MELT-EXTRUDED SOLID DISPERSIONS CONTAINING AN APOPTOSIS-INDUCING AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of provisional application Ser. No. 61/408,527, filed October 29, 2010, which is hereby incorporated by reference as if set forth in its entirety.

[0002] Cross-reference is also made, without claim to benefit of priority or admission as to prior art status, to the following pending U.S. application containing subject matter related to the present application: Serial No. 12/787,682 (U.S. 2010/0305122) titled "Apoptosis-inducing agents for the treatment of cancer and immune and autoimmune diseases," the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0003] The present invention relates to solid dispersions comprising an apoptosis-inducing agent, to pharmaceutical dosage forms comprising such dispersions, to processes for preparing such dispersions and dosage forms and to methods of use thereof for treating diseases characterized by overexpression of anti-apoptotic Bcl-2 family proteins.

BACKGROUND

[0004] Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system.

[0005] Evasion of apoptosis is a hallmark of cancer (Hanahan & Weinberg (2000) Cell 100:57–70). Cancer cells must overcome a continual bombardment by cellular stresses such as DNA damage, oncogene activation, aberrant cell cycle progression and harsh microenvironments that would cause normal cells to undergo apoptosis. One of the primary means by which cancer cells evade apoptosis is by up-regulation of anti-apoptotic proteins of the Bcl-2 family.

[0006] A particular type of neoplastic disease for which improved therapies are needed is non-Hodgkin's lymphoma (NHL). NHL is the sixth most prevalent type of new cancer in the U.S. and occurs primarily in patients 60–70 years of age. NHL is not a single disease but a family of related diseases, which are classified on the basis of several characteristics including clinical attributes and histology.

[0007] One method of classification places different histological subtypes into two major categories based on natural history of the disease, *i.e.*, whether the disease is indolent or aggressive. In general, indolent subtypes grow slowly and are generally incurable, whereas aggressive subtypes grow rapidly and are potentially curable. Follicular lymphomas are the most common indolent subtype, and diffuse large-cell lymphomas constitute the most common aggressive subtype. The oncoprotein Bcl-2 was originally described in non-Hodgkin's B-cell lymphoma.

[0008] Treatment of follicular lymphoma typically consists of biologically-based or combination chemotherapy. Combination therapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is routinely used, as is combination therapy with rituximab, cyclophosphamide, vincristine and prednisone (RCVP). Single-agent therapy with rituximab (targeting CD20, a phosphoprotein uniformly expressed on the surface of B-cells) or fludarabine is also used. Addition of rituximab to chemotherapy regimens can provide improved response rate and increased progression-free survival.

[0009] Radioimmunotherapy agents, high-dose chemotherapy and stem cell transplants can be used to treat refractory or relapsed NHL. Currently, there is not an approved treatment regimen that produces a cure, and current guidelines recommend that patients be treated in the context of a clinical trial, even in a first-line setting.

[0010] First-line treatment of patients with aggressive large B-cell lymphoma typically consists of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R).

[0011] Most lymphomas respond initially to any one of these therapies, but tumors typically recur and eventually become refractory. As the number of regimens patients receive increases, the more chemotherapy-resistant the disease becomes. Average response to first-line therapy is approximately 75%, 60% to second-line, 50% to third-line, and about 35–40% to fourth-line therapy. Response rates approaching 20% with a single agent in a multiple relapsed setting are considered positive and warrant further study.

[0012] Other neoplastic diseases for which improved therapies are needed include leukemias such as chronic lymphocytic leukemia (like NHL, a B-cell lymphoma) and acute lymphocyctic leukemia.

[0013] Chronic lymphoid leukemia (CLL) is the most common type of leukemia. CLL is primarily a disease of adults, more than 75% of people newly diagnosed being over the age of 50, but in rare cases it is also found in children. Combination chemotherapies are the prevalent treatment, for example fludarabine with cyclophosphamide and/or rituximab, or more complex combinations such as CHOP or R-CHOP.

[0014] Acute lymphocyctic leukemia, also known as acute lymphoblastic leukemia (ALL), is primarily a childhood disease, once with essentially zero survival but now with up to 75% survival due to combination chemotherapies similar to those mentioned above. New therapies are still needed to provide further improvement in survival rates.

[0015] Current chemotherapeutic agents elicit their antitumor response by inducing apoptosis through a variety of mechanisms. However, many tumors ultimately become resistant to these agents. Bcl-2 and Bcl-X_L have been shown to confer chemotherapy resistance in short-term survival assays *in vitro* and, more recently, *in vivo*. This suggests that if improved therapies aimed at suppressing the function of Bcl-2 and Bcl-X_L can be developed, such chemotherapy-resistance could be successfully overcome.

[0016] Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, CLL, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, spleen cancer and the like is described in International Patent Publication Nos. WO 2005/024636 and WO 2005/049593.

[0017] Involvement of Bcl-2 proteins in immune and autoimmune diseases is described, for example, by Puck & Zhu (2003) Current Allergy and Asthma Reports 3:378–384; Shimazaki *et al.* (2000) British Journal of Haematology 110(3):584–590; Rengan *et al.* (2000) Blood 95(4):1283–1292; and Holzelova *et al.* (2004) New England Journal of Medicine 351(14):1409–1418. Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in United States Patent Application Publication No. US 2008/0182845.

[0018] Compounds that occupy a binding site on Bcl-2 proteins are known. To be therapeutically useful by oral administration, such compounds must have high binding affinity, exhibiting for example K_i <1 nM, preferably <0.1 nM, more preferably <0.01 nM, to proteins of the Bcl-2 family, specifically Bcl-2, Bcl-X_L and Bcl-w. They must also be

formulated in a manner that provides high systemic exposure after oral administration. A typical measure of systemic exposure after oral administration of a compound is the area under the curve (AUC) resulting from graphing plasma concentration of the compound versus time from oral administration.

[0019] Where aqueous solubility of Bcl-2 binding compounds is very low, the formulator faces a significant challenge in assuring acceptable oral bioavailability, which is strongly dependent on solubility in the aqueous medium of the gastrointestinal tract. This is true even where binding affinity is very high. The challenge becomes even greater when considering the need to provide an adequate drug loading in the formulation, so that a therapeutically effective dose can be administered in an acceptably small volume of formulated product.

[0020] Liquid dosage forms (including encapsulated liquids) can be useful for some drugs of low aqueous solubility, provided a suitable pharmaceutically acceptable solvent system (generally lipid-based) can be found that provides adequate drug loading without posing solubility or storage-stability issues. Other approaches that have been proposed for such drugs include solid dispersions, which bring their own challenges.

[0021] For a variety of reasons, such as patient compliance and taste masking, a solid dosage form is usually preferred over a liquid dosage form. In most instances, however, oral solid dosage forms of a drug provide a lower bioavailability than oral solutions of the drug.

[0022] There have been attempts to improve the bioavailability provided by solid dosage forms by forming solid dispersions, or more particularly solid solutions, of drugs. Solid dispersions, or solutions, are preferred physical systems because the components therein readily form liquid solutions when contacted with a liquid medium, such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid dispersion, or solid solution, is less than that required for the dissolution of the components from a crystalline or microcrystalline solid phase. It is, however, important that the drug released from the solid dispersion, or solid solution, remains water-solubilized in the aqueous fluids of the gastrointestinal tract; otherwise, the drug may precipitate in the gastrointestinal tract, resulting in low bioavailability.

[0023] International Patent Publication WO 01/00175 relates to mechanically stable pharmaceutical dosage forms which are solid solutions of active ingredients in an auxiliary

agent matrix. The matrix contains a homopolymer or a copolymer of N-vinyl pyrrolidone and a liquid or semi-solid surfactant.

[0024] International Patent Publication WO 00/57854 relates to mechanically stable pharmaceutical dosage forms for oral administration, containing at least one active compound, at least one thermoplastically moldable, matrix-forming auxiliary and more than 10% and up to 40% by weight of a surface-active substance that has a hydrophilic-lipophilic balance (HLB) value of between 2 and 18 and is liquid at 20°C, or has a drop point between 20°C and 50°C.

[0025] U.S. Patent Application Publication No. 2005/0208082 relates to a solubilizing composition comprising a mixture of TPGS (α-tocopheryl polyethylene glycol succinate or vitamin E polyethylene glycol succinate) and linoleic acid. The solubilizing composition is used to disperse a lipophile in an aqueous phase.

[0026] Hot melt-extrusion, an enabling technology in increasing use for enhancing bioavailability of poorly water-soluble drug compounds, is a solvent-free, non-ambient process that has been said to afford many advantages over conventional solid dosage forms in terms of robustness and versatility (Crowley *et al.* (2007) Drug Development and Industrial Pharmacy 33:908–926).

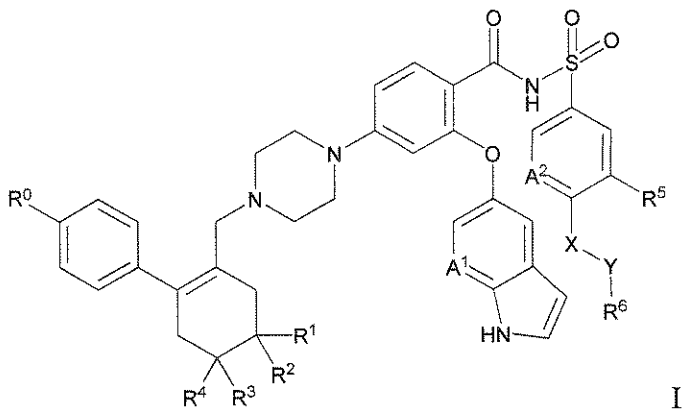
[0027] Proprietary melt-extrusion technology (Meltrex® of Abbott GmbH, Wiesbaden, Germany) has been shown to significantly improve the pharmacokinetic properties of certain drugs over alternative formulations. See, for example, Klein *et al.* (2007) J. Acquir. Immune Defic. Syndr. 44:401–410.

[0028] Apoptosis-inducing drugs that target Bcl-2 family proteins such as Bcl-2 and Bcl-X_L are best administered according to a regimen that provides continual, for example daily, replenishment of the plasma concentration, to maintain the concentration in a therapeutically effective range. This can be achieved by daily parenteral, *e.g.*, intravenous (i.v.) or intraperitoneal (i.p.) administration. However, daily parenteral administration is often not practical in a clinical setting, particularly for outpatients. To enhance clinical utility of an apoptosis-inducing agent, for example as a chemotherapeutic in cancer patients, a solid dosage form with acceptable oral bioavailability would be highly desirable. Such a dosage form, and a regimen for oral administration thereof, would represent an important advance in treatment of many types of cancer, including NHL, CLL and ALL, and would more readily

enable combination therapies with other chemotherapeutics.

SUMMARY

[0028a] In one aspect, there is provided a solid dispersion comprising, in essentially non-crystalline form, a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

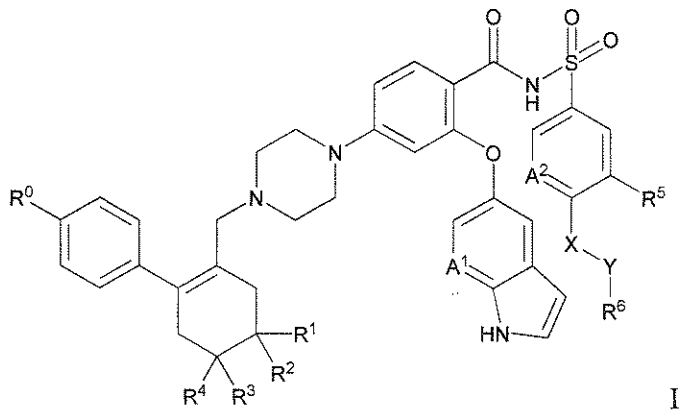
wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each

optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof; dispersed in a solid matrix that comprises (a) at least one pharmaceutically acceptable water-soluble polymeric carrier and (b) at least one pharmaceutically acceptable surfactant.

[0028b] In one aspect, there is provided a process for preparing a solid dispersion, comprising:

(a) subjecting to elevated temperature (i) an active pharmaceutical ingredient (API) that comprises a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or R^9–$(CH_2)_m$– groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each

optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

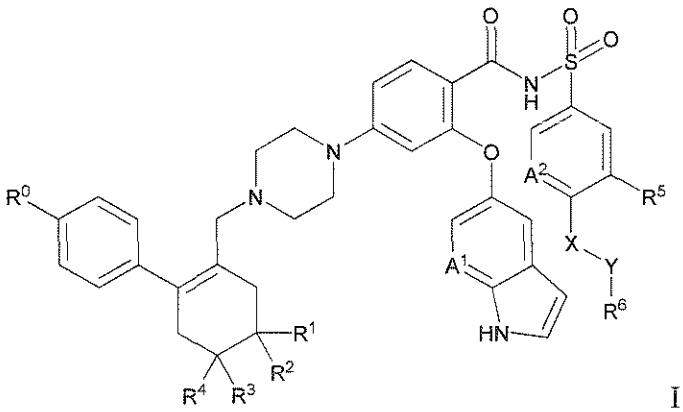
or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

(b) extruding the semi-solid mixture; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

[0028c] In one aspect, there is provided a process for preparing a solid dispersion, comprising:

(a) subjecting to elevated temperature (i) an active pharmaceutical ingredient (API) that comprises a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4}

alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

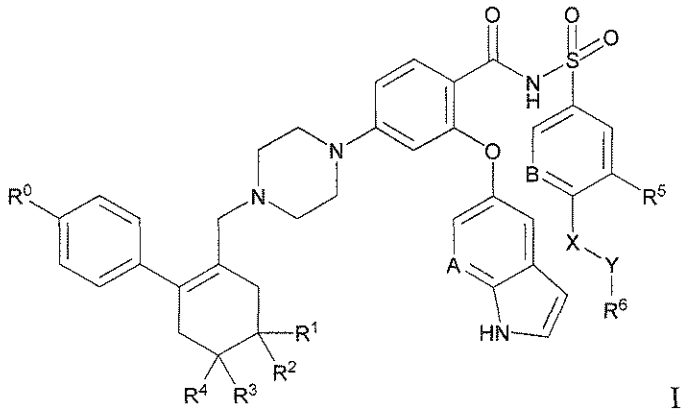
(b) extruding and calendering the semi-solid mixture; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

[0028d] In one aspect, there is provided an orally deliverable pharmaceutical dosage form comprising the solid dispersion as defined herein.

[0028e] In one aspect, there is provided the use of a therapeutically effective amount of the solid dispersion as defined herein, in the manufacture of a medicament for treating a neoplastic, immune or autoimmune disease.

[0029] In one embodiment, there is provided a solid dispersion comprising, in essentially non-crystalline, for example amorphous, form, a compound of Formula I:



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A and B are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups

being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt of such compound. The compound or salt thereof is dispersed in a solid matrix that comprises (a) a pharmaceutically acceptable water-soluble polymeric carrier and (b) a pharmaceutically acceptable surfactant.

[0030] There is further provided a solid orally deliverable dosage form comprising such a solid dispersion, optionally together with one or more additional excipients.

[0031] There is still further provided a process for preparing a solid dispersion as described above. This process comprises:

(a) subjecting to elevated temperature (i) an active pharmaceutical ingredient (API) that comprises a compound of Formula I or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

(b) extruding the semi-solid mixture, for example through a die; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

[0032] A "melt" herein is a liquid or semi-solid (*e.g.*, rubbery) state induced by elevated temperature wherein it is possible for a first component to become homogeneously distributed in a matrix comprising a second component. Typically, the second (matrix) component, for example a polymeric carrier, is in such a state and other components, for example including a compound of Formula I or a salt thereof, dissolve in the melt, thus forming a solution.

[0033] By "elevated temperature" herein is meant a temperature above a softening point of the polymeric carrier, as affected by other components if present, such as plasticizers or surfactants.

[0034] Preparation of the melt can take place in a variety of ways. Mixing of the components can take place before, during or after formation of the melt. For example, the components can be mixed first and then subjected to elevated temperature to form the melt; alternatively mixing and melting can take place simultaneously. In one embodiment the polymeric carrier is first melted, optionally with the surfactant component, and the API is then added to the resulting melt. Usually, the melt is thoroughly mixed while at elevated temperature in order to ensure homogeneous dispersion of the API.

[0035] There is still further provided a solid dispersion prepared by the process described above.

[0036] There is still further provided a method for treating a neoplastic, immune or autoimmune disease, comprising orally administering to a subject having the disease a therapeutically effective amount of a solid dispersion as described above, or one or more solid dosage forms comprising such a dispersion. Examples of neoplastic diseases include cancers. A specific illustrative type of cancer that can be treated according to the present method is non-Hodgkin's lymphoma (NHL). Another specific illustrative type of cancer that can be treated according to the present method is chronic lymphocytic leukemia (CLL). Yet another specific illustrative type of cancer that can be treated according to the present method is acute lymphocytic leukemia (ALL), for example in a pediatric patient.

[0037] Additional embodiments of the invention, including more particular aspects of those provided above, will be found in, or will be evident from, the detailed description that follows.

DRAWINGS

[0038] Drawings herein are for illustrative purposes only of selected embodiments and not all possible implementations, and do not limit the scope of the present disclosure.

[0039] Fig. 1 is a flow-chart for a process including melt extrusion useful to form a solid dispersion product according to an embodiment of the present technology.

DETAILED DESCRIPTION

[0040] Attempts to formulate a compound of Formula I or a salt thereof as an orally deliverable dosage form have been frustrated by the very limited number of pharmaceutically acceptable liquid solvent systems providing acceptable solubility of the compound or salt, and by a tendency with all such solvent systems tested for precipitation of insoluble solids during storage. It has now been found that a more successful approach is to formulate the compound or salt as a solid dispersion. Details of that approach, by which a combination of satisfactory drug loading, acceptable stability and adequate bioavailability are all achievable with a very unpromising class of active ingredient, are disclosed herein.

[0041] A solid dispersion in accordance with the present disclosure comprises an active ingredient in an essentially non-crystalline or amorphous form, which is usually more soluble than the crystalline form. The term "solid dispersion" herein encompasses systems having small solid-state particles (e.g., essentially non-crystalline or amorphous particles) of one phase dispersed in another solid-state phase. More particularly, the present solid dispersions comprise particles of one or more active ingredients dispersed in an inert carrier or matrix in solid state, and can be prepared by melting or solvent methods or by a combination of melting and solvent methods. According to the present invention a melt-extrusion method as described herein is particularly favored.

[0042] An "amorphous form" refers to a particle without definite structure, *i.e.*, lacking crystalline structure.

[0043] The term "essentially non-crystalline" herein means that no more than about 5%, for example no more than about 2% or no more than about 1% crystallinity, is observed by X-ray diffraction analysis. In a particular embodiment, no detectable crystallinity is observed by one or both of X-ray diffraction analysis or polarization microscopy. In this regard it is to be noted that, when no detectable crystallinity is observed, the solid dispersion referenced herein may additionally or alternatively be described as a solid solution.

A. Active Compound

[0044] Compounds of Formula I, including salts thereof, useful herein typically have very low solubility in water, being classed as essentially insoluble, *i.e.*, having a solubility of less

than about 10 μg/ml. Examples of such active ingredients are, for example, Biopharmaceutics Classification System (BCS) Class IV drug substances that are characterized by low solubility and low permeability (see "Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system", U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000). It will be recognized that aqueous solubility of many compounds is pH-dependent; in the case of such compounds the solubility of interest herein is at a physiologically relevant pH, for example a pH of about 1 to about 8. Thus, in various embodiments, the drug has a solubility in water, at least at one point in a pH range from about 1 to about 8, of less than about 10 μg/ml, in some cases less than about 1 μg/ml or even less than about 0.1 μg/ml. Illustratively, a particular compound useful herein has a solubility in water at pH 4 of <0.004 μg/ml.

[0045] Solid dispersions of the present invention comprise as active ingredient a compound of Formula I as defined above, or a pharmaceutically acceptable salt of such a compound. Optionally they may further comprise a second active ingredient, for example a therapeutic agent useful in combination therapy with the compound of Formula I as indicated hereinbelow.

[0046] In one embodiment, the compound has Formula I where R^0 is chloro.

[0047] In a further embodiment, the compound has Formula I where R^1 is methyl or methoxy, R^2 is methyl, and R^3 and R^4 are each H.

[0048] In a still further embodiment, the compound has Formula I where R^5 is trifluoromethyl, trifluoromethylsulfonyl, chloro, bromo or nitro. In a more particular embodiment, if A^2 is –CH– then R^5 is nitro; and if A^2 is –N– then R^5 is bromo.

[0049] In a more particular embodiment, the compound has Formula I where (a) R^0 is chloro, (b) R^1 is methyl or methoxy, R^2 is methyl, and R^3 and R^4 are each H, and (c) R^5 is trifluoromethyl, trifluoromethylsulfonyl, chloro, bromo or nitro.

[0050] Compounds useful herein vary considerably in the $–X–Y–R^6$ substituent, more particularly the R^6 group, of Formula I. In most embodiments, R^6 is a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted as defined above.

[0051] The term "carbocyclic" herein embraces saturated and partly and fully unsaturated ring structures having 3 to 7 ring carbon atoms, including bicyclic structures. In one

embodiment, R^6 is a saturated carbocyclic (*i.e.*, cycloalkyl) ring, for example but not limited to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in each case optionally substituted as more fully described below.

[0052] The term "heterocyclic" herein embraces saturated and partly and fully unsaturated ring structures having 4 to 7 ring atoms, one or more of which are heteroatoms independently selected from N, O and S. Typically the heterocyclic ring has no more than two such heteroatoms. In one embodiment, R^6 is a saturated heterocyclic ring, for example but not limited to azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imazolidinyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiophanyl, thiazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, 1,4-dioxanyl, morpholinyl or tetrahydrothiopyranyl, in each case optionally substituted as more fully described below.

[0053] Where R^6 is a carbocyclic or heterocyclic ring, for example a saturated ring as described immediately above, it can be unsubstituted or substituted at up to three positions on the ring. Substituents, if present, comprise no more than two Z^1 groups and/or no more than one Z^2 group.

[0054] Z^1 groups are independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups. Illustrative examples of such Z^1 groups include without limitation methyl, cyanomethyl, methoxy, fluoro, hydroxy, amino and methylsulfonyl.

[0055] The Z^2 group, if present, is a further 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as described above. Ring Z^2, if present, is typically but not necessarily saturated, and in most cases is not further substituted. In one embodiment Z^2 is a saturated carbocyclic ring, for example but not limited to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In another embodiment Z^2 is a saturated heterocyclic ring, for example but not limited to azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imazolidinyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiophanyl, thiazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, 1,4-dioxanyl, morpholinyl or tetrahydrothiopyranyl.

[0056] In some embodiments, R^6 is a group NR^7R^8, where R^7 and R^8 are each independently H or R^9–$(CH_2)_m$– groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, and each m is independently 0 or 1. Each of rings R^9 is typically but not necessarily saturated, and in most cases is unsubstituted. Illustrative carbocyclic rings at R^7 and/or R^8 include without limitation cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Illustrative heterocyclic rings at R^7 and/or R^8 include without limitation azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imazolidinyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiophanyl, thiazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, 1,4-dioxanyl, morpholinyl or tetrahydrothiopyranyl.

[0057] In particular embodiments, R^6 is selected from the group consisting of 4-methoxycyclohexyl, *cis*-4-hydroxy-4-methylcyclohexyl, *trans*-4-hydroxy-4-methylcyclohexyl, 4-morpholin-4-ylcyclohexyl, (3R)-1-(methylsulfonyl)pyrrolidin-3-yl, (3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl, tetrahydro-2H-pyran-4-yl, (3S)-tetrahydro-2H-pyran-3-yl, 4-methoxytetrahydro-2H-pyran-4-yl, 4-fluorotetrahydro-2H-pyran-4-yl, 4-aminotetrahydro-2H-pyran-4-yl, 1-(cyanomethyl)piperidin-4-yl, 4-fluoro-1-oxetan-3-ylpiperidin-4-yl, 1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl, 4-methylpiperazin-1-yl, 1,4-dioxan-2-yl, 4-methylmorpholin-2-yl and cyclopropyl(oxetan-3-yl)amino.

[0058] Compounds of Formula I may contain asymmetrically substituted carbon atoms in the R- or S-configuration; such compounds can be present as racemates or in an excess of one configuration over the other, for example in an enantiomeric ratio of at least about 85:15. The compound can be substantially enantiomerically pure, for example having an enantiomeric ratio of at least about 95:5, or in some cases at least about 98:2 or at least about 99:1.

[0059] Compounds of Formula I may alternatively or additionally contain carbon-carbon double bonds or carbon-nitrogen double bonds in the Z- or E-configuration, the term "Z" denoting a configuration wherein the larger substituents are on the same side of such a double bond and the term "E" denoting a configuration wherein the larger substituents are on opposite sides of the double bond. The compound can alternatively be present as a mixture of Z- and E-isomers.

[0060] Compounds of Formula I may alternatively or additionally exist as tautomers or

equilibrium mixtures thereof wherein a proton shifts from one atom to another. Examples of tautomers illustratively include keto-enol, phenol-keto, oxime-nitroso, nitro-aci, imine-enamine and the like.

[0061] In one embodiment, the API present in the solid dispersion is selected from compounds specifically identified in above-referenced U.S. application Serial No. 12/787,682 (U.S. 2010/0305122) in Examples 1–378 thereof, and pharmaceutically acceptable salts of such compounds, independently of whether these compounds are individually embraced by the present Formula I. Compounds 1–378 of these Examples, and illustrative procedures for their synthesis, are reproduced hereinbelow. In a further embodiment, the API present in the solid dispersion is selected from Compounds 1–378 and pharmaceutically acceptable salts thereof, but only to the extent that such Examples are individually embraced by the present Formula I. The entire disclosure of U.S. application Serial No. 12/787,682 (U.S. 2010/0305122) is expressly incorporated herein by reference.

[0062] Description of the synthesis of representative compounds is given below. Other compounds of Formula I can be prepared by substantially analogous methods, as will be clear to one of skill in the art. The exemplified compounds have been named using ACD/ChemSketch Version 5.06 (05 June 2001, Advanced Chemistry Development Inc., Toronto, Ontario), ACD/ChemSketch Version 12.01 (13 May 2009), Advanced Chemistry Development Inc., Toronto, Ontario), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA). Intermediates were named using ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA).

Compound 1

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 1A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)piperazine-1-carboxylate

[0063] 4'-Chlorobiphenyl-2-carboxaldehyde (4.1 g), tert-butyl piperazine-1-carboxylate (4.23 g), and sodium triacetoxyborohydride (5.61 g) in CH_2Cl_2 (60 ml) were stirred for 24 hours. The reaction was quenched with methanol and poured into ether. The solution was

washed with water and brine, concentrated, and chromatographed on silica gel with 2–25% ethyl acetate/hexanes.

Compound 1B

1-((4'-chlorobiphenyl-2-yl)methyl)piperazine

[0064] Compound 1A (3.0 g) and triethylsilane (1 ml) were stirred in CH_2Cl_2 (30 ml) and trifluoroacetic acid (30 ml) for 2 hours, and the reaction was concentrated, and then taken up in ether and concentrated again. The material was taken up in dichloromethane (200 ml) and $NaHCO_3$ solution (100 ml), and partitioned. The organic layer was dried over Na_2SO_4, and condensed to give the title compound.

Compound 1C

tert-butyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoate

[0065] Tert-butyl 4-bromo-2-fluorobenzoate (14.0 g), Compound 1B (16.05 g), $Pd_2(dba)_3$ (tris(dibenzylideneacetone)dipalladium(0))(1.40 g), 2-(di-tert-butylphosphino)biphenyl (1.82 g), and K_3PO_4 (16.2 g) were stirred in 1,2-dimethoxyethane (300 ml) at 80°C for 24 hours. The reaction was cooled and concentrated. The crude product was chromatographed on silica gel with 10–20% ethyl acetate/hexanes.

Compound 1D

tert-butyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

[0066] 1H-Pyrrolo[2,3-B]pyridine-5-ol (167 mg), Compound 1C (500 mg), and Cs_2CO_3 (508 mg) were stirred in dimethylsulfoxide (5 ml) at 130°C for 24 hours. The mixture was cooled, diluted with ethyl acetate, washed thee times with water, and brine, and dried (Na_2SO_4), filtered and concentrated. The crude product was chromatographed on silica gel with 25% ethyl acetate/hexanes.

Compound 1E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

[0067] Compound 1D (200 mg) and triethylsilane (1 ml) were stirred in dichloromethane (15 ml) and trifluoroacetic acid (15 ml) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with NaH_2PO_4, and brine, and dried (Na_2SO_4), filtered and concentrated.

Compound 1F

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0068] 4-Fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) were stirred in tetrahydrofuran (30 ml) for 24 hours. The solution was diluted with ethyl acetate, washed with NaH_2PO_4 solution and brine, and dried (Na_2SO_4), filtered and concentrated. The product was triturated from ethyl acetate.

Compound 1G

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0069] Compound 1E (115 mg), Compound 1F (67 mg), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (82 mg), and 4-dimethylaminopyridine (26 mg) were stirred in CH_2Cl_2 (3 ml) for 24 hours. The reaction was cooled and chromatographed on silica gel with 0–5% methanol/ethyl acetate. ^1H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.48 (brs, 1H), 8.34 (br s, 1H), 8.31 (m, 1H), 7.90 (d, 1H), 7.68 (m, 1H), 7.58 (m, 2H), 7.46 (m, 4H), 7.35 (m, 2H), 7.21 (dd, 1H), 6.76 (m, 4H), 6.28 (m, 2H), 3.02 (m, 2H), 2.89 (m, 4H), 2.80 (m, 4H), 2.40 (m, 3H), 1.59 (m, 2H), 1.25 (m, 4H), 0.87 (m, 2H).

Compound 2

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 2A

4-(3-morpholinopropylamino)-3-nitrobenzenesulfonamide

[0070] This Compound was prepared by substituting 3-(N-morpholinyl)-propylamine for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 2B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0071] This Compound was prepared by substituting Compound 2A for Compound 1F in the procedure for Compound 1G. ^1H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.60 (brs,

1H), 8.60 (m, 1H), 8.43 (d, 1H), 7.94 (d, 1H), 7.64 (m, 2H), 7.54 (d, 1H), 7.45 (m, 4H), 7.33 (m, 2H), 7.23 (dd, 1H), 6.96 (d, 1H), 6.85 (m, 2H), 6.32 (d, 1H), 6.26 (d, 1H), 3.60 (m, 4H), 3.10 (m, 4H), 3.05 (m, 10H), 2.40 (m, 2H), 2.33 (m, 2H), 1.77 (m, 2H).

Compound 3

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 3A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0072] To a suspension of hexane washed NaH (17 g) in dichloromethane (700 ml) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to –78°C and trifluoroacetic anhydride (40 ml) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the product.

Compound 3B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

[0073] Compound 3A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 dimethoxyethane/methanol (600 ml) were heated to 70°C for 24 hours. The mixture was concentrated. Ether (4 × 200 ml) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

Compound 3C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

[0074] To a mixture of $LiBH_4$ (13g), Compound 3B (53.8 g) and ether (400 ml), was added methanol (25 ml) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3 × 100 ml). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0–30% ethyl acetate/hexanes.

Compound 3D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

[0075] Mesyl chloride (7.5 ml) was added via syringe to Compound 3C (29.3 g) and triethylamine (30 ml) in CH_2Cl_2 (500 ml) at 0°C, and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10–20% ethyl acetate/hexanes.

Compound 3E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

[0076] Compound 3D (1 g) was stirred in dichloromethane (10 ml), trifluoroacetic acid (10 ml), and triethylsilane (1 ml) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 ml) and saturated aqueous Na_2CO_3 solution (20 ml) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated to give the product.

Compound 3F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

[0077] to a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 ml) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 ml), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 ml) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

Compound 3G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

[0078] To a mixture of Compound 3F (24.3 g) in tetrahydrofuran (500 ml) at –78°C was added 2.5M BuLi (30.3 ml). After 2 minutes, trimethylborate (11.5 ml) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted thee times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 ml) at 0°C,

and 1M NaOH (69 ml) was added, followed by 30% H_2O_2 (8.43 ml), and the solution was stirred for 1 hour. $Na_2S_2O_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 5–25% ethyl acetate/hexanes.

Compound 3H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

[0079] A mixture of Compound 3G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 ml) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 ml), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2–50% ethyl acetate/hexanes.

Compound 3I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0080] A mixture of Compound 3H (1.55 g), Compound 3E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 ml) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 ml), and washed with 3 × 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10–50% ethyl acetate/hexanes.

Compound 3J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0081] Compound 3I (200 mg) in dioxane (10 ml) and 1M NaOH (6 ml) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted thee times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

Compound 3K

tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

[0082] Tert-butyl piperidin-4-ylcarbamate (45.00 g, 225 mmol) and dihydro-2H-pyran-4(3H)-one (24.74 g, 247 mmol) were added to dichloromethane (1000 ml). Sodium triacetoxyborohydride (61.90 g, 292 mmol) was added, and the solution was stirred at room

temperature for 16 hours. The solution was extracted with 1M sodium hydroxide and dried over anhydrous sodium sulfate. The solution was filtered and concentrated and purified by flash column chromatography on silica gel with 10% methanol (in dichloromethane) increasing to 20% methanol (in dichloromethane).

Compound 3L

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-amine dihydrochloride

[0083] A solution of Compound 3K (52.57 g, 185 mmol) in dichloromethane (900 ml) was treated with 4M aqueous HCl (462 ml), and the solution was mixed vigorously at room temperature for 16 hours. Solvent was removed under vacuum to give crude product as the dihydrochloride salt, which was used without further purification.

Compound 3M

3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)benzenesulfonamide

[0084] Compound 3L (22.12 g, 86 mmol) was added to 1,4-dioxane (300 ml) and water (43 ml). Triethylamine (43.6 ml, 31.6 g, 313 mmol) was added, and the mixture was stirred at room temperature until Compound 3L had completely dissolved. 4-Chloro-3-nitrobenzenesulfonamide was added and the mixture was heated at 90°C for 16 hours. The mixture was cooled, and the solvents were removed under vacuum. 10% methanol (in dichloromethane) was added and the solution was stirred vigorously at room temperature until a fine suspension was obtained. The solid was isolated by vacuum filtration and washed with dichloromethane to give pure product.

Compound 3N

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0085] This Compound was prepared by substituting Compound 3J for Compound 1E and Compound 3M for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.65 (brs, 1H), 8.53 (br s, 1H), 8.18 (m, 1H), 8.00 (br s, 1H), 7.63 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.20 (d, 1H), 3.95 (m, 2H), 3.05 (m, 10H), 2.73 (m, 4H), 2.17 (m, 10H), 1.95 (m, 2H), 1.80 (m, 2H), 1.63 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 4

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 4A

4-(1-methylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

[0086] This Compound was prepared by substituting 4-amino-N-methylpiperidine for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 4B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0087] This Compound was prepared by substituting Compound 3J for Compound 1E and Compound 4A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.65 (brs, 1H), 8.55 (br s, 1H), 8.17 (m, 1H), 8.02 (d, 1H), 7.85 (dd, 1H), 7.51 (m, 3H), 7.35 (m, 2H), 7.18 (dd, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (d, 1H), 6.20 (d, 1H), 3.90 (m, 1H), 3.09 (m, 8H), 2.77 (m, 2H), 2.05-2.30 (m, 10H), 1.95 (s, 3H), 1.39 (t, 2H), 1.24 (m, 2H), 0.93 (s, 6H).

Compound 5

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 5A

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0088] A mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) in tetrahydrofuran (30 ml) were stirred overnight, neutralized with concentrated HCl and concentrated. The residue was suspended in ethyl acetate and the precipitates were collected, washed with water and dried to provide the title compound.

Compound 5B

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0089] To a suspension of hexane washed NaH (17 g) in dichloromethane (700 ml) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to –78°C and trifluoroacetic anhydride (40 ml) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the product.

Compound 5C

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

[0090] Compound 5B (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 dimethoxyethane/methanol (600 ml) were heated to 70°C for 24 hours. The mixture was concentrated. Ether (4 × 200 ml) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

Compound 5D

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

[0091] To a mixture of $LiBH_4$ (13g), Compound 5C (53.8 g) and ether (400 ml), was added methanol (25 ml) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3 × 100 ml). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0–30% ethyl acetate/hexanes.

Compound 5E

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

[0092] Mesyl chloride (7.5 ml) was added via syringe to Compound 5D (29.3 g) and triethylamine (30 ml) in CH_2Cl_2 (500 ml) at 0°C, and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10–20% ethyl acetate/hexanes.

Compound 5F

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

[0093] Compound 5E (200 mg) and triethylsilane (1 ml) were stirred in dichloromethane (15 ml) and trifluoroacetic acid (15 ml) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with NaH_2PO_4, and brine, and dried (Na_2SO_4), filtered and concentrated.

Compound 5G

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

[0094] To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 ml) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 ml), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 ml) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

Compound 5H

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

[0095] To a mixture of Compound 5G (24.3 g) in tetrahydrofuran (500 ml) at –78°C was added 2.5M BuLi (30.3 ml). After 2 minutes, trimethylborate (11.5 ml) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted thee times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 ml) at 0°C, and 1M NaOH (69 ml) was added, followed by 30% H_2O_2 (8.43 ml), and the solution was stirred for 1 hour. $Na_2S_2O_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 5–25% ethyl acetate/hexanes.

Compound 5I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

[0096] A mixture of Compound 5H (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 ml) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 ml), and washed twice with water, and brine, and

concentrated. The crude product was chromatographed on silica gel with 2–50% ethyl acetate/hexanes.

Compound 5J

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0097] A mixture of Compound 5I (1.55 g), Compound 5F (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 ml) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 ml), and washed with 3 × 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10–50% ethyl acetate/hexanes.

Compound 5K

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0098] Compound 5J (200 mg) in dioxane (10 ml) and 1M NaOH (6 ml) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted thee times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

Compound 5L

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0099] Compound 5K (3.39 g), Compound 5A (1.87 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.39 g), and 4-dimethylaminopyridine (1.09 g) were stirred in CH_2Cl_2 (40 ml) for 24 hours. The reaction was cooled and chromatographed on silica gel with 25-100% ethyl acetate/hexanes, then 10% methanol/ethyl acetate with 1% acetic acid,o give the product (1.62 g, 32%) as a white solid. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.65 (brs, 1H), 8.55 (br s, 1H), 8.04 (d, 1H), 7.89 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.08 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.84 (m, 1H), 3.30 (m, 4H), 3.07 (m, 4H), 2.73(m, 2H), 2.18 (m, 6H), 1.95 (m, 2H), 1.61 (dd, 2H), 1.38 (m, 2H), 1.24 (m, 4H), 0.92 (s, 6H).

Compound 6

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-

{(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 6A

4-(4-methylpiperazin-1-ylamino)-3-nitrobenzenesulfonamide

[0100] A 50 ml round-bottomed flask was charged with 4-chloro-3-nitrobenzenesulfonamide (1 g, 4.23 mmol), 4-methylpiperazin-1-amine dihydrochloride (1 g, 5.32 mmol), and N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine (3 ml, 20.01 mmol) in dioxane (10 ml). The reaction mixture was refluxed for 12 hours. After this time, the reaction mixture was cooled to room temperature, the salt filtered off via a Buchner funnel, and the solvent removed in vacuo. The crude product was added to a silica gel column (Analogix, SF65-200g) and purified by eluting with 0–5% methanol in dichloromethane.

Compound 6B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0101] This Compound was prepared by substituting Compound 3J for Compound 1E and Compound 6A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.65 (brs, 1H), 9.09 (br s, 1H), 8.47 (d, 1H), 8.24 (dd, 1H), 7.99 (d, 1H), 7.50 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.35 (d, 1H), 6.20 (d, 1H), 3.04 (m, 4H), 2.89 (m, 4H), 2.73 (m, 2H), 2.34 (s, 3H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t, 2H), 1.05 (m, 4H), 0.93 (s, 6H).

Compound 7

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

Compound 7A

ethyl 2-(9H-carbazol-4-yloxy)-4-fluorobenzoate

[0102] This Compound was prepared by substituting ethyl 2,4-difluorobenzoate for methyl 2,4-difluorobenzoate and 4-hydroxycarbazole for Compound 3G in the procedure for Compound 3H.

Compound 7B

ethyl 2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0103] This Compound was prepared by substituting Compound 7A for Compound 3H in the procedure for Compound 3I.

Compound 7C

2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0104] This Compound was prepared by substituting Compound 7B for Compound 3I in the procedure for Compound 3J, except here upon completion of the reaction, water and 2N HCl were added to adjust the pH to 2, and the HCl salt of the product was extracted using $CHCl_3/CH_3OH$.

Compound 7D

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0105] This Compound was prepared by substituting Compound 7C for Compound 1E and Compound 4A for Compound 1F in the procedure for Compound 1G, except here the purification was done by preparative HPLC using a C18 column, 250 × 50 mm, 10μ, and eluting with a gradient of 20–100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a bistrifluoroacetate salt. ^1H NMR (300 MHz, dimethylsulfoxide -d_6) δ 11.82 (br s, 1H), 11.40 (s, 1H), 9.70, 9.40 (both v br s, total 2H), 8.40 (d, 1H), 8.10 (br d, 1H), 7.90 (br d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.48 (d, 1H), 7.38 (m, 3H), 7.22 (m, 2H), 7.07 (m, 4H), 6.78 (dd, 1H), 6.43 (dd, 1H), 6.19 (s, 1H), 3.97 (m, 1H), 3.80 (m, 2H), 3.60, 3.30, 3.10, 2.80 (all br m, total 11H), 2.20, 2.10, 2.00 (all br m, total 8H), 1.78 (m, 2H), 1.42 (m, 2H), 1.25 (m, 2H), 0.92 (s, 6H).

Compound 8

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

Compound 8A

3-nitro-4-(3-(pyrrolidin-1-yl)propylamino)benzenesulfonamide

[0106] This Compound was prepared by substituting 3-(pyrrolidin-1-yl)propan-1-amine for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 8B

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

[0107] This Compound was prepared by substituting Compound 7C for Compound 1E and Compound 8A for Compound 1F in the procedure for Compound 1G, except here the purification was done by preparative HPLC using a C18 column, 250 × 50 mm, 10μ,and eluting with a gradient of 20–100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a bistrifluoroacetate salt. ^1H NMR (300 MHz, dimethylsulfoxide -d_6) δ 11.80 (br s, 1H), 11.42 (s, 1H), 9.50, 9.25 (both v br s, total 2H), 8.58 (br t, 1H), 8.43 (d, 1H), 7.91 (d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.38 (m, 3H), 7.23 (m, 2H), 7.07 (m, 3H), 6.93 (d, 1H), 6.78 (dd, 1H), 6.44 (dd, 1H), 6.18 (s, 1H), 3.70, 3.60, 3.20. 3.00 (all br m, total 18H), 2.18 (br m, 2H), 2.00-180 (envelope, 8H), 1.42 (m, 2H), 0.92 (s, 6H).

Compound 9

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 9A

trans-tert-butyl 4-morpholinocyclohexylcarbamate

[0108] A solution of tert-butyl-4-aminocyclohexylcarbamate (20.32 g, 95 mmol), bis(2-bromoethyl) ether (14.30 ml, 114 mmol) and triethylamine (33.0 ml, 237 mmol) in N,N-dimethylformamide (200 ml) was stirred for 16 hours at 70°C. The reaction mixture was cooled down to room temperature, concentrated and the product was extracted with ethyl acetate. The organic layer was washed with sodium carbonate solution (15% aq.), dried and concentrated. The product was used in next step without purification.

Compound 9B

trans-4-morpholinocyclohexanamine dihydrochloride

[0109] To a solution of trans-tert-butyl-4-morpholinocyclohexylcarbamate (19.2 g, 67.5 mmol) in dichloromethane (100 ml) was added HCl (100 ml, 400 mmol) (4M in dioxane) and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and solid salt was filtered off, and dried in an oven.

Compound 9C

trans-4-(4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

[0110] A solution of trans-4-morpholinocyclohexanamine dihydrochloride (5 g, 19.44 mmol), 4-fluoro-3-nitrobenzenesulfonamide (4.32 g, 19.63 mmol) and triethylamine (20 ml, 143 mmol) in tetrahydrofuran (60 ml) was stirred for 16 hours at room temperature. The solid product was filtered off, washed with tetrahydrofuran, ether, dichloromethane (3 ×) and dried under vacuum.

Compound 9D

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0111] This compound was prepared by substituting Compound 3J for Compound 1E and Compound 9C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.61 (brs, 1H), 8.49 (br s, 1H), 8.12 (m, 1H), 7.99 (br s, 1H), 7.71 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 7.01 (m, 1H), 6.65 (dd, 1H), 6.36 (d, 1H), 6.21 (d, 1H), 3.60 (m, 4H), 3.04 (m, 4H), 2.73 (m, 2H), 2.57 (m, 2H), 2.42 (m, 1H), 2.18 (m, 6H), 2.05 (m, 2H), 1.95 (m, 2H), 1.90 (m, 2H), 1.38 (m, 6H), 1.15 (m, 3H), 0.92 (s, 6H).

Compound 10

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 10A

4-(2-methoxyethylamino)-3-nitrobenzenesulfonamide

[0112] This compound was prepared by substituting 2-methoxyethylamine for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 10B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-

methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0113] This compound was prepared by substituting Compound 3J for Compound 1E and Compound 10A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.65 (brs, 1H), 8.58-8.49 (m, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.79 (m, 1H), 7.49 (m, 3H), 7.34 (m, 2H), 7.06 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.61-3.51 (m, 4H), 3.31 (s, 3H), 3.07 (m, 4H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 11

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 11A

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide and (R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

[0114] This racemic mixture was prepared by substituting (tetrahydro-2H-pyran-3-yl)methanamine for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 11B

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

[0115] The racemic mixture of Compound 11A was resolved by chiral SFC on an AD column (21mm i.d.x 250 mm in length) using a gradient of 10–30% 0.1% diethylamine methanol in CO_2 over 15 minutes (oven temperature: 40°C; flow rate: 40 ml/minute) to provide the title compound.

Compound 11C

(R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

[0116] The racemic mixture of Compound 11A was resolved by chiral SFC on an AD column (21mm i.d.x 250 mm in length) using a gradient of 10–30% 0.1% diethylamine methanol in CO_2 over 15 minutes (oven temperature: 40°C; flow rate: 40 ml/minute) to provide the title compound.

Compound 11D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-

nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0117] To a mixture of Compound 3J (59.8 mg, 0.105 mmol), Compound 11B (33mg, 0.105 mmol) and N,N-dimethylpyridin-4-amine (38.4 mg, 0.314 mmol) in dichloromethane (5 ml) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (24.07 mg, 0.13 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the title compound. ^1H NMR (500 MHz, dimethylsulfoxide -d_6) δ 11.68 (s, 1 H), 11.40 (s, br, 1 H), 8.53 - 8.58 (m, 2 H), 8.04 (d, 1 H), 7.80 (dd, 1 H), 7.47 - 7.54 (m, 3 H), 7.34 (d, 2 H), 7.02 - 7.09 (m, 3 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.79 (dd, 1 H), 3.69 - 3.73 (m, 1 H), 3.22 - 3.37 (m, 3 H), 3.16 - 3.21 (m, 1 H), 3.07 (s, 4 H), 2.74 (s, 2 H), 2.09 - 2.24 (m, 6 H), 1.95 (s, 2 H), 1.86 - 1.93 (m, 1 H), 1.79 - 1.85 (m, 1 H), 1.58 - 1.64 (m, 1 H), 1.42 - 1.51 (m, 1 H), 1.38 (t, 2 H), 1.25 - 1.34 (m, 1 H), 0.92 (s, 6 H).

Compound 12

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 12A

4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

[0118] (1,4-Dioxan-2-yl)methanol (380 mg, 3.22 mmol) in tetrahydrofuran (30 ml) was treated with sodium hydride (60%) (245 mg, 6.13 mmol) at room temperature for 30 minutes. The reaction mixture was cooled in an ice bath and 4-fluoro-3-nitrobenzenesulfonamide (675 mg, 3.06 mmol) was added. The resulting mixture was stirred at room temperature for 2 hours and another portion of sodium hydride (60%) (245 mg, 6.13 mmol) was added. The reaction mixture was stirred overnight and quenched with ice water (3 ml). The cloudy mixture was filtered and the filtrate was concentrated. The residue was triturated with methanol to give the title compound.

Compound 12B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0119] The title compound was prepared as described in the procedure for Compound 11D using Compound 12A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide -d_6) δ 11.67 (s, 1 H), 11.42 (s, br, 1 H), 8.34 (s, 1 H), 8.03 (d, 2 H), 7.48 - 7.55 (m, 3 H), 7.41 (d, 1 H), 7.35 (d, 2 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.20 - 4.28 (m, 2 H), 3.85 - 3.91 (m, 1 H), 3.82 (dd, 1 H), 3.74 - 3.78 (m, 1 H), 3.59 - 3.69 (m, 2 H), 3.41 - 3.51 (m, 2 H), 3.05 - 3.17 (m, 4 H), 2.83 (s, br, 2 H), 2.27 (s, br, 4 H), 2.15 (s, 2 H), 1.96 (s, 2 H), 1.39 (t, 2 H), 0.93 (s, 6 H).

Compound 13

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0120] The title compound was prepared as described in the procedure for Compound 11D using Compound 11C in place of Compound 11B. The proton NMR spectra of Compound 13 and Compound 11D are identical. ^{1}H NMR (500 MHz, dimethylsulfoxide -d_6) δ 11.68 (s, 1 H), 11.40 (s, br, 1 H), 8.53 - 8.58 (m, 2 H), 8.04 (d, 1 H), 7.80 (dd, 1 H), 7.47 - 7.54 (m, 3 H), 7.34 (d, 2 H), 7.02 - 7.09 (m, 3 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.79 (dd, 1 H), 3.69 - 3.73 (m, 1 H), 3.22 - 3.37 (m, 3 H), 3.16 - 3.21 (m, 1 H), 3.07 (s, 4 H), 2.74 (s, 2 H), 2.09 - 2.24 (m, 6 H), 1.95 (s, 2 H), 1.86 - 1.93 (m, 1 H), 1.79 - 1.85 (m, 1 H), 1.58 - 1.64 (m, 1 H), 1.42 - 1.51 (m, 1 H), 1.38 (t, 2 H), 1.25 - 1.34 (m, 1 H), 0.92 (s, 6 H).

Compound 14

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0121] The title compound was prepared as described in the procedure for Compound 11D using naphthalene-2-sulfonamide (47 mg, 0.227 mmol) in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.82 (s, 1 H), 11.69 (s, 1 H), 8.51 (s, 1 H), 8.08 (d, 1 H), 8.05 (d, 1 H), 7.97 (dd, 2 H), 7.82 (dd, 1 H), 7.66 - 7.71 (m, 1 H), 7.63 (t, 1 H), 7.54 (d, 1 H), 7.47 - 7.52 (m, 2 H), 7.34 (d, 2 H), 7.04 (d, 2 H), 6.65 (dd, 1 H), 6.39 (dd, 1 H), 6.18 (s,

1 H), 3.04 (s, 4 H), 2.72 (s, 2 H), 2.10 - 2.20 (m, 6 H), 1.95 (s, 2 H), 1.38 (t, 2 H), 0.92 (s, 6 H).

Compound 15

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 15A

methyl 6,6-dimethyl-4-oxotetrahydro-2H-pyran-3-carboxylate

[0122] To a suspension of hexane-washed NaH (0.72 g, 60% in mineral oil) in tetrahydrofuran (30 ml) was added a solution of 2,2-dimethyldihydro-2H-pyran-4(3H)-one (2.0 g) in tetrahydrofuran (20ml). The suspension was stirred at room temperature for 30 minutes. The dimethylcarbonate (6.31 ml) was added dropwise by syringe. The mixture was heated to reflux for 4h. LC/MS showed the expected product as the major product. The mixture was acidified with 5% HCl and extracted with dichloromethane (100 ml × 3) and washed with water, brine and dried over Na_2SO_4. After evaporation, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

Compound 15B

methyl 6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-5,6-dihydro-2H-pyran-3-carboxylate

[0123] To a cooled (0°C) stirring suspension of NaH (0.983 g, 60% in mineral oil) in ether (50 ml) was added Compound 15A (3.2 g). The mixture was stirred at 0°C for 30 minutes before the addition of Tf_2O (4.2 ml). The mixture was then stirred at room temperature overnight. The mixture was diluted with ether (200 ml) and washed with 5% HCl , water and brine. After drying over Na_2SO_4, evaporation of solvent gave the crude product which was used in the next step without further purification.

Compound 15C

methyl 4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carboxylate

[0124] To a solution of Compound 15B (2.88 g), 4-chlorophenylboronic acid (1.88 g) and $Pd(Ph_3P)_4$ (0.578 g) in toluene (40 ml) and ethanol (10 ml) was added 2N Na_2CO_3 (10 ml). The mixture was stirred at reflux overnight. The mixture was diluted ether (300 ml) and washed with water, brine and dried over Na_2SO_4. After evaporation of solvent, the residue was loaded on a column and eluted with 3% ethyl acetate in hexane to give the product.

Compound 15D

(4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methanol

[0125] To a solution of Compound 15C (1.6 g) in ether (20 ml) was added $LiAlH_4$ (1.2 g). The mixture was stirred for 4 hours. The mixture was acidified carefully with 5% HCl and extracted with ethyl acetate (100 ml × 3) and washed with water, brine and dried over Na_2SO_4. After concentration, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

Compound 15E

4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carbaldehyde

[0126] To a solution of oxalyl chloride (1.1 g) in dichloromethane (30 ml) at –78°C was added dimethylsulfoxide (6.12 ml). The mixture was stirred at the temperature for 30 minutes, and then a solution of Compound 15D (1.2 g) in dichloromethane (10 ml) was added . The mixture was stirred at –78°C for 2 hours before the addition of triethylamine (10 ml). The mixture was stirred overnight and the temperature was allowed to rise to room temperature. The mixture was diluted with ether (300 ml) and washed with water, brine and dried over Na_2SO_4. Concentration of the solvent and column purification (5% ethyl acetate in hexane) gave the product.

Compound 15F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(piperazin-1-yl)benzoate

[0127] A mixture of Compound 3H (20.5 g) and piperazine (37.0 g) in dimethylsulfoxide (200 ml) was heated to 110°C for 24 hours, and the mixture was allowed to cool to room temperature. The mixture was poured into water (1 L), extracted thee times with dichloromethane, and the combined extracts were washed with 2 × water, and brine and filtered and concentrated to give the pure product.

Compound 15G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

[0128] To a solution of Compound 15E (100 mg) and Compound 15F (177 mg) in dichloromethane (10 ml) was added sodium triacetoxyborohydride (154 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 ml) and washed with 2%NaOH, water and brine. After drying over Na_2SO_4, the mixture was filtered and the

solvent was evaporated under vacuum. The residue was loaded on a column and eluted with 30% ethyl acetate in hexane to give the pure product.

Compound 15H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

[0129] To a solution of Compound 15G (254 mg) in tetrahydrofuran (4 ml), methanol (2 ml) and water (2 ml) was added LiOH H_2O (126mg). The mixture was stirred overnight. The mixture was then neutralized with 5% HCl and diluted with ethyl acetate (200 ml). After washing with brine, it was dried over Na_2SO_4. Filtration and evaporation of solvent gave the product.

Compound 15I

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0130] The title compound was prepared as described in the procedure for Compound 1G, substituting Compound 1E with Compound 15H. ^{1}H NMR (300 MHz, dimethylsulfoxide -d_6) δ 11.68 (br s, 1H), 11.42 (s, 1H), 8.60 (m, 1H), 8.57 (d, 1H), 8.05(d, 1H), 7.80 (dd, 1H), 7.48-7.54 (m, 3H), 7.38 (d, 2H), 7.12 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.11(s, 2H), 3.85(m, 2H), 3.27(m, 6H), 3.07 (m, 2H), 2.84 (m, 2H), 2.14 (m, 5H), 1.92(m, 1H), 1.42 (m, 2H), 1.24(m, 2H), 1.10 (s, 6H).

Compound 16

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 16A

4-(2-methoxyethylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0131] 4-Fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (1.536 g, 5 mmol), 2-methoxyethanamine (0.376 g, 5mmol), and triethylamine (1.939 g, 15 mmol) in anhydrous tetrahydrofuran (30 ml) solution was heated at 55°C for 3 hours. The solution was diluted with ethyl acetate, washed with water and brine, and dried (Na_2SO_4), filtered and the filtrate was concentrated. The crude material was used in the next step without further purification.

Compound 16B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0132] This Compound was prepared by substituting Compound 3J for Compound 1E and Compound 16A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.67 (brs, 1H), 8.14 (m 1H), 8.03 (d, 1H), 7.91 (d, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (m, 3H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.06 (m, 4H), 2.75 (m, 2H), 2.17 (m, 6H), 1.95 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 17

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

Compound 17A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0133] This Compound was prepared by substituting 1-(tetrahydropyran-4-yl)methylamine for 2-methoxyethanamine in the procedure for Compound 16A.

Compound 17B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

[0134] This Compound was prepared by substituting Compound 3J for Compound 1E and Compound 17A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.70 (brs, 1H), 8.15 (m 1H), 8.04 (d, 1H), 7.92 (d, 1H), 7.51 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.05 (m, 3H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.18 (d, 1H), 3.85 (m, 2H), 3,25 (m, 4H), 3.07 (m, 4H), 2.77 (m, 2H), 2.17 (m, 6H), 1.95 (m, 2H), 1.84 (m,1 H), 1.54 (m, 2H), 1.39(t, 2H), 1.24 (m, 2H), 0.93 (s, 6H).

Compound 18

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-

ylmethyl)amino]phenyl}sulfonyl)benzamide

Compound 18A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

[0135] A mixture of 5-hydroxyindole (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 ml) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 ml), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2–50% ethyl acetate/hexanes.

Compound 18B

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0136] A mixture of Compound 18A (1.7 g), Compound 3E (1.8 g), and HK_2PO_4 (1.21 g) in dimethylsulfoxide (20 ml) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 ml), and washed with 3 × 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10–50% ethyl acetate/hexanes.

Compound 18C

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0137] Compound 18B (200 mg) in dioxane (10 ml) and 1M NaOH (6 ml) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted thee times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

Compound 18D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0138] The title compound was prepared as described in the procedure for Compound 11D by replacing Compound 3J with Compound 18C, and Compound 1F for Compound 11B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.18 (s, 2H), 8.59-8.64 (m, 2H), 7.80 (dd, 1H), 7.52 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.10 (d,1H), 7.03 (d, 2H), 6.8 (dd, 1H), 6.65 (dd, 1H), 6.40)s, 1H), 6.14 (d, 1H), 3.85 (dd, 2H), 3.24-3.32 (m, 4H), 3.03 (s, 3H),

2.73 (s, 2H), 2.12-2.17 (m, 5H), 1.68-1.94 (m, 3H), 1.61 (d, 2H), 1.37 (t, 2H), 1.24-1.27 (m, 2H), 0.92 (s, 6H).

Compound 19

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0139] The title compound was prepared as described in the procedure for Compound 11D by replacing Compound 11B with Compound 9B and Compound 3J with Compound 18C. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.29 (s, 1H), 9.29 (d, *J*=2.1 Hz, 1H), 8.37 (d, *J*=7.6 Hz, 1H), 8.32 (dd, *J*=9.3, 2.3 Hz, 1H), 8.18 (d, *J*=8.8 Hz, 1H), 7.52 - 7.57 (m, 2H), 7.39 - 7.47 (m, 3H), 7.10 (dd, *J*=8.7, 2.3 Hz, 1H), 7.05 - 7.08 (m, 2H), 6.90 (d, *J*=9.5 Hz, 1H), 6.74 (dd, *J*=9.0, 2.3 Hz, 1H), 6.59 - 6.63 (m, 1H), 6.55 (d, *J*=2.4 Hz, 1H), 3.72 - 3.78 (m, 4H), 3.33 - 3.43 (m, 1H), 2.99 - 3.09 (m, 4H), 2.76 (s, 2H), 2.46 - 2.54 (m, 4H), 2.16 - 2.29 (m, 3H), 2.09 - 2.14 (m, 4H), 2.05 (d, *J*=11.9 Hz, 2H), 1.97 (d, *J*=1.8 Hz, 2H), 1.87 (d, *J*=11.6 Hz, 2H), 1.19 - 1.42 (m, 6H), 0.93 (s, 6H).

Compound 20

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0140] The title compound was prepared as described in the procedure for Compound 11D by replacing Compound 11B with Compound 10A and Compound 3J with Compound 18C. ^{1}H NMR (400 MHz, dimethylsulfoxide - d_6) δ 11.20 (br. s, 1H) 11.15 (s, 1H) 8.59 (m, 2H) 7.81 (dd, 1H) 7.50 (d, 1H) 7.36 (m, 4H) 7.08 (m, 4H) 6.85 (dd, 1H) 6.65 (dd, 1H) 6.38 (m, 1H) 6.14 (m, 1H) 3.58 (m, 4H) 3.30 (s, 3H) 3.03 (m, 4H) 2.73 (s, 2H) 2.15 (m, 6H) 1.96 (s, 2H) 1.38 (t, 2H) 0.92 (s, 6H).

Compound 21

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide

[0141] The title compound was prepared as described in the procedure for Compound 11D by replacing Compound 3J with Compound 18C. ^{1}H NMR (400 MHz, dimethylsulfoxide -d_6) δ 11.17 (s, 2 H), 8.53 - 8.65 (m, 2 H), 7.80 (d, 1 H), 7.51 (d, 1 H), 7.38

- 7.44 (m, 2 H), 7.33 (d, 2 H), 7.15 (s, 1 H), 7.02 - 7.09 (m, 3 H), 6.82 - 6.92 (m, 1 H), 6.65 (d, 1 H), 6.39 (s, 1 H), 6.14 (s, 1 H), 3.68 - 3.82 (m, 2 H), 3.22 - 3.32 (m, 2 H), 3.13 - 3.22 (m, 1 H), 3.03 (s, 4 H), 2.72 (s, 2 H), 2.09 - 2.23 (m, 6 H), 1.78 - 1.98 (m, 4 H), 1.56 - 1.66 (m, 1 H), 1.43 - 1.51 (m, 1 H), 1.37 (t, 2 H), 1.22 - 1.33 (m, 1 H), 0.92 (s, 6 H).

Compound 22

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide

[0142] The title compound was prepared as described in the procedure for Compound 11D using Compound 11C in place of Compound 11B, and Compound 18C in place of Compound 3J. ^{1}H NMR (400 MHz, dimethylsulfoxide -d_6) δ 11.17 (s, 2 H), 8.53 - 8.65 (m, 2 H), 7.80 (d, 1 H), 7.51 (d, 1 H), 7.38 - 7.44 (m, 2 H), 7.33 (d, 2 H), 7.15 (s, 1 H), 7.02 - 7.09 (m, 3 H), 6.82 - 6.92 (m, 1 H), 6.65 (d, 1 H), 6.39 (s, 1 H), 6.14 (s, 1 H), 3.68 - 3.82 (m, 2 H), 3.22 - 3.32 (m, 2 H), 3.13 - 3.22 (m, 1 H), 3.03 (s, 4 H), 2.72 (s, 2 H), 2.09 - 2.23 (m, 6 H), 1.78 - 1.98 (m, 4 H), 1.56 - 1.66 (m, 1 H), 1.43 - 1.51 (m, 1 H), 1.37 (t, 2 H), 1.22 - 1.33 (m, 1 H), 0.92 (s, 6 H).

Compound 23

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

Compound 23A

methyl 2-(1H-indol-5-yloxy)-4-(piperazin-1-yl)benzoate

[0143] The title compound was prepared as described in the procedure for Compound 15F by replacing Compound 3H with Compound 18A.

Compound 23B

methyl 2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

[0144] The title compound was prepared as described in the procedure for Compound 15G by replacing Compound 15F with Compound 23A.

Compound 23C

2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-

yl)methyl)piperazin-1-yl)benzoic acid

[0145] The title compound was prepared as described in the procedure for Compound 15H by replacing Compound 15G with Compound 23B.

Compound 23D

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0146] The title compound was prepared as described in the procedure for Compound 11D by replacing Compound 11B with Compound 1F, and Compound 3J with Compound 23C. ^{1}H NMR (400 MHz, dimethylsulfoxide -d_6) δ 11.20 (br s, 1H), 11.17(s, 1H), 8.63 (t, 1 H), 8.59 (d, 1 H), 7.79 (dd, 1 H), 7.51 (d, 1 H), 7.36 (m, 3 H), 7.13 (m, 2 H), 6.86 (dd, 1 H), 6.66 (dd, 1 H), 6.39 (s, 1 H), 6.15 (d, 1 H), 4.10 (s, 2 H), 3.85 (m, 3 H), 3.50 (m, 2 H), 3.42 (m, 2 H), 3.24 (m, 4 H), 3.02 (m, 4 H), 2.82 (m, 2 H), 2.16 (m, 2 H), 1.61 (m, 3 H), 1.25 (m, 4 H), 1.17 (s, 6 H).

Compound 24

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 24A

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0147] (Tetrahydro-2H-pyran-4-yl)methanol (2.0 g) in tetrahydrofuran (20 ml) was treated with 60% NaH (1.377 g). The solution was stirred for 20 minutes at the room temperature. To this solution was added 4-fluoro-3-nitrobenzenesulfonamide (2.84 g) portion-wise. The reaction was stirred for another 2 hours. The mixture was poured into water, neutralized with 10% HCl, and extracted with ethyl acetate thee times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20-60% ethyl acetate in hexanes.

Compound 24B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-

yloxy)benzamide

[0148] The title compound was prepared by substituting Compound 24A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.33 (s, 1H), 8.00-8.02 (m, 2H), 7.50-7.53 (m, 3H), 7.34-7.36 (m, 3H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (d, 1H), 6.21 (s, 1H), 4.06 (d, 2H), 3.88 (dd, 2H), 3.08 (s, 4H), 2.80 (s, 2H), 2.25 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.52-1.55 (m, 1 H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

Compound 25

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 25A

4-((1,4-dioxan-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0149] The title compound was prepared as described in the procedure for Compound 1F using (1,4-dioxan-2-yl)methanamine in place of (tetrahydropyran-4-yl)methanamine.

Compound 25B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0150] The title compound was prepared as described in the procedure for Compound 11D using Compound 25A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 11.38 (s, 1H), 8.53 - 8.59 (m, 2H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.46 - 7.54 (m, 3H), 7.34 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.75 - 3.86 (m, 3H), 3.58 - 3.68 (m, 2H), 3.45 - 3.52 (m, 2H), 3.35 - 3.43 (m, 2H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 26

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 26A

3-nitro-4-(2,2,2-trifluoroethylamino)benzenesulfonamide

[0151] The title compound was prepared by substituting 2,2,2-trifluoroethanamine for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 26B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0152] The title compound was prepared by substituting Compound 26A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.48 (s, 1H), 8.40 (m, 2H), 7.90 (d, 1H), 7.71 (dd, 1H), 7.59 (d, 1H), 7.40 (t, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.06 (m, 3H), 6.61 (dd, 1H), 6.26 (m, 2H), 4.32 (m, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.19 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 27

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 27A

3-nitro-4-(3,3,3-trifluoropropylamino)benzenesulfonamide

[0153] The title compound was prepared by substituting 3,3,3-trifluoropropan-1-amine for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 27B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0154] The title compound was prepared by substituting Compound 27A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.47 (s, 1H), 8.37 (d, 1H), 8.29 (m, 1H), 7.89 (d, 1H), 7.61 (m, 2H), 7.39 (t, 1H), 7.35 (d, 2H), 7.22 (d, 1H), 7.05 (d, 2H), 6.75 (d, 1H), 6.62 (dd, 1H), 6.27 (m, 2H), 3.59 (q, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.66 (m, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (m, 6H).

Compound 28

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-

yloxy)benzamide

Compound 28A

(S)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

[0155] The racemic mixture of Compound 12A was resolved on a SFC chiral AD column to provide the title compound.

Compound 28B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0156] The title compound was prepared as described in the procedure for Compound 11D using Compound 28A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48 - 7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (s, 1H), 4.19 - 4.30 (m, 2H), 3.85 - 3.92 (m, 1H), 3.73 - 3.85 (m, 2H), 3.58 - 3.70 (m, 2H), 3.40 - 3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18 - 2.39 (m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 29

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 29A

Cis-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[0157] 4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and Compound 34A (1 g) in tetrahydrofuran (20 ml) was treated with N,N-diisopropylethylamine (0.871 ml) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, eluted with 40–55% acetonitrile in 0.1% trifluoroacetic acid in water over 25 min to give the *cis* isomer Compound 29A and *trans* isomer Compound 34B.

Compound 29B

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0158] The title compound was prepared as described in the procedure for Compound

11D using Compound 29A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.36 (s, 1H), 8.53 - 8.63 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47 - 7.56 (m, 3H), 7.34 (d, 2H), 7.00 - 7.12 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.37 (s, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.81 (dd, 2H), 1.64 - 1.74 (m, 1H), 1.48 (dd, 2H), 1.23 - 1.42 (m, 6H), 0.92 (s, 6H).

Compound 30

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 30A

(R)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

[0159] The racemic mixture of Compound 12A was resolved on a SFC chiral AD column to provide the title compound.

Compound 30B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0160] The title compound was prepared as described in the procedure for Compound 11D using Compound 30A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48 - 7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (s, 1H), 4.19 - 4.30 (m, 2H), 3.85 - 3.92 (m, 1H), 3.73 - 3.85 (m, 2H), 3.58 - 3.70 (m, 2H), 3.40 - 3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18 - 2.39 (m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 31

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0161] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 25A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 11.46 (m, 1H), 8.54

(m, 2H), 8.45 (m, 1H), 8.03 (d, 1H), 7.83 (m, 2H), 7.50 (m, 3H), 7.34 (m, 3H), 7.12 (m, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.11 (s, 2H), 3.79 (m, 4H), 3.51 (m, 6H), 3.05 (m, 4H), 2.17 (m, 3H), 1.17 (s, 6H).

Compound 32

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0162] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 12A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.37 (d, 1H), 8.03 (m, 2H), 7.50 (m, 3H), 7.37 (d, 2H), 7.13 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.25 (m, 2H), 4.12 (s, 2H), 3.84 (m, 3H), 3.63 (m, 2H), 3.45 (m, 2H), 3.06 (m, 4H), 2.86 (m, 2H), 2.24 (m, 6H), 1.20 (m, 6H).

Compound 33

trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0163] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 9C, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1H), 8.51 (d, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.76 (dd, 1H), 7.48 (m, 3H), 7.38 (d, 2H), 7.13 (d, 2H), 7.06 (d, 1H), 6.66 (dd, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 4.11 (s, 2H), 3.63 (m, 5H), 3.05 (m, 4H), 2.83 (s, 2H), 2.64 (m, 4H), 2.17 (m, 6H), 2.05 (m, 2H), 1.91 (s, 2H), 1.43 (m, 6H), 1.17 (m, 6H).

Compound 34

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 34A

(4-methoxycyclohexyl)methanamine

[0164] (4-Methoxyphenyl)methanamine (1 g, 1.29 mmol) in ethanol (10 ml) was treated with 5% Rh-Al_2O_3 (99.8 mg, 0.048 mmol) under H_2 atmosphere (500 psi) at 50°C for 16

hours. Additional 5% Rh-Al_2O_3 (0.4 g) was added. The resulting mixture was stirred under H_2 atmosphere (500 psi) at 60°C for 2 hours. The insoluble material was filtered off and the filtrate was concentrated to provide a mixture of *cis* and *trans* product as an oil, which was used in the next step without further purification.

Compound 34B

trans-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[0165] 4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and Compound 34A (1 g) in tetrahydrofuran (20 ml) was treated with N,N-diisopropylethylamine (0.871 ml) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, and was eluted with 40–55% acetonitrile in 0.1% trifluoroacetic acid in water over 25 minutes.

Compound 34C

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0166] The title compound was prepared as described in the procedure for Compound 11D using Compound 34B in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1 H), 11.37 (s, 1 H), 8.52 - 8.62 (m, 2 H), 8.04 (d, 1 H), 7.79 (dd, 1 H), 7.47 - 7.55 (m, 3 H), 7.34 (d, 2 H), 7.02 - 7.09 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.21 - 3.27 (m, 5 H), 3.02 - 3.12 (m, 5 H), 2.75 (s, 2 H), 2.20 (s, 4 H), 2.14 (s, 2 H), 1.93 - 2.04 (m, 4 H), 1.79 (d, 2 H), 1.55 - 1.65 (m, 1 H), 1.38 (t, 2 H), 0.97 - 1.12 (m, 4 H), 0.92 (s, 6 H).

Compound 35

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0167] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 36C, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.78 (s, 1H), 8.58 (s, 1H), 8.00 (d, 1H), 7.51 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.68 (dd, 1H), 6.37 (dd, 1H), 6.23 (d, 1H), 4.31 (d, 2H), 4.13 (s, 2H), 3.88 (dd, 2H), 3.11 (m, 5H), 2.16 (m, 6H), 1.65 (m, 2H),

1.35 (m, 2H), 1.19 (s, 6H).

Compound 36

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 36A

5-bromo-6-chloropyridine-3-sulfonamide

[0168] 5-Bromo-6-chloropyridine-3-sulfonyl chloride (8.2 g) in methanol (20 ml) was cooled to 0°C. To this solution was added 7N NH_3 in methanol (80 ml). The reaction mixture was stirred overnight. The solvent was removed at low temperature, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate thee times. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The solid was purified by flash column chromatography on silica gel using 20–100% ethyl acetate in hexanes to give the title compound.

Compound 36B

5-bromo-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0169] The title compound was prepared by substituting Compound 36A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 36C

5-cyano-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0170] A mixture of Compound 36B (0.702 g), dicyanozinc (0.129 g), and tetrakis(triphenylphosphine)palladium(0) (0.231 g) in N,N-dimethylformamide (2 ml) was degassed via vacuum/nitrogen cycle thee times. The reaction mixture was heated at 120 °C for 3 hours. After cooling, it was poured into water and extracted with ethyl acetate thee times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20%-60% ethyl acetate in hexanes to give the title compound.

Compound 36D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0171] The title compound was prepared by substituting Compound 36C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.56 (s, 1H), 8.66 (s, 1H), 8.44 (s, 1H), 7.94 (d, 1H), 7.55 (d, 1H), 7.44 (t, 1H), 7.34-7.35 (m, 3H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.32 (s, 1H), 6.24 (s, 1H), 4.26 (d, 2H), 3.86 (dd, 2H), 3.10 (s, 4H), 2.75 (s, 2H), 2.31-2.35 (m, 2H), 2.01-2.05 (m, 1H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

Compound 37

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 37A

1,6-dioxaspiro[2.5]octane-2-carbonitrile

[0172] A mixture of tetrahydropyran-4-one (10 ml) and chloroacetonitrile (6.4 ml) in tert-butanol (10 ml) was stirred for 10 minutes. To this solution was added a solution of potassium tert-butoxide (12.11 g) in 200 ml of tert-butanol at room temperature over 40 minutes. The reaction mixture was stirred for 16 hours, diluted with water and quenched slowly with 1 N HCl. The solvent was partially removed by rotary evaporation. It was then extracted with ether (5x 200 ml). The combined extracts was washed with brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated and purified by flash chromatography on silica with 3:7 to 1:1 ethyl acetate:hexanes to provide the title compound.

Compound 37B

2-(4-fluorotetrahydro-2H-pyran-4-yl)-2-hydroxyacetonitrile

[0173] Compound 37A (11.5 g) in dichloromethane (40 ml) in a polypropylene bottle was treated with 70% hydrogen fluoride-pyridine (10.4 ml) dropwise at 0 °C. The solution was allowed to warm to room temperature over 3 hours, and stirred for an additional 1.5 hours. The reaction mixture was diluted with ethyl acetate (200 ml) and poured into saturated aqueous $NaHCO_3$. Additional solid $NaHCO_3$ was used carefully until bubbling ceased. The organic layer was isolated, and the aqueous layer was extracted with additional ethyl acetate three times (150 ml each).The combined organic layers were washed with 5% HCl (50 ml each, twice), brine, dried over $MgSO_4$, filtered and concentrated to give the desired product which was used directly in the next step.

Compound 37C

(4-fluorotetrahydro-2H-pyran-4-yl)methanol

[0174] Compound 37B (11.7 g, 74 mmol) in 2-propanol (150 ml) and water (37.5 ml) was cooled to 0 °C. To this solution was added $NaBH_4$ (4.20 g, 111 mmol). The solution was stirred and allowed to warm to room temperature over 3 hours. It was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate (2 × 100 ml) was used to wash the solid, and the mixture was decanted. The combined organic solutions were concentrated. The residue was purified by flash chromatography, eluting with 1:1 ethyl acetate:hexanes to provide the title compound.

Compound 37D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0175] The title compound was prepared by substituting Compound 37C for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 37E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0176] The title compound was prepared as described in the procedure for Compound 11D using Compound 37D in place of Compound 11B. ^1H NMR (dimethylsulfoxide-d_6) δ 11.64 (s, 2H), 8.33 (s, 1H), 8.00-8.01 (m, 2H), 7.39-7.57 (m, 4H), 7.33 (d, J = 8.24 Hz, 2H), 7.03 (d, J = 8.54 Hz, 2H), 6.65 (dd, J = 9, 1.98 Hz, 1H), 6.37-6.38 (m, 1H), 6.19 (d, J = 1.53 Hz, 1H), 4.35 (d, J = 20.75 Hz, 2H), 3.74-3.78 (m, 2H), 3.55-3.60 (m, 2H), 3.07 (br, 4H), 2.80 (br, 2H), 2.25 (br, 4H), 2.13 (br, 2H), 1.81-1.94 (m, 6H), 1.38 (t, J = 6.26 Hz, 2H), 0.91 (s, 6H).

Compound 38

N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 38A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0177] The title compound was prepared by substituting 3-cyano-4-

fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 38B

5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)benzamide

[0178] To a solution of Compound 38A (0.455 g) in ethanol (3 ml) and tetrahydrofuran (1 ml) was added hydrogen peroxide (30% in water, 2 ml) followed by 1 N aqueous NaOH (1.024 ml) and heated to 35°C for 3 hours. The reaction was poured into dichloromethane (50 ml) and 1N aqueous HCl (25 ml). The aqueous layer was extracted with dichloromethane (3 × 50 ml). The precipitate contained in the combined organic layers was collected by filtration to give the title compound.

Compound 38C

N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0179] The title compound was prepared by substituting Compound 38B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.79 - 11.70 (m, 1H), 11.66 - 11.54 (m, 1H), 9.29 - 9.08 (m, 1H), 8.27 (d, 1H), 8.08 (d, 1H), 7.97 - 7.90 (m, 1H), 7.76 - 7.72 (m, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.50 (d, 1H), 7.39 (d, 1H), 7.23 (d, 1H), 7.08 (d, 1H), 6.74 - 6.67 (m, 1H), 6.44 (s, 1H), 6.22 (s, 1H), 4.03 (d, 6H), 3.74 - 3.52 (m, 4H), 3.33 (s, 4H), 3.11 - 2.90 (m, 2H), 2.01 (s, 4H), 1.79 - 1.58 (m, 2H), 1.24 (s, 5H), 0.94 (s, 6H).

Compound 39

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 39A

cis-tert-butyl-4-morpholinocyclohexylcarbamate

[0180] To a solution of morpholine (4.08 g) and tert-butyl 4-oxocyclohexylcarbamate (10 g) stirred for 24 hours at room temperature in titanium (IV) isopropoxide (27.5 ml), methanol (10 ml) was added followed by careful addition of sodium borohydride (3.55 g). The reaction mixture was quenched with water/NaOH solution, extracted with ether, dried over magnesium

sulfate, filtered, and concentrated. The product was separated from the trans isomer and purified by flash chromatography (silica gel, 50% - 100% acetone in hexanes) to provide the title compound.

Compound 39B

cis-4-morpholinocyclohexanamine bis(2,2,2-trifluoroacetate)

[0181] To a solution of Compound 39A (2.43 g) in dichloromethane (15 ml) was added trifluoroacetic acid (5 ml) and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was concentrated and the crude product was used without purification.

Compound 39C

4-(cis-4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

[0182] A solution of Compound 39B (0.40 g), 4-fluoro-3-nitrobenzenesulfonamide (0.478 g) and triethylamine (2 ml) in tetrahydrofuran (10 ml) was stirred for 3 days at room temperature. The reaction mixture was concentrated and purified by flash chromatography (silica gel, 0–30% methanol/dichloromethane) providing the product.

Compound 39D

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0183] The title compound was prepared by substituting Compound 39C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.07 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.67 (t, 2H), 7.44 (d, 2H), 7.06 (d, 2H), 6.91 (d, 1H), 6.74 (dd, 1H), 6.48 - 6.55 (m, 2H), 3.65 - 3.73 (m, 5H), 3.02 - 3.09 (m, 4H), 2.76 (s, 2H), 2.41 - 2.48 (m, 4H), 2.25 (t, 2H), 2.09 - 2.16 (m, 5H), 1.97 (s, 2H), 1.77 - 1.86 (m, 2H), 1.55 - 1.63 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 40

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 40A

5,6-dichloropyridine-3-sulfonamide

[0184] The title compound was prepared by substituting 5,6-dichloropyridine-3-sulfonyl chloride for 5-bromo-6-chloropyridine-3-sulfonyl chloride in the procedure for Compound 36A.

Compound 40B

5-chloro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0185] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 40C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0186] The title compound was prepared by substituting Compound 40B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.52 (s, 1H), 8.39 (d, 1H), 8.03 (d, 1H), 7.54 (d, 1H), 7.52 (d, 1H), 7.50 (dd, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.30 (m, 2H), 3.10 (v br s, 4H), 2.90 (v br s, 2H), 2.35 (v br s, 4H), 2.17 (br m, 2H), 2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.40 (t, 2H), 1.35 (ddd, 2H), 0.93 (s, 6H).

Compound 41

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0187] The title compound was prepared by substituting Compound 15H for Compound 3J and Compound 40B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.55 (d, 1H), 8.41 (d, 1H), 8.04 (d, 1H), 7.54 (m, 2H), 7.50 (dd, 1H), 7.38 (d, 2H), 7.14 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.25 (d, 2H), 4.12 (s, 2H), 3.87 (dd, 2H), 3.30 (m, 2H), 3.10 (v br s, 4H), 2.90 (v br s, 2H), 2.27 (v br s, 4H), 2.17 (br m, 2H), 2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.35 (ddd, 2H), 0.97 (s, 6H).

Compound 42

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-

ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide

Compound 42A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trifluoromethyl)benzenesulfonamide

[0188] A mixture of 4-fluoro-3-(trifluoromethyl)benzenesulfonamide (1.056 g), (tetrahydro-2H-pyran-4-yl)methanamine (0.5 g) and N,N-diisopropylethylamine (1.68 g) in anhydrous dimethylsulfoxide (15 ml) solution was heated at 90°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound.

Compound 42B

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide

[0189] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 42A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.73 (s, 1H), 11.25 (s, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.77 (m, 1H), 7.61 (d, 1H), 7.51 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 6.88 (d, 1H), 6.67 (dd, 1H), 6.53 (m, 1H), 6.43 (m, 1H), 6.15 (d, 1H), 4.11 (s, 2H), 3.82 (dd, 2H), 3.19 (m, 5H), 3.05 (m, 4H), 2.82 (s, 2H), 2.20 (m, 7H), 1.85 (m, 1H), 1.56 (m, 2H), 1.18 (s, 6H).

Compound 43

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

[0190] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 17A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.48 (m, 1H), 8.16 (d, 1H), 8.05 (d, 1H), 7.92 (dd, 1H), 7.52 (m, 3H), 7.37 (d, 2H), 7.27 (m, 1H), 7.11 (m, 3H), 6.68 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.11 (s, 2H), 3.84 (dd, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.84 (m, 2H), 2.23 (m, 5H), 1.84 (m, 1H), 1.55 (m, 2H), 1.25 (m, 3H), 1.18 (s, 6H).

Compound 44

trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 44A

trans-4-(4-morpholinocyclohexylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0191] The title compound was prepared as described in the procedure for Compound 16A by replacing 2-methoxyethanamine with Compound 9B.

Compound 44B

trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0192] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 44A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.62 (s, 1H), 8.08 (s, 1H), 8.00 (d, 1H), 7.85 (d, 1H), 7.47 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.98 (d, 1H), 6.65 (dd, 1H), 6.55 (m, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.54 (m, 6H), 3.04 (m, 4H), 2.83 (s, 2H), 2.57 (m, 3H), 2.24 (m, 6H), 1.91 (m, 5H), 1.34 (m, 4H), 1.20 (s, 6H).

Compound 45

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 45A

4-(1-methylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0193] The title compound was prepared as described in the procedure for Compound 16A by replacing 2-methoxyethanamine with 1-methyl-4-aminopiperidine.

Compound 45B

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0194] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 45A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.59 (s, 1H), 8.10 (s, 1H), 7.98 (d, 1H), 7.90 (dd, 1H), 7.49 (m, 3H), 7.39 (m, 3H), 7.14 (d, 2H), 7.02 (d, 1H), 6.65 (dd, 2H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.12 (s, 2H), 3.75 (m, 1H), 3.16 (m, 4H), 2.98 (m, 5H), 2.88 (m, 5H), 2.67 (s, 2H), 2.22 (m, 6H), 1.68 (m, 1H), 1.18 (s, 6H).

Compound 46

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

Compound 46A

5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)nicotinamide

[0195] To Compound 36C (0.025 g) in ethanol (1 ml) and tetrahydrofuran (1 ml) was added hydrogen peroxide (30% in water, 0.5 ml) followed by 1M aqueous sodium hydroxide (0.056 ml) then another 1 ml of tetrahydrofuran. The reaction was heated to 45°C for 2 hours, cooled, quenched with 1N aqueous HCl (5 ml), and the product extracted into dichloromethane (10 ml). The organic layer was dried over magnesium sulfate, filtered and concentrated to give the title compound.

Compound 46B

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

[0196] The title compound was prepared by substituting Compound 46A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 – 10.09 (m, 1H), 9.09 (s, 2H), 8.93 – 8.81 (m, 1H), 8.28 – 8.18 (m, 1H), 8.03 – 7.87 (m, 1H), 7.77 – 7.68 (m, 1H), 7.59 – 7.51 (m, 1H), 7.48 – 7.41 (m, 1H), 6.91 (d, 2H), 6.59 – 6.48 (m, 2H), 5.97 (s, 2H), 4.50 (d, 2H), 4.08 – 3.98 (m, 2H), 3.45 (s, 4H), 3.13 – 2.99 (m, 4H), 2.82 – 2.68 (m, 2H), 2.19 (s, 4H), 1.86 (s, 5H), 1.61 – 1.35 (m, 4H), 0.94 (s, 6H).

Compound 47

N-({5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-

chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 47A

5-bromo-6-((1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0197] To (1-methylpiperidin-4-yl)methanol (0.109 g) in tetrahydrofuran (2 ml) was added sodium hydride (0.136 g). After 30 minutes, Compound 36A (0.230 g) was added as a solution in tetrahydrofuran (1 ml) and the reaction was heated to 50°C. After 4 hours, the reaction was cooled, poured into water (10 ml) and dichloromethane (50 ml), and the pH was adjusted to pH~8. The aqueous layer was extracted with dichloromethane (3 × 50 ml), and the organic layers were combined, washed with brine (30 ml), dried over magnesium sulfate, filtered, and concentrated to give the title compound.

Compound 47B

N-({5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0198] The title compound was prepared by substituting Compound 47A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.51 (s, 1H), 8.35 (d, 1H), 8.17 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.44 – 7.40 (m, 1H), 7.33 (dd, 3H), 7.05 (d, 2H), 6.61 (d, 1H), 6.31 (dd, 1H), 6.24 (s, 1H), 4.25 (d, 2H), 3.40 (s, 4H), 3.01 (s, 4H), 2.73 (d, J = 8.2, 5H), 2.20 (s, 6H), 1.93 (d, 4H), 1.54 (s, 1H), 1.39 (s, 2H), 1.24 (s, 2H), 0.93 (s, 6H).

Compound 48

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 48A

4-((1-methylpiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0199] The title compound was prepared by substituting (1-methylpiperidin-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 48B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-

methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0200] The title compound was prepared by substituting Compound 48A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.54 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.87 – 7.77 (m, 1H), 7.58 (d, 1H), 7.43 (s, 1H), 7.40 – 7.00 (m, 7H), 6.70 – 6.56 (m, 1H), 6.31 (s, 1H), 6.24 (s, 1H), 4.05 (s, 2H), 3.46 – 3.33 (m, 2H), 3.02 (s, 6H), 2.72 (d, 5H), 2.21 (s, 6H), 1.96 (s, 5H), 1.70 – 1.48 (m, 2H), 1.39 (s, 2H), 0.93 (s, 6H).

Compound 49

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 49A

6-((1, 4-dioxan-2-yl)methoxy)-5-bromopyridine-3-sulfonamide

[0201] The title compound was prepared by substituting (1, 4-dioxan-2-yl)methanol for (tetrahydro-2*H*-pyran-4-yl)methanol and Compound 36A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 49B

6-((1,4-dioxan-2-yl)methoxy)-5-cyanopyridine-3-sulfonamide

[0202] The title compound was prepared by substituting Compound 49A for Compound 36B in the procedure for Compound 36C.

Compound 49C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0203] The title compound was prepared by substituting Compound 49B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.50 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 7.91 (d, 1H), 7.58 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.28 (s, 1H), 7.06 (d, 2H), 6.64 (dd, 1H), 6.29 (m, 2H), 4.40 (d, 2H), 3.90 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 4H), 3.07 (s, 4H), 2.85 (m, 2H), 2.34 (m, 4H), 2.16 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

Compound 50

N-{[5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0204] The title compound was prepared by substituting Compound 49A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.60 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.99 (d, 1H), 7.56 (d, 1H), 7.46 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.65 (dd, 1H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.34 (m, 2H), 3.88 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 2H), 3.06 (s, 4H), 2.81 (s, 2H), 2.26 (m, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.38 (m, 2H), 0.93 (s, 6H).

Compound 51

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 51A

4-((2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0205] The title compound was prepared as described in the procedure for Compound 12A by replacing (1,4-dioxan-2-yl)methanol with (2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol.

Compound 51B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0206] The title compound was prepared as described in the procedure for Compound 11D using Compound 51A in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 2H), 8.35 (s, 2H), 8.03 (d, 4H), 7.47 - 7.58 (m, 6H), 7.31 - 7.42 (m, 6H), 7.04 (d, 4H), 6.68 (dd, 2H), 6.40 (s, 2H), 6.20 (d, 2H), 3.96 - 4.09 (m, 2H), 3.54 - 3.68 (m, 2H), 3.09 (s, 4H), 2.83 (s, 2H), 2.09 - 2.37 (m, 7H), 1.96 (s, 2H), 1.55 - 1.69 (m, 2H), 1.39 (t, 2H), 1.19 (m, 8H), 0.92 (s, 6H).

Compound 52

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-

{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 52A

3-cyano-4-fluorobenzenesulfonamide

[0207] 3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) in 1,4-dioxane (10 ml) at 0 °C was treated dropwise with a 7 M ammonia solution in methanol (3.57 ml) and stirred for 30 minutes. A small amount of solid was removed by filtration and discarded. The filtrate was concentrated, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and triturated with diethyl ether to give the product.

Compound 52B

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0208] The title compound was prepared by substituting Compound 52A for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 52C

3-chloro-5-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0209] Compound 52B (0.148 g) in acetonitrile (5 ml) was treated with N-chlorosuccinimide (0.080 g), heated at 60 °C for 3 hours and filtered to remove a small amount of solid. The filtrate was concentrated and chromatographed on silica gel with 3-15% ethyl acetate in dichloromethane as eluent. The obtained solid was slurried in water, filtered, rinsed with additional water and dried under vacuum to give the product.

Compound 52D

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0210] The title compound was prepared by substituting Compound 52C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ11.70 (s, 1H), 11.41 (br s, 1H), 8.07 (d, 1H), 7.89 (s, 2H), 7.61 (m, 1H), 7.53 (m, 2H), 7.35 (d, 2H), 7.18 (m, 1H), 7.05 (d, 2H), 6.69 (m, 1H), 6.42 (dd, 1H), 6.18 (dd, 1H), 3.83 (m, 2H), 3.55 (t, 2H), 3.23 (m, 3H), 3.06 (m, 4H), 2.15 (m, 4H), 1.92 (m, 4H), 1.60 (m, 2H), 1.40 (m, 2H), 1.19 (m, 4H), 0.93 (s, 6H).

Compound 53

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 53A

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0211] The title compound was prepared by substituting Compound 3J for Compound 1E and 4-chloro-3-nitrobenzenesulfonamide for Compound 1F in the procedure for Compound 1G.

Compound 53B

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0212] A 5 ml round-bottomed flask was charged with Compound 53A (120 mg), 1-acetylpiperidin-4-amine (28 mg), and triethylamine (0.064 ml) in dioxane (2 ml). The reaction mixture was heated to 90°C for 24 hours. The reaction mixture was cooled to room temperature, and added to a silica gel column and purified by eluting with 0–5% methanol in dichloromethane. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.66 (br s, 1H), 8.65 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.19 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.28 (d, 1H), 3.97-3.75 (m, 2H), 3.07 (br s, 4H), 2.87-2.70 (m, 4H), 2.29-2.10 (m, 6H), 2.02 (s, 3H), 2.00-1.89 (m, 4H), 1.66-1.54 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

Compound 54

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 54A

2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0213] The title compound was prepared by substituting 2-chloro-4,5-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-

pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 54

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0214] The title compound was prepared by substituting Compound 54A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.76 (s, 1H), 11.31 (s, 1H), 8.08 (d, 1H), 7.69 (d, 1H), 7.60 (d, 1H), 7.55 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (s, 1H), 6.84 (d, 1H), 6.69 (dd, 1H), 6.45 (dd, 1H), 6.13 (d, 1H), 3.82 (dd, 2H), 3.24 (t, 2H), 3.05 (m, 6H), 2.73 (s, 2H), 2.14 (m, 6H), 1.95 (s, 2H), 1.81 (m, 1H), 1.61 (m, 2H), 1.38 (t, 2H), 1.17 (m, 2H), 0.92 (s, 6H).

Compound 55

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0215] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 2A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.66 (br s, 1H), 8.75 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.54-7.48 (m, 3H), 7.35 (d, 2H), 7.08-7.02 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.61 (t, 4H), 3.43 (q, 2H), 3.29 (m, 2H), 3.06 (br s, 4H), 2.73 (br s, 2H), 2.47 (br s, 4H), 2.18 (m, 6H), 1.95 (br s, 2H), 1.80 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 56

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 56A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0216] The title compound was prepared by substituting Compound 37C for tetrahydro-2H-pyran-4-yl)methanol and Compound 36A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 56B

5-cyano-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0217] The title compound was prepared by substituting Compound 56A for Compound 36B in the procedure for Compound 36C.

Compound 56C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0218] The title compound was prepared by substituting Compound 56B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.58 (s, 1H), 8.70 (s, 1H), 8.51 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.35-7.37 (m, 3H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.33 (d, 1H), 6.26 (s, 1H), 4.56 (d, 2H), 3.76-3.80 (s, 2H), 3.56-3.62 (m, 2H), 3.01-3.10 (m, 4H), 2.14-2.18 (m, 2H), 1.96 (s, 2H), 1.80-1.87 (m, 4H), 1.41 (t, 2H), 0.93 (s, 6H).

Compound 57

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 57A

5-bromo-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

[0219] The title compound was prepared by substituting 2-morpholinoethanol for tetrahydro-2H-pyran-4-yl)methanol and Compound 36A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 57B

5-cyano-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

[0220] The title compound was prepared by substituting Compound 57A for Compound 36A in the procedure for Compound 36B.

Compound 57C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0221] The title compound was prepared by substituting Compound 57B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.56 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.92 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.36 (d, 2H), 7.31 (s, 1H), 7.06 (d, 2H), 6.65 (dd, 1H), 6.31 (d, 1H), 6.27 (d, 1H), 4.59 (t, 2H), 3.59 (s, 4H), 3.08 (s, 4H), 2.89 (s, 2H), 2.65 (s, 4H), 2.16-2.18 (m, 2H), 1.97 (s, 2H), 1.41 (t, 2H), 0.93 (s, 6H).

Compound 58

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 58A

3-chloro-4-(2-(2-methoxyethoxy)ethylthio)benzenesulfonamide

[0222] In a 25 ml microwave tube was added sodium hydride (0.6 g) in terahydrofuran (10 ml) to give a suspension. 2-(2-Methoxyethoxy)ethanethiol (1 g) was added slowly. After stirring for 30 minutes, 3-chloro-4-fluorobenzenesulfonamide (1.54 g) dissolved in 10 ml tetrahydrofuran was added slowly. The mixture was heated at 110°C for 30 minutes in a Biotage Initiator microwave reactor. Water was added, the product was extracted with ether (20 ml × 3), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica eluting with 0–25% ethyl acetate in hexane.

Compound 58B

3-chloro-4-(2-(2-methoxyethoxy)ethylsulfonyl)benzenesulfonamide

[0223] Compound 58A (0.15 g) was suspended in acetic acid (3 ml). Peracetic acid (0.4 ml) was added slowly. The mixture was stirred at room temperature overnight, then poured into $Na_2S_2O_3$ solution, and the product precipitated. After filtration and washing with water, the product was dried under vacuum.

Compound 58C

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0224] The title compound was prepared by substituting Compound 58B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.52

(s, 1H), 7.92 (d, 1H), 7.84 (m, 2H), 7.68 (m, 1H), 7.62 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.29 (m, 1H), 7.05 (d, 2H), 6.62 (dd, 1H), 6.32 (m, 1H), 6.26 (d, 1H), 3.74 (t, 2H), 3.68 (t, 2H), 3.24 (m, 2H), 3.06 (m, 5H), 3.01 (m, 4H), 2.74 (s, 2H), 2.19 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 59

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 59A

4-(2-(2-methoxyethoxy)ethylthio)-3-nitrobenzenesulfonamide

[0225] The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 3-chloro-4-fluorobenzenesulfonamide in the procedure for Compound 58A.

Compound 59B

4-(2-(2-methoxyethoxy)ethylsulfonyl)-3-nitrobenzenesulfonamide

[0226] The title compound was prepared by substituting Compound 59A for Compound 58A in the procedure for Compound 58B.

Compound 59C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0227] The title compound was prepared by substituting Compound 59B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.51 (s, 1H), 8.17 (m, 1H), 7.94 (m, 3H), 7.64 (d, 1H), 7.42 (m, 1H), 7.35 (d, 2H), 7.28 (d, 1H), 7.05 (d, 2H), 6.62 (m, 1H), 6.28 (m, 2H), 3.83 (m, 4H), 3.16 (m, 2H), 3.08 (s, 3H), 3.01 (m, 4H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H)

Compound 60

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 60A

trans-4-(4-aminocyclohexyloxy)-3-nitrobenzenesulfonamide

[0228] To a solution of *tert*-butyl 4-hydroxycyclohexylcarbamate (0.250 g) in tetrahydrofuran (5 ml) was added sodium hydride (0.186 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.256 g) was added as a solution in tetrahydrofuran (1 ml). The reaction was heated to 60°C for 1.5 hours, cooled, and poured into a mixture of dichloromethane (100 ml) and water (25 ml). The aqueous layer was adjusted to pH~4 with 1N aqueous HCl and the organic layer was separated, washed with brine (50 ml), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolv 40 g) and eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes. This solid was treated with HCl (4.0M in dioxane, 5 ml) at room temperature for 1 hour and concentrated to give the title compound.

Compound 60B

4-(trans-4-morpholinocyclohexyloxy)-3-nitrobenzenesulfonamide

[0229] To Compound 60A (0.220 g) and 1-bromo-2-(2-bromoethoxy)ethane (0.177 g) in N,N-dimethylformamide (3 ml) was added triethylamine (0.338 ml) and the reaction heated to 70°C for 5 hours. The reaction was cooled and the resulting precipitate was removed by filtration. The reaction was concentrated and loaded onto silica gel and was eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane to give the title compound.

Compound 60C

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0230] The title compound was prepared by substituting Compound 60B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.62 (s, 1H), 8.23 (s, 1H), 7.99 (s, 1H), 7.96 – 7.88 (m, 1H), 7.54 (d, 1H), 7.48 (s, 2H), 7.34 (d, 3H), 7.04 (d, 2H), 6.72 – 6.58 (m, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.69 – 4.47 (m, 1H), 3.66 (s, 4H), 3.05 (s, 4H), 2.76 (s, 6H), 2.22 (s, 9H), 1.96 (s, 4H), 1.39 (s, 6H), 0.92 (s, 6H).

Compound 61

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]pyridin-3-

yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 61A

5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)pyridine-3-sulfonamide

[0231] A mixture of Compound 36A (1.0 g), Compound 3L (0.95 g) and triethylamine (3.08 ml) in anhydrous dioxane (20 ml) was heated at 110°C overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 2%-8% methanol/dichloromethane to give the title compound.

Compound 61B

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0232] The title compound was prepared by substituting Compound 61A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.59 (s, 1H), 8.35 (s, 1H), 8.00 (s, 2H), 7.55 (d, 1H), 7.46 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.49 (m, 1H), 6.36 (s, 1H), 6.20 (s, 1H), 4.05 (m, 1H), 3.94 (d, 2H), 3.28 (m, 6H), 3.01 (s, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.93 (m, 4H), 1.80 (m, 4H), 1.57 (m, 2H), 1.38 (t, 2H), 1.17 (t, 2H), 0.90 (s, 6H).

Compound 62

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 62A

4-(2-cyanoethylamino)-3-nitrobenzenesulfonamide

[0233] The title compound was prepared by substituting 3-aminopropanenitrile for Compound 39B in the procedure for Compound 39C.

Compound 62B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0234] The title compound was prepared by substituting Compound 62A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (501 MHz, pyridine-d_5) δ 13.04 (s, 1H),

9.24 (d, 1H), 9.04 (t, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.13 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (ddd, 2H), 7.07 (ddd, 2H), 7.02 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 3.83 (q, 2H), 3.07 (d, 4H), 2.98 (t, 2H), 2.77 (s, 2H), 2.26 (s, 2H), 2.11 - 2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 63

cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0235] The title compound was prepared by substituting Compound 15H for Compound 3J and Compound 39C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (501 MHz, pyridine-d_5) δ 13.09 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (dt, 2H), 7.46 (ddd, 2H), 7.12 (ddd, 2H), 6.91 (d, 1H), 6.72 (dd, 1H), 6.51 (dd, 1H), 6.49 (d, 1H), 5.69 (s, 2H), 4.40 (s, 2H), 3.69 - 3.73 (m, 4H), 3.68 (s, 1H), 2.95 - 3.02 (m, 4H), 2.84 (s, 2H), 2.40 - 2.46 (m, 4H), 2.21 (s, 2H), 2.08 - 2.15 (m, 5H), 1.76 - 1.84 (m, 2H), 1.55 - 1.63 (m, 6H), 1.29 (s, 6H).

Compound 64

trans-N-{[4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 64A

tert-butyl (trans)-4-(bis(cyclopropylmethyl)amino)cyclohexylcarbamate

[0236] The title compound was prepared by substituting cyclopropanecarbaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde and tert-butyl (trans)-4-aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 64B

(trans)-N^1,N^1-bis(cyclopropylmethyl)cyclohexane-1,4-diamine dihydrochloride

[0237] To a solution of Compound 64A (1.4 g) in dichloromethane (10 ml) was added hydrogen chloride (10 ml, 4M in dioxane) and the reaction was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and pure product was filtered off.

Compound 64C

trans-4-(4-(bis(cyclopropylmethyl)amino)cyclohexylamino)-3-nitrobenzenesulfonamide

[0238] The title compound was prepared by substituting Compound 64B for Compound 39B in the procedure for Compound 39C.

Compound 64D

trans-N-{[4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0239] The title compound was prepared by substituting Compound 64C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.30 (d, 1H), 8.44 (d, 1H), 8.41 (dd, 1H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.00 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.36 - 3.43 (m, 1H), 3.02 - 3.09 (m, 4H), 2.87 - 2.94 (m, 1H), 2.77 (s, 2H), 2.47 (d, 4H), 2.25 (t, 2H), 2.11 - 2.16 (m, 4H), 2.08 (d, 2H), 1.97 (s, 2H), 1.84 (d, 2H), 1.39 (t, 2H), 1.26 - 1.35 (m, 4H), 0.90 - 0.98 (m, 8H), 0.50 - 0.56 (m, 4H), 0.18 - 0.23 (m, 4H).

Compound 65

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 65A

4-((1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide

[0240] The title compound was prepared by substituting 4-aminomethyl-1-methyl piperidine for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 65B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0241] The title compound was prepared by substituting Compound 65A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, dichloromethane-d_2) δ 9.57 (bs, 1H), 8.78 (d, 1H), 8.41 (d, 1H), 8.14 (d, 1H), 7.90 (m, 2H), 7.64 (d, 1H), 7.45 (d, 1H), 7.23 (d, 2H), 6.95 (d, 2H), 6.76 (d, 1H), 6.59 (dd, 1H), 6.51 (d, 1H), 6.09 (d, 1H), 3.21 (m, 2H), 3.08 (m, 4H), 3.02 (m, 2H), 2.74 (s, 2H), 2.33 (s, 3H), 2.21-2.17 (m, 6H), 2.16-2.02 (m, 3H), 1.97 (br.s, 2H), 1.78 (m, 4H), 1.41 (t, 2H), 0.94 (s, 6H).

Compound 66

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 66A

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

[0242] The title compound was prepared by substituting tert-butyl 3-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 66B

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

[0243] The title compound was prepared by substituting Compound 66A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1F, with the exception that the product was purified on a silica gel column eluted with 4% methanol in dichloromethane.

Compound 66C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0244] A solution of Compound 66B in 50% trifluoroacetic acid and dichloromethane mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated and the residue was purified on a reverse phase HPLC using a gradient of 20-80% acetonitrile in water containing 10 mM ammonium acetate. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.61 (s, 1H), 8.52 (bs, 1H), 8.49 (d, 1H), 7.98 (d, 1H), 7.78 (d, 1H), 7.54 (d, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 7.34 (d, 2H), 7.04 (m, 3H), 6.65 (dd, 1H), 6.34 (s, 1H), 6.21 (d, 1H), 3.89 (d, 1H), 3.76 (d, 1H), 3.55-3.46 (m, 2H), 3.40-3.35 (m, 4H), 3.04 (m, 4H),2.91 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 67

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-

yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0245] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 15H and Compound 6A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.58 (s, 1H), 9.04 (s, 1H), 8.44 (d, 1H), 7.97 (d, 1H), 7.76 (dd, 1H), 7.49 (m, 4H), 7.38 (d, 2H), 7.14 (d, 2H), 6.64 (dd, 1H), 6.34 (d, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.03 (m, 6H), 2.85 (m, 5H), 2.29 (m, 4H), 2.18 (m, 6H), 1.20 (s, 6H).

Compound 68

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 68A

4-morpholinobut-2-yn-1-ol

[0246] To a solution of morpholine (4.36 g) in toluene (15 ml) was added 4-chlorobut-2-yn-1-ol (2.09 g) in toluene (5 ml). The solution was stirred at 85 °C for 3 hours. After cooling, the solid was filtered off. The filtrate was subjected to vacuum distillation to give the pure title compound.

Compound 68B

4-(4-morpholinobut-2-ynyloxy)-3-nitrobenzenesulfonamide

[0247] The title compound was prepared by substituting Compound 68A for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 68C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0248] The title compound was prepared by substituting Compound 68B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.08 (d, 1H), 8.03 (d, 1H), 7.47-7.53 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 5.15 (s, 2H), 3.52-3.55 (m, 4H), 3.09 (s, 4H), 2.84 (br s, 2H), 2.23-2.40 (m, 6H), 2.12-2.18 (m, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

Compound 69

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 69A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-((triisopropylsilyl)ethynyl)pyridine-3-sulfonamide

[0249] Compound 36B (0.176 g), bis(triphenylphosphine)palladium(II) chloride (0.176 g), copper(I) iodide (0.010 g), N,N-dimethylacetamide (2.5 ml) and triethylamine (0.105 ml) were combined, flushed with nitrogen and stirred for 2 minutes. (Triisopropylsilyl)acetylene (0.135 ml) was added and the reaction mixture was flushed with nitrogen again, heated at 60 °C overnight, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 10–30% ethyl acetate in hexanes as the eluent to give the product.

Compound 69B

5-ethynyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0250] Compound 69A (0.205 g) in tetrahydrofuran (3 ml) at ambient temperature was treated with tetrabutyl ammonium fluoride (1 M in tetrahydrofuran, 0.906 ml) and stirred at ambient temperature for 4 hours. Additional tetrabutyl ammonium fluoride (1 M in tetrahydrofuran, 1.8 ml) was added and the mixture was heated at 40 °C for 45 minutes. Solid tetrabutyl ammonium fluoride (0.253 g) was added and heating was continued for 30 minutes. The reaction mixture was concentrated and then chromatographed on silica gel using 0–2% methanol in dichloromethane as the eluent to give the product.

Compound 69C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0251] The title compound was prepared by substituting Compound 69B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.58 (d, 1H), 8.19 (d, 1H), 8.05 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.56 (s, 1H), 4.24 (d, 2H), 3.87 (dd, 2H), 3.38 (m, 3H), 3.07 (m, 4H), 2.86 (m, 2H), 2.29 (m, 5H), 2.04 (m, 3H), 1.64 (dd, 2H),

1.34 (m, 4H), 0.93 (s, 6H).

Compound 70

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 70A

4-amino-3-cyanobenzenesulfonamide

[0252] 3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) was dissolved in dioxane (4 ml). The solution was cooled to 0°C and 7 ml of an ammonia (7N in methanol) solution was added. After the addition was complete, the ice bath was removed and the reaction was stirred at room temperature for 24 hours. After concentration of the reaction mixture, the crude material was purified by flash chromatography eluting with a gradient of 30–100% ethyl acetate/hexanes.

Compound 70B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-cyanophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[0253] The title compound was prepared by substituting Compound 70A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G.

Compound 70C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-carbamoylphenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[0254] To a solution of Compound 70B (90 mg) in ethanol (2 ml) was added tetrahydrofuran (2 ml), hydrogen peroxide (30%, 1 ml) and 1M sodium hydroxide solution (0.48 ml), followed by an additional 2 ml of tetrahydrofuran. The reaction was heated to 45°C for 30 minutes, cooled, and then quenched with 5% HCl solution and extracted twice with dichloromethane. The extracts were combined and concentrated to obtain the product.

Compound 70D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0255] Compound 70C (80 mg) was combined with trimethyl orthoformate (2.3 ml) and trifluoroacetic acid (0.03 ml) and the resulting solution was stirred at room temperature for 4

hours. The mixture was purified by flash chromatography, eluting with a gradient of 3-10% methanol/dichloromethane. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 12.61 (s, 1H), 11.71 (s, 1H), 8.65 (d, 1H), 8.24 (s, 1H), 8.17 (dd, 1H), 8.04 (m, 1H), 7.73 (d, 1H), 7.57 (d, 1H), 7.51 (m, 2H), 7.39 (d, 2H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.40 (m, 1H), 6.24 (br s, 1H), 3.61 (m, 6H), 3.03 (m, 2H), 2.75 (m, 2H), 2.17 (m, 2H), 2.01 (m, 2H), 1.44 (m, 2H), 0.94 (s, 6H).

Compound 71

trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 71A

8-chlorospiro[4.5]dec-7-ene-7-carbaldehyde

[0256] To a solution of N,N-dimethylformamide (2.81 ml) in dichloromethane (40 ml) was added dropwise $POCl_3$ (2.78 ml) at 0°C. The reaction mixture was warmed up to room temperature and spiro[4.5]decan-8-one (3.95 g) in dichloromethane (5 ml) was added dropwise. The mixture was stirred overnight. The reaction was quenched with cold aqueous sodium acetate and the resulting mixture was extracted with ether and the organic layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

Compound 71B

8-(4-chlorophenyl)spiro[4.5]dec-7-ene-7-carbaldehyde

[0257] To a suspension of Compound 71A (3 g) in water (50 ml) was added 4-chlorophenylboronic acid (2.83 g), tetrabutylammonium (4.87 g), potassium carbonate (6.26 g) and palladium(II) acetate (0.169 g). The reaction mixture was stirred at 45°C for 5 hours and extracted with dichloromethane. The organic layer was concentrated and the residue was loaded onto a silica gel column, and eluted with 5-20% ethyl acetate in hexane to give the title compound.

Compound 71C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoate

[0258] To a solution of Compound 71B (274 mg) in dichloroethane (3.5 ml) was added Compound 15F (387 mg) and sodium triacetoxyborohydride (317 mg). The reaction mixture was stirred overnight. Sodium cyanoborohydride (37.6 mg) was added and the resulting

mixture stirred overnight. The reaction was quenched with water and diluted with dichloromethane. The mixture was washed with water extensively and the organic layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

Compound 71D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoic acid

[0259] The title compound was prepared as described in the procedure for Compound 3J using Compound 71C in place of Compound 3I.

Compound 71E

trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0260] The title compound was prepared as described in the procedure for Compound 11D using Compound 71D and Compound 9C in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 8.51 (s, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.76 (d, 1H), 7.44 - 7.53 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.20 (d, 1H), 3.50 - 3.70 (m, 5H), 3.04 (s, 4H), 2.55 - 2.76 (m, 5H), 2.34 - 2.39 (m, 1H), 2.20 (d, 6H), 2.03 (s, 4H), 1.91 (s, 2H), 1.61 (q, 4H), 1.51 (t, 2H), 1.36 - 1.46 (m, 8H).

Compound 72

cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0261] The title compound was prepared as described in the procedure for Compound 11D using Compound 15H and 29A in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.45 (s, 1H), 8.59 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.54 (d, 1H), 7.47 - 7.52 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 7.08 (d, 1H), 6.68 (dd, 1H), 6.35 - 6.42 (m, 1H), 6.19 (d, 1H), 4.11 (s, 2H), 3.37 (s, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.07 (s, 4H), 2.83 (s, 2H), 2.17 (d, 6H), 1.81 (dd, 2H), 1.64 - 1.73 (m, 1H), 1.48 (dd, 2H), 1.23 - 1.41 (m, 4H), 1.18 (s, 6H).

Compound 73

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0262] The title compound was prepared as described in the procedure for Compound 11D using Compound 71D and Compound 37D in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.37 (s, 1H), 7.98 - 8.11 (m, 2H), 4.38 (d, 2H), 3.74 - 3.82 (m, 2H), 3.54 - 3.64 (m, 2H), 3.44 (s, 1H), 3.08 (s, 3H), 2.58 - 2.89 (m, 2H), 2.13 - 2.35 (m, 4H), 2.04 (s, 2H), 1.78 - 1.93 (m, 4H), 1.57 - 1.65 (m, 4H), 1.52 (t, 2H), 1.36 - 1.47 (m, 4H).

Compound 74

trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0263] The title compound was prepared as described in the procedure for Compound 11D using Compound 71D and Compound 34B in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.58 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47 - 7.55 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.25 (t, 2H), 3.22 (s, 3H), 3.06 (s, 5H), 2.71 (s, 2H), 2.21 (s, 6H), 1.94 - 2.06 (m, 4H), 1.79 (d, 2H), 1.57 - 1.65 (m, 5H), 1.51 (t, 2H), 1.39 (t, 4H), 0.95 - 1.11 (m, 4H).

Compound 75

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 75A

methyl 5,5-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0264] The title compound was prepared by substituting 4,4-dimethyl-2-methoxycarbonylcyclohexanone for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in the procedure for Compound 3A.

Compound 75B

methyl 2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarboxylate

[0265] The title compound was prepared by substituting Compound 75A for Compound 3A in the procedure for Compound 3B.

Compound 75C

(2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methanol

[0266] The title compound was prepared by substituting Compound 75B for Compound 3B in the procedure for Compound 3C.

Compound 75D

2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarbaldehyde

[0267] To a solution of Compound 75C (2.8 g) in dichloromethane (50 ml) was added Dess-Martin Periodinane (5.68 g). The reaction mixture was stirred at room temperature for 3 hours and diluted with ether and washed with 5% NaOH and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography using 20% ethyl acetate in hexanes to provide the title compound.

Compound 75E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0268] The title compound was prepared by replacing 4'-chlorobiphenyl-2-carboxaldehyde with Compound 75D and tert-butyl piperazine-1-carboxylate with Compound 15F in the procedure for Compound 1A.

Compound 75F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0269] The title compound was prepared as described in the procedure for Compound 15H by replacing Compound 15G with Compound 75E.

Compound 75G

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0270] The title compound was prepared as described in the procedure for Compound

11D using Compound 75F and Compound 1F in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47 - 7.55 (m, 3H), 7.31 - 7.36 (m, 2H), 7.05 - 7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.18 (d, 1H), 3.85 (dd, 2H), 3.22 - 3.31 (m, 4H), 3.07 (s, 4H), 2.67 - 2.78 (m, 2H), 2.19 (s, 6H), 1.82 - 1.98 (m, 3H), 1.56 - 1.66 (m, 2H), 1.39 (t, 2H), 1.17 - 1.33 (m, 3H), 0.93 (s, 6H).

Compound 76

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0271] The title compound was prepared as described in the procedure for Compound 11D using Compound 75F and Compound 36C in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.62 (s, 1H), 8.73 (s, 1H), 8.52 (s, 1H), 7.98 (d, 1H), 7.56 (d, 1H), 7.45 - 7.51 (m, 1H), 7.43 (s, 1H), 7.37 (d, 2H), 7.10 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.25 (s, 1H), 4.29 (d, 2H), 3.88 (dd, 2H), 3.12 (d, 4H), 2.21 (s, 2H), 2.00 - 2.11 (m, 1H), 1.95 (s, 2H), 1.64 (dd, 2H), 1.27 - 1.46 (m, 4H), 0.95 (s, 6 H)

Compound 77

tert-butyl 3-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxy]methyl}morpholine-4-carboxylate

Compound 77A

tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

[0272] The title compound was prepared as described in the procedure for Compound 12A by replacing (1,4-dioxan-2-yl)methanol with tert-butyl 3-(hydroxymethyl)morpholine-4-carboxylate.

Compound 77B

tert-butyl 3-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxy]methyl}morpholine-4-carboxylate

[0273] The title compound was prepared as described in the procedure for Compound

11D using Compound 77A in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.01 - 8.11 (m, 2H), 7.47 - 7.61 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.20 (s, 1H), 4.41 - 4.52 (m, 2H), 4.15 - 4.28 (m, 1H), 3.59 - 3.95 (m, 3H), 3.51 (d, 1H), 3.34 - 3.43 (m, 1H), 3.10 (s, 5H), 2.84 (s, 2H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.20 - 1.45 (m, 12H), 0.92 (s, 6H).

Compound 78

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(morpholin-3-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0274] Compound 77B (100 mg) in dichloromethane (10 ml) at 0°C was treated with trifluoroacetic acid (5 ml) for 20 minutes. The reaction mixture was concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (10 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.56 (s, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.90 (dd, 1H), 7.57 (d, 1H), 7.42 - 7.46 (m, 1H), 7.31 - 7.37 (m, 3H), 7.25 (d, 1H), 7.01 - 7.09 (m, 2H), 6.64 (dd, 1H), 6.29 - 6.37 (m, 1H), 6.24 (d, 1H), 4.17 - 4.31 (m, 2H), 3.90 - 4.05 (m, 1H), 3.77 - 3.85 (m, 1H), 3.45 - 3.59 (m, 4H), 2.94 - 3.13 (m, 6H), 2.76 (s, 2H), 2.18 (d, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 79

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0275] The title compound was prepared as described in the procedure for Compound 11D using Compound 71D and Compound 1F in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.77 - 7.84 (m, 1H), 7.45 - 7.56 (m, 3H), 7.34 (d, 2H), 7.04 - 7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.85 (dd, 2H), 3.22 - 3.31 (m, 4H), 3.07 (s, 4H), 2.71 (s, 2H), 2.21 (s, 6H), 2.03 (s, 2H), 1.81 - 1.94 (m, 1H), 1.56 - 1.68 (m, 6H), 1.51 (t, 2H), 1.34 - 1.45 (m, 4H), 1.20 - 1.33 (m, 2H).

Compound 80

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0276] The title compound was prepared by substituting 1-(methylsulfonyl)piperidin-4-amine for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.67 (br s, 1H), 8.57 (d, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 3.80 (m, 1H), 3.57 (m, 2H), 3.08 (br s, 4H), 2.95 (td, 2H), 2.92 (s, 3H), 2.85-2.72 (m, 2H), 2.30-2.10 (m, 6H), 2.07-1.93 (m, 4H), 1.70 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 81

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 81A

1,1-dioxotetrahydro-2H-thiopyran-4-amine

[0277] N-Benzyl-1,1-dioxotetrahydro-2H-thiopyran-4-amine (2.00 g) was added to ethanol (40 ml) in a pressure bottle. Palladium hydroxide on carbon (0.587 g,) was added and the solution was stirred under 30 psi of hydrogen at room temperature for 2 hours. The mixture was filtered though a nylon membrane and the solvent was removed under vacuum.

Compound 81B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0278] The title compound was prepared by substituting Compound 81A for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.65 (br s, 1H), 8.55 (d, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.86 (dd, 1H), 7.52-7.47 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.21 (d, 1H), 4.05 (m, 1H), 3.22-3.00 (m, 8H), 2.79 (br s, 2H), 2.31-2.11 (m, 10H), 1.96 (br s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 82

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0279] The title compound was prepared by substituting Compound 3J for Compound 1E and 4-chloro-3-nitrobenzenesulfonamide for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.60 (br s, 1H), 8.38 (br s, 1H), 7.96 (d, 1H), 7.91 (d, 1H), 7.68 (d, 1H), 7.58 (d, 1H), 7.46 (t, 1H), 7.39-7.35 (m, 3H), 7.07 (d, 2H), 6.67 (dd, 1H), 6.34 (m, 1H), 6.28 (d, 1H), 3.31 (br s, 2H), 3.17 (br s, 8H), 2.18 (m, 2H), 1.98 (br s, 2H), 1.42 (t, 2H), 0.94 (s, 6H).

Compound 83

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 83A

3-Nitro-4-[1-(2,2,2-trifluoro-ethyl)-piperidin-4-ylamino]-benzenesulfonamide

[0280] The title compound was prepared by substituting 1-(2,2,2-trifluoroethyl)piperidin-4-amine hydrochloride for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 6A.

Compound 83B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0281] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 82A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.66 (br s, 1H), 8.56 (d, 1H), 8.24 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.52 (dd, 2H), 7.48 (d, 1H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.68 (m, 1H), 3.22 (q, 2H), 3.07 (br s, 4H), 2.90 (m, 2H), 2.75 (br s, 2H), 2.29-2.12 (m, 8H), 1.97-1.86 (m, 4H), 1.63 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 84

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]pyridin-3-yl}sulfonyl)-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 84A

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ol

[0282] Piperidin-4-ol (7.8 g) and dihydro-2H-pyran-4(3H)-one (5.0 g) were dissolved in titanium(IV) isopropoxide (30 ml) and the reaction was stirred at room temperature overnight. Methanol (40 ml) was added and the reaction was cooled to 0°C. Then $NaBH_4$ (3.8 g) was added in portions over one hour. After 2 hours 1N aqueous NaOH was added, followed by ethyl acetate addition. After filtration though celite the layers were separated, the aqueous layer extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4. The crude was purified by column chromatography using dichloromethane having 5-10% 7N NH_3 in methanol.

Compound 84B

5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

[0283] The title compound was prepared by substituting Compound 84A for (tetrahydro-2H-pyran-4-yl)methanol and Compound 36A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 84C

5-cyano-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

[0284] The title compound was prepared by substituting Compound 84B for Compound 36B in the procedure for Compound 36C.

Compound 84D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0285] The title compound was prepared by substituting Compound 84C for Compound 11B in the procedure for Compound 11D. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.50 (s, 1H), 8.60 (d, 1H), 8.37 (d, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.42 (dd, 1H), 7.35 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.28 (m, 1H), 6.24 (d, 1H), 5.30 (br s, 1H), 4.50 (d, 2H), 3.95 (dd, 2H), 3.30 (m, 5H), 3.02 (br s, 4H), 2.95 (br s, 2H), 2.24 (br s, 4H), 2.17 (br m, 4H), 1.96 (s, 2H), 1.90 (br m, 4H), 1.60 (br m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 85

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 85A

5-isopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0286] Compound 36B (0.176 g), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g), and palladium(II) acetate (0.011 g) were combined in a 10 ml oven-dried flask. Tetrahydrofuran (1 ml) was added and the mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2-Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 ml) was added and stirring was continued under nitrogen overnight. Additional 2-2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g) and palladium(II) acetate (0.011 g) were added. The mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2- Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 ml) was added and stirring was continued under nitrogen for 2.5 days. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel with 0 to 3% methanol in CH_2Cl_2 as the eluent. The obtained material was chromatographed on silica gel a second time with 10–40% ethyl acetate in CH_2Cl_2 as the eluent, triturated with diethyl ether and dried under vacuum at 45°C to give the product.

Compound 85B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0287] The title compound was prepared by substituting Compound 85A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.70 (s, 1H), 8.49 (m, 1H), 8.04 (d, 1H), 7.90 (m, 1H), 7.57 (m, 1H), 7.52 (t, 1H), 7.48 (dd, 1H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (s, 1H), 4.19 (m, 2H), 3.88 (m, 2H), 3.30 (m, 2H), 3.05 (m, 5H), 2.77 (s, 2H), 2.21 (s, 4H), 2.14 (s, 2H), 2.03 (m, 1H), 1.95 (s, 2H), 1.64 (m, 2H), 1.34 (m, 4H), 1.12 (d, 6H), 0.92 (s, 6H).

Compound 86

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 86A

3-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0288] The title compound was prepared by substituting 3,4-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 86B

3-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0289] The title compound was prepared by substituting Compound 86A for Compound 52B in the procedure for Compound 52C.

Compound 86C

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0290] The title compound was prepared by substituting Compound 86B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.72 (s, 1H), 11.20 (s, 1H), 8.08 (d, 1H), 7.61 (m, 2H), 7.50 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 6.09 (m, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.76 (s, 2H), 2.18 (m, 6H), 1.95 (s, 2H), 1.72 (m, 1H), 1.53 (d, 2H), 1.38 (t, 2H), 1.16 (m, 2H), 0.92 (s, 6H).

Compound 87

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl) benzamide

Compound 87A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

[0291] The title compound was prepared by substituting 5-hydroxyindole for Compound 3G in the procedure for Compound 3H.

Compound 87B

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0292] The title compound was prepared by substituting Compound 87A for Compound 3H in the procedure for Compound 3I.

Compound 87C

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0293] The title compound was prepared by substituting Compound 87B for Compound 3I in the procedure for Compound 3J.

Compound 87D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)[redacted]]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0294] The title compound was prepared by substituting Compound 87C for Compound 1E in the procedure for Compound 1G, except here the crude was purified by preparative HPLC using a 250 × 50 mm C18 column and eluting with 20–100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.40 (br s, 1H), 11.17 (s, 1H), 9.50 (v br s, 1H), 8.61 (t, 1H), 8.57 (d, 1H), 7.77 (dd, 1H), 7.70 (br s, 1H), 7.50 (m, 5H), 7.36 (m, 5H), 7.10 (s, 1H), 7.08 (d, 1H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.30 (br s, 1H), 3.84 (dd, 2H), 3.70 (br s, 1H), 3.30 (m, 6H), 3.20, 2.95, 2.80 (all br s, total 6H), 1.86 (m, 1H), 1.60 (m, 2H), 1.25 (m, 2H).

Compound 88

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0295] The title compound was prepared by substituting Compound 87C for Compound 1E and Compound 2A for Compound 1F in the procedure for Compound 1G, except here the crude was purified by preparative HPLC using a 250 × 50 mm C18 column and eluting with 20–100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.40 (br s, 1H), 11.19 (s, 1H), 9.60 (v br s, 1H), 8.69 (t, 1H), 8.60 (d, 1H), 7.83 (dd, 1H), 7.65 (br s, 1H), 7.50 (m, 5H),

7.38 (m, 5H), 7.12 (m, 2H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.38 (br s, 1H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.40 (m, 4H), 3.30-2.80 (envelope, 10H), 3.20 (m, 4H), 1.96 (m, 2H).

Compound 89

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

[0296] This Compound was prepared by substituting Compound 87C for Compound 1E and Compound 3M for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 1H), 8.56 (d, 1H), 8.20 (d, 1H), 7.84 (dd, 1H), 7.52 (d, 1H), 7.39 – 7.31 (m, 4H), 7.12 (d, 2H), 7.04 (d, 2H), 6.84 (dd, 1H), 6.65 (dd, 1H), 6.38 (t, 1H), 6.14 (d, 1H), 3.94 (m, 2H), 3.84 (m, 1H), 3.02 (m, 8H), 2.79 (m, 3H), 2.72 (s, 2H), 2.20-2.02 (m, 8H), 1.85 (m, 6H), 1.60 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 90

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0297] The title compound was prepared by substituting Compound 87C for Compound 1E and Compound 4A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.08 (s, 1H), 8.51 (d, 1H), 8.13 (d, 1H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.37 – 7.31 (m, 4H), 7.06 - 7.00 (m, 4H), 6.79 (dd, 1H), 6.59 (dd, 1H), 6.35 (t, 1H), 6.14 (d, 1H), 3.73 (m, 1H), 3.05 - 2.95 (m, 6H), 2.71 (s, 2H), 2.60 (m, 2H), 2.48 (s, 3H), 2.16 (m, 6H), 2.01 (m, 2H), 1.95 (s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 91

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0298] The title compound was prepared by substituting Compound 6A for Compound 11B and Compound 87C for Compound 3J in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 9.18 (s, 1H), 8.53 (d, 1H), 7.84 (dd, 1H), 7.56 (d, 1H), 7.51 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.12 (d, 1H), 7.03 (d, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.38 (m, 1H), 6.13 (d, 1H), 3.00 (m, 4H), 2.90 (m, 4H), 2.71 (s, 2H), 2.33 (s, 3H), 2.15 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

Compound 92

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

[0299] The title compound was prepared as described in the procedure for Compound 11D using Compound 87C and Compound 12A in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20 - 4.28 (m, 2H), 3.85 - 3.91 (m, 1H), 3.82 (dd, 1H), 3.74 - 3.78 (m, 1H), 3.59 - 3.69 (m, 2H), 3.40 - 3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 93

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

[0300] The title compound was prepared by substituting Compound 87C for Compound 3J and Compound 16A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.18 (d, 1H), 7.92 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.26 (m, 1H), 7.17 (d, 1H), 7.04 (m, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.03 (s, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 94

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

[0301] The title compound was prepared by substituting Compound 87C for Compound 3J and Compound 17A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.20 (s, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.53 (d, 1H), 7.40 (m, 4H), 7.33 (t, 1H), 7.17 (d, 1H), 7.07 (m, 3H), 6.86 (dd, 1H), 6.70 (dd, 1H), 6.41 (s, 1H), 6.21 (d, 1H), 3.84 (dd, 2H), 3.59 (m, 2H), 3.25 (m, 6H), 3.00 (m, 2H), 2.74 (s, 2H), 2.54 (m, 2H), 2.18 (s, 2H), 2.01 (s, 2H), 1.83 (m, 1H), 1.54 (m, 2H), 1.45 (t, 2H), 1.23 (m, 2H), 0.94 (s, 6H).

Compound 95

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 95A

1-(1,3-difluoropropan-2-yl)piperidin-4-amine

[0302] Tert-butyl piperidin-4-ylcarbamate (0.212 g), 1,3-difluoropropan-2-one (0.149 g) and sodium triacetoxyborohydride (0.337 g) were stirred together in dichloroethane at room temperature. After stirring overnight the reaction was quenched with water (10 ml) and extracted into dichloromethane (2 × 20 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was treated with hydrogen chloride (4.0M in dioxane, 1.323 ml) for 1 hour to give the title compound as the HCl salt after concentration.

Compound 95B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0303] Compound 95A (0.057 g) and Compound 53A (0.162 g) were suspended in dioxane (3 ml) and heated to 105°C overnight. The reaction was concentrated, loaded onto silica gel (GraceResolv 12 g) and eluted with a gradient of 0.5% to 4% methanol/dichloromethane. The product containing fractions were concentrated and loaded onto C18 (SF25-75g analogix column) and eluted using a gradient of 30% to 60% acetonitrile/water. The product was partitioned between dichloromethane (20 ml) and saturated aqueous $NaHCO_3$ solution (20 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.88 (d, 2H), 8.45 (d, 1H), 8.20 (s, 1H), 8.18 - 8.09 (m, 1H), 7.95 (d, 1H), 7.68 (d, 1H), 7.44 (s, 1H), 7.23 - 7.19 (m, 1H), 6.91 (d, 3H), 6.53 (d, 2H), 5.98 (d, 1H), 4.64 (dd, 4H), 3.68 - 3.50 (m, 1H), 3.01 (d, 6H), 2.72 (d, 4H), 2.19 (s, 11H), 1.69 (s, 2H), 1.41 (s, 2H), 0.94 (s, 6H).

Compound 96

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 96A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0304] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide and Compound 37C for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 96B

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0305] The title compound was prepared by substituting Compound 96A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.03 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.22 (s, 1H), 4.50 (d, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.12 (v br s, 4H), 2.93 (v br s, 2H), 2.38 (v br s, 4H), 2.17 (br m, 2H), 1.96 (s, 2H), 1.86 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

Compound 97

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 97A

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate

[0306] The title compound was prepared by substituting tert-butyl 4-aminopiperidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 97B

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide

[0307] Tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate was dissolved in dichloromethane (3 ml) and treated with 1N HCl in ether (4 ml). The reaction was stirred overnight then concentrated to give the title compound.

Compound 97C

4-(1-(2,2-difluoroethyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

[0308] 3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide hydrochloride (0.100g), 1,1-difluoro-2-iodoethane (0.063 ml) and diisopropylamine (0.156 ml) were stirred together in N,N-dimethylformamide (3 ml) and heated to 85°C. The reaction was diluted with dichloromethane (50 ml) and washed with water (50 ml), brine (50 ml), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolve 12g) and eluted using a gradient of 0.5% methanol/dichloromethane to 3% methanol/dichloromethane over 30 minutes to give the title compound.

Compound 97D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0309] The title compound was prepared by substituting Compound 97B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 11.54 - 11.27 (m, 1H), 8.55 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.81 (d, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.13 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.38 (dd, 1H), 6.15 (dt, 2H), 3.64 (s, 1H), 3.07 (s, 4H), 2.79 (ddd, 6H), 2.41 (t, 2H), 2.17 (d, 6H), 1.92 (d, 4H), 1.61 (d, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

Compound 98

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0310] The title compound was prepared as described in the procedure for Compound 53B by replacing 1-acetylpiperidin-4-amine with 4-amino-1-cyclopropylpiperidine. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.54 (d, 1H), 8.22 (d, 1H), 8.02 (d, 1H), 7.80 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.11 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.69 (m, 1H), 3.06 (m, 4H), 2.92 (m, 2H), 2.74 (s, 2H), 2.23 (m, 7H), 1.93 (m, 5H), 1.77 (m, 1H), 1.55 (m, 3H), 1.38 (t, 2H), 0.92 (s, 6H), 0.43 (m, 4H).

Compound 99

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-

{[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0311] The title compound was prepared as described in the procedure for Compound 53B by replacing 1-acetylpiperidin-4-amine with 1-(4-morpholino)cyclohexanemethylamine. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.70 (s, 1H), 9.06 (s, 1H), 8.59 (d, 1H), 8.06 (d, 1H), 7.83 (dd, 1H), 7.57 (d, 1H), 7.50 (m, 2H), 7.34 (m, 3H), 7.19 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (d, 1H), 3.56 (m, 6H), 3.44 (m, 2H), 3.07 (m, 5H), 2.57 (m, 5H), 2.24 (m, 6H), 1.95 (s, 3H), 1.45 (m, 6H), 1.23 (m, 3H), 0.92 (s, 6H).

Compound 100

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 100A

trans-tert-butyl-4-(dicyclopropylamino)cyclohexylcarbamate

[0312] A suspension of trans-tert-butyl-4-aminocyclohexylcarbamate (1 g), molecular sieves 3A (1 g), acetic acid (2.67 ml), (1-ethoxycyclopropoxy)trimethysilane (3.74 ml) and sodium cyanoborohydride (0.880 g) in dry methanol (10 ml) was heated at reflux for 3 hours. The insolubles were filtered off, the resulting solution was basified with aqueous NaOH (6 M) to pH 14, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (silica gel 80 g, 30 - 100% acetone/hexanes) to provide the title compound.

Compound 100B

(trans)-N^1,N^1-dicyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

[0313] The title compound was prepared by substituting Compound 100A for Compound 39A in the procedure for Compound 39B.

Compound 100C

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0314] A suspension of Compound 53A (0.14 g), Compound 100B (0.112 g) and N,N-diisopropylethylamine (0.310 ml) in dioxane (10 ml) was stirred for 3 days at 100°C. The

product was concentrated and purified by RP HPLC(C8, 30% - 100% CH_3CN/water/0.1% trifluoroacetic acid). ^1H NMR (500 MHz, pyridine-d_5) δ 13.07 (s, 1H), 9.28 (d, 1H), 8.41 - 8.45 (m, 2H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 - 6.51 (m, 1H), 3.43 (ddd, 1H), 3.03 - 3.09 (m, 4H), 2.72 - 2.79 (m, 3H), 2.22 - 2.28 (m, 2H), 2.11 - 2.16 (m, 4H), 2.10 (s, 2H), 2.00 - 2.05 (m, 2H), 1.97 (s, 2H), 1.89 (s, 1H), 1.86 (s, 3H), 1.62 - 1.71 (m, 2H), 1.39 (t, 2H), 1.19 - 1.29 (m, 2H), 0.93 (s, 6H), 0.48 (d, 8H).

Compound 101

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 101A

ethyl 2-hydroxy-6,6-dimethylcyclohex-1-enecarboxylate

[0315] Into a 500 ml flame dried round-bottomed flask was added copper(I) iodide (18 g) in ether (200 ml) to give a suspension. After cooling to –5°C, methyllithium (120 ml, 1.6M in ether) was added dropwise. After stirring at –5°C for 1 hour, 3-methylcyclohex-2-enone (5.15 ml) in 15 ml ether was added dropwise, and the mixture was stirred at –5°C for 1 hour. After cooling to –78°C, hexamethylphosphoramide (60 ml) was added dropwise. Ethyl carbonocyanidate (23.74 ml) was added. After stirring at –78°C for 20 minutes, the mixture was warmed up to room temperature, and stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3 × 20 ml). The combined organic layers were washed with saturated aqueous NH_4Cl (3 × 20 ml), dried over Na_2SO_4, filtered, and dried under vacuum. The crude product was added to a silica gel column and purified by eluting with 0–10% ethyl acetate in hexane.

Compound 101B

ethyl 6,6-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0316] Into a 500 ml round-bottomed flask was added hexane-washed sodium hydride (0.5 g) in dichloromethane (100 ml) to give a suspension. After cooling to –5°C, Compound 101A (2.0 g) was added. After stirring at –5°C for 30 minutes, the mixture was cooled to –78°C. Trifluoromethanesulfonic anhydride (2.2 ml) was added. The mixture was warmed to room temperature and stirred overnight. Water was added slowly to the mixture, the aqueous

layer was then extracted by dichloromethane (2 × 20 ml). The combined organic layers were washed with saturated NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated.

Compound 101C

ethyl 2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enecarboxylate

[0317] Into a 25 ml microwave tube was added Compound 101B (2.9 g), 4-chlorophenylboronic acid (2.2 g), and tetrakis(triphenylphosphine)palladium (0.05 g) in 1,2-dimethoxyethane/methanol(2:1, 10 ml) to give a solution. Cesium fluoride (4 g) was then added. The reaction mixture was stirred at 150°C under (100W) in a Biotage Initiator microwave reactor for 30 minutes. After removing the solvents, water was added, and the mixture was extracted with ethyl acetate (2 ×). The combined organic layers were dried by $MgSO_4$. After filtering, the crude product was purified by reverse phase chromatography eluting with 50–100% acetonitrile/water with 0.1% trifluoroacetic acid.

Compound 101D

(2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methanol

[0318] In a 100 ml round-bottomed flask was placed lithium aluminum hydride (1 g) in ether (20 ml) to give a suspension. Compound 101C (1 g) dissolved in ether (5 ml) was added slowly by syringe. The mixture was stirred at room temperature overnight. After cooling to 0°C, the reaction was quenched by water. Ether (2 × 10 ml) was used to extract the product. The crude product was purified by flash chromatography on silica by eluting with 0-15% ethyl acetate in hexane.

Compound 101E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0319] To a 0°C solution of Compound 101D (0.43 g) in dichloromethane (5 ml) was added triethylamine (1 ml). Methanesulfonyl chloride (0.134 ml) was then added slowly. After 5 minutes, Compound 15F (0.61 g) was added. The mixture was stirred at room temperature overnight. The crude product was purified by flash chromatography on silica with 0 to 25% ethyl acetate in hexanes to provide the title compound.

Compound 101F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0320] In a 5 ml microwave tube was added lithium hydroxide hydrate (15 mg) and Compound 101E (45 mg) in dioxane/water(2:1) (2 ml) to give a suspension. The mixture was heated to 130°C in a Biotage Initiator microwave reactor for 20 minutes. After cooling and neutralization by HCl, the crude product was added to a Prep HPLC column and was eluted with 20-80% acetonitrile/water with 0.1% trifluoroacetic acid.

Compound 101G

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0321] The title compound was prepared by substituting Compound 101F for Compound 3J and Compound 1F for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 11.47 (s, 1H), 8.58 (m, 2H), 8.03 (m, 1H), 7.79 (m, 1H), 7.51 (m, 3H), 7.31 (d, 2H), 7.10 (m, 1H), 7.02 (d, 2H), 6.65 (m, 1H), 6.39 (m, 1H), 6.15 (m, 1H), 3.85 (m, 2H), 3.27 (m, 4H), 2.97 (m, 4H), 2.76 (s, 2H), 2.14 (m, 6H), 1.70 (m, 2H), 1.61 (m, 2H), 1.44 (m, 2H), 1.26 (m, 3H), 1.16 (m, 6H)

Compound 102

N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 102A

(4-ethylmorpholin-3-yl)methanol

[0322] Morpholin-3-ylmethanol (500 mg) and iodoethane (666 mg) in N,N-dimethylformamide was treated with K_2CO_3 (1.1 g) overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

Compound 102B

5-bromo-6-((4-ethylmorpholin-3-yl)methoxy)pyridine-3-sulfonamide

[0323] The title compound was prepared as described in the procedure for Compound 12A by replacing 4-fluoro-3-nitrobenzenesulfonamide and (1,4-dioxan-2-yl)methanol with 5-bromo-6-fluoropyridine-3-sulfonamide and Compound 102A, respectively.

Compound 102C

N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0324] The title compound was prepared as described in the procedure for Compound 11D using Compound 102B in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.62 (s, 1H), 8.51 (s, 1H), 8.30 (s, 1H), 8.00 (d, 1H), 7.55 (d, 1H), 7.45 - 7.50 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.37 (s, 1H), 6.21 (d, 1H), 4.58 (dd, 1H), 4.39 - 4.50 (m, 1H), 3.78 - 3.90 (m, 1H), 3.67 - 3.77 (m, 1H), 3.50 - 3.65 (m, 2H), 3.08 (s, 4H), 2.59 - 3.00 (m, 4H), 2.20 - 2.39 (m, 2H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.99 - 1.11 (m, 3H), 0.93 (s, 6H)

Compound 103

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 103A

4-((4-ethylmorpholin-3-yl)methoxy)-3-nitrobenzenesulfonamide

[0325] The title compound was prepared as described in the procedure for Compound 12A by replacing (1,4-dioxan-2-yl)methanol with Compound 102A.

Compound 103B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0326] The title compound was prepared as described in the procedure for Compound 11D using Compound 103A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.33 (s, 1H), 7.99 - 8.06 (m, 2H), 7.47 - 7.57 (m, 3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.42 (dd, 1H), 4.23 (dd, 1H), 3.81 (d, 1H), 3.69 (d, 1H), 3.49 - 3.63 (m, 2H), 3.08 (s, 4H), 2.92 (s, 1H), 2.81 (s, 4H), 2.54 (s, 1H), 2.25 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 1.00 (t, 3H), 0.92 (s, 6H)

Compound 104

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0327] Compound 78 (20 mg) and dihydro-2H-pyran-4(3H)-one (10 mg) in dichloroethane (2 ml) was treated with $NaCNBH_3$ (9.74 mg) overnight. Additional dihydro-2H-pyran-4(3H)-one (20 mg) and titanium (IV) isoproxide (0.05 ml) were added. The resulting mixture was stirred at room temperature overnight and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the title compound. ^1H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.35 (s, 1H), 8.04 (s, 2H), 7.44 - 7.58 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 4.44 (s, 1H), 4.28 (s, 1H), 3.85 (d, 2H), 3.71 (d, 1H), 3.61 (s, 3H), 3.20 - 3.29 (m, 2H), 3.08 (s, 5H), 2.54 - 2.96 (m, 5H), 2.06 - 2.42 (m, 5H), 1.96 (s, 2H), 1.77 (d, 1H), 1.53 - 1.66 (m, 1H), 1.29 - 1.51 (m, 4H), 0.92 (s, 6H).

Compound 105

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 105A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-3-ylcarbamate

[0328] The title compound was prepared by substituting (S)-tert-butyl piperidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 105B

(S)-1-(tetrahydro-2H-pyran-4-yl)piperidin-3-amine

[0329] The title compound was prepared by substituting Compound 105A for Compound 1A in the procedure for Compound 1B.

Compound 105C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0330] The title compound was prepared by substituting Compound 105B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.68 (br s, 1H), 8.54 (br s, 1H), 8.02 (d, 1H), 7.77 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.98 (m, 2H), 3.90 (m, 2H), 3.52 (m, 2H), 3.09 (s, 2H), 3.05 (m, 4H), 2.77 (m, 2H), 2.60 (m, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.65 (m, 5H), 1.50 (m, 3H), 1.38 (m, 2H), 0.94 (s, 6H).

Compound 106

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 106 A

5-bromo-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

[0331] The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanamine for Compound 3L in the procedure for Compound 61A.

Compound 106B

5-cyano-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

[0332] The title compound was prepared by substituting Compound 106A for Compound 36B in the procedure for Compound 36C.

Compound 106C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0333] The title compound was prepared by substituting Compound 106B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.62 (s, 1H), 8.55 (s, 1H), 8.14 (s, 1H), 8.01 (d, 1H), 7.87 (s, 1H), 7.56 (d, 1H), 7.48 (d, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (m, 1H), 6.37 (s, 1H), 6.19 (d, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.04 (s, 4H), 2.74 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.87 (m, 1H), 1.53 (m, 2H), 1.37 (t, 2H),

1.18 (m, 2H), 0.91 (s, 6H).

Compound 107

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 107A

3-nitro-4-(4-aminothiomorpholine-1,1-dioxide)benzenesulfonamide

[0334] The title compound was prepared by substituting 4-aminothiomorpholine-1,1-dioxide for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 107B

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0335] The title compound was prepared by substituting Compound 107A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 9.58 (s, 1H), 8.50 (s, 1H), 8.02 (d, 1H), 7.78 (m, 2H), 7.50 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.38 (s, 1H), 6.19 (d, 1H), 3.48 (m, 4H), 3.23 (m, 4H), 3.05 (s, 4H), 2.73 (d, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 108

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 108A

4-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

[0336] The title compound was prepared by substituting 4-(aminomethyl)tetrahydro-2H-pyran-4-amine for (tetrahydro-2H-pyran-4-yl)methanamine in the procedure for Compound 1F.

Compound 108B

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0337] The title compound was prepared by substituting Compound 108A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.55 (s, 1H), 8.45 (s, 2H), 7.95 (d, 1H), 7.75-7.77 (m, 1H), 7.57 (d, 2H), 7.44 (s, 1H), 7.34 (d, 2H), 7.09 (d, J = 8.85 Hz, 1H), 7.05 (d, 2H), 6.69 (dd, 1H), 6.33 (d, 1H), 6.22 (d, 1H), 3.59-3.71 (m, 6H), 3.01 (s, 4H), 2.73 (s, 2H), 2.15-2.19 (m, 6H), 1.95 (s, 2H), 1.71-1.74 (m, 2H), 1.59-1.61 (m, 1H), 1.38 (t, 2H), 0.93 (s, 6H).

Compound 109

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 109A

trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyridine-3-sulfonamide

[0338] The title compound was prepared by substituting Compound 9B for Compound 3L in the procedure for Compound 61A.

Compound 109B

trans-5-cyano-6-(4-morpholinocyclohexylamino)pyridine-3-sulfonamide

[0339] The title compound was prepared by substituting Compound 109A for Compound 36B in the procedure for Compound 36C.

Compound 109C

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0340] The title compound was prepared by substituting Compound 109B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.59 (s, 1H), 8.56 (d, 1H), 8.13 (s, 1H), 8.00 (d, 1H), 7.55 (d, 1H), 7.47 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.36 (d, 1H), 6.19 (d, 1H), 4.00 (m, 1H), 3.65 (m, 4H), 3.28 (m, 4H), 3.03 (m, 4H), 2.73 (m, 4H), 2.16 (m, 6H), 1.90 (m, 6H), 1.40 (m, 6H), 0.93 (s, 6H).

Compound 110

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0341] The title compound was prepared by substituting Compound 52B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.71 (s, 1H), 11.23 (s, 1H), 8.08 (d, 1H), 7.91 (d, 1H), 7.74 (dd, 1H), 7.60 (d, 1H), 7.52 (m, 2H), 7.34 (m, 2H), 7.16 (s, 1H), 7.04 (m, 2H), 6.83 (d, 1H), 6.68 (dd, 1H), 6.43 (dd, 1H), 6.16 (d, 1H), 3.83 (dd, 2H), 3.23 (m, 2H), 3.12 (t, 2H), 3.06 (m, 4H), 2.73 (m, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.82 (m, 1H), 1.58 (m, 2H), 1.38 (m, 2H), 1.18 (m, 2H), 0.92 (s, 6H).

Compound 111

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 111A

benzyl (1S,3R)-3-(tert-butoxycarbonylamino)cyclopentylcarbamate

[0342] (1S,3R)-3-(tert-butoxycarbonylamino)cyclopentanecarboxylic acid (1.03 g), diphenylphosphoryl azide (DPPA, 1.00 ml), triethylamine (0.929 ml), and benzyl alcohol (0.931 ml) were combined in toluene (10 ml) and stirred at 100°C for 24 hours. The solution was cooled and chromatographed on silica gel using 10% ethyl acetate/hexanes to give the pure product.

Compound 111B

benzyl (1S,3R)-3-aminocyclopentylcarbamate

[0343] The title compound was prepared by substituting Compound 111A for Compound 1A in the procedure for Compound 1B.

Compound 111C

benzyl (1S,3R)-3-morpholinocyclopentylcarbamate

[0344] A solution of Compound 111B (400 mg), 1-bromo-2-(2-bromoethoxy)ethane (0.246 ml), and triethylamine (0.595 ml) in N,N-dimethylformamide (6 ml) was stirred at 70°C for 24 hours. The solution was cooled and poured into ethyl acetate (200 ml). The solution was extracted with 3 × water, washed with brine, concentrated, and chromatographed on silica gel using 10% methanol/ethyl acetate to give the pure product.

Compound 111D

(1S,3R)-3-morpholinocyclopentanamine

[0345] Compound 111C (300 mg) and ethanol (20 ml) were added to wet 20% $Pd(OH)_2$-C

(60.0 mg) in a 50 ml pressure bottle and stirred for 8 hours at 30 psi. The mixture was filtered through a nylon membrane and condensed to give the product.

Compound 111E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0346] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 111D for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.45 (d, 1H), 8.28 (dd, 1H), 7.97 (d, 1H), 7.68 (d, 1H), 7.52 (d, 1H), 7.44 (d, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.92 (dd, 1H), 6.85 (dd, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 4.08 (m, 1H), 3.60 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.48 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.07 (m, 1H), 1.95 (s, 2H), 1.79 (m, 2H), 1.63 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

Compound 112

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 112A

tert-butyl (1R,3S)-3-aminocyclopentylcarbamate

[0347] The title compound was prepared by substituting Compound 111A for Compound 111C in the procedure for Compound 111D.

Compound 112B

tert-butyl (1R,3S)-3-morpholinocyclopentylcarbamate

[0348] The title compound was prepared by substituting Compound 112A for Compound 111B in the procedure for Compound 111C.

Compound 112C

(1R,3S)-3-morpholinocyclopentanamine

[0349] The title compound was prepared by substituting Compound 112B for Compound 1A in the procedure for Compound 1B.

Compound 112D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-

{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0350] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 112C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (dimethylsulfoxide -d_6) δ 11.35 (s, 1H), 8.51 (d, 1H), 8.44 (dd, 1H), 8.00 (d, 1H), 7.77 (d, 1H), 7.50 (d, 1H), 7.48 (s, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 7.02 (dd, 1H), 6.67 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.11 (m, 1H), 3.61 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.50 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.06 (m, 1H), 1.95 (s, 2H), 1.77 (m, 2H), 1.66 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 113

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 113A

tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

[0351] The title compound was prepared by substituting tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 113B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

[0352] The title compound was prepared by substituting Compound 113A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G, with the exception that the product was purified on a silica gel column eluted with 4% methanol in dichloromethane.

Compound 113C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0353] The title compound was prepared by substituting Compound 113B for Compound

66B in the procedure for Compound 66C. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.60 (s, 1H), 8.55 (br, s, 1H), 8.51 (s, 1H), 8.00 (d, 1H), 7.80 (d, 1H), 7.52 (d, 1H), 7.49-7.46 (m, 2H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04(d, 2H), 6.66 (dd, 1H), 6.36 (s, 1H), 6.20 (d, 1H), 4.00 (dd, 1H), 3.91 (m, 1H), 3.70 (t, 1H), 3.60 (m, 1H), 3.58 (m, 1H), 3.32 (m, 1H), 3.16 (d, 1H), 3.05 (m, 4H), 2.98 (td, 1H), 2.86 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 114

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 114A

3-nitro-4-((tetrahydrofuran-3-yl)methylamino)benzenesulfonamide

[0354] The title compound was prepared by substituting 3-aminomethyl-tetrahydrofuran for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 114B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0355] The title compound was prepared by substituting Compound 114A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 11.42 (bs, 1H), 8.63 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.53-7.48 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.82-3.79 (m, 1H),3.71 (t, 1H), 3.62 (dd, 1H), 3.50 (dd, 1H), 3.38 (m, 1H), 3.32 (m, 1H), 3.07 (m, 4H), 2.76 (s, 2H), 2.58 (m, 1H), 2.25-2.00 (m, 6H), 1.98 (m, 1H), 1.95 (s, 2H), 1.65 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 115

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 115A

cis-tert-butyl 1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

[0356] The title compound was prepared as a racemate of the cis diastereomer by substituting tert-butyl piperidin-4-ylcarbamate for piperidin-4-ol and 3-fluorodihydro-2H-pyran-4(3H)-one (prepared by the method described in US 2005/0101628, incorporated herein by reference) for dihydro-2H-pyran-4(3H)-one) in the procedure for Compound 84A.

Compound 115B

cis-1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-amine

[0357] Compound 115A (0.29 g) was dissolved in CH_2Cl_2 (9 ml), then 4*N* HCl in dioxane (4 ml) was added and the reaction stirred at room temperature for 16 hours. The reaction was diluted with CH_2Cl_2 (30 ml), then 4*N* aqueous NaOH (5 ml) was added. After shaking and separating the layers the aqueous layer was saturated with solid NaCl and extracted with more CH_2Cl_2 (10 ml). The combined organic layers were dried over Na_2SO_4. After filtration and concentration the amine was used with no further purification.

Compound 115C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0358] The title compound was prepared by substituting Compound 115B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 8.54 (d, 1H), 8.43 (br d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.11 (d, 1H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 4.92 (d, 1H), 3.95 (m, 2H), 3.70 (v br m, 1H), 3.50, 3.40, 3.30 (all m, total 5H), 3.05, 3.00 (both v br m, total 5H), 2.74 (s, 2H), 2.55 (v br m, 1H), 2.18 (br m, 6H), 1.95 (m, 4H), 1.88 (ddd, 1H), 1.63 (v br m, 3H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 116

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 116A

1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine

[0359] Tert-butyl azetidin-3-ylcarbamate (0.46 g), dihydro-2H-pyran-4(3H)-one (0.29 g) and sodium triacetoxyborohydride (0.85 g) were stirred together in dichloromethane (5 ml)

overnight. The reaction was poured into dichloromethane (50 ml) and saturated aqueous $NaHCO_3$ solution (25 ml). The organic layer was separated, washed with brine (25 ml), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane over 20 minutes gave the Boc-protected intermediate. Treatment with HCl (4.0M in dioxane, 2 ml) and methanol (1 ml) for 1 hour gave the title compound after concentration as the di-HCl salt.

Compound 116B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0360] A suspension of 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-chloro-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin1-yl)benzamide (0.180 g), 1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine (0.078 g), and triethylamine (0.159 ml) in dioxane (2 ml) was degassed with nitrogen for 30 seconds then sealed. The reaction was heated to 110°C. After stirring for 16 hours, more triethylamine (10 equivalents total) and dimethylsulfoxide (1 ml) were added and the reaction stirred for an additional 18 hours at 110°C. The reaction was cooled, diluted with water (50 ml) and extracted with dichloromethane (2 × 150 ml). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane (flow = 36 ml/minutes) gave the title compound. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.59 (s, 1H), 8.49 (d, 1H), 8.40 (s, 1H), 7.97 (d, 1H), 7.77 (s, 1H), 7.47 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 – 6.78 (m, 1H), 6.65 (d, 1H), 6.35 (s, 1H), 6.21 (s, 1H), 4.47 – 4.23 (m, 1H), 3.83 (s, 3H), 3.05 (s, 6H), 2.73 (s, 2H), 2.18 (s, 8H), 1.95 (s, 2H), 1.68 (s, 2H), 1.38 (s, 2H), 1.24 (s, 4H), 0.92 (s, 6H).

Compound 117

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 117A

1-(tetrahydrofuran-3-yl)azetidin-3-amine

[0361] Tert-butyl azetidin-3-ylcarbamate (0.550 g), dihydrofuran-3(2H)-one (0.412 g) and sodium triacetoxyborohydride (1.015 g) were stirred together in dichloromethane (5 ml). After stirring overnight, the reaction was poured into saturated aqueous $NaHCO_3$ solution (25 ml) and extracted with dichloromethane (50 ml). The organic layer was washed with brine (25 ml), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes gave tert-butyl 1-(tetrahydrofuran-3-yl)azetidin-3-ylcarbamate. The resulting material was treated with HCl/dioxane for 1 hour, and then concentrated to give the title compound.

Compound 117B

3-nitro-4-(1-(tetrahydrofuran-3-yl)azetidin-3-ylamino)benzenesulfonamide

[0362] 4-Fluoro-3-nitrobenzenesulfonamide (0.084 g), 1-(tetrahydrofuran-3-yl)azetidin-3-amine (0.090 g) and triethylamine (0.266 ml) in tetrahydrofuran (3 ml) were heated to 60°C. After stirring for 4 hours, the reaction was cooled, the tetrahydrofuran was removed and the residue was partitioned between dichloromethane (200 ml) and water (20 ml). The organic layer was separated, washed with brine (25 ml), dried over magnesium sulfate, filtered, and concentrated to give the title compound.

Compound 117C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0363] The title compound was prepared by substituting Compound 117B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^1H NMR (300 MHz, $CDCl_3$) δ 10.39 - 9.79 (m, 1H), 9.17 (s, 1H), 8.87 (d, 1H), 8.51 (d, 1H), 8.15 (dd, 2H), 7.94 (d, 1H), 7.68 (d, 1H), 7.48 - 7.42 (m, 1H), 7.23 (d, 2H), 6.91 (d, 2H), 6.69 (d, 1H), 6.54 (dd, 2H), 5.99 (d, 1H), 4.29 (d, 1H), 4.01 - 3.73 (m, 4H), 3.66 (d, 2H), 3.08 (s, 6H), 2.76 (s, 2H), 2.21 (s, 6H), 2.03 - 1.83 (m, 3H), 1.64 (s, 2H), 1.42 (d, 2H), 0.93 (s, 6H).

Compound 118

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 118A

(R)-tert-butyl (1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

[0364] The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 118B

(R)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

[0365] The title compound was prepared by substituting Compound 118A for Compound 1A in the procedure for Compound 1B.

Compound 118C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0366] The title compound was prepared by substituting Compound 118B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.57 (s, 1H), 8.59 (br s, 1H), 8.45 (br s, 1H), 8.02 (d, 1H), 7.95 (m, 1H), 7.71 (m, 1H), 7.56 (d, 1H), 7.45 (m, 1H), 7.35 (m, 3H), 7.05 (m, 2H), 6.90 (br s, 1H), 6.64 (d, 1H), 6.33 (m, 1H), 6.22 (m, 1H), 3.90 (m, 2H), 3.44 (m, 2H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (m, 3H), 2.59 (m, 2H), 2.19 (m, 6H), 1.95 (m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.39 (m, 2H), 1.23 (m, 1H), 0.94 (s, 6H).

Compound 119

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0367] The title compound was prepared as described in the procedure for Compound 11D using Compound 75F and Compound 37D in place of Compound 3J and Compound 11B, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.39 (s, 1H), 8.08 (d, 1H), 8.04 (d, 1H), 7.41 - 7.59 (m, 4H), 7.35 (d, 2H), 7.08 (d, 2H), 6.68 (dd, 1H), 6.37 - 6.43 (m, 1H), 6.20 (s, 1H), 4.38 (d, 2H), 3.73 - 3.82 (m, 2H), 3.54 - 3.63 (m, 2H), 3.09 (s, 4H), 2.81 (s, 2H), 2.16 - 2.39 (m, 5H), 1.94 (s, 2H), 1.79 - 1.93 (m, 4H), 1.40 (t, 2H), 0.94 (s, 6H).

Compound 120

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

Compound 120A

trans-4-(aminomethyl)cyclohexanol

[0368] Tert-butyl ((1r,4r)-4-hydroxycyclohexyl)methylcarbamate (1 g) in dichloromethane (10 ml) was treated with trifluoroacetic acid (5 ml) at 0°C for 10 minutes and at room temperature for 30 minutes. The reaction mixture was concentrated and dried in vacuo to provide the title compound as a trifluoroacetic acid salt.

Compound 120B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

[0369] A mixture of Compound 53A (211 mg), Compound 120A (104 mg) and N-ethyl-N-isopropylpropan-2-amine (0.3 ml) in dimethylsulfoxide (2 ml) was heated at 150°C in a Biotage Initiator microwave synthesizer for 1.5 hours and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (30 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound. ^1H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.61 (t, 1H), 8.53 - 8.58 (m, 1H), 8.04 (d, 1H), 7.76 - 7.83 (m, 1H), 7.47 - 7.56 (m, 3H), 7.34 (d, 2H), 7.07 - 7.11 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.82 - 4.99 (m, 1H), 4.50 (d, 1H), 3.26 - 3.31 (m, 2H), 3.23 (t, 1H), 3.07 (s, 4H), 2.76 (s, 2H), 2.10 - 2.28 (m, 6H), 2.05 (dd, 1H), 1.95 (s, 2H), 1.84 (t, 2H), 1.52 - 1.76 (m, 2H), 1.41 - 1.51 (m, 1H), 1.38 (t, 2H), 0.95 - 1.25 (m, 4H), 0.92 (s, 6H).

Compound 121

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

Compound 121A

(4-methoxycyclohexyl)methanol

[0370] 4-Methoxycyclohexanecarboxylic acid (7 g) in tetrahydrofuran (20 ml) was treated with 1 M (in tetrahydrofuran) borane-tetrahydrofuran complex (100 ml) overnight. The mixture was concentrated and the residue was dissolved in methanol (100 ml) and concentrated HCl (10 ml). The resulting mixture was stirred for 1 hour and concentrated. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give the title compound.

Compound 121B

4-((4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[0371] The title compound was prepared as described in the procedure for Compound 12A by replacing (1,4-dioxan-2-yl)methanol with Compound 121A.

Compound 121C

4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[0372] Separation of the cis and trans mixture of Compound 121B on a reverse phase HPLC (gradient: 40–55% acetonitrile in 0.1% TFA in water over 25 minutes) provided the title compound.

Compound 121D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

[0373] The title compound was prepared as described in the procedure for Compound 11D using Compound 121C in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.34 (s, 1H), 7.96 - 8.07 (m, 2H), 7.48 - 7.56 (m, 3H), 7.31 - 7.42 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.39 (s, 1H), 3.20 (s, 3H), 3.09 (s, 4H), 2.82 (s, 2H), 2.09 - 2.34 (m, 6H), 1.96 (s, 2H), 1.78 - 1.86 (m, 3H), 1.54 (dd, 2H), 1.28 - 1.46 (m, 6H), 0.92 (s, 6H).

Compound 122

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 122A

cis-tert-butyl-4-(cyclopropylamino)cyclohexylcarbamate

[0374] The title compound was prepared by substituting tert-butyl 4-oxocyclohexylcarbamate for 4'-chlorobiphenyl-2-carboxaldehyde and cyclopropylamine for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 122B

cis-N^1-cyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

[0375] The title compound was prepared by substituting Compound 122A for Compound 39A in the procedure for Compound 39B.

Compound 122C

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0376] The title compound was prepared by substituting Compound 122B for Compound 100B in the procedure for Compound 100C. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.28 (d, 1H), 8.59 (d, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 2H), 7.43 (t, 2H), 7.07 (d, 2H), 6.90 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.50 (dd, 1H), 3.56 - 3.63 (m, 1H), 3.02 - 3.08 (m, 4H), 2.77 (s, 3H), 2.26 (t, 2H), 2.10 - 2.16 (m, 4H), 2.06 (ddd, 1H), 1.97 (s, 2H), 1.74 - 1.82 (m, 2H), 1.61 - 1.71 (m, 5H), 1.39 (t, 2H), 0.93 (s, 6H), 0.39 - 0.44 (m, 4H).

Compound 123

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 123A

trans-tert-butyl-4-(tetrahydro-2H-pyran-4-ylamino)cyclohexylcarbamate

[0377] The title compound was prepared by substituting trans-tert-butyl-4-aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 123B

trans-N1-(tetrahydro-2H-pyran-4-yl)cyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

[0378] The title compound was prepared by substituting Compound 123A for Compound 39A in the procedure for Compound 39B.

Compound 123C

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0379] The title compound was prepared by substituting Compound 123B for Compound 100B in the procedure for Compound 100C. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.01 (s, 1H), 9.28 (d, 1H), 8.48 (d, 1H), 8.38 (dd, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 7.67 - 7.69 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.91 (d, 1H), 6.78 (dd, 1H), 6.59 (d, 1H), 6.48 (dd, 1H), 4.01 (d, 2H), 3.44 - 3.49 (m, 1H), 3.37 - 3.43 (m, 2H), 3.01 - 3.09 (m, 5H), 2.85 (t, 1H), 2.78 (s, 2H), 2.27 (t, 2H), 2.13 - 2.18 (m, 4H), 2.05 (t, 4H), 1.97 (s, 2H), 1.93 (d, 2H), 1.52 - 1.60 (m, 2H), 1.44 - 1.50 (m, 2H), 1.39 (t, 2H), 1.25 - 1.34 (m, 2H), 0.94 (s, 6H).

Compound 124

trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 124A

trans-4-morpholinocyclohexanol

[0380] Trans-4-Aminocyclohexanol (0.5 g), 1-bromo-2-(2-bromoethoxy)ethane (1.07 g) and triethylamine (2.42 ml) were dissolved in anhydrous acetonitrile (20 ml). The reaction mixture was heated at 60°C overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 7%-10% methanol in dichloromethane to give the title compound.

Compound 124B

trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyridine-3-sulfonamide

[0381] The title compound was prepared by substituting Compound 124A for (tetrahydro-2*H*-pyran-4-yl)methanol and Compound 36A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 124C

trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-

chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0382] The title compound was prepared by substituting Compound 124B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).

Compound 125

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 125A

4-(((trans)-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[0383] Separation of the *cis* and *trans* mixture of Compound 121B on a reverse phase HPLC provided the title compound.

Compound 125B

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0384] The title compound was prepared as described in the procedure for Compound 11D using Compound 125A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.34 (s, 1H), 7.96 - 8.09 (m, 2H), 7.51 (dd, 3H), 7.32 - 7.39 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.24 (s, 3H), 3.00 - 3.15 (m, 5H), 2.83 (s, 2H), 2.09 - 2.36 (m, 6H), 2.03 (d, 2H), 1.96 (s, 2H), 1.77 - 1.86 (m, 2H), 1.73 (s, 1H), 1.39 (t, 2H), 1.02 - 1.17 (m, 4H), 0.92 (s, 6H).

Compound 126

tert-butyl 4-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxy]methyl}-4-fluoropiperidine-1-carboxylate

Compound 126A

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

[0385] 1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 ml) was treated with 1.0 N $LiAlH_4$ in THF (2.54 ml) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 ml) was added to the reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 ml). The reaction was stirred for another 1 hour. The solid was removed by filtration via a pack of Celite and washed with ethyl acetate. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the product.

Compound 126B

tert-butyl 4-fluoro-4-((2-nitro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

[0386] The title compound was prepared by substituting Compound 126A for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 126C

tert-butyl 4-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxy]methyl}-4-fluoropiperidine-1-carboxylateyl)oxy]benzamide

[0387] The title compound was prepared by substituting Compound 126B for Compound 11B in the procedure for Compound 11D. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.36 (s, 2H), 8.02-8.06 (m, 2H), 7.49-7.53 (m, 3H), 7.40 (d, 1H), 7.35 (d, 2H), 7.04 (d, 1H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.83-3.85 (m, 2H), 3.09 (s, 4H), 2.33 (s, 2H), 2.27-2.32 (m, 4H), 2.13-2.16 (m, 2H), 1.96 (s, 2H), 1.83-1.92 (m, 2H), 1.67-1.75 (m, 2H), 1.38-1.41 (m, 11H), 0.92 (s, 6H).

Compound 127

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0388] The title compound was prepared by substituting Compound 126C for Compound 1A in the procedure for Compound 1B. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.50 (s, 1H), 8.14 (d, 1H), 7.90 (d, 2H), 7.80 (dd, 1H), 7.60 (d, 1H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 7.13 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.30 (dd, 1H), 6.26 (d, 1H), 4.28 (d, 2H), 3.10-

3.13 (m, 2H), 2.91-3.00 (m, 6H), 2.73 (s, 2H), 1.96-2.02 (m, 4H), 1.77-1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 128

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-ylpiperazin-1-yl)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 128A

tert-butyl 4-(tetrahydro-2H-pyran-4-yl)piperazine-1-carboxylate

[0389] The title compound was prepared by substituting tert-butyl piperazine-1-carboxylate for morpholine and dihydro-2H-pyran-4(3H)-one for tert-butyl 4-oxocyclohexylcarbamate in the procedure for Compound 39A.

Compound 128B

1-(tetrahydro-2H-pyran-4-yl)piperazine dihydrochloride

[0390] To a solution of Compound 128A (3.92 g) in ether was added HCl (25 ml, 2M in ether) and the reaction mixture was stirred for 16 hours at room temperature. The solid product was filtered off, dried and used in next step without further purification.

Compound 128C

trans-tert-butyl-4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexylcarbamate

[0391] The title compound was prepared by substituting Compound 128B for morpholine in the procedure for Compound 39A.

Compound 128D

trans-4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexanamine tris(2,2,2-trifluoroacetate)

[0392] The title compound was prepared by substituting Compound 128C for Compound 39A in the procedure for Compound 39B.

Compound 128E

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-ylpiperazin-1-yl)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0393] The title compound was prepared by substituting Compound 128D for Compound 100B in the procedure for Compound 100C. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.07 (s,

1H), 9.28 - 9.32 (m, 1H), 8.44 (t, 1H), 8.34 - 8.39 (m, 2H), 8.10 - 8.14 (m, 1H), 7.66 - 7.69 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (t, 1H), 6.73 - 6.77 (m, 1H), 6.52 - 6.55 (m, 1H), 6.49 - 6.52 (m, 1H), 3.99 - 4.06 (m, 2H), 3.29 - 3.36 (m, 2H), 3.03 - 3.09 (m, 4H), 2.77 (s, 2H), 2.62 (s, 8H), 2.24 - 2.29 (m, 3H), 2.10 - 2.16 (m, 5H), 2.05 (s, 2H), 1.97 (s, 2H), 1.92 (s, 2H), 1.70 (d, 2H), 1.57 (td, 2H), 1.34 - 1.43 (m, 4H), 1.20 - 1.30 (m, 2H), 0.93 (s, 6H).

Compound 129

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 129A

(1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methanol

[0394] A suspension of piperidin-4-ylmethanol (0.250 g), sodium triacetoxyborohydride (0.690 g) and 1,3-difluoropropan-2-one (0.245 g) were stirred together in dichloromethane. After stirring overnight the reaction was poured into saturated aqueous $NaHCO_3$ solution (10 ml) and stirred for 15 minutes. The reaction was extracted with dichloromethane (3 × 25 ml), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 3% methanol/dichloromethane gave the title compound.

Compound 129B

4-((1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0395] To a solution of (1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methanol (0.068 g) in tetrahydrofuran (1 ml) was added sodium hydride (0.056 g) and the reaction stirred for 30 minutes at room temperature. 4-Fluoro-3-nitrobenzenesulfonamide (0.077 g) was added in one portion and stirring was continued for 1 hour. The reaction was poured into water (20 ml) and extracted with dichloromethane. The pH of the aqueous layer was adjusted to pH~8 and it was extracted with dichloromethane (50 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

Compound 129C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0396] The title compound was prepared by substituting Compound 129B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 11.47 - 10.98 (m, 1H), 8.33 (d, 1H), 8.03 (d, 2H), 7.50 (dd, 3H), 7.36 (t, 3H), 7.04 (d, 2H), 6.67 (d, 1H), 6.39 (dd, 1H), 6.20 (s, 1H), 4.62 (dd, 4H), 4.06 (d, 2H), 3.18 - 2.71 (m, 11H), 2.20 (d, 6H), 1.96 (s, 2H), 1.73 (d, 3H), 1.35 (d, 4H), 0.92 (s, 6H).

Compound 130

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 130A

(R)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

[0397] The title compound was prepared by substituting dihydro-2H-pyran-4(3H)-one for 4′-chlorobiphenyl-2-carboxaldehyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 130B

(R)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

[0398] A solution of Compound 130A (550 mg) in dichloromethane (25 ml) was cooled in an ice bath under nitrogen. 2,2,2-Trifluoroacetic acid (8.333 ml) was added and the reaction was stirred for 2 hours. The product was obtained by concentration and high vacuum drying.

Compound 130C

(R)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)benzenesulfonamide

[0399] The title compound was prepared by substituting Compound 130B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 130D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0400] To a solution of Compound 3J (90 mg), Compound 130C (64.2 mg), triethylamine (0.077 ml), N,N-dimethylpyridin-4-amine (38.5 mg) in a mixture of dichloromethane (5 ml)

and N,N-dimethylformamide (0.5 ml) was added N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine, hydrochloric acid (60.4 mg) and the mixture was stirred 18 hours. This was concentrated on high vacuum and the crude was purified by reverse phase chromatography with ammonium acetate buffer/acetonitrile. 1H NMR (500 MHz, pyridine-d_5) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.59 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.65 - 7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H), 3.35 (t, 2H), 3.07 (m, 4H), 2.73 - 2.80 (m, 4H), 2.68 - 2.72 (m, 1H), 2.36 (q, 1H), 2.11 - 2.30 (m, 9H), 1.97 (m, 2H), 1.62 - 1.71 (m, 3H), 1.48 - 1.58 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 131

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 131A

tert-butyl (3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

[0401] The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-4(3H)-one for 4′-chlorobiphenyl-2-carboxaldehyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 131B

(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

[0402] The title compound was prepared by substituting Compound 131A for Compound 130A in the procedure for Compound 130B.

Compound 131C

4-((3R)-(1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

[0403] The title compound was prepared by substituting Compound 131B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 131D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0404] The title compound was prepared by substituting Compound 131C for Compound 130C in the procedure for Compound 130D. 1H NMR (500 MHz, pyridine-d_5) δ 13.03 (d, 1H), 9.28 (m, 1H), 8.61 (m, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71 - 2.82 (m, 5H), 2.37 - 2.44 (m, 2H), 2.19 - 2.29 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.32 - 1.49 (m, 4H), 1.28 (d, 3H), 1.20 (s, 3H), 0.94 (s, 6H).

Compound 132

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 132A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

[0405] The title compound was prepared by substituting dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 132B

(S)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

[0406] The title compound was prepared by substituting Compound 132A for Compound 130A in the procedure for Compound 130B.

Compound 132C

(S)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)benzenesulfonamide

[0407] The title compound was prepared by substituting Compound 132B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Comound 132D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0408] The title compound was prepared by substituting Compound 132C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500 MHz, pyridine- d_5) δ 13.04 (m, 1H), 9.27 (d, 1H), 8.58 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H),

7.44 (d, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H), 3.36 (t, 2H), 3.07 (m, 4H), 2.68 - 2.80 (m, 5H), 2.36 (m, 1H), 2.09 - 2.29 (m, 9H), 1.97 (s, 2H), 1.62 - 1.72 (m, 3H), 1.48 - 1.60 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 133

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 133A

tert-butyl (3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

[0409] The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-4(3H)-one for 4′-chlorobiphenyl-2-carboxaldehyde and (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 133B

(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

[0410] The title compound was prepared by substituting Compound 133A for Compound 130A in the procedure for Compound 130B.

Compound 133C

4-(3S)-(1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitro benzenesulfonamide

[0411] The title compound was prepared by substituting Compound 133B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 133D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0412] The title compound was prepared by substituting Compound 133C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500 MHz, pyridine- d_5) δ 13.03 (d, 1H), 9.28 (m, 1H), 8.61 (m, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71 - 2.82 (m, 5H), 2.37 - 2.44 (m, 2H), 2.19 - 2.29 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.33 - 1.48 (m,

4H), 1.28 (d, 3H), 1.20 (s, 3H), 0.94 (s, 6H).

Compound 134

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 134A

4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

[0413] A solution of Compound 113A (0.8 g) in dichloromethane (10 ml) and trifluoroacetic acid (10 ml) was stirred at room temperature for 2 hours. The solvents were evaporated and the residue triturated with diethyl ether. The resulting solid was dissolved in 5% aqueous sodium carbonate solution (20 ml). The solution was concentrated to dryness and the resulting solid was triturated with a solution of 10% methanol in dichloromethane several times. Evaporation of the organic solvents gave the title compound.

Compound 134B

4-((4-methylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0414] To a solution of Compound 134A (158 mg) in anhydrous *N,N*-dimethylformamide (4 ml) was added sodium carbonate (64 mg) and methyl iodide (78 mg). After stirring overnight at room temperature, the mixture was evaporated to dryness. The crude product was then absorbed on silica gel (6 g) and purified on a silica gel column eluting with 10% methanol in dichloromethane to give the title compound.

Compound 134C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0415] The title compound was prepared by substituting Compound 134B for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92 (m, 1H),3.86 (d, 1H), 3.67 (dt, 1H), 3.49-3.39 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 3.71 (m, 1H), 2.49 (d, 1H), 2.26 (m, 2H), 2.16 (s, 3H), 2.14 (m, 4H), 2.03 (dt, 1H), 1.97 (s, 2H), 1.90 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 135

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 135A

4-((4-(2-methoxyethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0416] The title compound was prepared by substituting 2-methoxyethyl bromide for methyl iodide in the procedure for Compound 134B.

Compound 135B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0417] The title compound was prepared by substituting Compound 135A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.98 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H),3.87 (d, 1H), 3.70 (dt, 1H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.27 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H), 2.77 (s, 2H), 2.70 (m, 1H), 2.57 (t, 2H), 2.27-2.07 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 136

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 136A

4-((4-acetylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0418] The title compound was prepared by substituting acetic anhydride for methyl iodide in the procedure for Compound 134B.

Compound 136B

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0419] The title compound was prepared by substituting Compound 136A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (s, 1H), 8.85 (s, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (dd, 1H), 6.75 (dd, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.73 (dd, 1H), 3.93-3.65 (m, 2H), 3.60-3.40 (m, 4H), 3.12 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.57 (t, 2H), 2.14 (s, 3H), 2.27-2.07 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 137

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 137A

ethyl 4-fluorobut-2-enoate

[0420] Ethyl 2-fluoroacetate (21.0 g) in CH_2Cl_2 (200 ml) at –78°C was treated dropwise over 45 min with a 1.0 M solution of diisobutylaluminum hydride in CH_2Cl_2 (200 ml) maintaining the internal temperature below –70°C. Stirring was continued at –78°C for 30 minutes and then (carbethoxymethylene)triphenylphosphorane (70.0 g) was added in one portion. The reaction mixture was allowed to slowly reach room temperature while stirring overnight. It was then quenched with methanol, filtered and concentrated to give the product as a mixture of isomers (E/Z = 3:1).

Compound 137B

trans-ethyl 1-benzyl-4-(fluoromethyl)pyrrolidine-3-carboxylate

[0421] A mixture of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (4.5 g) and Compound 137A (2.5 g) in dichloromethane (50 ml) was cooled to 0°C, treated dropwise with trifluoroacetic acid (0.15 ml), stirred for 4 hours at 0°C and neutralized with saturated aqueous Na_2CO_3 solution. The mixture was poured into a separatory funnel and the layers separated. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 0–20% ethyl acetate in hexanes as eluent to give both the cis and trans isomers of the product. Only the trans diastereomers were carried on in the following steps.

Compound 137C

trans-ethyl 4-(fluoromethyl)pyrrolidine-3-carboxylate

[0422] Compound 137B (0.83 g) in ethanol (9 ml) was treated with 10% Pd/C (0.208 g) and ammonium formate (1.97 g), refluxed for 1.5 hours, concentrated, dissolved in dichloromethane, filtered though a pad of celite rinsing with dichloromethane, and concentrated to give the product.

Compound 137D

trans-1-benzyl 3-ethyl 4-(fluoromethyl)pyrrolidine-1,3-dicarboxylate

[0423] Compound 137C (0.44 g) in dioxane (4 ml) and water (4 ml) at 0°C was treated sequentially with Na_2CO_3 (0.89 g) and benzyl chloroformate (0.48 ml). The reaction mixture was stirred at 0°C for 3 hours and was then allowed to slowly warm to room temperature over 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 10–25% ethyl acetate in hexanes as eluent to give the product.

Compound 137E

trans-1-(benzyloxycarbonyl)-4-(fluoromethyl)pyrrolidine-3-carboxylic acid

[0424] The title compound was prepared by substituting Compound 137D for Compound 15G in the procedure for Compound 15H.

Compound 137F

trans-benzyl 3-(fluoromethyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

[0425] Compound 137E (0.563 g) in tetrahydrofuran (10 ml) at 0°C was treated dropwise with a 1 M solution of borane in tetrahydrofuran (4 ml), stirred for 3 hours and then slowly quenched with saturated aqueous NH_4Cl solution. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered and concentrated to give the product.

Compound 137G

trans-benzyl 3-(fluoromethyl)-4-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

[0426] The title compound was prepared by substituting Compound 137F for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 137H

trans-4-((4-(fluoromethyl)pyrrolidin-3-yl)methoxy)-3-nitrobenzenesulfonamide

[0427] Compound 137G (0.232g) in acetic acid (2.5 ml) was treated with hydrobromic

acid (33 wt % in acetic acid) (0.875 ml) at ambient temperature, stirred for 1 hour and concentrated. The product was free-based using a MEGA BE-SCX column with 1:1 CH_2Cl_2/methanol as eluent for the hydrobromic acid and acetic acid. The product was released from the column with 10% (7 M ammonia in methanol) in CH_2Cl_2 as eluent.

Compound 137I

trans-4-((4-(fluoromethyl)-1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)-3-nitrobenzenesulfonamide

[0428] The title compound was prepared by substituting Compound 137H for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 137J

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0429] The title compound was prepared by substituting Compound 137I for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.35 (d, 1H), 8.03 (m, 2H), 7.51 (m, 3H), 7.37 (m, 3H), 7.04 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.45 (m, 6H), 4.21 (d, 2H), 3.62 (m, 1H), 3.08 (m, 4H), 2.72 (m, 5H), 2.31 (m, 9H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 138

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 138A

(4-fluorotetrahydro-2H-pyran-4-yl)methyl methanesulfonate

[0430] A mixture of Compound 37C (1.4 g), methanesulfonyl chloride (1.054 ml), triethylamine (2.99 ml), and 4-dimethylaminopyridine (0.051 g) in CH_2Cl_2 (20 ml) was stirred at 0°C for 2 hours, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

Compound 138B

2-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)isoindoline-1,3-dione

[0431] A mixture of Compound 138A (1.8 g) and potassium phthalimide (2.356 g) in N,N-dimethylformamide (30 ml) was heated at 150°C overnight, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

Compound 138C

(4-fluorotetrahydro-2H-pyran-4-yl)methanamine

[0432] A mixture of Compound 138B (1.4 g) and hydrazine (1.548 ml) in ethanol (40 ml) was heated at 70 °C overnight, cooled to room temperature, slurried with CH_2Cl_2 (200 ml) and the solid removed by filtration. The filtrate was concentrated and chromatographed on silica gel eluting with 100:5:1 ethyl acetate/methanol/NH_4OH to give the product.

Compound 138D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

[0433] A mixture of 4-fluoro-3-nitrobenzenesulfonamide (0.44 g), Compound 138C (0.266 g), and triethylamine (1.11 ml) in tetrahydrofuran (10 ml) was heated at 70°C overnight, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel eluting with 50% ethyl acetate in hexanes to give the product.

Compound 138E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0434] The title compound was prepared by substituting Compound 138D for Compound 11B in the procedure for Compound 11D. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.82 (dd, 1H), 7.48-7.54 (m, 3H), 7.34 (d, 2H), 7.24 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.70-3.77 (m, 4H), 3.50-3.55 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H), 1.76-1.84 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 139

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 139A

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

[0435] The title compound was prepared as described in the procedure for Compound 53B by replacing 1-acetylpiperidin-4-amine with 4-amino-piperidine-1-carboxylic acid tert-butyl ester.

Compound 139B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenylsulfonyl)benzamide

[0436] To a cooled (0°C) solution of Compound 139A (960 mg) in dichloromethane (10 ml) was added dropwise trifluoroacetic acid (5 ml). The mixture was stirred at the temperature for 3 hours. Then, the mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (200 ml) and washed with aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the mixture was filtered, and evaporation of the solvent from the filtrate gave the title compound.

Compound 139C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0437] To a solution of Compound 139B (120 mg) in tetrahydrofuran (3 ml) and acetic acid (1 ml) was added oxetan-3-one (50.8 mg) and MP-cyanoborohydride (2.15 mmol/g, 150 mg). The mixture was stirred at room temperature overnight. The mixture was filtered. The filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5-10% 7N NH_3 in methanol in dichloromethane to give the title compound. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.62 (s, 1H), 8.51 (d, 1H), 8.20 (d, 1H), 7.99 (d, 1H), 7.74 (m, 1H), 7.48 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.36 (dd, 1H), 6.20 (d, 1H), 4.54 (t, 2H), 4.43 (t, 2H), 3.66 (m, 1H), 3.44 (m, 3H), 3.04 (m, 5H), 2.73 (s, 2H), 2.61 (m, 2H), 2.12 (m, 11H), 1.61 (m, 2H), 1.38 (t, 2H), 0.93 (m, 6H).

Compound 140

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-

[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0438] The title compound was prepared as described in the procedure for Compound 139C by replacing oxetan-3-one with cyclobutanone. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.58 (s, 1H), 8.47 (d, 1H), 8.12 (d, 1H), 7.97 (d, 1H), 7.74 (d, 1H), 7.53 (d, 1H), 7.45 (m, 1H), 7.36 (m, 3H), 7.02 (m, 3H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 3.74 (m, 1H), 2.97 (m, 6H), 2.73 (s, 3H), 2.15 (m, 15H), 1.67 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

Compound 141

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0439] The title compound was prepared as described in the procedure for Compound 139C by replacing oxetan-3-one with 2,2-dimethyltetrahydropyran-4-one. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.60 (s, 1H), 8.50 (d, 1H), 8.15 (m, 1H), 7.99 (d, 1H), 7.78 (m, 1H), 7.62 (m, 1H), 7.47 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.65 (m, 2H), 6.35 (dd, 1H), 6.21 (d, 1H), 4.56 (d, 3H), 3.89 (m, 3H), 3.67 (m, 6H), 3.45 (m, 2H), 3.04 (m, 3H), 2.75 (m, 3H), 2.14 (m, 3H), 1.71 (m, 5H), 1.16 (s, 9H).

Compound 142

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 142A

(S)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

[0440] (S)-tert-butyl pyrrolidin-3-ylcarbamate (415 mg), (1-ethoxycyclopropoxy)trimethylsilane (1.8 ml) and molecular sieves (500 mg) were combined in methanol (4.5 ml). Acetic acid (1.3 ml) was added, followed by sodium cyanoborohydride (420 mg). The resulting mixture was heated to reflux for 4 hours. Insoluble material was filtered off and reaction was made basic to pH 14 with addition of 6M aqueous NaOH solution. The solution was extracted three times with diethyl ether, and the combined extracts were dried over $MgSO_4$, filtered and concentrated to obtain an oil, which was purified by flash chromatography, eluting first with 100% dichloromethane, followed by 5%

methanol/dichloromethane and 10% methanol/dichloromethane.

Compound 142B

(S)-1-cyclopropylpyrrolidin-3-amine

[0441] The title compound was prepared by substituting Compound 142A for Compound 1A in the procedure for Compound 1B.

Compound 142C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0442] The title compound was prepared by substituting Compound 142B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 8.51 (m, 2H), 8.30 (m, 1H), 8.00 (br s, 1H), 7.77 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.97 (br s, 1H), 6.67 (dd, 1H), 6.36 (m, 1H), 6.21 (m, 1H), 4.19 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.78 (br s, 1H), 1.68 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

Compound 143

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0443] The title compound was prepared as described in the procedure for Compound 139C by replacing oxetan-3-one with 3-oxotetrahydrofuran. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.53 (d, 1H), 8.21 (m, 1H), 8.02 (m, 1H), 7.80 (dd, 1H), 7.49 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.29 (m, 3H), 3.73 (m, 6H), 3.09 (m, 4H), 2.76 (m, 2H), 2.05 (m, 8H), 1.68 (m, 2H), 1.37 (m, 2H), 0.94 (s, 6H).

Compound 144

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 144A

(R)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

[0444] The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for (S)-tert-butyl pyrrolidin-3-ylcarbamate in the procedure for Compound 142A.

Compound 144B

(R)-1-cyclopropylpyrrolidin-3-amine

[0445] The title compound was prepared by substituting Compound 144A for Compound 1A in the procedure for Compound 1B.

Compound 144C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0446] The title compound was prepared by substituting Compound 144B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.53 (d, 2H), 8.32 (d, 1H), 8.02 (d, 1H), 7.81 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.20 (d, 1H), 4.21 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.74 (br s, 1H), 1.66 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

Compound 145

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 145A

(S)-tert-butyl (1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

[0447] The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 145B

(S)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

[0448] The title compound was prepared by substituting Compound 145A for Compound 1A in the procedure for Compound 1B.

Compound 145C

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylamino)phenylsulfonyl)benzamide

[0449] The title compound was prepared by substituting Compound 145B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.58 (s, 1H), 8.61 (br s, 1H), 8.46 (s, 1H), 7.96 (d, 1H), 7.72 (m, 1H), 7.54 (d, 1H), 7.45 (t, 1H), 7.37 (br s, 2H),7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.22 (d, 1H), 3.89 (m, 2H), 3.38 (m, 4H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (s, 2H), 2.61 (m, 1H), 2.18 (m, 6H), 2.05 (m, 1H), 1.95 (m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.38 (m, 2H), 0.94 (s, 6H).

Compound 146

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0450] The title compound was prepared as described in the procedure for Compound 120B using 3-amino-2,2-dimethylpropan-1-ol in place of Compound 120A. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 11.35 (s, 1H), 8.96 (t, 1H), 8.56 (d, 1H), 8.05 (d, 1H), 7.79 (dd, 1H), 7.46 - 7.56 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 5.10 (t, 1H), 3.29 (d, 1H), 3.24 (d, 1H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (d, 12H).

Compound 147

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 147A

tert-butyl (1-(methylsulfonyl)piperidin-3-yl)methylcarbamate

[0451] tert-Butyl piperidin-3-ylmethylcarbamate(500 mg) was dissolved in anhydrous dichloromethane (10 ml), and methanesulfonyl chloride (0.181 ml) was added followed by the addition of triethylamine (1.3 ml). The reaction mixture was stirred at room temperature overnight. The organic solvent was removed under vacuum. The residue was purified with

flash column chromatography on silica gel eluting with 0–70% ethyl acetate in hexane to give the title compound.

Compound 147B

(1-(methylsulfonyl)piperidin-3-yl)methanamine

[0452] Compound 147A (400 mg) was suspended in 4N HCl in dioxane (10 ml) followed by the addition of anhydrous methanol (1 ml). The clear solution was stirred at room temperature for 2 hours. The organic solvent was removed under vacuum. The solid residue was used in the next step without further purification.

Compound 147C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0453] Compound 53A (50 mg), Compound 147B (26 mg) and triethylamine (0.088 ml) were dissolved in anhydrous dioxane (1ml) and N,N-dimethylformamide (0.2 ml). The reaction vial was heated in a Biotage Initiator microwave reactor at 130°C for 25 minutes. The solvent was removed under vacuum. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 20-80% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the title compound. ^1H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.52 (m, 1H), 3.40 (m, 2H), 3.06 (m, 4H), 2.84 (s, 3H), 2.75 (m, 2H), 2.75 (m, 4H), 2.58 (m, 1H), 2.16 (m, 6H), 1.95 (s, 3H), 1.76 (m, 2H), 1.52 (m, 1H), 1.37 (m, 2H), 0.92 (s, 6H).

Compound 148

N-[(4-{[(1-acetylpiperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 148A

tert-butyl (1-acetylpiperidin-3-yl)methylcarbamate

[0454] The title compound was prepared by substituting acetyl chloride for

methanesulfonyl chloride in the procedure for Compound 147A.

Compound 148B

1-(3-(aminomethyl)piperidin-1-yl)ethanone

[0455] The title compound was prepared by substituting Compound 148A for Compound 147A in the procedure for Compound 147B.

Compound 148C

N-[(4-{[(1-acetylpiperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0456] The title compound was prepared by substituting Compound 148B for Compound 147B in the procedure for Compound 147C. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).

Compound 149

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 149A

(R)-tert-butyl 1-(methylsulfonyl)pyrrolidin-3-ylcarbamate

[0457] The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in the procedure for Compound 147A.

Compound 149B

(R)-1-(methylsulfonyl)pyrrolidin-3-amine

[0458] The title compound was prepared by substituting Compound 149A for Compound 147A in the procedure for Compound 147B.

Compound 149C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-

b]pyridin-5-yloxy)benzamide

[0459] The title compound was prepared by substituting Compound 149B for Compound 147B in the procedure for Compound 147C. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 8.02 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.33 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.41 (m, 1H), 3.69 (m, 1H), 3.39 (m, 3H), 3.06 (m, 4H), 2.97 (s, 3H), 2.76 (m, 2H), 2.27 (m, 8H), 1.93 (m, 2H), 1.54 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 150

4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 150A

ethyl 2-hydroxy-3,3-dimethylcyclohex-1-enecarboxylate

[0460] Into a 500 ml round-bottomed flask was added diisopropylamine (3.5 ml) in ether (200 ml). After cooling to –30°C, butyllithium (16 ml) (1.6M in hexane) was added slowly. After stirring 30 minutes, the temperature was cooled to –5 °C. 2,2-Dimethylcyclohexanone (3 g) was added slowly. The mixture was warmed up to 0°C and stirred for 1 hour. After cooling to –5 °C, hexamethylphosphoramide (8 ml) and ethyl carbonocyanidate (2.5 ml) were added. After stirring at –5 °C for 20 minutes, and warming to room temperature, the reaction was stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3 × 20 ml). The combined the organic layers were washed with saturated aqueous NH_4Cl (3 × 20 ml). After drying over Na_2SO_4, the mixture was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography on silica with 0–10% ethyl acetate in hexanes to provide the title compound.

Compound 150B

ethyl 3,3-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0461] The title compound was prepared by substituting Compound 150A for Compound 101A in the procedure for Compound 101B.

Compound 150C

ethyl 2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarboxylate

[0462] The title compound was prepared by substituting Compound 150B for Compound 101B in the procedure for Compound 101C.

Compound 150D

(2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methanol

[0463] In a 200 ml round-bottomed flask was added Compound 150C (0.97 g) and lithium borohydride (0.47 g) in ether (20 ml) to give a suspension. Methanol (2.2 ml) was added slowly. The mixture was refluxed overnight. The reaction was then cooled, and methanol was added to quench the reaction. 1N aqueous HCl was then added until the pH<7, and ether (3 × 30 ml) was used to extract the product. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography on silica with 0–25% ethyl acetate in hexanes to provide the title compound.

Compound 150E

2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarbaldehyde

[0464] Into a 100 ml round-bottomed flask was added Compound 150D (0.3 g) and Dess-Martin Periodinane (0.6 g) in dichloromethane (10 ml) to give a suspension. The mixture was stirred at room temperature overnight. After filtration, the mixture was washed with saturated aqueous $NaHCO_3$ (2 × 20 ml), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica with 0–25% ethyl acetate in hexanes to provide the title compound.

Compound 150F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0465] The title compound was prepared by substituting Compound 150E for 4'-chlorobiphenyl-2-carboxaldehyde and Compound 15F for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 150G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0466] The title compound was prepared by substituting Compound 150F for Compound 101E in the procedure for Compound 101F.

Compound 150H

4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0467] The title compound was prepared by substituting Compound 150G for Compound 3J and Compound 1F for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethyl sulfoxide-d_6) δ 11.50 (s, 1H), 8.36 (m, 1H), 8.32 (m, 1H), 7.91 (d, 1H), 7.59 (m, 2H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (m, 1H), 6.94 (d, 2H), 6.79 (d, 1H), 6.60 (m, 1H), 6.29 (m, 1H), 6.24 (d, 1H), 3.83 (m, 2H), 3.25 (m, 4H), 2.98 (m, 4H), 2.42 (s, 2H), 2.14 (m, 6H), 1.60 (m, 6H), 1.25 (m, 3H), 0.86 (s, 6H).

Compound 151

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 151A

1-(1,3-difluoropropan-2-yl)azetidin-3-amine

[0468] To a solution of tert-butyl azetidin-3-ylcarbamate (0.256 g) and 1,3-difluoropropan-2-one (0.154 g) in dichloromethane (2 ml) was added sodium triacetoxyborohydride (0.473 g) and the reaction was allowed to stirred at room temperature. After 16 hours, the reaction was quenched with saturated $NaHCO_3$ solution (10 ml) and extracted into dichloromethane (25 ml). The organic layer was dried and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.5% to 3.5% methanol/dichloromethane followed by treatment with HCl (4.0M in dioxane, 3 ml) and methanol (0.5 ml) for 2 hours gave the title compound after concentration.

Compound 151B

4-(1-(1,3-difluoropropan-2-yl)azetidin-3-ylamino)-3-nitrobenzenesulfonamide

[0469] To a suspension of 4-chloro-3-nitrobenzenesulfonamide (0.225 g) and 1-(1,3-difluoropropan-2-yl)azetidin-3-amine (0.193 g) in dioxane (5 ml) was added diisopropylamine (0.832 ml). The reaction was sonicated and then heated to 100°C. After stirring overnight, the reaction was concentrated and loaded onto silica gel (GraceResolv 12 g) and eluted with a gradient of 0.5% to 3.5% methanol/dichloromethane to give the title

compound.

Compound 151C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0470] The title compound was prepared by substituting Compound 151B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 11.54 - 11.28 (m, 1H), 8.54 (d, 1H), 8.45 (s, 1H), 8.01 (d, 1H), 7.82 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (d, 1H), 6.67 (d, 1H), 6.37 (s, 1H), 6.20 (s, 1H), 4.64 - 4.23 (m, 6H), 3.81 (s, 2H), 3.08 (s, 4H), 2.75 (s, 3H), 2.15 (s, 7H), 1.95 (s, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

Compound 152

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 152A

tert-butyl (1-(methylsulfonyl)pyrrolidin-3-yl)methylcarbamate

[0471] The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in the procedure for Compound 147A.

Compound 152B

(1-(methylsulfonyl)pyrrolidin-3-yl)methanamine

[0472] The title compound was prepared by substituting Compound 152A for Compound 147A in the procedure for Compound 147B.

Compound 152C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0473] The title compound was prepared by substituting Compound 152B for Compound 147B in the procedure for Compound 147C. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.60 (s, 1H), 8.49 (m, 2H), 7.99 (s, 1H), 7.73 (m, 1H), 7.53 (d, 1H), 7.47 (s, 1H), 7.42 (m,

1H), 7.34 (d, 2H), 7.04 (m, 3H), 6.65 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 3.41 (m, 4H), 3.22 (m, 2H), 3.03 (m, 4H), 2.89 (s, 3H), 2.73 (m, 2H), 2.59 (m, 1H), 2.17 (m, 6H), 2.00 (m, 4H), 1.68 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 153

N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 153A

tert-butyl (1-acetylpyrrolidin-3-yl)methylcarbamate

[0474] The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate and acetyl chloride for methanesulfonyl chloride in the procedure for Compound 147A.

Compound 153B

1-(3-(aminomethyl)pyrrolidin-1-yl)ethanone

[0475] The title compound was prepared by substituting Compound 153A for Compound 147A in the procedure for Compound 147B.

Compound 153C

N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0476] The title compound was prepared by substituting Compound 153B for Compound 147B in the procedure for Compound 147C. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.62 (m, 1H), 8.54 (s, 1H), 8.03 (m, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.35 (t, 2H), 7.09 (s, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.20 (s, 1H), 3.56 (m, 1H), 3.42 (m, 4H), 3.43 (m, 4H), 3.23 (m, 1H), 3.07 (m, 4H), 2.74 (m, 2H), 2.16 (m, 6H), 1.93 (m, 5H), 1.38 (t, 2H), 0.93 (s, 6H).

Compound 154

N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 154A

(R)-tert-butyl 1-acetylpyrrolidin-3-ylcarbamate

[0477] The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate and acetyl chloride for methanesulfonyl chloride in the procedure for Compound 147A.

Compound 154B

(R)-1-(3-aminopyrrolidin-1-yl)ethanone

[0478] The title compound was prepared by substituting Compound 154A for Compound 147A in the procedure for Compound 147B.

Compound 154C

N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0479] The title compound was prepared by substituting Compound 154B for Compound 147B in the procedure for Compound 147. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.61 (s, 1H), 8.50 (s, 1H), 8.17 (d, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.10 (m, 1H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.34 (m, 1H), 3.81 (m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 3.05 (m, 4H), 2.74 (s, 2H), 2.19 (m, 9H), 1.96 (m, 5H), 1.38 (t, 2H), 0.94 (s, 6H).

Compound 155

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0480] The title compound was prepared as described in the procedure for Compound 120B using 3-methoxy-2,2-dimethylpropan-1-amine in place of Compound 120A. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.32 (s, 1H), 8.92 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.46 - 7.55 (m, 3H), 7.34 (d, 2H), 7.08 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36 - 6.42 (m, 1H), 6.19 (d, 1H), 3.25 - 3.30 (m, 5H), 3.19 (s, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.96 (s, 6H), 0.92 (s, 6H).

Compound 156

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-

({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 156A

4-(((1R,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

[0481] The title compound was prepared by substituting (1R,3R)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 156B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0482] The title compound was prepared by substituting Compound 156A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.29 (s, 1H), 8.62 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.85 (d, 1H), 6.74 (dd, 1H), 6.54 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H), 2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s, 2H), 1.90 (m, 1H), 1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

Compound 157

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 157A

4-(((1S,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

[0483] The title compound was prepared by substituting (1S, 3S)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 157B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0484] The title compound was prepared by substituting Compound 157A for Compound

130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.03 (s, 1H), 9.29 (s, 1H), 8.60 (t, 1H), 8.44 (d, 1H), 8.32 (dd, 1H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.55 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H), 2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s, 2H), 1.90 (m, 1H), 1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

Compound 158

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 158A

4-(((1S,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

[0485] The title compound was prepared by substituting (1S, 3R)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 158B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0486] The title compound was prepared by substituting Compound 158A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.94 (s, 1H), 9.25 (d, 1H), 8.59 (t, 1H), 8.48 (d, 1H), 8.27 (m, 2H), 7.66 (m, 2H), 7.45 (d, 2H), 7.08 (d, 2H), 6.77 (dd, 1H), 6.72 (d, 1H), 6.60 (d, 1H), 6.47 (m, 1H), 4.53 (m, 1H), 3.30 (m, 2H), 3.06 (m, 4H), 2.78 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.98 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 159

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 159A

4-(((1R,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

[0487] The title compound was prepared by substituting (1R, 3S)-3-

hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 159B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0488] The title compound was prepared by substituting Compound 158A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.02 (s, 1H), 9.28 (d, 1H), 8.59 (t, 1H), 8.44 (d, 1H), 8.29 (d, 1H), 8.13 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.82 (dd, 1H), 6.74 (d, 1H), 6.55 (d, 1H), 6.48 (m, 1H), 4.53 (m, 1H), 3.34 (m, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.97 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 160

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0489] The title compound was prepared by substituting (S)-3-aminopiperidin-2-one for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.68 (br s, 1H), 8.88 (d, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.95 (br s, 1H), 7.83 (dd, 1H), 7.55-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.41 (m, 1H), 3.22 (m, 2H), 3.09 (br s, 4H), 2.78 (br s, 2H), 2.35-2.09 (m, 8H), 1.96 (br s, 2H), 1.86 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 161

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}methyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 161A

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)azetidine-1-carboxylate

[0490] Compound 82 (305 mg). tert-butyl 3-(aminomethyl)azetidine-1-carboxylate (86

mg) and diisopropyl amine (0.202 ml) in dioxane (3 ml) were heated to 110°C. After stirring overnight, the reaction was concentrated. Silica gel chromatography (Reveleris, 12 g) eluting with a gradient of 0.5% to 3% methanol/dichloromethane (flow = 36 ml/minute) gave the title compound.

Compound 161B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(azetidin-3-ylmethylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[0491] To a solution of Compound 161A (0.257 g) in dichloromethane (5 ml) was added trifluoroacetic acid (0.211 ml). After 30 minutes an additional 0.2 ml of trifluoroacetic acid was added. After 3 hours, the reaction was concentrated to give the title compound.

Compound 161C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}methyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0492] A solution of Compound 161B (0.118 g), sodium triacetoxyborohydride (0.035 g) and 1,3-difluoropropan-2-one (0.012 g) were stirred together in dichloromethane (1 ml) overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 ml) and extracted into dichloromethane (30 ml). The organic layer was dried and concentrated. Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.5% to 3.5% methanol/dichloromethane over 30 minutes (flow = 36 ml/min) gave the title compound. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 11.47 - 11.21 (m, 1H), 8.85 (s, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.54 - 7.45 (m, 3H), 7.33 (s, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.43 (dt, 4H), 3.56 (t, 2H), 3.46 (s, 2H), 3.12 (m, 6H), 2.74 (m, 3H), 2.17 (m, 7H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

Compound 162

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0493] The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in the procedure for Compound 161C. ^{1}H NMR (300 MHz,

dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 11.51 - 11.03 (m, 1H), 8.81 (s, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.57 (s, 2H), 4.43 - 4.35 (m, 2H), 3.82 (s, 1H), 3.59 (t, 2H), 3.44 (t, 2H), 3.20 (s, 2H), 3.06 (s, 4H), 2.73 (s, 3H), 2.18 (s, 6H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

Compound 163

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 163A

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)piperidine-1-carboxylate

[0494] The title compound was prepared by substituting tert-butyl 4-(aminomethyl)piperidine-1-carboxylate for 1-acetylpiperidin-4-amine in the procedure for Compound 53B.

Compound 163B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylmethylamino)phenylsulfonyl)benzamide

[0495] The title compound was prepared by substituting Compound 163A for Compound 1A in the procedure for Compound 1B.

Compound 163C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0496] The title compound was prepared by substituting Compound 163B for Compound 161B and oxetan-3-one for 1,3-difluoropropan-2-one in the procedure for Compound 161C. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.60 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.55 (t, 2H), 4.46 (t, 2H), 3.52 (br s, 1H), 3.28 (m, 2H), 3.17 (d, 1H), 3.06 (m, 4H), 2.82 (m, 2H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (m, 3H), 1.72 (m, 3H), 1.38 (t,

2H), 1.28 (m, 2H), 0.92 (s, 6H).

Compound 164

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0497] The title compound was prepared by substituting Compound 163B for (S)-tert-butyl pyrrolidin-3-ylcarbamate in the procedure for Compound 142A. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.96 (br s, 1H), 11.62 (br s, 1H), 8.50 (m, 2H), 7.98 (d, 1H), 7.72 (m, 1H), 7.52 (d, 1H), 7.45 (m, 2H), 7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.22 (d, 1H), 3.28 (m, 3H), 3.04 (m, 5H), 2.72 (s, 2H), 2.64 (m, 1H), 2.64 (m, 1H), 2.36 (m, 1H), 2.16 (m, 7H), 1.95 (s, 2H), 1.68 (m, 3H), 1.38 (t, 2H), 1.18 (m, 3H), 0.94 (s, 6H), 0.35 (m, 3H).

Compound 165

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 165A

4-((4-(2-fluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0498] The title compound was prepared by substituting 2-fluoro-ethyl bromide for methyl iodide in the procedure for Compound 134B.

Compound 165B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0499] The title compound was prepared by substituting Compound 165A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 3.93 (m, 1H), 4.63, 4.51(dt, 2H), 3.95-3.85 (m, 2H), 3.68 (dt, 1H), 3.43-3.37 (m, 2H), 3.07 (m, 4H), 2.92 (d, 1H), 2.77 (s, 2H), 2.65 (m, 2H), 2.59 (m, 1H), 2.26 (m, 2H), 2.17-2.08 (m, 5H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 166

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 166A

4-((4-(2,2-difluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0500] The title compound was prepared by substituting 2,2-difluoro-ethyl bromide for methyl iodide in the procedure for Compound 134B.

Compound 166B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0501] The title compound was prepared by substituting Compound 166A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 6.31, 6.20, 6.09 (tt, 1H), 3.90 (m, 1H), 3.85 (d, 1H), 3.67 (dt, 1H), 3.49-3.30 (m, 2H), 3.07 (m, 4H), 2.84 (d, 1H), 2.82-2.75 (m, 4H), 2.69 (d, 1H), 2.33 (dt, 1H), 2.27-2.20 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 167

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 167A

4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0502] The title compound was prepared by substituting Compound 173A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 167B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-

b]pyridin-5-yloxy)benzamide

[0503] The title compound was prepared by substituting Compound 167A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) 11.69 (s, 1H), 8.39 (s, 1H), 8.09 (d, 1H), 8.04 (d, 1H), 7.52 (m, 4H), 7.35 (d, 2H), 7.05 (m, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.57 (t, 2H), 4.48 (m, 2H), 4.38 (d, 2H), 4.02 (m, 1H), 3.63 (m, 2H), 3.08 (m, 4H), 2.74 (m, 4H), 2.17 (m, 6H), 1.88 (m, 6H), 1.40 (t, 2H), 0.93 (s, 6H).

Compound 168

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 168A

(S)-methyl 4,4-difluoropyrrolidine-2-carboxylate

[0504] (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate (0.472 g) in CH_2Cl_2 (1 ml) was treated with trifluoroacetic acid (1.4 ml), stirred at ambient temperature for 4 hours, and concentrated. The product was free-based using a MEGA BE-SCX column with 1:1 CH_2Cl_2/methanol as eluent for the trifluoroacetic acid. The product was released from the column with 5% (7 M ammonia in methanol) in CH_2Cl_2 as eluent.

Compound 168B

(S)-methyl 4,4-difluoro-1-(oxetan-3-yl)pyrrolidine-2-carboxylate

[0505] The title compound was prepared by substituting Compound 168A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 168C

(S)-(4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl)methanol

[0506] Compound 168B (0.180 g) in tetrahydrofuran (3 ml) was treated sequentially with a solution of calcium chloride (0.245 g) in ethanol (3 ml) and $NaBH_4$ (0.167 g) and then stirred at ambient temperature for 7 hours. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 50% ethyl acetate in hexanes as eluent to give the product.

Compound 168D

(S)-4-((4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl)methoxy)-3-nitrobenzenesulfonamide

[0507] The title compound was prepared by substituting Compound 168C for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 168E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0508] The title compound was prepared by substituting Compound 168D for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.38 (s, 1H), 8.06 (m, 2H), 7.49 (m, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.21 (s, 1H), 4.54 (m, 3H), 4.43 (t, 1H), 4.23 (m, 1H), 4.12 (m, 2H), 3.44 (m, 2H), 3.12 (m, 7H), 2.58 (m, 1H), 2.29 (m, 7H), 1.97 (s, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

Compound 169

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 169A

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

[0509] The title compound was prepared as described in the procedure for Compound 53B by replacing 1-acetylpiperidin-4-amine with tert-butyl 3-(aminomethyl)morpholine-4-carboxylate.

Compound 169B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-(morpholin-3-ylmethylamino)-3-nitrophenylsulfonyl)benzamide

[0510] The title compound was prepared as described in the procedure for Compound 139B by replacing Compound 139A with Compound 169A.

Compound 169C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0511] The title compound was prepared as described in the procedure for Compound 139C by replacing Compound 139B and oxetan-3-one with Compound 169B and tetrahydropyran-4-one, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.77 (m, 1H), 8.57 (d, 1H), 8.05 (d, 1H), 7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 2H), 7.03 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 3.86 (m, 2H), 3.72 (m, 2H), 3.11 (m, 6H), 2.74 (m, 4H), 2.20 (m, 6H), 1.95 (m, 3H), 1.51 (m, 7H), 0.92 (s, 6H).

Compound 170

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclobutylmorpholin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0512] The title compound was prepared as described in the procedure for Compound 139C by replacing Compound 139B and oxetan-3-one with Compound 169B and cyclobutanone. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.72 (s, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 3H), 7.03 (m, 4H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.18 (d, 1H), 3.47 (m, 3H), 3.10 (m, 6H), 2.72 (m, 6H), 2.25 (m, 8H), 1.95 (m, 4H), 1.56 (m, 3H), 1.38 (m, 2H), 0.92 (s, 6H).

Compound 171

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0513] The title compound was prepared as described in the procedure for Compound 139C by replacing Compound 139B and oxetan-3-one with Compound 169B and 3-oxotetrahydrofuran, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 8.66 (s, 1H), 8.53 (d, 1H), 8.01 (d, 1H), 7.80 (d, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.98 (d, 1H), 6.66 (dd, 1H), 6.37 (d, 1H), 6.19 (d, 1H), 3.68 (m, 8H), 3.05 (m, 6H), 2.85 (m, 3H), 2.73 (s, 2H), 2.25 (m, 6H), 1.91 (m, 3H), 1.37 (m, 3H), 0.95 (m, 6H).

Compound 172

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0514] The title compound was prepared by substituting Compound 163B for tert-butyl piperazine-1-carboxylate and 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 11.40 (br s, 1H), 8.57 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (m 1H), 6.19 (d, 1H), 4.63 (d, 2H), 4.53 (d, 2H), 3.28 (m, 2H), 3.07 (m, 4H), 2.89 (m, 2H), 2.74 (m, 2H), 2.40 (m, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.67 (m, 3H), 1.38 (t, 2H), 1.23 (m, 3H), 0.94 (s, 6H).

Compound 173

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 173A

4-((4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0515] The title compound was prepared by substituting Compound 126B for Compound 1A in the procedure for Compound 1B.

Compound 173B

4-((1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0516] To Compound 173A (0.24 g) in methanol (3 ml) was added 3Å molecular sieves (0.1 g), followed sequentially by acetic acid (0.31 ml), (1-ethoxycyclopropoxy)trimethylsilane (0.64 ml), and sodium cyanoborohydride (0.148 g). The reaction was heated under reflux overnight. After cooling, the reaction mixture was loaded onto a silica gel column. After drying, the column was eluted with 100:2:0.2 ethyl acetate/methanol/NH_4OH to give the title compound.

Compound 173C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0517] The title compound was prepared by substituting Compound 173B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.33 (s, 1H), 8.01 (m, 2H), 7.53 (d, 1H), 7.48-7.49 (m, 2H), 7.34-7.38 (m, 3H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 3.70-3.77 (m, 2H), 3.07 (s, 4H), 2.92 (s, 2H), 2.80 (s, 2H), 2.58 (s, 2H), 2.25 (s, 4H), 2.13-2.16 (m 2H), 1.38 (t, 2H), 0.92 (s, 6H), 0.40-0.49 (m, 4H).

Compound 174

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0518] A suspension of Compound 53A (120 mg), (4-methoxyphenyl)methanamine (31 mg) and Hunig's Base (0.159 ml) in dimethylsulfoxide (2 ml) was heated for 2 hours at 150°C in a Biotage Initiator microwave reactor. The reaction mixture was diluted with methanol (2 ml) and purified by reverse phase HPLC (C8, 30% – 100% CH_3CN/water/0.1% trifluoroacetic acid). ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.07 (s, 1H), 9.32 (d, 1H), 9.17 (t, 1H), 8.43 (d, 1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.38 (d, 2H), 7.07 (d, 2H), 6.97 - 7.02 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.55 (d, 2H), 3.68 (s, 3H), 3.03 - 3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 175

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0519] The title compound was prepared by substituting (3-trifluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in the procedure for Compound 174. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.38 (t, 1H), 9.31 (d, 1H), 8.42 (d, 1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.65 (ddd, 2H), 7.41 - 7.46 (m, 3H), 7.36 - 7.40 (m, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (d, 1H), 4.73 (d, 2H), 3.02 - 3.08 (m, 4H), 2.77 (s, 2H), 2.22 - 2.28 (m, 2H), 2.09 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 176

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0520] The title compound was prepared by substituting (3-methoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in the procedure for Compound 174. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.27 - 9.32 (m, 2H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.64 - 7.67 (m, 2H), 7.44 (d, 2H), 7.32 (t, 1H), 7.14 (s, 1H), 7.04 - 7.09 (m, 3H), 6.88 - 6.94 (m, 2H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.48 - 6.50 (m, 1H), 4.64 (d, 2H), 3.68 (s, 3H), 3.03 - 3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.18 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 177

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0521] The title compound was prepared by substituting (4-difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in the procedure for Compound 174. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.32 (d, 1H), 9.28 (t, 1H), 8.42 (d, 1H), 8.28 (dd, 1H), 8.07 (d, 1H), 7.66 (t, 1H), 7.64 (d, 1H), 7.58 (s, 1H), 7.44 (s, 2H), 7.26 (s, 1H), 7.25 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.03 - 3.10 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.11 - 2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 178

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0522] The title compound was prepared by substituting 1,4-dioxa-spiro[4.5]dec-8-ylamine for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.26 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.89 (s, 4H), 3.78 (m, 1H), 3.07 (br s, 4H), 2.78 (br s, 2H), 2.28-2.11

(m, 6H), 2.00-1.88 (m, 4H), 1.75-1.57 (m, 4H), 1.54-1.35 (m, 4H), 0.92 (s, 6H).

Compound 179

trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 179A

tert-butyl trans-4-acetamidocyclohexylcarbamate

[0523] Tert-butyl (trans)-4-aminocyclohexylcarbamate (1.500 g) and triethylamine (2.93 ml, 2.125 g) were added to dichloromethane and stirred until the tert-butyl (trans)-4-aminocyclohexylcarbamate had dissolved completely. Acetyl chloride (0.577 g) was added slowly, and the solution was stirred at room temperature for 16 hours. The solvent was removed, and the residue taken up in ethyl acetate, washed with pH 4 buffer, washed with brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum.

Compound 179B

N-(trans-4-aminocyclohexyl)acetamide

[0524] The title compound was prepared by substituting Compound 179A for Compound 1A in the procedure for Compound 1B.

Compound 179C

trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0525] The title compound was prepared by substituting Compound 179B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.20 (d, 1H), 8.04 (d, 1H), 7.82-7.76 (m, 2H), 7.53-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.57 (m, 2H), 3.07 (br s, 4H), 2.75 (br s, 2H), 2.28-2.10 (m, 6H), 2.03-1.94 (m, 4H), 1.83 (d, 2H), 1.80 (s, 3H), 1.55-1.24 (m, 6H), 0.92 (s, 6H).

Compound 180

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 180A

(R)-tert-butyl 1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

[0526] To a solution of (R)-tert-butyl pyrrolidin-3-ylcarbamate (500 mg) and 1,1-difluoro-2-iodoethane (618 mg) in N,N-dimethylformamide (6 ml) was added N-ethyl-N-isopropylpropan-2-amine (1.403 ml) and the mixture was stirred at 70°C for 72 hours. The reaction mixture was concentrated and the crude product was purified on silica gel with methanol/dichloromethane.

Compound 180B

(R)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

[0527] To a solution of Compound 180A (525 mg) in a mixture of dichloromethane (3 ml) and methanol (4.0 ml) was added hydrogen chloride, 4M in dioxane (5.24 ml) and the reaction was stirred for 1.5 hours. The reaction was concentrated and the crude material was taken up in dichloromethane and the solvent evaporated, then taken up in ether and the solvent evaporated, and then dried on high vacuum.

Compound 180C

(R)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

[0528] The title compound was prepared by substituting Compound 180B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 180D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0529] The title compound was prepared by substituting Compound 180C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500 MHz, pyridine- d_5) δ 13.02 (m, 1H), 9.27 (d, 1H), 8.55 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04 - 6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83 - 2.95 (m, 4H), 2.74 - 2.82 (m, 3H), 2.47 (m, 1H), 2.09 - 2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 181

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-

{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 181A

(S)-tert-butyl 1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

[0530] The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane and (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl pyrrolidin-3-ylcarbamate in the procedure for Compound 180A.

Compound 181B

(S)-1-(2-fluoroethyl)pyrrolidin-3-amine

[0531] The title compound was prepared by substituting Compound 181A for Compound 180A in the procedure for Compound 180B.

Compound 181C

(S)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

[0532] The title compound was prepared by substituting Compound 181B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 181D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0533] The title compound was prepared by substituting Compound 181C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500 MHz, pyridine- d_5) δ 13.00 (m, 1H), 9.26 (d, 1H), 8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63 - 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.51 (t, 1H), 4.05 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66 - 2.79 (m, 6H), 2.39 (q, 1H), 2.20 - 2.29 (m, 3H), 2.15 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 182

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 182A

(S)-tert-butyl 1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

[0534] The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl pyrrolidin-3-ylcarbamate in the procedure for Compound 180A.

Compound 182B

(S)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

[0535] The title compound was prepared by substituting Compound 182A for Compound 180A in the procedure for Compound 180B.

Compound 182C

(S)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

[0536] The title compound was prepared by substituting Compound 182B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 182D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0537] The title compound was prepared by substituting Compound 182C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500 MHz, pyridine- d_5) δ 13.02 (m, 1H), 9.27 (d, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04 - 6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83 - 2.95 (m, 4H), 2.74 - 2.82 (m, 3H), 2.47 (m, 1H), 2.09 - 2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 183

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,b]pyridin-5-yloxy)benzamide

Compound 183A

(R)-tert-butyl 1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

[0538] The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane in the procedure for Compound 180A.

Compound 183B

(R)-1-(2-fluoroethyl)pyrrolidin-3-amine

[0539] The title compound was prepared by substituting Compound 183A for Compound

180A in the procedure for Compound 180B.

Compound 183C

(R)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

[0540] The title compound was prepared by substituting Compound 183B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 183D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0541] The title compound was prepared by substituting Compound 183C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500 MHz, pyridine- d_5) δ 13.00 (m, 1H), 9.26 (d, 1H), 8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63 - 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.50 (t, 1H), 4.04 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66 - 2.79 (m, 6H), 2.39 (q, 1H), 2.19 - 2.28 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 184

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 184A

(S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

[0542] To a solution of (S)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 ml) was added sodium hydride (0.238 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.295 g) was added and reaction stirred at room temperature. After 1 hour, the reaction was partitioned between water (25 ml) and dichloromethane (50 ml) and the reaction quenched with 1N aqueous HCl (5.96 ml). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.2% to 2% methanol/dichloromethane over 30 minutes (flow = 36 m/minute) gave the title compound.

Compound 184B

(S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)benzenesulfonamide

[0543] To (S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate (0.433 g) was added hydrogen chloride (4.0M in dioxane, 1.0 ml). After stirring for 1 hour, the reaction was concentrated and partitioned between dichloromethane (50 ml) and saturated aqueous $NaHCO_3$ solution (50 ml). The aqueous layer was separated and concentrated. The residue was triturated with methanol (100 ml), filtered and concentrated and treated with sodium cyanoborohyde (0.068 g) and cyclobutanone (0.078 g) and stirred overnight. The reaction was partitioned between dichloromethane (50 ml) and water (25 ml) and saturated aqueous $NaHCO_3$ (10 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

Compound 184C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0544] The title compound was prepared by substituting Compound 184B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 11.45 – 11.01 (m, 1H), 8.30 (d, 1H), 7.98 (dd, 2H), 7.60 – 7.43 (m, 3H), 7.33 (t, 3H), 7.04 (d, 2H), 6.74 – 6.59 (m, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.49 (td, 2H), 4.33 (s, 1H), 4.13 (dd, 2H), 3.79 (s, 2H), 3.44 (dd, 2H), 3.07 (s, 4H), 2.74 (d, 6H), 2.19 (d, 6H), 1.98 (d, 2H), 1.74 – 1.52 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

Compound 185

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0545] The title compound was prepared by substituting (4-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in the procedure for Compound 174. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.32 (d, 1H), 9.14 (s, 1H), 8.44 (d, 1H), 8.28 (dd, 1H), 8.09 (d, 1H), 7.65 - 7.68 (m, 2H), 7.44 (d, 2H), 7.37 - 7.41 (m, 2H), 7.19 (s, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.54 (d, 2H), 3.02 - 3.09 (m, 4H), 2.77 (s, 2H), 2.22 - 2.29 (m, 2H), 2.10 - 2.17 (m, 4H), 1.97 (d, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 186

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0546] The title compound was prepared by substituting (3-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in the procedure for Compound 174. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.27 - 9.32 (m, 2H), 8.43 (d, 1H), 8.20 (dd, 1H), 8.08 (d, 1H), 7.66 (t, 2H), 7.44 (d, 2H), 7.33 (t, 1H), 7.25 (s, 1H), 7.13 (dd, 1H), 7.07 (d, 2H), 6.98 (d, 1H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.02 - 3.09 (m, 4H), 2.77 (s, 2H), 2.22 - 2.28 (m, 2H), 2.09 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 187

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0547] The title compound was prepared by substituting (3-difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in the procedure for Compound 174. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.34 (t, 1H), 9.30 (d, 1H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.66 (ddd, 2H), 7.40 - 7.45 (m, 3H), 7.36 (t, 1H), 7.27 - 7.30 (m, 2H), 7.19 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.69 (d, 2H), 3.02 - 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.09 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 188

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 188A

cis-methyl 3-morpholinocyclopentanecarboxylate

[0548] The title compound was prepared by substituting methyl 3-oxocyclopentanecarboxylate for 4'-chlorobiphenyl-2-carboxaldehyde and morpholine for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 188B

cis-3-morpholinocyclopentyl)methanol

[0549] The title compound was prepared by substituting Compound 188A for Compound 101C in the procedure for Compound 101D.

Compound 188C

4-((cis-3-morpholinocyclopentyl)methoxy)-3-nitrobenzenesulfonamide

[0550] The title compound was prepared by substituting Compound 188B for (1,4-dioxan-2-yl)methanol in the procedure for Compound 12A.

Compound 188D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0551] The title compound was prepared by substituting Compound 188C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.57 (s, 1H), 8.17 (m, 1H), 7.94 (m, 1H), 7.82 (m, 1H), 7.56 (d, 1H), 7.44 (t, 1H), 7.34 (m, 3H), 7.16 (m, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.24 (d, 1H), 4.06 (m, 2H), 3.62 (m, 4H), 3.03 (m, 4H), 2.75 (s, 2H), 2.35 (m, 2H), 2.19 (m, 6H), 2.03 (m, 2H), 1.96 (s, 2H), 1.78 (m, 2H), 1.51 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H)

Compound 189

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 189A

trans-(4-methanesulfonylamino-cyclohexyl)-carbamic acid tert-butyl ester

[0552] The title compound was prepared by substituting methanesulfonyl chloride for acetyl chloride in the procedure for Compound 179A.

Compound 189B

trans-N-(4-aminocyclohexyl)-methanesulfonamide

[0553] The title compound was prepared by substituting Compound 189A for Compound 1A in the procedure for Compound 1B.

Compound 189C

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0554] The title compound was prepared by substituting Compound 189B for 1-acetylpiperidin-4-amine in the procedure for Compound 53B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.68 (br s, 1H), 8.55 (d, 1H), 8.18 (d, 1H), 8.04 (d, 1H), 7.84 (d, 1H), 7.79 (dd, 1H), 7.56-7.47 (m, 3H), 7.34 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.56 (m, 1H), 3.17 (m, 1H), 3.07 (br s, 4H), 2.93 (s, 3H), 2.75 (br s, 2H), 2.28-2.10 (m, 6H), 2.05-1.90 (m, 6H), 1.55-1.32 (m, 6H), 0.92 (s, 6H).

Compound 190

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 190A

4-(1-cyclopropylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0555] The title compound was prepared as described in the procedure for Compound 17A by replacing (tetrahydropyran-4-yl)methylamine with 4-amino-1-cyclopropylpiperidine.

Compound 190B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0556] The title compound was prepared as described in the procedure for Compound 1G by replacing Compound 1E and Compound 1F with Compound 3J and Compound 190A, respectively. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.13 (d, 1H), 8.02 (d, 1H), 7.91 (m, 1H), 7.48 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (m, 2H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.64 (m, 1H), 3.13 (m, 5H), 2.73 (m, 5H), 2.22 (m, 6H), 1.92 (m, 5H), 1.70 (m, 1H), 1.41 (m, 5H), 0.94 (s, 6H), 0.41 (m, 4H).

Compound 191

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-

b]pyridin-5-yloxy)benzamide

Compound 191A

3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide

[0557] To a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 ml) was added sodium hydride (0.223 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.276 g) was added and reaction stirred at room temperature. After 1 hour the reaction was partitioned between water (25 ml) and dichloromethane (50 ml) and the reaction quenched with 1N aqueous HCl (5.57 ml). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Treatment with HCl (4.0M in dioxane, 2 ml) and methanol (2 ml) for 1 hour, followed by concentration, trituration with dichloromethane and filtration gave the title compound.

Compound 191B

3-nitro-4-((1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

[0558] To a suspension of 3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide (0.100 g) and cyclobutanone (0.030 g) in methanol (1 ml) was added sodium cyanoborohydride (0.027 g). After stirring overnight, the reaction was quenched with saturated $NaHCO_3$ (5 ml) and extracted into dichloromethane (2 × 10 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

Compound 191C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0559] The title compound was prepared by substituting Compound 191B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 11.46 - 10.46 (m, 1H), 8.29 (s, 1H), 8.00 (d, 2H), 7.61 - 7.41 (m, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.66 (d, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.67 - 4.40 (m, 4H), 4.08 (d, 2H), 3.06 (s, 4H), 2.78 (s, 4H), 2.19 (m, 6H), 1.96 (s, 4H), 1.79 (m, 4H), 1.39 (s, 4H), 0.93 (s, 6H).

Compound 192

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 192A

4-((4-fluoro-1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0560] A mixture of Compound 173A (0.4 g), dihydro-2H-pyran-4(3H)-one (0.179 g), sodium cyanoborohydride (0.112 g), and acetic acid (0.5 ml) in tetrahydrofuran (3 ml) was stirred overnight. The solvents were removed under reduced pressure. The residue was purified with flash column chromatography on silica gel eluting with 100:5:0.5 ethyl acetate/methanol/NH_4OH to give the desired product.

Compound 192B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0561] The title compound was prepared by substituting Compound 192A for Compound 11B in the procedure for Compound 11D. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.58 (s, 1H), 8.25 (s, 1H), 7.96 (d, 1H), 7.93 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.34-7.37 (m, 3H), 7.26 (d, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.34 (dd, 1H), 6.23 (d, 1H), 4.34 (d, 2H), 3.93 (dd, 2H), 3.03 (s, 6H), 2.76 (s, 4H), 2.09-2.22 (m, 6H), 1.96 (s, 2H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 193

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 193A

4-((4-fluoro-1-(tetrahydrofuran-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0562] The title compound was prepared by substituting dihydrofuran-3(2H)-one for dihydro-2H-pyran-4(3H)-one in the procedure for Compound 192A.

Compound 193B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0563] The title compound was prepared by substituting Compound 193A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1H), 8.31 (s, 1H), 7.99-8.00 (m, 2H), 7.54 (d, 1H), 7.46-7.48 (m, 2H), 7.34-7.35 (m, 3H), 7.05 (d2H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.34 (d, 2H), 3.76-3.83 (m, 3H), 3.62-3.65 (m, 2H), 3.03 (s, 4H), 2.79 (s, 4H), 2.24 (s, 2H), 2.15 (s, 2H), 1.84-1.99 (m, 8H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 194

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 194A

4-((4-fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0564] A mixture of Compound 173A (0.4 g), methanesulfonyl chloride (0.113 g), and triethylamine (0.64 ml) in dichloromethane (5 ml) was stirred overnight. The reaction mixture was loaded onto a silica gel column and eluted with 100:1 ethyl acetate:methanol to give the clean product.

Compound 194B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0565] The title compound was prepared by substituting Compound 194A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.37 (s, 1H), 8.06 (d, 1H), 8.02 (d, 1H), 7.49-7.53 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38-6.39 (m, 1H), 6.21 (d, 1H), 4.40 (d, 2H), 3.51-3.54 (m, 2H), 3.09 (s, 4H), 2.96-3.01 (m, 4H), 2.92 (s, 3H), 2.82 (s, 2H), 2.25-2.34 (m, 4H), 2.13-2.16 (m, 6H), 2.01-2.07 (m, 2H0, 1.99 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 195

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 195A

(R)-tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)pyrrolidine-1-carboxylate

[0566] The title compound was prepared by substituting (R)-tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate for 1-acetylpiperidin-4-amine in the procedure for Compound 53B.

Compound 195B

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(pyrrolidin-3-ylmethylamino)phenylsulfonyl)benzamide

[0567] The title compound was prepared by substituting Compound 195A for Compound 1A in the procedure for Compound 1B.

Compound 195C

(R)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methylamino)phenylsulfonyl)benzamide

[0568] The title compound was prepared by substituting Compound 195B for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.81 (t, 1H), 8.55 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.35 (m, 2H), 7.04 (m, 3H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.57 (m, 2H), 4.48 (m, 2H), 3.68 (m, 2H), 3.30 (m, 2H), 3.06 (m, 4H), 2.74 (m, 3H), 2.56 (m, 3H), 2.44 (m, 1H), 2.18 (m, 5H), 1.95 (m, 3H), 1.58 (m, 1H), 1.36 (m, 2H), 0.94 (s, 6H).

Compound 196

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 196A

trans-4-(4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[0569] The title compound was prepared as described in the procedure for Compound

12A by replacing (1,4-dioxan-2-yl)methanol with trans-(4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol (made according to the procedures in WO 2008/124878, incorporated herein by reference).

Compound 196B

trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(((1r,4r)-4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[0570] The title compound was prepared as described in the procedure for Compound 1G using Compound 196A in place of Compound 1F and Compound 3J in place of Compound 1E.

Compound 196C

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0571] Compound 196B (150 mg) in dichloromethane (5 ml) and methanol (2 ml) was treated with 10% aqueous HCl (3 ml) for 1 hour and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40–60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (30 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.27 (s, 1H), 8.34 (d, 1H), 7.95 - 8.08 (m, 2H), 7.47 - 7.55 (m, 3H), 7.32 - 7.40 (m, 3H), 7.01 - 7.07 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.54 (d, 1H), 3.96 - 4.06 (m, 2H), 3.10 (s, 4H), 2.84 (s, 2H), 2.05 - 2.39 (m, 6H), 1.96 (s, 2H), 1.46 - 1.93 (m, 5H), 1.39 (t, 2H), 0.98 - 1.29 (m, 4H), 0.92 (s, 6H).

Compound 197

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 197A

3-(4-(aminomethyl)phenoxy)-N,N-dimethylpropan-1-amine

[0572] 4-(3-(Dimethylamino)propoxy)benzonitrile (300 mg) in methanol (20 ml) was treated with Raney nickel (wet, 1.5 g) under H_2 (30 psi) for 4 hour. The insoluble material was filtered off and the filtrate was concentrated to provide the title compound.

Compound 197B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0573] The title compound was prepared as described in the procedure for Compound 120B using Compound 197A in place of Compound 120A. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.56 (s, 1H), 8.80 (t, 1H), 8.42 (d, 1H), 7.93 (d, 1H), 7.52 - 7.61 (m, 2H), 7.41 - 7.47 (m, 1H), 7.26 - 7.36 (m, 5H), 7.03 - 7.08 (m, 2H), 6.89 (d, 2H), 6.73 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H), 6.22 (d, 1H), 4.52 (d, 2H), 3.99 (t, 2H), 2.90 - 3.05 (m, 7H), 2.72 (s, 2H), 2.61 (s, 6H), 2.09 - 2.24 (m, 6H), 1.89 - 2.04 (m, 5H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 198

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 198A

(4-(2-morpholinoethoxy)phenyl)methanamine

[0574] The title compound was prepared as described in the procedure for Compound 197A using 4-(2-morpholinoethoxy)benzonitrile in place of 4-(3-(dimethylamino)propoxy)benzonitrile.

Compound 198B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0575] The title compound was prepared as described in the procedure for Compound 120B using Compound 198A in place of Compound 120A. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 9.00 (t, 1H), 8.56 (d, 1H), 8.02 (d, 1H), 7.72 (dd, 1H), 7.46 - 7.54 (m, 3H), 7.27 - 7.36 (m, 4H), 7.01 - 7.07 (m, 2H), 6.89 - 6.95 (m, 3H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.18 (d, 1H), 4.56 (d, 2H), 4.07 (t, 2H), 3.54 - 3.61 (m, 4H), 3.06 (s, 4H),

2.71 - 2.78 (m, 4H), 2.07 - 2.24 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 199

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(*E*)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 199A

4-[((*E*)-4-hydroxy-adamantan-1-ylmethyl)-amino]-3-nitro-benzenesulfonamide

[0576] 4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 ml) were treated with triethylamine (1 ml) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40–60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as Compound 199A and Compound 199B, respectively.

Compound 199B

4-[((*Z*)-4-hydroxy-adamantan-1-ylmethyl)-amino]-3-nitro-benzenesulfonamide

[0577] 4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 ml) were treated with triethylamine (1 ml) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40–60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as Compound 199A and Compound 199B, respectively.

Compound 199C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(*E*)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0578] The title compound was prepared as described in the procedure for Compound 11D using Compound 199A in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 11.40 (s, 1H), 8.55 (d, 1H), 8.50 (t, 1H), 8.03 (d, 1H), 7.77 (dd, 1H), 7.46 - 7.54 (m, 3H), 7.31 - 7.38 (m, 2H), 7.14 (d, 1H), 7.01 - 7.06 (m, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.63 (d, 1H), 3.02 - 3.16 (m, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 2.04 (d, 2H), 1.95 (s, 2H), 1.76 - 1.88 (m, 3H), 1.49 - 1.61 (m, 6H), 1.38 (t, 2H), 1.29 (d, 2H), 0.92 (s, 6H).

Compound 200

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(*Z*)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0579] The title compound was prepared as described in the procedure for Compound 11D using Compound 199B in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 11.39 (s, 1H), 8.55 (d, 1H), 8.51 (t, 1H), 8.04 (d, 1H), 7.77 (dd, 1H), 7.46 - 7.55 (m, 3H), 7.31 - 7.37 (m, 2H), 7.14 (d, 1H), 7.01 - 7.06 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.61 (d, 1H), 3.08 (d, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 1.79 - 1.99 (m, 7H), 1.55 - 1.69 (m, 4H), 1.49 (s, 2H), 1.38 (t, 2H), 1.22 (d, 2H), 0.92 (s, 6H).

Compound 201

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 201A

4-((1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy)-3-nitrobenzenesulfonamide

[0580] The title compound was prepared as described in the procedure for Compound 12A by replacing (1,4-dioxan-2-yl)methanol with (1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethanol.

Compound 201B

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0581] The title compound was prepared as described in the procedure for Compound 11D using Compound 201A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.35 (d, 1H), 7.95 - 8.10 (m, 2H), 7.47 - 7.58 (m, 3H), 7.30 - 7.45 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (d, 1H), 5.92 - 6.23 (m, 3H), 3.65 - 4.39 (m, 3H), 3.00 - 3.22 (m, 4H), 2.76 - 2.98 (m, 4H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.71 - 1.91 (m, 1H), 1.33 - 1.47 (m, 3H), 1.20 - 1.32 (m, 2H), 0.92 (s, 6H), 0.50 - 0.66 (m, 1H).

Compound 202

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0582] Compound 82 (140 mg) was dissolved in dioxane (3.0 ml), and 4-amino-1-methylpyrrolidin-2-one hydrochloride (30 mg) and triethylamine (0.100 ml) were added. The reaction mixture was heated at 110°C for 40 hours. The reaction was concentrated and the crude material was purified by preparative HPLC using a C18 column, 250 × 50 mm, 10μ, and eluting with a gradient of 20–100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the title compound. ^1H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.74 (d, 1H), 8.37 (br d, 1H), 8.02 (d, 1H), 7.83 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.46 (m, 1H), 3.81 (dd, 1H), 3.38 (dd, 1H), 3.08 (br m, 4H), 2.82 (dd, 1H), 2.75 (s, 5H), 2.43 (dd, 1H), 2.21 (br m, 4H), 2.16 (br t, 2H), 1.95 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 203

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 203A

4-(((1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-nitrobenzenesulfonamide

[0583] To a solution of Compound 201A (340 mg) in tetrahydrofuran (10 ml) and water (1 ml) was added N-methylmorpholine N-oxide (184 mg) and OsO_4 (2.5% in 2-methyl-2-propanol) (1.05 ml). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as Compound 203A and Compound 203B, respectively.

Compound 203B

4-(((1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-nitrobenzenesulfonamide

[0584] To a solution of Compound 201A (340 mg) in tetrahydrofuran (10 ml) and water (1 ml) was added N-methylmorpholine N-oxide (184 mg) and OsO_4 (2.5% in 2-methyl-2-propanol) (1.05 ml). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as Compound 203A and Compound 203B, respectively.

Compound 203C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0585] The title compound was prepared as described in the procedure for Compound 11D using Compound 203A in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.97 - 8.07 (m, 2H), 7.48 - 7.55 (m, 3H), 7.41 (d, 1H), 7.32 - 7.37 (m, 2H), 7.02 - 7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.07 - 4.19 (m, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09 - 2.34 (m, 8H), 2.04 - 2.09 (m, 2H), 1.93 - 2.01 (m, 3H), 1.62 - 1.77 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.67 - 0.76 (m, 1H).

Compound 204

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0586] The title compound was prepared as described in the procedure for Compound 11D using Compound 203B in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.98 - 8.07 (m, 2H), 7.49 - 7.54 (m, 3H), 7.41 (d, 1H), 7.32 - 7.36 (m, 2H), 7.02 - 7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.13 (dd, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09 - 2.35 (m, 8H), 2.07 (s, 2H), 1.93 - 2.02 (m, 3H), 1.61 - 1.80 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.66 - 0.78 (m, 1H).

Compound 205

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 205A

methyl 1,4-dioxaspiro[4.5]decane-7-carboxylate

[0587] To a solution of trimethylsilyltrifluoromethanesulfonate (0.034 ml) in dry dichloromethane (5 ml) was added 1,2-bis(trimethylsiloxy)ethane (4.55 ml) followed by methyl 3-oxocyclohexanecarboxylate (2.9 g). The reaction mixture was stirred for 3 hours at –78°C. The reaction mixture was quenched with dry pyridine (0.5 ml), poured into saturated aqueous $NaHCO_3$, and extracted with ether. The ether layer was dried over Na_2CO_3/Na_2SO_4. The reaction mixture was concentrated and purified by flash chromatography on silica with 5 to 30% ethyl acetate in hexanes to provide the title compound.

Compound 205B

1,4-dioxaspiro[4.5]decan-7-ylmethanol

[0588] The title compound was prepared by substituting Compound 205A for Compound 101C in the procedure for Compound 101D.

Compound 205C

3-nitro-4-((3-oxocyclohexyl)methoxy)benzenesulfonamide

[0589] Into a 250 ml round-bottomed flask was added sodium hydride (0.5 g) in tetrahydrofuran (10 ml) and then 1,4-dioxaspiro[4.5]decan-7-ylmethanol (0.5 g) was added. After the mixture stirred at room temperature for 20 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.65 g) was added. The mixture was stirred at room temperature for overnight. Water (20 ml) was added slowly. The aqueous layer was extracted by dichloromethane (3 × 20 ml). The combined organic layers were dried over Na_2SO_4. After filtration, and concentration of the filtrate, the residue was purified by reverse phase chromatography, eluting with 30–60% acetonitrile in water with 0.1% trifluoroacetic acid.

Compound 205D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0590] The title compound was prepared by substituting Compound 205C for Compound 11B in the procedure for Compound 11D. ^1H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.59 (s, 1H), 8.22 (s, 1H), 7.96 (d, 1H), 7.87 (m, 1H), 7.55 (d, 1H), 7.45 (t, 1H), 7.35 (m, 3H), 7.20 (m, 1H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.23 (d, 1H), 4.07 (d, 2H), 3.04 (m, 4H),

2.76 (s, 2H), 2.35 (m, 2H), 2.20 (m, 8H), 1.96 (m, 4H), 1.58 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 206

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 206A

2-chloro-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

[0591] In a 250 ml round-bottomed flask was added N,N-dimethylformamide (3.5 ml) in dichloromethane (30 ml), and the mixture was cooled to −10°C. Phosphoryl trichloride (4 ml) was added dropwise, and the solution was warmed up to room temperature. 4,4-Dimethylcyclohex-2-enone (5.5 ml) was then added slowly, and the mixture was heated to reflux overnight. The reaction mixture was cooled and quenched with a 0°C solution of sodium acetate (25 g in 50 ml water). The aqueous layer was extracted with diethyl ether (200 ml × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the product.

Compound 206B

2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

[0592] Into a 1 L round-bottomed flask was added Compound 206A (6.8 g), 4-chlorophenylboronic acid (6.5 g), and palladium (II) acetate (0.2 g) in water (100 ml) to give a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing, the mixture was stirred at 45°C for 4 hours. After cooling and filtering though silica gel in a funnel, diethyl ether (4 × 200ml) was used to extract the product. The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0–10% ethyl acetate in hexanes to provide the title compound.

Compound 206C

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoate

[0593] The title compound was prepared by substituting Compound 206B for 4'-chlorobiphenyl-2-carboxaldehyde and Compound 15F for tert-butyl piperazine-1-carboxylate

in the procedure for Compound 1A.

Compound 206D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoic acid

[0594] The title compound was prepared by substituting Compound 206C for Compound 101E in the procedure for Compound 101F.

Compound 206E

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0595] The title compound was prepared by substituting Compound 206D for Compound 3J and Compound 1F for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.61 (s, 1H), 8.49 (m, 2H), 7.99 (m, 1H), 7.72 (m, 1H), 7.53 (d, 1H), 7.41 (m, 4H), 7.12 (d, 2H), 6.99 (m, 1H), 6.66 (dd, 1H), 6.35 (m, 1H), 6.23 (d, 1H), 5.74 (d, 1H), 5.58 (d, 1H), 3.84 (m, 2H), 3.26 (m, 4H), 3.06 (m, 4H), 2.88 (s, 2H), 2.24 (m, 6H), 1.61 (m, 2H), 1.26 (m, 3H), 1.00 (s, 6H).

Compound 207

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 207A

(R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-amine

[0596] The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl azetidin-3-ylcarbamate in the procedure for Compound 151A.

Compound 207B

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

[0597] The title compound was prepared by substituting Compound 207A for Compound 151A in the procedure for Compound 151B.

Compound 207C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-

(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0598] The title compound was prepared by substituting Compound 207B for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 11.52 - 11.24 (m, 1H), 8.55 (d, 1H), 8.37 (d, 1H), 8.03 (d, 1H), 7.83 (dd, 1H), 7.57 - 7.45 (m, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.70 (d, 2H), 4.54 (d, 2H), 4.23 (s, 1H), 3.11 - 2.87 (m, 7H), 2.74 (dd, 4H), 2.35 - 2.13 (m, 7H), 1.95 (s, 2H), 1.70 (s, 1H), 1.39 (d, 2H), 0.92 (s, 6H).

Compound 208

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 208A

2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-iodo-3-(trifluoromethyl)pyridine

[0599] A mixture of Compound 37C (0.537 g), 5-iodo-3-(trifluoromethyl)pyridin-2-ol (1.156 g), and triphenylphosphine (1.574 g) in tetrahydrofuran (20 ml) was cooled to 0 °C. To this solution was added (E)-di-tert-butyl diazene-1,2-dicarboxylate (0.921 g). The reaction mixture was stirred overnight. The solvent was removed, and the residue was purified with column flash chromatography on silica gel eluting with 4:1 hexanes/ethyl acetate to give the desired product.

Compound 208B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

[0600] Compound 207A (1.3 g) in tetrahydrofuran (10 ml) was cooled to -42°C with a cold bath of CH_3CN/dry ice. To this solution was added 2.0 M isopropylmagnesium chloride (1.6 ml) dropwise over 5 minutes. The reaction mixture was stirred for 30 minutes at -42°C, then allowed to warm to 0°C over 10 minutes. The reaction mixture was cooled again to -42°C, and SO_2 was bubbled though it for 10 minutes. The reaction mixture was stirred for another 30 minutes. To this solution was sulfuryl dichloride (0.433 g). On warming to room temperature, concentrated NH_4OH (10 ml) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was

purified by flash column chromatography on silica gel eluting with 3:1 hexanes/ethyl acetate to give the title compound.

Compound 208C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0601] The title compound was prepared by substituting Compound 208B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.61 (s, 1H), 8.72 (s, 1H), 8.36 (s, 1H), 7.98 (d, 1H), 7.55 (d, 1H), 7.42-7.47 (m, 2H), 7.36 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.23 (s, 1H), 4.56 (d, 2H), 3.75-3.79 (m, 2H), 3.56-3.61 (m, 2H), 3.09 (s, 4H), 2.32-2.37 (m, 2H), 2.16(s, 2H), 1.97-1.99 (m, 2H), 1.79-1.86 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

Compound 209

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 209A

(S)-tert-butyl (1-(oxetan-3-yl)pyrrolidin-3-yl)methylcarbamate

[0602] The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 209B

(S)-(1-(oxetan-3-yl)pyrrolidin-3-yl)methanamine

[0603] The title compound was prepared by substituting Compound 209A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in the procedure for Compound 168A.

Compound 209C

(S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methylamino)benzenesulfonamide

[0604] The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and Compound 209B for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 209D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0605] The title compound was prepared by substituting Compound 209C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.30 (d, 1H), 9.02 (t, 1H), 8.42 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.67 (dd, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (m, 1H), 6.52 (m, 2H), 4.82 (t, 1H), 4.75 (t, 1H), 4.67 (t, 2H), 3.57 (m, 1H), 3.24 (t, 2H), 3.07 (m, 4H), 2.75 (m, 3H), 2.57 (dd, 1H), 2.45 (s, 1H), 2.36 (t, 1H), 2.26 (s, 2H), 2.18 (m, 5H), 1.93 (m, 3H), 1.56 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 210

trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 210A

(4-methoxycyclohexyl)methanol

[0606] The title compound was prepared by substituting 4-methoxycyclohexanecarboxylic acid for 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate in the procedure for Compound 126A.

Compound 210B

trans-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

[0607] The title compound was prepared by substituting Compound 210A for tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 210C

trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0608] The title compound was prepared by substituting Compound 210C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H),

6.67 (dd, J 1H), 6.39 (s, 1H), 6.21 (s, 1H), 4.20 (d, 2H), 3.23 (s, 3H), 3.06-3.09 (m, 4H), 2.15-2.37 (m, 4H), 1.96-2.03 (m, 4H), 1.74-1.84 (m, 2H), 1.40 (t, 2H), 1.04-1.13 (m, 4H), 0.93 (s, 6H).

Compound 211

cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 211A

cis-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

[0609] The title compound was isolated as a by-product in the synthesis of Compound 210B.

Compound 211B

cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0610] The title compound was prepared by substituting Compound 211A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 4.21 (d, 2H), 3.20 (s, 3H), 3.06 (s, 4H), 2.15-2.37 (m, 4H), 1.96 (s, 2H), 1.80-1.84 (m, 2H), 1.50-1.54 (m, 2H), 1.34-1.44 (m, 6H), 0.93 (s, 6H).

Compound 212

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 212A

(S)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbamate

[0611] The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 212B

(S)-1-(oxetan-3-yl)pyrrolidin-3-amine

[0612] The title compound was prepared by substituting Compound 212A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in the procedure for Compound 168A.

Compound 212C

(S)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino)benzenesulfonamide

[0613] The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and Compound 212B for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 212D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0614] The title compound was prepared by substituting Compound 212C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.58 (d, 1H), 8.42 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H), 4.09 (m, 1H), 3.59 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.69 (m, 2H), 2.62 (dd, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.68 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 213

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 213A

4-((4-(2-(2-methoxyethoxy)ethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0615] The title compound was prepared by substituting 2-(2′-methoxyethoxy)ethyl bromide for methyl iodide in the procedure for Compound 134B.

Compound 213B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0616] The title compound was prepared by substituting Compound 213A for Compound

130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.98 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.96-3.86 (m, 2H),3.72 (dd, 1H), 3.67-3.61 (m, 4H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H), 2.77 (s, 2H), 2.70 (m, 1H), 2.60 (t, 2H), 2.30-2.05 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 214

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 214A

4-((4-(cyanomethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0617] The title compound was prepared by substituting 2-bromoacetonitrile for methyl iodide in the procedure for Compound 134B.

Compound 214B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0618] The title compound was prepared by substituting Compound 214A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H),3.87 (d, 1H), 3.77 (s, 2H), 3.65 (dt, 1H), 3.51-3.40 (m, 2H), 3.07 (m, 4H), 2.87 (d, 1H), 2.77 (s, 2H), 2.60 (d, 1H), 2.50 (m, 1H), 2.38 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 215

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 215A

4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0619] The title compound was prepared by substituting 2-dimethylaminoacetyl chloride hydrochloride for methyl iodide in the procedure for Compound 134B.

Compound 215B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0620] The title compound was prepared by substituting Compound 215A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H),3.60-3.40 (m, 3H),3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 216

(2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholin-4-yl)acetic acid

Compound 216A

tert-butyl 2-(2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholino)acetate

[0621] The title compound was prepared by substituting *tert*-butyl 2-bromoacetate for methyl iodide in the procedure for Compound 134B.

Compound 216B

tert-butyl 2-(2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholino)acetate

[0622] The title compound was prepared by substituting Compound 216A for Compound 130C in the procedure for Compound 130D.

Compound 216C

(2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholin-4-yl)acetic acid

[0623] The title compound was prepared by treating Compound 216B with 50% trifluoroacetic acid in dichloromethane. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.97 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.30 (dd, 1H), 8.12 (d, 1H), 7.69 (t, 1H), 7.64 (d, 1H), 7.43 (d, 2H), 7.08 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.47 (m, 1H), 4.05-4.00 (m, 1H),3.91 (d, 1H), 3.79 (dt, 1H), 3.50 (s, 2H), 3.45 (m, 2H), 3.13 (d, 1H), 3.07 (m, 4H), 2.88 (d, 1H), 2.78 (s, 2H), 2.57 (dt, 1H), 2.43 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 217

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 217A

3-nitro-4-(((4-(oxetan-3-yl)morpholin-2-yl)methyl)amino)benzenesulfonamide

[0624] The title compound was prepared by substituting Compound 134A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 217B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0625] The title compound was prepared by substituting Compound 217A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H),3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 218

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 218A

4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0626] The title compound was prepared by substituting Compound 134A for Compound 173A in the procedure for Compound 173B.

Compound 218B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0627] The title compound was prepared by substituting Compound 218A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H),3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

Compound 219

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 219A

5-(methylthio)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0628] A mixture of Compound 36B (0.1 g) and sodium methanethiolate (0.04 g) in N,N-dimethylformamide (2 ml) was heated at 80°C overnight. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

Compound 219B

5-(methylsulfonyl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0629] A mixture of Compound 219A (0.15 g) and 75% meta-chloroperoxybenzoic acid

(0.217 g) in chloroform (4 ml) was stirred at room temperature. The reaction mixture was stirred overnight. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

Compound 219C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0630] The title compound was prepared by substituting Compound 219B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.81 (s, 1H), 8.55 (d, 1H), 8.01 (d, 1H), 7.55 (d, 1H), 7.49-7.50 (m, 2H), 7.37 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.88 (dd, 2H), 3.13 (s, 4H), 2.95 (s, 2H), 2.36-2.38 (m, 2H), 2.03-2.16 (m, 4H), 1.97 (s, 3H), 1.66-1.69 (m, 2H), 1.38-1.402 (m, 4H), 0.93 (s, 6H).

Compound 220

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 220A

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0631] To a solution of Compound 37C (0.500 g) in tetrahydrofuran (5 ml) was added sodium hydride (0.596 g). Additional tetrahydrofuran (25 ml) was added and the mixture stirred for 30 minutes, then 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (1.145 g) was added as a solution in tetrahydrofuran (5 ml). After stirring for 2 hours, the reaction mixture was partioned between 1N aqueous HCl (50 ml) and dichloromethane (200 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting solid was chromatographed over silica gel (Reveleris 80g) eluting with a gradient of 0.5% to

7.5% methanol/dichloromethane over 30 minutes (flow = 40 ml/min) to provide the title compound.

Compound 220B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0632] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 220A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.42 (s, 1H), 8.35 - 8.22 (m, 1H), 8.01 (s, 1H), 7.49 (d, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (s, 1H), 6.38 (s, 1H), 6.21 (s, 1H), 4.42 (d, 2H), 3.76 (s, 2H), 3.59 (s, 2H), 3.10 (s, 6H), 2.15 (s, 6H), 2.02 - 1.74 (m, 6H), 1.40 (s, 2H), 0.93 (s, 6H).

Compound 221

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 221A

4-((4-methyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0633] The title compound was prepared by substituting (4-methyltetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 221B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0634] The title compound was prepared by substituting Compound 221A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.36 (s, 1H), 8.04-8.06 (m, 2H), 7.50-7.53 (m, 3H), 7.41 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.00 (s, 2H), 3.63-3.67 (m, 2H), 3.53-3.58 (m, 2H), 3.09 (s, 4H), 2.82 (s, 2H), 2.27 (s, 2H), 2.15 (s, 2H), 1.58-1.63 (m, 2H), 1.39 (t, 2H), 1.30-1.34 (m, 2H), 1.09 (s, 3H), 0.92 (s, 6H).

Compound 222

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)piperazine-1-carboxylate

Compound 222A

ethyl 4-(2-nitro-4-sulfamoylphenyl)piperazine-1-carboxylate

[0635] The title compound was prepared by substituting ethyl piperazine-1-carboxylate for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 222B

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)piperazine-1-carboxylate

[0636] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 222A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.52 (br. s, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.59 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.23 (d, 1H), 7.05 (d, 2H), 6.94 (d, 1H), 6.63 (dd, 1H), 6.29 (m, 2H), 4.07 (q, 2H), 3.47 (m, 4H), 3.17 (d, 2H), 3.00 (m, 8H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 1.20 (t, 3H), 0.93 (s, 6H).

Compound 223

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 223A

4-(4-morpholinopiperidin-1-yl)-3-nitrobenzenesulfonamide

[0637] The title compound was prepared by substituting 4-(piperidin-4-yl)morpholine for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 223B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0638] The title compound was prepared by substituting Compound 3J for Compound 1E

and Compound 223A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.53 (br. s, 1H), 8.05 (d, 1H), 7.91 (d, 1H), 7.58 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.26 (d, 1H), 7.05 (d, 2H), 6.91 (d, 1H), 6.62 (dd, 1H), 6.29 (m, 2H), 5.76 (s, 1H), 3.57 (m, 4H), 3.20 (m, 2H), 3.01 (m, 4H), 2.80 (t, 2H), 2.73 (s, 2H), 2.47 (m, 4H), 2.32 (m, 1H), 2.18 (m, 6H), 1.96 (m, 3H), 1.82 (m, 2H), 1.44 (m, 4H), 0.93 (s, 6H).

Compound 224

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 224A

(R)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbamate

[0639] The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 224B

(R)-1-(oxetan-3-yl)pyrrolidin-3-amine

[0640] The title compound was prepared by substituting Compound 224A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in the procedure for Compound 168A.

Compound 224C

(R)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino)benzenesulfonamide

[0641] The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and Compound 224B for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 224D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0642] The title compound was prepared by substituting Compound 224C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.03 (s, 1H), 9.26 (d, 1H), 8.57 (d, 1H), 8.42 (d, 1H), 8.36 (dd, 1H), 8.09 (d, 1H), 7.66 (m, 1H), 7.64 (d,

1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H), 3.58 (m, 1H), 3.07 (m, 4H), 2.77 (m, 2H), 2.68 (m, 2H), 2.61 (m, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (m, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 225

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 225A

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0643] To Compound 207A (0.217 g) and 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (0.281 g) in tetrahydrofuran (5 ml) was added diisopropylethylamine (0.559 ml) and the reaction was allowed to stir at room temperature for 1 hour and was then heated to 50°C for 1 hour. The reaction was concentrated, the residue was loaded onto silica gel (Reveleris 40 g) and eluted with a gradient of 0.75% methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

Compound 225B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0644] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 225A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.52 - 11.23 (m, 1H), 8.17 (d, 1H), 8.04 (d, 1H), 7.95 (d, 1H), 7.54 (d, 1H), 7.53 - 7.50 (m, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.10 - 6.97 (m, 4H), 6.67 (d, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 4.60 (dd, 4H), 4.20 (s, 1H), 3.11 - 2.63 (m, 12H), 2.19 (d, 6H), 1.95 (s, 2H), 1.58 (s, 1H), 1.40 (d, 2H), 0.92 (s, 6H).

Compound 226

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 226A

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

[0645] To a solution of Compound 82 (800 mg) and tert-butyl 4-aminopiperidine-1-carboxylate (203 mg) in dioxane (10 ml) was added Hunig's Base (1 ml). The mixture was stirred at 120°C overnight. The mixture was diluted with ethyl acetate (200 ml) and washed with water, brine and dried over Na_2SO_4. After filtration and evaporation of solvent, the residue was loaded on a silica gel cartridge and eluted with 3% methanol in dichloromethane to give the title compound.

Compound 226B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenylsulfonyl)benzamide

[0646] To a solution of Compound 226A (902 mg) in dichloromethane (10 ml) was added trifluoroacetic acid (5 ml). The mixture was stirred at room temperature for 3 hours. The mixture was concentrated under vacuum and co-concentrated with dichloromethane twice to afford the crude product which was used in the next step without further purification.

Compound 226C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0647] To a solution of Compound 226B (79 mg) in tetrahydrofuran (3 ml) and acetic acid (1 ml) was added acetone (54 mg) and MP-cyanoborohydride (150 mg, 2.25mmol/g). The mixture was stirred overnight. The mixture was filtered. The filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH_3 in methanol in dichloromethane to provide the title compound. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.09 (s, 1 H), 8.34 (m, 1 H), 7.93 (m, 2 H), 7.66 (m, 4 H), 7.35 (d, 2 H), 7.06 (d, 2 H), 6.89 (m, 1 H), 6.74 (dd, 1 H), 6.59 (dd, 1 H), 6.50 (d, 1 H), 3.11 (m, 6 H), 2.73 (m, 4 H), 2.26 (m, 9 H), 1.97 (s, 3 H), 1.40 (t, 2 H), 1.23 (s, 8 H), 0.94 (s, 6 H).

Compound 227

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-

chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 227A

1-tert-butylpiperidin-4-amine

[0648] To a solution of 1-tert-butylpiperidin-4-one (5.0 g) in methanol (100 ml) and water (10 ml) was added ammonium formate (20.3 g) and 0.5 g of Pd/C (10%). The mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under vacuum and the residue was diluted with ethyl acetate (500 ml) and washed with water and brine. After drying over Na_2SO_4 and filtration, the solvent was evaporated under vacuum to provide the title compound.

Compound 227B

4-(1-tert-butylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

[0649] To a mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.2 g) and Compound 227A (1.56 g) in tetrahydrofuran (20 ml) was added Hunig's Base (6 ml). The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 ml) and water (100 ml) and stirred until the solid disappeared into the solution. The layers were separated and the organic phase was washed with water and brine, dried over Na_2SO_4, and filtered. The combined aqueous layers were extracted again with ethyl acetate and the combined organic phases were dried over Na_2SO_4. After filtration, the solvent was evaporated to provide the title compound.

Compound 227C

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0650] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 227B for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.51 (s, 1 H), 8.43 (d, 1 H), 8.04 (m, 1 H), 7.93 (d, 1 H), 7.72 (m, 1 H), 7.56 (dd, 1 H), 7.42 (m, 1 H), 7.34 (m, 3 H), 7.05 (d, 2 H), 6.93 (dd, 1 H), 6.62 (dd, 1 H), 6.28 (m, 1 H), 3.04 (m, 6 H), 2.73 (s, 3 H), 2.25 (m, 9 H), 1.95 (s, 2 H), 1.68 (m, 2 H), 1.32 (m, 9 H), 0.93 (s, 6 H).

Compound 228

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-

({[1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 228A

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)piperidine-1-carboxylate

[0651] The title compound was prepared by substituting *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 228B

3-nitro-4-(piperidin-3-ylmethylamino)benzenesulfonamide

[0652] The title compound was prepared by substituting Compound 228A for Compound 113A in the procedure for Compound 134A.

Compound 228C

4-((1-(2-methoxyethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide

[0653] The title compound was prepared by substituting Compound 228B for Compound 134A and 2-methoxyethyl bromide for methyl iodide in the procedure for Compound 134B.

Compound 228D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0654] The title compound was prepared by substituting Compound 228C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5, 90 °C) δ 12.40 (s, 1H), 8.52 (s, 1H), 8.43 (s, 1H), 8.20 (m, 2H),7.95 (bs, 1H), 7.80 (s, 1H), 7.46 (d, 1H), 7.36 (d, 2H), 7.07 (d, 2H), 7.05 (s, 1H), 6.75 (d, 1H), 6.59 (s, 1H), 6.47 (s, 1H), 3.65-3.50 (m, 5H),3.20 (s, 3H), 3.04 (m, 5H), 2.81 (s, 3H), 2.74 (m, 1H), 2.24 (m, 7H), 2.06 (s, 2H), 2.00 (s, 2H), 1.75 (m, 1H), 1.57 (m, 2H), 1.42 (t, 2H), 1.15 (m, 1H), 0.95 (s, 6H).

Compound 229

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 229A

4-((1-(cyanomethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide

[0655] The title compound was prepared by substituting Compound 228B for Compound 134A and 2-bromoacetonitrile for methyl iodide in the procedure for Compound 134B.

Compound 229B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0656] The title compound was prepared by substituting Compound 229A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.03 (s, 1H), 8.42 (s, 1H), 8.30 (d, 1H), 8.10 (d, 1H), 7.68 (m, 2H), 7.44 (d, 2H), 7.08 (m, 3H), 6.99 (d, 1H), 6.75 (d, 1H), 6.51 (m, 2H), 3.78 (m, 2H), 3.43 (d, 1H), 3.13 (m, 1H), 3.04 (m, 4H), 2.76 (s, 2H), 2.71-2.65 (m, 3H), 2.52 (m, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.84 (m, 1H), 1.68 (m, 1H), 1.50 (m, 2H), 1.39 (t, 2H), 1.07-0.99 (m, 1H), 0.93 (s, 6H).

Compound 230

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 230A

4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0657] To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.315 g) in tetrahydrofuran (5 ml) was added sodium hydride (0.342 g). After stirring for 15 minutes, 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (0.658 g) was added as a solution in tetrahydrofuran (2 ml) followed by additional tetrahydrofuran (5 ml). After stirring for 1 hour, the reaction was poured in dichloromethane (50 ml) and water (25 ml) and the pH of the water layer was adjusted to 8. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was chromatographed over silica gel (Reveleris 40 g) eluting with a gradient of 1.0% to 10% 7N NH_3 in methanol/dichloromethane over 20 minutes then maintaining 10% 7N NH_3 in methanol/dichloromethane for 5 minutes (flow = 30 ml/min) to provide the title compound.

Compound 230B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0658] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 230A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.63 - 11.57 (m, 1H), 8.40 - 8.36 (m, 1H), 8.28 - 8.17 (m, 1H), 7.97 (s, 1H), 7.53 (d, 1H), 7.50 - 7.32 (m, 5H), 7.05 (d, 1H), 7.05 (d, 1H), 6.68 - 6.61 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.55 - 4.40 (m, 2H), 3.06 (s, 8H), 2.79 (s, 4H), 2.06 (d, 13H), 1.39 (s, 2H), 0.93 (s, 6H).

Compound 231

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 231A

(R)-5-chloro-6-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)pyridine-3-sulfonamide

[0659] To Compound 207A (0.051 g) and Compound 40A (0.049 g) in dioxane (5 ml) was added diisopropylethylamine (0.131 ml) and the reaction was heated to 75°C for 1 hour then 85°C for 2 days. The reaction was concentrated, loaded onto silica gel (Reveleris 12 g) and eluted with a gradient of 0.75% methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

Compound 231B

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0660] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 231A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.71 (s, 1H), 11.44 - 11.11 (m, 1H), 8.44 (d, 1H), 8.07 (d, 1H), 7.90 (d, 1H), 7.61 (d, 1H), 7.52 (dd, 2H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.16 (s, 1H), 4.77 - 4.39 (m, 5H), 3.19 - 2.63 (m, 11H), 2.19 (s, 7H), 1.91 (d, 3H), 1.38 (s, 2H), 0.92 (s, 6H).

Compound 232

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]piperazine-1-carboxylate

Compound 232A

tert-butyl 4-nitrosopiperazine-1-carboxylate

[0661] In a 500 ml round-bottomed flask, 6N aqueous HCl (30 ml) was cooled to –10 °C, and tert-butyl piperazine-1-carboxylate (10 g) was added. Sodium nitrite (4.5 g) dissolved in 35 ml water was added slowly. NaOH (10 g in 20 ml water) was used to neutralize the solution. Dichloromethane (3 × 50 ml) was used to extract the product. After drying over Na_2SO_4 and filtration, the solution was concentrated. The crude product was added to a silica gel column (Analogix, SF65-400 g,) and purified by eluting with 0-30% ethyl acetate in hexane.

Compound 232B

tert-butyl 4-aminopiperazine-1-carboxylate

[0662] In a 100 ml round-bottomed flask was added Compound 232A (0.15 g) and zinc (1 g) in water/methanol (1:1, 10 ml) to give a suspension. The mixture was cooled to 0°C. 12N Aqueous HCl (2 ml) was added slowly, and the mixture was stirred at 0 °C for 30 minutes. 2N Aqueous NaOH solution was used to adjust the mixture to basic pH. The mixture was filtered, and extracted with ether (3 × 30 ml). After drying over Na_2SO_4, filtration, and concentration, the crude product was added to a silica gel column (Analogix, SF15-12g,) and purified by eluting with 0–25% ethyl acetate in hexane.

Compound 232C

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperazine-1-carboxylate

[0663] The title compound was prepared by substituting Compound 232B for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 232D

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]piperazine-1-carboxylate

[0664] The title compound was prepared by substituting Compound 3J for Compound 1E

and Compound 232C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.47 (br. s, 1H), 8.86 (s, 1H), 8.34 (d, 1H), 7.90 (d, 1H), 7.59 (m, 2H), 7.36 (m, 4H), 7.23 (m, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.27 (m, 2H), 2.99 (m, 5H), 2.76 (m, 6H), 2.19 (m, 6H), 1.96 (s, 2H), 1.41 (m, 11H), 1.24 (m, 4H), 0.93 (s, 6H).

Compound 233

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro-lambda~6~-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 233A

2-(5-bromo-2-nitrophenyl)sulfur pentafluoride

[0665] To a solution of 3-bromophenylsulfur pentafluoride (2.18 g) in concentrated H_2SO_4 (5 ml) was added KNO_3 (780 mg). The mixture was stirred overnight. The mixture was diluted with diethyl ether (100 ml) and washed with water and brine. After drying over Na_2SO_4 and filtration, the solvent was evaporated under vacuum to provide the title compound.

Compound 233B

2-(5-bromo-2-aminophenyl)sulfur pentafluoride

[0666] Compound 233A (6.4g) and tetrahydrofuran (300 ml) were added to Ra-Ni, (12.80 g) in a 50 ml pressure bottle and the mixture stirred for 2 hours at 30 psi and room temperature. The mixture was filtered though a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

Compound 233C

4-bromo-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

[0667] To a solution of Compound 233B (4.4 g) in methanol (50 ml) was added tetrahydro-2H-pyran-4-carbaldehyde (1.68 g) and decaborane (1.1 g). The mixture was stirred and monitored by thin layer chromatography. More tetrahydro-2H-pyran-4-carbaldehyde (500 mg) was added to the stirring mixture to drive the reaction to completion. The reaction mixture was concentrated under vacuum and ethyl acetate (500 ml) and brine (200 ml) were added. The organic phase was dried over Na_2SO_4. Filtration and evaporation of the solvent and flash chromatography (20% ethyl acetate in hexane) gave the title compound.

Compound 233D

4-thioacetoxy-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

[0668] To a solution of Compound 233C (456 mg) and potassium ethanethioate (197 mg) in dioxane (4 ml) was added tris(dibenzylideneacetone)dipalladium(0) (27 mg) and xantphos (33 mg) followed by N,N-diisopropylethylamine (0.5 ml). The mixture was purged with argon, sealed and stirred under microwave irradiation for 60 minutes at 120°C. The mixture was dissolved in ethyl acetate (300 ml) and water (100 ml). The organic phase was washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent followed by flash chromatography (20% ethyl acetate in hexane) provided the title compound.

Compound 233E

3-pentafluorosulfanyl-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenylsulfonamide

[0669] N-chlorosuccinimide (527 mg) was added to a mixture of 2N aqueous HCl (1.5 ml) and acetonitrile (12 ml) and then cooled to 0°C. A solution of Compound 233D (386 mg) in acetonitrile (3 ml) was added to the mixture which was then stirred at 0°C for 2 hours, and then diluted with ethyl acetate (300 ml) and washed with brine and dried over Na_2SO_4. After filtration and evaporation of solvent, the residue was dissolved in isopropyl alcohol (20 ml) and cooled to 0°C with stirring. Then, ammonium hydroxide (conc. 10 ml) was added to mixture. After stirring for 2 hours, the mixture was concentrated under vacuum and the residue was added to ethyl acetate (400 ml) and water (150 ml). The organic layer was washed with brine and dried over Na_2SO_4. After filtration and evaporation of solvent, the residue was purified by flash column (20% ethyl acetate in dichloromethane) to provide the title compound.

Compound 233F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro-lambda~6~-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0670] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 233E for Compound 1F in the procedure for Compound 1G. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.71 (s, 1 H), 11.33 (m, 1 H), 8.12 (m, 2 H), 7.72 (d, 1 H), 7.54 (m, 3 H), 7.33 (m, 2 H), 7.02 (m, 3 H), 6.67 (m, 2 H), 6.42 (m, 1 H), 6.16 (d, 1 H), 3.82 (m, 2 H), 3.21 (m, 4 H), 3.05 (m, 4 H), 2.73 (s, 2 H), 2.21 (m, 8 H), 1.97 (m, 3 H), 1.29 (m, 4

H), 0.92 (s, 6 H).

Compound 234

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 234A

4-vinyltetrahydro-2H-pyran-4-ol

[0671] Dihydro-2H-pyran-4(3H)-one (8.01 g) in anhydrous ethyl ether (50 ml) was treated with 1.0 M vinylmagnesium bromide (104 ml) over 20 minutes at 0°C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with additional ethyl ether three times. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 20% ethyl acetate in hexanes to provide the title compound.

Compound 234B

4-methoxy-4-vinyltetrahydro-2H-pyran

[0672] To a solution of Compound 234A (9.4 g) in tetrahydrofuran (150 ml) was added 60 % sodium hydride (5.28 g) at 0°C portionwise. After the addition was complete, the solution was heated under reflux for three hours. After cooling, to this suspension was added dimethyl sulfate (8.41 ml) slowly. The solution was heated under reflux overnight, cooled to room temperature, and hydrolyzed with cool saturated aqueous NH_4Cl. After extraction with diethyl ether several times, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatograph on silica gel using 1–10% ethyl acetate in hexanes to provide the title compound.

Compound 234C

4-methoxytetrahydro-2H-pyran-4-carbaldehyde

[0673] Compound 234B (4.3 g) in tetrahydrofuran (200 ml) and water (67 ml) was treated with 4% osmium tetroxide in water (9.24 ml). To this solution was added potassium periodate (13.91 g) portionwise over 2 hours. The solution was stirred overnight at room temperature. Water was added to the mixture followed by repeat extractions with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was

purified by flash column chromatography on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

Compound 234D

(4-methoxytetrahydro-2H-pyran-4-yl)methanol

[0674] Compound 234C (1.8 g) in 2-propanol (28 ml) and water (7 ml) was cooled to 0°C. To this solution was added sodium borohydride (0.709 g). The solution was stirred and allowed to warm to room temperature over 3 hours. The reaction was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate was used to wash the solid, and was the mixture was decanted. The combined organic solutions were concentrated. The residue was purified by flash chromatography on silica gel eluting 1:1 ethyl acetate: hexane to provide the title compound.

Compound 234E

4-((4-methoxytetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

[0675] The title compound was prepared by substituting Compound 234D for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 234F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0676] The title compound was prepared by substituting Compound 234E for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.04-8.07 (m, 2H), 7.50-7.53 (m, 3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.21 (s, 2H), 3.65-3.67 (m, 2H), 3.53-3.56 (m, 2H), 3.19 (s, 3H), 3.10 (s, 4H), 2.86 (s, 2H), 2.30 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.61-1.74 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 235

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 235A

(R)-*tert*-butyl 3-(2-nitro-4-sulfamoylphenoxy)pyrrolidine-1-carboxylate

[0677] The title compound was prepared by substituting (R)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 235B

(R)-*tert*-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenoxy)pyrrolidine-1-carboxylate

[0678] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 235A for Compound 1F in the procedure for Compound 1G.

Compound 235C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0679] To a solution of Compound 235B (0.230 g) in dichloromethane (3 ml) was added trifluoroacetic acid (0.377 ml). After stirring for 4 hours, the reaction was concentrated then dissolved in dichloromethane (3 ml) and treated with 1,3-difluoropropan-2-one (0.028 g) followed by sodium triacetoxyborohydride (0.078 g). After stirring for 4 hours, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and dichloromethane (5 ml). The reaction was diluted with dichloromethane (250 ml) and saturated aqueous $NaHCO_3$ (100 ml) was added. The organic layer was separated, washed with brine (100 ml), dried over magnesium sulfate, filtered and concentrated. Trituration with acetonitrile gave the title compound. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.67 (s, 1H), 8.34 (s, 1H), 8.03 (s, 2H), 7.52 (d, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.75 - 6.60 (m, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 5.17 - 5.06 (m, 1H), 4.60 (d, 4H), 2.98 (d, 12H), 2.37 - 2.02 (m, 6H), 1.96 (s, 3H), 1.39 (s, 2H), 0.93 (s, 6H).

Compound 236

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 236A

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-

enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperazin-1-ylamino)phenylsulfonyl)benzamide

[0680] The title compound was prepared by substituting Compound 232D for Compound 1A in the procedure for Compound 1B.

Compound 236B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0681] The title compound was prepared by substituting Compound 236A for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.67 (br. s, 1H), 9.20 (s, 1H), 8.53 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.53 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44 (t, 2H), 3.47 (m, 1H), 3.06 (m, 4H), 2.88 (m, 4H), 2.74 (m, 4H), 2.09 (m, 11H), 1.38 (t, 2H), 0.91 (s, 6H).

Compound 237

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0682] The title compound was prepared by substituting Compound 236A for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.05 (br. s, 1H), 9.27 (d, 1H), 9.23 (s, 1H), 8.44 (m, 2H), 8.12 (d, 1H), 7.68 (m, 3H), 7.44 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.02 (m, 2H), 3.31 (m, 2H), 3.06 (m, 4H), 2.91 (m, 5H), 2.76 (s, 2H), 2.38 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.65 (m, 2H), 1.39 (m, 7H), 0.93 (s, 6H).

Compound 238

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 238A

(R)-3-nitro-4-(tetrahydrofuran-3-ylamino)benzenesulfonamide

[0683] The title compound was prepared by substituting (R)-tetrahydrofuran-3-amine for

4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 238B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0684] The title compound was prepared by substituting Compound 238A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.59 (s, 1H), 8.47 (d, 1H), 8.19 (m, 2H), 7.97 (d, 1H), 7.74 (m, 1H), 7.52 (d, 1H), 7.46 (t, 1H), 7.34 (m, 2H), 7.05 (m, 2H), 6.96 (d, 1H), 6.89 (d, 1H), 6.65 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 4.31 (m, 1H), 3.92 (m, 1H), 3.87 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.04 (m, 4H), 2.73 (m, 2H), 2.33 (m, 1H), 2.18 (m, 6H), 1.95 (m, 2H), 1.88 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

Compound 239

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 239A

tert-butyl (4,4-difluorocyclohexyl)methylcarbamate

[0685] Tert-butyl (4-oxocyclohexyl)methylcarbamate (5 g) and diethylaminosulfur trifluoride (7.45 g) were stirred in dichloromethane (100 ml) for 24 hours. The mixture was quenched with pH 7 buffer (100 ml), and poured into ether (400 ml). The resulting solution was separated, and the organic layer was washed twice with water, and once with brine, and then concentrated to give the crude product and fluoroolefin by-product in a 3:2 ratio. The crude material was taken up in tetrahydrofuran (70 ml) and water (30 ml), and N-methylmorpholine-N-oxide (1.75 g), and OsO_4 (2.5 wt % solution in t-butanol) were added, and the mixture was stirred for 24 hours. $Na_2S_2O_3$ (10 g) was then added, and the mixture was stirred for 30 minutes. The mixture was then diluted with ether (300 ml), and the resulting solution was separated, and rinsed twice with water, and once with brine, and concentrated. The crude product was chromatographed on silica gel using 5–10% ethyl acetate in hexanes to provide the title compound.

Compound 239B

(4,4-difluorocyclohexyl)methanamine

[0686] A solution of Compound 239A (3 g) in dichloromethane (35 ml), trifluoroacetic acid (15 ml), and triethylsilane (1 ml) was stirred for 2 hours. The solution was concentrated, then concentrated from toluene, and left on high vacuum for 24 hours. The semi-solid was taken up in ether/hexane and filtered to provide the title compound as its trifluoroacetic acid salt.

Compound 239C

4-((4,4-difluorocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[0687] The title compound was prepared by substituting Compound 239B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 239D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0688] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 239C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 12.40 (s, 1H), 11.61 (br s, 1H), 8.53 (m, 1H), 8.50 (d, 1H), 7.99 (d, 1H), 7.73 (d, 1H), 7.49 (m, 2H), 7.32 (d, 2H), 7.04 (d, 2H), 7.00 (d, 1H), 6.65 (d, 1H), 6.32 (s, 1H), 6.21 (s, 1H), 3.37 (m, 4H), 3.06 (m, 4H), 2.73 (m, 2H), 2.18 (m, 4H), 1.97 (m, 4H), 1.81 (m, 4H), 1.38 (m, 2H), 1.20 (m, 4H), 0.92 (s, 6H).

Compound 240

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 240A

4-(1-tert-butylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

[0689] To a mixture of 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (307 mg) and Compound 227A (156 mg) in tetrahydrofuran (4 ml) was added Hunig's Base (1 ml). The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 ml) and water (100 ml) and stirred until the solid disappeared into the solution. The layers were separated

and the organic phase was washed with water, brine and dried over Na_2SO_4. After filtration, the combined aqueous layers were extracted again with ethyl acetate and the combined organic phase was dried over Na_2SO_4. After filtration, the solvent was evaporated to provide the title compound.

Compound 240B

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0690] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 240A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.53 (s, 1 H), 8.04 (s, 1 H), 7.94 (d, 1 H), 7.86 (m, 1 H), 7.55 (d, 2 H), 7.44 (d, 1 H), 7.33 (m, 3 H), 7.05 (d, 2 H), 6.92 (m, 1 H), 6.62 (dd, 1 H), 6.43 (m, 1 H), 6.29 (d, 2 H), 3.79 (m, 1 H), 3.05 (m, 6 H), 2.73 (s, 3 H), 2.19 (m, 8 H), 1.96 (s, 3 H), 1.27 (m, 12 H), 0.92 (s, 6 H).

Compound 241

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 241A

tert-butyl 2-((4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)methyl)morpholine-4-carboxylate

[0691] The title compound was prepared by substituting tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine and 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 1F.

Compound 241B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)methyl)morpholine-4-carboxylate

[0692] The title compound was prepared by substituting Compound 241A for Compound

1F and Compound 3J for Compound 1E in the procedure for Compound 1G.

Compound 241C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-(morpholin-2-ylmethylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide

[0693] The title compound was prepared by substituting Compound 241B for Compound 1A in the procedure for Compound 1B.

Compound 241D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0694] The title compound was prepared by substituting Compound 241C for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4′-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.15 (d, 1H), 8.04 (d, 1H), 7.92 (dd, 1H), 7.54 (d, 1H), 7.51 (t, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.25 (m, 1H), 7.04 (m, 3H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.19 (d, 1H), 4.54 (t, 2H), 4.43 (m, 2H), 3.85 (m, 1H), 3.69 (m, 1H), 3.52 (m, 1H), 3.48 (m, 1H), 3.39 (m, 2H), 3.07 (m, 4H), 2.77 (br s, 2H), 2.69 (d, 1H), 2.56 (d, 1H), 2.21 (br s, 4H), 2.15 (t, 2H), 1.94 (m, 3H), 1.76 (t, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 242

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 242A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

[0695] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 138D.

Compound 242B

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0696] The title compound was prepared by substituting Compound 242A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.71 (s, 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.51-7.53 (m, 2H), 7.40 (s, 1H), 7.33-7.35 (m, 2H), 7.03-7.05 (m, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 3.77 (d, 1H), 3.69-3.71 (m, 3H), 3.48-3.53 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H),1.96 (s, 2H), 1.65-1.76 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

Compound 243

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 243A

5-chloro-6-(1-cyclopropylpiperidin-4-ylamino)pyridine-3-sulfonamide

[0697] The title compound was prepared by substituting Compound 40A for 4-chloro-3-nitrobenzenesulfonamide, 1-cyclopropylpiperidin-4-amine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine in the procedure for Compound 6A.

Compound 243B

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0698] The title compound was prepared by substituting Compound 243A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.40 (d, 1H), 8.05 (d, 1H), 7.88 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.34 (d, 2H), 7.03 (d, 2H), 6.97 (br d, 1H), 6.66 (dd, 1H), 6.40 (m, 1H), 6.16 (d, 1H), 4.04 (m, 1H), 3.03 (br m, 6H), 2.73 (s, 2H), 2.42 (br m, 2H), 2.18 (br m, 6H), 1.95 (s, 2H), 1.80 (m, 3H), 1.62 (m , 2H), 1.38 (t, 2H), 0.91 (s, 6H), 0.47 (m, 2H), 0.40 (br m, 2H).

Compound 244

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 244A

(S)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

[0699] The title compound was prepared by substituting (S)-tert-butyl 2-(hydroxymethyl)-morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 244B

(S)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

[0700] The title compound was prepared by substituting Compound 244A for Compound 113A in the procedure for Compound 134A.

Compound 244C

(S)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

[0701] The title compound was prepared by substituting Compound 244B for Compound 134A and 2-bromoacetonitrile for methyl iodide in the procedure for Compound 134B.

Compound 244D

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0702] The title compound was prepared by substituting Compound 244C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.99 (s, 1H), 9.09 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H),4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76 (s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 245

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 245A

(S)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

[0703] The title compound was prepared by substituting Compound 244B for Compound

134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in the procedure for Compound 134B.

Compound 245B

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0704] The title compound was prepared by substituting Compound 245A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.09 (d, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 4.85-4.46 (m, 3H),4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H), 3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 246

N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 246A

(R)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

[0705] The title compound was prepared by substituting (R)-tert-butyl 2-(hydroxymethyl)-morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 246B

(R)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

[0706] The title compound was prepared by substituting Compound 246A for Compound 113A in the procedure for Compound 134A.

Compound 246C

(R)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

[0707] The title compound was prepared by substituting Compound 246B for Compound 134A and 2-bromoacetonitrile for methyl iodide in the procedure for Compound 134B.

Compound 246D

N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-

{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0708] The title compound was prepared by substituting Compound 246C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.99 (s, 1H), 9.09 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H),4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76 (s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 247

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 247A

(R)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

[0709] The title compound was prepared by substituting Compound 246B for Compound 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in the procedure for Compound 134B.

Compound 247B

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0710] The title compound was prepared by substituting Compound 247A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.09 (d, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 4.85-4.46 (m, 3H),4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H), 3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 248

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 248A

5-bromo-3-fluoro-2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine

[0711] The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide and Compound 37C for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 248B

tert-butyl 5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

[0712] Compound 248A (0.308 g), tert-butyl carbamate (0.141 g), palladium(II) acetate (0.011 g), Xantphos (0.043 g) and cesium carbonate (0.489 g) were combined with dioxane (5.0 ml) in a 20-ml vial equipped with a magnetic stir bar. The vial was flushed with nitrogen, capped and stirred at 100°C overnight. Additional palladium(II) acetate (0.011 g), Xantphos (0.043 g) and tert-butyl carbamate (0.141 g) were added and heating was continued at 100°C for 8 hours. The cooled reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on silica gel with 7-25% ethyl acetate in hexanes as the eluent.

Compound 248C

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

[0713] Under ice-cooling, thionyl chloride (1.563 ml) was added dropwise over 20 minutes to water (9 ml). The mixture was stirred for 12 hours to give a SO_2-containing solution. Separately, Compound 248B (0.295 g) was added to a mixture of 1,4-dioxane (3.2 ml) and concentrated HCl (8 ml) at 0°C. After stirring for 15 minutes, a solution of sodium nitrite (0.065 g) in water (2 ml) was added dropwise and stirring was continued at 0°C for 3 hours. Copper(I) chloride (0.042 g) and then the freshly prepared solution of diazotized material were added sequentially to the previously prepared SO_2-containing solution. The resulting solution was stirred for 30 minutes and then extracted with ethyl acetate (2 × 125 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on silica gel with 5% ethyl acetate in hexanes as the eluent.

Compound 248D

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0714] Compound 248C (0.08 g) in isopropanol (2 ml) at 0°C was treated with

ammonium hydroxide (1.697 ml), stirred overnight and then concentrated to dryness. The obtained solid was slurried in water, filtered, rinsed with water and dried under high vacuum to provide the title compound.

Compound 248E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0715] The title compound was prepared by substituting Compound 248D for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.03 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.55 (d, 2H), 3.80 (m, 4H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.88 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 250

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 250A

5-chloro-6-((3-methyloxetan-3-yl)methoxy)pyridine-3-sulfonamide

[0716] The title compound was prepared by substituting (3-methyloxetan-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 250B

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0717] The title compound was prepared by substituting Compound 250A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.22 (d, 1H), 8.51 (d, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.66 (t, 2H), 7.43 - 7.46 (m, 2H), 7.04 - 7.09 (m, 2H), 6.75 (dd, 1H), 6.45 - 6.54 (m, 2H), 4.47 (s, 2H), 3.81 - 3.84 (m, 2H), 3.74 (d, 2H), 3.03 - 3.11 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t,

2H), 1.16 (s, 3H), 0.94 (s, 6H).

Compound 251

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 251A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0718] The title compound was prepared by substituting (4-fluorotetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and 5-bromo-6-chloropyridine-3-sulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 251B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0719] To a suspension of 5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide (200 mg) and cyclohexene (0.549 ml) in ethyl acetate (10 ml) was added 10% palladium on carbon (57.6 mg). The suspension was stirred for 60 minutes at 120°C. The reaction mixture was filtered and concentrated. The product was purified by reverse-phase flash chromatography (C18, 150g, 10%–100% acetonitrile/H_2O/trifluoroacetic acid 0.1%).

Compound 251C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0720] The title compound was prepared by substituting Compound 251B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 9.29 (d, 1H), 8.50 (dd, 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.66 - 7.70 (m, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.84 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.50 (d, 2H), 3.81 - 3.89 (m, 2H), 3.70 - 3.81 (m, 2H), 3.02 - 3.12 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.18 (m, 4H), 1.97 (s, 2H), 1.77 - 1.94 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 252

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-

(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 252A

tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate

[0721] The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and tert-butyl morpholin-2-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 252B

(4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methanamine

[0722] A solution of Compound 252A (538 mg) in dioxane (4 ml) was treated with 4.0M HCl in dioxane solution (1.8 ml). The reaction was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and used without further purification.

Compound 252C

4-((4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0723] The title compound was prepared by substituting Compound 252B for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 252D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0724] The title compound was prepared by substituting Compound 252C for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 8.59 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.07 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.69 (t, 2H), 4.57 (t, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 3.52 (m, 2H), 3.41 (m, 2H), 3.07 (br s, 4H), 2.91 (d, 1H), 2.74 (m, 3H), 2.59 (m, 1H), 2.43 (m, 1H), 2.20 (m, 4H), 2.15 (m, 2H), 1.95 (br s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

Compound 253

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 253A

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)piperidine-1-carboxylate

[0725] The title compound was prepared by substituting tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate for tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 253B

5-chloro-6-(piperidin-4-ylmethoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

[0726] The title compound was prepared by substituting Compound 253A for Compound 39A in the procedure for Compound 39B.

Compound 253C

5-chloro-6-((1-(cyanomethyl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0727] Compound 253B (0.061 g), 2-chloroacetonitrile (0.017 g), sodium carbonate (0.025 g) and N,N-dimethylformamide (1 ml) were combined in a 4-ml vial and heated at 60°C overnight. The cooled reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on silica gel with 2–10% methanol in CH_2Cl_2 as the eluent.

Compound 253D

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0728] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 253C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.04 (s, 1H), 9.14 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (t, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.74 (dd, 1H), 6.50 (m, 2H), 4.18 (d, 2H), 3.64 (s, 2H), 3.05 (s, 4H), 2.77 (m, 4H), 2.24 (m, 4H), 2.13 (m, 4H), 1.97 (s, 2H), 1.69 (m, 3H), 1.41 (m, 4H), 0.93 (s, 6H).

Compound 254

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 254A

(R)-tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)pyrrolidine-1-carboxylate

[0729] The title compound was prepared by substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 254B

(R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesufonamide

[0730] The title compound was prepared by substituting Compound 254A for Compound 113A in the procedure for Compound 134A.

Compound 254C

(R)-4-(1-(2-(2-methoxyethoxy)ethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesufonamide

[0731] To a solution of (R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide (440 mg) in N,N-dimethylformamide (10 ml) was added sodium carbonate (132 mg) and 1-bromo-2-(2-methoxyethoxy)ethane (0.155 ml). The reaction mixture was heated at 60°C for 18 hours and after an aqueous workup, the crude product was purified on silica gel with a 2.5 - 10% methanol in methylene chloride gradient to provide the title compound.

Compound 254D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yl-oxy)benzamide

[0732] The title compound was prepared by substituting Compound 254C for Compound 130C in the procedure for Compound 130D. 1H NMR (500 MHz, pyridine-d_5) δ 12.96 (m, 1H), 9.25 (m, 1H), 8.57 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (t, 1H) 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.47 (m, 1H), 5.26 (br s, 1H), 4.02 (m, 1H), 3.63 (m, 4H), 3.53 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.89 - 2.81 (m, 2H), 2.78 (s, 2H), 2.75 - 2.66 (m, 3H), 2.37 (m, 1H), 2.26 (m, 2H), 2.24 - 2.18 (m, 1H), 2.15 (m, 4H), 1.97 (s, 2H), 1.65 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 255

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 255A

(R)-4-(1-(2-(dimethylamino)acetyl)pyrrolidin-3-ylamino)-3-nitrobenzenesufonamide

[0733] The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride, hydrochloric acid for 1-bromo-2-(2-methoxyethoxy)ethane in the procedure for Compound 254C except the reaction was stirred at ambient temperature for 18 hours.

Compound 255B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0734] The title compound was prepared by substituting Compound 255A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500 MHz, pyridine - d_5) δ 13.01 (d, 1H), 9.26 (m, 1H), 8.46 - 8.33 (m, 3H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01 – 6.89 (m, 1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.48 (m, 1H), 5.32 (br s, 1H), 4.27 - 4.14 (m, 1H), 4.05- 3.95 (m, 1H), 3.82 - 3.62 (m, 3H), 3.27 - 3.15 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.34 (2, 3H), 2.32 (s, 3H), 2.30 - 2.20 (m, 3H), 2.15 (m, 4H), 1.97 (s, 2H), 1.87 - 1.81 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 256

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 256A

tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)azetidine-1-carboxylate

[0735] The title compound was prepared by substituting tert-butyl 3-aminoazetidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in the procedure for Compound 6A.

Compound 256B

4-(azetidin-3-ylamino)-3-nitrobenzenesulfonamide

[0736] The title compound was prepared by substituting Compound 256A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in the procedure for Compound 168A.

Compound 256C

3-nitro-4-(1-(oxetan-3-yl)azetidin-3-ylamino)benzenesulfonamide

[0737] The title compound was prepared by substituting Compound 256B for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 256D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0738] The title compound was prepared by substituting Compound 256C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.04 (s, 1H), 9.27 (d, 1H), 8.62 (d, 1H), 8.42 (d, 1H), 8.35 (dd, 1H), 8.09 (d, 1H), 7.67 (m, 1H), 7.63 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.67 (d, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 4.66 (t, 2H), 4.58 (m, 2H), 4.23 (m, 1H), 3.71 (m, 3H), 3.12 (dd, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (t, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 257

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 257A

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

[0739] The title compound was prepared by substituting Compound 126A for (tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 257B

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

[0740] The title compound was prepared by substituting Compound 257A for Compound 39A in the procedure for Compound 39B.

Compound 257C

5-chloro-6-((1-(cyanomethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0741] Compound 257B (0.166 g) in acetonitrile (3 ml) was treated with 2-

chloroacetonitrile (0.027 g) and sodium carbonate (0.064 g), heated at 60°C overnight, cooled to room temperature and chromatographed on silica gel with 0 to 3% methanol in CH_2Cl_2 as the eluent. The obtained solid was slurried in water, filtered, rinsed with water and diethyl ether, and dried in a vacuum oven at 80°C.

Compound 257D

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0742] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 257C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.49 (d, 2H), 3.72 (s, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.73 (m, 4H), 2.26 (t, 2H), 2.13 (m, 4H), 2.07 (m, 2H), 1.90 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 258

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 258A

(S)-tert-butyl 2-(tosyloxymethyl)morpholine-4-carboxylate

[0743] To a solution of (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (1 g) in dichloromethane (50 ml) was added triethylamine (1.604 ml) and 4-methylbenzene-1-sulfonyl chloride (1.097 g). The mixture was stirred at ambient temperature under nitrogen for 72 hours. The reaction was diluted with methylene chloride (50 ml) and brine (100 ml). The brine layer was extracted with methylene chloride (75 ml). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude material was purified on a silica gel column eluting with a 15-65 % ethyl acetate in hexane gradient to provide the title compound.

Compound 258B

(S)-tert-butyl 2-(azidomethyl)morpholine-4-carboxylate

[0744] A solution of Compound 258A (1.66 g) and sodium azide (0.581 g) in anhydrous

N,N-dimethylformamide (10 ml) was stirred at 90°C for 4 hours. The mixture was cooled and concentrated to dryness. The residue was taken up in 5% aqueous sodium carbonate solution and extracted with methylene chloride. The organic solution was dried ($MgSO_4$), filtered and concentrated to give a solid.

Compound 258C

(R)-tert-butyl 2-(aminomethyl)morpholine-4-carboxylate

[0745] This compound was obtained by hydrogenation of Compound 258B under 60 psi of hydrogen over 10% palladium on carbon in methanol for 24 hours, followed by filtration and evaporation of the solvent.

Compound 258D

(R)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

[0746] The title compound was prepared by substituting Compound 258C for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 258E

(S)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

[0747] The title compound was prepared by substituting Compound 258D for Compound 113A in the procedure for Compound 134A.

Compound 258F

(R)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0748] The title compound was prepared by substituting Compound 258E for Compound 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in the procedure for Compound 134B.

Compound 258G

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0749] The title compound was prepared by substituting Compound 258F for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20

(dd, 1H), 3.95-3.76 (m, 2H),3.60-3.40 (m, 3H),3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 259

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 259A

(R)-tert-butyl 2-(tosyloxymethyl)morpholine-4-carboxylate

[0750] The title compound was prepared by substituting (R)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate in the procedure for Compound 258A.

Compound 259B

(R)-tert-butyl 2-(azidomethyl)morpholine-4-carboxylate

[0751] The title compound was prepared by substituting Compound 259A for Compound 258A in the procedure for Compound 258B.

Compound 259C

(S)-tert-butyl 2-(aminomethyl)morpholine-4-carboxylate

[0752] The title compound was prepared by substituting Compound 259B for Compound 258B in the procedure for Compound 258C.

Compound 259D

(S)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

[0753] The title compound was prepared by substituting Compound 259C for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 259E

(R)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

[0754] The title compound was prepared by substituting Compound 259D for Compound 113A in the procedure for Compound 134A.

Compound 259F

(S)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0755] The title compound was prepared by substituting Compound 259E for Compound 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in the procedure for Compound 134B.

Compound 259G

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0756] The title compound was prepared by substituting Compound 259F for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H),3.60-3.40 (m, 3H),3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 260

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 260A

5-chloro-6-((1-(2-(dimethylamino)acetyl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0757] Compound 253B (0.061 g), 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.061 g), and sodium carbonate (0.032 g) were combined in a 4-ml vial with N,N-dimethylformamide (2 ml). The mixture was stirred at ambient temperature for 3 days. Additional 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.037 g), sodium carbonate (0.032 g) and N,N-dimethylformamide (1 ml) were added and stirring was continued for 24 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 0 to 20% methanol in CH_2Cl_2 as the eluent.

Compound 260B

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0758] The title compound was prepared by substituting Compound 260A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, pyridine-d_5) δ 12.91 (s, 1H), 9.16 (d, 1H), 8.75 (d, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 7.70 (d, 1H), 7.62 (d, 1H), 7.45 (m, 2H), 7.09 (m, 2H), 6.77 (dd, 1H), 6.60 (d, 1H), 6.45 (d, 1H), 4.81 (d, 1H), 4.15 (m, 3H), 3.24 (m, 2H), 3.04 (m, 4H), 2.89 (m, 1H), 2.79 (s, 2H), 2.53 (m, 1H), 2.29 (m, 6H), 2.26 (m, 2H), 2.18 (m, 4H), 1.98 (m, 2H), 1.91 (m, 1H), 1.71 (m, 2H), 1.39 (t, 2H), 1.25 (m, 2H), 0.94 (s, 6H).

Compound 261

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 261A

(R)-tert-Butyl 3-(3-chloro-5-sulfamoylpyridin-2-yloxy)pyrrolidine-1-carboxylate

[0759] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide and (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 261B

(R)-5-Chloro-6-(pyrrolidin-3-yloxy)pyridine-3-sulfonamide

[0760] The title compound was prepared by substituting Compound 261A for tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in the procedure for Compound 252B.

Compound 261C

(R)-5-chloro-6-(1-(2,2-difluoroethyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

[0761] A mixture of Compound 261B (353 mg), 1, 1-difluoro-2-iodoethane (268 mg), sodium carbonate (283 mg) in N,N-dimethylformamide (10ml) was heated at 80°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel column and eluted using a gradient of 0.5 to 3 % methanol in dichloromethane to provide the title compound.

Compound 261D

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-

{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0762] The title compound was prepared by substituting Compound 261C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.55 (s, 1 H), 8.04 (s, 1 H), 7.95 (d, 1 H), 7.58 (d, 1 H), 7.44 (t, 1 H), 7.35 (m, 3 H), 7.05 (d, 2 H), 6.64 (dd, 1 H), 6.33 (m, 1 H), 6.24 (d, 1 H), 6.25-5.97 (m, 1 H), 5.39 (m, 1 H), 2.98 (m, 6 H), 2.86 (m, 6 H), 2.55 (m, 2 H), 2.24 (m, 7 H), 1.96 (s, 2 H), 1.83 (m, 1 H), 1.39 (t, 2 H), 0.93 (s, 6 H)

Compound 262

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 262A

(R)-4-(1-(cyanomethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesufonamide

[0763] The title compound was prepared by substituting 2-bromoacetonitrile for 1-bromo-2-(2-methoxyethoxy)ethane in the procedure for Compound 254C.

Compound 262B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0764] The title compound was prepared by substituting Compound 262A for Compound 130C in the procedure for Compound 130D. 1H NMR (400 MHz, pyridine - d_5) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.53 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.67 - 7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.81 (d, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 5.15 (br s, 1H), 4.10 (m, 1H), 3.89 (s, 2H), 3.07 (m, 4H), 2.93 - 2.86 (m, 2H), 2.80 - 2.77 (m, 3H), 2.61 - 2.53 (m, 1H), 2.31 - 2.21 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.75 - 1.68 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H).

Compound 263

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 263A

tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

[0765] Sodium hydride (6.63 g, 60% in mineral oil) was added to trimethylsulfoxonium iodide (36.5 g) in dimethyl sulfoxide (150 ml) and tetrahydrofuran (150 ml), was and stirred for 30 minutes. tert-Butyl 4-oxopiperidine-1-carboxylate (25.4 g) was added and the reaction was stirred for 3 hours. The reaction was poured into water (800 ml) and extracted three times with ether. The combined extracts were washed three times with water, and brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude product which was used without further purification.

Compound 263B

tert-butyl 4-(2-(benzyloxy)benzyl)-4-hydroxypiperidine-1-carboxylate

[0766] (2-(Benzyloxy)phenyl)magnesium bromide (33.8 ml, 1M) was added to a solution of Compound 263A (6.0 g) and CuI (1.07 g) in tetrahydrofuran (220 ml) at 0°C over 10 minutes. The reaction was quenched with pH 7 buffer (20 ml), extracted twice with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 2-20% ethyl acetate in hexanes to provide the title compound.

Compound 263C

tert-butyl 4-hydroxy-4-(2-hydroxybenzyl)piperidine-1-carboxylate

[0767] Compound 263B (11.5 g) and methanol (120 ml) were added to Raney Nickel (1.150 g) in a 250 ml SS pressure bottle and stirred for 1 hour at 30 psi under hydrogen. The mixture was filtered through a nylon membrane and the solution was concentrated to yield the title compound.

Compound 263D

tert-butyl 4-hydroxy-4-(2-(trifluoromethylsulfonyloxy)benzyl)piperidine-1-carboxylate

[0768] A mixture of Compound 263C (4.6 g), N-phenylbis(trifluoromethanesulfonimide) (5.88 g), and Hunig's base (2.88 ml) in dichloromethane (100 ml) was stirred for 24 hours. The mixture was concentrated and chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

Compound 263E

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-hydroxypiperidine-1-carboxylate

[0769] A mixture of Compound 263D (4.3 g), 4-chlorophenylboronic acid (1.84 g), K_3PO_4 (2.91 g), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.36 g) in 2-methyltetrahydrofuran (50 ml) was stirred at 70°C for 24 hours. The reaction was cooled and quenched with water (50 ml), extracted twice with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-30% ethyl acetate in hexanes to provide the title compound.

Compound 263F

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine-1-carboxylate

[0770] Sodium hydride (0.36 g, 60% in mineral oil) was added to Compound 263E (4.3 g), in tetrahydrofuran (40 ml) and the reaction was stirred for 10 minutes. Hexamethylphosphoramide (5 ml) and CH_3I (2.34 ml) were added and the reaction was stirred at 50°C for 18 hours. The reaction was cooled and quenched with water (50 ml), extracted twice with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 5–25% ethyl acetate in hexanes to provide the title compound.

Compound 263G

4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine

[0771] The title compound was prepared by substituting Compound 263F for Compound 1A in the procedure for Compound 1B.

Compound 263H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoate

[0772] A solution of Compound 263G (1.4 g), Compound 3H (1.06 g) and Hunig's base (0.75 ml) in dimethylsulfoxide (20 ml) was stirred at 120°C for 18 hours. The reaction was cooled and quenched with water (200 ml), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

Compound 263I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-

methoxypiperidin-1-yl)benzoic acid

[0773] The title compound was prepared by substituting Compound 263H for Compound 3I in the procedure for Compound 3J.

Compound 263J

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0774] The title compound was prepared by substituting Compound 263I for Compound 1E and Compound 96A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.71 (s, 1H), 11.58 (br s, 1H), 8.58 (d, 1H), 8.28 (d, 1H), 8.05 (d, 1H), 7.56 (d, 1H), 7.52 (m, 1H), 7.46 (d, 1H), 7.44 (d, 2H), 7.28 (m, 5H), 7.11 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 4.54 (d, 2H), 3.75 (m, 2H), 3.59 (m, 2H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.74 (m, 2H), 1.89 (m, 2H), 1.83 (m, 2H), 1.36 (m, 2H), 1.09 (m, 2H).

Compound 264

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0775] The title compound was prepared by substituting Compound 263I for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.71 (s, 1H), 11.40 (br s, 1H), 8.62 (t, 1H), 8.58 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.54 (m, 2H), 7.44 (m, 3H), 7.28 (m, 5H), 7.13 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.31 (m, 4H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.73 (m, 2H), 1.89 (m, 1H), 1.62 (m, 2H), 1.38 (m, 2H), 1.25 (m, 2H), 1.09 (m, 2H).

Compound 265

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 265A

benzyl 4-(piperidin-1-ylmethylene)piperidine-1-carboxylate

[0776] To a solution of benzyl 4-formylpiperidine-1-carboxylate (12.5g) in toluene (120

ml) was added piperidine (6.46g). The mixture was stirred at reflux under a Dean-Stark trap overnight. The mixture was then concentrated under vacuum and the residue was used directly in the next step.

Compound 265B

benzyl 9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate

[0777] To a solution of Compound 265A (15.88g) in ethanol (300 ml) was added but-3-enone (3.89 g). The mixture was stirred at reflux overnight. Then acetic acid (30 ml) was added to the mixture which was stirred at reflux again overnight. The mixture was then concentrated under vacuum and the residue was diluted with ethyl acetate (400 ml) and washed with water and brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, column purification gave the title compound.

Compound 265C

benzyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate

[0778] Compound 265B (21 g) and tetrahydrofuran (160 ml) were added to 5% Pt-C wet (3.15 g) in a 250 ml pressure bottle and stirred for 1 hour at 30 psi and room temperature. The mixture was filtered though a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

Compound 265D

benzyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate

[0779] To a solution of Compound 265C (8.0 g) in dichloromethane (200 ml) was added Dess-Martin Periodinane (11.2 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 ml) and washed with 2N aqueous NaOH, water, and brine. After drying over Na_2SO_4 and filtration, concentration of the solvent gave the crude product which was used directly in the next reaction without further purification.

Compound 265E

benzyl 9-chloro-8-formyl-3-azaspiro[5.5]undec-8-ene-3-carboxylate

[0780] Phosphorus oxychloride (2.33 ml) was added dropwise to a cooled (0°C) solution of Compound 265D (7.5 g) in N,N-dimethylformamide (10 ml) and dichloromethane (30 ml). The mixture was then stirred overnight before it was diluted with ethyl acetate (300 ml) and washed with aqueous sodium acetate, water (3 ×), and brine and dried over Na_2SO_4. After

filtration and concentration, the crude product was used directly in the next reaction without further purification.

Compound 265F

benzyl 9-(4-chlorophenyl)-8-formyl-3-azaspiro[5.5]undec-8-ene-3-carboxylate

[0781] To a mixture of 4-chlorophenylboronic acid (5.94 g), Compound 265E (11.01 g), palladium(II) acetate (142 mg), K_2CO_3 (13.2 g) and tetrabutylammonium bromide (10.2 g) was added water (120 ml). The mixture was stirred at 50°C overnight. The mixture was diluted with ethyl acetate (400 ml) and washed with water (3 ×) and brine and dried over Na_2SO_4. After filtration and concentration, the residue was loaded on a column and eluted with 5 to 20% ethyl acetate in hexane to provide the title compound.

Compound 265G

benzyl 8-((4-(3-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(methoxycarbonyl)phenyl)piperazin-1-yl)methyl)-9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-ene-3-carboxylate

[0782] To a solution of Compound 15F (1.37 g) and Compound 265F (1.65 g) in dichloromethane (20 ml) was added sodium triacetoxyborohydride (1.24 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 ml) and washed with 2N aqueous NaOH, water and brine. After drying over Na_2SO_4, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

Compound 265H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

[0783] Compound 265G (2 g) and tetrahydrofuran (10 ml) were added to 20% $Pd(OH)_2$-C, wet (0.400 g) in a 50 ml pressure bottle and stirred for 16 hours at 30 psi and room temperature. The mixture was filtered though a nylon membrane and evaporation of the solvent gave the title compound.

Compound 265I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

[0784] To a solution of Compound 265H (320 mg) in dichloromethane (5 ml) was added 1,3-difluoroacetone (139 mg) and sodium triacetoxyborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 ml) and washed with 2N

aqueous NaOH, water and brine. After drying over Na_2SO_4, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

Compound 265J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

[0785] To a solution of Compound 265I (320 mg) in tetrahydrofuran (4 ml) and methanol (2 ml) was added LiOH H_2O (120 mg) and the solution was stirred overnight. The reaction was cooled, carefully neutralized with 1N aqueous HCl and extracted with dichloromethane (3 × 50 ml). The combined organic layers were washed with brine (25 ml), dried over sodium sulfate, filtered and concentrated under vacuum to provide the title compound.

Compound 265K

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0786] The title compound was prepared by substituting Compound 265J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.61 (s, 1 H), 8.49 (d, 2 H), 7.72 (m, 1 H), 7.49 (m, 2 H), 7.32 (d, 2 H), 7.07 (m, 3 H), 6.65 (dd, 1 H), 6.35 (d, 1 H), 6.20 (m, 1 H), 4.66 (m, 2 H), 4.50 (m, 2 H), 3.84 (m, 2 H), 3.04 (m, 5 H), 2.70 (m, 6 H), 2.23 (m, 6 H), 2.00 (m, 4 H), 1.35 (m, 12 H).

Compound 266

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 266A

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

[0787] To a solution of Compound 265H (320 mg) in dichloromethane (5 ml) was added acetone (143 mg) and sodium triacetoxyborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 ml) and washed with 2N aqueous NaOH, water and brine. After drying over Na_2SO_4, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

Compound 266B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

[0788] The title compound was prepared by substituting Compound 266A for Compound 265I in the procedure for Compound 265J.

Compound 266C

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0789] The title compound was prepared by substituting Compound 266B for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.54 (s, 1 H), 8.38 (m, 2 H), 7.93 (d, 1 H), 7.60 (m, 3 H), 7.39 (m, 4 H), 7.09 (d, 2 H), 6.85 (d, 1 H), 6.63 (dd, 1 H), 6.27 (dd, 2 H), 3.84 (m, 3 H), 3.08 (m, 8 H), 2.71 (s, 3 H), 2.15 (m, 8 H), 1.71 (m, 9 H), 1.24 (m, 11 H).

Compound 267

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0790] The title compound was prepared by substituting Compound 265J for Compound 1E and Compound 40B for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.56 (s, 1 H), 8.38 (s, 1 H), 8.06 (m, 1 H), 7.57 (d, 1 H), 7.38 (m, 5 H), 7.07 (m, 3 H), 6.64 (dd, 1 H), 6.33 (d, 1 H), 6.23 (m, 1 H), 4.68 (d, 2 H), 4.52 (d, 2 H), 4.21 (d, 2 H), 3.86 (dd, 2 H), 3.08 (m, 8 H), 2.71 (m, 6 H), 2.10 (m, 12 H), 1.42 (m, 7 H).

Compound 268

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0791] The title compound was prepared by substituting Compound 266B for Compound 1E and Compound 40B for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.49 (s, 1 H), 8.28 (d, 1 H), 7.94 (dd, 2 H), 7.60 (d, 1 H), 7.35 (m, 4 H), 7.08 (m, 2 H), 6.61 (dd, 1 H), 6.28 (dd, 2 H), 4.18 (d, 2 H), 3.85 (m, 2 H), 3.05 (m, 7

H), 2.71 (s, 3 H), 2.25 (m, 6 H), 2.02 (m, 2 H), 1.63 (m, 8 H), 1.30 (m, 9 H).

Compound 269

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 269A

5-chloro-6-((4-fluoro-1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0792] Compound 257B (0.131 g) in N,N-dimethylformamide (3.0 ml) was treated with iodomethane (0.043 g) and sodium carbonate (0.079 g) and stirred at ambient temperature for 3 days. The N,N-dimethylformamide was removed on high vacuum and the concentrate was chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH_2Cl_2 as the eluent.

Compound 269B

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0793] The title compound was prepared by substituting Compound 269A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.01 (s, 1H), 9.11 (d, 1H), 8.71 (d, 1H), 8.44 (d, 1H), 8.16 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.49 (dd, 1H), 4.49 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.68 (m, 2H), 2.38 (m, 2H), 2.26 (m, 5H), 2.14 (t, 4H), 1.97 (m, 6H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 270

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 270A

5-chloro-6-((1-(2-(dimethylamino)acetyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0794] Compound 257B (0.131 g), 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g), and sodium carbonate (0.048 g) were combined in a 5-ml vial with N,N-dimethylformamide (3.0 ml) and stirred overnight at ambient temperature. Additional sodium

carbonate (0.048 g) was added followed by 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g) and stirring was continued over a second night. The reaction mixture was concentrated under high vacuum, slurried in CH_2Cl_2, filtered, concentrated and chromatographed on amine functionalized silica gel with 0 to 4% methanol in CH_2Cl_2 as the eluent.

Compound 270B

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0795] The title compound was prepared by substituting Compound 270A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.04 (s, 1H), 9.12 (d, 1H), 8.73 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.66 (d, 1H), 4.52 (dd, 2H), 4.07 (d, 1H), 3.46 (m, 1H), 3.40 (m, 1H), 3.30 (m, 1H), 3.11 (m, 1H), 3.06 (m, 4H), 2.77 (s, 2H), 2.35 (s, 6H), 2.26 (t, 2H), 2.14 (m, 4H), 2.05 (m, 2H), 1.97 (s, 2H), 1.81 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 271

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 271A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine-1-carboxylate

[0796] A solution of Compound 263E (2.0 g) and diethylaminosulfur trifluoride (1.39 ml) in dichloromethane (40 ml) was stirred for 24 hours. The reaction was quenched with water (30 ml), extracted twice with ether, and the combined extracts were washed with water, and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 5% ethyl acetate in hexanes to provide the title compound.

Compound 271B

4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine

[0797] The title compound was prepared by substituting Compound 271A for Compound 1A in the procedure for Compound 1B.

Compound 271C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoate

[0798] The title compound was prepared by substituting Compound 271B for Compound 263G in the procedure for Compound 263H.

Compound 271D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoic acid

[0799] The title compound was prepared by substituting Compound 271C for Compound 3I in the procedure for Compound 3J.

Compound 271E

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0800] The title compound was prepared by substituting Compound 271D for Compound 1E Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 11.46 (br s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.52 (m, 3H), 7.44 (d, 2H), 7.28 (m, 5H), 7.14 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 3.84 (dd, 2H), 3.31 (m, 9H), 2.95 (d, 2H), 2.81 (m, 2H), 1.91 (m, 1H), 1.62 (m, 2H), 1.45 (m, 2H), 1.29 (m, 2H).

Compound 272

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0801] The title compound was prepared by substituting Compound 271D for Compound 1E and Compound 96A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1H), 11.64 (br s, 1H), 8.58 (m, 1H), 8.25 (m, 1H), 8.03 (d, 1H), 7.70 (dd, 1H), 7.50 (m, 4H), 7.43 (m, 3H), 7.28 (m, 4H), 7.15 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 4.54 (d, 2H), 4.04 (m, 1H), 3.75 (m, 2H), 3.58 (m, 2H), 2.95 (d, 2H), 2.80 (m, 2H), 1.88 (m, 2H), 1.82 (m, 2H), 1.48 (m, 2H), 1.28 (m, 2H), 0.85 (m, 2H).

Compound 273

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-

1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide

[0802] The title compound was prepared by substituting Compound 266B for Compound 1E and Compound 42A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.57 (s, 1 H), 7.97 (d, 1 H), 7.77 (s, 1 H), 7.55 (m, 2 H), 7.45 (m, 1 H), 7.36 (m, 3 H), 7.08 (d, 2 H), 6.62 (dd, 2 H), 6.35 (dd, 1 H), 6.21 (d, 1 H), 3.82 (m, 3 H), 3.06 (m, 9 H), 2.72 (m, 3 H), 2.25 (m, 8 H), 2.09 (m, 2 H), 1.56 (m, 9 H), 1.20 (m, 10 H).

Compound 274

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 274A

(R)-5-chloro-6-(1-(3-fluoro-2-(fluoromethyl)propyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

[0803] The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and Compound 261B for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 274B

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0804] The title compound was prepared by substituting Compound 274A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.52 (s, 1 H), 8.32 (d, 1 H), 8.01 (d, 1 H), 7.93 (d, 1 H), 7.59 (d, 1 H), 7.42 (m, 1 H), 7.33 (m, 3 H), 7.05 (d, 2 H), 6.63 (dd, 1 H), 6.31 (dd, 1 H), 6.25 (d, 1 H), 5.38 (m, 1 H), 4.65 (t, 2 H), 4.53 (t, 2 H), 3.02 (s, 4 H), 2.94 (m, 5 H), 2.75 (s, 2 H), 2.66 (m, 1 H), 2.23 (m, 7 H), 1.96 (s, 2 H), 1.82 (m, 1 H), 1.39 (t, 2 H), 0.93 (s, 6 H).

Compound 275

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 275A

3-(2-(benzyloxy)ethoxy)tetrahydrofuran

[0805] Tetrahydrofuran-3-ol (0.881 g) in tetrahydrofuran (15 ml) was treated with 60% sodium hydride (0.8 g). After 10 minutes, ((2-bromoethoxy)methyl)benzene (3.23 g) was added. The solution was stirred for 16 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was separated, and was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 1:1 ethyl acetate: hexane to provide the title compound.

Compound 275B

2-(tetrahydrofuran-3-yloxy)ethanol

[0806] Compound 275A (0.85 g) and 5% palladium on carbon (0.1 g) in ethanol (10 ml) was treated with a balloon of hydrogen. The reaction was stirred overnight. The solid was filtered off, and the filtrate was concentrated to give the title compound.

Compound 275C

3-nitro-4-(2-(tetrahydrofuran-3-yloxy)ethoxy)benzenesulfonamide

[0807] The title compound was prepared by substituting Compound 275B for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 275D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0808] The title compound was prepared by substituting Compound 275C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.32 (s, 1H), 8.00-8.02 (m, 2H), 7.49-7.52 (m, 2H), 7.39-7.41 (m, 1H), 7.38 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.33-4.35 (m, 2H), 4.18-4.21 (m, 1H), 3.62-3.67 (m, 4H), 3.09 (s, 4H), 2.83 (s, 2H), 2.26 (s, 2H), 2.15 (s, 2H), 1.96 (s, 2H), 1.85-1.94 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

Compound 276

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-

b]pyridin-5-yloxy)benzamide

Compound 276A

trans-4-(aminomethyl)cyclohexanecarbonitrile

[0809] To a solution of tert-butyl (trans-4-(cyanomethyl)cyclohexyl)methylcarbamate (500 mg) in dichloromethane (10 ml) was slowly added trifluoroacetic acid (2 ml) at 0°C. The reaction mixture was warmed to room temperature, stirred for 1 hour and concentrated to provide the title compound.

Compound 276B

4-((trans-4-cyanocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[0810] A mixture of 4-fluoro-3-nitrobenzenesulfonamide (347 mg) and Compound 276A (300 mg) in tetrahydrofuran (20 ml) was treated with triethylamine (1.4 ml) overnight and concentrated. The residue was triturated with ethyl acetate to provide the title compound.

Compound 276C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0811] The title compound was prepared as described in the procedure for Compound 11D using Compound 276B in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1 H), 11.36 (s, 1 H), 8.60 (t, 1 H), 8.56 (d, 1 H), 8.04 (d, 1 H), 7.79 (dd, 1 H), 7.47 - 7.54 (m, 3 H), 7.34 (d, 2 H), 7.01 - 7.09 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.25 (t, 2 H), 3.07 (s, 4 H), 2.76 (s, 2 H), 2.57 - 2.68 (m, 1 H), 2.17 (d, 6 H), 1.92 - 2.06 (m, 4 H), 1.78 (d, 2 H), 1.66 (s, 1 H), 1.35 - 1.53 (m, 4 H), 0.96 - 1.10 (m, 2 H), 0.92 (s, 6 H).

Compound 277

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 277A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0812] To a suspension of hexane washed NaH (17 g) in dichloromethane (700 ml) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After

stirring for 30 minutes, the mixture was cooled to –78°C and trifluoroacetic anhydride (40 ml) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the product.

Compound 277B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

[0813] Compound 277A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 dimethoxyethane/methanol (600 ml) were heated to 70°C for 24 hours. The mixture was concentrated. Ether (4 × 200 ml) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

Compound 277C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

[0814] To a mixture of $LiBH_4$ (13g), Compound 277B (53.8 g) and ether (400 ml), was added methanol (25 ml) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3 × 100 ml). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

Compound 277D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

[0815] Mesyl Chloride (7.5 ml) was added via syringe to Compound 277C (29.3 g) and triethylamine (30 ml) in CH_2Cl_2 (500 ml) at 0°C, and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10–20% ethyl acetate/hexanes.

Compound 277E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

[0816] Compound 277D (1 g) was stirred in dichloromethane (10 ml), trifluoroacetic acid

(10 ml), and triethylsilane (1 ml) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 ml) and saturated aqueous Na_2CO_3 solution (20 ml) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated to give the product.

Compound 277F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

[0817] To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 ml) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 ml), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 ml) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

Compound 277G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

[0818] To a mixture of Compound 277F (24.3 g) in tetrahydrofuran (500 ml) at –78°C was added 2.5M BuLi (30.3 ml). After 2 minutes, trimethylborate (11.5 ml) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted thee times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 ml) at 0°C, and 1M NaOH (69 ml) was added, followed by 30% H_2O_2 (8.43 ml), and the solution was stirred for 1 hour. $Na_2S_2O_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 5–25% ethyl acetate/hexanes.

Compound 277H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

[0819] A mixture of Compound 277G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 ml) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 ml), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2–50% ethyl acetate/hexanes.

Compound 277I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0820] A mixture of Compound 277H (1.55 g), Compound 277E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 ml) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 ml), and washed three times with 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

Compound 277J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0821] Compound 277I (200 mg) in dioxane (10 ml) and 1M NaOH (6 ml) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted thee times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

Compound 277K

5,6-dichloropyridine-3-sulfonamide

[0822] To a solution of 5,6-dichloropyridine-3-sulfonyl chloride (32.16 g) in isopropyl alcohol (300 ml) at 0°C was added a 30% aqueous solution of NH_4OH (50.8 ml). After stirring overnight, the solvent was reduced to 1/3 of the original volume. It was then partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel. The material was then slurried in 1:9 ethyl acetate/hexanes, filtered and dried under vacuum to give the title compound.

Compound 277L

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

[0823] 1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 ml) was treated with 1.0 N $LiAlH_4$ in tetrahydrofuran (2.54 ml) at 0°C. The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 ml) was added to the reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 ml). The reaction was

stirred for another 1 hour. The solid was removed by filtration via a pack of diatomaceous earth and washed with ethyl acetate. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the product.

Compound 277M

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

[0824] To a solution of Compound 277L (1 g) in tetrahydrofuran (15 ml) was added NaH (60% dispersion in mineral oil, 685 mg), and the solution was stirred for 10 minutes. Compound 227K (1 g) was added and the reaction stirred for 24 hours. The mixture was poured into water, neutralized with 10% HCl, and extracted with ethyl acetate thee times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 30% ethyl acetate in hexanes.

Compound 277N

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

[0825] Compound 277M (13 ml) was treated with trifluoroacetic acid (2.363 ml), stirred at ambient temperature for 2 hours, concentrated and dried to give the title compound.

Compound 277O

5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0826] Compound 277N (0.088 g) and oxetan-3-one (0.014 g) were combined in dichloromethane (2.0 ml) and dimethylformamide (1.0 ml) and stirred at ambient temperature for 45 minutes. Sodium triacetoxyborohydride (0.064 g) was added in portions. Stirring was continued overnight at ambient temperature. Additional oxetan-3-one (0.014 g) was added and stirring was continued for 30 minutes at ambient temperature before more sodium triacetoxyborohydride (0.064 g) was added. The reaction mixture was stirred for 72 hours at ambient temperature, concentrated, chromatographed on silica gel with 0 to 5% methanol in dichloromethane as the eluent, and dried in a vacuum oven at 80 °C to give the title compound.

Compound 277P

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0827] Compound 277J (0.063 g), Compound 277O (0.042 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.032 g), and 4-dimethylaminopyridine (0.027 g) were combined in a 4-ml vial with dichloromethane (1.0 ml) and stirred overnight at ambient temperature. The reaction mixture was chromatographed directly without aqueous workup on silica gel with 0-4% methanol in dichloromethane as the eluent. Fractions containing the desired product were concentrated, slurried in acetonitrile, concentrated and dried overnight in a vacuum oven at 80°C to give the title compound. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.13 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.66 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.51 (m, 2H), 4.63 (m, 4H), 4.53 (d, 2H), 3.39 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.51 (m, 2H), 2.25 (m, 2H), 2.18 (m, 2H), 2.13 (m, 4H), 2.06 (t, 2H), 1.97 (s, 2H), 1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 278

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 278A

5-bromo-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

[0828] The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 36B.

Compound 278B

5-cyano-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

[0829] The title compound was prepared by substituting Compound 278A for Compound 36B in the procedure for Compound 36C.

Compound 278C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0830] The title compound was prepared by substituting Compound 278B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.60 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 7.96 (d, 1H), 7.56 (d, 1H), 7.45-7.47 (m, 1H), 7.40 (s, 1H), 7.36 (d, 2H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.34 (dd, 1H), 6.25 (d, 1H), 4.47 (d, 2H), 3.80-3.84

(m, 2H), 3.24-3.28 (m, 2H), 3.12 (s, 2H), 2.16 (s, 2H), 1.97 (s, 2H), 1.61-1.71 (m, 4H), 1.40 (t, 2H), 1.21-1.25 (m, 2H), 0.93 (s, 6H).

Compound 279

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 279A

4-(furan-3-ylmethoxy)-3-nitrobenzenesulfonamide

[0831] The title compound was prepared by substituting furan-3-ylmethanol for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 279B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0832] The title compound was prepared by substituting Compound 279A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.34 (s, 1H), 8.03-8.06 (m, 2H), 7.83 (s, 1H), 7.69 (t, 1H), 7.51-7.53 (m, 4H), 7.34-7.36 (m, 2H), 7.04-7.06 (m, 2H), 6.68 (dd, 1H), 6.57 (s, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 5.23 (s, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.32 (m, 6H), 1.39 (t, 2H), 0.92 (s, 6H).

Compound 280

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 280A

(R)-tert-butyl 3-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)pyrrolidine-1-carboxylate

[0833] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide and (R)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 280B

(R)-5-chloro-6-(pyrrolidin-3-ylmethoxy)pyridine-3-sulfonamide

[0834] The title compound was prepared by substituting Compound 280A for tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in the procedure for Compound

252B.

Compound 280C

(R)-5-chloro-6-((1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

[0835] The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4′-chlorobiphenyl-2-carboxaldehyde and Compound 280B for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 280D

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0836] The title compound was prepared by substituting Compound 280C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.57 (s, 1 H), 8.38 (d, 1 H), 8.07 (d, 1 H), 7.96 (d, 1 H), 7.57 (d, 1 H), 7.44 (m, 1 H), 7.35 (m, 3 H), 7.05 (d, 2 H), 6.64 (dd, 1 H), 6.33 (dd, 1 H), 6.23 (d, 1 H), 4.65 (d, 2 H), 4.53 (dd, 2 H), 2.92 (m, 8 H), 2.75 (m, 4 H), 2.58 (m, 2 H), 2.20 (m, 6 H), 1.96 (m, 4 H), 1.53 (m, 1 H), 1.39 (t, 2 H), 0.89 (s, 6 H).

Compound 281

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 281A

(R)-5-chloro-6-((1-(2,2-difluoroethyl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

[0837] The title compound was prepared by substituting Compound 280B for Compound 261B in the procedure for Compound 261C.

Compound 281B

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0838] The title compound was prepared by substituting Compound 281A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.59 (s, 1 H), 8.41 (d, 1 H), 8.10 (d, 1 H), 7.98 (d, 1 H), 7.56 (d, 1 H), 7.46 (m, 1 H), 7.41 (d, 1 H),

7.34 (d, 2 H), 7.04 (d, 2 H), 6.65 (dd, 1 H), 6.35 (dd, 1 H), 6.23 (m, 1 H), 6.03 (m, 1 H), 3.06 (s, 4 H), 2.84 (m, 6 H), 2.63 (m, 4 H), 2.20 (m, 6 H), 1.94 (m, 3 H), 1.53 (m, 1 H), 1.39 (t, 2 H), 0.91 (s, 6 H).

Compound 282

N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 282A

5-chloro-6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0839] Compound 257B (0.088 g) and 1,3-difluoropropan-2-one (0.028 g) were combined in dichloromethane (2 ml) and N,N-dimethylformamide (0.500 ml) and stirred at ambient temperature for 45 minutes. Sodium triacetoxyborohydride (0.064 g) was added in portions and then the reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred at ambient temperature for 72 hours. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated under high vacuum to remove N,N-dimethylformamide and then chromatographed on silica gel with 0 to 4% methanol in CH_2Cl_2 as the eluent.

Compound 282B

N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0840] The title compound was prepared by substituting Compound 282A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.12 (t, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m,

2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.77 (dd, 1H), 4.65 (dd, 1H), 4.52 (dd, 2H), 3.06 (m, 4H), 2.93 (t, 1H), 2.80 (m, 5H), 2.52 (m, 1H), 2.26 (t, 2H), 2.13 (m, 4H), 2.04 (m, 2H), 1.97 (s, 2H), 1.85 (m, 2H), 1.39 (t, 2H), 1.28 (m, 2H), 0.93 (s, 6H).

Compound 283

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 283A

3-chloro-4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)benzenesulfonamide

[0841] To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.265 g) in tetrahydrofuran (2 ml) was added sodium hydride (0.288 g). After 15 minutes, 3-chloro-4-fluorobenzenesulfonamide (0.377 g) was added as a solution in tetrahydrofuran (1 ml). The reaction was stirred for 2 hours, quenched with water (5 ml), adjusted to pH~7 with 1N aqueous HCl, and extracted with dichloromethane (2 × 25 ml). The organic layer was washed with brine (25 ml), dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.1% to 10% methanol containing 2N NH_3/dichloromethane over 30 minutes gave the title compound.

Compound 283B

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0842] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 283A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.60 (s, 1H), 10.68 – 9.84 (m, 1H), 7.99 (d, 1H), 7.79 (d, 1H), 7.63 (t, 1H), 7.54 (d, 1H), 7.50 – 7.38 (m, 2H), 7.34 (d, 2H), 7.04 (d, 3H), 6.64 (dd, 1H), 6.36 (dd, 1H), 6.22 (s, 1H), 4.23 (d, 2H), 3.03 (s, 6H), 2.71 (m, 4H), 2.07 (m, 12H), 1.38 (s, 3H), 1.24 (s, 2H), 0.92 (s, 6H).

Compound 284

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 284A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0843] To a solution of (tetrahydro-2H-pyran-4-yl)methanol (0.258 g) in tetrahydrofuran (5 ml) was added sodium hydride (0.355 g) and the reaction stirred at room temperature for 15 minutes. Compound 52A (0.400 g) was added and the reaction stirred for an additional 1 hour. The reaction was poured into ethyl acetate (50 ml) and 1N aqueous HCl (35 ml). The organic layer was washed with brine (35 ml) dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 10% to 100% ethyl acetate/hexanes over 30 minutes gave the title compound.

Compound 284B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0844] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 284A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.69 (s, 1H), 11.60 - 11.16 (m, 1H), 8.15 (s, 1H), 8.08 - 8.01 (m, 2H), 7.58 - 7.46 (m, 3H), 7.35 (d, J = 8.4, 2H), 7.29 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.05 (d, 2H), 3.89 (d, 2H), 3.37 (d, 4H), 3.09 (s, 4H), 2.81 (s, 2H), 2.21 (d, 7H), 1.96 (s, 2H), 1.67 (d, 2H), 1.39 (s, 2H), 0.92 (s, 6H).

Compound 285

N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 285A

5-chloro-6-((1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

[0845] Compound 257B (0.263 g), 1,1-difluoro-2-iodoethane (0.23 g), and sodium carbonate (0.254 g) were combined in a 20-ml vial with N,N-dimethylformamide (6 ml) and stirred at 70°C overnight. The reaction mixture was concentrated under high vacuum and then chromatographed on silica gel with 0 to 5% methanol in CH_2Cl_2 as the eluent.

Compound 285B

N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-

yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0846] The title compound was prepared by substituting Compound 285A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.43 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 6.18 (tt, 2H), 4.51 (d, 2H), 3.07 (m, 4H), 2.80 (m, 6H), 2.60 (td, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 2.03 (t, 2H), 1.97 (s, 2H), 1.93 (m, 1H), 1.85 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 286

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 286A

3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0847] The title compound was prepared by substituting Compound 37C for (4-fluoro-1-methylpiperidin-4-yl)methanol in the procedure for Compound 283A.

Compound 286B

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0848] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 286A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.71 (s, 1H), 11.56 - 11.16 (m, 1H), 8.06 (d, 1H), 7.90 (d, 1H), 7.81 (d, 1H), 7.64 - 7.45 (m, 3H), 7.34 (d, 2H), 7.26 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.28 (d, 2H), 3.78 (d, 2H), 3.61 (dd, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.87 (dd, 6H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 287

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 287A

(4,4-difluorocyclohexyl)methanol

[0849] Ethyl 4,4-difluorocyclohexanecarboxylate (1.0 g, 5.20 mmol) in diethyl ether (2 ml) was added dropwise to lithium aluminium hydride (0.24 g) in diethyl ether (15 ml), and heated under reflux for 4 hours. The reaction was then cooled to 0°C, and water was added (0.24 ml), followed by 5*N* aqueous NaOH (0.24 ml) and water (0.72 ml). Then Na_2SO_4 and more diethyl ether (40 ml) were added, and the mixture was stirred for 30 minutes, then filtered through celite. After concentration, the residue was diluted with CH_2Cl_2 and Na_2SO_4 was added, and the mixture was filtered and concentrated to provide the title compound.

Compound 287B

5-chloro-6-((4,4-difluorocyclohexyl)methoxy)pyridine-3-sulfonamide

[0850] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide and Compound 287A for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 287C

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0851] The title compound was prepared by substituting Compound 287B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1H), 8.46 (d, 1H), 8.14 (d, 1H), 8.00 (d, 1H), 7.56 (d, 1H), 7.47 (m, 2H), 7.35 (d, 2H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.07 (br m, 4H), 2.82 (br s, 2H), 2.30 (br m, 4H), 2.16 (br m, 2H), 2.00, 1.95, 1.85 (all m, total 9H), 1.40 (t, 2H), 1.37 (m, 2H), 0.92 (s, 6H).

Compound 288

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 288A

5-nitro-3-(trifluoromethyl)pyridin-2-ol

[0852] 3-(Trifluoromethyl)pyridin-2-ol (2.3 g) was added to concentrated sulfuric acid

(15 ml) at 0 °C. The mixture was stirred at 0°C for 5 minutes. To this solution was added fuming nitric acid (6 ml) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 2 hours, and then heated at 50°C for 3 hours. After cooling, the reaction mixture was poured onto ice (200 g), and the mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the title compound.

Compound 288B

2-chloro-5-nitro-3-(trifluoromethyl)pyridine

[0853] A mixture of Compound 288A (1.69 g), phosphorus pentachloride (2.03 g), and phosphoryl trichloride (0.97 ml) was heated at 90°C for 3 hours. After cooling, the reaction mixture was poured into ice, and extracted with ethyl acetate three times. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in hexanes to provide the title compound.

Compound 288C

6-chloro-5-(trifluoromethyl)pyridin-3-amine

[0854] A mixture of iron (1.5 g) and ammonium chloride (2.38 g) in water (40 ml) was stirred at room temperature for 5 minutes. To this suspension was added Compound 288B in methanol (40 ml). The reaction mixture was stirred at room temperature for 1 hour. More iron (1.8 g) was added to the reaction mixture, and it was stirred for another 3 hours. The solid from the reaction mixture was filtered off, and the filtrate was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 20% ethyl acetate in hexanes to provide the title compound.

Compound 288D

6-chloro-5-(trifluoromethyl)pyridine-3-sulfonyl chloride

[0855] Under ice-cooling, thionyl chloride (4 ml) was added dropwise over 20 minutes to water (27 ml). The mixture was stirred overnight for 12 hours to give a SO_2 containing solution. Separately, Compound 288C (1.14 g) in dioxane (5 ml) was added to concentrated HCl (20 ml) at 0°C. The solution was stirred for 5 minutes. To this suspension/solution was

added sodium nitrite (0.44 g) in water (6 ml) dropwise at 0°C. The solution was stirred at 0°C for 3 hours. During this time, any solid formed was crushed with a glass rod to make sure that Compound 288C was completely reacted. To the SO_2 containing solution was added copper(I) chloride (0.115 g). Then, to this solution was added the diazotized Compound 288C at 0°C. The solution was stirred for 30 minutes. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to provide the title compound.

Compound 288E

6-chloro-5-(trifluoromethyl)pyridine-3-sulfonamide

[0856] Compound 288D (2.03 g) in dioxane (20 ml) solution was cooled to 0°C. Ammonium hydroxide solution was added dropwise. The reaction mixture was stirred at 0°C for 2 hours followed by room temperature over night. The solvent was partially removed, and the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 0-3% methanol in dichloromethane to afford the title compound.

Compound 288F

tert-butyl 4-fluoro-4-((5-sulfamoyl-3-(trifluoromethyl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate

[0857] The title compound was prepared by substituting Compound 288E for 4-fluoro-3-nitrobenzenesulfonamide and Compound 322A for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 288G

6-((4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

[0858] The title compound was prepared by substituting Compound 288F for tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in the procedure for Compound 252B.

Compound 288H

6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-

3-sulfonamide

[0859] The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and Compound 288G for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A.

Compound 288I

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0860] The title compound was prepared by substituting Compound 288H for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.50 (s, 1 H), 8.57 (s, 1 H), 8.27 (d, 1 H), 7.91 (d, 1 H), 7.58 (d, 1 H), 7.40 (m, 1 H), 7.35 (d, 2 H), 7.28 (d, 1 H), 7.05 (d, 2 H), 6.61 (dd, 1 H), 6.29 (dd, 1 H), 6.24 (d, 1 H), 4.67 (d, 2 H), 4.55 (d, 2 H), 4.50 (s, 1 H), 4.44 (s, 1 H), 3.06 (m, 5 H), 2.73 (m, 6 H), 2.19 (d, 6 H), 1.90 (m, 7 H), 1.39 (t, 2 H), 0.93 (s, 6 H).

Compound 289

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 289A

5-chloro-6-(2-(tetrahydrofuran-2-yl)ethoxy)pyridine-3-sulfonamide

[0861] The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for Compound 36A in the procedure for Compound 36B.

Compound 289B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0862] The title compound was prepared by substituting Compound 289A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.52 (d, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.50-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.39-4.51 (m, 4H), 3.87-3.94 (m, 1H), 3.73-3.78

(m, 1H), 3.57-3.62 (m, 1H), 3.11 (s, 4H), 2.89 (s, 2H), 2.33 (s, 4H), 2.15 (s, 2H), 1.77-2.01 (m, 7H), 1.45-1.54 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H).

Compound 290

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 290A

2-chloro-4,4-dimethylcyclohex-1-enecarbaldehyde

[0863] Into a 250 ml round-bottomed flask was added N,N-dimethylformamide (3.5 ml) in dichloromethane (30 ml). The mixture was cooled to –10°C, and phosphoryl trichloride (4 ml) was added dropwise. The solution was warmed up to room temperature and 3,3-dimethylcyclohexanone (5.5 ml) was added slowly. The mixture was heated to reflux overnight. The reaction mixture was quenched by 0°C solution of sodium acetate (25 g in 50 ml water). The aqueous layer was extracted with ether (3 × 200 ml). The organic layers were combined, dried over Na_2SO_4, filtered, and dried under vacuum.

Compound 290B

2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarbaldehyde

[0864] Into a 1 L round-bottomed flask was added Compound 290A (6.8 g), 4-chlorophenylboronic acid (6.5 g) and palladium(II) acetate (0.2 g) in water (100 ml) to give a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing after subjecting to vacuum and nitrogen, the mixture was stirred at 45°C for 4 hours. After filtering through silica gel, diethyl ether (4 × 200 ml) was used to extract the product. The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0–10% ethyl acetate in hexanes to provide the title compound.

Compound 290C

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazine-1-carboxylate

[0865] To a solution of *tert*-butyl 3-methylpiperazine-1-carboxylate (0.256 g) and Compound 290B (0.350 g) in dichloromethane (2 ml) was added sodium triacetoxyborohydride (0.406 g) and the reaction was stirred at room temperature overnight.

The reaction was quenched with $NaHCO_3$ solution (50 ml) and extracted with dichloromethane (50 ml). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 2.5% methanol/dichloromethane gave the title compound.

Compound 290D

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-2-methylpiperazine

[0866] A solution of Compound 290C (0.298 g) and HCl (4.0M in dioxane, 2 ml) were stirred for 1 hour. The reaction was concentrated and partioned between dichloromethane (100 ml) and $NaHCO_3$ (100 ml). The organic layer was washed with brine (50 ml), dried over magnesium sulfate, filtered and concentrated to provide the title compound.

Compound 290E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoate

[0867] The title compound was prepared by substituting Compound 290D for Compound 3E in the procedure for Compound 3I.

Compound 290F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoic acid

[0868] The title compound was prepared by substituting Compound 290E for Compound 15G in the procedure for Compound 15H.

Compound 290G

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0869] The title compound was prepared by substituting Compound 290F for Compound 1E in the procedure for Compound 1G. ^1H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.66 (s, 1H), 11.54 - 11.30 (m, 1H), 8.62 - 8.53 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.68 (d, 1H), 6.38 (dd, 1H), 6.21 (s, 1H), 3.84 (d, 2H), 3.23 (s, 4H), 2.75 (s, 4H), 1.64 (s, 8H), 1.62 (d, 2H), 1.42 - 1.17 (m, 6H), 0.92 (s, 6H), 0.87 (s, 3H).

Compound 291

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-

{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 291A

tert-butyl 2-cyanoethyl(cyclopropyl)carbamate

[0870] To a solution of 3-(cyclopropylamino)propanenitrile (5.0g) in tetrahydrofuran (30 ml) was added di-*tert*-butyl dicarbonate (9.91g) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 ml) and washed with 5% aqueous HCl, water and brine. After drying over Na_2SO_4, the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

Compound 291B

tert-butyl 3-aminopropyl(cyclopropyl)carbamate

[0871] Compound 291A (9.75 g) and 7M NH_3-methanol (25 ml) were added to a Ra-Ni 2800, water slurry (19.50 g, 332 mmol) in a 250 ml pressure bottle and stirred for 2 hours at 30 psi and room temperature. The mixture was filtered though a nylon membrane and evaporation of the solvent gave the title compound.

Compound 291C

tert-butyl cyclopropyl(3-(2-nitro-4-sulfamoylphenylamino)propyl)carbamate

[0872] To a solution of 4-chloro-3-nitrobenzenesulfonamide (2.5 g), and Compound 291B (2.26 g) in dioxane (20 ml) was added N,N-diisopropylethylamine (5 ml). The mixture was stirred at reflux overnight. The mixture was diluted with ethyl acetate (400 ml) and washed with water and brine. After drying over Na_2SO_4, the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

Compound 291D

tert-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)propyl(cyclopropyl)carbamate

[0873] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 291C for Compound 1F in the procedure for Compound 1G.

Compound 291E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-

(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0874] To a solution of Compound 291D (2.56 g) in dichloromethane (10 ml) was added trifluoroacetic acid(10 ml). The mixture was stirred for 2 hours. The mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, and brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the crude product. The title compound was obtained by dissolving 200 mg of the crude material in dimethylsulfoxide/methanol (1:1, 10 ml) and loaded on Gilson, C18(100A) 250x121.2 mm(10micron), eluting with 30% acetonitrile to 65% acetonitrile over 40 minutes. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.54 (s, 1 H), 8.43 (m, 2 H), 7.94 (d, 1 H), 7.71 (dd, 1 H), 7.57 (d, 1 H), 7.43 (m, 1 H), 7.34 (m, 3 H), 7.05 (d, 2 H), 6.90 (d, 1 H), 6.63 (dd, 1 H), 6.29 (d, 2 H), 3.43 (m, 2 H), 2.96 (m, 6 H), 2.73 (m, 2 H), 2.22 (m, 7 H), 1.87 (m, 4 H), 1.38 (m, 3 H), 0.94 (m, 6 H), 0.62 (m, 4 H).

Compound 292

N-{[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 292A

5-chloro-6-(2-methoxyethoxy)pyridine-3-sulfonamide

[0875] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide and 2-methoxyethanol for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 292B

N-{[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0876] The title compound was prepared by substituting Compound 292A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1H), 8.48 (d, 1H), 8.17 (d, 1H), 8.01 (d, 1H), 7.56 (d, 1H), 7.49 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.52 (m, 2H), 3.70 (m, 2H), 3.28 (s, 3H), 3.13 (br m, 4H), 2.88 (br s, 2H), 2.34 (br m, 4H), 2.16 (br m, 2H), 1.97 (s, 2H), 1.40 (t, 2H),

0.92 (s, 6H).

Compound 293

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 293A

5-bromo-3-fluoro-2-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine

[0877] The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 293B

tert-butyl 5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

[0878] The title compound was prepared by substituting Compound 293A for Compound 248A in the procedure for Compound 248B.

Compound 293C

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

[0879] The title compound was prepared by substituting Compound 293B for Compound 248B in the procedure for Compound 248C.

Compound 293D

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

[0880] The title compound was prepared by substituting Compound 293C for Compound 248C in the procedure for Compound 248D.

Compound 293E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0881] The title compound was prepared by substituting Compound 293D for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.07 (s, 1H), 9.05 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.21 (d, 2H), 3.96 (dd, 2H), 3.31 (td, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (m, 3H), 1.58 (dd, 2H), 1.38 (m, 4H), 0.94 (s, 6H).

Compound 294

N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 294A

tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

[0882] The title compound was prepared by substituting *tert*-butyl-4-(hydroxymethyl)piperidine-1-carboxylate for (4-fluoro-1-methylpiperidin-4-yl)methanol in the procedure for Compound 283A.

Compound 294B

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-chlorophenoxy)methyl)piperidine-1-carboxylate

[0883] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 294A for Compound 1F in the procedure for Compound 1G.

Compound 294C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(3-chloro-4-(piperidin-4-ylmethoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[0884] To Compound 294B (0.286 g) in dichloromethane (3 ml) was added trifluoroacetic acid (1 ml) and the reaction stirred at room temperature. After 3 hours the reaction was concentrated to provide the title compound.

Compound 294D

N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0885] To Compound 294C (0.75 g) as a solution in dichloromethane (1 ml) was added N,N-diisopropylethylamine (0.055 ml) followed by 2-methoxyacetyl chloride (6 µl). After stirring for 10 minutes the reaction was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.5% to 3.5% methanol/dichloromethane over 30 minutes (flow = 40 ml/minutes) to provide the title compound. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.71 (s, 1H), 11.55 - 11.24 (m, 1H), 8.06 (d, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.57 (s, 1H),

7.51 (s, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.21 (d, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.42 - 4.32 (m, 1H), 4.03 (dd, 4H), 3.86 - 3.74 (m, 1H), 3.28 (s, 3H), 3.07 (s, 5H), 2.77 (s, 3H), 2.30 - 1.92 (m, 9H), 1.77 (s, 2H), 1.31 (d, 4H), 0.92 (s, 6H).

Compound 295

N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0886] The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride for 2-methoxyacetyl chloride in the procedure for Compound 294D. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.58 (s, 1H), 10.35 – 9.94 (m, 1H), 7.96 (d, 1H), 7.74 (d, 1H), 7.55 (d, 2H), 7.45 (s, 1H), 7.41 – 7.29 (m, 3H), 7.05 (d, 3H), 6.63 (d, 1H), 6.37 – 6.32 (m, 1H), 6.22 (d, 1H), 4.39 (d, 1H), 3.94 (s, 6H), 3.01 (s, 6H), 2.73 (m, 4H), 2.55 (m, 5H), 2.19 (s, 6H), 1.95 (m, 2H), 1.82 (m, 2H), 1.38 (s, 4H), 0.93 (s, 6H).

Compound 296

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 296A

tert-butyl 4-((4,4-dimethyl-2-oxocyclohexyl)methyl)piperidine-1-carboxylate

[0887] 3,3-Dimethylcyclohexanone (5.60 ml) was added to sodium bis(trimethylsilyl)amide (45.3 ml, 1M in tetrahydrofuran), and the reaction was stirred for 1 hour. tert-Butyl 4-(bromomethyl)piperidine-1-carboxylate (11.1 g) in dimethylsulfoxide (30 ml) was added, and the reaction was stirred at 50°C for 24 hours. The reaction was cooled, poured into water (300 ml), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

Compound 296B

tert-butyl 4-((2-(4-chlorophenyl)-2-hydroxy-4,4-dimethylcyclohexyl)methyl)piperidine-1-carboxylate

[0888] (4-Chlorophenyl)magnesium bromide (14.1 ml, 1M in ether) was added to

Compound 296A (3.25 g) in tetrahydrofuran (40 ml) at –78°C, and the reaction was stirred for 20 minutes, and then allowed to warm to room temperature overnight. The reaction was quenched with pH 7 buffer (20 ml), extracted with 2 × ether, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 1-20% ethyl acetate in hexanes to provide the title compound.

Compound 296C

trans-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidine

[0889] The title compound was prepared by substituting Compound 296B for Compound 1A in the procedure for Compound 1B.

Compound 296D

trans-methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoate

[0890] The title compound was prepared by substituting Compound 296C for Compound 263G in the procedure for Compound 263H.

Compound 296E

trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoic acid

[0891] The title compound was prepared by substituting Compound 296D for Compound 3I in the procedure for Compound 3J.

Compound 296F

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0892] The title compound was prepared by substituting Compound 296E for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.36 (br s, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.78 (dd, 1H), 7.52 (m, 3H), 7.27 (d, 2H), 7.16 (d, 2H), 7.09 (m, 1H), 6.63 (dd, 1H), 6.38 (dd, 1H), 6.11 (d, 1H), 3.83 (dd, 2H), 3.52 (m, 2H), 3.26 (m, 4H), 2.61 (m, 2H), 2.35 (m, 1H), 1.89 (m, 2H), 1.76 (m, 1H), 1.62 (m, 2H), 1.38 (m, 4H), 1.25 (m, 6H), 1.12 (m, 2H), 0.95 (m, 2H), 0.94 (s, 3H), 0.88 (s, 3H).

Compound 297

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}benzamide

Compound 297A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

[0893] The title compound was prepared by substituting Compound 288E for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 297B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}benzamide

[0894] The title compound was prepared by substituting Compound 297A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.49 (s, 1 H), 8.56 (d, 1 H), 8.23 (d, 1 H), 7.90 (d, 1 H), 7.58 (d, 1 H), 7.40 (m, 1 H), 7.34 (m, 2 H), 7.26 (d, 1 H), 7.05 (d, 2 H), 6.61 (dd, 1 H), 6.28 (dd, 1 H), 6.24 (d, 1 H), 4.24 (d, 2 H), 3.86 (dd, 2 H), 3.30 (m, 4 H), 3.00 (s, 4 H), 2.73 (s, 2 H), 2.16 (m, 6 H), 1.97 (m, 2 H), 1.61 (dd, 2 H), 1.33 (m, 4 H), 0.93 (s, 6 H).

Compound 298

N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 298A

6-((trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-5-chloropyridine-3-sulfonamide

[0895] The title compound was prepared by substituting (trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for Compound 36A in the procedure for Compound 36B.

Compound 298B

N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0896] The title compound was prepared by substituting Compound 298A for Compound 11B in the procedure for Compound 11D. After the reaction was over, the solvent was removed, and the residue was treated with 1:1 trifluoroacetic acid/dichloromethane for two hours. The solvents were removed, and the residue was purified by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ, C18(2), 250X21.20 mm, 5 Å) eluting with 20-80% acetonitrle in water with 0.1% trifluoroacetic acid to provide the title compound. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.21 (s, 1H), 4.53 (t, 1H), 4.18 (d, 2H), 3.08 (s, 4H), 2.84 (s, 2H), 2.29 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.79-1.83 (m, 5H), 1.39 (t, 2H), 1.08-1.13 (m, 5H), 0.93 (s, 6H).

Compound 299

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 299A

3-cyano-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0897] The title compound was prepared by substituting Compound 37C for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 284A.

Compound 299B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0898] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 299A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.72 (s, 1H), 10.24 - 9.27 (m, 1H), 8.21 (d, 1H), 8.12 (dd, 1H), 8.05 (d, 1H), 7.63 - 7.46 (m, 3H), 7.45 - 7.31 (m, 3H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 4.38 (d, 2H), 3.91 - 3.73 (m, 2H), 3.68 - 3.51 (m, 2H), 3.22 - 2.96 (m, 10H), 2.31 - 2.12 (m, 2H), 1.99 (s, 6H), 1.43 (t, 2H), 0.93 (s, 6H).

Compound 300

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 300A

6-((trans-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

[0899] The title compound was prepared by substituting Compound 288E for 4-fluoro-3-nitrobenzenesulfonamide and Compound 121A for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 300B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0900] The title compound was prepared by substituting Compound 300A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.50 (s, 1 H), 8.56 (d, 1 H), 8.23 (d, 1 H), 7.90 (d, 1 H), 7.58 (d, 1 H), 7.40 (m, 1 H), 7.35 (d, 2 H), 7.27 (d, 1 H), 7.05 (d, 2 H), 6.61 (dd, 1 H), 6.28 (dd, 1 H), 6.24 (d, 1 H), 4.20 (d, 2 H), 3.23 (s, 3 H), 3.03 (m, 5 H), 2.73 (s, 2 H), 2.18 (m, 6 H), 1.98 (m, 5 H), 1.80 (m, 3 H), 1.39 (t, 2 H), 1.09 (m, 4 H), 0.93 (s, 6 H).

Compound 301

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 301A

6-((cis-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

[0901] The title compound was prepared by substituting Compound 288E for 4-fluoro-3-nitrobenzenesulfonamide and Compound 121A for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 301B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3b]pyridin-5-yloxy)benzamide

[0902] The title compound was prepared by substituting Compound 301A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.49

(m, 1 H), 8.54 (m, 1 H), 8.23 (d, 1 H), 7.91 (d, 1 H), 7.59 (d, 1 H), 7.40 (m, 1 H), 7.34 (m, 2 H), 7.27 (d, 1 H), 7.04 (d, 2 H), 6.61 (dd, 1 H), 6.29 (dd, 1 H), 6.24 (d, 1 H), 4.20 (d, 2 H), 3.37 (m, 2 H), 3.19 (s, 3 H), 3.00 (s, 4 H), 2.73 (s, 2 H), 2.18 (m, 6 H), 1.96 (s, 2 H), 1.80 (m, 3 H), 1.50 (dd, 2 H), 1.37 (m, 6 H), 0.93 (s, 6 H).

Compound 302

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-({[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 302A

4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidine

[0903] Compound 296B (1.0 g) was stirred in dichloromethane (15 ml) and trifluoroacetic acid (15 ml) at 35°C for 48 hours. The mixture was concentrated, taken up in dichloromethane (100 ml), and stirred, and saturated Na_2CO_3 solution (20 ml) was added slowly. The solution was separated and the organic layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

Compound 302B

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoate

[0904] The title compound was prepared by substituting Compound 302A for Compound 263G in the procedure for Compound 263H.

Compound 302C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoic acid

[0905] The title compound was prepared by substituting Compound 302B for Compound 3I in the procedure for Compound 3J.

Compound 302D

1,1-difluoro4-methylenecyclohexane

[0906] Butyllithium (12.32 ml, 2.5 M solution in hexanes) was added to a solution of methyltriphenylphosphonium chloride (9.63 g) in tetrahydrofuran (50 ml) at 0°C, and the reaction was stirred for 5 minutes. 4,4-Difluorocycleohexanone (3.76 g) in dioxane (150 ml)was then added, and the reaction was stirred for 30 minutes. Water (3 ml) was added, and

then hexane (150 ml) was slowly added, the reaction was filtered, and the solution carried on.

Compound 302E

4,4-difluoro-1-(hydroxymethyl)cyclohexanol

[0907] To the solution from Compound 302D was added water (75 ml), then N-metthylmorpholine-N-oxide (6.4 ml, 50% solution in water) and OsO_4 (14.2 g, 2.5 wt % solution in tert-butanol) were added, and the reaction was stirred for 96 hours at 50°C. The solution was cooled to room temperature, treated with saturated aqueous $Na_2S_2O_3$ solution (100 ml) for 30 minutes, and then acidified with concentrated aqueous HCl. The solution was then extracted three times with ethyl acetate, and the organic layers were combined, washed with 1M HCl, and brine, and concentrated. The crude mixture was chromatographed on silica gel using 10–100% ethyl acetate in hexanes, and then 5% methanol in ethyl acetate to give the product.

Compound 302F

5-chloro-6-((4,4-difluoro-1-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

[0908] This compound was prepared by substituting Compound 302E for tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 302G

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0909] The title compound was prepared by substituting Compound 302C for Compound 1E and Compound 302F for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.65 (br s, 2H), 8.51 (s, 1H), 8.18 (s, 1H), 8.02 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.69 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.88 (s, 1H), 4.27 (s, 2H), 3.10 (m, 4H), 2.88 (m, 1H), 2.33 (m, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.91 (m, 2H), 1.73 (m, 4H), 1.52 (m, 1H), 1.40 (m, 2H), 1.31 (m, 1H), 0.93 (s, 3H), 0.91 (m, 2H).

Compound 303

N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 303A

trans-4-morpholinocyclohexyl)methanol

[0910] To *tert*-butyl trans-4-(hydroxymethyl)cyclohexylcarbamate (0.500 g) was added hydrogen chloride (4.0M in dioxane, 2.2 ml) and the reaction was stirred for 1 hour and concentrated. The resulting solid was dissolved in acetonitrile (4 ml) and treated with N,N-diisopropylethylamine (1.523 ml) followed by 1-bromo-2-(2-bromoethoxy)ethane (0.556 g) and heated to 60°C. After stirring overnight the reaction was concentrated, loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 1% to 10% methanol/dichloromethane over 30 minutes (flow = 40 ml/min) to provide the title compound.

Compound 303B

3-chloro-4-(((1r,4r)-4-morpholinocyclohexyl)methoxy)benzenesulfonamide

[0911] The title compound was prepared by substituting Compound 303A for (4-fluoro-1-methylpiperidin-4-yl)methanol in the procedure for Compound 283A.

Compound 303C

N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0912] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 303B for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.65 (s, 1H), 10.96 – 10.59 (m, 1H), 8.02 (d, 1H), 7.82 (d, 1H), 7.69 (s, 1H), 7.50 (dd, 3H), 7.38 – 7.30 (m, 2H), 7.15 – 6.99 (m, 3H), 6.65 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 3.91 (d, 2H), 3.64 (s, 4H), 3.04 (s, 4H), 2.73 (s, 7H), 2.18 (s, 6H), 1.93 (m, 6H), 1.80 – 1.65 (m, 1H), 1.32 (m, 6H), 0.92 (s, 6H).

Compound 304

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0913] To a solution of Compound 291E (95 mg) in dichloromethane (2 ml) and acetic acid (0.5 ml) was added thiazole-5-carbaldehyde (13 mg) followed by sodium triacetoxyborohydride (35 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, and brine and dried

over Na_2SO_4. Filtration and evaporation of the solvent gave crude product which was dissolved in dimethylsulfoxide/methanol (6 ml, 1:1) and loaded on Gilson, C18(100A) 250x121.2 mm(10micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1 H), 8.95 (s, 1 H), 8.57 (m, 2 H), 8.03 (d, 1 H), 7.78 (m, 2 H), 7.49 (m, 3 H), 7.35 (m, 2 H), 7.02 (m, 3 H), 6.67 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H), 4.00 (s, 2 H), 3.05 (d, 4 H), 2.73 (m, 2 H), 2.60 (m, 2 H), 2.18 (m, 7 H), 1.95 (s, 2 H), 1.79 (m, 3 H), 1.37 (m, 3 H), 0.92 (s, 6 H), 0.45 (m, 4 H).

Compound 305

N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 305A

3-chloro-4-((trans-4-hydroxycyclohexyl)methoxy)benzenesulfonamide

[0914] (Trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol (275 mg, prepared according to a procedures in WO 2008/124878) and 3-chloro-4-fluorobenzenesulfonamide (259 mg) in tetrahydrofuran (15 ml) were treated with sodium hydride (180 mg, 60%) overnight. The reaction was quenched with water (1 ml) and trifluoroacetic acid (4 ml) was added. The resulting mixture was stirred for 1 hour and concentrated. The residue was triturated with water and methanol to provide the title compound.

Compound 305B

N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0915] The title compound was prepared as described in the procedure for Compound 11D using Compound 305A in place of Compound 11B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.71 (s, 1 H), 11.38 (s, 1 H), 8.06 (d, 1 H), 7.87 (d, 1 H), 7.76 (dd, 1 H), 7.57 (d, 1 H), 7.51 - 7.55 (m, 1 H), 7.49 (d, 1 H), 7.34 (d, 2 H), 7.18 (d, 1 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.42 (dd, 1 H), 6.18 (d, 1 H), 4.54 (d, 1 H), 3.91 (d, 2 H), 3.07 (s, 4 H), 2.75 (s, 2 H), 2.17 (d, 6 H), 1.95 (s, 2 H), 1.78 - 1.90 (m, 4 H), 1.63 - 1.75 (m, 1 H), 1.38 (t, 2 H), 1.00 - 1.25 (m, 4 H), 0.92 (s, 6 H).

Compound 306

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 306A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

[0916] The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide, (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine in the procedure for Compound 6A.

Compound 306B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0917] The title compound was prepared by substituting Compound 306A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.80 (s, 1H), 11.17 (br s, 1H), 8.09 (d, 1H), 7.71 (d, 1H), 7.63 (d, 1H), 7.58 (dd, 1H), 7.53 (dd, 1H), 7.50 (d, 1H), 7.34 (d, 2H), 7.03 (d, 2H), 6.74 (d, 1H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.40 (t, 1H), 6.16 (d, 1H), 3.83 (m, 2H), 3.24 (m, 2H), 3.10 (m, 2H), 3.06 (br m, 4H), 2.72 (s, 2H), 2.17 (br m, 6H), 1.95 (s, 2H), 1.83 (m, 1H), 1.59 (br m, 2H), 1.38 (t, 2H), 1.20 (ddd, 2H), 0.92 (s, 6H).

Compound 307

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 307A

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethyl)benzenesulfonamide

[0918] The title compound was prepared by substituting 4-fluoro-3-(trifluoromethyl)benzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and Compound 37C for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 307B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0919] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 307A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.07 (s, 1H), 8.78 (d, 1H), 8.58 (dd, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.43 (m, 2H), 7.16 (d, 1H), 7.06 (m, 2H), 6.74 (dd, 1H), 6.51 (m, 2H), 4.21 (d, 2H), 3.87 (m, 2H), 3.78 (td, 2H), 3.06 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 1.95 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 308

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 308A

4-(3-(cyclopropylamino)propylamino)-3-nitrobenzenesulfonamide

[0920] To a solution of Compound 291C (4.14 g) in dichloromethane (10 ml) was added trifluoroacetic acid(10 ml). The mixture was stirred for 2 hours. The mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, and brine and dried over Na_2SO_4. Filtration and evaporation of solvent gave the title compound.

Compound 308B

4-(3-(cyclopropyl(2,2,2-trifluoroethyl)amino)propylamino)-3-nitrobenzenesulfonamide

[0921] To a solution of Compound 308A (314 mg) in dichloromethane (6 ml) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (255 mg) and N,N-diisopropylethylamine (258 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. Filtration and evaporation of solvent gave the title compound.

Compound 308C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0922] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 308B for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1 H), 11.38 (m, 1 H), 8.55 (d, 2 H), 8.03 (d, 1 H), 7.81 (dd, 1 H), 7.50 (m, 3 H), 7.34 (d, 2 H), 7.05 (m, 3 H), 6.67 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H), 3.07 (m, 4 H), 2.82 (m, 4 H), 2.18 (m, 7 H), 1.38 (m, 2 H), 0.92 (s, 6 H), 0.44 (m, 4 H).

Compound 309

N-[(3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0923] To a solution of Compound 294B (0.150 g) in dichloromethane (2 ml) was added trifluoroacetic acid (1 ml). After stirring for 1 hour the reaction was concentrated and dried under high vacuum. The residue was dissolved in dichloromethane (2 ml) and treated with sodium triacetoxyborohydride (0.050 g) and oxetan-3-one (0.017 g) and stirred overnight at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 ml) and extracted into dichloromethane (50 ml). The organic layer was separated, washed with brine (25 ml), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 5% methanol/dichloromethane over 30 minutes (flow = 40 ml/min) provided the title compound. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.70 (s, 1H), 11.21 (s, 1H), 8.05 (d, 1H), 7.87 (d1H), 7.75 (dd, 1H), 7.61 - 7.42 (m, 3H), 7.42 - 7.26 (m, 2H), 7.18 (d, 1H), 7.14 - 6.97 (m, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.51 (dt, 4H), 3.99 (d, 2H), 3.56 - 3.32 (m, 1H), 3.06 (s, 4H), 2.89 - 2.68 (m, 4H), 2.16 (d, 6H), 2.01 - 1.69 (m, 7H), 1.50 - 1.07 (m, 4H), 0.92 (s, 6H).

Compound 310

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 310A

3,5-difluoro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0924] Compound 37C (0.423 g) in tetrahydrofuran (30 ml) was treated with NaH (60% oil dispersion) (0.480 g), stirred 20 minutes at ambient temperature, treated with 3,4,5-

trifluorobenzenesulfonamide (0.633 g) and stirred 30 minutes. N,N-Dimethylacetamide (15 ml) was added to increase solubility of the reactants and stirring was continued overnight at ambient temperature. Additional NaH (60% oil dispersion) (0.480 g) and N,N-dimethylacetamide (15 ml) were added and the mixture was heated overnight at 50°C. The reaction was quenched with saturated aqueous NH_4Cl solution and then partitioned between saturated aqueous NH_4Cl solution and ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH_2Cl_2 as the eluent. The residue was further purified by reverse phase HPLC on a C18 column using a gradient of 10–70% acetonitrile/0.1% trifluoroacetic acid in water to provide the title compound.

Compound 310B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0925] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 310A for Compound 1F in the procedure for Compound 1G. ^1H NMR (500 MHz, pyridine-d_5) δ 13.06 (s, 1H), 8.41 (d, 1H), 8.11 (m, 2H), 8.08 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 4.26 (d, 2H), 3.85 (dd, 1H), 3.83 (dd, 1H), 3.74 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.87 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 311

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 311A

4-(3-(cyclopropyl(oxetan-3-yl)amino)propylamino)-3-nitrobenzenesulfonamide

[0926] To a solution of Compound 308A (314 mg) in dichloromethane (5 ml) was added oxetan-3-one (72 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water and brine and dried over Na_2SO_4. After filtration, evaporation of the

solvent gave the crude title compound.

Compound 311B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0927] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 311A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1 H), 11.37 (s, 1 H), 8.68 (s, 1 H), 8.54 (d, 1 H), 8.02 (d, 1 H), 7.79 (d, 1 H), 7.49 (m, 3 H), 7.34 (d, 2 H), 7.03 (m, 3 H), 6.67 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H), 4.62 (m, 2 H), 4.48 (t, 2 H), 3.98 (m, 1 H), 3.37 (m, 2 H), 3.06 (m, 4 H), 2.73 (d, 2 H), 2.59 (m, 2 H), 2.23 (m, 6 H), 1.95 (s, 2 H), 1.74 (m, 3 H), 1.38 (t, 2 H), 0.92 (s, 6 H), 0.41 (m, 4 H).

Compound 312

N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0928] To Compound 294B (0.065 g) was added hydrogen chloride (4.0M in dioxane, 0.339 ml) and a few drops of methanol. After 30 minutes, the reaction was concentrated, and (S)-1-methylpyrrolidine-2-carboxylic acid (0.013 g), N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (0.026 g), suspended in dichloromethane (0.5 ml) were added followed by diisopropylethylamine (0.036 ml). The mixture stirred at room temperature. After stirring overnight, the reaction mixture was loaded onto silica gel (Reveleris 40g) and eluted using a gradient of 1% to 10% methanol (containing 1N NH_3)/dichloromethane over 30 minutes (flow = 40 ml/minutes) to provide the title compound. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.51 (s, 1H), 10.00 – 9.22 (m, 1H), 7.92 (d, 1H), 7.68 (d, 1H), 7.57 (d, 1H), 7.47 (dd, 1H), 7.44 – 7.38 (m, 1H), 7.38 – 7.31 (m, 2H), 7.29 (d, 1H), 7.12 – 7.01 (m, 2H), 6.90 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H), 6.25 (d, 1H), 5.85 (d, 1H), 4.40 (s, 1H), 3.92 (s, 4H), 3.17 – 2.89 (m, 8H), 2.73 (s, 4H), 2.38 (s, 3H), 2.18 (m, 6H), 1.96 (s, 2H), 1.80 (m, 2H), 1.57 (s, 2H), 1.39 (s, 2H), 1.22 (m, 2H), 0.96 (m, 6H).

Compound 313

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-

({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 313A

3,4-difluoro-5-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0929] The title compound was obtained as a side product in the procedure for Compound 310A.

Compound 313B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0930] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 313A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.05 (s, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.98 (m, 2H), 7.66 (m, 1H), 7.63 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.12 (d, 2H), 3.83 (m, 2H), 3.75 (m, 2H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.82 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 314

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 314A

(S)-5-chloro-6-((4-cyclopropylmorpholin-2-yl)methoxy)pyridine-3-sulfonamide

[0931] A solution of Compound 244B (250 mg), anhydrous methanol (6 ml), (1-ethoxycyclopropoxy)trimethylsilane (0.474 ml), and acetic acid (0.509 ml) was heated at 70°C for 30 minutes. After cooling to ambient temperature, sodium cyanoborohydride (112 mg) was added and the mixture was stirred for 18 hours. Additional sodium cyanoborohydride (75 mg) was added and stirring was continued 18 hours. The reaction was concentrated and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The crude product was isolated from the dried methylene chloride layer and was purified on silica gel and was eluted with a 1, 2.5, 5, 10% methanol in methylene chloride step gradient to provide the title compound.

Compound 314B

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0932] The title compound was prepared by substituting Compound 314A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (400 MHz, pyridine- d_5) δ 12.98 (s, 1H), 9.09 (d, 1H), 8.69 (d, 1H), 8.41 (d, 1H), 8.11 (d, 1H), 7.66 - 7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (m, 1H), 6.48 (m, 1H), 5.72 (br s, 1H), 4.62 - 4.57 (m, 1H), 4.51 - 4.47 (m, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 3.57 (m, 1H), 3.08 - 3.01 (m, 5H), 2.77 (s, 2H), 2.69 (m, 1H), 2.39 - 2.24 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.57 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H), 0.48 - 0.3 (m, 4H).

Compound 315

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0933] The title compound was prepared by substituting Compound 302C for Compound 1E and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.70 (s, 1H), 11.35 (br s, 1H), 8.61 (m, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.82 (dd, 1H), 7.45-7.57 (m, 3H), 7.33 (d, 2H), 7.15 (d, 1H), 7.01 (d, 2H), 6.65 (dd, 1H), 6.40 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.53 (m, 2H), 3.27 (m, 4H), 2.63 (m, 2H), 2.04 (m, 2H), 1.91 (s, 2H), 1.77 (m, 2H), 1.62 (m, 4H), 1.45 (m, 2H), 1.38 (m, 2H), 1.27 (m, 1H), 1.23 (m, 4H), 0.92 (s, 6H).

Compound 316

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 316A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

[0934] The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanol for (4-fluoro-1-methylpiperidin-4-yl)methanol in the procedure for Compound 283A.

Compound 316B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0935] The title compound was prepared by substituting Compound 302C for Compound 1E and Compound 316A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.77 (s, 1H), 11.35 (br s, 1H), 8.06 (m, 1H), 7.88 (d, 1H), 7.79 (dd, 1H), 7.58 (s, 1H), 7.53 (t, 1H), 7.46 (d, 1H), 7.34 (d, 2H), 7.22 (d, 1H), 7.01 (d, 2H), 6.66 (dd, 1H), 6.42 (dd, 1H), 6.11 (d, 1H), 3.99 (d, 2H), 3.88 (dd, 2H), 3.52 (m, 2H), 3.34 (m, 4H), 2.62 (m, 2H), 2.04 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.46 (m, 2H), 1.38 (m, 4H), 0.92 (s, 6H), 0.75 (m, 2H).

Compound 317

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate

Compound 317A

methyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

[0936] The title compound was prepared by substituting methyl chloroformate for methyl iodide in the procedure for Compound 134B.

Compound 317B

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate

[0937] The title compound was prepared by substituting Compound 317A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.35 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (bs, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.29-4.03 (m, 1H),3.89-3.70 (m, 3H), 3.71 (s, 3H), 3..55-3.38 (m, 3H), 3.07 (m, 4H), 2.96 (dt, 1H), 2.86 (dd, 1H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 318

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-

yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

Compound 318A

N-ethyl-N-methyl-2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxamide

[0938] The title compound was prepared by substituting *N*-methyl-*N*-ethyl carbamyl chloride for methyl iodide in the procedure for Compound 134B.

Compound 318B

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

[0939] The title compound was prepared by substituting Compound 318A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.44 (d, 1H), 8.33 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92-3.85 (m, 2H), 3.75 (d, 1H), 3.62 (dt, 1H), 3.55-3.48 (m, 1H), 3.45-3.39 (m, 2H), 3.21 (q, 2H), 3.07 (m, 4H), 2.99 (dt, 1H), 2.90 (dd, 1H), 2.77 (s, 2H), 2.76 (s, 3H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.06 (t, 3H), 0.93 (s, 6H).

Compound 319

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 319A

4-((4-(methylsulfonyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0940] The title compound was prepared by substituting methanesulfonyl chloride for methyl iodide in the procedure for Compound 134B.

Compound 319B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0941] The title compound was prepared by substituting Compound 319A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H),

9.25 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.13 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.99 (m, 1H), 3.92-3.88 (m, 2H), 3.64 (m, 2H), 3.56 (m, 1H), 3.50 (m, 1H), 3.07 (m, 4H), 3.04 (s, 3H), 2.95-2.88 (m, 2H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 320

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclobutyl(cyclopropyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 320A

4-(3-(cyclobutyl(cyclopropyl)amino)propylamino)-3-nitrobenzenesulfonamide

[0942] To a solution of Compound 308A (314 mg) in dichloromethane (5 ml) was added cyclobutanone (70 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water and brine and dried over Na_2SO_4. After filtration, evaporation of solvent gave the title compound.

Compound 320B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclobutyl(cyclopropyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0943] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 320A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1 H), 8.70 (m, 1 H), 8.54 (d, 1 H), 8.02 (d, 1 H), 7.79 (dd, 1 H), 7.49 (m, 3 H), 7.34 (d, 2 H), 7.03 (m, 3 H), 6.66 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H), 3.37 (q, 2 H), 3.06 (m, 4 H), 2.73 (s, 2 H), 2.63 (m, 2 H), 2.21 (m, 8 H), 1.82 (m, 3 H), 1.53 (m, 2 H), 1.38 (t, 2 H), 0.94 (m, 6 H), 0.41 (m, 4 H).

Compound 321

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 321A

ethyl 5,5-difluoro-2-oxocyclohexanecarboxylate

[0944] To a solution of diethyl 4,4-difluoroheptanedioate (4.3 g) in toluene (50 ml) was added potassium 2-methylpropan-2-olate (2.87 g) and the reaction stirred overnight at room temperature. The reaction was quenched with 1N aqueous HCl (100 ml) and extracted with diethyl ether (150 ml). The ether layer was washed with brine (50 ml), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 5% ethyl acetate/hexanes gave the title compound.

Compound 321B

ethyl 5,5-difluoro-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0945] To a solution of Compound 321A (2.37 g) in dichloromethane (40 ml) at 0°C was added N,N-diisopropylethylamine (5.02 ml) followed by trifluoromethanesulfonic anhydride (2.33 ml) and the reaction was allowed to slowly warm to room temperature. After stirring overnight the reaction was quenched with 10 ml of water then 1N aqueous HCl (100 ml). The reaction was extracted with dichloromethane (3 × 75 ml), and the combined organics were washed with brine (50 ml) and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 25% ethyl acetate/hexanes gave the title compound.

Compound 321C

ethyl 2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarboxylate

[0946] A solution of Compound 321B (3.47 g), 4-chlorophenylboronic acid (1.925 g) and cesium fluoride (3.43 g) in 30 ml of 1,2-dimethoxyethane and 15 ml of ethanol was degassed with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.237 g) was added and the reaction was heated to 70°C. The reaction was diluted with ether (200 ml) and washed with 1N aqueous HCl (100 ml) and brine (100 ml), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 8% ethyl acetate/hexanes over 40 minutes gave the title compound.

Compound 321D

(2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methanol

[0947] To a solution of Compound 321C (1.84 g) in diethyl ether (25 ml) at 0°C was added lithium aluminum hydride (1.0M, 4.28 ml). The reaction was quenched with the dropwise addition of water, then 1N aqueous HCl (50 ml) was added and the reaction diluted with diethyl ether (100 ml). The organic layer was separated, washed with brine (50 ml) dried over magnesium sulfate, filtered and concentrated to provide the title compound.

Compound 321E

2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarbaldehyde

[0948] To a solution of Compound 321D (1.38 g) in dichloromethane (25 ml) was added Dess-Martin periodinane (2.489 g) and the reaction stirred for 1 hour at room temperature. The reaction was quenched with 1N aqueous NaOH solution (75 ml) and the product was extracted into dichloromethane (2 × 100 ml). The combined organics were washed with brine (75 ml), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveris 80 g) eluting with a gradient of 1% to 10% ethyl acetate/hexanes over 40 minutes gave the title compound.

Compound 321F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[0949] The title compound was prepared by substituting Compound 321E for Compound 15E in the procedure for Compound 15G.

Compound 321G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[0950] The title compound was prepared by substituting Compound 321F for Compound 15G in the procedure for Compound 15H.

Compound 321H

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0951] The title compound was prepared by substituting Compound 321G for Compound 1E and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.74 - 11.63 (m, 1H), 11.53 - 11.29 (m, 1H), 8.57 (d, 2H), 8.05 (d, 1H), 7.85 - 7.77 (m, 1H), 7.49 (d, 3H), 7.38 (d, 2H), 7.16 - 7.06 (m, 3H), 6.73 - 6.64 (m, 1H), 6.43 - 6.36 (m, 1H), 6.21 - 6.14 (m, 1H), 3.93 - 3.77 (m, 2H), 3.29 (d, 4H), 3.07 (s, 4H), 2.79 - 2.57 (m, 4H), 2.45 (dd, 2H), 2.19 (s, 6H), 1.99 - 1.80 (m, 1H), 1.70 - 1.54 (m, 2H), 1.38 - 1.13 (m, 2H).

Compound 322

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 322A

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

[0952] 1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (2 g) was taken up in tetrahydrofuran (20 ml) and cooled in an ice bath. Lithium aluminum hydride (1.0M in dioxane, 5.09 ml) was added dropwise. The reaction was stirred at room temperature for 2 hours. The reaction was quenched with water and with 1M aqueous NaOH solution and then stirred another 1 hour at room temperature. The mixture was extracted with ethyl acetate, and the extracts were combined and washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was used without further purification.

Compound 322B

tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)-4-fluoropiperidine-1-carboxylate

[0953] The title compound was prepared by substituting Compound 322A for (tetrahydro-2H-pyran-4-yl)methanol and 3-chloro-4-fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 322C

3-chloro-4-((4-fluoropiperidin-4-yl)methoxy)benzenesulfonamide

[0954] The title compound was prepared by substituting Compound 322B for Compound 1A in the procedure for Compound 1B.

Compound 322D

3-chloro-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

[0955] To a solution of Compound 322C (830 mg) in tetrahydrofuran (15 ml) and acetic acid (5 ml) was added oxetan-3-one (163 mg) and MP-cyanoborohydride (2.38 mmol/g, 1.9 g). The mixture was stirred at room temperature overnight. The reaction was then filtered and the filtrate was concentrated under vacuum. The residue was slurried in ether and the solid product was collected by filtration.

Compound 322E

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-

(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0956] The title compound was prepared by substituting Compound 322D for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.71 (s, 1H), 8.06 (d, 1H), 7.89 (d, 1H), 7.79 (m, 1H), 7.58 (d, 1H), 7.52 (t, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.42 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44(t, 2H), 4.24 (d, 2H), 3.44 (m, 2H), 3.07 (br s, 4H), 2.74 (m, 2H), 2.59 (m, 2H), 2.14 (m, 7H), 1.95 (m, 4H), 1.78 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Compound 323

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 323A

3-chloro-4-((tetrahydrofuran-3-yl)methoxy)benzenesulfonamide

[0957] The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydrofuran-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A, except here, dimethylformamide was used in place of tetrahydrofuran and the reaction was heated at 70°C for two days.

Compound 323B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0958] The title compound was prepared by substituting Compound 323A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.73 (s, 1H), 8.07 (d, 1H), 7.89 (d, 1H), 7.80 (dd, 1H), 7.59 (d, 1H), 7.51 (dd, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.23 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.19 (d, 1H), 4.07 (m, 2H), 3.80 (m, 2H), 3.68 (m, 1H) 3.56 (m, 1H), 3.10 (br m, 4H), 2.85 (br s, 2H), 2.69 (m, 1H), 2.32 (br m, 4H), 2.17 (br m, 2H), 2.02 (m, 1H), 1.96 (s, 2H), 1.69 (m, 1H), 1.40 (t, 2H), 0.92 (s, 6H).

Compound 324

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-[(4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide

Compound 324A

4-((trans-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[0959] The title compound was prepared by substituting Compound 120A for Compound 39B in the procedure for Compound 39C.

Compound 324B

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-[(4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide

[0960] The title compound was prepared by substituting Compound 321G for Compound 1E and Compound 324A for Compound 1Fin the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.65 - 8.50 (m, 2H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.60 - 7.44 (m, 3H), 7.41 - 7.34 (m, 2H), 7.14 - 7.02 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.17 (d, 1H), 4.50 (d, 1H), 3.23 (t, 2H), 3.06 (s, 4H), 2.70 (d4H), 2.44 (s, 2H), 2.33 - 1.94 (m, 6H), 1.78 (dd, 4H), 1.51 (d, 2H), 1.23 (s, 2H), 1.16 - 0.92 (m, 2H).

Compound 325

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 325A

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

[0961] The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in the procedure for Compound 265G.

Compound 325B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

[0962] The title compound was prepared by substituting Compound 325A for Compound

15G in the procedure for Compound 15H.

Compound 325C

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0963] The title compound was prepared by substituting Compound 325B for Compound 1E and Compound 286A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.67 (s, 1H), 11.13 (s, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.80 - 7.70 (m, 1H), 7.59 - 7.46 (m, 3H), 7.34 (d, 2H), 7.21 (d, 1H), 7.11 - 7.03 (m, 2H), 6.66 (d, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.50 (dd, 4H), 4.26 (d, 2H), 3.85 - 3.69 (m, 2H), 3.61 (d, 3H), 3.05 (s, 4H), 2.69 (s, 2H), 2.37 (s, 4H), 2.17 (s, 6H), 2.04 (s, 2H), 1.87 (d, 4H), 1.49 (d, 6H).

Compound 326

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 326A

(R)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0964] The title compound was prepared by substituting Compound 258E for Compound 173A in the procedure for Compound 173B.

Compound 326B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0965] The title compound was prepared by substituting Compound 326A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H),3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

Compound 327

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 327A

(S)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

[0966] The title compound was prepared by substituting Compound 259E for Compound 173A in the procedure for Compound 173B.

Compound 327B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0967] The title compound was prepared by substituting Compound 327A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H),3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

Compound 328

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 328A

spiro[2.5]octan-5-one

[0968] To a solution of 3-ethoxycyclohex-2-enone (48.1 ml) in ether (1000 ml) was added titanium(IV) isopropoxide (110 ml) followed by addition of ethylmagnesium bromide (357 ml) at ambient temperature. The reaction mixture was stirred for 2 hours at ambient temperature and was then quenched with water (500 ml). The organic layer was separated (decanted) and the water layer was extracted with ether (3 × 300 ml). The combined extracts were partially concentrated to approximately 300 ml. p-Toluenesulfonic acid monohydrate

(3.0 g) was added and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then washed with saturated aqueous $NaHCO_3$ solution., dried ($MgSO_4$), filtered and concentrated. The concentrate was purified by fractional distillation (1st fraction b.p. 27°C at 23 torr (not product), 2nd fraction (product) b.p. 75°C at 8 torr).

Compound 328B

5-chlorospiro[2.5]oct-5-ene-6-carbaldehyde

[0969] N,N-dimethylformamide (2.1 ml) in dichloromethane (3.2 ml) at -5 °C was treated slowly with $POCl_3$ (2.33 ml) keeping the bath temperature less than 0°C. The cooling bath was removed and the mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was returned to the cooling bath and Compound 328A (2.484 g) in dichloromethane (4 ml) was added slowly to the reaction mixture. The reaction mixture was heated at 45°C for 15 hours, cooled to room temperature and then poured into a mixture of ice and saturated aqueous sodium acetate solution. After the ice melted, the mixture was extracted with diethyl ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed with 0 to 10% CH_2Cl_2 in hexanes, then 25% CH_2Cl_2 in hexanes and then 100% CH_2Cl_2 as the eluents.

Compound 328C

5-(4-chlorophenyl)spiro[2.5]oct-5-ene-6-carbaldehyde

[0970] Compound 328B (2.9 g), 4-chlorophenylboronic acid (2.87 g), palladium(II) acetate (0.103 g), K_2CO_3 (5.28 g) and tetrabutylammonium bromide (4.93 g) were combined in a 100-ml round bottomed flask with water (17.0 ml). The flask was flushed with nitrogen and stirred at 45°C for 14 hours. The reaction mixture was partitioned between brine and diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered through a plug of celite, concentrated and chromatographed on silica gel with 0 to 2% ethyl acetate in hexanes as the eluent.

Compound 328D

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoate

[0971] The title compound was prepared by substituting Compound 15F for tert-butyl piperazine carboxylate and Compound 328C for 4-chlorobiphenyl-2-carboxaldehyde in the

procedure for Compound 1A.

Compound 328E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoic acid hydrochloride

[0972] Compound 328D (0.85 g) in a mixture of tetrahydrofuran (4.8 ml), methanol (2.4 ml) and water (2.4 ml) was treated with $LiOH \cdot H_2O$ (0.184 g) and heated overnight at 50°C. The reaction mixture was cooled to room temperature, concentrated to remove tetrahydrofuran and methanol and acidified with 1 N aqueous HCl causing precipitation of the product. The solid was collected by filtration, rinsed with water and dried overnight in a vacuum oven at 80°C to provide the title compound.

Compound 328F

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0973] The title compound was prepared by substituting Compound 328E for Compound 1E in the procedure for Compound 1G. ^1H NMR (500 MHz, pyridine-d_5) 13.07 (s, 1H), 9.32 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.43 (m, 2H), 7.10 (m, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.51 (m, 2H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.16 (t, 2H), 3.06 (m, 4H), 2.81 (s, 2H), 2.37 (t, 2H), 2.16 (m, 4H), 2.11 (s, 2H), 1.81 (m, 1H), 1.58 (dd, 2H), 1.45 (t, 2H), 1.32 (qd, 2H), 0.38 (s, 4H).

Compound 329

N-{[5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 329A

ethyl 4-(cyclopropylamino)cyclohexanecarboxylate

[0974] To a solution of ethyl 4-oxocyclohexanecarboxylate (3.4 g) in dichloromethane (30 ml) was added cyclopropanamine (1.14 g) followed by sodium triacetoxyborohydride (4.24 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 ml) and washed with 2N NaOH, water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 329B

ethyl 4-(cyclopropyl(oxetan-3-yl)amino)cyclohexanecarboxylate

[0975] To a solution of Compound 329A (1.05g) in dichloromethane (10 ml) was added oxetan-3-one (0.358 g) followed by sodium triacetoxyborohydride (1.05 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 ml) and washed with 2N aqueous NaOH, water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 329C

(4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methanol

[0976] To a solution of Compound 329B (1.2 g) in tetrahydrofuran (20 ml) was added lithium aluminum hydride (0.681 g). The mixture was stirred overnight. 2N aqueous NaOH solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl acetate (300 ml) and washed with water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 329D

5-chloro-6-((4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methoxy)pyridine-3-sulfonamide

[0977] To a solution of Compound 329C (706 mg) in N,N-dimethylformamide (6 ml) was added NaH (60% in mineral oil, 300 mg) . The mixture was stirred for 30 minutes, and then 5,6-dichloropyridine-3-sulfonamide (706 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH_4Cl and extracted with ethyl acetate (3 × 200 ml). The combined organic layers were washed with water, brine and dried over Na_2SO_4. After filtration and evaporation of the solvent the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH_3 in methanol in dichloromethane to provide the title compound.

Compound 329E

N-{[5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0978] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 329D for Compound 1F in the procedure for Compound 1G. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1 H), 8.50 (m, 1 H), 8.16 (s, 1 H), 8.02 (d, 1 H), 7.51 (m, 3 H), 7.35 (d, 2 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.38 (m, 1 H), 6.21 (s, 1 H), 4.70 (m, 2

H), 4.43 (t, 3 H), 4.19 (m, 2 H), 3.12 (m, 4 H), 2.84 (m, 2 H), 2.19 (m, 6 H), 1.96 (s, 3 H), 1.77 (m, 3 H), 1.38 (m, 7 H), 0.93 (s, 6 H), 0.44 (m, 4 H).

Compound 330

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0979] The title compound was prepared by substituting Compound 328E for Compound 3J and Compound 218A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (400 MHz, pyridine-d_5) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.95 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.84 (m, 2H), 3.58 (td, 1H), 3.45 (m, 2H), 3.06 (m, 4H), 2.93 (d, 1H), 2.81 (s, 2H), 2.69 (d, 1H), 2.35 (m, 3H), 2.19 (m, 5H), 2.11 (s, 2H), 1.58 (m, 1H), 1.45 (t, 2H), 0.42 (m, 8H).

Compound 331

N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 331A

tert-butyl 2-((2-chloro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

[0980] To a solution of *tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (0.478 g) in anhydrous N,N-dimethylformamide (5 ml) was added sodium hydride (0.280 g). The mixture was stirred at room temperature for 30 minutes, followed by addition of 3-chloro-4-fluorobenzenesulfonamide (0.419 g). The mixture was stirred at 40°C overnight. The reaction was quenched with water (10 ml), and the mixture was adjusted to ~pH 7 and extracted with ethyl acetate. The crude product was purified on a silica gel column eluting with 60% ethyl acetate in hexane to provide the title compound.

Compound 331B

3-chloro-4-(morpholin-2-ylmethoxy)benzenesulfonamide

[0981] The title compound was prepared by substituting Compound 331A for Compound 113A in the procedure for Compound 134A.

Compound 331C

3-chloro-4-((4-cyclopropylmorpholin-2-yl)methoxy)benzenesulfonamide

[0982] The title compound was prepared by substituting Compound 331B for Compound 173A in the procedure for Compound 173B.

Compound 331D

N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0983] The title compound was prepared by substituting Compound 331C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.04 (s, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.27 (dd, 1H), 8.09 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.05 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 4.20 (dd, 1H), 4.10 (dd, 1H), 3.94 (m, 1H), 3.86 (d, 1H), 3.58 (dt, 1H), 3.06 (m, 5H), 2.77 (s, 2H), 2.69 (d, 1H), 2.40-2.20 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.60 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

Compound 332

N-[(3-chloro-4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 332A

tert-butyl 2-((2-chloro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

[0984] A solution of 3-chloro-4-fluorobenzenesulfonamide (1.0 g), tert-butyl 2-(aminomethyl)morpholine-4-carboxylate (1.135 g) and N-ethyl-N-isopropylpropan-2-amine (1.246 ml) in dimethylsulfoxide (15 ml) was stirred at 115°C for 72 hours. The mixture was concentrated, and the residue was purified on a silica gel column eluting with 60% ethyl acetate to provide the title compound.

Compound 332B

3-chloro-4-(morpholin-2-ylmethylamino)benzenesulfonamide

[0985] The title compound was prepared by substituting Compound 332A for Compound 113A in the procedure for Compound 134A.

Compound 332C

3-chloro-4-(((4-cyclopropylmorpholin-2-yl)methyl)amino)benzenesulfonamide

[0986] The title compound was prepared by substituting Compound 332B for Compound 173A in the procedure for Compound 173B.

Compound 332D

N-[(3-chloro-4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0987] The title compound was prepared by substituting Compound 332C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.05 (s, 1H), 8.45 (m, 2H), 8.21 (dd, 1H), 8.12 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.78 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 6.37 (m, 1H), 3.84 (d, 1H), 3.77 (m, 1H), 3.54 (dt, 1H), 3.35 (m, 2H), 3.05 (m, 4H), 2.94 (d, 1H), 2.77 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.26 (m, 2H), 2.18-2.12 (m, 5H), 1.97 (s, 2H), 1.55 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

Compound 333

2-{[(2-chloro-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}phenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

Compound 333A

2-((2-chloro-4-sulfamoylphenylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

[0988] The title compound was prepared by substituting Compound 332B for Compound 134A and *N*-methyl-*N*-ethyl carbamyl chloride for methyl iodide in the procedure for Compound 134B.

Compound 333B

2-{[(2-chloro-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}phenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

[0989] The title compound was prepared by substituting Compound 333A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.05 (s, 1H), 8.46 (s, 1H), 8.45 (s, 1H), 8.20 (dd, 1H), 8.10 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H),

7.07 (d, 2H), 6.79 (d, 1H), 6.73 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 6.43 (m, 1H), 3.83 (d, 2H),3.73 (d, 1H), 3.59 (dt, 1H), 3.41-3.35 (m, 3H), 3.20 (q, 2H), 3.05 (m, 4H), 2.95 (t, 1H), 2.84 (dd, 1H), 2.76 (s, 2H), 2.73 (s, 3H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.04 (t, 3H), 0.94 (s, 6H).

Compound 334

(2S)-2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)oxy]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

Compound 334A

(S)-2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

[0990] The title compound was prepared by substituting Compound 244B for Compound 134A and *N*-methyl-*N*-ethyl carbamyl chloride for methyl iodide in the procedure for Compound 134B.

Compound 334B

(2S)-2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)oxy]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

[0991] The title compound was prepared by substituting Compound 334A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.98 (s, 1H), 9.08 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.58 (dd, 1H),4.47 (dd, 1H), 4.03 (m, 1H), 3.84 (m, 2H), 3.63 (dt, 1H), 3.45 (d, 1H), 3.22 (q, 2H), 3.07 (m, 4H), 3.05-2.95 (m, 2H), 2.78 (s, 3H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.07 (t, 3H), 0.94 (s, 6H).

Compound 335

N-[(5-chloro-6-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 335A

tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)morpholine-4-carboxylate

[0992] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide and tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 335B

5-chloro-6-(morpholin-2-ylmethylamino)pyridine-3-sulfonamide

[0993] The title compound was prepared by substituting Compound 335A for Compound 113A in the procedure for Compound 134A.

Compound 335C

5-chloro-6-((4-cyclopropylmorpholin-2-yl)methylamino)pyridine-3-sulfonamide

[0994] The title compound was prepared by substituting Compound 335B for Compound 173A in the procedure for Compound 173B.

Compound 335D

N-[(5-chloro-6-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[0995] The title compound was prepared by substituting Compound 335C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.02 (s, 1H), 9.15 (d, 1H), 8.49 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.80 (t, 1H), 7.69 (d, 1H), 7.65 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.73 (dd, 1H), 6.52 (m, 1H), 6.49 (d, 1H), 3.92 (m, 1H),3.84 (m, 2H), 3.70 (m, 1H), 3.54 (dt, 1H), 3.05 (m, 4H), 2.99 (d, 1H), 2.76 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.25 (m, 2H), 2.12 (m, 5H), 1.97 (s, 2H), 1.53 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H), 0.40 (m, 4H).

Compound 336

2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

Compound 336A

2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)-N-ethyl-N-methylmorpholine-4-

carboxamide

[0996] The title compound was prepared by substituting Compound 335B for Compound 134A and *N*-methyl-*N*-ethyl carbamyl chloride for methyl iodide in the procedure for Compound 134B.

Compound 336B

2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

[0997] The title compound was prepared by substituting Compound 336A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.03 (s, 1H), 9.14 (d, 1H), 8.51 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.89 (m, 1H), 7.69 (d, 1H), 7.66 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.74 (dd, 1H), 6.51 (m, 1H), 6.48 (d, 1H), 3.96 (m, 1H),3.90-3.70 (m, 4H), 3.59 (dt, 1H), 3.43 (d, 1H), 3.17 (q, 2H), 3.05 (m, 4H), 2.95 (dt, 1H), 2.81 (dd, 1H), 2.76 (s, 2H), 2.72 (s, 3H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.03 (t, 3H), 0.93 (s, 6H).

Compound 337

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 337A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[0998] To a suspension of hexane washed NaH (17 g) in dichloromethane (700 ml) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to −78°C and trifluoroacetic anhydride (40 ml) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the product.

Compound 337B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

[0999] Compound 337A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 dimethoxyethane/methanol (600 ml)

were heated to 70°C for 24 hours. The mixture was concentrated. Ether (4 × 200 ml) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

Compound 337C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

[01000] To a mixture of $LiBH_4$ (13g), Compound 337B (53.8 g) and ether (400 ml), was added methanol (25 ml) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3 × 100 ml). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

Compound 337D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

[01001] Mesyl Chloride (7.5 ml) was added via syringe to Compound 337C (29.3 g) and triethylamine (30 ml) in CH_2Cl_2 (500 ml) at 0°C, and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10–20% ethyl acetate/hexanes.

Compound 337E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

[01002] Compound 337D (1 g) was stirred in dichloromethane (10 ml), trifluoroacetic acid (10 ml), and triethylsilane (1 ml) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 ml) and saturated aqueous Na_2CO_3 solution (20 ml) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na_2SO_4, and concentrated to give the product.

Compound 337F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

[01003] To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 ml) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 ml), and after 10

minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 ml) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

Compound 337G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

[01004] To a mixture of Compound 337F (24.3 g) in tetrahydrofuran (500 ml) at –78°C was added 2.5M BuLi (30.3 ml). After 2 minutes, trimethylborate (11.5 ml) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted thee times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 ml) at 0°C, and 1M aqueous NaOH (69 ml) was added, followed by 30% aqueous H_2O_2 (8.43 ml), and the solution was stirred for 1 hour. $Na_2S_2O_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 5–25% ethyl acetate/hexanes.

Compound 337H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

[01005] A mixture of Compound 337G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 ml) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 ml), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2–50% ethyl acetate/hexanes.

Compound 337I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[01006] A mixture of Compound 337H (1.55 g), Compound 337E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 ml) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 ml), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50%

ethyl acetate/hexanes.

Compound 337J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[01007] Compound 337I (200 mg) in dioxane (10 ml) and 1M aqueous NaOH (6 ml) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted thee times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

Compound 337K

tert-butyl (4-hydroxy-4-methylcyclohexyl)methylcarbamate

[01008] To a vigorous stirring solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.7 g) in tetrahydrofuran (40 ml) at –78°C was dropwise added 1.6 M methyllithium (14.02 ml) in ether. After completion of the addition, the mixture was stirred at –78°C for 1.2 hours and poured into a cold NH_4Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 ml, three times) and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in dichloromethane and loaded onto an Analogix purification system, and it was eluted with 0 - 50% ethyl acetate in dichloromethane to provide the title compound.

Compound 337L

4-(aminomethyl)-1-methylcyclohexanol

[01009] Compound 337K (1.3 g) in dichloromethane (5 ml) at 0°C was treated with trifluoroacetic acid (2.1 ml) and a few drops of water for 1 hour. The reaction mixture was concentrated and the residue was directly used for next step.

Compound 337M

4-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[01010] Compound 337L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 ml) was treated with triethylamine overnight. The reaction mixture, was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30% - 50% acetonitrile in 0.1% trifluoroacetic acid water solution to isolate the title compound.

Compound 337N

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01011] A mixture of Compound 337J (3.0 g), Compound 337M (1.98 g), N, N-dimethylpyridin-4-amine (1.93 g) and N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (1.31 g) in dichloromethane (50 ml) was stirred overnight and concentrated. The residue was purified by reverse chromatography, eluted with 40%-70% acetonitrile in 0.1% TFA water. The desired fractions were concentrated to remove acetonitrile, neutralized with $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, concentrated and dried to provide the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1 H), 8.52 - 8.58 (m, 2 H), 8.04 (d, 1 H), 7.79 (dd, 1 H), 7.53 (d, 1 H), 7.47 - 7.52 (m, 2 H), 7.30 - 7.37 (m, 2 H), 7.07 (d, 1 H), 7.01 - 7.06 (m, 2 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 4.25 (s, 1 H), 3.25 - 3.32 (m, 4 H), 3.07 (s, 4 H), 2.75 (s, 2 H), 2.09 - 2.24 (m, 6 H), 1.95 (s, 2 H), 1.50 - 1.73 (m, 5 H), 1.28 - 1.43 (m, 4 H), 1.06 - 1.18 (m, 5 H), 0.92 (s, 6 H).

Compound 338

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 338A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

[01012] To a suspension of hexane washed NaH (17 g) in dichloromethane (700 ml) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to –78°C and trifluoroacetic anhydride (40 ml) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the product.

Compound 338B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

[01013] Compound 338A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and

tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 dimethoxyethane/methanol (600 ml) were heated to 70°C for 24 hours. The mixture was concentrated. Ether (4 × 200 ml) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

Compound 338C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

[01014] To a mixture of $LiBH_4$ (13g), Compound 338B (53.8 g) and ether (400 ml), was added methanol (25 ml) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N aqueous HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3 × 100 ml). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

Compound 338D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

[01015] Mesyl Chloride (7.5 ml) was added via syringe to Compound 338C (29.3 g) and triethylamine (30 ml) in CH_2Cl_2 (500 ml) at 0°C, and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10–20% ethyl acetate/hexanes.

Compound 338E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

[01016] Compound 338D (1 g) was stirred in dichloromethane (10 ml), trifluoroacetic acid (10 ml), and triethylsilane (1 ml) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 ml) and saturated aqueous Na_2CO_3 solution (20 ml) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated to give the product.

Compound 338F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

[01017] To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 ml) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 ml), and after 10

minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 ml) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

Compound 338G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

[01018] To a mixture of Compound 338F (24.3 g) in tetrahydrofuran (500 ml) at –78°C was added 2.5M BuLi (30.3 ml). After 2 minutes, trimethylborate (11.5 ml) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted thee times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 ml) at 0°C, and 1M aqueous NaOH (69 ml) was added, followed by 30% aqueous H_2O_2 (8.43 ml), and the solution was stirred for 1 hour. $Na_2S_2O_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 5–25% ethyl acetate/hexanes.

Compound 338H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

[01019] A mixture of Compound 338G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 ml) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 ml), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2–50% ethyl acetate/hexanes.

Compound 338I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[01020] A mixture of Compound 338H (1.55 g), Compound 338E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 ml) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 ml), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50%

ethyl acetate/hexanes.

Compound 338J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[01021] Compound 338I (200 mg) in dioxane (10 ml) and 1M NaOH (6 ml) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted thee times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

Compound 338K

tert-butyl (4-hydroxy-4-methylcyclohexyl)methylcarbamate

[01022] To a vigorous stirring solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.7 g) in tetrahydrofuran (40 ml) at –78°C was dropwise added 1.6 M methyllithium (14.02 ml) in ether. After completion of the addition, the mixture was stirred at –78°C for 1.2 hours and poured into a cold NH_4Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 ml, three times) and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in dichloromethane and loaded onto an Analogix purification system, and it was eluted with 0 - 50% ethyl acetate in dichloromethane to provide the title compound.

Compound 338L

4-(aminomethyl)-1-methylcyclohexanol

[01023] Compound 338K (1.3 g) in dichloromethane (5 ml) at 0°C was treated with trifluoroacetic acid (2.1 ml) and a few drops of water for 1 hour. The reaction mixture was concentrated and the residue was directly used for next step.

Compound 338M

4-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[01024] Compound 338L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 ml) was treated with triethylamine overnight. The reaction mixture, was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30% - 50% acetonitrile in 0.1% trifluoroacetic acid water solution to isolate the title compound.

Compound 338N

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01025] A mixture of Compound 338J (144 mg), Compound 338M (95 mg), N, N-dimethylpyridin-4-amine (123 mg) and N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (62.7 mg) in dichloromethane (7 ml) was stirred overnight and concentrated. The residue was purified by reverse chromatography, eluted with 40%-70% acetonitrile in 0.1% TFA water. The desired fractions were concentrated, neutralized with $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, concentrated and dried to provide the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1 H), 11.38 (s, 1 H), 8.59 (t, 1 H), 8.55 (d, 1 H), 8.04 (d, 1 H), 7.79 (dd, 1 H), 7.54 (d, 1 H), 7.46 - 7.52 (m, 2 H), 7.30 - 7.38 (m, 2 H), 7.00 - 7.10 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.95 (s, 1 H), 3.25 (t, 4 H), 3.07 (s, 4 H), 2.75 (s, 2 H), 2.10 - 2.26 (m, 6 H), 1.95 (s, 2 H), 1.29 - 1.62 (m, 8 H), 1.16 - 1.30 (m, 2 H), 1.08 (s, 3 H), 0.92 (s, 6 H).

Compound 339

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 339A

(1R,4S)-methyl spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-carboxylate

[01026] A reaction mixture of 1,4-dioxaspiro[4.4]non-6-ene (5 g), methyl acrylate (10.24 g), and hydroquinone (0.13 g) was heated at 100°C in acetonitrile (12 ml) for three days. After cooling, the solvent was removed, and residue was purified by flash chromatography on silica gel eluting with 4:1 hexane/ethyl acetate to provide the title compound as a mixture of two isomers.

Compound 339B

(1R,4S)-spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-ylmethanol

[01027] Compound 339A (1.0 g) in tetrahydrofuran was cooled to 0°C. To this solution was added 1.0 N lithium aluminum hydride (2.8 ml) dropwise. The reaction mixture was

stirred for 2 hours. Water (0.4 ml) was added followed by 2 N aqueous NaOH (0.2 ml). The solid was filtered off, and the filtrate was concentrated. Toluene was added, and it was then distilled to remove any trace amount of water. The title compound was used for the next reaction without further purification.

Compound 339C

5-chloro-6-(((1S,2R,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

[01028] The title compound was prepared by substituting Compound 339B for (tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for Compound 36A in the procedure for Compound 36B. The two stereoisomers at the 5 position were isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ, C18(2), 250X21.20 mm, 5 Å) eluting with 20-80% acetonitrle in water with 0.1% trifluoroacetic acid. The desired fractions were collected, and the solvents were removed under reduced vacuum at 60°C. During this process, a lot of solid formed. It was then partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the title compound.

Compound 339D

5-chloro-6-(((1S,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

[01029] Compound 339C (0.44 g) in tetrahydrofuran (15 ml) was treated with 3.0 M methylmagnesium bromide (5.3 ml) at 0°C. The solution was stirred for 16 hours. The reaction mixture was then partitioned between ethyl acetate and 0.05 N aqueous HCl (20 ml). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

Compound 339E

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01030] The title compound was prepared by substituting Compound 339D for Compound

11B in the procedure for Compound 11D.^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 8.02 (d,1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.20 (s, 1H), 4.40-4.48 (m, 2H), 4.31 (s, 1H), 3.09 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 7H), 1.96 (s, 2H), 1.87 (d, 1H), 1.65-1.69 (m, 1H), 1.54-1.56 (m, 2H), 1.36-1.47 (m, 6H), 1.26-1.30 (m, 1H), 1.19 (s, 3H), 0.93 (s, 6H).

Compound 340

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 340A

4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrobenzenesulfonamide

[01031] To a solution of 4-fluoro-3-nitrobenzenesulfonamide (1.4 g) in tetrahydrofuran (30 ml) was added 1,4-dioxaspiro[4.5]decan-8-amine (1.0 g) and diisopropylethylamine (5 ml) . The mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 ml) and washed with water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 340B

N-(4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrophenylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[01032] To a solution of Compound 3J (617 mg) and Compound 340A (386 mg) in dichloromethane (10 ml) was added 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (288 mg) and 4-(dimethylamino)pyridine (183 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 340C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(4-oxocyclohexylamino)phenylsulfonyl)benzamide

[01033] To a solution of Compound 340B (386 mg) in acetone (10 ml) and water (5 ml) was added para-toluenesulfonic acid monohydrate (50 mg). The mixture was stirred at 120°C

in a Biotage Initiator microwave reactor for 30 minutes. The mixture was diluted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 340D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01034] To a solution of Compound 340C (240 mg) and 3-(cyclopropylamino)propanenitrile (62 mg) in tetrahydrofuran (10 ml) was added acetic acid (2 ml) and MP-cyanoborohydride (300 mg, 2.15mmol/g). The mixture was stirred overnight. The mixture was filtered and concentrated under vacuum and the residue was dissolved in dimethylsulfoxide/methanol (1:1, 10 ml) and loaded on Gilson, C18(100A) 250x121.2 mm(10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1 H), 8.55 (dd, 1 H), 8.17 (d, 1 H), 8.03 (d, 1 H), 7.79 (d, 1 H), 7.49 (m, 3 H), 7.34 (d, 2 H), 7.11 (m, 1 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.38 (d, 1 H), 6.19 (d, 1 H), 4.01 (m, 1 H), 3.56 (m, 1 H), 3.06 (m, 4 H), 2.88 (t, 2 H), 2.65 (m, 6 H), 2.19 (m, 6 H), 2.00 (m, 7 H), 1.51 (m, 6 H), 0.92 (s, 6 H), 0.42 (m, 4 H).

Compound 341

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 341A

ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate

[01035] To a solution of ethyl 4-oxocyclohexanecarboxylate (31.8 g) in toluene (100 ml) was added ethylene glycol (36.5 ml) and p-toluenesulfonic acid monohydrate (0.426 g). The two phase mixture was stirred rapidly at ambient temperature for 72 hours. The reaction was diluted with water (900 ml) and extracted with ether (900 ml). The organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. After filtration, the title compound was obtained by concentration under high vacuum.

Compound 341B

1,4-dioxaspiro[4.5]decan-8-ylmethanol

[01036] To a suspension of lithium aluminum hydride (8.19 g) in tetrahydrofuran (400 ml) was added dropwise a solution of Compound 341A (37.8 g) in tetrahydrofuran (75 ml). The mixture was then heated at reflux for 2 hours. The reaction mixture was cooled in an ice bath and quenched very slowly with water (8 ml). Then added sequentially were 4N sodium hydroxide (8 ml), ether (200 ml), water (24 ml), ether (500 ml) and anhydrous sodium sulfate (250 g). The resulting mixture was stirred rapidly for 2 hours and was filtered. The title compound was isolated by concentration of the filtrate.

Compound 341C

8-(benzyloxymethyl)-1,4-dioxaspiro[4.5]decane

[01037] To a suspension of sodium hydride (60% oil dispersion, 8.86 g) in tetrahydrofuran (170 ml) was added a solution of Compound 341B (30.52 g) in tetrahydrofuran (100 ml). This mixture was stirred for 30 minutes and benzyl bromide (24 ml) was added. After stirring for 72 hours, the reaction was quenched with saturated ammonium chloride solution (400 ml) and diluted with ether (500 ml). The layers were separated and the aqueous layer was extracted with ether (2 X 150 ml). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with a 0, 10, 15, 75 % ethyl acetate in hexanes step gradient to provide the title compound.

Compound 341D

4-(benzyloxymethyl)cyclohexanone

[01038] To a solution of Compound 341C (43.02 g) in dioxane (500 ml) was added water (125 ml) and 2M hydrochloric acid (90 ml). The mixture was heated at 85°C for 18 hours. Upon cooling, the reaction mixture was diluted with brine (1500 ml), saturated sodium bicarbonate solution (300 ml) and ether (1000 ml). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with a 5- 50% ethyl acetate in hexanes step gradient to provide the title compound.

Compound 341E

trans-4-(benzyloxymethyl)-1-methylcyclohexanol

[01039] To 2,6-di-t-butyl-4-methylphenol (83.4 g) in toluene (1100 ml) was added 2.0M (in hexanes) trimethylaluminum (95 ml) somewhat carefully to control methane evolution and

a small exotherm. The reaction mixture was stirred at ambient temperature under N_2 for 75 minutes and was then cooled to –77°C. A solution of Compound 341D (14 g) in toluene (15 ml) was added dropwise, keeping the temperature below –74 °C. Methyllithium (1.6M in diethyl ether, 120 ml) was then added dropwise, keeping the temperature below –65°C. The resulting mixture was stirred at –77°C under N_2 for 2 hours. The reaction mixture was then poured into 1N aqueous HCl (1600 ml), rinsing the flask with toluene. The organic layer was washed with brine and the combined aqueous layers were extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The concentrate was chromatographed on 650 g of spherical silica gel using 2.5 L of 80/20 hexanes/ethyl acetate, then 3.0 L of 75/25 hexanes/ethyl acetate, and finally 4.0 L of 70/30 hexanes/ethyl acetate as the eluents to provide the title compound.

Compound 341F

trans-4-(hydroxymethyl)-1-methylcyclohexanol

[01040] Compound 341E (12.6 g) and ethanol (120 ml) were added to 20% $Pd(OH)_2/C$, wet (1.260 g) in a 500 ml SS pressure bottle. The reaction mixture was stirred at ambient temperature under 30 psi hydrogen gas. Hydrogen uptake ceased at 5 minutes. The mixture was filtered through a nylon membrane rinsing with ethanol. The filtrate was concentrated and then azeotroped with toluene (100 ml) to remove any remaining ethanol. The concentrate was dried under high vacuum for 40 minutes to provide the title compound.

Compound 341G

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

[01041] The title compound was prepared by substituting Compound 40A for 4-fluoro-3-nitrobenzenesulfonamide and Compound 341F for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 341H

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01042] The title compound was prepared by substituting Compound 328E for Compound 3J and Compound 341G for Compound 11B in the procedure for Compound 11D. ^1H NMR (500 MHz, pyridine-d_5) δ 13.09 (s, 1H), 9.18 (d, 1H), 8.74 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H),

7.67 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.74 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 4.29 (d, 2H), 3.05 (m, 4H), 2.80 (s, 2H), 2.37 (t, 2H), 2.15 (m, 4H), 2.11 (s, 2H), 1.89 (m, 6H), 1.75 (m, 2H), 1.45 (t, 2H), 1.41 (s, 3H), 1.32 (m, 2H), 0.37 (m, 4H).

Compound 342

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 342A

methyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate

[01043] To a 50 ml pressure bottle were placed methyl imidazo[1,2-a]pyridine-6-carboxylate (0.26 g), acetic acid (10 ml), and wet 5% palladium on carbon (0.052 g). The reaction mixture was stirred for 16 hours at 30 psi and 50°C. The solid was filtered off, and the filtrate was concentrated. The residue was taken up in ethyl acetate. It was then washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10–100% ethyl acetate in hexanes to provide the title compound.

Compound 342B

(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methanol

[01044] The title compound was prepared by substituting Compound 342A for Compound 339A in the procedure for Compound 339B.

Compound 342C

5-chloro-6-((5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methoxy)pyridine-3-sulfonamide

[01045] The title compound was prepared by substituting Compound 342B for (tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for Compound 36A in the procedure for Compound 36B.

Compound 342D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01046] The title compound was prepared by substituting Compound 342C for Compound 11B in the procedure for Compound 11D.^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.54

(s, 1H), 8.36 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.58 (d, 1H), 7.41-7.44 (m, 2H), 7.2-7.36 (m, 4H), 7.05 (d, 2H), 6.63 (dd, 1H), 6.32 (dd, 1H), 6.24 (d, 1H), 4.42-4.51 (m, 1H), 4.37-4.40 (m, 1H), 4.29 (dd, 1H), 3.91 (dd, 1H), 3.03 (s, 4H), 2.90-2.95 (m, 2H), 2.77 (s, 2H), 2.51-2.52 (m, 1H), 2.07-2.23 (m, 7H), 1.96 (s, 2H), 1.76-1.82 (m, 1H), 1.65-1.69 (m, 2H), 1.54-1.56 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Compound 343

N-[(5-chloro-6-{[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 343A

5-chloro-6-(((1S,2S,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

[01047] The title compound was isolated as another isomer in the procedure for Compound 339C.

Compound 343B

5-chloro-6-(((1S,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

[01048] The title compound was prepared by substituting Compound 343A for Compound 339B in the procedure for Compound 339C.

Compound 343C

N-[(5-chloro-6-{[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01049] The title compound was prepared by substituting Compound 343B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.27 (s, 1H), 4.11-4.19 (m, 2H), 3.11 (s, 4H), 2.87 (s, 2H), 1.96-2.23 (m, 10H), 1.88 (d, 1H), 1.50 (dd, 1H), 1.33-1.44 (m, 2H), 1.13-1.19 (m, 4H), 0.88-0.93 (m, 8H).

Compound 344

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 344A

4-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[01050] Compound 347A (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.2 g) in tetrahydrofuran (40 ml) were treated with 60% sodium hydride (1.6 g) for 3 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30-50% CH_3CN in 0.1% trifluoroacetic acid water to provide the title compound as a single enantiomer.

Compound 344B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01051] The title compound was prepared by substituting Compound 344A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 8.34 (d, 1H), 8.04 (m, 2H), 7.52 (m, 3H), 7.40 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.96 (s, 1H), 3.10 (br s, 4H), 2.85 (m, 2H), 2.29 (m, 3H), 2.15 (t, 2H), 1.96 (br s, 2H), 1.68 (m, 1H), 1.55(m, 4H),1.42 (m, 4H), 1.27 (m, 2H), 1.10 (s, 3H), 0.92 (s, 6H).

Compound 345

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01052] The title compound was prepared by substituting Compound 328E for Compound 3J and Compound 277O for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.07 (s, 1H), 9.13 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.68 (t, 1H), 7.66 (d, 1H), 7.42 (m, 2H), 7.09 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.64 (d, 4H), 4.53 (d, 2H), 3.39 (m, 1H), 3.06 (m, 4H), 2.81 (s, 2H), 2.51 (m, 2H), 2.37 (m, 2H), 2.12 (m, 10H), 1.90 (m, 2H), 1.45 (t, 2H), 0.38 (s, 4H).

Compound 346

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01053] The title compound was prepared by substituting 3,3-difluoropyrrolidine hydrochloride for 3-(cyclopropylamino)propanenitrile in the procedure for Compound 340D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1 H), 11.38 (m, 1 H), 8.55 (m, 1 H), 8.36 (d, 1 H), 8.03 (d, 1 H), 7.80 (m, 1 H), 7.50 (m, 3 H), 7.34 (d, 2 H), 7.13 (d, 1 H), 7.04 (d, 2 H), 6.83 (m, 1 H), 6.68 (m, 1 H), 6.38 (d, 1 H), 6.19 (s, 1 H), 4.02 (s, 1 H), 3.83 (m, 1 H), 3.06 (m, 4 H), 2.96 (m, 2 H), 2.73 (m, 4 H), 2.26 (m, 8 H), 1.97 (m, 4 H), 1.68 (m, 4 H), 1.37 (m, 2 H), 0.92 (s, 6 H).

Compound 347

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 347A

4-(hydroxymethyl)-1-methylcyclohexanol

[01054] 4-(Hydroxymethyl)cyclohexanone (800 mg) in tetrahydrofuran (15 ml) was treated with 3 M methylmagnesium chloride in tetrahydrofuran (6.24 ml) at 0°C. The reaction was warmed to room temperature over 2 hours and quenched with methanol and water. The resulting mixture was concentrated and the residue was suspended in ethyl acetate. The precipitates were filtered off and the filtrate was concentrated. The residue was purified by chromatography, eluting with 0–100% ethyl acetate in hexane to provide the title compound.

Compound 347B

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

[01055] Compound 347A (970 mg) and Compound 40A (1.6 g) in N,N-dimethylformamide (8 ml) were treated with sodium hydride (1.8 g, 60%) at room temperature for 2 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30–45% acetonitrile in 0.1% trifluoroacetic acid water to isolate

the title compound.

Compound 347C

5-chloro-6-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

[01056] The title compound was prepared and isolated as described in the procedure for Compound 347B.

Compound 347D

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01057] The title compound was prepared as described in the procedure for Compound 11D using Compound 347B in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1 H), 8.51 (d, 1 H), 8.18 (d, 1 H), 8.03 (d, 1 H), 7.48 - 7.56 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.17 - 4.34 (m, 3 H), 3.11 (s, 4 H), 2.89 (s, 2 H), 2.24 - 2.42 (m, 4 H), 2.15 (s, 2 H), 1.96 (s, 2 H), 1.66 - 1.82 (m, 3 H), 1.55 (d, 2 H), 1.31 - 1.44 (m, 4 H), 1.12 - 1.27 (m, 2 H), 1.10 (s, 3 H), 0.93 (s, 6 H).

Compound 348

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01058] The title compound was prepared as described in the procedure for Compound 11D using Compound 347C in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1 H), 8.51 (d, 1 H), 8.18 (d, 1 H), 8.03 (d, 1 H), 7.47 - 7.58 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.21 (d, 2 H), 3.95 (s, 1 H), 3.11 (s, 4 H), 2.89 (s, 2 H), 2.33 (d, 4 H), 2.15 (s, 2 H), 1.96 (s, 2 H), 1.63 - 1.77 (m, 1 H), 1.48 - 1.60 (m, 4 H), 1.35 - 1.48 (m, 4 H), 1.20 - 1.33 (m, 2 H), 1.09 (s, 3 H), 0.93 (s, 6 H).

Compound 349

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01059] The title compound was prepared by substituting 2,2-difluorocyclopropanamine hydrochloride for 3-(cyclopropylamino)propanenitrile in the procedure for Compound 340D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.60 (s, 1 H), 8.47 (m, 2 H), 8.12 (m, 1 H), 7.98 (m, 1 H), 7.72 (m, 2 H), 7.47 (m, 3 H), 7.34 (m, 3 H), 7.05 (m, 3 H), 6.65 (dd, 1 H), 6.35 (m, 1 H), 6.22 (d, 1 H), 3.54 (m, 2 H), 3.08 (m, 4 H), 2.74 (m, 4 H), 2.25 (m, 4 H), 2.01 (m, 4 H), 1.38 (m, 4 H), 0.92 (s, 6 H).

Compound 350

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 350A

ethyl spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

[01060] To a solution of ethyl 4-oxocyclohexanecarboxylate (22.75 g) and pyrocatechol (14.75 g) in toluene (200 ml) was added catalytic amount of para-toluenesulfonic acid monohydrate and the mixture was stirred under reflux and a Dean-Stark trap overnight. The mixture was diluted with diethyl ether (600 ml) and washed with aqueous $NaHCO_3$, water and brine. After drying over Na_2SO_4, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

Compound 350B

ethyl 4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

[01061] A solution of Compound 350A (5.25g) in tetrahydrofuran (40 ml) was added dropwise to a solution of lithium diisopropylamide (12 ml, 2.0M in tetrahydrofuran/heptane/ethylbenzene) at 0°C. The solution was stirred at 0°C for 30 minutes, and then was transferred by cannula to a pre-cooled (0°C) stirring solution of N-fluorobenzenesulfonnimide (7.89g) in dry tetrahydrofuran (20 ml). The reaction mixture was stirred at 0°C for 30 minutes, and then at 20°C for 18 hours. The reaction mixture was poured over aqueous NH_4Cl and extracted with diethyl ether (3 × 200 ml). The combined organic layers were washed with water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the crude product.

Compound 350C

(4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methanol

[01062] To a solution of Compound 350B (23 g) in tetrahydrofuran (150 ml) was added lithium aluminum hydride (3.11 g). The mixture was stirred overnight. Aqueous 2N NaOH solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl acetate (600 ml) and washed with water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the crude product which was loaded on a 600 g analogics column and eluted with 10% to 20% ethyl acetate in hexane to provide the title compound.

Compound 350D

5-chloro-6-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)pyridine-3-sulfonamide

[01063] To a solution of Compound 350C (89 mg) in N,N-dimethylformamide (3 ml) was added NaH (65% in mineral oil, 36 mg) . The mixture was stirred for 30 minutes, and then 5, 6-dichloropyridine-3-sulfonamide (85 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH_4Cl and extracted with ethyl acetate (100 ml). The combined organic layers were washed with water, brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and eluted with 30% ethyl acetate in hexane to provide the title compound.

Compound 350E

5-chloro-6-((1-fluoro-4-oxocyclohexyl)methoxy)pyridine-3-sulfonamide

[01064] To a solution of Compound 350D (1.6g) and pyridinium p-toluenesulfonate (1.2 g) in acetone (10 ml) was added water (2 ml) and the mixture was stirred under microwave irradiation at 100°C for 10 minutes. The mixture was diluted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 350F

5-chloro-6-((cis-1-fluoro-4-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

[01065] To a solution of Compound 350E (336 mg) in tetrahydrofuran(10 ml) was added $NaBH_4$ (75 mg). The mixture was stirred for 45 minutes. The mixture was diluted with ethyl acetate (300 ml) and washed with 2N aqueous NaOH, water, and brine. After drying over Na_2SO_4, the mixture was filtered and the solvent was evaporated to give the crude product.

Compound 350G

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-

(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01066] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 350F for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1 H), 8.48 (s, 1 H), 8.18 (s, 1 H), 8.01 (d, 1 H), 7.50 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.67 (dd, 1 H), 6.37 (dd, 1 H), 6.21 (d, 1 H), 4.62 (d, 1 H), 4.47 (s, 1 H), 4.40 (s, 1 H), 3.46 (m, 1 H), 3.06 (m, 4 H), 2.88 (m, 1 H), 2.25 (m, 6 H), 1.99 (m, 4 H), 1.58 (m, 8 H), 0.93 (s, 6 H).

Compound 351

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 351A

diethyl 1,4-dioxaspiro[4.5]decane-8,8-dicarboxylate

[01067] A 500 ml round-bottomed flask was charged with diisopropylamine (16 ml) and tetrahydrofuran (311 ml). The solution was cooled to –78°C under N_2 and n-BuLi (2.5 M in hexanes, 44.8 ml)) was added. The reaction was stirred for 30 minutes at –78°C and ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (20 g) was added as a tetrahydrofuran solution (ca. 10 ml). The solution was stirred at –78°C for 1 hour and ethyl chloroformate (9 ml) was added neat. After stirring at –78°C for 10 minutes, the reaction was warmed to room temperature over 2 hours. The reaction was quenched with saturated aqueous NH_4Cl and was diluted with diethyl ether. The layers were separated, the aqueous layer was extracted with diethyl ether and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes/ethyl acetate).

Compound 351B

1,4-dioxaspiro[4.5]decane-8,8-diyldimethanol

[01068] To a 1 L round-bottomed flask was added Compound 351A (26.6 g) and tetrahydrofuran (310 ml) to give a colorless solution. The solution was cooled to 0°C and lithium aluminum hydride (2M in tetrahydrofuran, 62 ml) was added via syringe. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was

cooled back down to 0°C and quenched slowly with 4.7 ml water, 4.7 ml 10% aqueous NaOH and 14 ml water. The mixture was allowed to stir until salts were formed and was then filtered through a Supelco 90 mm silica gel Buchner funnel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-80% hexanes/ethyl acetate).

Compound 351C

2,8,11-trioxa-dispiro[3.2.4]tridecane

[01069] To a 1 L round-bottomed flask was added Compound 351B (13 g) in tetrahydrofuran (321 ml). The solution was cooled to –78°C under N_2 and n-BuLi (25.7 ml) was added dropwise via syringe. After addition was complete, the mixture stirred for 30 minutes and a tetrahydrofuran solution of 4-toluenesulfonyl chloride (12.25 g) was added via addition funnel. The reaction was allowed to stir overnight, and gradually warm to room temperature. The reaction mixture was cooled to –78°C and n-BuLi (25.7ml) was added. The mixture was warmed to room temperature and stirred for 3 hours. The reaction was quenched with sat aqueous NH_4Cl and diluted with diethyl ether. The layers were separated, the aqueous layers extracted with diethyl ether and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0–20% acetone/hexanes).

Compound 351D

2-oxaspiro[3.5]nonan-7-one

[01070] To a 500 ml round-bottomed flask was added Compound 351C (11 g) in 80 % aqueous acetic acid (200 ml). The reaction was heated to 65°C and stirred for about 4 hours. Most of the acetic acid and water were removed by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes/ethyl acetate).

Compound 351E

7-methylene-2-oxaspiro[3.5]nonane

[01071] To a 250 ml round-bottomed flask was added methyltriphenylphosphonium iodide (4.33 g) in tetrahydrofuran (35.7 ml) to give a suspension. The suspension was cooled to -15°C. n-BuLi (2.5 M in hexanes, 4.28 ml) was added dropwise and the mixture was stirred at -15°C for 40 minutes and Compound 351D (1 g) was added as a tetrahydrofuran (ca. 5 ml)

solution. The mixture was stirred at -15°C for about 15 minutes and warmed to room temperature. After 1.5 hours, the reaction was complete and was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted (2 ×) with diethyl ether. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase chromatography (Analogix, 80 g Grace silica gel column, 0-50% hexanes/ethyl acetate).

Compound 351F

2-oxaspiro[3.5]nonan-7-ylmethanol

[01072] To a 25 ml round-bottomed flask was added Compound 351E (568 mg) and Compound 351F tetrahydrofuran (4.11 ml) to give a colorless solution. 9-Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 24.7 ml) was added and the reaction was allowed to stir for 2 hours at room temperature. Ethanol (11 ml) was added followed by aqueous NaOH (5M, 4.11 ml) and then hydrogen peroxide (2.1 ml) was added. The reaction was heated at 50°C for 2 hours. The mixture was concentrated by rotary evaporation, and diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 ×) and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 80 g Grace, 0–70 % hexanes/ethyl acetate).

Compound 351G

4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrobenzenesulfonamide

[01073] Compound 351G was prepared substituting Compound 351F for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 351H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[01074] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 351G for Compound 1F in the procedure for Compound 1G. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1 H) 8.34 (s, 1 H) 8.03 (d, 2 H) 7.45 - 7.57 (m, 3 H) 7.30 - 7.40 (m, 3 H) 7.04 (d, 2 H) 6.67 (dd, 1 H) 6.39 (dd, 1 H) 6.17 - 6.23 (m, 1 H) 4.29 (s, 2

H) 4.20 (s, 2 H) 4.00 (d, 2 H) 3.08 (s, 4 H) 2.73 - 2.90 (m, 2 H) 2.72 (s, 1 H) 2.01 - 2.32 (m, 6 H) 1.96 (s, 2 H) 1.64 - 1.78 (m, 4 H) 1.33 - 1.50 (m, 6 H) 0.96 - 1.15 (m, 2 H) 0.92 (s, 6 H).

Compound 352

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 352A

4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[01075] The title compound was prepared by substituting Compound 341F for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 352B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01076] The title compound was prepared by substituting Compound 352A for Compound 1F and Compound 3J for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1H), 8.31 (br s, 1H), 8.01 (m, 2H), 7.49 (m, 3H), 7.33 (m, 3H), 7.03 (m, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.27 (s, 1H), 4.05 (d, 2H), 3.40 (m, 2H), 3.17 (s, 1H), 3.07 (m, 3H), 2.79 (m, 1H), 2.24 (m, 3H), 2.14 (m, 2H), 1.94 (m, 2H), 1.71 (m, 3H), 1.52 (m, 2H), 1.38 (m, 4H), 1.22 (m, 2H), 1.09 (s, 3H), 0.91 (s, 6H).

Compound 353

4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 353A

1,4-dioxaspiro[4.5]decane-8,8-diylbis(methylene) bis(4-methylbenzenesulfonate)

[01077] To a 500 ml round-bottomed flask was added Compound 351B (10 g) and dichloromethane (165 ml) to give a colorless solution. Triethylamine (24.1 ml) and toluene-2-sulfonyl chloride (19.8 g) were added followed by 4-dimethylaminopyridine (0.604 g). The reaction was refluxed overnight. Saturated aqueous NH_4Cl was added followed by dilution with water and additional dichloromethane. The aqueous layer was extracted with

dichloromethane (2 ×) and the combined organics were dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-55% hexanes/ethyl acetate).

Compound 353B

8,8-bis(fluoromethyl)-1,4-dioxaspiro[4.5]decane

[01078] To a 500 ml round-bottomed flask was added Compound 353A (20 g). tetra-*n*-Butylammonium fluoride (1M in tetrahydrofuran, 200 ml) was added and the resulting solution was refluxed for 6 days. The reaction was cooled, diluted with diethyl ether and washed with water (3 ×). The organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-30% hexanes/ethyl acetate).

Compound 353C

4,4-bis(fluoromethyl)cyclohexanone

[01079] To a 250 ml round bottom flask was added Compound 353B (1.1 g) and 80% aqueous acetic acid (50 ml). The reaction was heated at 65°C for 3 hours, cooled and concentrated by rotary evaporation to remove most of the acetic acid and water. The residue was purified by regular phase flash column chromatography (Analogix, 0-50% hexanes/ethyl acetate).

Compound 353D

2-chloro-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

[01080] To a 100 ml pear flask was added N,N-dimethylformamide (498 µl) and dichloromethane (8.9 ml) to give a colorless solution. The solution was cooled to 0°C and $POCl_3$ (550 µl) was added dropwise and then the mixture was warmed to room temperature for 30 minutes. In the meantime, to a 100 ml pear shaped flask was added Compound 353C (870 mg, 5.36 mmol) in dichloromethane (8941 µl) to give a colorless solution. The Vilsmeier reagent was then taken up in a syringe and added dropwise to the 4,4-bis(fluoromethyl)cyclohexanone (870 mg) solution at room temperature. The resulting solution was stirred overnight. The reaction was poured into saturated aqueous $NaHCO_3$ and ice, warmed to room temperature and extracted with dichloromethane (3 × 30 ml). The organics were combined, dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix (0–60%

hexanes/ethyl acetate).

Compound 353E

2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

[01081] To a 20 ml vial was added Compound 353D (460 mg), 4-chlorophenylboronic acid (414 mg), potassium carbonate (762 mg), tetrabutylammonium bromide (711 mg), palladium (II) acetate (14.85 mg) and water (2450 μl) to give a suspension which was degassed with N_2 for 2 minutes. The reaction was stirred at 45°C overnight, cooled, and poured over a Supelco silica gel Buchner funnel, washing with ethyl acetate several times. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0–60% hexanes/ethyl acetate).

Compound 353F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[01082] To a 20 ml vial was added Compound 353E (240 mg), Compound 15F (297 mg) and dichloromethane (4.2 ml). Sodium triacetoxyborohydride (268 mg) was added and the reaction was stirred overnight at room temperature. The reaction was loaded directly onto silica gel and purified by regular phase flash column chromatography (Analogix, 0-80% hexanes/ethyl acetate).

Compound 353G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[01083] The title compound was prepared by substituting Compound 353F for Compound 15G in the procedure for Compound 15H.

Compound 353H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

[01084] Compound 353H was prepared by replacing Compound 3J with Compound 353G and Compound 11B with Compound 1F in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1 H) 11.44 (s, 1 H) 8.48 - 8.70 (m, 1 H) 8.05 (d, 2 H) 7.81 (dd, 1 H) 7.46 - 7.59 (m, 3 H) 7.35 (d, 2 H) 7.12 (d, 2 H) 6.68 (dd, 1 H) 6.40 (dd, 1 H)

6.16 (d, 1 H) 4.39 - 4.49 (m, 2 H) 4.23 - 4.35 (m, 2 H) 3.85 (dd, *J*=11.87, 2.71 Hz, 2 H) 3.20 - 3.30 (m, 4 H) 2.98 - 3.10 (m, 4 H) 2.66 - 2.77 (m, 2 H) 2.11 - 2.30 (m, 6 H) 2.02 - 2.12 (m, 3 H) 1.99 (s, 1 H) 1.82 - 1.97 (m, 1 H) 1.54 - 1.67 (m, 4 H) 1.20 - 1.34 (m, 2 H).

Compound 354

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 354A

tert-butyl 2-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

[01085] The title compound was prepared by substituting tert-butyl 2-(hydroxymethyl)-morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol Compound 24A.

Compound 354B

4-(morpholin-2-ylmethoxy)-3-nitrobenzenesulfonamide

[01086] The title compound was prepared by substituting Compound 354A for Compound 113A in the procedure for Compound 134A.

Compound 354C

4-((4-cyclopropylmorpholin-2-yl)methoxy)-3-nitrobenzenesulfonamide

[01087] The title compound was prepared by substituting Compound 354B for Compound 173A in the procedure for Compound 173B.

Compound 354D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01088] The title compound was prepared by substituting Compound 354C for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 12.98 (s, 1H), 9.06 (d, 1H), 8.50 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.66 (t, 1H), 7.62 (d, 1H), 7.44 (d, 2H), 7.26 (d, 1H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.31 (dd, 1H),4.22 (dd, 1H), 3.92 (m, 1H), 3.83 (d, 1H), 3.56 (dt, 1H), 3.07 (m, 5H), 2.77 (s, 2H), 2.68 (d, 1H), 2.35 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.59 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.40 (m, 4H).

Compound 355

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 355A

5-chloro-6-((trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

[01089] To a cooled (0°C) solution of Compound 350E (1.2 g) in tetrahydrofuran (30 ml) was added dropwise a solution of methylmagnesium bromide (5 ml, 3.0M in ether). Upon addition, the reaction mixture solidified. More tetrahydrofuran (10 ml) was added to the mixture and stirring was continued for 1 hour. The mixture was poured over aqueous NH_4Cl and extracted with ethyl acetate (3 × 150 ml). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The mixture was filtered and concentrated. The residue was dissolved in dimethylsulfoxide/methanol (20 ml, 1:1) and loaded on loaded on Gilson, C18(100A) 250x121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes to separate the two isomers and isolate the title compound.

Compound 355B

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01090] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 355A for Compound 1F in the procedure for Compound 1G. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1 H), 8.47 (s, 1 H), 8.17 (s, 1 H), 7.54 (d, 1 H), 7.48 (m, 2 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.67 (dd, 1 H), 6.37 (d, 1 H), 6.22 (d, 1 H), 4.49 (s, 1 H), 4.42 (s, 1 H), 4.15 (s, 1 H), 3.06 (m, 4 H), 2.84 (m, 1 H), 2.25 (m, 6 H), 1.96 (s, 3 H), 1.83 (m, 4 H), 1.44 (m, 6 H), 1.14 (s, 3 H), 0.93 (s, 6 H).

Compound 356

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 356A

5-chloro-6-((cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

[01091] The title compound was prepared as described for Compound 355A.

Compound 356B

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01092] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 356A for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1 H), 8.52 (s, 1 H), 8.20 (s, 1 H), 8.03 (d, 1 H), 7.51 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.55 (s, 1 H), 4.48 (s, 1 H), 4.34 (s, 1 H), 3.08 (m, 4 H), 2.89 (d, 2 H), 2.27 (m, 5 H), 1.93 (m, 4 H), 1.66 (m, 4 H), 1.43 (m, 4 H), 1.11 (s, 3 H), 0.93 (s, 6 H).

Compound 357

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 357A

ethyl 4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

[01093] To 1-*tert*-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.000 g) was added HCl (4.0M in dioxane, 4.54 ml). After 1 hour the reaction was concentrated and dried under high vacuum. The resulting solid was dissolved in dichloromethane (5 ml) and treated with sodium triacetoxyborohydride (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution (20 ml) and extracted into dichloromethane (2 × 25 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 3.75% methanol/dichloromethane over 40 minutes (flow = 30 ml/min) gave the title compound.

Compound 357B

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

[01094] To a solution of Compound 357A (0.59 g) in tetrahydrofuran (5 ml) was added lithium aluminum hydride (1.80 ml) at 0°C. The reaction was removed from the ice bath and allowed to warm to room temperature. The reaction was quenched by the dropwise addition

of 0.6 ml of water followed by 0.2 ml of 2N aqueous NaOH. The reaction was filtered through celite and rinsed with ethyl acetate (50 ml). The mixture and the residue was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minutes (flow = 40 ml/min) to provide the title compound.

Compound 357C

3-cyano-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

[01095] The title compound was prepared by substituting Compound 357B for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 284A.

Compound 357D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01096] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 357C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide- d_6) δ 11.67 (s, 1H), 11.49 - 11.14 (m, 1H), 8.17 (d, 1H), 8.03 (d, 2H), 7.51 (dd, 3H), 7.43 - 7.26 (m, 3H), 7.12 - 6.96 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.55 (t, 2H), 4.45 (t, 2H), 4.34 (d, 2H), 3.49 (s, 1H), 3.09 (s, 8H), 2.39 - 1.66 (m, 14H), 1.39 (s, 2H), 0.92 (s, 6H).

Compound 358

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 358A

benzyl (4-ethyl-4-hydroxycyclohexyl)methylcarbamate

[01097] To a vigorous stirring solution of benzyl (4-oxocyclohexyl)methylcarbamate (1 g) in tetrahydrofuran (20 ml) at –78°C was slowly added 1 M ethylmagnesium bromide (11.48 ml, 11.48 mmol) in ether. After completion of the addition, the mixture was stirred at –78°C for 2 hours and was warmed to 0°C, and stirred in an ice bath for 30 minutes. The reaction was quenched with a cold NH_4Cl aqueous solution. The precipitates were filtered off and washed with ethyl acetate. The filtrate was concentrated. The residue was dissolved in dichloromethane and loaded onto Analogix purification system, and was eluted with 0 - 50%

ethyl acetate in dichloromethane to provide the title compound.

Compound 358B

4-(aminomethyl)-1-ethylcyclohexanol

[01098] A mixture of Compound 358A (500 mg) and 10% Pd/C (100 mg) in tetrahydrofuran (15 ml) was stirred under H_2 for 3 hours. The insoluble material was removed by filtration, and the filtrate was concentrated to provide the title compound.

Compound 358C

4-((trans-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[01099] Compound 358B (270 mg) and 4-fluoro-3-nitrobenzenesulfonamide (417 mg) in tetrahydrofuran were treated with triethylamine (0.8 ml) overnight. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by a reverse phase chromatography, eluting with 40-55% acetonitrile in 0.1% trifluoroacetic acid water to isolate the title compound.

Compound 358D

4-((cis-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[01100] The title compound was prepared and isolated as described for Compound 358C.

Compound 358E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01101] The title compound was prepared as described in the procedure for Compound 11D using Compound 358C in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1 H), 11.35 (s, 1 H), 8.56 (d, 2 H), 8.05 (d, 1 H), 7.80 (dd, 1 H), 7.45 - 7.57 (m, 3 H), 7.34 (d, 2 H), 7.00 - 7.10 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.98 (s, 1 H), 3.24 - 3.31 (m, 4 H), 3.07 (s, 4 H), 2.75 (s, 2 H), 2.17 (d, 6 H), 1.95 (s, 2 H), 1.54 - 1.73 (m, 5 H), 1.35 - 1.47 (m, 4 H), 1.20 - 1.32 (m, 2 H), 1.03 - 1.18 (m, 2 H), 0.92 (s, 6 H), 0.81 (t, 3 H).

Compound 359

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01102] The title compound was prepared as described in the procedure for Compound 11D using Compound 358D in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d $_6$) δ 11.69 (s, 1 H), 11.34 (s, 1 H), 8.60 (t, 1 H), 8.56 (d, 1 H), 8.05 (d, 1 H), 7.80 (dd, 1 H), 7.54 (d, 1 H), 7.47 - 7.52 (m, 2 H), 7.34 (d, 2 H), 7.01 - 7.10 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.77 (s, 1 H), 3.26 (t, 2 H), 3.07 (s, 4 H), 2.76 (s, 2 H), 2.10 - 2.26 (m, 6 H), 1.95 (s, 2 H), 1.46 - 1.61 (m, 5 H), 1.28 - 1.46 (m, 6 H), 1.12 - 1.24 (m, 2 H), 0.92 (s, 6 H), 0.82 (t, 3 H).

Compound 360

4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 360A

ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

[01103] Into a 500 ml round-bottomed flask was added diisopropylamine (7.98 ml) in tetrahydrofuran (233 ml) to give a colorless solution. The mixture was cooled to –78°C under N_2 and n-BuLi (2.5 M in hexanes, 22.40 ml) was added. The reaction was stirred for 30 minutes and ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (10 g) was added. The reaction was allowed to stir for 1.5 hours upon which time CH_3I (4.38 ml) was added. The reaction was allowed to warm to room temperature overnight with stirring. Water was added and the aqueous layer was extracted with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by normal phase flash column chromatography (Analogix, 0-50% hexanes/ethyl acetate).

Compound 360B

(8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol

[01104] In a 500 ml round-bottomed flask was lithium aluminum hydride (1.772 g) in tetrahydrofuran (234 ml) to give a suspension. This suspension was cooled to 0°C and ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (10.66 g) was added via addition funnel. The reaction was stirred overnight at room temperature and then cooled back down to 0°C. The excess lithium aluminum hydride was slowly quenched with 1.8 ml water, 1.8 ml aqueous NaOH (5N) and 5.6 ml water. The suspension was stirred until the salts turned white

and was then filtered through a plug of silica gel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0–75% hexanes/ethyl acetate).

Compound 360C

8-(methoxymethyl)-8-methyl-1,4-dioxaspiro[4.5]decane

[01105] To a 250 ml round-bottomed flask was added NaH (0.902 g) and tetrahydrofuran (37.6 ml) to give a suspension. Compound 360B was added as a tetrahydrofuran solution at room temperature. The suspension was stirred for 30 minutes and then CH_3I (0.611 ml) was added. The reaction was stirred under N_2 overnight, carefully quenched with brine and diluted with water and ether. The aqueous layer was extracted with ether (2 ×) and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (Analogix, 0–60% hexanes/ethyl acetate).

Compound 360D

4-(methoxymethyl)-4-methylcyclohexanone

[01106] The title compound was prepared by substituting Compound 360C for Compound 353B in the procedure for Compound 353C.

Compound 360E

2-chloro-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

[01107] The title compound was prepared by substituting Compound 360D for Compound 353C in the procedure for Compound 353D.

Compound 360F

2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

[01108] The title compound was prepared by substituting Compound 360E for Compound 353D in the procedure for Compound 353E.

Compound 360G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[01109] The title compound was prepared by substituting Compound 360F for Compound 353E in the procedure for Compound 353F.

Compound 360H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[01110] The title compound was prepared by substituting Compound 360G for Compound 15G in the procedure for Compound 15H.

Compound 360I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

[01111] The title compound was prepared by replacing Compound 3J with Compound 360H and Compound 11B with Compound 1F in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.68 (s, 1 H) 11.43 (s, 1 H) 8.45 - 8.72 (m, 2 H) 8.04 (d,1 H) 7.80 (dd,1 H) 7.44 - 7.61 (m, 3 H) 7.34 (d, 2 H) 6.99 - 7.20 (m, 3 H) 6.68 (dd, 1 H) 6.39 (dd, 1 H) 6.18 (d, 1 H) 3.85 (dd, 2 H) 3.25 - 3.30 (m, 4 H) 3.24 (s, 3 H) 3.02 - 3.17 (m, 6 H) 2.72 (dd, 2 H) 2.18 (s, 5 H) 2.03 - 2.13 (m, 2 H) 1.81 - 1.93 (m, 2 H) 1.57 - 1.67 (m, 2 H) 1.47 - 1.56 (m, 1 H) 1.17 - 1.41 (m, 3 H) 0.91 (s, 3 H).

Compound 361

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 361A

(S)-3-nitro-4-((4-(oxetan-3-yl)morpholin-2-yl)methylamino)benzenesulfonamide

[01112] The title compound was prepared by substituting Compound 259E for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in the procedure for Compound 1A.

Compound 361B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01113] The title compound was prepared by substituting Compound 361A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.00 (s, 1H),

9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.96 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H),3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 362

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 362A

3-chloro-4-(((1*r*, 4*r*)-4-hydroxy-4-methylcyclohexyl)methoxy)benzenesulfonamide

[01114] To a solution of Compound 34lF (300 mg) in N,N-dimethylformamide (10 ml) was added sodium hydride (416 mg) portionwise. The resulting suspension was stirred for 15 minutes. 3-Chloro-4-fluorobenzenesulfonamide (425 mg) was added and stirring was continued for 72 hours. The reaction was quenched with water and the pH was adjusted to ca. 7. The mixture was diluted with brine (75 ml) and extracted with methylene chloride. The crude product was isolated from the dried methylene chloride layer by concentration and was purified on silica gel eluted with a 10, 25, 50 % ethyl acetate in methylene chloride step gradient to provide the title compound.

Compound 362B

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01115] The title compound was prepared by substituting Compound 362A for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (400 MHz, pyridine- d_5) δ 13.07 (m, 1H), 8.58 (d, 1H), 8.45 (d, 1H), 8.31 (dd, 1H), 8.11 (d, 1H), 7.69 - 7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.97 (d, 1H), 6.74 (dd, 1H), 6.52 (m, 2H), 5.34 (br s, 2H), 3.82 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 - 1.85 (m, 7H), 1.82 - 1.73 (m, 2H), 1.44 - 1.32 (m, 7H), 0.94 (m, 6H).

Compound 363

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-

({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 363A

4-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)-3-nitrobenzenesulfonamide

[01116] To a solution of Compound 350C (495 mg) in N,N-dimethylformamide (6 ml) was added NaH (65% in mineral oil, 320 mg). The mixture was stirred for 30 minutes, and then 4-fluoro-3-nitrobenzenesulfonamide (457 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH_4Cl and extracted with ethyl acetate (300 ml). The combined organic layers were washed with water, brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and was eluted with 30% ethyl acetate in hexane to provide the title compound.

Compound 363B

4-((1-fluoro-4-oxocyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[01117] To a solution of Compound 363A (860 mg) in ethanol (30 ml) was added concentrated HCl (10 ml) and the mixture was stirred at 100°C for 3 hours. The mixture was neutralized with solid Na_2CO_3 and extracted with dichloromethane (300 ml) and washed with aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 363C

4-((4-((2-cyanoethyl)(cyclopropyl)amino)-1-fluorocyclohexyl)methoxy)-3-nitrobenzenesulfonamide

[01118] To a solution of Compound 363B (200 mg) in dichloromethane (6 ml) was added 3-(cyclopropylamino)propanenitrile (64 mg) followed by sodium triacetoxyborohydride (184 mg). The mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (400 ml) and washed with 2N aqueous NaOH, water, and brine. After drying over Na_2SO_4, the mixture was filtered and evaporation of the solvent gave the title compound.

Compound 363D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01119] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 363C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.66 (s, 1 H), 8.35 (s, 1 H), 8.02 (d, 2 H), 7.51 (m, 3 H), 7.40 (m, 1 H), 7.35 (d, 2 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.39 (d, 1 H), 6.20 (s, 1 H), 4.27 (d, 2 H), 3.13 (m, 4 H), 2.88 (m, 3 H), 2.67 (m, 4 H), 2.09 (m, 10 H), 1.49 (m, 9 H), 0.93 (s, 6 H), 0.45 (m, 4 H).

Compound 364

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 364A

6-amino-5-nitropyridine-3-sulfonic acid

[01120] 6-Aminopyridine-3-sulfonic acid (20 g) in concentrated H_2SO_4 (80 ml) was heated at 50°C until it was completely dissolved. To this solution was added fuming HNO_3 slowly over 20 minutes, so the internal temperature did not exceed 55°C. After the addition was complete, the reaction mixture was heated at 50°C for 1 hour. After it was cooled to room temperature, it was poured into 150 g of ice. The mixture was stirred for another hour. The flask was cooled to 0°C, and was kept at 0°C for another 2 hours. The solid was collected by filtration, and washed with cold 1:1 water/ethanol (20 ml), followed by diethyl ether (10 ml). The solid was dried in a vacuum oven overnight to provide the title compound.

Compound 364B

6-hydroxy-5-nitropyridine-3-sulfonic acid

[01121] Compound 364A (4.0 g) in aqueous HCl (37%, 12 ml) and water (50 ml) was treated with sodium nitrite (1.19 g) in water (8 ml) dropwise at 0°C. After the addition was complete, the reaction mixture was stirred at 0°C for 1 hour. The mixture was heated at reflux for 2 hours. Water was distilled off to give a dry residue. After the residue was cooled to room temperature, a solution of 1:1 ethano/water (20 ml) was added. The resulting suspension was cooled to 0°C, and kept at 0°C for 1 hour. The solid was collected by filtration to provide the title compound.

Compound 364C

6-chloro-5-nitropyridine-3-sulfonyl chloride

[01122] A mixture of Compound 364B (2.6 g), PCl_5 (5.91 g), and $POCl_3$ (10 ml) was heated at 120°C for 4 hours. The initial suspension became a clear solution. The excess of $POCl_3$ was distilled off. After it was cooled to room temperature, the residue was poured into 50 g of crushed ice. The solid was extracted into ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give crude product that was used in the next step without further purification.

Compound 364D

6-chloro-5-nitropyridine-3-sulfonamide

[01123] Compound 364C in tetrahydrofuran (10 ml) was cooled to –10°C. To this solution was added concentrated ammonium hydroxide (0.82 ml) dropwise. The solution was stirred at –10°C for 10 minutes. The solvent was removed under pressure at room temperature. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

Compound 364E

5-nitro-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

[01124] The title compound was prepared by substituting Compound 364D for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for (4-fluorotetrahydro-2H-pyran-4-yl)methanamine in the procedure for Compound 138D.

Compound 364F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01125] The title compound was prepared by substituting Compound 364E for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1H), 8.93 (s, 1H), 8.73 (d, 1H), 8.69 (d, 1H), 8.00 (d, 1H), 7.54 (d, 1H), 7.47-7.48 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.22 (d, 1H), 3.83 (dd, 2H), 3.51 (t, 2H), 3.21-3.27 (m, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 1.90-2.27 (m, 12H), 1.58 (dd, 2H), 1.39 (t, 2H), 1.18-1.28 (m, 2H), 0.88-0.93 (m, 8H).

Compound 365

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 365A

7-(azidomethyl)-2-oxaspiro[3.5]nonane

[01126] To a 250 ml round-bottomed flask was Compound 351F (350 mg) in tetrahydrofuran (75.0 ml) to give a colorless solution. The solution was cooled to 0°C, triphenylphosphine (2.94 g), diisopropyl azodicarboxylate (2.18 ml) and diphenyl phosphorazidate (2.32 ml) were added and the reaction was stirred for 30 minutes at room temperature. The mixture was concentrated and purified the residue by regular phase flash column chromatography (Analogix, 0–20% hexanes/ethyl acetate).

Compound 365B

2-oxaspiro[3.5]nonan-7-ylmethanamine

[01127] To a 50 ml round-bottomed flask was added 10% palladium on carbon (58.7 mg). The flask was flushed with N_2 and Compound 365A (400 mg) was added as a methanol solution (10.5 ml). The flask was then flushed several times with H_2 (via balloon) and heated to 45°C for 2 hours. The reaction was cooled to room temperature, filtered through celite and the filtrate was concentrated by rotary evaporation. The residue was used in the next step without further purification.

Compound 365C

4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrobenzenesulfonamide

[01128] The title compound was prepared by substituting Compound 365B for 1-(tetrahydropyran-4-yl)methylamine in the procedure for Compound 1F.

Compound 365D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[01129] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 365C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1 H) 11.25 - 11.49 (m, 1 H) 8.48 - 8.66 (m, 2 H) 8.03

(d, 1 H) 7.79 (dd, 1 H) 7.41 - 7.61 (m, 3 H) 7.27 - 7.40 (m, 2 H) 7.05 (t, 3 H) 6.67 (dd, 1 H) 6.39 (dd, 1 H) 6.18 (d, 1 H) 4.29 (s, 2 H) 4.19 (s, 2 H) 3.17 - 3.27 (m, 2 H) 2.99 - 3.14 (m, 4 H) 2.69 - 2.79 (m, 2 H) 2.09 - 2.28 (m, 6 H) 2.04 (d, 2 H) 1.95 (s, 2 H) 1.66 (d, 2 H) 1.49 - 1.61 (m, 1 H) 1.29 - 1.45 (m, 4 H) 0.93 - 1.05 (m, 2 H) 0.92 (s, 6 H).

Compound 366

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 366A

tert-butyl (4-cyano-4-methylcyclohexyl)methylcarbamate

[01130] To a cooled (–78°C) solution of tert-butyl (4-cyanocyclohexyl)methylcarbamate (500 mg) in tetrahydrofuran (10 ml) was added lithium diisopropylamide (2.0 ml, 2M in heptane). The mixture was stirred at –78°C for 30 minutes before the addition of CH_3I (1 ml). The mixture was then stirred and the temperature was allowed to warm to room temperature. The reaction was quenched with aqueous NH_4Cl and the mixture was extracted with ethyl acetate (300 ml) and washed with water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent and silica gel chomatography (40% ethyl acetate in hexane) of the crude material gave the title compound.

Compound 366B

4-(aminomethyl)-1-methylcyclohexanecarbonitrile

[01131] To a solution of Compound 366A (480 mg) in dichloromethane (10 ml) was added trifluoroacetic acid (10 ml). The mixture was stirred for 3 hours. The mixture was then concentrated under vacuum and was used directly in the next reaction without further purification.

Compound 366C

4-((4-cyano-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[01132] To a solution of 4-fluoro-3-nitrobenzenesulfonamide (362 mg) in tetrahydrofuran (10 ml) was added Compound 366B (250 mg) and N,N-diisopropylethylamine (2 ml) . The mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 ml) and washed with water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the title compound.

Compound 366D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01133] The title compound was prepared by substituting Compound 3J for Compound 1E and Compound 366C for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.67 (s, 1 H), 11.37 (m, 1 H), 8.59 (m, 2 H), 8.04 (d, 1 H), 7.80 (d, 1 H), 7.51 (m, 3 H), 7.34 (d, 2 H), 7.10 (d, 1 H), 7.04 (d, 2 H), 6.68 (dd, 1 H), 6.39 (m, 1 H), 6.19 (s, 1 H), 3.07 (m, 4 H), 2.75 (m, 2 H), 2.17 (m, 7 H), 1.76 (m, 9 H), 1.32 (m, 9 H), 0.92 (s, 6 H).

Compound 367

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)amino}methyl pivalate

[01134] This compound was prepared by substituting chloromethyl pivalate for chloromethyl butyrate in the procedure for Compound 368. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ11.72 (s, 1H), 8.43 (d, 1H), 8.22 (dd, 1H), 8.01 (d, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 7.03 (d, 2H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.17 (d, 1H), 5.83 (s, 2H), 4.40 (d, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 3.08 (br m, 4H), 2.73 (br s, 2H), 2.18 (br m, 6H), 1.96 (s, 2H), 1.84 (m, 4H), 1.39 (m, 2H), 1.00 (s, 9H), 0.92 (s, 6H).

Compound 368

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)amino}methyl butyrate

[01135] Compound 37E (500 mg) was dissolved in acetonitrile (3.7 ml) and chloromethyl butyrate (77 mg) and Hunig's base (73 mg) were added. The reaction was heated under reflux for one day. After cooling and dilution with dimethylsulfoxide (4 ml) the reaction was purified by preparative HPLC using a 250 × 50 mm C18 column and eluting with 20–100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and

concentrated to provide the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.72 (s, 1H), 8.43 (d, 1H), 8.22 (dd, 1H), 8.01 (d, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 7.03 (d, 2H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.17 (d, 1H), 5.83 (s, 2H), 4.40 (d, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 3.08 (br m, 4H), 2.73 (br s, 2H), 2.18 (m, 8H), 1.96 (s, 2H), 1.84 (m, 4H), 1.39 (m, 4H), 0.92 (s, 6H), 0.75 (t, 3H).

Compound 369

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}($^2H_8$)piperazin-1-yl]-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide

Compound 369A

methyl 4-[(2,2,3,3,5,5,6,6-$^2H_8$)piperazin-1-yl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzoate

[01136] Into a 40 ml vial were added Compound 3H (1.55 g) and piperazine-d_8 (2.040 g) in dimethylsulfoxide (13 ml). The solution was heated to 85°C for 2.5 hours, and was then allowed to cool to room temperature overnight. The mixture was transferred to a 120 ml flask and was cooled to 5–10°C. Dichloromethane (30 ml) was added, then water (10 ml) was added via syringe over 5 minutes maintaining temp at no more than 15°C. The layers were separated and the organic layer was washed with water (4 × 10–15 ml) until pH of aqueous layer was 8–9. The organic layer was filtered through Na_2SO_4 and rinsed with dichloromethane (5 ml), and concentrated to provide the title compound.

Compound 369B

methyl 4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}($^2H_8$)piperazin-1-yl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzoate

[01137] In a 100 ml round-bottomed flask, Compound 369A (3.4 g), Compound 290B (1.321 g) and dichloromethane (3 ml) were added to a 100 ml round bottom flask at room temperature. To a separate 50 ml 3 neck round bottom flask, sodium triacetoxyborohydride (1.330 g) and dichloromethane (12 ml) were added to give a slurry. After cooling the 50 ml round bottom flask to 18–20°C, the piperazine adduct/aldehyde solution was added via syringe over 5 minutes. The triacetoxyborohydride gradually dissolved to give a clear solution after ~5 minutes. After an additional 10 minutes, the solution became hazy. After 16 hours, the reaction was cooled to 5–10°C. Saturated aqueous $NaHCO_3$ (12 ml) was added over 5 minutes maintaining the temperature at no more than 10°C. The layers were separated and the organic

layer was washed with saturated aqueous $NaHCO_3$, and 10% NaCl (12 ml), and then filtered through Na_2SO_4 and rinsed with dichloromethane (4 ml). The solution was concentrated on a rotovap, and chase concentrated with methanol (40 ml). The resulting solution was cooled to 5–10°C, and the product precipitated. The solution was mixed at room temperature for 30 minutes, then filtered and rinsed with methanol (5 ml), and the product was air dried.

Compound 369C

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}($^2H_8$)piperazin-1-yl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzoic acid

[01138] The title compound was prepared by substituting Compound 369B for Compound 15G in the procedure for Compound 15H.

Compound 369D

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}($^2H_8$)piperazin-1-yl]-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide

[01139] To a mixture of Compound 369C (2.0g), Compound 1F (1.1g) and N,N-dimethylpyridin-4-amine (0.7 g) in dichloromethane (20 ml) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.8 g). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with N,N-dimethylethane-1,2-diamine (0.6g) and stirred at room temperature for 3 hours. The mixture was extracted with 20% aqueous acetic acid and washed with 5% aqueous NaCl. Methanol (2 ml) and ethyl acetate (18 ml) were added and the precipitate was collected by filtration to provide the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide -d_6) 11.71 (s, 1H), 11.37 (s, br, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47 - 7.54 (m, 3H), 7.31 - 7.34 (m, 2H), 7.09 (d, 1H), 7.01 - 7.03 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.83 (dd, 2H), 3.21 - 3.30 (m, 4H), 3.00 – 3.10 (s, 4H), 2.75 (s, 2H), 2.05 - 2.24 (m, 6H), 1.95 (s, 2H), 1.80 - 1.93 (m, 1H), 1.55 - 1.64 (m, 2H), 1.37 (t, 2H), 1.18 - 1.31 (m, 2H), 0.90 (s, 6H).

Compound 370

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl}benzamide

Compound 370A

5-amino-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

[01140] A mixture of Compound 364E (0.16 g) and 5% palladium on carbon (0.025 g) in ethanol (5 ml) was treated with a balloon of hydrogen. The reaction mixture was stirred overnight. The solid was filtered off. The filtrate was concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

Compound 370B

3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridine-6-sulfonamide

[01141] Compound 370A (0.085 g) in water (10 ml) was treated with concentrated H_2SO_4 (0.5 ml). The solution was cooled to 0°C. To this solution was added $NaNO_2$ (0.023 g) in water (1 ml) dropwise. The solution was stirred for 1 hour at 0°C. The reaction mixture was poured into saturated $NaHCO_3$ solution, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the title compound.

Compound 370C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylsulfonyl)benzamide

[01142] This compound was prepared by substituting Compound 370B for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.60 (s, 1H), 9.11 (s, 1H), 8.92 (d, 1H), 7.96 (d, 1H), 7.55 (d, 1H), 7.45-7.46 (m, 1H), 7.42 (s, 1H), 7.36 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.32 (s, 1H), 6.22 (s, 1H), 4.63 (d, 2H), 3.80 (dd, 2H), 3.21-3.30 (m, 2H), 3.16 (s, 4H), 2.83 (s, 2H), 2.19-2.29 (m, 6H), 1.97 (s, 2H), 1.33-1.41 (m, 6H), 0.93 (s, 2H).

Compound 371

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 371A

6-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

[01143] This compound was prepared by substituting Compound 364D for 4-fluoro-3-

nitrobenzenesulfonamide and Compound 376B for Compound 138C in the procedure for Compound 138D. The title compound was isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ, C18(2), 250X21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% TFA.

Compound 371B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01144] The title compound was prepared by substituting Compound 371A for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.63 (s, 1H), 11.53 - 10.99 (m, 1H), 8.91 (s, 1H), 8.71 (dd, 2H), 8.01 (d, 1H), 7.61 - 7.44 (m, 3H), 7.44 - 7.28 (m, 2H), 7.12 - 6.97 (m, 2H), 6.76 - 6.61 (m, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.92 (s, 1H), 3.48 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.24 (dd, 6H), 1.96 (s, 2H), 1.37 (ddd, 11H), 1.07 (s, 3H), 0.93 (s, 6H).

Compound 372

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 372A

ethyl 4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

[01145] To 1-*tert*-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.00 g) was added HCl (4.0M in dioxane, 4.54 ml). After 1 hour the reaction was concentrated and dried under high vacuum. The resulting solid was dissolved in dichloromethane (5 ml) and treated with sodium triacetoxyborohydride (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight. The reaction was quenched with saturated NaHCO3 solution (20 ml) and extracted into dichloromethane (2 × 25 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 3.75% methanol/dichloromethane over 40 minutes (flow = 30 ml/minute) gave the title compound.

Compound 372B

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

[01146] To a solution of Compound 372A (0.59 g) in tetrahydrofuran (5 ml) was added lithium aluminum hydride (1.80 ml) at 0°C. The reaction was removed from the ice bath and allowed to warm to room temperature. The reaction was quenched by the dropwise addition of 0.6 ml of water followed by 0.2 ml of 2N aqueous NaOH. The reaction was filtered through diatomaceous earth and rinsed with ethyl acetate (50 ml). The organics were concentrated and loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minute (flow = 40 ml/minutes) to give the title compound.

Compound 372C

5-bromo-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

[01147] This compound was prepared by substituting Compound 372B for (tetrahydro-2H-pyran-4-yl)methanol and Compound 36A for 4-fluoro-3-nitrobenzenesulfonamide in the procedure for Compound 24A.

Compound 372D

5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

[01148] This compound was prepared by substituting Compound 372C for Compound 36B in the procedure for Compound 36C.

Compound 372E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)benzamide

[01149] The title compound was prepared by substituting Compound 372D for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.58 (s, 1H), 8.71 (s, 1H), 8.52 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.48 - 7.30 (m, 4H), 7.06 (d, 2H), 6.68 (d, 1H), 6.37 - 6.22 (m, 2H), 4.65 - 4.40 (m, 6H), 3.58 (s, 1H), 3.12 (s, 6H), 2.84 - 2.59 (m, 4H), 2.17 (s, 6H), 1.96 (d, 6H), 1.41 (s, 2H), 0.93 (s, 6H).

Compound 373

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide

Compound 373A

morpholine-4-carboxamide

[01150] A solution of morpholine-4-carbonyl chloride (2.0 g) in methanol (10 ml) and 7 N NH_3 in methanol (5 ml) was stirred at 45°C overnight. The mixture was concentrated to give a solid, which was dried under vacuum.

Compound 373B

N-(2-nitro-4-sulfamoylphenyl)morpholine-4-carboxamide

[01151] This compound was prepared by substituting Compound 373A for (tetrahydro-2H-pyran-4-yl)methanol in the procedure for Compound 24A.

Compound 373C

N-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenyl)morpholine-4-carboxamide

[01152] This compound was prepared by substituting Compound 373B for Compound 130C in the procedure for Compound 130D. ^{1}H NMR (500MHz, pyridine-d_5) δ 13.02 (s, 1H), 10.41 (s, 1H), 9.27 (d, 1H), 8.81 (d, 1H), 8.50 (dd, 1H), 8.40 (d, 1H), 8.09 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.67 (m, 4H),3.58 (m, 4H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Compound 374

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 374A

(4,4-diethoxycyclohexyl)methanol

[01153] Ethyl 4,4-diethoxycyclohexanecarboxylate (6.67 g) synthesized according to a literature procedure (European Journal of Organic Chemistry (2008) 5:895) in tetrahydrofuran (60 ml) was treated with 2 M lithium aluminum hydride in tetrahydrofuran (14.5 ml) at 0°C for 1 hour. Water (3 ml) was slowly added to quench the reaction. The precipitates were filtered off and washed with ethyl acetate. The filtrate was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

Compound 374B

1,1-diethoxy-4-(methoxymethyl)cyclohexane

[01154] Compound 374A (665 mg) in tetrahydrofuran (20 ml) was treated with NaH (394 mg) for 30 minutes and then CH_3I (0.267 ml) was slowly added. The resulting mixture was stirred overnight and the reaction was quenched with a few drops of water. The mixture was concentrated and the residue was suspended in water and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography, and was eluted with 0-15% ethyl acetate in dichloromethane to provide the title compound.

Compound 374C

4-(methoxymethyl)cyclohexanone

[01155] Compound 374B (2.2 g) in a mixture of water (3 ml) and acetic acid (12 ml) was heated at 65°C for 2 hours. The reaction mixture was concentrated. The residue was mixed with water and saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The dichloromethane layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

Compound 374D

4-(methoxymethyl)cyclohexanecarbonitrile

[01156] To a cold (–10°C) solution of Compound 374C (1.18 g) and toluenesulfonylmethyl isocyanide (2.268 g) in dimethoxyethane (3 ml) and absolute ethanol (0.1 ml) was added (in small portions) potassium tert-butoxide (2.235 g). The reaction mixture was continued to stir at <5°C for 30 minutes, warmed to room temperature, heated at 35°C for 30 minutes and then at room temperature for 2 hours. The reaction mixture was concentrated and the residue was dissolved in water-brine, and extracted with dichloromethane. The dichloromethane layer was purified by flash chromatography, and was eluted with 5% ethyl acetate in dichloromethane to provide the title compound.

Compound 374E

(4-(methoxymethyl)cyclohexyl)methanamine

[01157] To a solution of Compound 374D (460 mg) in tetrahydrofuran (15 ml) was added 2M lithium aluminum hydride in tetrahydrofuran (2.252 ml) slowly. The reaction mixture was stirred at room temperature for 1 hour, refluxed for 1 hour and cooled. 2 ml of 2M

aqueous NaOH and water (5 ml) was added. The solid was filtered off and washed with ether. The filtrate was concentrated. The residue was mixed with dichloromethane (50 ml) and the resulting mixture was dried over Na_2SO_4 and concentrated to provide the title compound.

Compound 374F

4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrobenzenesulfonamide

[01158] Compound 374E (450 mg) and 4-fluoro-3-nitrobenzenesulfonamide (693 mg) in tetrahydrofuran (10 ml) were stirred overnight. The reaction mixture was concentrated and the residue was suspended in a mixture of CH_3CN, methanol and water. The precipitates were collected, washed with water and dried to give the title compound.

Compound 374G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrophenylsulfonyl)benzamide

[01159] The title compound was prepared as described in the procedure for Compound 11D using Compound 374F in place of Compound 11B. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.69 (s, 1H), 11.40 (s, 1H), 8.53 - 8.61 (m, 2H), 8.04 (d, 1H), 7.77 - 7.82 (m, 1H), 7.47 - 7.55 (m, 3H), 7.34 (d, 2H), 7.02 - 7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.18 - 3.27 (m, 5H), 3.04 - 3.14 (m, 5H), 2.75 (s, 2H), 2.11 - 2.24 (m, 6H), 1.95 (s, 2H), 1.69 - 1.84 (m, 3H), 1.33 - 1.63 (m, 7H), 0.84 - 1.05 (m, 9H).

Compound 375

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 375A

methyl 1-(thiazol-2-yl)piperidine-4-carboxylate

[01160] A mixture of methyl piperidine-4-carboxylate (2.045 g), 2-bromothiazole (1.64 g), and Cs_2CO_3 (5.86 g) in dimethylformamide (15 ml) was heated at 100°C overnight. After it cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on

silica gel to give the title compound.

Compound 375B

(1-(thiazol-2-yl)piperidin-4-yl)methanol

[01161] This compound was prepared by substituting Compound 375A for Compound 339A in the procedure for Compound 339B.

Compound 375C

5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

[01162] This compound was prepared by substituting Compound 375B for (tetrahydro-2H-pyran-4-yl)methanol and Compound 40A for Compound 36A in the procedure for Compound 36B.

Compound 375D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

[01163] This compound was prepared by substituting Compound 375C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.65 (s, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 2H), 7.35 (d, 2H), 7.14 (d, 1H), 7.05 (d, 2H), 6.80 (d, 1H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.28 (d, 2H), 3.92 (d, 2H), 2.98-3.10 (m, 6H), 2.86 (s, 2H), 2.30 (m, 4H), 2.03-2.15 (m, 3H), 1.96 (s, 2H), 1.96 (s, 2H), 1.82-1.86 (m, 2H), 1.33-1.44 (m, 4H), 0.93 (s, 6H).

Compound 376

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 376A

tert-butyl (4-hydroxy-4-methylcyclohexyl)methylcarbamate

[01164] A solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.00 g) was dissolved in tetrahydrofuran (20 ml) and cooled to –78°C. Methylmagnesium bromide (4.40 ml) was added dropwise. The reaction was stirred for 2 hours at –78°C then allowed to warm to 0°C and stirred for 30 minutes. The resulting suspension was quenched with water (10 ml), diluted with ether (50 ml), washed with ammonium chloride (25 ml), washed with brine (25

ml), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting using a gradient of 5% to 50% ethyl acetate/dichloromethane over 30 minutes (flow = 60 ml/min) gave the title compound as a ~2:1 mixture of cis and trans isomers.

Compound 376B

4-(aminomethyl)-1-methylcyclohexanol

[01165] To a solution of Compound 376A (0.75 g) in dichloromethane (3 ml) was added a few drops of water followed by trifluoroacetic acid (1.19 ml) and the reaction stirred at room temperature. After stirring for 2h added added additional trifluoroacetic acid (0.5 ml). After an additional 4 h the reaction was concentrated and dried under high vacuum. The resulting oily solid was triturated with diethyl ether with sonication. Filtration and washing with diethyl ether gave the title compound as a trifluoroacetic acid salt and a mixture of cis and trans isomers.

Compound 376C

6-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

[01166] This compound was prepared by substituting Compound 364D for 4-fluoro-3-nitrobenzenesulfonamide and Compound 376B for (4-fluorotetrahydro-2H-pyran-4-yl)methanamine in the procedure for Compound 138D. The title compound was isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ, C18(2), 250X21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% TFA.

Compound 376D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01167] This compound was prepared by substituting Compound 376C for Compound 11B in the procedure for Compound 11D. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 8.91 (s, 1H), 8.72 (d, 1H), 8.70 (d, 1H), 8.01 (d, 1H), 7.47-7.54 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.93 (s, 1H), 3.48 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 6H), 1.96 (s, 1H), 1.34-1.59 (m, 9H), 1.17-1.24 (m, 2H), 1.07 (s, 2H), 0.92 (s, 6H).

Compound 377

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

[01168] The title compound was prepared by substituting Compound 378D for Compound 1E and Compound 337M for Compound 1F in the procedure for Compound 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.92 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.20 (m, 5H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.49 (m, 1H), 2.17 (m, 6H), 1.86 (m, 5H), 1.69 (m, 4H), 1.40 (s, 3H), 1.23 (m, 5H).

Compound 378

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound 378A

2-chloro-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

[01169] Dimethylformamide (1.298 ml) in dichloromethane (2.0 ml) at −10°C was treated dropwise with $POCl_3$ (1.426 ml) to give a colorless solution. The mixture was stirred 5 minutes and then warmed to room temperature and stirred 30 minutes. The solution was cooled to −10°C, treated dropwise with a solution of 4-methoxy-4-methylcyclohexanone (1.74 g) in dichloromethane (2.5 ml), and stirred for 4 hours at ambient temperature. The reaction mixture was poured over a mixture of ice and 25% aqueous sodium acetate solution. After the ice melted, the reaction mixture was poured into a separatory funnel and extracted with diethyl ether (4 × 125 ml). The diethyl ether extracts were washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on silica gel with 0 to 5% ethyl acetate in hexanes as the eluent.

Compound 378B

2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

[01170] Compound 378A (1.55 g), 4-chlorophenylboronic acid (1.542 g), $PdOAc_2$ (0.055 g), K_2CO_3 (2.84 g) and tetrabuylammonium bromide (2.65 g) were combined in a 50-ml round-bottomed flask equipped with a magnetic stir bar. Water (9.13 ml) was added. The

vial was flushed with nitrogen, capped and stirred at 45°C for 14 hours. The reaction mixture was cooled to room temperature and partitioned between brine and diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered through a plug of celite, concentrated and chromatographed on silica gel with 5 to 20% ethyl acetate in hexanes as the eluent.

Compound 378C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

[01171] The title compound was prepared by substituting Compound 378B for 4′-chlorobiphenyl-2-carboxaldehyde and Compound 15F for tert-butyl piperazine-1-carboxylate in the procedure for Compound 1A except that a small amount of DMSO was added to the reaction mixture.

Compound 378D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

[01172] The title compound was prepared by substituting Compound 378C for Compound 15G in the procedure for Compound 15H.

Compound 378E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

[01173] The title compound was prepared by substituting Compound 378D for Compound 1E in the procedure for Compound 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.21 (s, 3H), 3.15 (m, 2H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.50 (m, 1H), 2.16 (m, 6H), 1.81 (m, 2H), 1.63 (m, 1H), 1.57 (dd, 2H), 1.32 (m, 2H), 1.21 (s, 3H).

[01174] Table 1 below presents the inhibition constant (K_i) for binding of representative compounds to Bcl-2 protein, as determined by a TR-FRET (Time-Resolved Fluorescence-Resonance-Energy-Transfer) assay. The smaller the K_i value, the greater is the binding

affinity. It will be noted that the overwhelming majority of the compounds have K_i <0.0001 μM (<0.1 nM), and very many have K_i <0.00001 μM (<0.01 nM).

Table 1. Bcl-2 binding K_i (μM)

Compound	K_i	Compound	K_i
1	0.000225	190	0.000026
2	< 0.000010	191	< 0.000010
3	0.000013	192	< 0.000010
4	< 0.000010	193	< 0.000010
5	< 0.000010	194	< 0.000010
6	0.000018	195	< 0.000010
7	0.00492	196	< 0.000010
8	0.000153	197	< 0.000010
9	< 0.000010	198	< 0.000010
10	< 0.000010	199	< 0.000010
11	0.000016	200	< 0.000010
12	< 0.000010	201	0.000014
13	< 0.000010	202	< 0.000010
14	0.002798	203	< 0.000010
15	< 0.000010	204	< 0.000010
16	0.000219	205	< 0.000010
17	0.00009	206	0.000036
18	0.000017	207	0.00003
19	0.000226	208	0.000104
20	0.000181	209	< 0.000010
21	0.000912	210	0.000011
22	0.000291	211	0.000058
23	0.000083	212	0.0001330
24	< 0.000010	213	< 0.000010
25	< 0.000010	214	< 0.000010
26	0.000011	215	< 0.000010
27	0.000134	216	< 0.000010
28	< 0.000010	217	< 0.000010
29	< 0.000010	218	0.000013
30	< 0.000010	219	0.001192
31	< 0.000010	220	0.000988
32	< 0.000010	221	0.000049
33	< 0.000010	222	0.000938
34	0.00001	223	0.000053
35	< 0.000010	224	< 0.000010
36	0.000017	225	0.000196
37	< 0.000010	226	0.000139
38	0.0003	227	< 0.000010

Compound	K_i	Compound	K_i
39	0.000012	228	0.026761
40	< 0.000010	229	0.002109
41	< 0.000010	230	0.000031
42	0.000439	231	0.000770
43	0.000012	232	0.001631
44	< 0.000010	233	0.001654
45	< 0.000010	234	0.000115
46	0.000935	235	0.000023
47	< 0.000010	236	0.000033
48	< 0.000010	237	0.000024
49	0.000074	238	< 0.000010
50	0.000021	239	0.000026
51	< 0.000010	240	< 0.000010
52	0.000114	241	< 0.000010
53	< 0.000010	242	0.000057
54	0.002071	243	0.000546
55	< 0.000010	244	0.000281
56	0.000037	245	0.000015
57	0.000063	246	0.000144
58	< 0.000010	247	0.000019
59	0.000203	248	0.000029
60	< 0.000010	250	0.000412
61	0.000091	251	0.000571
62	< 0.000010	252	< 0.000010
63	< 0.000010	253	0.000052
64	< 0.000010	254	< 0.000010
65	< 0.000010	255	< 0.000010
66	< 0.000010	256	< 0.000010
67	< 0.000010	257	0.000052
68	0.000012	258	< 0.000010
69	0.001157	259	< 0.000010
70	0.003964	260	0.000016
71	0.00001	261	0.000134
72	< 0.000010	262	< 0.000010
73	< 0.000010	263	0.000156
74	0.000029	264	0.000036
75	< 0.000010	265	< 0.000010
76	0.000196	266	< 0.000010
77	0.000213	267	0.000035
78	< 0.000010	268	< 0.000010
79	< 0.000010	269	0.000016
80	< 0.000010	270	< 0.000010

Compound	K_i	Compound	K_i
81	< 0.000010	271	0.000039
82	0.000328	272	0.000031
83	0.000071	273	0.000035
84	0.000123	274	0.000040
85	0.000391	275	< 0.000010
86	0.000498	276	< 0.000010
87	0.000618	277	< 0.000010
88	0.000672	278	0.000252
89	0.000073	279	0.000035
90	0.000013	280	0.000071
91	0.000487	281	0.000145
92	0.000128	282	< 0.000010
93	0.003461	283	< 0.000010
94	0.000678	284	0.000024
95	0.000014	285	< 0.000010
96	0.000014	286	< 0.000010
97	0.000017	287	0.000081
98	< 0.000010	288	0.000251
99	0.000233	289	0.000090
100	< 0.000010	290	< 0.000010
101	0.000021	291	< 0.000010
102	0.000094	292	0.000190
103	< 0.000010	293	0.000093
104	0.000016	294	0.000046
105	< 0.000010	295	< 0.000010
106	0.000895	296	0.000512
107	0.000035	297	0.000174
108	< 0.000010	298	< 0.000010
109	0.000127	299	0.000039
110	0.000557	300	0.001627
111	< 0.000010	301	0.002065
112	< 0.000010	302	0.000332
113	< 0.000010	303	0.000044
114	< 0.000010	304	nd
115	< 0.000010	305	0.000033
116	< 0.000010	306	0.002067
117	< 0.000010	307	0.000130
118	< 0.000010	308	0.000141
119	< 0.000010	309	0.000023
120	< 0.000010	310	0.000165
121	< 0.000010	311	< 0.000010
122	< 0.000010	312	< 0.000010

Compound	K_i	Compound	K_i
123	< 0.000010	313	0.001102
124	< 0.000010	314	0.000042
125	< 0.000010	315	0.000052
126	< 0.000010	316	0.000601
127	< 0.000010	317	< 0.000010
128	< 0.000010	318	< 0.000010
129	0.000002	319	< 0.000010
130	< 0.000010	320	< 0.000010
131	< 0.000010	321	< 0.000010
132	< 0.000010	322	< 0.000010
133	< 0.000010	323	0.000104
134	< 0.000010	324	< 0.000010
135	< 0.000010	325	< 0.000010
136	< 0.000010	326	< 0.000010
137	< 0.000010	327	< 0.000010
138	< 0.000010	328	< 0.000010
139	< 0.000010	329	0.000030
140	< 0.000010	330	< 0.000010
141	< 0.000010	331	0.001086
142	0.00013	332	0.000621
143	< 0.000010	333	0.000511
144	< 0.000010	334	0.000572
145	< 0.000010	335	0.000150
146	< 0.000010	336	0.000198
147	< 0.000010	337	< 0.000010
148	< 0.000010	338	0.000013
149	< 0.000010	339	0.000036
150	< 0.000010	340	< 0.000010
151	0.000017	341	< 0.000010
152	< 0.000010	342	< 0.000010
153	< 0.000010	343	< 0.000010
154	< 0.000010	344	< 0.000010
155	0.000059	345	< 0.000010
156	< 0.000010	346	0.000042
157	< 0.000010	347	0.000013
158	< 0.000010	348	0.000034
159	< 0.000010	349	0.000023
160	< 0.000010	350	< 0.000010
161	< 0.000010	351	< 0.000010
162	< 0.000010	352	0.000014
163	< 0.000010	353	< 0.000010
164	< 0.000010	354	0.000010

Compound	K_i	Compound	K_i
165	< 0.000010	355	0.000014
166	< 0.000010	356	0.000039
167	< 0.000010	357	< 0.000010
168	< 0.000010	358	< 0.000010
169	0.000021	359	< 0.000010
170	0.000022	360	< 0.000010
171	< 0.000010	361	< 0.000010
172	< 0.000010	362	0.000016
173	< 0.000010	363	0.000017
174	< 0.000010	364	< 0.000010
175	0.000119	365	< 0.000010
176	0.000023	366	0.000024
177	0.000111	367	nd
178	0.000076	368	nd
179	< 0.000010	369	< 0.000010
180	< 0.000010	370	0.000285
181	0.000017	371	< 0.0000010
182	0.000068	372	nd
183	< 0.000010	373	< 0.0000010
184	< 0.000010	374	< 0.0000010
185	0.000022	375	0.00010999
186	0.000047	376	< 0.0000010
187	0.00008	377	< 0.0000010
188	< 0.000010	378	< 0.0000010
189	0.000018		

nd = not determined

[01175] Table 2 below presents data for log D (a parameter related to lipophilicity) at pH 7.4, as determined by an HPLC method, for representative compounds. It will be noted that all compounds have high log D values (most in excess of 5.3), indicating a high degree of lipophilicity and very poor solubility in water at pH 7.4.

Table 2. log D at pH 7.4

Compound	log D
5	5.37
6	5.74
9	5.71
12	5.17
18	6.35
20	6.24
24	5.72

Compound	log D
37	5.27
87	5.86
89	6.21
90	6.69
91	6.59
92	5.60
120	5.40
208	5.57
239	5.92
242	5.51
276	5.59
277	5.26
286	5.66
303	6.24
311	5.60
312	6.47
322	5.48
337	5.48
338	5.67

B. Exemplary Compounds

[01176] Compounds believed to be particularly useful in preparation of solid dispersions of the invention include without limitation:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}-sulfonyl)benzamide – Compound 89;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-benzamide – Compound 91;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 5;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-

b]pyridin-5-yloxy)benzamide – Compound 9;

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 29;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 34;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 37;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 277;

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 61;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 378;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 149;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*trans*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 337;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*cis*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 338;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 311;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]-sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 118;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 134;

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 253;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 108;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 234;

and pharmaceutically acceptable salts thereof.

C. Compound Forms

[01177] In some embodiments, a compound of Formula I is present in the solid dispersion in its parent-compound form, alone or together with a salt form of the compound.

[01178] Compounds of Formula I may form acid addition salts, basic addition salts or zwitterions. Salts of compounds of Formula I can be prepared during isolation or following purification of the compounds.

[01179] Acid addition salts are those derived from reaction of a compound of Formula I with an acid. For example, salts including the acetate, adipate, alginate, ascorbate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, ethanedisulfonate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 1-hydroxy-2-naphthoate, lactate, lactobionate, malate, maleate,

malonate, mesitylenesulfonate, methanesulfonate, naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, sulfate, tartrate, thiocyanate, trichloroacetate, trifluoroacetate, para-toluenesulfonate and undecanoate salts of a compound of Formula I can be used in a composition of the invention.

[01180] Basic addition salts, including those derived from reaction of a compound with the bicarbonate, carbonate, hydroxide or phosphate of cations such as lithium, sodium, potassium, calcium and magnesium, can likewise be used.

[01181] A compound of Formula I typically has more than one protonatable nitrogen atom and is consequently capable of forming acid addition salts with more than one, for example about 1.2 to about 2, about 1.5 to about 2 or about 1.8 to about 2, equivalents of acid per equivalent of the compound.

[01182] Without being bound by theory, it is believed that the therapeutic efficacy of compounds of Formula I is due at least in part to their ability to bind to a Bcl-2 family protein such as Bcl-2, Bcl-X_L or Bcl-w in a way that inhibits the anti-apoptotic action of the protein, for example by occupying the BH3 binding groove of the protein. It will generally be found desirable to select a compound having high binding affinity for a Bcl-2 family protein, for example a K_i <1 nM, preferably <0.1 nM, more preferably <0.01 nM.

[01183] A compound of Formula I or a salt thereof is present in a solid dispersion of the invention in an amount that can be therapeutically effective when the composition is administered to a subject in need thereof according to an appropriate regimen. Dosage amounts are expressed herein as parent-compound-equivalent amounts unless the context requires otherwise. Typically, a unit dose (the amount administered at a single time), which can be administered at an appropriate frequency, *e.g.*, twice daily to once weekly, is about 10 to about 1,000 mg, depending on the compound in question. Where frequency of administration is once daily (q.d.), unit dose and daily dose are the same. Illustratively, the unit dose is typically about 25 to about 1,000 mg, more typically about 50 to about 500 mg, for example about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450 or about 500 mg. Where the dosage form comprises a capsule shell enclosing the solid dispersion, or a tablet wherein the solid dispersion is formulated with other ingredients, a unit dose can be deliverable in a single dosage form or a plurality of dosage forms, most typically 1 to about 10 dosage forms.

D. Formulations

[01184] The higher the unit dose, the more desirable it becomes to prepare a solid dispersion having a relatively high concentration of the drug therein. Typically, the concentration of drug in the solid dispersion is at least about 1%, *e.g.*, about 1% to about 50%, by parent-compound-equivalent weight, but lower and higher concentrations can be acceptable or achievable in specific cases. Illustratively, the drug concentration in various embodiments is at least about 2%, *e.g.*, about 2% to about 50%, or at least about 5%, *e.g.*, about 5% to about 40%, for example about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35% or about 40%, by parent-compound-equivalent weight. In some embodiments, the drug concentration may be between about 5% and about 15%, such as between about 5% and about 12%, such as about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, or about 12%.

[01185] The major component of the matrix of a solid dispersion product is a polymer that is hydrophilic or water-soluble at least in a part of the pH scale, more particularly at a pH occurring in the gastrointestinal (GI) tract, or a combination of such polymers. A polymer or polymer mixture useful herein is solid at ambient temperature and, in the interests of good storage stability at a range of temperatures, should remain solid even at the highest temperatures typically experienced during storage, transport and handling of the product. A useful property of a polymer determining its usefulness herein is therefore its glass transition temperature (T_g). Suitable water-soluble polymers include, but are not limited to, those having a T_g of at least about 40°C, at least about 50°C, at least about 60°C, or more, and more particularly about 80°C to about 180°C. Methods for determining T_g values of organic polymers are described for example in Sperling, ed. (1992) Introduction To Physical Polymer Science, 2nd edition, John Wiley & Sons, Inc.

[01186] Polymers are considered water-soluble if they form a clear homogeneous solution in water (e.g., a solution that is essentially uniform throughout, and that appears clear under visual inspection or alternatively using an instrument such as a turbidimeter, the solution for example exhibiting little or no scattering of a light beam going therethrough). When

dissolved at 20°C in an aqueous solution at 2% (w/v), a suitable water-soluble polymer illustratively has an apparent viscosity of about 1 to about 5000 mPa.s, for example about 1 to about 700 mPa.s, or about 5 to about 100 mPa.s. Water-dispersable or water-swellable polymers can also be used.

[01187] Non-limiting examples of polymeric carriers useful herein include:

- homopolymers and copolymers of N-vinyl lactams, especially homopolymers and copolymers of N-vinyl pyrrolidone, *e.g.*, the homopolymer polyvinylpyrrolidone (PVP or povidone) and copolymers such as those comprising monomers of N-vinyl pyrrolidone and vinyl acetate (copovidone) or N-vinyl pyrrolidone and vinyl propionate;
- cellulose esters and cellulose ethers, in particular methylcellulose, ethylcellulose, (hydroxyalkyl)celluloses such as hydroxypropylcellulose, (hydroxyalkyl)alkyl-celluloses such as hydroxypropylmethylcellulose (HPMC or hypromellose), cellulose phthalates and succinates such as cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate (HPMC-P), hydroxypropylmethylcellulose succinate (HPMC-S) and hydroxypropylmethylcellulose acetate succinate (HPMC-AS);
- high molecular weight polyalkylene oxides such as polyethylene oxides (PEGs or PEOs) and copolymers of ethylene oxide and propylene oxide (poloxamers);
- polyacrylates and polymethacrylates such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/ 2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates) and poly(hydroxyalkyl methacrylates);
- polyacrylamides;
- vinyl acetate polymers such as copolymers of vinyl acetate and crotonic acid, polyvinyl acetate, polyvinyl alcohol and partially hydrolyzed polyvinyl acetate (also referred to as partially saponified polyvinyl alcohol);
- graft copolymers of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate (*e.g.*, Soluplus™ of BASF or equivalent product);
- oligo- and polysaccharides such as carrageenans, galactomannans and xanthan

gum;

and mixtures of two or more thereof.

[01188] Suitable povidones include, without limitation, those having a K-value (a measure of viscosity of an aqueous solution of the povidone) of about 12, about 15, about 17, about 25, about 30 or about 90, and mixtures thereof. A particular example of a useful povidone is povidone (or PVP) K30.

[01189] Another suitable polymer is a mixture of PVP and polyvinyl acetate such as that sold under the name Kollidon™ SR by BASF AG. In some embodiments, a vinylpyrrolidone-vinyl acetate copolymer commercially available as Kollidon VA 64, which is soluble both in water and in alcohol, is suitable in the formulations of the present invention.

[01190] A particular example of a useful copovidone is one consisting of about 60% N-vinyl pyrrolidone and about 40% vinyl acetate monomers, referred to herein as "copovidone 60/40".

[01191] Suitable HPMCs and derivatives thereof include, without limitation, HPMC E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC-AS LF, HPMC-AS MF, HPMC-AS HF, HPMC-AS LG, HPMC-AS MG, HPMC-AS HG, HPMC-P 50, HPMC-P 55 and mixtures thereof.

[01192] Suitable ethylcelluloses include, without limitation, those sold under the Ethocel™ trademark of Dow Chemical Company as Ethocel™ 4, Ethocel™ 7, Ethocel™ 10, Ethocel™ 14 and Ethocel™ 20, products of other manufacturers equivalent thereto, and mixtures thereof.

[01193] Suitable methacrylic acid/methyl methacrylate copolymers include, without limitation, those sold under the Eudragit™ trademark of Rohm GmbH as Eudragit™ L100, Eudragit™ L100-55 and Eudragit™ S100, products of other manufacturers equivalent thereto, and mixtures thereof.

[01194] Suitable PEGs include, without limitation, PEG 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and mixtures thereof. Lower molecular-weight PEGs such as PEG 400 and PEG 600 may be unsuitable as the sole polymeric carrier but can be useful in combination with other polymers.

[01195] Suitable poloxamers include, without limitation, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, poloxamer 407 and mixtures thereof. It will be noted that

poloxamers have surfactant properties and can be included primarily for these properties as well as their polymeric nature.

[01196] In one embodiment, the solid dispersion matrix comprises one or more polymeric carriers selected from the group consisting of povidones, copovidones, HPMCs, polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate graft copolymers and mixtures thereof. In a more particular embodiment, the solid dispersion matrix comprises one or more polymeric carriers selected from the group consisting of povidone K30, copovidone 60/40, HPMC E5, Soluplus™ polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate graft copolymer and products equivalent to Soluplus™.

[01197] One or more polymeric carriers typically constitute in total about 20% to about 95%, such as about 20% to about 90%, for example about 40% to about 85%, or about 60% to about 85%, or about 70% to about 85%, or even about 75% to about 85%, by weight of the solid dispersion.

[01198] Upon oral administration and exposure to GI fluid, it is believed without being bound by theory that, through interplay between the polymeric carrier and a surfactant component of the solid dispersion, a suitable release rate and inhibition of crystallization or recrystallization of the active ingredient are provided, thereby permitting bioabsorption.

[01199] The surfactant component can be anionic, non-ionic or can comprise a combination of anionic and non-ionic surfactants. Useful pharmaceutically acceptable anionic surfactants include alkyl sulfates (*e.g.*, sodium lauryl sulfate), alkylcarboxylates, alkylbenzole sulfates and secondary alkane sulfonates.

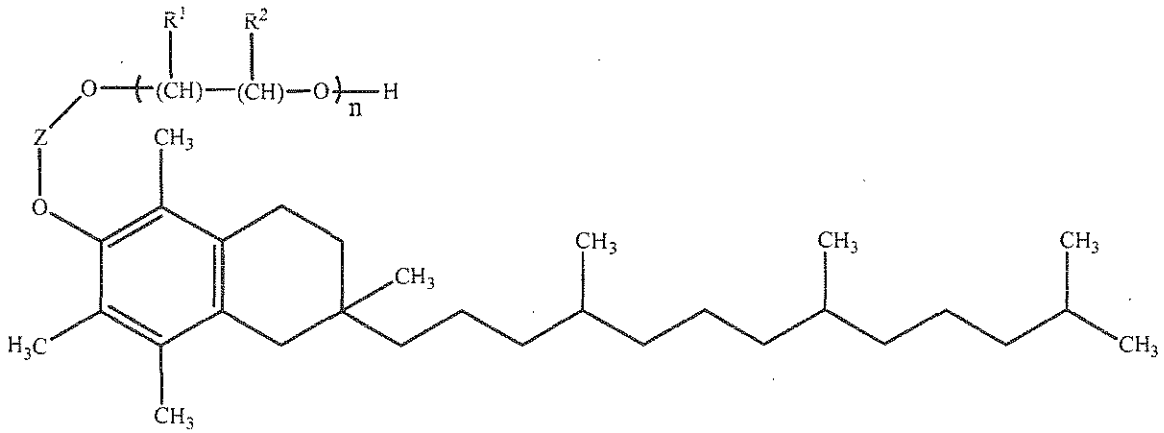
[01200] Particularly useful as surfactants herein are pharmaceutically acceptable non-ionic surfactants, especially those having a hydrophilic-lipophilic balance (HLB) value of about 12 to about 18, for example about 13 to about 17, or about 14 to about 16. The HLB system (see Fiedler (2002) Encyclopedia of Excipients, 5th edition, Aulendorf: ECV-Editio-Cantor-Verlag) assigns numeric values to surfactants, with lipophilic substances receiving lower HLB values and hydrophilic substances receiving higher HLB values.

[01201] Non-limiting examples of non-ionic surfactants useful herein include:

- polyoxyethylene castor oil derivatives such as PEG-35 castor oil (*e.g.*, Cremophor EL™ of BASF or equivalent product), PEG-40 hydrogenated castor oil (*e.g.*, Cremophor RH™ 40 or equivalent product) and PEG-60 hydrogenated castor oil

(*e.g.*, Cremophor RH™ 60 or equivalent product);

- other polyoxyethylene glycerides such as PEG-32 glyceryl laurate (*e.g.*, Gelucire™ 44/14 of Gattefossé or equivalent product) and PEG-32 glyceryl palmitostearate (*e.g.*, Gelucire™ 50/13 or equivalent product), and Labrafil M1944 CS (oleoyl macrogol 6 glycerides prepared by transesterification of apricot kernel oil with PEG 300);
- fatty acid monoesters of sorbitan, for example sorbitan monooleate (*e.g.*, Span™ 80 or equivalent product), sorbitan monostearate (*e.g.*, Span™ 60 or equivalent product), sorbitan monopalmitate (*e.g.*, Span™ 40 or equivalent product) and sorbitan monolaurate (*e.g.*, Span™ 20 or equivalent product);
- other fatty acid esters of sorbitan, for example, sorbitan tristearate and sorbitan trioleate;
- fatty acid monoesters of polyoxyethylene sorbitan (polysorbates) such as PEG-20 sorbitan monooleate (polysorbate 80, *e.g.*, Tween™ 80 or equivalent product) PEG-20 sorbitan monostearate (polysorbate 60, *e.g.*, Tween™ 60 or equivalent product), PEG-20 sorbitan monopalmitate (polysorbate 40, *e.g.*, Tween™ 40 or equivalent product), or PEG-20 sorbitan monolaurate (polysorbate 20, *e.g.*, Tween™ 20 or equivalent product);
- other fatty acid esters of polyoxyethylene sorbitan, for example, polyoxyethylene (20) sorbitan tristearate (Tween 65), polyoxyethylene (20) sorbitan trioleate (Tween 85);
- fatty acid ester of polyalkylene glycols such as, for example, PEG 660 hydroxy-stearic acid (polyglycol ester of 12-hydroxystearic acid (70 mol %) with 30 mol % ethylene glycol);
- polyalkoxylated ethers of fatty alcohols such as, for example, PEG (2) stearyl ether (Brij 72), macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether;
- A tocopheryl compound corresponding to the structure below:



wherein Z is a linking group, R^1 and R^2 are, independently of one another, hydrogen or C_1-C_4 alkyl and n is an integer from 5 to 100, preferably 10 to 50. Typically, Z is the residue of an aliphatic dibasic acid such as glutaric, succinic, or adipic acid. Preferably, both R^1 and R^2 are hydrogen. The preferred tocopheryl compound is α-tocopheryl polyethylene glycol succinate, which is commonly abbreviated as vitamin E-TPGS. Vitamin E-TPGS is a water-soluble form of natural-source vitamin E prepared by esterifying d-alpha-tocopheryl acid succinate with polyethylene glycol 1000;

and mixtures of two or more thereof.

[01202] In one embodiment, the solid dispersion comprises one or more surfactants selected from the group consisting of polyoxyethylene glycerides (including polyoxyethylene castor oil derivatives), polysorbates, TPGS and mixtures thereof. In a more particular embodiment, the solid dispersion matrix comprises one or more polymeric carriers selected from the group consisting of PEG-40 hydrogenated castor oil, polysorbate 80, polysorbate 20 and TPGS.

[01203] One or more surfactants typically constitute in total about 2% to about 25%, for example about 5% to about 20%, such as between about 5% and about 15%, or between about 5% and about 10% by weight of the solid dispersion.

[01204] Other, optional, components of the solid dispersion include, without limitation, one or more lubricants, glidants or flow regulators. Such a material, for example colloidal silicon dioxide or fumed silica (e.g., Aerosil), can reduce adhesion of the extrudable mixture to the screw and wall of the extruder and can facilitate the smooth passage of extrudate through the die. Illustratively, colloidal silicon dioxide can constitute zero to about 5%, for

example about 0.1% to about 2%, by weight of the solid dispersion. The solid dispersion can also optionally contain one or more bulking agents (fillers), disintegrants, cosolvents such as propylene glycol esters of fatty acids (*e.g.*, propylene glycol laurate), plasticizers and/or stabilizers such as antioxidants, light stabilizers, free radical scavengers or antimicrobial agents.

[01205] A dosage form of the invention can consist of, or consist essentially of, a solid dispersion as described above. However, in some embodiments a dosage form contains additional excipients and requires additional processing of the solid dispersion. For example, the solid dispersion can be ground to a powder and filled into a capsule shell or molded or compressed to form a tablet, with additional excipients as may be conventionally used in such dosage forms.

[01206] Thus orally deliverable solid dosage forms of the invention include but are not limited to capsules, dragees, granules, pills, powders and tablets. Excipients commonly used to formulate such dosage forms include encapsulating materials or formulation additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers and mixtures thereof. Many excipients have two or more functions in a pharmaceutical composition. Characterization herein of a particular excipient as having a certain function, *e.g.*, diluent, disintegrant, binding agent, *etc.*, should not be read as limiting to that function. Further information on excipients can be found in standard reference works such as Handbook of Pharmaceutical Excipients, 3rd ed. (Kibbe, ed. (2000), Washington: American Pharmaceutical Association).

[01207] Suitable diluents illustratively include, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; lactitol; maltitol; mannitol; sorbitol; xylitol; dextrose and dextrose monohydrate; fructose; sucrose and sucrose-based diluents such as compressible sugar, confectioner's sugar and sugar spheres; maltose; inositol; hydrolyzed cereal solids; starches (*e.g.*, corn starch, wheat starch, rice starch, potato starch, tapioca starch, *etc.*), starch components such as amylose and dextrates, and modified or processed starches such as pregelatinized starch; dextrins; celluloses including powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, food grade sources

of α- and amorphous cellulose and powdered cellulose, and cellulose acetate; calcium salts including calcium carbonate, tribasic calcium phosphate, dicalcium phosphate (*e.g.*, dibasic calcium phosphate dihydrate), monobasic calcium sulfate monohydrate, calcium sulfate and granular calcium lactate trihydrate; magnesium carbonate; magnesium oxide; bentonite; kaolin; sodium chloride; and the like. Such diluents, if present, typically constitute in total about 1% to about 95%, for example about 5% to about 50%, or about 10% to about 30%, by weight of the composition. The diluent or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

[01208] Microcrystalline cellulose and silicified microcrystalline cellulose are particularly useful diluents, and are optionally used in combination with a water-soluble diluent such as mannitol. Illustratively, a suitable weight ratio of microcrystalline cellulose or silicified microcrystalline cellulose to mannitol is about 10:1 to about 1:1, but ratios outside this range can be useful in particular circumstances.

[01209] Suitable disintegrants include, either individually or in combination, starches including pregelatinized starch and sodium starch glycolate; clays; magnesium aluminum silicate; cellulose-based disintegrants such as powdered cellulose, microcrystalline cellulose, methylcellulose, low-substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium and croscarmellose sodium; alginates; povidone; crospovidone; polacrilin potassium; gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums; colloidal silicon dioxide; and the like. One or more disintegrants, if present, typically constitute in total about 0.2% to about 30%, for example about 0.5% to about 20%, or about 1% to about 10%, by weight of the composition.

[01210] Sodium starch glycolate is a particularly useful disintegrant, and typically constitutes in total about 1% to about 20%, for example about 2% to about 15%, or about 5% to about 10%, by weight of the composition.

[01211] Binding agents or adhesives are useful excipients, particularly where the composition is in the form of a tablet. Such binding agents and adhesives should impart sufficient cohesion to the blend being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable binding agents and adhesives include, either individually or in combination, acacia; tragacanth; glucose; polydextrose;

starch including pregelatinized starch; gelatin; modified celluloses including methylcellulose, carmellose sodium, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxyethylcellulose and ethylcellulose; dextrins including maltodextrin; zein; alginic acid and salts of alginic acid, for example sodium alginate; magnesium aluminum silicate; bentonite; polyethylene glycol (PEG); polyethylene oxide; guar gum; polysaccharide acids; polyvinylpyrrolidone (povidone or PVP), for example povidone K-15, K-30 and K-29/32; polyacrylic acids (carbomers); polymethacrylates; and the like. One or more binding agents and/or adhesives, if present, typically constitute in total about 0.5% to about 25%, for example about 1% to about 15%, or about 1.5% to about 10%, by weight of the composition.

[01212] Povidone and hydroxypropylcellulose, either individually or in combination, are particularly useful binding agents for tablet formulations, and, if present, typically constitute about 0.5% to about 15%, for example about 1% to about 10%, or about 2% to about 8%, by weight of the composition.

[01213] Wetting agents can be added to the formulation if desired, in addition to the surfactant component of the solid dispersion. Non-limiting examples of surfactants that can be used as wetting agents include, either individually or in combination, quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride; dioctyl sodium sulfosuccinate; polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10 and octoxynol 9; poloxamers (polyoxyethylene and polyoxypropylene block copolymers); polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides, polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example ceteth-10, laureth-4, laureth-23, oleth-2, oleth-10, oleth-20, steareth-2, steareth-10, steareth-20, steareth-100 and polyoxyethylene (20) cetostearyl ether; polyoxyethylene fatty acid esters, for example polyoxyethylene (20) stearate, polyoxyethylene (40) stearate and polyoxyethylene (100) stearate; sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate; polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80; propylene glycol fatty acid esters, for example propylene glycol laurate; sodium lauryl sulfate; fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate; glyceryl fatty acid esters, for example glyceryl monooleate, glyceryl monostearate and glyceryl palmitostearate; α-

tocopherol polyethylene glycol (1000) succinate (TPGS); tyloxapol; and the like. One or more wetting agents, if present, typically constitute in total about 0.1% to about 15%, for example about 0.2% to about 10%, or about 0.5% to about 7%, by weight of the composition, excluding surfactant present in the solid dispersion.

[01214] Nonionic surfactants, more particularly poloxamers, are examples of wetting agents that can be useful herein. Illustratively, a poloxamer such as Pluronic™ F127, if present, can constitute about 0.1% to about 10%, for example about 0.2% to about 7%, or about 0.5% to about 5%, by weight of the composition, excluding surfactant present in the solid dispersion.

[01215] Lubricants reduce friction between a tableting mixture and tableting equipment during compression of tablet formulations. Suitable lubricants include, either individually or in combination, glyceryl behenate; stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils; glyceryl palmitostearate; talc; waxes; sodium benzoate; sodium acetate; sodium fumarate; sodium stearyl fumarate; PEGs (*e.g.*, PEG 4000 and PEG 6000); poloxamers; polyvinyl alcohol; sodium oleate; sodium lauryl sulfate; magnesium lauryl sulfate; and the like. One or more lubricants, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 5%, or about 0.2% to about 2%, by weight of the composition. Sodium stearyl fumarate is a particularly useful lubricant.

[01216] Anti-adherents reduce sticking of a tablet formulation to equipment surfaces. Suitable anti-adherents include, either individually or in combination, talc, colloidal silicon dioxide, starch, DL-leucine, sodium lauryl sulfate and metallic stearates. One or more anti-adherents, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 7%, or about 0.2% to about 5%, by weight of the composition. Colloidal silicon dioxide is a particularly useful anti-adherent.

[01217] Glidants improve flow properties and reduce static in a tableting mixture. Suitable glidants include, either individually or in combination, colloidal silicon dioxide, starch, powdered cellulose, sodium lauryl sulfate, magnesium trisilicate and metallic stearates. One or more glidants, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 7%, or about 0.2% to about 5%, by weight of the composition, excluding glidant present in the solid dispersion. Colloidal silicon dioxide is a particularly

useful glidant.

[01218] Other excipients such as buffering agents, stabilizers, antioxidants, antimicrobials, colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in compositions of the present invention. Tablets can be uncoated or can comprise a core that is coated, for example with a nonfunctional film or a release-modifying or enteric coating. Capsules can have hard or soft shells comprising, for example, gelatin (in the form of hard gelatin capsules or soft elastic gelatin capsules), starch, carrageenan and/or HPMC, optionally together with one or more plasticizers.

E. Method of Preparation

[01219] As indicated above, the solid dispersion of the present invention can be prepared by a process comprising melt-extrusion. Accordingly, the solid dispersion product is a melt-processed, solidified mixture. The melt-extrusion process comprises the steps of preparing a homogeneous melt of the active ingredient or the combination of active ingredients, the pharmaceutically acceptable polymer and the solubilizers, and cooling the melt until it solidifies. "Melting" refers to a transition from a solid to a liquid (or alternatively from a solid to a softened or rubbery state), such that it is possible for one component to become homogeneously mixed with or embedded in the other. Typically, one component will melt and the other components will dissolve in the melt, thus forming a solution. In accordance with the present disclosure, melting generally involves heating above the softening point of the pharmaceutically acceptable polymer. The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or simultaneously mixed and melted. Usually, the melt is homogenized in order to disperse the active ingredients efficiently. Also, it may be convenient first to melt the pharmaceutically acceptable polymer and then to admix and homogenize the active ingredients.

[01220] In a first step of this process, at least three components are subjected to elevated temperature to provide an extrudable mixture: a compound of Formula I or a pharmaceutically acceptable salt thereof; at least one pharmaceutically acceptable water-soluble polymeric carrier; and at least one pharmaceutically acceptable surfactant. Other components can

optionally be included at this stage, for example one or more additional active ingredients and/or one or more additional excipients, for example a glidant.

[01221] The components can be mixed together before, during or after melting or softening of the polymeric carrier. In one embodiment, the components are mixed first and then subjected to elevated temperature to form the extrudable mixture. In another embodiment, the components are mixed while at elevated temperature to form the extrudable mixture. In yet another embodiment the polymeric carrier is first melted or softened, optionally with the surfactant component, and the compound of Formula I or salt thereof is then added to the resulting melt. In yet another embodiment, the surfactant is added to the polymer/API melt. According to all these embodiments, it will be found preferable to thoroughly mix the melt while at elevated temperature in order to ensure homogeneous dispersion or dissolution of the active ingredient in the partially or completely molten matrix. In one embodiment, the polymeric carrier, the surfactant, and optionally the glidant are mixed first into a pre-blend. The API is then added and the mixture is blended, in order to achieve a sufficiently homogeneous blend.

[01222] The melting and mixing takes place in an apparatus customary for this purpose. Particularly suitable are extruders or kneaders. Suitable extruders include single-screw extruders, intermeshing screw extruders and multiscrew extruders, for example twin-screw extruders, which can be co-rotating or counter-rotating and, optionally, equipped with kneading disks or other screw elements for mixing or dispersing the components of the melt. In some preferred embodiments, a single screw extruder may be used for small (e.g., benchtop) and large scale (commercial) production of extrudates.

[01223] The elevated temperature attained during this part of the process can suitably be about 70°C to about 250°C, preferably 80°C to about 250°C, such as for example about 80°C to about 180°C, about 100°C to about 180°C, or about 90°C to about 160°C, or 120°C to about 160°C. Illustratively the temperature at the feeding end of the extruder is maintained at a relatively moderate temperature, for example about 80°C to about 120°C, about 80°C to about 110°C, or about 90°C to about 100°C; in the middle portion of the extruder at a higher temperature, for example about 130°C to about 180°C, or about 140°C to about 160°C; and near the extrusion die at a somewhat lower temperature, for example about 110°C to about 160°C, or about 120°C to about 150°C. It will be appreciated that appropriate working

temperatures are determined in part by the kind of extruder and the configuration of elements within the extruder used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, friction and shearing of the material in the extruder can also impart a substantial amount of thermal energy to the mixture and aid in the formation of a homogeneous melt of the components.

[01224] Other process parameters such as screw speed and feed rate will depend on the particular composition and equipment used and can readily be optimized by one of ordinary skill in the art without undue experimentation.

[01225] An API such as a compound of Formula I or a salt thereof can be added as a solid powder or in solution or dispersion in a suitable liquid solvent such as an alcohol or aliphatic hydrocarbon or ester, or liquid carbon dioxide. Such solvent is removed, *e.g.*, evaporated, in preparation of the melt.

[01226] The extrudate emerging from the extruder die is semi-solid, for example pasty or viscous in texture. Before cooling to ambient temperature, the extrudate can, if desired, be shaped into any desired shape, for example by use of a calender with two counter-rotating rollers having mutually matching depressions on their surface. Typically such a procedure results in "lentils" (small lenticular tablets). If the rollers do not have depressions on their surfaces, films can be obtained. In one embodiment, extrudate is fed directly from the extrusion equipment to the calender. Alternatively, the extrudate can molded into a desired shape by injection-molding, or simply cut into pieces, either before solidification (hot-cut) or after solidification (cold-cut).

[01227] In a variant of the above process, a foam can be formed if the extrudate contains a propellant such as a gas, *e.g.*, carbon dioxide, or volatile compound, *e.g.*, a low molecular-weight hydrocarbon, or a compound that is thermally decomposable to a gas. The propellant is dissolved in the extrudate under the relatively high pressure conditions within the extruder and, when the extrudate emerges from the die, the sudden release of pressure causes the propellant to come out of solution and vaporize, resulting in formation of a foam.

[01228] According to empirical results to-date, it has been observed that the manufacturability and quality of the extrudates may be affected and improved by the selection of matrix polymer and surfactant, as well as the percentage of API (i.e. drug load) in the extrusion blend. In general, the maximum drug load in a desirably clear, homogenous

extrudate may be improved via the selection of polymer and surfactant in the extrusion blend and selection of the concentrations of the API, the polymer, and the surfactant in the extrusion blend. In some embodiments of the invention, copovidone (Kollidon VA64) or Soluplus is used as polymer carrier, at a concentration of for example about 70% to about 90%, about 75% to about 84%, or about 78% to 82%. In these or other embodiments of the invention, the surfactant (*e.g.,* Vitamin E TPGS, Tween20, Tween80, poloxamer F68NF, Span 20, Sucroester WP15, Lauroglycol FCC, SDS, or PEG 400) may be employed at about 2% to about 15%, preferably about 5% to about 12%, most preferably about 6% to about 9% level. In these or still other preferred embodiments, the API content in the extrusion blend may range from about 1% to about 25%, preferably about 5% to 20%, most preferably about 10% to about 15%. Optionally, glidant (*e.g.,* Aerosil) can also be included in the extrusion blend at about 0% to about 3%, preferably about 0.5% to about 1.5% level.

[01229] In this regard, it is to be noted that, in one or more embodiments, it may be desirable to control the weight% ratio of two or more of the components (e.g., the API and the surfactant) of the extrusion blend, in order for example to optimize the processability of the blend (e.g., to optimize the physical properties of the blend for manufacturing purposes, such as degradation, glass transition temperature (Tg), release time, etc.). Thus, these ratios may vary as a function of, for example, the process conditions and/or components utilized in the extrusion blend. However, in various exemplary embodiments, the weight% ratio of, for example, the API to surfactant may range from about 15:1 to about 1:15, from about 10:1 to about 1:10, from about 5:1 to about 1:5, from about 4:1 to about 1:4, or from about 2:1 to about 1:2 (e.g., about 2:1, about 1.5:1, about 1:1, about :1.5 or about 1:2). In this regard it is to be further noted that, in these or yet additional embodiments, two or more APIs (e.g., two or more compounds falling within the scope of Formula I, or alternatively a compound falling within the scope of Formula I and another compound or active, such as another chemotherapeutic compound disclosed elsewhere herein) may be utilized in the extrusion blend (provided, for example, the compounds are suitable stable under the processing conditions and there is little or no interaction between the compounds that would lead to chemical instability of the compounds).

[01230] In this regard it is to be still further noted that selection or choice of the polymer carrier may impact various performance properties of the resulting extrudate (or composition).

For example, in some instances, it has been observed that as the drug load increases relative to the amount of polymer carrier, the release rate is slower. However, it has also been observed that the release rate may vary, in at least some instances, from one polymer carrier to the other; for example, it has been observed that the release rate using Soluplus was slower than when comparable copovidone polymer carriers were used. Empirical results to-date also suggest that the release rate, as well as the variations therein, are in at least some instances independent of the surfactant (e.g., poloxamer, Tween80, solutol, cremophor, etc.) that is used; for example, it has been observed that the amount of surfactant (e.g., poloxamer) has little if any impact on the release rate when used with Soluplus (alone or in combination with a copovidone polymer carrier). Without being held to any particular theory, it is generally believed that this may be due, at least in part, to Soluplus acting as a surfactant, as well. Empirical results to-date still further suggest that differences in release rate occur when mixtures of polymer carriers are used, as well; for example, it has been observed that an equal parts mixture of Soluplus and a copovidone polymer carrier results in a release rate that is slower than the release rate observed when only Soluplus is used. In addition, it has been observed that as the amount of the copovidone polymer carrier increases in this mixture, the more the release rate decreases.

[01231] Bioavailability of the solid dispersion produced by melt extrusion may be assessed by dispersibility studies. The release rate of API from the extrudates may measured in samples after dispensing the extrudates in acidic environment (*e.g.,* 0.1N HCl) at about physiological temperature (*e.g.,* 37°C) to simulate drug release in the gastrointestinal tract in human. Generally, current empirical results to-date have shown that the formulations with higher drug load have slower API release rate. It is also observed that although higher surfactant level leads to faster API release rate, excessive surfactant may affect the manufacturability of the extrudates.

[01232] Once cooled to ambient temperature, the melt-extruded solid dispersion can be stored until ready for use or further processing. It has been determined, e.g., by differential scanning calorimetry (DSC), that extrudates manufactured by the process of the present invention generally are monophasic systems in which the risk of phase separation is negligible even for extended storage durations. If desired, the solid dispersion can be milled or ground to form granules suitable for filling into capsules or for molding or compression to form a

tablet, with additional excipients as may be conventionally used in such dosage forms, for example those listed hereinabove.

[01233] In one embodiment, a milling apparatus (e.g., a Quadro U5 Comil) equipped with screens having various aperture sizes (in the range of 100 to 1000 μm) may be used for milling the extrudates. The distribution of the sizes of the particles produced by the milling is substantially consistent throughout the milling process and is not significantly affected by the batch size (*e.g.,* from about 100 g to about 45 kg) of the extrudates. The milled extrudate can be further blended with filler (*e.g.,* dicalcium phosphate (DCP) or crosarmellose sodium), or lubricant (*e.g.,* sodium stearyl fumarate). Tabletability, characterized by the tensile strength as a function of compaction pressure, can be assessed on a tablet press simulator (*e.g.,* Presster, Metropolitan Computing Corporation). In general, formulations made from clear extrudates typically show better tabletability than those made from cloudy extrudates. Further, the addition of DCP or other fillers and reduction of particle size (as determined by the screen aperture sizes of Comil), as well as an increase in moisture content in the milled extrudate, all improve tabletability.

[01234] Bioavailability of the tablets produced from the milled extrudates may be assessed by *in vitro* dissolution studies using, for example, USP apparatus Type 2 method. It has been observed in preferred embodiments that about 90% to about 100% of the API may be released from 50 mg tablets within 6 to 8 hours. Similar results may be obtained using either phosphate buffer or 0.01 N HCl. Based on empirical results to-date, the dissolution rate appears to be independent of the particle size of the milled extrudates before compression and the moisture content in the tablets, and is only slightly decreased by the addition of DCP. This appears to support an erosion-based drug release mechanism in the tablets, with the dissolution rate apparently being a function of the tablet composition.

F. Dosage Forms and Regimen

[01235] The terms "orally deliverable", "oral administration" and "orally administered" herein refer to administration to a subject *per os* (p.o.), that is, administration wherein the composition is immediately swallowed, for example with the aid of a suitable volume of water or other potable liquid. "Oral administration" is distinguished herein from intraoral

administration, *e.g.*, sublingual or buccal administration or topical administration to intraoral tissues such as periodontal tissues, that does not involve immediate swallowing of the composition.

[01236] The active ingredient form (*e.g.*, parent compound or salt), the polymeric carrier(s), surfactant(s) and other optional ingredients should be selected, and relative amounts of these components should be used, to provide a solid dispersion or dosage form having acceptable bioabsorption when administered orally. Such bioabsorption can be evidenced, for example, by the pharmacokinetic (PK) profile of the solid dispersion or dosage form, more particularly by the C_{max} or AUC, for example AUC_{0-24} or $AUC_{0-\infty}$ at a particular dose or over a range of doses. Illustratively, bioavailability can be expressed as a percentage, for example using the parameter F, which computes AUC for oral delivery of a test composition as a percentage of AUC for intravenous (i.v.) delivery of the drug in a suitable solvent, taking into account any difference between oral and i.v. doses.

[01237] Bioavailability can be determined by PK studies in humans or in any suitable model species. For present purposes, a dog model is generally suitable. In various illustrative embodiments, compositions of the invention exhibit oral bioavailability of at least about 15%, at least about 20%, at least about 25% or at least about 30%, up to or exceeding about 50%, in a dog model, when administered as a single dose of about 2.5 to about 10 mg/kg to fasting or non-fasting animals.

[01238] Compositions embraced herein, including compositions described generally or with specificity herein, are useful for orally delivering a drug that is a compound of Formula I or a pharmaceutically acceptable salt thereof to a subject. Accordingly, a method of the invention for delivering such a drug to a subject comprises orally administering a composition as described above.

[01239] The subject can be human or non-human (*e.g.*, a farm, zoo, work or companion animal, or a laboratory animal used as a model) but in an important embodiment the subject is a human patient in need of the drug, for example to treat a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein. A human subject can be male or female and of any age. The patient is typically an adult, but a method of the invention can be useful to treat a childhood cancer such as leukemia, for example acute lymphocytic leukemia, in a pediatric patient.

[01240] The composition is normally administered in an amount providing a therapeutically effective daily dose of the drug. The term "daily dose" herein means the amount of drug administered per day, regardless of the frequency of administration. For example, if the subject receives a unit dose of 150 mg twice daily, the daily dose is 300 mg. Use of the term "daily dose" will be understood not to imply that the specified dosage amount is necessarily administered once daily. However, in a particular embodiment the dosing frequency is once daily (q.d.), and the daily dose and unit dose are in this embodiment the same thing.

[01241] What constitutes a therapeutically effective dose depends on the particular compound, the subject (including species and body weight of the subject), the disease (*e.g.*, the particular type of cancer) to be treated, the stage and/or severity of the disease, the individual subject's tolerance of the compound, whether the compound is administered in monotherapy or in combination with one or more other drugs, *e.g.*, other chemotherapeutics for treatment of cancer, and other factors. Thus the daily dose can vary within wide margins, for example from about 10 to about 1,000 mg. Greater or lesser daily doses can be appropriate in specific situations. It will be understood that recitation herein of a "therapeutically effective" dose herein does not necessarily require that the drug be therapeutically effective if only a single such dose is administered; typically therapeutic efficacy depends on the composition being administered repeatedly according to a regimen involving appropriate frequency and duration of administration. It is strongly preferred that, while the daily dose selected is sufficient to provide benefit in terms of treating the cancer, it should not be sufficient to provoke an adverse side-effect to an unacceptable or intolerable degree. A suitable therapeutically effective dose can be selected by the physician of ordinary skill without undue experimentation based on the disclosure herein and on art cited herein, taking into account factors such as those mentioned above. The physician may, for example, start a cancer patient on a course of therapy with a relatively low daily dose and titrate the dose upwards over a period of days or weeks, to reduce risk of adverse side-effects.

[01242] Illustratively, suitable doses of a compound of Formula I are generally about 25 to about 1,000 mg/day, more typically about 50 to about 500 mg/day or about 200 to about 400 mg/day, for example about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450 or about 500 mg/day, administered at an average dosage interval of

about 3 hours to about 7 days, for example about 8 hours to about 3 days, or about 12 hours to about 2 days. In most cases a once-daily (q.d.) administration regimen is suitable.

[01243] An "average dosage interval" herein is defined as a span of time, for example one day or one week, divided by the number of unit doses administered over that span of time. For example, where a drug is administered three times a day, around 8 am, around noon and around 6 pm, the average dosage interval is 8 hours (a 24-hour time span divided by 3). If the drug is formulated as a discrete dosage form such as a tablet or capsule, a plurality (*e.g.*, 2 to about 10) of dosage forms administered at one time is considered a unit dose for the purpose of defining the average dosage interval.

[01244] Where the composition is in the form of a capsule, one to a small plurality of capsules can be swallowed whole, typically with the aid of water or other imbibable liquid to help the swallowing process. Suitable capsule shell materials include, without limitation, gelatin (in the form of hard gelatin capsules or soft elastic gelatin capsules), starch, carrageenan and HPMC.

[01245] Administration can be with or without food, *i.e.*, in a non-fasting or fasting condition. It is generally preferred to administer the present compositions to a non-fasting patient.

G. Montherapies and Combination Therapies

[01246] Compositions of the invention are suitable for use in monotherapy or in combination therapy, for example with other chemotherapeutics or with ionizing radiation. A particular advantage of the present invention is that it permits once-daily oral administration, a regimen which is convenient for the patient who is undergoing treatment with other orally administered drugs on a once-daily regimen. Oral administration is easily accomplished by the patient him/herself or by a caregiver in the patient's home; it is also a convenient route of administration for patients in a hospital or residential care setting.

[01247] Combination therapies illustratively include administration of a composition of the present invention concomitantly with one or more of bortezomib, carboplatin, cisplatin, cyclophosphamide, dacarbazine, dexamethasone, docetaxel, doxorubicin, etoposide, fludarabine, irinotecan, paclitaxel, rapamycin, rituximab, vincristine and the like, for example

with a polytherapy such as CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone), RCVP (rituximab + cyclophosphamide + vincristine + prednisone), R-CHOP (rituximab + CHOP) or DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab).

[01248] A composition of the invention can be administered in combination therapy with one or more therapeutic agents that include, but are not limited to, alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, other apoptosis inducing agents (for example, Bcl-xL, Bcl-w and Bfl-1 inhibitors), activators of a death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (bi-specific T-cell engager) antibodies, antibody-drug conjugates, biological response modifiers, cyclin-dependent kinase (CDK) inhibitors, cell cycle inhibitors, cyclooxygenase-2 (COX-2) inhibitors, dual variable domain binding proteins (DVDs), human epidermal growth factor receptor 2 (ErbB2 or HER/2neu) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, JAK2 inhibitors, mammalian target of rapamycin (mTOR) inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly-ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids, deltoids, plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like.

[01249] BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include, but are not limited to, adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by

T-cells when targeted to cancer cells (Sutton *et al.* (1997) J. Immunol. 158:5783–5790).

[01250] siRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH_3-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (*e.g.*, 10–200 bps) and structures (*e.g.*, hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1–2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand. For example, siRNAs targeting Mcl-1 have been shown to enhance the activity of ABT-263 or ABT-737 in various tumor cell lines (Tse *et al.* (2008) Cancer Res. 68:3421–3428 and references therein).

[01251] Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (*i.e.*, capable of binding one antigen) or multispecific (*i.e.*, capable of binding two or more antigens). DVD binding proteins comprising two heavy-chain DVD polypeptides and two light-chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy-chain DVD polypeptide, a light-chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy -chain variable domain and a light-chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

[01252] Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, Cloretazine™ (laromustine, VNP 40101M), cyclophosphamide, dacarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide,

melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, treosulfan, trofosfamide and the like.

[01253] Angiogenesis inhibitors include epidermal growth factor receptor (EGFR) inhibitors, endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

[01254] Antimetabolites include Alimta™ (pemetrexed disodium, LY231514, MTA), 5-azacitidine, Xeloda™ (capecitabine), carmofur, Leustat™ (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethenylcytidine, fludarabine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, Gemzar™ (gemcitabine), hydroxyurea, Alkeran™ (melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, ribavirin, S-1, triapine, trimetrexate, TS-1, tiazofurin, tegafur, vidarabine, UFT and the like.

[01255] Antivirals include ritonavir, hydroxychloroquine and the like.

[01256] Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, aurora A-specific kinase inhibitors, aurora B-specific kinase inhibitors, pan-aurora kinase inhibitors and the like.

[01257] Bcl-2 family protein inhibitors other than compounds of Formula I herein include AT-101 ((–)gossypol), Genasense™ Bcl-2-targeting antisense oligonucleotide (G3139 or oblimersen), IPI-194, IPI-565, ABT-737, ABT-263, GX-070 (obatoclax) and the like.

[01258] Bcr-Abl kinase inhibitors include dasatinib (BMS-354825), Gleevec™ (imatinib) and the like.

[01259] CDK inhibitors include AZD-5438, BMI-1040, BMS-387032, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202 or R-roscovitine), ZK-304709 and the like.

[01260] COX-2 inhibitors include ABT-963, Arcoxia™ (etoricoxib), Bextra™ (valdecoxib), BMS-347070, Celebrex™ (celecoxib), COX-189 (lumiracoxib), CT-3,

Deramaxx™ (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole, MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, Vioxx™ (rofecoxib) and the like.

[01261] EGFR inhibitors include ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, Erbitux™ (cetuximab), HR3, IgA antibodies, Iressa™ (gefitinib), Tarceva™ (erlotinib or OSI-774), TP-38, EGFR fusion protein, Tykerb™ (lapatinib) and the like.

[01262] ErbB2 receptor inhibitors include CP-724714, CI-1033 (canertinib), Herceptin™ (trastuzumab), Tykerb™ (lapatinib), Omnitarg™ (2C4, petuzumab), TAK-165, GW-572016 (ionafamib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecific antibodies, mAB AR-209, mAB 2B-1 and the like.

[01263] Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

[01264] HSP-90 inhibitors include 17AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, Mycograb™ (human recombinant antibody to HSP-90), nab-17AAG, NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090, VER-49009 and the like.

[01265] Inhibitors of apoptosis proteins include HGS-1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

[01266] Antibody-drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19A, SGN-35, SGN-75 and the like.

[01267] Activators of death receptor pathway include TRAIL and antibodies or other agents that target TRAIL or death receptors (*e.g.*, DR4 and DR5) such as apomab, conatumumab, ETR2-ST01, GDC0145 (lexatumumab), HGS-1029, LBY-135, PRO-1762, trastuzumab and the like.

[01268] Kinesin inhibitors include Eg5 inhibitors such as AZD-4877 and ARRY-520, CENPE inhibitors such as GSK-923295A, and the like.

[01269] JAK2 inhibitors include CEP-701 (lesaurtinib), XL019, INCB-018424 and the like.

[01270] MEK inhibitors include ARRY-142886, ARRY-438162, PD-325901, PD-98059 and the like.

[01271] mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30 and Torin 1, and the like.

[01272] Non-steroidal anti-inflammatory drugs include Amigesic™ (salsalate), Dolobid™ (diflunisal), Motrin™ (ibuprofen), Orudis™ (ketoprofen), Relafen™ (nabumetone), Feldene™ (piroxicam), ibuprofen cream, Aleve™ and Naprosyn™ (naproxen), Voltaren™ (diclofenac), Indocin™ (indomethacin), Clinoril™ (sulindac), Tolectin™ (tolmetin), Lodine™ (etodolac), Toradol™ (ketorolac), Daypro™ (oxaprozin) and the like.

[01273] PDGFR inhibitors include CP-673451, CP-868596 and the like.

[01274] Platinum chemotherapeutics include cisplatin, Eloxatin™ (oxaliplatin), eptaplatin, lobaplatin, nedaplatin, Paraplatin™ (carboplatin), picoplatin, satraplatin and the like.

[01275] Polo-like kinase inhibitors include BI-2536 and the like.

[01276] Phosphoinositide-3 kinase inhibitors include wortmannin, LY-294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

[01277] Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

[01278] VEGFR inhibitors include Avastin™ (bevacizumab), ABT-869, AEE-788, Angiozyme™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, CO) and Chiron (Emeryville, CA)), axitinib (AG-13736), AZD-2171, CP-547632, IM-862, Macugen™ (pegaptanib), Nexavar™ (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787 or ZK-222584), Sutent™ (sunitinib or SU-11248), VEGF trap, Zactima™ (vandetanib or ZD-6474) and the like.

[01279] Antibiotics include intercalating antibiotics such as aclarubicin, actinomycin D, amrubicin, annamycin, Adriamycin™ (doxorubicin), Blenoxane™ (bleomycin), daunorubicin, Caelyx™ and Myocet™ (liposomal doxorubicin), elsamitrucin, epirubicin, glarubicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, Valstar™ (valrubicin), zinostatin and the like.

[01280] Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, Camptosar™ (irinotecan hydrochloride), camptothecin, Cardioxane™ (dexrazoxane), diflomotecan, edotecarin, Ellence™ and

Pharmorubicin™ (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

[01281] Antibodies include Avastin™ (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, Erbitux™ (cetuximab), Humax-CD4™ (zanolimumab), IGF1R-specific antibodies, lintuzumab, Panorex™ (edrecolomab), Rencarex™ (WX G250), Rituxan™ (rituximab), ticilimumab, trastuzumab, CD20 antibodies types I and II and the like.

[01282] Hormonal therapies include Arimidex™ (anastrozole), Aromasin™ (exemestane), arzoxifene, Casodex™ (bicalutamide), Cetrotide™ (cetrorelix), degarelix, deslorelin, Desopan™ (trilostane), dexamethasone, Drogenil™ (flutamide), Evista™ (raloxifene), Afema™ (fadrozole), Fareston™ (toremifene), Faslodex™ (fulvestrant), Femara™ (letrozole), formestane, glucocorticoids, Hectorol™ (doxercalciferol), Renagel™ (sevelamer carbonate), lasofoxifene, leuprolide acetate, Megace™ (megestrol), Mifeprex™ (mifepristone), Nilandron™ (nilutamide), tamoxifen including Nolvadex™ (tamoxifen citrate), Plenaxis™ (abarelix), prednisone, Propecia™ (finasteride), rilostane, Suprefact™ (buserelin), luteinizing hormone releasing hormone (LHRH) including Trelstar™ (triptorelin), histrelin including Vantas™ (histrelin implant), Modrastane™ (trilostane), Zoladex™ (goserelin) and the like.

[01283] Deltoids and retinoids include seocalcitol (EB1089 or CB1093), lexacalcitol (KH1060), fenretinide, Panretin™ (alitretinoin), tretinoin including Atragen™ (liposomal tretinoin), Targretin™ (bexarotene), LGD-1550 and the like.

[01284] PARP inhibitors include ABT-888, olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

[01285] Plant alkaloids include vincristine, vinblastine, vindesine, vinorelbine and the like.

[01286] Proteasome inhibitors include Velcade™ (bortezomib), MG132, NPI-0052, PR-171 and the like.

[01287] Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, Actimmune™ (interferon gamma-1b), interferon gamma-n1, combinations thereof and the like. Other agents include Alfaferone (IFN-α), BAM-002 (oxidized glutathione), Beromun™ (tasonermin), Bexxar™ (tositumomab),

Campath™ (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), dacarbazine, denileukin, epratuzumab, Granocyte™ (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, Mylotarg™ (gemtuzumab ozogamicin), Neupogen™ (filgrastim), OncoVAC-CL, Ovarex™ (oregovomab), pemtumomab (Y-muHMFG1), Provenge™ (sipuleucel-T), sargaramostim, sizofiran, teceleukin, Theracys™ (BCG or Bacillus Calmette-Guerin), ubenimex, Virulizin™ (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama or SSM), WF-10 (tetrachlorodecaoxide or TCDO), Proleukin™ (aldesleukin), Zadaxin™ (thymalfasin), Zenapax™ (daclizumab), Zevalin™ (90Y-ibritumomab tiuxetan) and the like.

[01288] Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity, and include krestin, lentinan, sizofiran, picibanil, PF-3512676 (CpG-8954), ubenimex and the like.

[01289] Pyrimidine analogs include cytarabine (cytosine arabinoside, ara C or arabinoside C), doxifluridine, Fludara™ (fludarabine), 5-FU (5-fluorouracil), floxuridine, Gemzar™ (gemcitabine), Tomudex™ (raltitrexed), triacetyluridine, Troxatyl™ (troxacitabine) and the like.

[01290] Purine analogs include Lanvis™ (thioguanine), Purinethol™ (mercaptopurine) and the like.

[01291] Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxy-phenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS-247550), paclitaxel, Taxotere™ (docetaxel), larotaxel (PNU-100940, RPR-109881 or XRP-9881), patupilone, vinflunine, ZK-EPO (synthetic epothilone) and the like.

[01292] Ubiquitin ligase inhibitors include MDM2 inhibitors such as nutlins, NEDD8 inhibitors such as MLN4924, and the like.

[01293] Compositions of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include, but are not limited to, external beam radiotherapy (XBRT), teletherapy, brachytherapy, sealed-source radiotherapy, unsealed-source radiotherapy and the like.

[01294] Additionally or alternatively, a composition of the present invention can be administered in combination therapy with one or more antitumor or chemotherapeutic agents

selected from Abraxane™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), Advexin™ (Ad5CMV-p53 vaccine or contusugene ladenovec), Altocor™ or Mevacor™ (lovastatin), Ampligen™ (poly(I)-poly(C12U), a synthetic RNA), Aptosyn™ (exisulind), Aredia™ (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), Avage™ (tazarotene), AVE-8062 (combretastatin derivative), BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), Canvaxin™ (melanoma vaccine), CeaVac™ (cancer vaccine), Celeuk™ (celmoleukin), histamine including Ceplene™ (histamine dihydrochloride), Cervarix™ (AS04 adjuvant-adsorbed human papilloma virus (HPV) vaccine), CHOP (Cytoxan™ (cyclophosphamide) + Adriamycin™ (doxorubicin) + Oncovin™ (vincristine) + prednisone), combretastatin A4P, Cypat™ (cyproterone), DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor), dacarbazine, dactinomycin, Dimericine™ (T4N5 liposome lotion), 5,6-dimethylxanthenone-4-acetic acid (DMXAA), discodermolide, DX-8951f (exatecan mesylate), eniluracil (ethynyluracil), squalamine including Evizon™ (squalamine lactate), enzastaurin, EPO-906 (epothilone B), Gardasil™ (quadrivalent human papilloma virus (Types 6, 11, 16, 18) recombinant vaccine), Gastrimmune™, Genasense™ (oblimersen), GMK (ganglioside conjugate vaccine), GVAX™ (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon-α, interferon-γ, Junovan™ and Mepact™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), Neovastat™ (AE-941), Neutrexin™ (trimetrexate glucuronate), Nipent™ (pentostatin), Onconase™ (ranpirnase, a ribonuclease enzyme), Oncophage™ (vitespen, melanoma vaccine treatment), OncoVAX™ (IL-2 vaccine), Orathecin™ (rubitecan), Osidem™ (antibody-based cell drug), Ovarex™ MAb (murine monoclonal antibody), paclitaxel albumin-stabilized nanoparticle, paclitaxel, Pandimex™ (aglycone saponins from ginseng comprising 20(S)-protopanaxadiol (aPPD) and 20(S)-protopanaxatriol (aPPT)), panitumumab, Panvac™-VF (investigational cancer vaccine), pegaspargase, peginterferon alfa (PEG interferon A), phenoxodiol, procarbazine, rebimastat, Removab™ (catumaxomab), Revlimid™ (lenalidomide), RSR13 (efaproxiral), Somatuline™ LA (lanreotide), Soriatane™ (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), Targretin™ (bexarotene), Taxoprexin™ (docosahexaenoic acid (DHA) + paclitaxel), Telcyta™ (canfosfamide, TLK-

286), Temodar™ (temozolomide), tesmilifene, tetrandrine, thalidomide, Theratope™ (STn-KLH vaccine), Thymitaq™ (nolatrexed dihydrochloride), TNFerade™ (adenovector: DNA carrier containing the gene for tumor necrosis factor-α), Tracleer™ or Zavesca™ (bosentan), TransMID-107R™ (KSB-311, diphtheria toxins), tretinoin (retin-A), Trisenox™ (arsenic trioxide), Ukrain™ (derivative of alkaloids from the greater celandine plant), Virulizin™, Vitaxin™ (anti-αvβ3 antibody), Xcytrin™ (motexafin gadolinium), Xinlay™ (atrasentan), Xyotax™ (paclitaxel poliglumex), Yondelis™ (trabectedin), ZD-6126 (N-acetylcolchinol-O-phosphate), Zinecard™ (dexrazoxane), zoledronic acid, zorubicin and the like.

[01295] In one embodiment, a composition of the invention is administered in a therapeutically effective amount to a subject in need thereof to treat a disease during which is overexpressed one or more of antiapoptotic Bcl-2 protein, antiapoptotic Bcl-X_L protein and antiapoptotic Bcl-w protein.

[01296] In another embodiment, a composition of the invention is administered in a therapeutically effective amount to a subject in need thereof to treat a disease of abnormal cell growth and/or dysregulated apoptosis.

[01297] Examples of such diseases include, but are not limited to, cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central

nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma or a combination thereof.

[01298] In a more particular embodiment, a composition of the invention is administered in a therapeutically effective amount to a subject in need thereof to treat bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer or spleen cancer.

[01299] According to any of these embodiments, the composition is administered in monotherapy or in combination therapy with one or more additional therapeutic agents.

[01300] For example, a method for treating mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma or a combination thereof in a subject comprises

administering to the subject therapeutically effective amounts of (a) a composition of the invention and (b) one or more of etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib.

[01301] In particular embodiments, a composition of the invention is administered in a therapeutically effective amount to a subject in need thereof in combination therapy with etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib in a therapeutically effective amount, for treatment of a lymphoid malignancy such as B-cell lymphoma or non-Hodgkin's lymphoma.

[01302] In other particular embodiments, a composition of the invention is administered in a therapeutically effective amount to a subject in need thereof in monotherapy or in combination therapy with etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib in a therapeutically effective amount, for treatment of chronic lymphocytic leukemia or acute lymphocytic leukemia.

[01303] The present invention also provides a method for maintaining in bloodstream of a human cancer patient a therapeutically effective plasma concentration of a compound of Formula I and/or one or more metabolites thereof, comprising administering to the subject a solid dispersion of the compound or a pharmaceutically acceptable salt thereof in essentially non-crystalline form in a matrix that comprises a pharmaceutically acceptable water-soluble polymeric carrier and a pharmaceutically acceptable surfactant, in a parent-compound-equivalent dosage amount of about 50 to about 500 mg per day, at an average dosage interval of about 3 hours to about 7 days.

[01304] What constitutes a therapeutically effective plasma concentration depends *inter alia* on the particular compound of Formula I, the particular cancer present in the patient, the stage, severity and aggressiveness of the cancer, and the outcome sought (*e.g.*, stabilization, reduction in tumor growth, tumor shrinkage, reduced risk of metastasis, *etc.*). It is strongly preferred that, while the plasma concentration is sufficient to provide benefit in terms of treating the cancer, it should not be sufficient to provoke an adverse side-effect to an unacceptable or intolerable degree.

[01305] In another embodiment, a composition of the invention is administered in a therapeutically effective amount to a subject in need thereof to treat an immune or autoimmune disorder. Such disorders include acquired immunodeficiency disease syndrome

(AIDS), autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, thrombocytopenia, acute and chronic immune diseases associated with organ transplantation, Addison's disease, allergic diseases, alopecia, alopecia areata, atheromatous disease/arteriosclerosis, atherosclerosis, arthritis (including osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis and reactive arthritis), autoimmune bullous disease, abetalipoprotemia, acquired immunodeficiency-related diseases, acute immune disease associated with organ transplantation, acquired acrocyanosis, acute and chronic parasitic or infectious processes, acute pancreatitis, acute renal failure, acute rheumatic fever, acute transverse myelitis, adenocarcinomas, aerial ectopic beats, adult (acute) respiratory distress syndrome, AIDS dementia complex, alcoholic cirrhosis, alcohol-induced liver injury, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allergy and asthma, allograft rejection, alpha-l-antitrypsin deficiency, Alzheimer's disease, amyotrophic lateral sclerosis, anemia, angina pectoris, ankylosing spondylitis-associated lung disease, anterior horn cell degeneration, antibody mediated cytotoxicity, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, arthropathy, asthenia, asthma, ataxia, atopic allergy, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, atrophic autoimmune hypothyroidism, autoimmune haemolytic anaemia, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), autoimmune mediated hypoglycemia, autoimmune neutropenia, autoimmune thrombocytopenia, autoimmune thyroid disease, B-cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bronchiolitis obliterans, bundle branch block, burns, cachexia, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy-associated disorders, chlamydia, choleosatatis, chronic alcoholism, chronic active hepatitis, chronic fatigue syndrome, chronic immune disease associated with organ transplantation, chronic eosinophilic pneumonia, chronic inflammatory pathologies, chronic mucocutaneous candidiasis, chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal common varied immunodeficiency (common variable hypogammaglobulinemia), conjunctivitis, connective tissue disease-

associated interstitial lung disease, contact dermatitis, Coombs-positive hemolytic anemia, cor pulmonale, Creutzfeldt-Jakob disease, cryptogenic autoimmune hepatitis, cryptogenic fibrosing alveolitis, culture-negative sepsis, cystic fibrosis, cytokine therapy-associated disorders, Crohn's disease, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatitis scleroderma, dermatologic conditions, dermatomyositis/ polymyositis-associated lung disease, diabetes, diabetic arteriosclerotic disease, diabetes mellitus, diffuse Lewy body disease, dilated cardiomyopathy, dilated congestive cardiomyopathy, discoid lupus erythematosus, disorders of the basal ganglia, disseminated intravascular coagulation, Down's Syndrome in middle age, drug-induced interstitial lung disease, drug-induced hepatitis, drug-induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, enteropathic synovitis, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hematophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, female infertility, fibrosis, fibrotic lung disease, fungal sepsis, gas gangrene, gastric ulcer, giant cell arteritis, glomerular nephritis, glomerulonephritides, Goodpasture's syndrome, goitrous autoimmune hypothyroidism (Hashimoto's disease), gouty arthritis, graft rejection of any organ or tissue, graft versus host disease, gram-negative sepsis, gram-positive sepsis, granulomas due to intracellular organisms, group B streptococci (GBS) infection, Graves' disease, hemosiderosis-associated lung disease, hairy cell leukemia, Hallerrorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hematopoietic malignancies (leukemia and lymphoma), hemolytic anemia, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, Henoch-Schoenlein purpura, hepatitis A, hepatitis B, hepatitis C, HIV infection/HIV neuropathy, Hodgkin's disease, hypoparathyroidism, Huntington's chorea, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hyperthyroidism, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic leucopenia, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia, idiosyncratic liver disease, infantile spinal muscular atrophy, infectious diseases, inflammation of the aorta, inflammatory bowel disease, insulin dependent diabetes mellitus, interstitial pneumonitis, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile

pernicious anemia, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, Kawasaki's disease, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, linear IgA disease, lipidema, liver transplant rejection, Lyme disease, lymphederma, lymphocytic infiltrative lung disease, malaria, male infertility idiopathic or NOS, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, microscopic vasculitis of the kidneys, migraine headache, mitochondrial multisystem disorder, mixed connective tissue disease, mixed connective tissue disease-associated lung disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel, Dejerine-Thomas, Shy-Drager and Machado-Joseph), myalgic encephalitis/Royal Free Disease, myasthenia gravis, microscopic vasculitis of the kidneys, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodyplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, nephrotic syndrome, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, non-alcoholic steatohepatitis, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, organ transplant rejection, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoarthrosis, osteoporosis, ovarian failure, pancreas transplant rejection, parasitic diseases, parathyroid transplant rejection, Parkinson's disease, pelvic inflammatory disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, perennial rhinitis, pericardial disease, peripheral atherlosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, phacogenic uveitis, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post-perfusion syndrome, post-pump syndrome, post-MI cardiotomy syndrome, postinfectious interstitial lung disease, premature ovarian failure, primary biliary cirrhosis, primary sclerosing hepatitis, primary myxoedema, primary pulmonary hypertension, primary sclerosing cholangitis, primary vasculitis, progressive supranuclear palsy, psoriasis, psoriasis type 1, psoriasis type 2, psoriatic arthropathy, pulmonary hypertension secondary to connective tissue disease, pulmonary manifestation of polyarteritis nodosa, post-inflammatory interstitial lung disease, radiation fibrosis, radiation therapy, Raynaud's phenomenon and disease, Raynoud's disease, Refsum's disease, regular narrow QRS tachycardia, Reiter's disease, renal disease NOS, renovascular hypertension, reperfusion injury, restrictive

cardiomyopathy, rheumatoid arthritis-associated interstitial lung disease, rheumatoid spondylitis, sarcoidosis, Schmidt's syndrome, scleroderma, senile chorea, senile dementia of Lewy body type, sepsis syndrome, septic shock, seronegative arthropathies, shock, sickle cell anemia, Sjögren's disease-associated lung disease, Sjögren's syndrome, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, sperm autoimmunity, multiple sclerosis (all subtypes), spinal ataxia, spinocerebellar degenerations, spondyloarthropathy, sporadic polyglandular deficiency type I, sporadic polyglandular deficiency type II, Still's disease, streptococcal myositis, stroke, structural lesions of the cerebellum, subacute sclerosing panencephalitis, sympathetic ophthalmia, syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic lupus erythematosus-associated lung disease, lupus nephritis, systemic sclerosis, systemic sclerosis-associated interstitial lung disease, T-cell or FAB ALL, Takayasu's disease/arteritis, telangiectasia, Th2-type and Th1-type mediated diseases, thromboangitis obliterans, thrombocytopenia, thyroiditis, toxicity, toxic shock syndrome, transplants, trauma/hemorrhage, type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), type B insulin resistance with acanthosis nigricans, type III hypersensitivity reactions, type IV hypersensitivity, ulcerative colitic arthropathy, ulcerative colitis, unstable angina, uremia, urosepsis, urticaria, uveitis, valvular heart diseases, varicose veins, vasculitis, vasculitic diffuse lung disease, venous diseases, venous thrombosis, ventricular fibrillation, vitiligo acute liver disease, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wegener's granulomatosis, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, yersinia and salmonella-associated arthropathy and the like.

EXAMPLES

[01306] The following examples are merely illustrative, and do not limit this disclosure in any way. For example, it will be appreciate that lab-scale compositions or formulations, or extrusion blends, referenced herein may in general be scaled up in view of the details provided without departing from the intended scope of the present application.

[01307] Trademarked ingredients used in the examples, which can be substituted with comparable ingredients from other suppliers, include Tween™ 80 of Uniqema (polysorbate 80 surfactant), and Soluplus™ of BASF (graft copolymer of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate).

[01308] In the examples, "API" (active pharmaceutical ingredient) can be any compound of Formula I, added in essentially anhydrous parent-compound (*i.e.*, not salt) form. The following compounds are more specifically contemplated for formulation according to the examples:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}-sulfonyl)benzamide – Compound 89;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-benzamide – Compound 91;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 5;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 9;

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 29;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 34;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 37;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-

(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 277;

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 61;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 378;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 149;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*trans*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 337;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*cis*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 338;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 311;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]-sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 118;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 134;

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 253;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-

pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 108; and

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide – Compound 234.

Example 1: Melt extrusion

[01309] Referring now to Fig. 1, an embodiment of a process including melt extrusion useful to form a solid dispersion product is shown at **100**. A granulation step **105** includes combining one or more pharmaceutically acceptable polymers, one or more surfactants, and one or more other optional ingredients and transforming these components into a granular form. For example, a pharmaceutically acceptable polymer may be provided in a stock form, such as pellets, which are then ground and mixed with a surfactant. Other ingredients, such as an anti-caking agent or emulsifier, can be included in the granulation step **105**.

[01310] The granulated polymer(s), surfactant(s), and optional ingredient(s) are then blended/sieved at **115** with the addition of the API **120**. For example, once the API is suitably blended with the granulated polymer(s), surfactant(s), and optional ingredient(s) to form an essentially uniform mixture, the mixture can be further sieved to select a uniform size.

[01311] At this point, the blended and sieved mixture can be processed by an extrusion and calendering step **125** where the mixture is subjected to pressure and/or heat suitable to melt at least a portion of the mixture. For example, a screw-type extruder can be used in this step. Suitable screw-type extruders include a Leistritz Micro 18 or Micro 27 twin-screw extruder.

[01312] Following extrusion, the mixture or extrudate can be subjected to calendering by pressing with a roller or a series of rollers. That is, as shown at **125**, the mixture from the blending/sieving step **115** is first extruded and then calendered. Calendering can include subjecting the extrudate to a roller having one or more cavities that press the extrudate into a lentil form or other shape. Optionally, the extrudate is not calendered at **125** (not shown) but can continue through the remainder of the illustrated process in Fig. 1.

[01313] The extruded and calendered material is cooled and allowed to return to a substantially solid phase prior to being milled, as shown at **130**, where the solid is ground, pulverized or broken down into smaller particles. The milled material is then blended and/or sieved **135** following addition of one or more optional ingredients **140**.

[01314] A compression step **145** forces the blended and/or sieved material into the desired final form, such as a tablet providing a particular dosage of the API. Finally, a coating may be applied to the compressed material as shown at **150**. The coating, such as a polymer coating, can make the compressed material smoother and easier to swallow, can control the release rate of the API, can make the material more resistant to the environment (extending shelf life), and/or can enhance the tablet's appearance.

[01315] In an alternative embodiment, rather than introducing the surfactant into the composition as part of the granulation step **105**, a liquid dosing system (not shown) may be used to dose a liquid surfactant (e.g., Tween80) into the composition at a different point in the process. For example, in one alternative embodiment a liquid surfactant may be dosed using a liquid dosing system into the composition during the extrusion step, **125**.

Example 2: Tablets formed by a process including melt-extrusion

[01316] The following components (in weight %) are combined and melt-extruded to form an extrudate:

12% API;
80% copovidone 60/40;
7% Tween™ 80; and
1% colloidal silicon dioxide.

[01317] In particular, these components can be processed as shown in Fig. 1 by granulation **105**, blending and/or sieving **115**, extrusion and calendering **125**. The copovidone, Tween™ 80 and colloidal silicon dioxide can be provided at **110** into the granulation step **105** and the API can be provided at **120** into the blending/sieving step **115**.

[01318] The extrusion/calendering step **125** is performed using a screw-type extruder where the extrusion process parameters include:

Temperature:	heating block 1	95°C
	heating blocks 2–5	155°C
	heating block 6 (die)	140°C
Screw speed:		150 rpm
Feed rate:		1.5 kg/h
Vacuum:		200 mbar

[01319] The resulting extrudate can then be processed as shown in Fig. 1 by milling **130**, blending/sieving **135**, compression **145**, and coating **150**. The extrudate is further combined with the following ingredients (provided at **140** as per Fig. 1) to provide the following tablet formulation:

extrudate	78.5%
dicalcium phosphate	20.0%
sodium stearyl fumarate	0.5%
colloidal silicon dioxide	1.0%

Example 3: Solid dispersion prepared by melt-extrusion

[01320] The following components (in weight %) are combined and melt-extruded to form an extrudate, by a process as described in Example 2:

10% API;
82% copovidone 60/40;
7% TPGS;
1% colloidal silicon dioxide.

[01321] The resulting extrudate can then be processed as described in Example 2.

Example 4: Solid dispersion prepared by melt-extrusion

[01322] The following components (in weight %) are combined and melt-extruded to form an extrudate, by a process as described in Example 2:

12% API;
78% copovidone 60/40;
7% TPGS;
2% propylene glycol laurate; and
1% colloidal silicon dioxide.

[01323] The resulting extrudate can then be processed as described in Example 2.

Example 5: Solid dispersion prepared by melt-extrusion

[01324] The following components (in weight %) are combined and melt-extruded to form an extrudate, by a process as described in Example 2:

12% API;

80% Soluplus™;

7% poloxamer; and

1% colloidal silicon dioxide.

[01325] The resulting extrudate can then be processed as described in Example 2.

Example 6. Melt Extrusion Feasibility Study

[01326] Feasibility experiments were performed to evaluate the influence of different excipients on extrudates with embedded amorphous drug. In these experiments, the formulations included copovidone (Kollidon VA 64; vinylpyrrolidone-vinyl acetate copolymer) as the matrix polymer, compound 5 as the active pharmaceutical ingredient (API), and a variety of surfactants/plasticizers.

[01327] Batches in the sizes of 10 g to 30 g were prepared. Surfactant/plasticizer and matrix polymer were pre-blended using a lab-mill (e.g. a IKA lab-mill A10 basic or Rotor GT95). The pre-blended mixture was left standing for 4-48 hours before blending compound 5 into the pre-blended mixture. The entire blend was extruded with a small-scale single screw extruder (e.g., a MicroCompounder Haake MiniLab extruder). The following Table 1 displays the appearance of the extrudate as a function of the extrusion temperature and the surfactant/plasticizer.

[01328] It was observed, from the single screw extrusions, that appearance is a function of temperature, as well as the concentration of the various components present in the mixture / blend. For example, in some cases, extrusion temperatures as low as 135°C did not lead to uniformly clear extrudates, while extrusion temperature up to 160°C led to an observable improvement. Notably, however, the extrudates were free of crystals.

Table 1. Feasibility Formulations and Extrudate Appearance

Batch	Drug Load [%]	Kollidon VA64 [%]	Surfactant [%]	Temperature [°C]	Appearance
9P01-01	5%	85%	10% Vitamin E TPGS	130°C	almost clear
9P01-02	5%	85%	10% Vitamin E TPGS	135°C	almost clear
9P01-03	5%	85%	10% Vitamin E TPGS	140°C	almost clear
9P01-04	5%	85%	10% Vitamin E TPGS	145°C	almost clear
9P01-05	5%	85%	10% Vitamin E TPGS	150°C	almost clear
9P02-01	10%	80%	10% Vitamin E TPGS	150°C	almost clear

9P02-02	10%	80%	10% Vitamin E TPGS	160°C	clear
9P03-01	12%	78%	10% Vitamin E TPGS	155°C	clear
9P03-02	12%	78%	10% Vitamin E TPGS	135°C	clear
9P04-01	5%	85%	10% Span20	140°C	clear
9P04-02	5%	85%	10% Span20	150°C	clear
9P05-01	5%	85%	10% Tween20	140°C	clear
9P05-02	5%	85%	10% Tween20	150°C	clear
9P06-01	5%	85%	10% Span20	140°C	clear
9P06-02	5%	85%	10% Span20	150°C	clear
9P07-01	5%	85%	7% Lauroglycol FCC 3% Vitamin E TPGS	150°C	cloudy
9P07-02	5%	85%	7% Lauroglycol FCC 3% Vitamin E TPGS	155°C	cloudy
9P08-01	5%	95%	0	140°C	almost clear
9P08-02	5%	95%	0	150°C	clear
9P09-01	10%	80%	5% SDS 5% PEG400	140°C	clear

[01329] Dispersibility of selected extrudates from the feasibility study above were tested by dispensing capsules (containing 500 mg milled extrudate and 250 mg Mannitol/Aerosil (99:1)) in 250 mL 0.1 N HCl at 37°C. After predetermined time points samples were taken and analyzed by HPLC (HPLC Conditions: Agilent 1100 Series; Column: Agilent Zorbax XDB C18, 150 x 4.6 mm, 3.5 μm; flow: 1.0 mL/min; injection volume: 25 μL; oven temperature: 30°C; detection wavelength: 314 nm; solvent A: 0.1% TFA (trifluoroacetic acid) in water; solvent B: ACN (acetonitrile): Methanol (50:50); method used a gradient: 0 min = 60% B; 7 min = 95% B; 7.1 min = 60% B; 10 min = 60% B). Several formulations (e.g. 9P01-05) were able to release a satisfactory amount of compound 5, but not all of the dispersions were stable over a long period of time. Vitamin E-TPGS and Tween20 appeared from the feasibility and dispersibility studies to be more suitable candidates for surfactant.

Example 7. Extrusion Trials Series I

[01330] Further studies were performed to evaluate the effect of drug load, surfactant level, and extrusion temperature on the appearance of the extrudate. Compound 5 and Aerosil (1%) were used in each batch as drug and glidant, respectively. The extrudates were free of residual crystal. The results are summarized in Table 2. These results indicate that a more suitable extrusion temperature is 150°C.

Table 2. Extrusion Trials Series I

Batch	Drug Load [%]	Polymer [%]	Surfactant [%]	Temperature [°C]	Appearance
0P01-01	5%	87.5% Copovidone	6.6% Vitamin E TPGS	130°C	cloudy
0P01-02	5%	87.5% Copovidone	6.6% Vitamin E TPGS	140°C	cloudy
0P01-03	5%	87.5% Copovidone	6.6% Vitamin E TPGS	150°C	cloudy
0P02-01	10%	82.8% Copovidone	6.2% Vitamin E TPGS	140°C	cloudy
0P02-02	10%	82.8% Copovidone	6.2% Vitamin E TPGS	150°C	clear
0P03-01	15%	78.1% Copovidone	5.9% Vitamin E TPGS	140°C	cloudy
0P03-02	15%	78.1% Copovidone	5.9% Vitamin E TPGS	150°C	clear
0P04-01	20%	73.5% Copovidone	5.5% Vitamin E TPGS	140°C	cloudy
0P04-02	20%	73.5% Copovidone	5.5% Vitamin E TPGS	150°C	clear
0P05-01	10%	82.8% Copovidone	6.2% Tween 80	140°C	cloudy
0P05-02	10%	82.8% Copovidone 6	6.2% Tween 80	150°C	clear
0P06-01	15%	78.1% Copovidone 5	5.9% Tween 80	140°C	cloudy
0P06-02	15%	78.1% Copovidone	5.9% Tween 80	150°C	clear
0P07-01	5%	82.8% copovidone	6.2% Tween 20	140°C	cloudy
0P07-02	5%	82.8% Copovidone	6.2% Tween 20	150°C	clear
0P08-01	15%	78.1% Copovidone	5.9% Tween 20	140°C	cloudy
0P08-02	15%	78.1% Copovidone	5.9% Tween 20	150°C	clear
0P09-01	10%	82.8% Copovidone	6.2% Sucroester WP15	140°C	cloudy
0P09-02	10%	82.8% Copovidone	6.2% Sucroester WP15	150°C	clear
0P10-01	15%	78.1% Copovidone	5.9% Sucroester WP15	140°C	cloudy
0P10-02	15%	78.1% Copovidone	5.9% Sucroester WP15	150°C	clear
0P11-01	5%	94% Soluplus	0%	140°C	cloudy
0P11-02	5%	94% Soluplus	0%	150°C	nearly clear
0P12-01	10	89% Soluplus	0%	140°C	cloudy
0P12-02	10	89% Soluplus	0%	150°C	nearly clear
0P13-01	15%	84% Soluplus	0%	140°C	cloudy
0P13-02	15%	84% Soluplus	0%	150°C	nearly clear
0P14-01	10%	82.8% Copovidone	6.2% Span 20	140°C	cloudy
0P14-02	10%	82.8% Copovidone	6.2% Span 20	150°C	clear
0P15-01	20%	79% Soluplus	0%	145°C	cloudy
0P15-02	20%	79% Soluplus	0%	155°C	nearly clear

[01331] Dispersibility of selected extrudates was tested by dispensing 5 mg compound 5 equivalent of unmilled extrudate in 75 mL 0.1 N HCl at 37°C. After predetermined time points samples were taken and analyzed by HPLC (200 µL of the dispersion was diluted with 800 µL acetonitrile to obtain a clear solution) (HPLC Conditions: Agilent 1100 Series; Column: Phenomenex Gemini-NX3µ C18 110 A; flow: 0.3 mL/min; injection volume: 5 µL;

oven temperature: 30°C; detection wavelength: 220 nm; solvent A: 0.1% TFA (trifluoroacetic acid) in water; solvent B: ACN (acetonitrile); method was isocratic solvent A 45%, solvent B 55%; peak elutes between 2.5 and 3.5 mins). Several formulations were able to release a satisfying amount of compound 5. As a general tendency, it was observed that the lower the drug load the better the drug release, and 20% drug load resulted in poor dispersibility. HPLC analysis of the extrudates showed that the content of the extrudates was inhomogeneous and correlates with the content found in dispersibility testing. This was believed to be the result of inhomogeneous blending of the API and other components prior to the extrusion process.

Example 8. Extrusion Trials Series II

[01332] To determine whether a drug loading of 12% was achievable, the appearance of extrusion blends containing 10-12% of compound 5 were recorded at 150°C (Table 3). The blends showed inhomogeneity and were therefore neither extruded nor tested for dispersibility.

Table 3. Extrusion Trials Series II - Extrusion Blend with 10-12% Drug Load

Batch	Drug Load [%]	Polymer [%]	Surfactant [%]	Glidant [%]	Appearance
0P16-01	12%	80% Kollidon VA64	7% Vitamin E TPGS	1% Aerosil	clear
0P17-01	12%	82% Kollidon VA64	5% Vitamin E TPGS	1% Aerosil	clear
0P18-01	12%	84% Kollidon VA64	3% Vitamin E TPGS	1% Aerosil	cloudy
0P19-01	12%	78% Kollidon VA64	7% Vitamin E TPGS 2% Lauroglycol	1% Aerosil	n. n.
0P20-01	12%	80% Kollidon VA64	7% Tween 20	1% Aerosil	clear
0P21-01	12%	80% Kollidon VA64	7% Tween 80	1% Aerosil	clear
0P22-01	12%	88% Soluplus	0%	0%	almost clear
0P23-01	12%	80% Soluplus	7% Poloxamer F68NF	1% Aerosil	clear
0P24-01	12%	84% Soluplus	3% Poloxamer F68NF	1% Aerosil	clear
0P25-01	10%	89% HMPC-E5	0%	0%	- -
0P26-01	10%	82% HMPC-E5	7% Sucroester WP15	1% Aerosil	- -

n.n.: not noted

Example 9. Blending Experiments to Improve Blend Homogeneity

[01333] To improve the homogeneity of extrusion blends and therefore the quality of the extrudates, the results from using a blender with fast rotating knives (IKA mill, Rotor Swiss) and from manual blending (accomplished by using a bowl with either a plastic mortar or the

gloves-protected hands) were compared. In order to check blend uniformity, five random samples were taken and the content of compound 5 (API) (extrusion blend: 12% Compoun 5; 80% Kollidon VA64; 7% Tween 80; and, 1% Aerosil) in each determined by HPLC (Table 5) (HPLC Conditions: Agilent 1100 Series; Column: Phenomenex Gemini-NX3μ C18 110 A; flow: 0.3 mL/min; injection volume: 5 μL; oven temperature: 30°C; detection wavelength: 220 nm; solvent A: 0.1% TFA (trifluoroacetic acid) in water; solvent B: ACN (acetonitrile); method was isocratic solvent A 45%, solvent B 55%; peak elutes between 2.5 and 3.5 mins). These results indicated that manual blending resulted in a homogeneous blend.

Table 5. Uniformity of Blends from Machine and Manual Blending

Blending Type	Content [%]: Random Sample 1	Content [%]: Random Sample 2	Content [%]: Random Sample 3	Content [%]: Random Sample 4	Content [%]: Random Sample 5	Mean [%]
manual blending by hand	101.9	110.5	103.5	102.7	111.1	105.9
IKA without API	89.4	101.3	91.5	88.4	98.3	93.8
IKA with API	87.4	99.9	91.6	92.8	91.8	93.1
manual blending with plastic mortar	98.9	100.2	98.8	100.9	99.4	99.6

Example 10. Extrusion Trials Series III

[01334] In this series, formulations with 10% drug load (compound 5 as API) were compared to formulations with 12% drug load (1% Aerosil as glidant, 150°C) (Table 6).

Table 6. Extrusion of Formulations with Compound 5 at 10% vs. 12% Drug Load

Batch	Drug Load [%]	Polymer [%]	Surfactant [%]	Appearance
0P27-02	10%	82% Kollidon VA64	7% Vitamin E TPGS	clear
0P28-01	12%	80% Kollidon VA64	7% Vitamin E TPGS	n. n.
0P29-01	10%	82% Kollidon VA64	7% Vitamin E TPGS	cloudy

			2% Laurogiykol	
0P30-01	12%	80% Kollidon VA64	7% Vitamin E TPGS 2% Lauroglykol	cloudy
0P31-01	10%	82% Kollidon VA64	7% Tween 20	clear
0P32-01	12%	80% Kollidon VA64	7% Tween 20	clear
0P33-01	10%	82% Kollidon VA64	7% Tween 80	n. n.
0P21-01	12%	80% Kollidon VA64	7% Tween 80	clear
0P35-01	10%	82% Kollidon VA64	7% Poloxamer F68NF	almost clear
0P36-01	12%	80% Kollidon VA64	7% Poloxamer F68NF	almost clear

n.n.: not noted

[01335] Dispersibility of the selected extrudates was tested by dispensing a 25 mg-compound 5 equivalent of unmilled extrudate in 75 mL 0.1 N HCl at 37°C. After predetermined time points, samples were taken and analyzed by HPLC (HPLC Conditions: Agilent 1100 Series; Column: Phenomenex Gemini-NX3μ C18 110 A; flow: 0.3 mL/min; injection volume: 5 μL; oven temperature: 30°C; detection wavelength: 220 nm; solvent A: 0.1% TFA (trifluoroacetic acid) in water; solvent B: ACN (acetonitrile); method was isocratic solvent A 45%, solvent B 55%; peak elutes between 2.5 and 3.5 mins). In general, most of the formulations in this study released substantially all (90-100%) of the API within 240 minutes. Both Tween 20 formulations (0P31-01 and 0P32-01) showed slow release rate and released more than about 60% API. While formulations with 7% Vitamin E TPGS and a 10% drug load (0P27-02) released substantially all API, formulations with the same surfactant and a 12% drug load (0P28-01) released only about 60% API. Both Tween 80 formulations (0P33-01 and 0P21-01) released API in a similar manner (about 100% within 240 minutes).

Example 11. Extrusion Trials Series IV – Tween 80 Formulations

[01336] In this series, Tween 80 formulations were studied to find the proper temperature and surfactant levels for the manufacture of extrudates containing 12% (Table 7), 13% (Table 8), 14% (Table 9), and 15% (Table 10) compound 5 as API. All batches have 1% Aerosil as glidant.

Table 7. Evaluation of Surfactant Level, Extrusion Temperature at 12% Drug Load

Batch	Polymer [%]	Surfactant [%]	Temperature [°C]	Appearance
0P65-01	78% Kollidon VA64	9% Tween 80	120°C	turbid
0P65-02			130°C	turbid
0P65-03			140°C	almost clear

0P65-04			150°C	almost clear
0P65-05			160°C	almost clear
0P66-01	80% Kollidon VA64	7% Tween 80	120°C	- -
0P66-02			130°C	- -
0P66-03			140°C	almost clear
0P66-04			150°C	clear
0P66-05			160°C	clear
0P66-06			170°C	clear
0P67-01	82% Kollidon VA64	5% Tween 80	130°C	- -
0P67-02			140°C	almost clear
0P67-03			150°C	almost clear
0P67-04			160°C	clear
0P67-05			170°C	clear
0P68-01	84% Kollidon VA64	3% Tween 80	130°C	- -
0P68-02			140°C	turbid
0P68-03			150°C	almost clear
0P68-04			160°C	clear
0P68-05			170°C	clear

Table 8. Evaluation of Surfactant Level, Extrusion Temperature at 13% Drug Load

Batch	Polymer [%]	Surfactant [%]	Temperature [°C]	Appearance
0P69-01	77% Kollidon VA64	9% Tween 80	130°C	- -
0P69-02			140°C	- -
0P69-03			150°C	- -
0P70-01	79% Kollidon VA64	7% Tween 80	- -	- -
0P71-01	81% Kollidon VA64	5% Tween 80	130°C	turbid
0P71-02			140°C	turbid
0P71-03			150°C	almost clear
0P71-04			160°C	clear
0P71-05			170°C	clear
0P72-01	83% Kollidon VA64	3% Tween 80	130°C	- -
0P72-02			140°C	turbid
0P72-03			150°C	turbid
0P72-04			160°C	clear
0P72-05			170°C	clear

Table 9. Evaluation of Surfactant Level, Extrusion Temperature at 14% Drug Load

Batch	Polymer [%]	Surfactant [%]	Temperature [°C]	Appearance
0P73-01	76% Kollidon VA64	9% Tween 80	- -	- -
0P74-01	78% Kollidon VA64	7% Tween 80	- -	- -
0P75-01	80% Kollidon	5% Tween 80	130°C	- -

0P75-02	VA64		140°C	turbid
0P75-03			150°C	almost clear
0P75-04			160°C	clear
0P75-05			170°C	clear
0P76-01	82% Kollidon VA64	3% Tween 80	130°C	- -
0P76-02			140°C	turbid
0P76-03			150°C	almost clear
0P76-04			160°C	clear
0P76-05			170°C	clear

Table 10. Evaluation of Surfactant Level, Extrusion Temperature at 15% Drug Load

Batch	Polymer [%]	Surfactant [%]	Temperature [°C]	Appearance
0P77-01	75% Kollidon VA64	9% Tween 80	- -	- -
0P78-01	77% Kollidon VA64	7% Tween 80	- -	- -
0P79-02	79% Kollidon VA64	5% Tween 80	140°C	turbid
0P79-03			150°C	almost clear
0P79-04			160°C	clear
0P79-05			170°C	clear
0P80-02	81% Kollidon VA64	3% Tween 80	140°C	turbid
0P80-03			150°C	almost clear
0P80-04			160°C	clear
0P80-05			170°C	clear

[01337] Dispersibility of selected extrudates was tested by dispensing 25 mg compound 5 equivalent of unmilled extrudate in 75 mL 0.1 N HCl at 37°C. After predetermined time points samples were taken and analyzed by HPLC (HPLC Conditions: Agilent 1100 Series; Column: Phenomenex Gemini-NX3μ C18 110 A; flow: 0.3 mL/min; injection volume: 5 μL; oven temperature: 30°C; detection wavelength: 220 nm; solvent A: 0.1% TFA (trifluoroacetic acid) in water; solvent B: ACN (acetonitrile); method was isocratic solvent A 45%, solvent B 55%; peak elutes between 2.5 and 3.5 mins). The results indicated that at least extrudates manufactured at 160°C released 80-100% of API within 240 minutes. In general, formulations with higher drug load showed slower release rate, and higher surfactant level led to faster release rate.

Example 12. Pharmacokinetic Profile of Extrudates

[01338] Based on the results of dispersibility testing, a pharmacokinetic study in dogs was performed for extrudates of three formulations:

Formulation 1 (batch 0P21-02):	12% compound 5, 80% copovidone, 7% Tween80, 1% Aerosil
Formulation 2 (batch 0P27-01):	10% compound 5, 82% copovidone, 7% Vitamin E TPGS, 1% Aerosil
Formulation 3 (batch0P38-01):	12% compound 5, 78% copovidone, 7% Tween 80, 2% Lauroglykol, 1% Aerosil

[01339] Capsules of 50 mg dosage strength were made using Aerosil/Mannitol as filler. Two capsules (100 mg) were orally administrated to each of four Beagle dogs (two male and two female). The animals were fasted overnight and received food 30 min prior to dosing and throughout the duration of the study. Plasma samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hours post-dose administration. Compound 5 levels in plasma samples were analyzed by LC-MS/MS (Table 11). The following primary pharmacokinetic parameters were determined:

$AUC_{(0\text{-}Inf)}$	Area under the concentration versus time curve from time 0 to infinity calculated as $AUC_{(0-\infty)} = AUC_{last} + (C_{last}/K_{el})$, where C_{last} is the last quantifiable concentration
Dose-normalized $AUC_{(0\text{-}Inf)}$	Dose-normalized area under the concentration versus time curve from time 0 to infinity ($AUC_{(0-\infty)}$:) $AUC_{(0\text{-}Inf)\,norm} = AUC_{(0-Inf)} * \frac{normalized\,dose}{actual\,dose}$
C_{max}	Maximum observed plasma concentration
Dose-normalized C_{max}	Dose-normalized maximum observed plasma concentration: $C_{max\,norm} = C_{max} * \frac{\text{normalized dose}}{\text{actual dose}}$
Point Estimate	C_{max} or AUC for an experimental formulation is divided by the C_{max} from the reference formulation for each dog separately. The log of this ratio is calculated and then the mean of the log transformed values for all dogs is calculated for each formulation. The point estimate for the C_{max} or AUC is then determined by calculating the anti-log.

T_{max}	Time of maximum plasma concentration

Table 11. Pharmacokinetic Parameters of Extrudate Capsules (Mean (n=4) ± SEM)

	$t_{1/2}$	C_{max}	T_{max}	$AUC_{(0-\infty)}$	Point Estimate	
	(h)	(µg/mL)	(h)	(µg•h/mL)	C_{max}	$AUC_{(0-\infty)}$
Formulation 1	**11.2**	**7.9** ± 1.1	**6.0** ± 1.2	**205.7** ± 18.1	**1.55**	**1.64**
Formulation 2	**10.5**	**5.7** ± 1.2	**9.3** ± 5.1	**134.6** ± 26.4	**1.07**	**1.02**
Formulation 3	**9.6**	**5.6** ± 1.2	**3.5** ± 1.7	**104.0** ± 20.4	**1.06**	**0.78**
lipid reference	**10.4**	**5.2** ± 0.9	**6.5** ± 1.0	**127.6** ± 17.2	--	--

AUC and C_{max} were normalized to a dose of 10 mg/kg.

Point estimates were calculated with non–normalized data.

[01340] The results indicate that all four formulations showed satisfying pharmacokinetic profile. The results from Formulations 2 and 3 were comparable to a reference lipid formulation. Formulation 1 showed exceptionally higher pharmacokinetic rate than the reference.

Example 13. Phase Separation Studies on Compound 5 Extrudates

[01341] To investigate phase separation potentials, differential scanning calorimetry (DSC) cycle tests were performed on extrudate of Formulation 1 in Example 13. The extrudate was milled using a standard laboratory ball mill, weighted into closed DSC crucibles and placed into the instrument (Mettler Toledo DSC 1/700/183). The samples were heated from -60°C to 100°C following a cooling to -60°C (1 Cycle). This procedure was repeated up to 5 times (5 Cycles). The results indicated that extrudate of Formulation 1 was a monophasic system after manufacture and phase separation was not likely to happen when the formulation was stored at long term and accelerated conditions below or even close to its glass transition temperature.

Example 14. Scale-up Extrusion Formulation and Conditions

[01342] Due to its results in the dog PK study, Formulation 1 (12% compound 5, 80% copovidon, 7% Tween 80, 1% Aerosil) was chosen for larger scale production. The extruder, type Micro 18, was equipped with a gravimetric feeder system and a calendar to realize a continuous process from blend to extrudate lentils, as an intermediate product. Experiments were conducted to evaluate the influence of feed rate, screw speed and temperature on product

quality. The screw design (Micro18-24) was chosen due to the good mixing properties. Samples were taken periodically every 30 min during the process and analyzed with respect to crystallinity, assay, and water content. The process parameters were stable over the whole run and the product did not show any significant deviation. Analytical results on the samples confirmed the stability of the process. The extruder conditions for batch production were as follows:

Block No.	Set	Range
Block 1	100°C	90-110°C
Block 2-5	155°C	145-165°C
Block 6 (die)	140°C	135-145°C
feed rate	1,50 kg/h	1,25-1,75 kg/h
screw speed	150 rpm	140-160 rpm

[01343] In view of the results obtained here, it was determined that further scale up was possible, using these or appropriately modified process conditions for a larger extruder (e.g., a Micro 27 extruder).

Example 15. Extrudate Milling

[01344] Active extrudates of compound 5 of Formulation 1 (glass transition temperature (Tg) at approximately 78°C) in batch sizes of a few hundred grams were milled using Quadro U5 Comil and Conidure (C type) screens with 813, 610 or 406 micron aperture sizes. Screens with larger aperture size resulted in an increase in milled extrudate particle size. There was no difference in particle size distribution in the beginning of the run compared to the end. Variation in milling batch size (from 127 g to 500 g) resulted in negligible change in particle size distribution. The particle size distribution of milled compound 5 and placebo extrudates were measured by laser diffraction using a Malvern Mastersizer 2000, and the results are summarized in Table 12.

Table 12. Particle Size Data for Milled Extrudates

Batch Size (g)	Conidur Screen used (μm)	Impeller speed (rpm)	Sampling	Particle size (in micron)		
				d_{10}	d_{50}	d_{90}
150	813	3500	Composite	119	407	802

153	610	3500	Composite	82	350	663
127	406	3500	Composite	32	156	360
500	406	3500	Initial sample	45	184	381
500	406	3500	Final sample	33	182	391

[01345] During the milling process, both the screen and product temperature reached a plateau, with the screen temperature maximized at about 43°C and the product temperature below 30°C. Under this condition, the risk of screen clogging due to extrudate melting was minimal. Scanning electronic microphotographs (SEM) indicated that all samples were composed of irregular shaped particles with a mixture of smooth surfaces, surfaces with adherent smaller particles and fines, and areas with conchodial fractures. The sample obtained from 813 micron screen had the fewest fines.

Example 16. Tablet Production by Compression

[01346] The Presster (Metropolitan Computing Corporation) was used to perform tablet compression testing. Compression was executed using a 10 mm diameter flat-faced tooling, with a target tablet weight between 360 mg to 370 mg, and a dwell time of 6 ms. Alternatively, tablets may be compressed manually on using Carver Laboratory press Model C (Fred S. Carver Inc, asset # LC013794). Tooling used to compress the 50 mg and 100 mg tablets were P29628-10B and A-2238, respectively. Different compound 5 formulations were evaluated using the Presster (Table 13). Data generated from compressing these formulations on the MCC Presster tablet press simulator were gathered regarding 1) compressibility (solid fraction as a function of compaction pressure); 2) compactibility (tensile strength as a function of solid fraction); and 3) tabletability (tensile strength as a function of compaction pressure).

Table 13. Compositions of Compound 5 Blends Used for Presster Evaluation

Ingredients	*No Filler Formula*	*5% SCC Formula*	*15% DCP Formula*	*20% DCP Formula*
Extrudate*	98.5	93.5	83.5	78.5
Croscarmellose Sodium	0	5	0	0
Dicalcium Phosphate	0	0	15	20
Sodium Stearyl Fumarate	0.5	0.5	0.5	0.5
Aerosil (Colloidal	1	1	1	1

Silicon Dioxide)				
Total	100	100	100	100

*API extrudate: 12% Compound 5, 7% Tween-80, 80% copovidone, and 1% of Aerosil
Placebo extrudate: 7% Tween-80, 92% copovidone, and 1% of Aerosil

[01347] The clarity of the extrudates was found to have an effect on tabletability of formulations made with either the 20% DCP Formula or the No Filler Formula. Compound 5 formulations prepared using clear extrudates generally resulted in higher tensile strength over a compaction pressure range (e.g. 50 to 400 MPa) than those prepared using cloudy extrudates. At 7% Tween 80, placebo extrudates remained cloudy even when extrusion temperature was increased to 180°C. Comparison of tabletability between clear and cloudy placebo extrudates was therefore not performed. Further, blends prepared with cloudy placebo extrudates milled under the same condition as that of clear compound 5 extrudates were assessed for tabletability using the Presster. However, the placebo blends did not compress into strong enough tablets with either the 20% DCP Formula or the No Filler Formula.

[01348] Addition of 5% croscarmellose sodium (SCC) to the milled, slightly cloudy compound 5 extrudate showed no improvement on tabletability. However, addition of 15% of dicalcium phosphate (DCP) to the same milled extrudate resulted in improvement on tabletability. Further, it was shown that adding 20% DCP to the extragranular blend of milled extrudates (using both 406 and 610 μm C-screen) of compound 5 improved tabletability. Extrudates milled through Comil screens with apperture sizes larger than 406 micron all demonstrated poor tabletability, with tensile strength less than 1 MPa at a compaction pressure of 200 MPa, even with addition of 20% DCP. In contrast, the fine material milled through a 406 micron C-screen can compress to yield relatively strong tablets (approximately 1.5 MPa tensile strength at 200 MPa compaction pressure).

[01349] Based on the results above, a composition of tablet ingredients was determined for clinical studies (Table 14). The average hardness of the 50 mg compound 5 tablets was 13 kp, the average table weight was 532 mg, and the table thickness was about 5.2 mm. X-ray tomography showed no internal cracks or fissures in the 50 mg tablets.

Table 14. Composition of 50 mg tablets of Compound 5

Process	Component	Quality Standard	Function	% (w/w)	mg/tablet
Extrudate	Compound 5, free base	In-house standard	Drug Substance	9.420	50.0
	Copovidone	USP-NF/ Ph. Eur.	Carrier polymer	62.800	333.3
	Polysorbate 80	USP-NF	Surfactant/ Plasticizer	5.495	29.2
	Colloidal Silicon Dioxide	USP-NF / Ph. Eur./ JP	Glidant	0.785	4.2
Post Extrusion	Dicalcium Phosphate	USP, Ph. Eur.	Filler	20.000	106.2
	Sodium Stearyl Fumarate	USP-NF / Ph. Eur.	Lubricant	0.500	2.7
	Colloidal Silicon Dioxide	USP-NF / Ph. Eur./ JP	Glidant	1.000	5.3
Total				100.000	530.9

Example 17. Dissolution Profile of Compound 5 Tablets

[01350] Dissolution tests on Compound 5 tablets (50 mg) were performed using USP apparatus 2 method in 900 ml dissolution medium (0.05M sodium phosphate buffer, pH 6.8, with 0.2% SDS). A paddle speed of 75 rpm was used for 180 minutes, after which it was increased to 150 rpm. Samples are collected at predetermined time points, and the concentration of compound 5 was analyzed by HPLC. Substantially all compound 5 (about 90-100%) was released from tablets within 6 to 8 hours. The use of different dissolution medium (e.g. 0.05M sodium phosphate buffer, pH 6.8, with 0.5% CTAB, or 0.01 N HCl with 0.5% CTAB) resulted in similar dissolution profiles. The dissolution profile was independent of particle size of the milled extrudate, and addition of 20% DCP as a post-extrusion filler slightly decreased the drug release rate from the tablet. Further, the dissolution profile remained unchanged after exposure to 25°C/60% RH open dish condition for 2 weeks and a significant increase in moisture content (>9%) in the tablets. These results indicate that the compound 5 tablets erode rather than disintegrate during dissolution, and drug release is controlled by erosion mechanism.

Example 18. Dog Pharmacokinetic Profiles of Compound 5 Tablets

[01351] Dog studies were performed in groups of 6 fed dogs. The dogs received a single

100 mg oral dose of a lipid formulation (10 mg/mL in Cremophor EL:PEG-400:Oleic acid, 10:10:80 by weight; dosed in 10 mL/dog) in Period 1, No Filler Formulation (Example 17) in Period 2, and 20% DCP Formulation (Example 17) in Period 3. A washout period of one week separated the adjacent dosing periods. The dogs were fasted overnight and food was returned to the animals about 30 minutes prior to dosing (fed dogs). Plasma concentrations of compound 5 were determined by HPLC-MS/MS at the completion of the dosing periods (Table 15). Compared with the reference lipid formulation, the plasma concentration profiles obtained from the two tablets were similar, with an initial T_{max} in 7-10 hours after dosing followed by a second peak in 12-24 hours. Peak concentrations obtained from 20% DCP Formulation tablet were slightly higher than those obtained from the No Filler formulation tablet. The difference in AUC between the two formulations was not significant. Point estimates for comparison of Formulation C to the lipid reference averaged 1.1 for Cmax and 0.73 for AUC. These results confirmed good bioavailability of API in these tablets, and showed that the addition of 20% DCP as extragranular tablet excipient did not change the bioavailability of API in dogs.

Table 15. Pharmacokinetic Parameters in Dogs (Mean ± SEM, n=6)

Period	Formulation	$t_{1/2}$ (hr)	C_{max}(µg/mL)	T_{max} (hr)	AUC (µg•hr/mL)	AUC/D (µg•hr/mL per mg/kg)
1	reference lipid formulation	14.6	8.16 *(1.24)*	9.3 *(1.6)*	273 *(48)*	22.5 *(2.9)*
2	100 mg tablet, No Filler Formulation	18.2	8.04 *(1.60)*	7.3 *(3.7)*	183 *(36)*	14.9 *(2.3)*
3	100 mg tablet, 20% DCP Formulation	14.4	9.34 *(1.35)*	9.8 *(4.5)*	195 *(31)*	16.2 *(2.0)*

Example 19. Pharmacokinetic Profiles in Human - Phase 1 Study of Compound 5

[01352] A first-in-human Phase 1 open-label study was conducted to determine the safety, PK, MTD, and preliminary efficacy profile of compound 5 in human subjects with relapsed or refractory chronic lymphocytic leukemia (CLL; Arm A) or Non-Hodgkin's Lymphoma (NHL; Arm B). Three subjects were enrolled in the first cohort of CLL arm. All subjects had

tumor lysis syndrome (TLS) after the first dose of compound 5 (in 50 mg tablet form).

Subject 1: bulky disease, initial dose = 200 mg

Subject 2: non-bulky disease, initial dose = 200 mg

Subject 3: bulky disease, initial dose = 100 mg

The dosing scheme for CLL arm was as follows: single dose on Week 1 Day -3; QD dose started on Week 1 Day 1. PK sampling was done on Week 1 Day -3 and Week 3 Day 1.

[01353] From the dose-normalized mean plasma concentration-time profiles of compound 5 in these three human subjects, preliminary PK results were obtained as summarized in Table 16.

Table 16. Preliminary Pharmacokinetic Parameters in Human

Week/ Day	ID	Dose (mg)	T_{max}(h)	C_{max} (μg/mL)	C_{max}/ Dose (μg/mL) /mg)	$t_{1/2}$$ (h)	AUC* (μg•h/ mL)	AUC/ Dose (μg•h/mL)/ mg	CL/F (L/h)
Week 1 Day -3	Subject 1	200	6	0.73	0.0037	30.6	23.3	0.12	8.6
	Subject 2	200	8	1.57	0.0079	50.9	76	0.38	2.6
	Subject 3	100	8	1.19	0.0119	22.1	36.3	0.36	2.8
	N		3	3	3	3	3	3	3
	Mean		7.3	- -	0.008	30.7	- -	0.29	4.7
	SD		1.2	- -	0.004	12.6	- -	0.15	3.4
	CV%		15.7	- -	52.8	42.9	- -	51.5	73.2
Week 3 Day 1	101	150	8	1.34	0.0089	- -	21.1	0.14	7.1

(*) AUC = AUC_{INF} on Week 1 Day -3 and $AUC_{ss,24}$ on Week 3 Day 1

($) Harmonic Mean and Pseudo Standard Deviation

[01354] As indicated by these data, compound 5 reached C_{max} around 7 hours. The terminal elimination half-life of compound 5 was 31 hrs (which was observed to be longer than a predicted value of 15 hrs). The observed average AUC normalized to 200 mg dose (58 μg•h/mL) was about 2-fold higher than the predicted AUC (30 μg•h/mL). Compound 5

clearance was 4.7 L/h (which was smaller than the predicted value of 10 L/h).

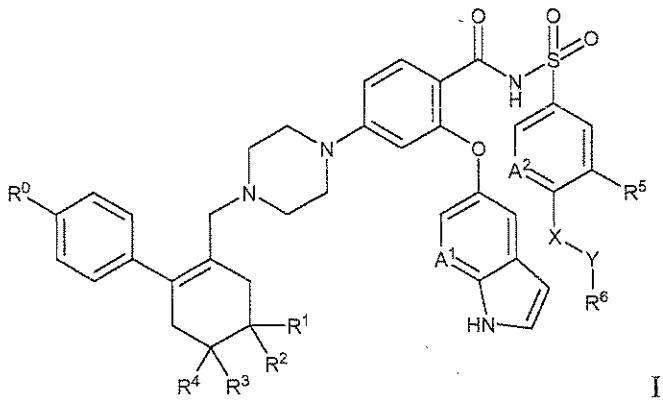
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[01355] When introducing elements of the present disclosure or the preferred embodiments(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[01356] As various changes could be made in the above apparatus and methods without departing from the scope of the disclosure, it is intended that all matter contained in the above description and shown in the accompanying figures shall be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A solid dispersion comprising, in essentially non-crystalline form, a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy,

C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof; dispersed in a solid matrix that comprises (a) at least one pharmaceutically acceptable water-soluble polymeric carrier and (b) at least one pharmaceutically acceptable surfactant.

2. The solid dispersion of Claim 1, wherein, in the compound of Formula I, R^0 is chloro.

3. The solid disperson of Claim 2, wherein, in the compound of Formula I, R^3 and R^4 are each methyl.

4. The solid disperson of Claim 3, wherein, in the compound of Formula I, R^1 and R^2 are each hydrogen.

5. The solid disperson of Claim 4, wherein, in the compound of Formula I, A^1 is N and A^2 is CH.

6. The solid disperson of Claim 5, wherein, in the compound of Formula I, R^5 is nitro.

7. The solid disperson of Claim 6, wherein, in the compound of Formula I, X is –NH–.

8. The solid disperson of Claim 7, wherein, in the compound of Formula I, Y is $–(CH_2)_n–$ where n is 1.

9. The solid disperson of Claim 8, wherein, in the compound of Formula I, R^6 is tetrahydropyran.

10. The solid dispersion of Claim 9, wherein the compound is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

11. The solid dispersion of Claim 1, wherein, in the compound of Formula I, R^1 is methyl or methoxy, R^2 is methyl, and R^3 and R^4 are each H.

12. The solid dispersion of Claim 1, wherein, in the compound of Formula I, if A^2 is –CH– then R^5 is nitro; and if A^2 is –N– then R^5 is bromo.

13. The solid dispersion of Claim 1, wherein, in the compound of Formula I, R^6 is a 3- to 7-membered carbocyclic or heterocyclic ring, unsubstituted or substituted with no more than two Z^1 groups and/or no more than one Z^2 group.

14. The solid dispersion of Claim 13, wherein, in the compound of Formula I, said carbocyclic or heterocyclic ring is a saturated ring.

15. The solid dispersion of Claim 14, wherein, in the compound of Formula I, said saturated ring is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imazolidinyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiophanyl, thiazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, 1,4-dioxanyl, morpholinyl and tetrahydrothiopyranyl rings.

16. The solid dispersion of Claim 1, wherein the compound is selected from the group consisting of

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)-sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]pyridin-3-yl}-sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}-sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)-sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*trans*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)-sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*cis*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)-sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]-sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-

N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}-amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and pharmaceutically acceptable salts thereof.

17. The solid dispersion of Claim 1, wherein the compound or salt is present in a parent-compound-equivalent amount of about 5% to about 40% by weight.

18. The solid dispersion of Claim 1, wherein the at least one polymeric carrier is present in an amount of about 40% to about 85% by weight and the at least one surfactant is present in an amount of about 5% to about 20% by weight.

19. The solid dispersion of Claim 1, wherein the at least one polymeric carrier is selected from the group consisting of homopolymers and copolymers of N-vinyl lactams, cellulose esters, cellulose ethers, high molecular weight polyalkylene oxides, polyacrylates, polymethacrylates, polyacrylamides, vinyl acetate polymers, graft copolymers of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, oligo- and polysaccharides and mixtures thereof.

20. The solid dispersion of Claim 1, wherein the at least one polymeric carrier is selected from the group consisting of povidones, copovidones, HPMCs, polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate graft copolymers and mixtures thereof.

21. The solid dispersion of Claim 1, wherein the at least one surfactant is non-ionic.

22. The solid dispersion of Claim 1, wherein the at least one surfactant is selected from the group consisting of polyoxyethylene glycerides, fatty acid monoesters of sorbitan, polysorbates, α-tocopheryl polyethylene glycol succinate (TPGS) and mixtures thereof.

23. The solid dispersion of Claim 1, further comprising at least one glidant.

24. The solid dispersion of Claim 23, wherein the at least one glidant comprises colloidal silicon dioxide.

25. The solid dispersion of Claim 1, wherein the compound or salt is present in a parent-compound-equivalent amount of about 5% to about 40% by weight, the at least one polymeric carrier is present in an amount of about 40% to about 85% by weight and the at least one surfactant is present in an amount of about 5% to about 20% by weight.

26. The solid dispersion of Claim 25, wherein the compound or salt is present in a parent-compound-equivalent amount of about 5% to about 15% by weight, the at least one polymeric carrier is present in an amount of about 70% to about 85% by weight and the at least one surfactant is present in an amount of about 5% to about 15% by weight.

27. The solid dispersion of Claim 26, wherein the compound is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

28. The solid dispersion of Claim 27, wherein the at least one polymeric carrier is a copovidone.

29. The solid dispersion of Claim 28, wherein the at least one surfactant is a polysorbate.

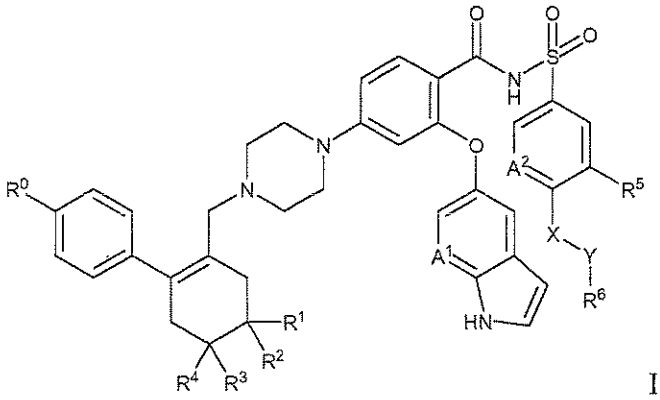
30. The solid dispersion of Claim 30, further comprising at least one glidant.

31. The solid dispersion of Claim 30, wherein the at least one glidant comprises colloidal silicon dioxide.

32. A process for preparing a solid dispersion, comprising:

(a) subjecting to elevated temperature (i) an active pharmaceutical ingredient (API)

that comprises a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each

optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

(b) extruding the semi-solid mixture; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

33. The process of Claim 32, wherein the API, polymeric carrier and surfactant are mixed together before said subjecting to elevated temperature.

34. The process of Claim 32, wherein the API, polymeric carrier and surfactant are mixed together while subjecting to elevated temperature.

35. The process of Claim 32, wherein said elevated temperature is about 70°C to about 250°C.

36. The process of Claim 32, wherein said elevated temperature is about 90°C to about 160°C.

37. The process of Claim 32, further comprising calendering the extrudate before or while cooling.

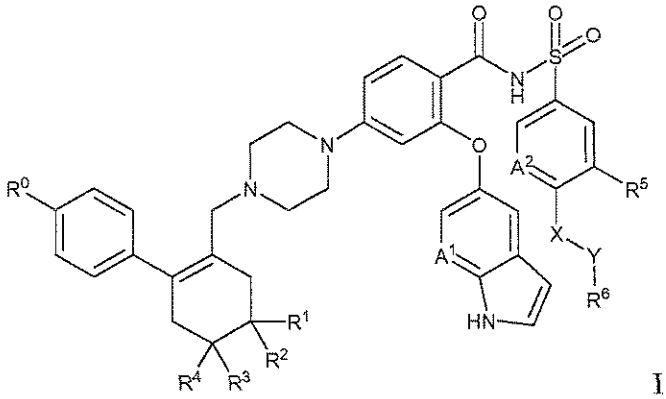
38. The process of Claim 32, wherein API is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

39. The process of claim 38, wherein the polymeric carrier is a copovidone.

40. The process of Claim 39, wherein the surfactant is a polysorbate.

41. A process for preparing a solid dispersion, comprising:

(a) subjecting to elevated temperature (i) an active pharmaceutical ingredient (API) that comprises a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $–(CH_2)_n–$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9–(CH_2)_m–$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon

are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

(b) extruding and calendering the semi-solid mixture; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

42. The process of Claim 41, wherein API is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

43. The process of claim 42, wherein the polymeric carrier is a copovidone.

44. The process of Claim 43, wherein the surfactant is a polysorbate.

45. An orally deliverable pharmaceutical dosage form comprising the solid dispersion of Claim 1.

46. Use of a therapeutically effective amount of the solid dispersion of Claim 1, in the manufacture of a medicament for treating a neoplastic, immune or autoimmune disease.

47. The use of Claim 46, wherein the disease is a neoplastic disease.

48. The use of Claim 47, wherein the neoplastic disease is selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof.

49. The use of Claim 47, wherein the neoplastic disease is a lymphoid malignancy.

50. The use of Claim 49, wherein the lymphoid malignancy is non-Hodgkin's lymphoma.

51. The use of Claim 47, wherein the neoplastic disease is chronic lymphocytic leukemia or acute lymphocytic leukemia.

52. The use of Claim 46, wherein the disease is an immune or autoimmune disease.

53. The use of Claim 46, wherein the solid dispersion is administered in a parent-compound-equivalent dose of about 50 to about 500 mg per day of the compound of

Formula I or salt thereof at an average treatment interval of about 3 hours to about 7 days.

54. The use of Claim 46, wherein the solid dispersion is administered once daily in a parent-compound-equivalent dose of about 50 to about 500 mg per day of the compound of Formula I or salt thereof.

55. The use of Claim 46, wherein the compound is selected from the group consisting of

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)-sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]pyridin-3-yl}-sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}-sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)-sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*trans*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)-sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*cis*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)-sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]-sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}-amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-

N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and pharmaceutically acceptable salts thereof.

56. The use of Claim 46, wherein the compound is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.