichloromethane
 25 with slight amounts of methanol, washed with 4 N aqueous sodium hydroxide, and the aqueous layer was back-extracted with THF (brine was added to assist in separation of

layers). The organic layers were combined, dried over magnesium sulfate, and concentrated. ¹H NMR of the solids obtained revealed that *p*-tosic acid (~5%) was still present. At this point the solids were dissolved in methanol/dichloromethane, adsorbed over silica gel, purified via flash silica gel chromatography (0 to 20% 2M ammonia in MeOH/CH₂Cl₂). Relevant fractions were concentrated and the solids obtained triturated to provide 3-[(2-[[6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (250 mg, 0.46 mmol, 22% over three steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.45 - 1.57 (m, 4 H), 1.84 - 1.94 (m, 2 H), 2.36 - 2.48 (m, 4 H), 2.70 (s, 2 H), 3.35 - 3.46 (m, 2 H), 3.69 - 3.76 (m, 2 H), 3.85 (s, 3 H), 6.26 (s, 1 H), 6.85 (s, 1 H), 7.01 (s, 1 H), 7.62 (s, 4 H), 8.38 - 8.49 (m, 2 H), 11.37 - 11.47 (m, 2 H); ESIMS (M+H)⁺ = 547.

Example 72

3-[(2-[[4,4-dimethyl-6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

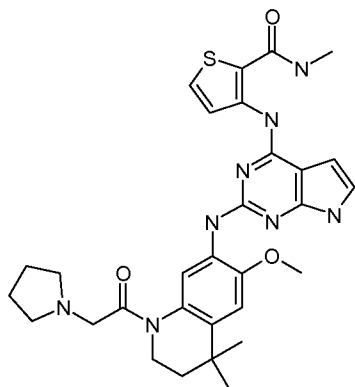


A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido [1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride (90% pure, 600 mg, 1.16 mmol) and 4,4-dimethyl-6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinamine (395 mg, 1.24 mmol) was taken in 2,2,2-trifluoroethanol (25 mL) and refluxed for 3 h. The reaction was cooled, diluted with excess saturated aqueous sodium bicarbonate, and then extracted with dichloromethane. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. The crude material 5-[[4,4-dimethyl-6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-3-[(4-

5 methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one was divided approximately into two equal parts. One part (assumed ~0.58 mmol) was added to a sealed tube, diluted with tetrahydrofuran (10 mL), treated with excess 28% aqueous ammonia (10 mL), and stirred overnight at 50 °C. The reaction was cooled, the organic layer was separated, dried over magnesium sulfate, filtered, concentrated, and subjected to purification via flash silica gel chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol:2M ammonia in methanol). The product obtained, 3-({2-([4,4-dimethyl-6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide (ESIMS (M+H)⁺ = 729) was dissolved in THF (3 mL), MeOH (6 mL), treated with excess sodium methoxide (200 mg, 3.70 mmol), and stirred at 70 °C for 2 h. The reaction was cooled, diluted with water, EtOAc, and transferred to a separatory funnel and shaken. Brine was added to assist in the separation of layers. The organic layer was separated, dried over sodium sulfate, filtered, and subjected to purification via flash silica gel column chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol:2M ammonia in methanol). Relevant fractions were combined, concentrated, and suspended in diethyl ether/ethyl acetate. The solids obtained were filtered to obtain 3-[(2-([4,4-dimethyl-6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (82 mg, 0.14 mmol, ~24% over three steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.28 (s, 6 H), 1.49 (br. s., 4 H), 1.70 - 1.76 (m, 2 H), 2.38 (br. s., 4 H), 3.36 (br. s., 2 H), 3.77 (t, *J*=6.1 Hz, 2 H), 3.89 (s, 3 H), 6.24 - 6.26 (m, 1 H), 6.96 (s, 1 H), 7.01 (s, 1 H), 7.53 - 7.69 (m, 4 H), 8.36 - 8.43 (m, 2 H), 11.39 - 11.46 (m, 2 H); ESIMS (M+H)⁺ = 575.

Example 73

3-[(2-([4,4-dimethyl-6-(methyloxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide



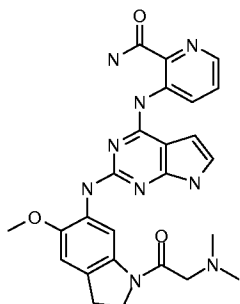
A part of the crude material 5-[[4,4-dimethyl-6-(methoxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino]-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one (assumed ~0.58 mmol-see Example 5 72) was added to a sealed tube, diluted with tetrahydrofuran (5 mL), treated with excess methyl amine (10 mL, 20 mmol, 2M in tetrahydrofuran), and stirred overnight at 50 °C. The reaction was cooled, concentrated, and subjected to purification via flash silica gel chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol:2M ammonia in methanol). The product obtained, 3-[(2-{[4,4-dimethyl-6-(methoxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-*N*-methyl-2-thiophenecarboxamide (ESIMS (M+H)⁺ = 743) was dissolved in THF (5 mL), MeOH (10 mL), treated with excess sodium methoxide (200 mg, 3.70 mmol), and stirred at 70 °C for 2 h. The reaction was cooled, 15 diluted with water, EtOAc, and transferred to a separatory funnel and shaken. Brine was added to assist in the separation of layers. The organic layer was separated, dried over sodium sulfate, filtered, and subjected to purification via flash silica gel column chromatography (dichloromethane to 8:1:1 mixture of dichloromethane:methanol:2M ammonia in methanol). Relevant fractions were combined, concentrated, and subjected 20 to further purification under reverse phase HPLC (10 to 70% acetonitrile/water with 0.05% trifluoroacetic acid). Relevant fractions were collected, treated with excess potassium carbonate, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, concentrated, suspended in diethyl ether/ethyl acetate. The solids obtained were filtered to obtain 3-[(2-{[4,4-dimethyl-6-(methoxy)-1-(1-pyrrolidinylacetyl)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (43 mg, 0.07 mmol, ~13% over three 25

steps). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.28 (s, 6 H), 1.50 (br. s., 4 H), 1.69 - 1.75 (m, 2 H), 2.40 (br. s., 4 H), 2.79 (d, $J=4.4$ Hz, 3 H), 3.38 (br. s, 2 H), 3.73 - 3.81 (m, 2 H), 3.89 (s, 3 H), 6.27 - 6.31 (m, 1 H), 6.95 - 7.03 (m, 2 H), 7.62 - 7.66 (m, 2 H), 8.16 (s, 1 H), 8.35 - 8.43 (m, 2 H), 11.34 (s, 1 H), 11.43 (br. s., 1 H); ESIMS ($\text{M}+\text{H}$) $^+$ = 589.

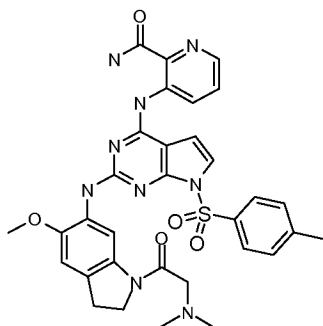
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Example 74

3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-pyridinecarboxamide



- 10 Step A/Intermediate C16: 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-pyridinecarboxamide



A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrido[3,2-

- 15 d]pyrrolo[2',3':4,5]pyrimido[1,6-*a*]pyrimidin-7(3*H*)-one hydrogen chloride (69 mg, 0.149 mmol) and 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (37.2 mg, 0.149 mmol) in THF (6 mL) was stirred at rt for 4 h. The resulting orange slurry was treated with a 27% aqueous NH_4OH solution (50 mL). The resulting clear mixture was stirred at rt. After 2 h EtOAc (100 mL) and a saturated NaCl solution (50 mL) were
- 20 added. The organic layer was washed with a saturated NaCl solution (50 mL). The aqueous layers were back extracted with CHCl_3 (100 mL). The combined organic layers were concentrated onto Celite and purified by silica gel chromatography using 1-10%

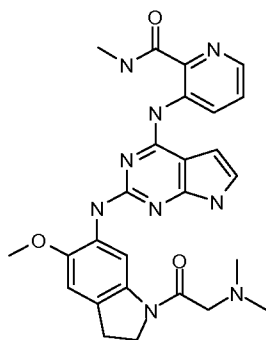
MeOH (containing 0.2% NH₃)/CH₂Cl₂. The product was triturated using CH₂Cl₂ and Et₂O to afford 3-({2-([1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-2-pyridinecarboxamide as a white solid (42.5 mg, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.23 (s, 6H), 2.35 (s, 3H), 3.15-3.27 (m, 4H), 3.74 (s, 3H), 4.24 (t, *J*=7.89 Hz, 2H), 6.44-6.55 (m, 1H), 7.09 (s, 1H), 7.20-7.50 (m, 4H), 7.88-8.11 (m, 3H), 8.16 (br s, 1H), 8.22 (s, 1H), 8.52 (s, 2H), 9.18 (d, *J*=7.89 Hz, 1H), 12.59 (s, 1H); ESIMS (M+H)⁺ = 656.35.

Step B/Example 73: 3-[(2-([1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-2-pyridinecarboxamide

A mixture of 3-({2-([1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-2-pyridinecarboxamide (40 mg, 0.061 mmol) and a 2M aqueous NaOH solution (1 mL) in dioxane (5 mL) was heated at 90 °C. After 2.5 h the reaction mixture was allowed to cool to rt and maintained overnight. The resulting slurry was filtered, the solids were washed with dioxane and E₂O to obtain 3-[(2-([1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-2-pyridinecarboxamide as a yellow solid (17.7 mg, 58%). ¹H NMR (400 MHz, THF-*d*₈) δ ppm 2.30 (s, 6H), 3.04-3.21 (m, 4H), 3.87 (s, 3H), 4.25 (t, *J*=8.31 Hz, 2H), 6.47 (d, *J*=3.16 Hz, 1H), 6.83 (s, 1H), 6.90 (d, *J*=3.02 Hz, 1H), 7.13 (s, 1H), 7.33-7.50 (m, 2H), 8.07 (d, *J*=4.26 Hz, 1H), 8.31 (s, 1H), 9.36 (s, 1H), 9.66 (d, *J*=8.65 Hz, 1H), 10.67 (s, 1H), 12.55 (s, 1H); ESIMS (M+H)⁺ = 502.35.

Example 75

3-[(2-([1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-*N*-methyl-2-pyridinecarboxamide

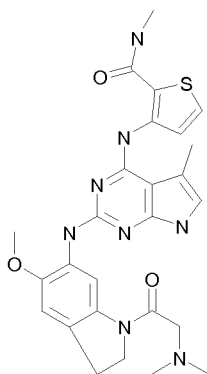


A solution of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrido[3,2-d]pyrrolo[2',3':4,5]pyrimido[1,6-a]pyrimidin-7(3H)-one hydrogen chloride (10 mg, 0.022 mmol) and 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1H-indol-6-amine (5.39 mg, 0.022 mmol) in 2,2,2-trifluoroethanol (1 mL) was stirred at rt. After 1 h a 2M MeNH₂ solution in THF (4 mL) was added and the reaction mixture was maintained at rt for 18 h. A 2N aqueous NaOH solution (1 mL) was added and the reaction mixture was heated at 80 °C for 4 h. The resulting mixture was allowed to cool to rt. EtOAc (50 mL) was added and the layers were separated. The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford 3-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-pyridinecarboxamide as a white solid (5 mg, 44%).
¹H NMR (400 MHz, THF-*d*₈) δ ppm 2.30 (s, 6H), 2.96 (d, *J*=4.94 Hz, 3H), 3.06-3.18 (m, 4H), 3.87 (s, 3H), 4.24 (t, *J*=8.51 Hz, 2H), 6.52 (dd, *J*=3.11, 1.83 Hz, 1H), 6.82 (s, 1H), 6.89-6.96 (m, 1H), 7.36-7.45 (m, 2H), 8.05 (d, *J*=3.66 Hz, 1H), 8.79 (d, 4.94 Hz, 1H), 9.41 (s, 1H), 9.65 (d, *J*=8.79 Hz, 1H), 10.76 (s, 1H), 12.59 (s, 1H); ESIMS (*M*+*H*)⁺ = 516.16.

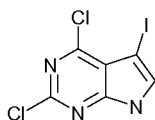
Example 76

3-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide

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Step A/Intermediate C17: 2,4-dichloro-5-iodo-1*H*-pyrrolo[2,3-*d*]pyrimidine



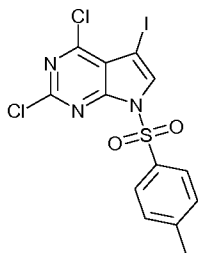
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2,4-dichloro-1*H*-pyrrolo[2,3-*d*]pyrimidine (0.5 g, 2.66 mmol) was dissolved in anhydrous DMF (20 mL) and *N*-iodo succinimide (718 mg, 3.19 mmol) was added. After stirring for 45 minutes at room temperature, the reaction mixture was poured into water (400 mL) and extracted with EtOAc (2x500 mL). Organics were combined and washed with brine (500 mL) and dried over sodium sulfate. Solvents were removed under reduced pressure and purified via column chromatography to afford 2,4-dichloro-5-iodo-1*H*-pyrrolo[2,3-*d*]pyrimidine (660 mg, 2.103 mmol) as a yellow solid. ESIMS (*M*+*H*)⁺=315

10

Step B/Intermediate C18: 2,4-dichloro-5-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine

15



2,4-dichloro-5-iodo-1*H*-pyrrolo[2,3-*d*]pyrimidine (660 mg, 2.103 mmol) and *p*-toluenesulfonyl chloride (441 mg, 2.31 mmol) were combined in dry dichloromethane

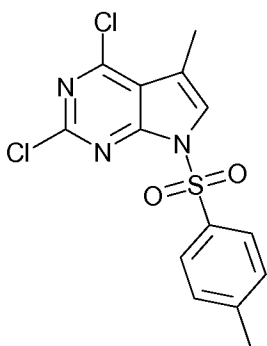
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(20 ml). Diisopropylethylamine (0.734 mL, 4.21 mmol) was added and the reaction mixture was let stir at rt for 18 h. The reaction was then diluted with dichloromethane and the organic layer was washed with a saturated solution of sodium bicarbonate, water and a saturated solution of brine, then dried over sodium sulfate. Solvents were removed under reduced pressure and the residue purified by chromatography on SiO₂ to afford 2,4-dichloro-5-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (901 mg, 1.94 mmol) as a yellow solid.

(ESIMS (M+H)⁺ =469)

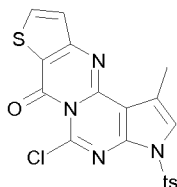
- 10 Step C/Intermediate C19: 2,4-dichloro-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine



- 2,4-dichloro-5-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (800 mg, 1.71 mmol) and Pd(PPh₃)₄ (40 mg, 0.034 mmol) were combined in dry THF (20 ml) and a 2M solution of methylzinc chloride in THF (1.28 ml, 2.56 mmol) was added under N₂. The reaction mixture was let stir at 60°C for 18 h at which time the reaction was diluted with ethyl acetate and the organic layer was washed with a saturated solution of sodium bicarbonate, water and a saturated brine solution, then dried over sodium sulfate. Solvents were removed under reduced pressure and the residue purified by chromatography on SiO₂ to afford 2,4-dichloro-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (487 mg, 1.37 mmol) as a tan solid. This reaction was repeated to synthesize sufficient material as needed for subsequent reactions. (ESIMS(M+H)⁺ =357)

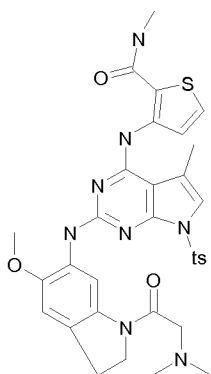
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Step D/Intermediate C20: 5-chloro-1-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one HCl salt



To a suspension of 2,4-dichloro-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.27 g, 3.57 mmol) and methyl 3-amino-2-thiophenecarboxylate (0.841 g, 5.35 mmol) in TFE (20 mL) was added trifluoroacetic acid (2.03 g, 17.83 mmol) and the mixture was heated at 85°C for ~30 h. At this time the reaction was terminated and the solids filtered and washed with TFE. Residual solvent was removed under reduced pressure to afford a solid containing about 90% methyl 3-({2-chloro-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-thiophenecarboxylate (614 mg, 1.29 mmol). This material (and 423 mg of material obtained following the procedure for the reaction described above) was dissolved in THF (50 mL) and a solution of lithium hydroxide (521 mg, 21.74 mmol) in water (15 ml) was added. Additional water (50 ml) and THF (35 ml) were added in efforts to solublize the reactants. The reaction was let stir at rt for 50 h at which time an additional 5 eq of LiOH was added. After several hours of stirring, little change occurred so reaction was worked up by diluting with EtOAc and washing with a saturated solution of NaCl. The organics were concentrated in vacuo to give a white residue which was dissolved in THF (10 ml) and DMF (few drops) and a solution of 2M oxalyl chloride in dichloromethane (0.960 mL, 1.92 mmol) was added dropwise. LCMS analysis indicated some starting material remained so an additional 0.5 eq of oxalyl chloride was added. The reaction mixture was then concentrated in vacuo to afford 5-chloro-1-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one HCl salt (754 mg, 1.695 mmol) (~70% clean). (ESIMS (M+H)⁺ = 445)

Step E/ Intermediate C21: 3-({2-[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-*N*-methyl-2-thiophenecarboxamide



To a flask containing 5-chloro-1-methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3*H*)-one HCl salt (747 mg, 1.09 mmol) in
2,2,2-trifluoroethanol (20 mL) was added 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-
dihydro-1*H*-indol-6-amine (352 mg, 1.41 mmol). The resulting slurry was stirred at 60°C
for 6 h and then rt for 16h, followed by 2h at 40°C. Solvents were removed under
reduced pressure to afford a green residue. Half of this material was dissolved in a 2M
solution of methyl amine in THF (15 ml). The reaction was let stir at rt for 48 h, at which
time the reaction mixture was diluted with ethyl acetate and washed with a saturated
solution of sodium bicarbonate, water and saturated brine solution. Organics were dried
over sodium sulfate and solvents removed under reduced pressure to afford a solid that
was purified via chromatography on SiO₂ to afford 3-({2-[[1-(*N,N*-dimethylglycyl)-5-
(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-
pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-*N*-methyl-2-thiophenecarboxamide (292 mg, 0.424
mmol). (ESIMS (M+H)⁺ = 689)

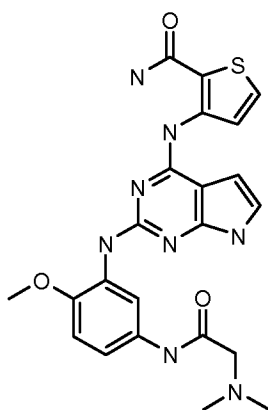
Step F/Example 76: 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-
yl]amino}-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-*N*-methyl-2-
thiophenecarboxamide

3-({2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-5-methyl-
7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-*N*-methyl-2-
thiophenecarboxamide (292 mg, 0.424 mmol) was dissolved in dioxane (6 mL) and 2*N*
NaOH (2 mL) was added in a microwave safe vessel. The reaction was then heated in a
microwave at 120°C for 15 min. Reaction was diluted with EtOAc and the organic layer

was washed with water and a saturated brine solution and dried over sodium sulfate. Solvents were removed under reduced pressure and the residue purified by chromatography on SiO₂ and then reverse phase HPLC to afford 3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (52 mg, 0.097 mmol) as a tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.25 (s, 6 H) 2.76 (d, *J*=4.39 Hz, 3 H) 3.13 (t, *J*=8.24 Hz, 2 H) 3.18 (s, 2 H) 3.77 (s, 3 H) 4.18 (t, *J*=8.24 Hz, 2 H) 6.66 (s, 1 H) 6.96 (s, 1 H) 7.53 (d, *J*=5.31 Hz, 1 H) 7.62 (s, 1 H) 8.05 (d, *J*=4.58 Hz, 1 H) 8.44 (d, *J*=5.49 Hz, 1 H) 8.53 (s, 1 H) 10.89 (s, 1 H) 11.15 (s, 1 H) (3H hidden under DMSO peak at 2.5). (ESIMS (M+H)⁺ = 535

Example 77

3-[(2-[[5-[(*N,N*-dimethylglycyl)amino]-2-(methoxy)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride (400 mg, 0.856 mmol) and N1-[3-amino-4-(methoxy)phenyl]-N2,N2-dimethylglycinamide hydrogen chloride (222 mg, 0.856 mmol) in 2,2,2-trifluoroethanol (40 mL) was heated at 50 °C for 3 days. LCMS indicated incomplete reaction, therefore more N1-[3-amino-4-(methoxy)phenyl]-N2,N2-dimethylglycinamide hydrogen chloride (120 mg, 0.46 mmol) was added and the mixture was heated at 80 °C for 4 h. After allowing to cool to rt THF (50 mL) and a 27% aqueous NH₄OH solution (150 mL) were added. The reaction mixture was heated at 80 °C for 18 h, allowed to cool to rt and diluted with CHCl₃ (200 mL). The organic layer was washed with a saturated NaCl solution (100 mL),

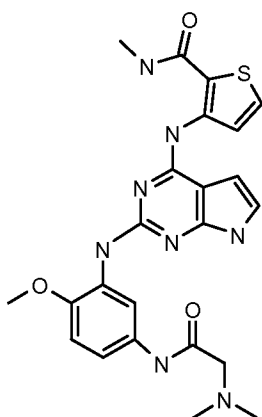
275

concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to obtain 3-[(2-[(5-[(*N,N*-dimethylglycyl)amino]-2-(methoxy)phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-

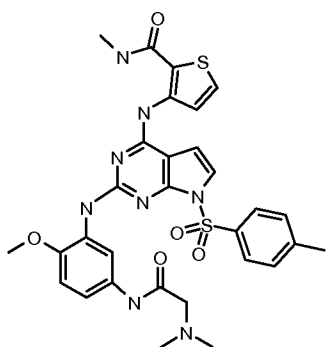
thiophenecarboxamide as a white solid (86 mg, 21%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.27 (s, 6H), 3.03 (s, 2H), 3.83 (s, 3H), 6.26 (dd, $J=3.30, 1.83$ Hz, 1H), 6.96 (d, $J=8.79$ Hz, 1H), 7.01 (dd, $J=3.30, 2.38$ Hz, 1H), 7.37 (dd, $J=8.79, 2.56$ Hz, 1H), 7.58 (br s, 1H), 7.66 (d, $J=5.31$ Hz, 1H), 7.69 (s, 1H), 8.16 (d, $J=2.56$ Hz, 1H), 8.41 (d, $J=5.49$ Hz, 1H), 9.42 (s, 1H), 11.38 (s, 1H), 11.44 (s, 1H); ESIMS ($\text{M}+\text{H}$) $^+$ = 484.14.

10 Example 78

3-[(2-[(5-[(*N,N*-dimethylglycyl)amino]-2-(methoxy)phenyl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide



15 Step A/Intermediate C22: 3-[(2-[(5-[(*N,N*-dimethylglycyl)amino]-2-(methoxy)phenyl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide



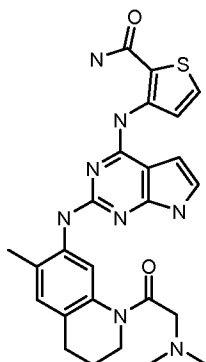
A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride (400 mg, 0.856 mmol) and N1-[3-amino-4-(methyloxy)phenyl]-N2,N2-dimethylglycinamide hydrogen chloride (222 mg, 0.856 mmol) in 2,2,2-trifluoroethanol (40 mL) was heated at 50 °C for 3 days. LCMS indicated starting material remained, therefore more N1-[3-amino-4-(methyloxy)phenyl]-N2,N2-dimethylglycinamide hydrogen chloride (120 mg, 0.46 mmol) was added. The reaction mixture was heated at 80 °C for 4 h. A 2M MeNH₂ solution in THF (10 mL) was added and the mixture was heated at 80 °C. After 40 h the resulting mixture was allowed to cool to rt, concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford 3-{2-[[5-[(N,N-dimethylglycyl)amino]-2-(methyloxy)phenyl]amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-N-methyl-2-thiophenecarboxamide as a yellow solid (436 mg, 79%). ESIMS (M+H)⁺ = 649.20.

Step B/Example 78: 3-[(2-[[5-[(N,N-dimethylglycyl)amino]-2-(methyloxy)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-methyl-2-thiophenecarboxamide

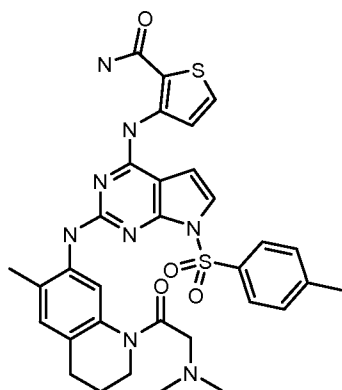
A mixture of 3-{2-[[5-[(N,N-dimethylglycyl)amino]-2-(methyloxy)phenyl]amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-N-methyl-2-thiophenecarboxamide (434 mg, 0.669 mmol) and a 1M aqueous KOH solution (6.69 mL, 6.69 mmol) in dioxane (20 mL) was heated at 80 °C for 7 h. The resulting mixture was allowed to cool to rt. EtOAc (50 mL) and a saturated NaHCO₃ solution (50 mL) were added. The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂. The product was dissolved in a mixture of CH₂Cl₂ and Et₂O and concentrated again to afford 3-[(2-[[5-[(N,N-dimethylglycyl)amino]-2-(methyloxy)phenyl]amino]-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-methyl-2-thiophenecarboxamide (160 mg, 48%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.27 (s, 6H), 2.79 (d, *J*=4.40 Hz, 3H), 3.03 (s, 2H), 3.83 (s, 3H), 6.60 (dd, *J*=3.39, 1.74 Hz, 1H), 6.96 (d, *J*=8.79 Hz, 1H), 6.99-7.05 (m, 1H), 7.37 (dd, *J*=8.70, 2.47 Hz, 1H), 7.65 (d, *J*=5.31 Hz, 1H), 7.69 (s, 1H), 8.08-8.21 (m, 2H), 8.41 (d, *J*=5.49 Hz, 1H), 9.42 (s, 1H), 11.35 (s, 1H), 11.38 (br s, 1H); ESIMS (M+H)⁺ = 495.13.

Example 79

3-[(2-{[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



- 5 Step A/Intermediate C23: 3-({2-[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-2-thiophenecarboxamide



A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-

- 10 e]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride (300 mg, 0.642 mmol) and 1-[(dimethylamino)acetyl]-6-methyl-1,2,3,4-tetrahydro-7-quinolinamine (159 mg, 0.642 mmol) in THF (50 mL) was heated at 70 °C for 20 h. The resulting mixture was allowed to cool to rt and treated with a 27% aqueous NH₄OH solution (100 mL). The reaction mixture was stirred at rt for 3 days. LCMS indicated incomplete reaction,
- 15 therefore more 27% aqueous NH₄OH solution (100 mL) was added. The mixture was heated at 80 °C for 40 h, then was allowed to cool to rt. EtOAc (200 mL) and a saturated NaCl solution (100 mL) were added. The organic layer was washed with a saturated NaCl solution, concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH(containing 0.2% NH₃)/CH₂Cl₂ to afford 3-({2-[1-(*N,N*-dimethylglycyl)-6-

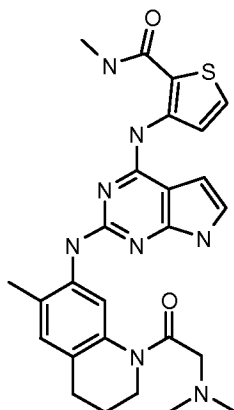
methyl-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino)-2-thiophenecarboxamide as a beige solid (55 mg, 13%). ESIMS (M+H)⁺ = 659.11.

- 5 Step B/Example 79: 3-[(2-{[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

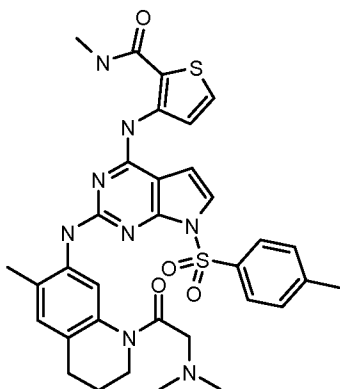
A mixture of 3-[(2-{[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide (53 mg, 0.080 mmol) and a 1M aqueous KOH solution (0.805 mL, 0.805 mmol) in dioxane (10 mL) was heated at 80 °C for 11 h. LCMS indicated incomplete reaction, therefore more 1M aqueous KOH solution (0.805 mL, 0.805 mmol) was added. The mixture was heated at 80 °C for 7 h, then was allowed to cool to rt. EtOAc (50 mL) and a saturated NaHCO₃ solution (50 mL) were added. The organic layer
15 was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂. The product was taken up into a mixture of CH₂Cl₂ and hexanes and concentrated to obtain 3-[(2-{[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-2-thiophenecarboxamide as a white solid (40 mg,
20 99%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.84-41.96 (m, 2H), 2.12 (s, 6H), 2.17 (s, 3H), 2.71 (t, *J*=6.41 Hz, 2H), 3.19 (s, 2H), 3.73 (t, *J*=5.95 Hz, 2H), 6.20 (dd, *J*=3.48, 1.83 Hz, 1H), 6.89-7.97 (m, 1H), 7.02 (s, 1H), 7.36-7.69 (m, 3H), 7.76 (br s, 1H), 8.17 (s, 1H), 8.28 (d, *J*=5.31 Hz, 1H), 11.24 (s, 1H), 11.38 (s, 1H). ESIMS (M+H)⁺ = 504.87.

25 **Example 80**

3-[(2-{[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide



Step A/Intermediate C24: 3-({2-([1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinoliny]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-*N*-methyl-2-thiophenecarboxamide



5

A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride (300 mg, 0.642
mmol) and 1-[(dimethylamino)acetyl]-6-methyl-1,2,3,4-tetrahydro-7-quinolinamine (159
mg, 0.642 mmol) in THF (50 mL) was heated at 70 °C. After 20 h a 2M MeNH₂ solution
10 in THF (10 mL) was added and the reaction mixture was stirred at rt for 3 days, then was
heated at 80 °C for 40 h. The resulting mixture was allowed to cool to rt, concentrated
onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing
0.2% NH₃)/CH₂Cl₂ to obtain 3-({2-([1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-
quinoliny]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-*N*-
15 methyl-2-thiophenecarboxamide as a yellow solid (162 mg, 38%). ¹H NMR (400 MHz,
DMSO-*d*₆) δ ppm 1.86-2.01 (m, 2H), 2.12 (br s, 6H), 2.17 (s, 3H), 2.32 (s, 3H), 2.73-2.85
(m, 5H), 3.17 (br s, 2H), 3.79 (t, *J*=5.86 Hz, 2H), 6.49 (d, *J*=4.03 Hz, 1H), 7.14 (s, 1H),
7.24 (d, *J*=7.64 Hz, 2H), 7.32 (d, *J*=4.03 Hz, 1H), 7.56 (d, *J*=5.49 Hz, 1H), 7.67 (br s,

1H), 7.83 (d, $J=5.68$ Hz, 2H), 8.00-8.24 (m, 2H), 8.76 (s, 1H), 11.43 (s, 1H); ESIMS (M+H)⁺ = 673.17

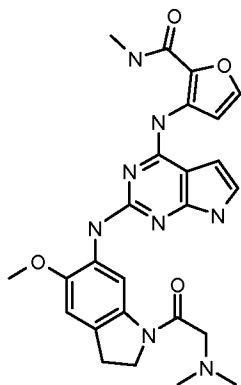
Step B/Example 80: 3-[(2-[[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinoliny]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide

A solution of 3-[(2-[[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinoliny]amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (160 mg, 0.238 mmol) in dioxane (20 mL) and a 1M aqueous KOH solution (2.378 mL, 2.378 mmol) was heated at 80 °C for 5 h. LCMS indicated incomplete reaction, therefore more 1M aqueous KOH solution (0.805 mL, 0.805 mmol) was added and the reaction mixture was heated at 80 °C for 7 h. the resulting mixture was allowed to cool to rt, diluted with EtOAc (100 mL) and a saturated NaHCO₃ solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford 3-[(2-[[1-(*N,N*-dimethylglycyl)-6-methyl-1,2,3,4-tetrahydro-7-quinoliny]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide as a white solid (74 mg, 60%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.83-1.97 (m, 2H), 2.11 (s, 6H), 2.17 (s, 3H), 2.71 (t, $J=6.50$ Hz, 2H), 2.78 (d, $J=4.39$ Hz, 3H), 3.18 (s, 2H), 3.73 (t, $J=6.04$ Hz, 2H), 6.23 (dd, $J=3.30, 1.83$ Hz, 1H), 6.89-6.96 (m, 1H), 7.01 (s, 1H), 7.54 (d, $J=5.31$ Hz, 1H), 7.76 (br s, 1H), 8.10 (q, $J=4.21$ Hz, 1H), 8.16 (s, 1H), 8.29 (d, $J=5.31$ Hz, 1H), 11.23 (s, 1H), 11.30 (s, 1H); ESIMS (M+H)⁺ = 519.08.

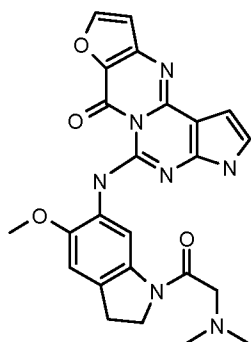
Example 81

3-[(2-[[1-(*N,N*-dimethylglycyl)-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-furancarboxamide

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Step A/Intermediate C25: 5-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]furo[3,2-*d*]pyrrolo[2',3':4,5]pyrimido[1,6-*a*]pyrimidin-7(3*H*)-one



5

A slurry of 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-2-furancarboxylic acid (1.925 g, 4.45 mmol) in CH_2Cl_2 (100 mL) was treated with a drop of DMF, followed by oxalyl chloride (0.779 mL, 8.89 mmol). The reaction mixture was stirred at rt. The resulting mixture was divided in half and both batches were concentrated. One batch of this crude intermediate 5-chloro-3-[(4-methylphenyl)sulfonyl]furo[3,2-*d*]pyrrolo[2',3':4,5]pyrimido[1,6-*a*]pyrimidin-7(3*H*)-one hydrogen chloride was dissolved in THF (50 mL) and 1-[(dimethylamino)acetyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (555 mg, 2.225 mmol) was added. After 6 h a 2M MeNH_2 solution in THF (11.13 mL, 22.25 mmol) was added. After 3 days at rt the resulting mixture was concentrated onto Celite and purified column chromatography to obtain 5-[[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino]furo[3,2-*d*]pyrrolo[2',3':4,5]pyrimido[1,6-*a*]pyrimidin-7(3*H*)-one as a yellow solid (25 mg). ESIMS ($\text{M}+\text{H}$)⁺ = 628.19.

10

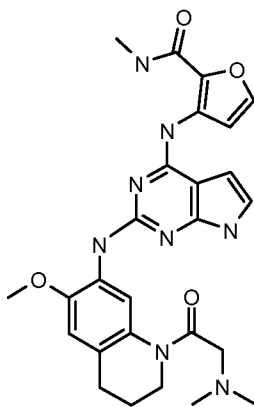
15

Step B/Example 81: 3-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-furancarboxamide

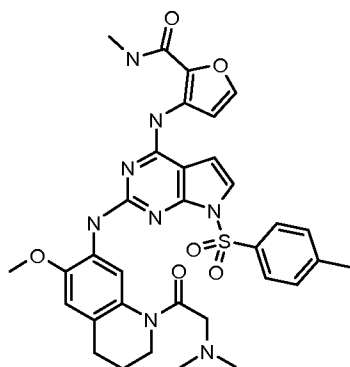
A solution of 5-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-3-[(4-methylphenyl)sulfonyl]furo[3,2-*d*]pyrrolo[2',3':4,5]pyrimido[1,6-*a*]pyrimidin-7(3*H*)-one (23 mg, 0.037 mmol) in a 2M MeNH₂ solution in THF (10 mL, 20.00 mmol) was stirred at rt for 20 h. The resulting mixture was concentrated. The residue was dissolved in dioxane (1.5 mL), treated with a 2M aqueous NaOH solution (1.5 mL, 3.00 mmol) and heated in the uW at 120 °C for 12 min. The two layers were separated, the organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford 3-[(2-{[1-(*N,N*-dimethylglycyl)-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-furancarboxamide as a brown solid (11 mg). ¹H NMR (400 MHz, THF-*d*₈) δ ppm 2.31 (s, 6H), 2.89 (d, *J*=4.76 Hz, 3H), 3.09 (t, *J*=8.24 Hz, 2H), 3.14 (s, 2H), 3.87 (s, 3H), 4.33 (t, *J*=8.33 Hz, 2H), 6.35 (s, 1H), 6.81 (s, 1H), 6.89 (s, 1H), 7.32-7.49 (m, 3H), 7.81 (s, 1H), 9.51 (s, 1H), 9.79 (s, 1H), 10.86 (s, 1H); ESIMS (M+H)⁺ = 505.14.

Example 82

3-[(2-{[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-furancarboxamide



Step A/Intermediate C26: 3-[(2-{[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-furancarboxamide



A slurry of 3-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-2-furancarboxylic acid (1.925 g, 4.45 mmol) in CH₂Cl₂ (100 mL) was treated with a drop of DMF, followed by oxalyl chloride (0.779 mL, 8.89 mmol). The reaction mixture was stirred at rt. The resulting mixture was divided in half and both batches were concentrated. One batch of this crude intermediate 5-chloro-3-[(4-methylphenyl)sulfonyl]furo[3,2-d]pyrrolo[2',3':4,5]pyrimido[1,6-a]pyrimidin-7(3H)-one hydrogen chloride and 1-[(dimethylamino)acetyl]-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinamine (586 mg, 2.225 mmol) in 2,2,2-trifluoroethanol (50 mL) were stirred at rt. After 3 days the resulting mixture was diluted with EtOAc (200 mL) and a saturated NaHCO₃ solution (100 mL). The organic layer was washed with a saturated NaCl solution (100 mL), dried (Na₂SO₄) and concentrated. The residue was triturated using Et₂O. This crude intermediate was dissolved in THF (10 mL) and a 2M MeNH₂ solution in THF (20 mL). The reaction mixture was heated at 80 °C for 6 h. The resulting mixture was allowed to cool to rt, concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-({2-[[1-(*N,N*-dimethylglycyl)-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-*N*-methyl-2-furancarboxamide as a brown solid (88 mg). ESIMS (M+H)⁺ = 673.17.

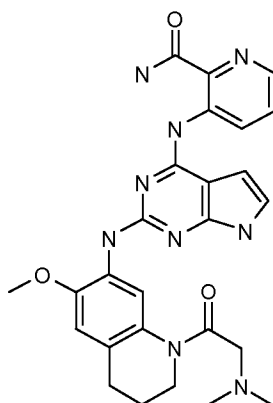
Step B/Example 82: 3-[(2-[[1-(*N,N*-dimethylglycyl)-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-*N*-methyl-2-furancarboxamide

A mixture of 3-({2-[[1-(*N,N*-dimethylglycyl)-6-(methyloxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-*N*-methyl-2-furancarboxamide (88 mg, 0.131 mmol) and a 2M aqueous NaOH solution (5

mL) in dioxane (5 mL) was heated in the MW at 120 °C for 12 min. The resulting mixture was diluted with EtOAc (50 mL) and a saturated NaHCO₃ solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford 3-[(2-[[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinoliny]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-furancarboxamide as a beige solid (82 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.79-1.97 (m, 2H), 2.12 (br s, 6H), 2.59-2.76 (m, 2H), 2.79 (d, *J*=4.58 Hz, 3H), 3.26 (s, 2H), 3.71 (t, *J*=6.04 Hz, 2H), 3.84 (s, 3H), 6.26 (dd, *J*=3.20, 1.56 Hz, 1H), 6.84 (s, 1H), 6.94-7.06 (s, 1H), 7.63-7.77 (m, 3H), 8.26 (q, *J*=4.27 Hz, 1H), 8.36 (s, 1H), 9.66 (s, 1H), 11.40 (br s, 1H); ESIMS (M+H)⁺ = 519.21.

Example 83

3-[(2-[[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinoliny]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-pyridinecarboxamide

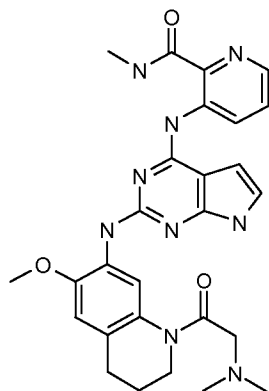


A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrido[3,2-*d*]pyrrolo[2',3':4,5]pyrimido[1,6-*a*]pyrimidin-7(3*H*)-one hydrogen chloride (300 mg, 0.649 mmol) and 1-[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (171 mg, 0.649 mmol) in 2,2,2-trifluoroethanol (10 mL) was stirred at rt. After 3 days THF (10 mL) was added, followed by a 27% aqueous NH₄OH solution (30 mL). The reaction mixture was stirred at rt. After 5 h a 2M aqueous NaOH solution (2 mL) was added and the reaction mixture was heated at 80 °C for 6 h. The resulting mixture was allowed to cool to rt, diluted with EtOAc (100 mL) and a saturated NaCl solution (50 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford 3-[(2-[[1-(*N,N*-

dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-pyridinecarboxamide as a white solid (65 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.79-1.97 (m, 2H), 2.08 (br s, 6H), 2.71 (br s, 2H), 3.21 (s, 2H), 3.73 (t, *J*=5.59 Hz, 2H), 3.84 (s, 3H), 6.28-6.35 (m, 1H), 6.85 (s, 1H), 7.04 (s, 1H), 7.48 (dd, *J*=8.42, 4.2 Hz, 1H), 7.72 (s, 1H), 7.80 (d, *J*=1.83 Hz, 1H), 8.15-8.27 (m, 1H), 8.38 (s, 1H), 8.53 (d, *J*=1.65 Hz, 1H), 9.45 (d, *J*=8.61 Hz, 1H), 11.44 (br s, 1H), 12.45 (s, 1H); ESIMS (M+H)⁺ = 516.38.

Example 84

3-[(2-{[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-pyridinecarboxamide

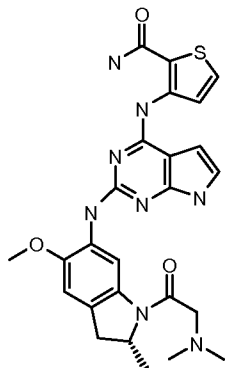


A mixture of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrido[3,2-*d*]pyrrolo[2',3':4,5]pyrimido[1,6-*a*]pyrimidin-7(3*H*)-one hydrogen chloride (300 mg, 0.649 mmol) and 1-[(dimethylamino)acetyl]-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinamine (171 mg, 0.649 mmol) in 2,2,2-trifluoroethanol (10 mL) was stirred at rt. After 3 days THF (10 mL) was added, followed by a 2M MeNH₂ solution in THF (20 mL). The reaction mixture was stirred at rt. After 5 h a 2M aqueous NaOH solution (2 mL) was added and the reaction mixture was heated at 80 °C for 6 h. The resulting mixture was allowed to cool to rt, concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-{[1-(*N,N*-dimethylglycyl)-6-(methoxy)-1,2,3,4-tetrahydro-7-quinolinyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-pyridinecarboxamide as a yellow solid (197 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.82-1.96 (m, 2H), 2.08 (br s, 6H), 2.71 (br s, 2H), 2.87 (d, *J*=4.94 Hz, 3H), 3.22 (s, 2H), 3.66-3.79 (m, 2H), 3.85 (s, 3H), 6.36 (dd, *J*=3.20, 1.74 Hz, 1H), 6.85 (s, 1H), 7.04 (s, 1H), 7.48 (dd, *J*=8.52, 4.30 Hz, 1H), 7.72 (s, 1H), 8.21 (dd,

$J=4.39$, 1.46 Hz, 1H), 8.39 (s, 1H), 9.18 (q, $J=4.58$ Hz, 1H), 9.44 (dd, $J=8.61$, 0.92 Hz, 1H), 11.44 (br s, 1H), 12.43 (s, 1H); ESIMS (M+H)⁺ = 530.39.

Example 85

5 **3-[(2-[(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide**

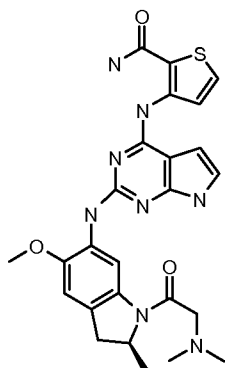


A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 10 e]thieno[3',2':4,5]pyrimido[1,2-c]pyrimidin-7(3H)-one hydrogen chloride (0.600 mg, 1.284 μ mol) and (2*R*)-1-[(dimethylamino)acetyl]-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (0.338 mg, 1.284 μ mol) in 2,2,2-trifluoroethanol (10 mL) was stirred at rt for 18 h. The resulting deep green slurry was split into 2 equal batches. One of the batches was treated with a 27% aqueous NH_4OH solution (10 mL). The orange slurry was heated
 15 at 80 °C for 20 h. The resulting mixture was diluted with EtOAc (50 mL) and a saturated NaHCO_3 solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 . This crude intermediate was dissolved in dioxane (10 mL) and a 2M aqueous NaOH solution (2 mL) and was heated at 80 °C for 5 h. The
 20 resulting mixture was allowed to cool to rt, diluted with EtOAc (50 mL) and a saturated NaCl solution (10 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to afford 3-[(2-[(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide as a yellow
 25 solid (122 mg, 55%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.27 (d, $J=5.13$ Hz, 3H), 2.26 (s, 6H), 2.60 (d, $J=15.38$ Hz, 1H), 3.08 (d, $J=14.28$ Hz, 1H), 3.26-3.49 (m, 2H), 3.80 (s,

3H), 4.72-4.88 (m, 1H), 6.24 (s, 1H), 6.99 (s, 2H), 7.39-7.80 (m, 4H), 8.40 (d, $J=5.13$ Hz, 1H), 8.59 (s, 1H), 11.33 (s, 1H), 11.43 (s, 1H); ESIMS (M+H)⁺ = 521.34; Optical rotation +14.2 (1mg/mL MeOH, rt).

5 Example 86

3-[(2-[(2S)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide

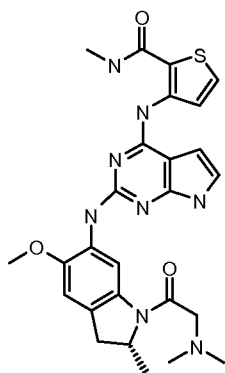


A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-
 10 e]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride (0.600 mg, 1.284 μ mol) and (2*S*)-1-[(dimethylamino)acetyl]-2-methyl-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-amine (0.338 mg, 1.284 μ mol) in 2,2,2-trifluoroethanol (10 mL) was stirred at rt for 18 h. The resulting deep green slurry was split into 2 equal batches. One of the batches was treated with a 27% aqueous NH_4OH solution (10 mL). The resulting orange slurry
 15 was stirred at rt for 20 h. The resulting mixture was diluted with EtOAc (50 mL) and a saturated NaHCO_3 solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 . This crude intermediate was taken up into dioxane (10 mL) and a 2M aqueous NaOH solution (2
 20 mL), and was heated at 80 $^\circ\text{C}$ for 5 h. The resulting mixture was allowed to cool to rt, diluted with EtOAc (50 mL) and a saturated NaCl solution (10 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH_3)/ CH_2Cl_2 to afford 3-[(2-[(2*S*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-
 25 yl)amino]-2-thiophenecarboxamide as a yellow solid (129 mg, 74%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.27 (d, $J=5.49$ Hz, 3H), 2.26 (s, 6H), 2.60 (d, $J=15.57$ Hz, 1H), 3.08

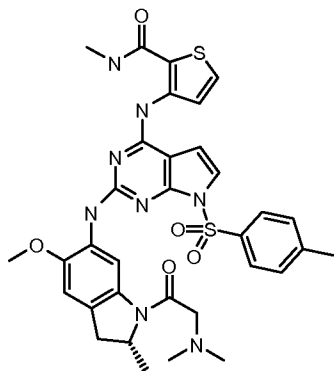
(d, $J=14.28$ Hz, 1H), 3.23-3.47 (m, 2H), 3.80 (s, 3H), 4.72-4.86 (m, 1H), 6.25 (s, 1H), 6.99 (s, 2H), 7.38-7.78 (m, 4H), 8.40 (d, $J=5.31$ Hz, 1H), 8.59 (s, 1H), 11.33 (s, 1H), 11.43 (s, 1H); ESIMS (M+H)⁺ = 521.32; Optical rotation -10.6 (1mg/mL MeOH, rt).

5 Example 87

3-[(2-[(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide



- 10 Step A/Intermediate C27: 3-[(2-[(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide



A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-

- 15 e]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride (0.600 mg, 1.284 μ mol) and (2*R*)-1-[(dimethylamino)acetyl]-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (0.338 mg, 1.284 μ mol) in 2,2,2-trifluoroethanol (10 mL) was stirred at rt for 18 h. The resulting deep green slurry was split into 2 equal batches. One of the batches was treated with a 2M MeNH₂ solution in THF (10 mL). The orange slurry was stirred at

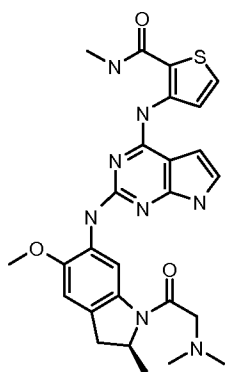
rt for 2 days. The resulting mixture was diluted with EtOAc (50 mL) and a saturated NaCl solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂, followed by trituration using Et₂O to obtain 3-({2-[[{(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-*N*-methyl-2-thiophenecarboxamide as a yellow solid (68 mg, 16%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.30 (s, 3H), 2.31 (s, 6H), 2.33 (s, 3H), 2.59-2.84 (m, 4H), 3.16-3.58 (m, 3H), 3.77 (s, 3H), 4.73-4.89 (m, 1H), 6.50 (d, *J*=3.48 Hz, 1H), 7.10 (s, 1H), 7.20-7.41 (m, 3H), 7.52 (s, 1H), 7.84-8.02 (m, 2H), 8.05-8.31 (m, 3H), 8.39 (s, 1H), 11.43 (s, 1H); ESIMS (M+H)⁺ = 689.26.

Step B/Example 87: 3-[(2-[[{(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-*N*-methyl-2-thiophenecarboxamide

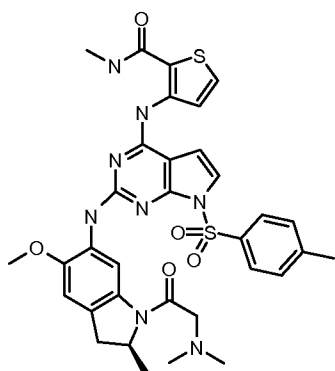
A solution of 3-({2-[[{(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-*N*-methyl-2-thiophenecarboxamide (66 mg, 0.096 mmol) in dioxane (10 mL) and a 2M aqueous NaOH solution (2 mL) was heated at 80 °C for 6 h. The resulting mixture was allowed to cool to rt, diluted with EtOAc (50 mL) and a saturated NaCl solution (10 mL). The organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to obtain 3-[(2-[[{(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methyloxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino)-*N*-methyl-2-thiophenecarboxamide as a yellow solid (48 mg, 94%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 (d, *J*=5.31 Hz, 3H), 2.26 (s, 6H), 2.61 (d, *J*=15.02 Hz, 1H), 2.79 (d, *J*=4.58 Hz, 3H), 3.08 (d, *J*=14.28 Hz, 1H), 3.22-3.47 (m, 2H), 3.80 (s, 3H), 4.72-4.86 (m, 1H), 6.28 (s, 1H), 6.92-7.08 (m, 2H), 7.52-7.63 (m, 1H), 7.66 (s, 1H), 8.13 (s, 1H), 8.40 (d, *J*=5.49 Hz, 1H), 8.58 (s, 1H), 11.33 (s, 1H), 11.34 (s, 1H). ESIMS (M+H)⁺ = 535.35; Optical rotation +13.7 (1mg/mL MeOH, rt).

Example 88

3-[(2-[(2S)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide



- 5 Step A/Intermediate C28: 3-({2-[(2S)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-*N*-methyl-2-thiophenecarboxamide



A slurry of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-

- 10 e]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrogen chloride (0.600 mg, 1.284 μ mol) and (2S)-1-[(dimethylamino)acetyl]-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-amine (0.338 mg, 1.284 μ mol) in 2,2,2-trifluoroethanol (10 mL) was stirred at rt for 18 h. The resulting deep green slurry was split into 2 equal batches. One of the batches was treated with a 2M MeNH₂ solution in THF (10 mL). The orange slurry was stirred at
15 rt for 2 days. The resulting mixture was diluted with EtOAc (50 mL) and a saturated NaCl solution (50 mL). The organic layer was washed with a saturated NaCl solution (50 mL), concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford as a yellow solid (300 mg, 70%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (s, 3H), 2.26 (s, 6H), 2.33 (s, 3H), 2.68 (d, *J*=15.75 Hz, 1H),

2.76 (d, $J=4.58$ Hz, 3H), 3.15 (d, 14.47 Hz, 1H), 3.28-3.52 (m, 2H), 3.76 (s, 3H), 4.76-4.87 (m, 1H), 6.51 (d, $J=3.66$ Hz, 1H), 7.09 (s, 1H), 7.21-7.38 (m, 3H), 7.52 (br s, 1H), 7.95 (d, $J=6.59$ Hz, 2H), 8.07-8.27 (m, 3H), 8.39 (s, 1H), 11.43 (s, 1H); ESIMS (M+H)⁺ = 689.30.

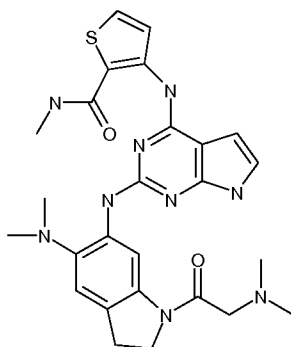
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StepB/Example 88: 3-[(2-[(2*S*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide

- 10 A solution of 3-[(2-[(2*R*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide (296 mg, 0.430 mmol) in dioxane (10 mL) and a 2M aqueous NaOH solution (2 mL) was heated at 80 °C for 7 h. The resulting mixture was allowed to cool to rt, diluted with EtOAc (50 mL) and a saturated NaCl solution (10 mL). The
- 15 organic layer was concentrated onto Celite and purified by silica gel chromatography using 1-10% MeOH (containing 0.2% NH₃)/CH₂Cl₂ to afford 3-[(2-[(2*S*)-1-(*N,N*-dimethylglycyl)-2-methyl-5-(methoxy)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide as a yellow solid (180 mg, 78%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 (d, $J=5.31$ Hz, 3H), 2.26 (s, 6H), 2.60
- 20 (d, $J=15.20$ Hz, 1H), 2.79 (d, $J=4.58$ Hz, 3H), 3.08 (d, $J=14.28$ Hz, 1H), 3.25-3.47 (m, 2H), 3.80 (s, 3H), 4.72-4.86 (m, 1H), 6.28 (s, 1H), 6.92-7.08 (m, 2H), 7.52-7.63 (m, 1H), 7.66 (s, 1H), 8.13 (s, 1H), 8.40 (d, $J=5.31$ Hz, 1H), 8.59 (s, 1H), 11.33 (s, 1H), 11.34 (s, 1H); ESIMS (M+H)⁺ = 535.41; Optical rotation -8.5 (1mg/mL MeOH, rt).

25 **Example 89**

3-[(2-[(5-(dimethylamino)-1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl]amino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide

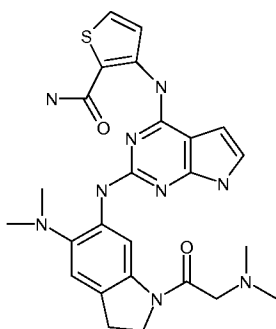


In a manner analogous to a procedure outlined previously, 3-[(2-[[5-(dimethylamino)-1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-*N*-methyl-2-thiophenecarboxamide was prepared from 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one hydrochloride, 1-[(dimethylamino)acetyl]-*N*5,*N*5-dimethyl-2,3-dihydro-1*H*-indole-5,6-diamine, and methyl amine to afford the title compound (0.2 g, 50% over 3 steps).

ESIMS (*M*+*H*)⁺ = 534. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.25 (s, 6 H) 2.60 (s, 6 H) 2.79 (d, *J*=4.41 Hz, 3 H) 3.04 - 3.12 (m, 2 H) 3.18 (s, 2 H) 4.14 - 4.21 (m, 2 H) 6.29 (br. s., 1 H) 6.99 (br. s., 1 H) 7.07 (s, 1 H) 7.62 (d, *J*=5.62 Hz, 1 H) 7.73 (s, 1 H) 8.09 - 8.19 (m, 1 H) 8.42 (d, *J*=5.22 Hz, 1 H) 8.75 (s, 1 H) 11.33(s, 1 H) 11.36(s, 1 H).

Example 90

3-[(2-[[5-(dimethylamino)-1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide



In a manner analogous to a procedure outlined previously, 3-[(2-[[5-(dimethylamino)-1-(*N,N*-dimethylglycyl)-2,3-dihydro-1*H*-indol-6-yl]amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-2-thiophenecarboxamide was prepared from 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*e*]thieno[3',2':4,5]pyrimido[1,2-*c*]pyrimidin-7(3*H*)-one

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hydrochloride, 1-[(dimethylamino)acetyl]-N5,N5-dimethyl-2,3-dihydro-1H-indole-5,6-diamine, and ammonium hydroxide to afford the title compound (0.25 g, 63% over 2 steps). ESIMS (M+H)⁺ = 520. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.25 (br. s., 6 H) 2.60 (s, 6 H) 3.08 (t, *J*=6.72 Hz, 2 H) 3.18 (br. s., 2 H) 4.17 (t, *J*=7.93 Hz, 2 H) 6.26 (br. s., 1 H) 6.99 (br. s., 1 H) 7.07 (br. s., 1 H) 7.5-7.64 (m, 3 H) 7.73 (br. s., 1 H) 8.42 (d, *J*=5.02 Hz, 1 H) 8.75 (s, 1 H) 11.33 (br. s., 1 H) 11.44 (br. s., 1 H).

10

ASSAYS

Time Resolved Fluorescence Resonance Energy Transfer (TR-FRET) assays were carried out on the exemplified compounds as follows:

The source of substrate peptide

The biotinylated substrate peptide, (sequence - Biotin-aminohexyl-AEEEEY*MMMAK KKK-NH₂) is purchased from QCB, Inc. (Hopkinton, MA). Purity is determined by HPLC. The calculated molecular mass of the peptide is 2216 dalton. Tyrosine phosphorylation by human IGF1R (hIGF1R) or human IR (hIR) occurs as indicated (Y*) in the peptide sequence described. Solid peptide sample is dissolved to approximately 1 mM in DMSO, aliquoted, and stored at -20°C until use. True peptide concentration is determined by amino acid analysis.

25

The source of enzyme:

hIGF1R: GST-rTEV-IGF-1R(957-1367) containing amino acid residues 957-1367 of human IGF1R (as annotated by National Center for Biotechnology Information (NCBI) accession number NP_000866) is purified from a baculovirus expression system in Sf9 cells using Glutathione Sepharose 4FF column chromatography followed by Sephadex-200 size exclusion column chromatography. Enzyme purity of approximately 95% is achieved. Samples, in 25 mM Tris-HCl, 250 mM NaCl, 5% glycerol, 1 mM DTT, pH 7.5, are stored at -80°C until use.

30

hIR: GST-rTEV-IR(979-1382) containing amino acid residues 979-1382 of human IR (as annotated by NCBI accession number NP_000199) is expressed and purified by the same process as hIGF1R. Enzyme purity of approximately 92% is achieved. Samples, in 25 mM Tris-HCl, 250 mM NaCl, 5% glycerol, 1 mM DTT, pH 7.5, are stored at -80°C until use.

Activation of hIGF1R and hIR by autophosphorylation:

hIGF1R: Activation of GST-rTEV-IGF-1R(957-1367) is achieved by a 4 minute incubation of hIGF1R (2.7 μ M final) with 2 mM ATP in 50 mM HEPES, 20 mM MgCL₂, 0.1 mg/ml BSA, at room temperature. Autophosphorylation is stopped by addition of EDTA (to 100 mM final). Aliquoted samples are flash frozen in liquid nitrogen and stored at -80°C until use.

hIR: Activation of GST-rTEV-IGF-1R(957-1367) is achieved by a 5 minute incubation of hIR (2.7 μ M final) with 2 mM ATP in 100 mM HEPES, 10 mM MgCL₂, 0.1 mg/ml BSA, at room temperature. Autophosphorylation is stopped by addition of EDTA (to 100 mM final). Aliquoted samples are flash frozen in liquid nitrogen and stored at -80°C until use.

Kinase assay of purified hIGF1R or hIR:

Assays are performed in 384-well (Greiner, Catalog No. 784076) microtiter plates. Reaction buffer (50 mM HEPES buffer, pH 7.5; 10 mM MgCL₂; 3 mM DTT; 1 mM CHAPS; 0.1 mg/ml BSA) for peptide phosphorylation (10 μ l volume) contained, in final concentrations, 500 nM biotinylated peptide substrate; 10 μ M ATP; and purified, activated hIGF1R or hIR (0.5 nM). Compounds, titrated in DMSO, are evaluated at eleven concentrations ranging from 50 μ M to 0.2 nM. Final assay concentrations of DMSO do not exceed 10%. No effect on activity relative to controls without DMSO is observed for hIGF1R or IR at these DMSO amounts. Reactions are incubated for 1 hour at room temperature and are stopped by a 5 μ l addition of EDTA (to 33 mM). A further addition of 5 μ l detection reagents (for final 7 nM Streptavidin-APC (PerkinElmer #CR¹³⁰-150), 1 nM Europium-labeled anti-phosphotyrosine monoclonal antibody (PerkinElmer #AD0067), added in reaction buffer (without DTT), is required for signal generation. After 30 minutes, signal is read on PerkinElmer Viewlux microplate imager or Wallac Victor fluorometer.

The data for compound concentration responses were plotted as % Inhibition, calculated with the data reduction formula $100 * (1 - [(U1 - C2) / (C1 - C2)])$, versus concentration of compound, where

- 5 U is the unknown value,
 C1 is the average control value obtained for DMSO only, and
 C2 is the average control value obtained for reactions stopped with EDTA at t=0.

Data were fitted to the curve described by:

$$y = ((V_{\max} * x) / (K + x)) \text{ where}$$

- 10 Vmax is the upper asymptote and
 K is the IC₅₀.

The results for each compound were recorded as pIC₅₀ calculated as follows:

$$pIC_{50} = -\text{Log}_{10}(K).$$

- 15 pIC50 values for the compounds of the examples (if available) were categorized by relative inhibition of IGF-1R and IR. The results are summarized in the tables below.

IGF-1R pIC ₅₀	Example no.
9.0-9.6	2, 3, 7, 11, 13, 14, 20, 31, 32, 33, 36, 44, 46, 48, 58-62, 68-74, 76-79, 83, 86, and 88
8.4-8.9	1, 5, 6, 8, 9, 12, 15, 16, 21-28, 34, 35, 41-43, 47, 52, 53, 55, 57, 63-67, 75, 80, 82, 84, and 85
7.0-8.3	4, 10, 17, 18, 19, 29, 30, 37-40, 45, 50, 51, 54, 56, 81, and 87

IR pIC ₅₀	Example No.
9.0-9.6	2, 3, 7, 11-15, 20, 22, 25, 31-33, 36, 44, 48, 58-62, 66, 68-74, 76-80, 82-84, 86, and 88
8.4-8.9	1, 5, 6, 8, 9, 16-18, 21, 23, 24, 26-28, 34, 35, 37, 38, 41-43, 45-47, 49, 50, 52-57, 63-65, 67, 75, 81, and 85
7.0-8.3	4, 10, 19, 29, 30, 39, 40, 51, and 87

20

Cell Proliferation Data

A. Inhibition of cell proliferation by IGF-1R inhibitors

Cell proliferation was measured by either CellTiter-Glo (measures cellular ATP level as a surrogate for total cell number) or by InCell analyzer (counts number of nuclei as a measure of cell number).

For CellTiter-Glo assay, exponentially growing cell lines of different tumor
5 origins, cultured in appropriate media containing 10% fetal bovine serum at 37°C in a 5% CO₂ incubator, were plated at low density (less than 2000cells/well) in 96-well plates. Twenty four hours post-plating, cells were treated with different concentrations of test compounds ranging from 30uM to 1.5nM. Several wells were left untreated as a control. Seventy two hours post-treatment, cell numbers were determined using 50-100ul per
10 well of CellTiter-Glo (Promega #G7573). Plates were incubated at 37°C for 30 minutes and the chemiluminescent signal was read on the Victor V or Envision 2100 reader. Percent inhibition of cell growth was expressed as percent proliferation relative to 100% proliferation (control). Concentration of test compound that inhibited 50% of cell growth (IC₅₀) was determined by 4 parameter fit of data using XLfit, (value of no cell control was
15 subtracted from all samples for background).

For InCell Analyser assay, various cell lines of different tumor origins were grown to 70-80% confluency in appropriate culture media containing 10% fetal bovine serum at 37°C in a 5% CO₂ incubator. On day -1, cells were seeded at 2 densities in 384-well plates and incubated at 37°C overnight. Stock compound plates were prepared in
20 advance which contained dimethyl sulfoxide (DMSO) alone and a 9-point half-log decreasing dose range of the compound in DMSO. The compound plates were stored at -80°C and each plate was only thawed once and used. On day 0, the main assay plates received compound or DMSO via a sonic delivery system (ECHO). The highest final concentration of compound of the dose range in the culture plates was 10uM. These
25 plates were cultured at 37°C for 3 days. A parallel set of cell line plates, which did not receive compound, were processed and read on day 0 to provide a T=0 (time zero). On day 3, the compound treated plates were stained and fixed to measure proliferation, apoptosis, and mitotic index using an InCell₁₀₀₀ analyser. A nuclear stain was used to identify cells in the wells. By counting the number of nuclei, the proliferation index of
30 compound treated groups were calculated as a percentage relative to the DMSO control, which was set to 100%. The IC₅₀ values were calculated using model 205 in ExcelFit.

IC₅₀ (nM) values for compounds of select examples were categorized by relative inhibition of cell proliferation. The results are summarized in the tables below.

IC50 for Colo205	Example No.
< 250 nM	1-3, 5-7, 9, 11, 12, 14, 15, 17, 22, 23, 25, 34, 35, 44, 46, 49, 53, 57, 58, 59, 68-73, and 77-79
250 nM to 1000 nM	5, 8, 12, 16, 18, 20, 21, 24, 26, 27, 28, 30, 37-43, 45, 47, 52, 55, 56, 66, 67, 80, and 81
> 1000 nM	10, 19, 29, 50, 51, and 54

IC50 for NCI-H929	Example No.
< 250 nM	1-8, 11-18, 20-28, 30, 34, 35, 37, 40-47, 49, 50, 52, 53, 55-59, 66-73, 77-80
250 nM to 1000 nM	10, 38, 39, 54, and 81
> 1000 nM	9, 19, 29, and 51

5 B. IGF-1R and IR Cellular Autophosphorylation

NIH-3T3 cells overexpressing human IGF-1R or IR were plated in 96-well plates (10,000 cells/well) in culture media containing 10% fetal bovine serum and incubated at 37°C in a 5% CO₂ incubator. Twenty four hours post-plating, cells were treated with different concentrations of test compounds ranging from 30uM to 1.5nM.

- 10 Two hours after compound addition, cells were stimulated with either human IGF-1 (30 ng/ml) or insulin (3 ug/ml) for 15 minutes. Cell lysates are analyzed for phosphorylated receptors using dissociation enhanced lanthanide fluor-immuno assay (DELFI) with anti-IGF-1R (MAB391, R&D Systems, Minneapolis, MN) or anti-IR β (sc-711, Santa Cruz Biotechnology, Santa Cruz, CA) capture antibody and europium-labeled anti-pTyr
- 15 antibody (Eu-N1 PT66, Perkin Elmer, Waltham, MA) for detection. The fluorescence signal for cells treated with compounds was expressed as percent relative to 100% stimulation (IGF-1 or insulin stimulated signal). Concentration of test compound that inhibited 50% of ligand-induced receptor phosphorylation (IC₅₀) was determined by 4
- 20 parameter fit of data using XLfit, (value of no cell control was subtracted from all samples for background).

IC50 values for the compounds of the examples (if available) were categorized by relative inhibition of IGF-1R and IR. The results are summarized in the tables below.

IGF-1R IC ₅₀	Example no.
< 100 nM	2-4, 11-16, 18, 20-28, 30-34, 37, 25, 43-

	47, 49, 52, 53, 56-60, 66-74, 76-79, 81-83, 85, 86, 88
100 nM – 500 nM	1, 5-8, 17, 29, 35, 38, 42, 50, 55, 61, 62, 64, 84, and 87
> 500 nM	9, 10, 19, 39, 40, 51, 54, 63, 75, and 80

IR IC ₅₀	Example No.
< 100 nM	2-5, 11, 13-16, 20-23, 27, 31-34, 37, 41, 43-47, 49, 52, 53, 57-60, 66-74, 76-79, 82, 83, 86, and 88
100 nM – 500 nM	1, 6, 7, 12, 17, 18, 24, 25, 26, 28-30, 35, 38, 42, 50, 54-56, 61, 62, 81, 84, 85, and 87
> 500 nM	8-10, 19, 39, 40, 51, 63, 64, 75, and 80

ALK Enzyme Assay:

5 The method measures the ability of the isolated enzyme to catalyse the transfer of the gamma-phosphate from ATP onto the tyrosine residue of a biotinylated synthetic peptide. The extent of tyrosine phosphorylation was measured using an anti-phosphotyrosine antibody, and quantified by homogenous time-resolved fluorescence (HTRF) assay purchased from CisBio (62TK0PEJ).

10 Reactions were performed in black 384-well polystyrene low volume plates in a final volume of 5 μ l. Assays were performed by adding 2.5 μ l of each of the following solutions, enzyme mix and substrate: The enzyme mix, final concentration in plate, contained 50 mM MOPS (pH 7.0); 10 nM supplement enzymatic buffer; 0.03 % NaN₃; 0.01 % BSA, 0.1 mM orthovanadate, 5 mM MgCl₂, 1 mM CHAPS, 1 mM dithiothreitol
15 and 0.25 nM ALK. The Substrate mix, final concentration in plate, contained 50 mM MOPS (pH 7.0); 10 nM supplement enzymatic buffer; 0.03 % NaN₃; 0.01 % BSA, 0.1 mM orthovanadate, 5 mM MgCl₂, 1 mM CHAPS, 1 mM dithiothreitol, 15.0 μ M ATP, and 0.25 μ M TK substrate-biotin.

20 To quantify compound potencies, the enzyme mix was added to the compound plates and the plates were incubated at 20°C for 30 minutes. The reactions were then started by adding the substrate mix. The reactions were allowed to proceed for 120 minutes at 20°C. The reactions were then terminated by the addition of 5 μ l HTRF detection mix to each well. The final concentrations of the detection reagents were: 50 mM HEPES (pH7.0); 0.1 % BSA; 0.8 M KF; 20 mM EDTA; 1 mM CHAPS; TK-antibody
25 Europium Cryptate; and 41 nM streptavidin-XL665. Assay plates were left unsealed,

stacked and incubated at 20° for 60 minutes. Quantification of activity was achieved by counting in an Envision Counter (PerkinElmer).

Compounds under analysis were dissolved in Me₂SO to 1.0 mM and serially diluted 1 to 3 with Me₂SO through twelve dilutions. 0.05 µl of each concentration was transferred to the corresponding well of an assay plate. This creates a final compound concentration range from 0.00017 to 10 µM.

The data for dose responses were plotted as % Inhibition calculated with the data reduction formula $100 \cdot (1 - (U1 - C2) / (C1 - C2))$ versus concentration of compound where U is the unknown value, C1 is the average control value obtained for 1% DMSO, and C2 is the average control value obtained for 0.1 M EDTA. Data were fitted with a curve described by:

$$y = A + \frac{B - A}{1 + \left[\frac{10^x}{10^c} \right]^D}$$

where A is the minimum y, B is the maximum y concentration [M], D is the slope factor, and x is the log₁₀ of the compound. The results for each compound were recorded as pIC₅₀s, calculated as follows:

$$\text{pIC}_{50} = -\text{Log}_{10}(K)$$

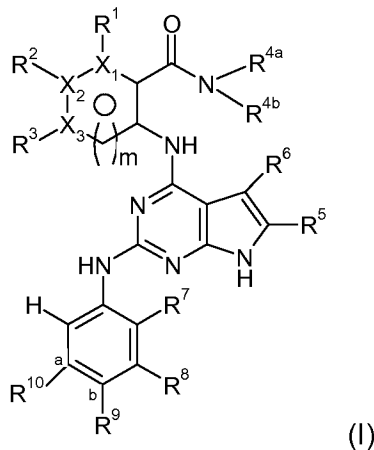
pIC₅₀ values for the compounds of the examples (if available) were categorized by relative inhibition of IGF-1R and IR. The results are summarized in the tables below.

ALK pIC ₅₀	Example no.
9.0-9.6	1-7, 12, 15-17, 21-25, 28, 33, 38, 41, 46, 48, 53-60, 68, 70-73, 78, 80, 81, 86, 87, 89, 91-102, 108, 110, 112, 113, 115, 116, 120, 126, 127, 139, 151-153, 156, 158, 171, 173, 167, 178-180, 182, 183, 190, 194, 199, 201, 203, 204, 208-210, 218, 219, 223, 225, 224, 234, 240, 244, 245, 251, 253, and 256-258
8.4-8.9	5, 6, 12, 36, 41, 46-48, 54, 58, 59, 65, 67, 73, 74, 76, 79, 83, 84, and 88
6.7-8.3	7, 34, 43, 44, 45, 51, 66, 75, 80, 85, and 87

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We claim:

1. A compound of formula (I):



or a pharmaceutically acceptable salt or solvate thereof wherein:

R^{4a} and R^{4b} are each independently selected from H, alkyl_{C1-C6}, -OH, -alkylene_{C1-C6}-OH, -alkylene_{C1-C6}-phenyl (optionally substituted with a halo), and -alkylene_{C1-C6}-C(O)NH₂;

one or two of X^1 , X^2 , and X^3 are independently selected from N, O, and S, while the remaining one or two of X^1 , X^2 , and X^3 are C;

m is 0 or 1;

R^1 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^1 is C, otherwise R^1 is absent;

R^2 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^2 is C, otherwise R^2 is absent;

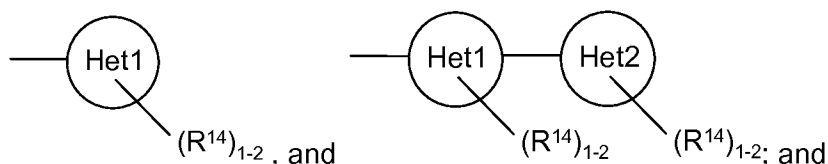
R^3 is selected from H, halo, alkyl_{C1-C6}, -alkylene_{C1-C3}-halo₁₋₃, and -O-alkyl_{C1-C6} when X^3 is C, otherwise R^3 is absent;

R^7 is selected from alkyl_{C1-C6}, -O-alkyl_{C1-C6}, halo, -NR²²R²³, and -O-alkylene_{C1-C6}-halo₁₋₃;

R^8 is selected from H, halo, and alkyl_{C1-C6};

one of R^9 and R^{10} is selected from -alkylene_{C1-C6}-SO₂-alkyl_{C1-C6}, -N-alkylene_{C0-C6}-C(O)-alkylene_{C0-C6}-NR²²R²³, -O-alkylene_{C0-C6}(optionally substituted with -OH)-NR²²R²³,

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the other of R^9 and R^{10} is selected from H, $\text{alkyl}_{\text{C1-C6}}$, $\text{-O-alkyl}_{\text{C1-C6}}$, and halo;

wherein Het1 and Het2 are each independently a five or six membered heterocyclic ring having an N atom and optionally one or two additional heteroatoms selected from N and O, and

each R^{14} is independently selected from H, OH, halo, $\text{alkyl}_{\text{C1-C6}}$, $\text{-O-alkyl}_{\text{C1-C6}}$, -cyclopropyl , $\text{-C(O)-alkyl}_{\text{C1-C6}}$, $\text{SO}_2\text{-alkyl}_{\text{C1-C6}}$, $\text{-(CH}_2\text{)}_{1-4}\text{-halo}$, and $\text{-(CH}_2\text{)}_{1-4}\text{-SO}_2\text{-alkyl}_{\text{C1-C6}}$; $\text{-C(O)-alkylene}_{\text{C0-C6}}\text{-NR}^{22}\text{R}^{23}$, $\text{-NR}^{22}\text{R}^{23}$;

or

R^9 and R^{10} , together with the atoms to which they are attached form a five, six, or seven-membered heterocyclic ring containing one or two N atom and the remainder C atoms, wherein at least one N atom is substituted with R^{15} , and the C atoms of the heterocyclic ring are optionally substituted with $(\text{R}^{19})_{1-2}$;

wherein R^{15} is selected from H, $\text{-alkyl}_{\text{C1-C4}}$, $\text{-alkylene}_{\text{C1-C4}}\text{-halo}$, $\text{-C(O)-alkylene}_{\text{C0-C6}}\text{-NR}^{22}\text{R}^{23}$, $\text{-C(O)-alkyl}_{\text{C1-C6}}$, $\text{-alkylene}_{\text{C1-C4}}\text{-NR}^{22}\text{R}^{23}$, $\text{-alkylene}_{\text{C1-C4}}\text{-C(O)-NR}^{22}\text{R}^{23}$, $\text{-C(O)-alkylene}_{\text{C1-C4}}\text{-O-alkyl}_{\text{C1-C6}}$, -C(O)-pyrrolidine , and $\text{-C(O)-pyrrolidine-alkyl}_{\text{C1-C6}}$; and,

each R^{19} is independently selected from H and $\text{alkyl}_{\text{C1-C6}}$;

each R^{22} is selected from H, $\text{alkyl}_{\text{C1-C6}}$, $\text{-O-alkyl}_{\text{C1-C6}}$, $\text{-alkylene}_{\text{C1-C6}}\text{-O-alkyl}_{\text{C1-C6}}$; and,

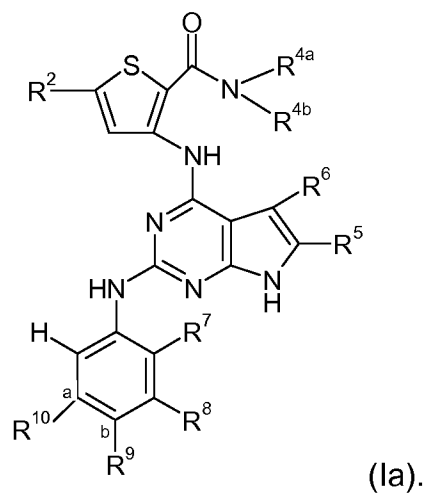
each R^{23} is selected from H and $\text{alkyl}_{\text{C1-C6}}$; or

R^{22} and R^{23} combine to form a four, five, or six membered, heterocyclic ring containing the N atom to which they are attached and optionally an additional heteroatom selected from N and O, wherein the ring is optionally substituted with -OH or $\text{-alkyl}_{\text{C1-C6}}$.

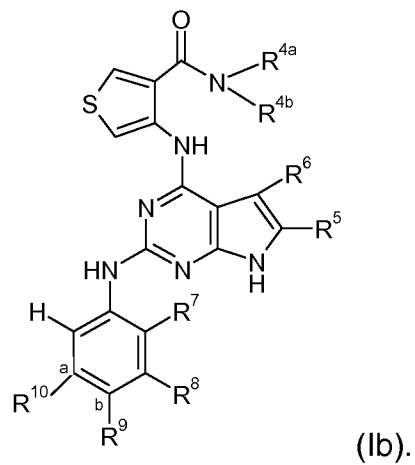
2. The compound of claim 1, wherein R^7 is $\text{-O-alkyl}_{\text{C1-C6}}$.

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3. The compound of claim 1 or 2, wherein R^7 is -O-methyl.
4. The compound of claim 1 having a formula (Ia)

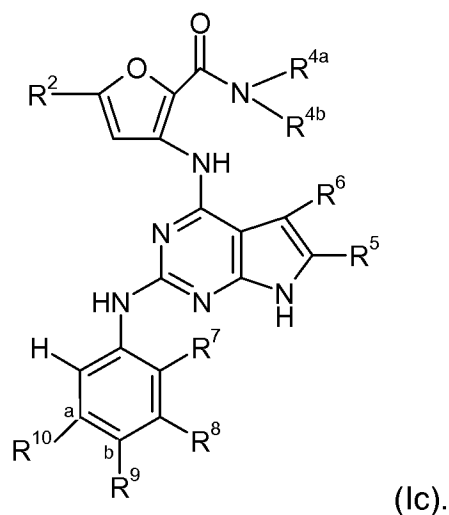


5. The compound of claim 1 having a formula (Ib)

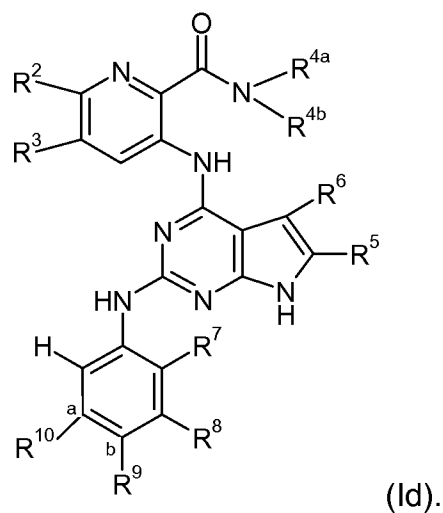


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6. The compound of claim 1 having a formula (Ic)

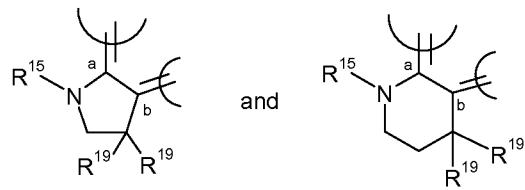


7. The compound of claim 1 having a formula (Id)



8. The compound of any of claims 1-7, wherein R⁹ and R¹⁰, together with the atoms to which they are attached form a five, six, or seven-membered heterocyclic ring containing one or two N atom and the remainder C atoms, wherein at least one N atom is substituted with R¹⁵, and the C atoms of the heterocyclic ring are optionally substituted with one or more groups selected from (R¹⁹)₁₋₂.

9. The compound of any of claims 1-8, wherein R^9 and R^{10} , together with the atoms to which they are attached form a five or six-membered heterocyclic ring selected from



10. The compound of any of claims 1-9, wherein R^{4a} and R^{4b} , are H.
11. A pharmaceutical composition comprising a compound according to any of claims 1 through 10 and a pharmaceutically acceptable carrier, diluent or excipient.
12. The pharmaceutical composition according to claim 11 further comprising a chemotherapeutic agent.
13. A method for treating a susceptible neoplasm in an mammal in need thereof, said method comprising administering to the mammal a therapeutically effective amount of a compound according to any of claims 1 through 10.
14. The method according to claim 13, wherein said susceptible neoplasm is selected from breast cancer, sarcomas, lung cancer, prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers, neuroblastomas, gliomas, head and neck cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer, testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor and skin cancer.
15. A compound according to any of claims 1 through 10 for use in the treatment of a condition mediated by IGF-1R in a mammal.
16. The compound according to any of claims 1 through 10 for use in the treatment of a susceptible neoplasm.

17. The compound according to claim 16, wherein the susceptible neoplasm is selected from breast cancer, sarcomas, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers (including multiple myeloma), neuroblastomas, gliomas, head and neck cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer, testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor and skin cancer (including melanoma).

18. The use of a compound according to any of claims 1 through 10 for the preparation of a medicament for the treatment of a condition mediated by IGF-1R in a mammal.

19. The use of a compound according to any of claims 1 through 10 for the preparation of a medicament for the treatment of a susceptible neoplasm in a mammal.

20. The use according to claim 19, wherein the susceptible neoplasm is selected from breast cancer, sarcomas, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers (including multiple myeloma), neuroblastomas, gliomas, head and neck cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer, testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor and skin cancer (including melanoma).

21. A pharmaceutical composition for use in the treatment of the susceptible neoplasm selected from breast cancer, sarcomas, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, renal cancer, pancreatic cancer, hematologic cancers (including multiple myeloma), neuroblastomas, gliomas, head and neck cancer, thyroid cancer, hepatocarcinoma, ovarian cancer, vulval cancer, cervical cancer, endometrial cancer, testicular cancer, bladder cancer, esophageal cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor and skin cancer (including melanoma), wherein the composition comprises a compound of any of claims 1 through 10.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/60830

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/505 (2009.01)

USPC - 514/267

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/505 (2009.01)

USPC - 514/267

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

IPC(8) - C07D 491/00, 487/00 (2009.01)

USPC - 544/250,280

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

PubWest (PGPB,USPT,USOC,EPAB,JPAB); Google

Search Terms Used: pyrrolopyrimidine, insulin growth factor receptor, receptor tyrosine kinase +cancer, igf-1r inhibitors, igf-1r overexpression disease

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0211678 A1 (AHMED et al.) 21 September 2006 (21.09.2006), para [0033-0040]	1-7
Y	WO 2007/140222 A2 (BRAIN et al.) 06 December 2007 (06.12.2007), page 7, 51	1-7

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 December 2009 (04.12.2009)

Date of mailing of the international search report

29 DEC 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/60830

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 8-21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.