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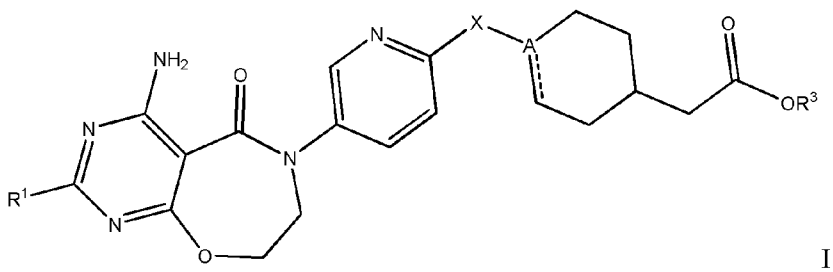
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(54) Title: PYRIDINE DERIVATIVES AS DGAT-1 INHIBITORS



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(57) Abstract: Described herein are compounds of formula (I): The compounds of formula (I) act as DGAT1 inhibitors and can be useful in preventing, treating or acting as a remedial agent for hyperlipidemia, diabetes mellitus and obesity.

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PYRIDINE DERIVATIVES AS DGAT-1 INHIBITORS

TECHNICAL FIELD

The present invention is directed to pyridine derivative compounds. Specifically, the compounds act as diacylglycerol O-acyltransferase type 1 inhibitors (hereinafter also referred to as "DGAT1"), and can be useful in preventing, treating or acting as a remedial agent for hyperlipidemia, diabetes mellitus and obesity.

BACKGROUND

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after meals. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In Type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

The available treatments for Type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat which results in the accumulation of triacylglycerol (TG) in adipose tissue.

In the body there are two TG synthesis pathways, a glycerol phosphate pathway, which is present in most organs and causes *de novo* TG synthesis, and a monoacylglycerol pathway, which is involved principally in absorption of aliphatic acid from the small intestine. Diacylglycerol acyltransferases (DGATs, EC 2.3.1.20), which are membrane-bound enzymes present in the endoplasmic reticulum, catalyze the final step of the TG synthesis common to the two TG synthesis pathways. The final reaction consists of transferring an acyl group from acyl-coenzyme A to the 3-position of 1,2-diacylglycerol to generate TG (Prog. Lipid Res., 43, 134-176, 2004 and Ann. Med., 36, 252-261, 2004). There are two subtypes of DGATs, DGAT-1 and DGAT-2. There is no significant homology at the generic or amino acid level between the DGAT-1 and DGAT-2, which are encoded by different genes (Proc. Natl. Acad. Sci. USA., 95, 13018-13023, 1998 and JBC, 276, 38870-38876, 2001). DGAT-1 is present in the small intestine, adipose tissue and liver and is believed to be involved in lipid absorption in the small intestine; lipid accumulation in the fat cell; and VLDL secretion and lipid accumulation in the liver (Ann. Med., 36, 252-261, 2004 and JBC, 280, 21506-21514, 2005).

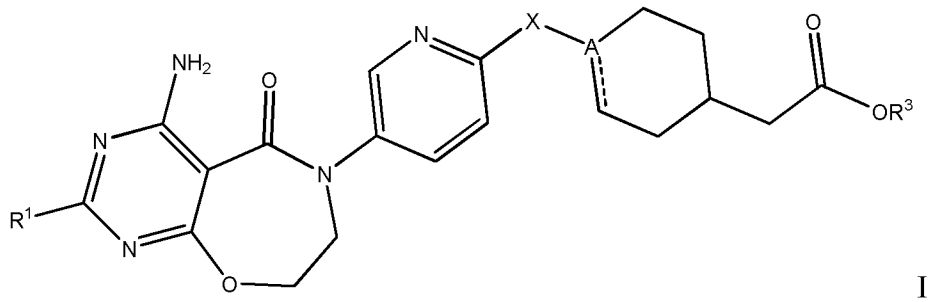
In order to carry out *in vivo* examination of the physiological function(s) of DGAT-1 and inhibitory activity against DGAT-1, DGAT-1-knockout (KO) mice deficient in DGAT-1 at the genetic level was produced and analyzed. DGAT1 KO mice show a lack of postprandial rise of plasma TG, suggesting an important role for DGAT1 in the regulation of fat absorption. DGAT1-deficient mice are resistant to high fat diet-induced obesity and have increased

sensitivity to insulin and leptin. Moreover, the KO mice are protected against hepatic steatosis and were shown to have decreased levels of tissue TG. In addition, the DGAT1 KO mice have improved glucose metabolism, with lower plasma glucose levels after glucose load or insulin injection. Furthermore, in a hyperinsulinemic–euglycemic clamp study, the DGAT1 KO mice required higher glucose infusion rates relative to the WT controls to maintain euglycemia. (Nature Genetics, 25, 87-90, 2000 and JCI, 109, 1049-1055, 2002). Dgat1 KO mice exhibit other post-prandial phenotypes including prolonged release of PYY and GLP-1 as well as delayed gastric emptying (*Biochem Biophys Res Commun. 390(3):377-81*, 2009). Currently, there is an incomplete understanding of the mechanism or the site of action by which DGAT1 inhibition leads to improvement in these metabolic parameters. Genetic data suggests that inhibition of the intestine DGAT1 is the prime driver for body weight loss (*J Lipid Res. 51:1770-80,* 2010). Other reports suggest adipose is the main site of action (*J. Med Chem 52, 1558-1568*, 2009.

From the results, DGAT-1 inhibitors are likely to be therapeutic drugs with efficacy for type 2 diabetes mellitus, obesity, lipidosis, hypertension, fatty liver, arteriosclerosis, cerebrovascular disorder, coronary artery disease and metabolic syndrome.

SUMMARY OF THE INVENTION

A compound of formula (I):



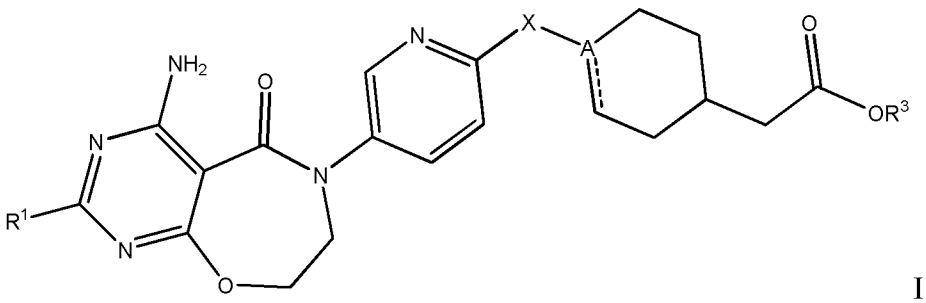
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or pharmaceutically acceptable salts thereof, wherein R^1 is further described below. The compounds described herein are DGAT-1 inhibitors, which are useful in the treatment of type 2 diabetes mellitus, obesity, lipidosis, hypertension, fatty liver, arteriosclerosis, cerebrovascular disorder, coronary artery disease and metabolic syndrome, particularly, obesity and diabetes.

DETAILED DESCRIPTION OF THE INVENTION

Compounds

Described herein are compounds of formula (I):



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or pharmaceutically acceptable salts thereof, wherein

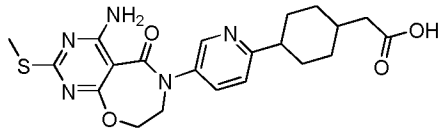
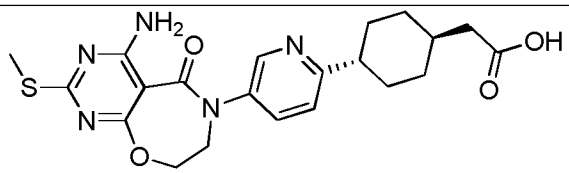
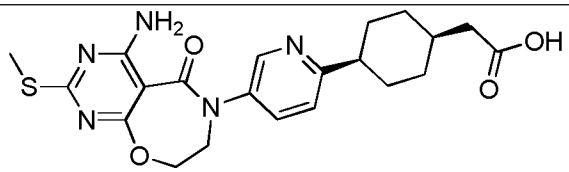
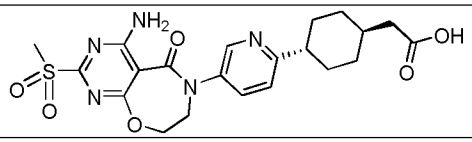
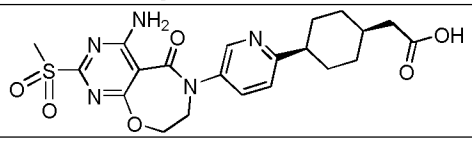
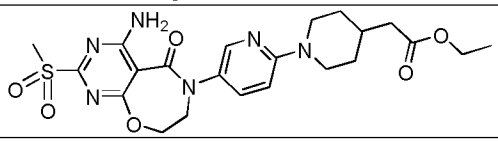
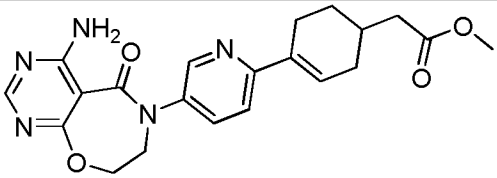
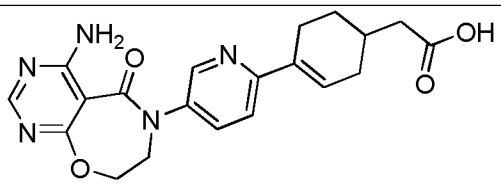
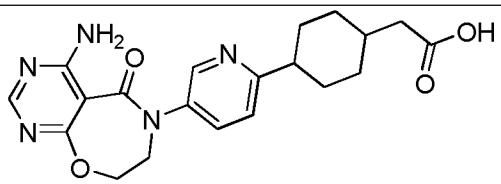
R^1 is selected from the group consisting of: hydrogen, C_1-C_{10} alkyl SO_2 , C_1-C_{10} alkyl S, C_1-C_{10} alkyl, and C_1-C_{10} alkoxy; wherein in the C_1-C_{10} alkyl may be unsubstituted or substituted with C_1-C_{10} alkyl, halogen, -OH, or $N(R^2)_2$; wherein each R^2 is independently selected from hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, or C(O) C_1-C_{10} alkyl;

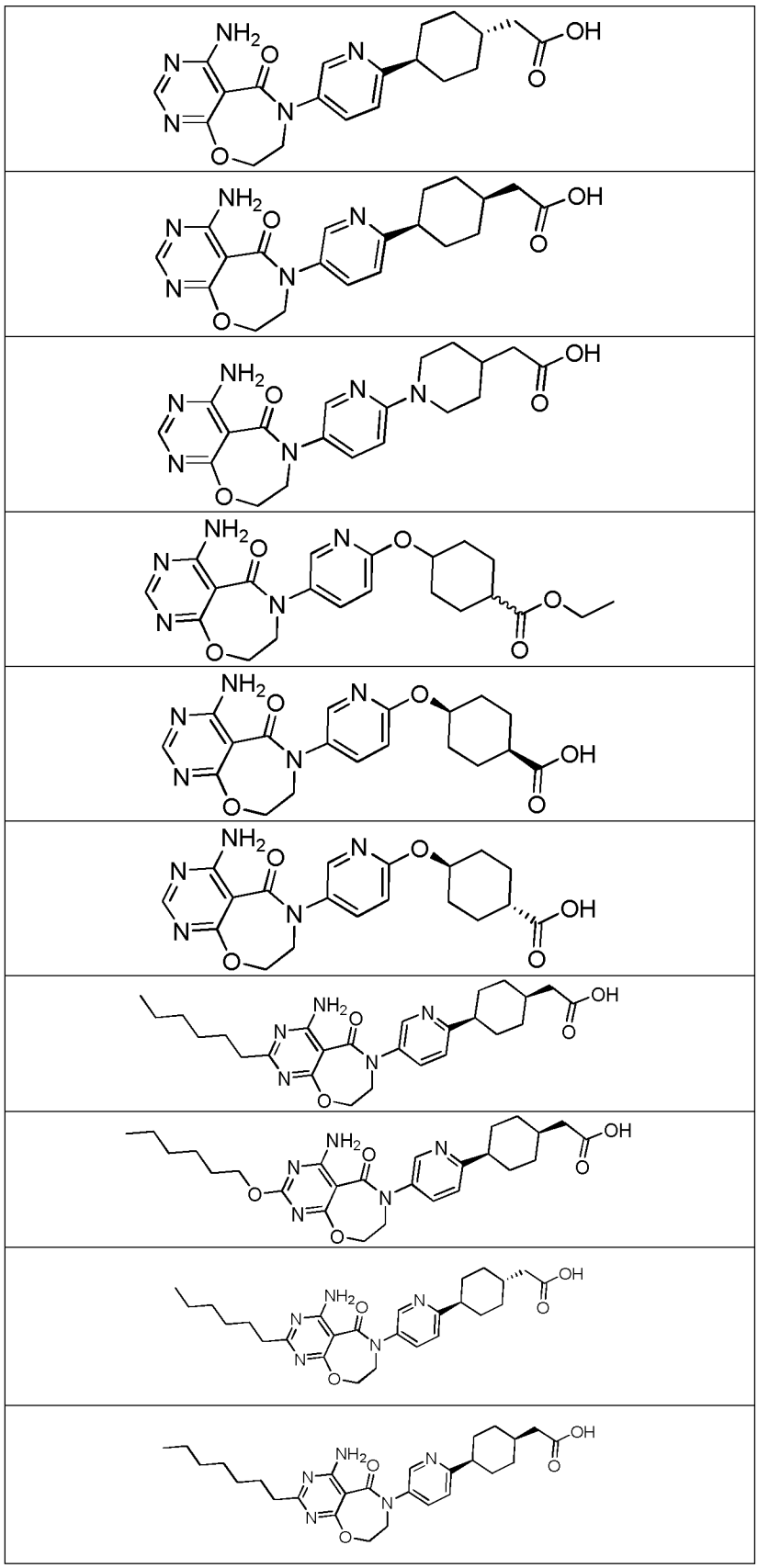
R^3 is selected from the group consisting of: hydrogen and C_1-C_{10} alkyl; wherein in the C_1-C_{10} alkyl may be unsubstituted or substituted with C_1-C_{10} alkyl, halogen, -OH, or $N(R^2)_2$; wherein each R^2 is independently selected from hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, or C(O) C_1-C_{10} alkyl;

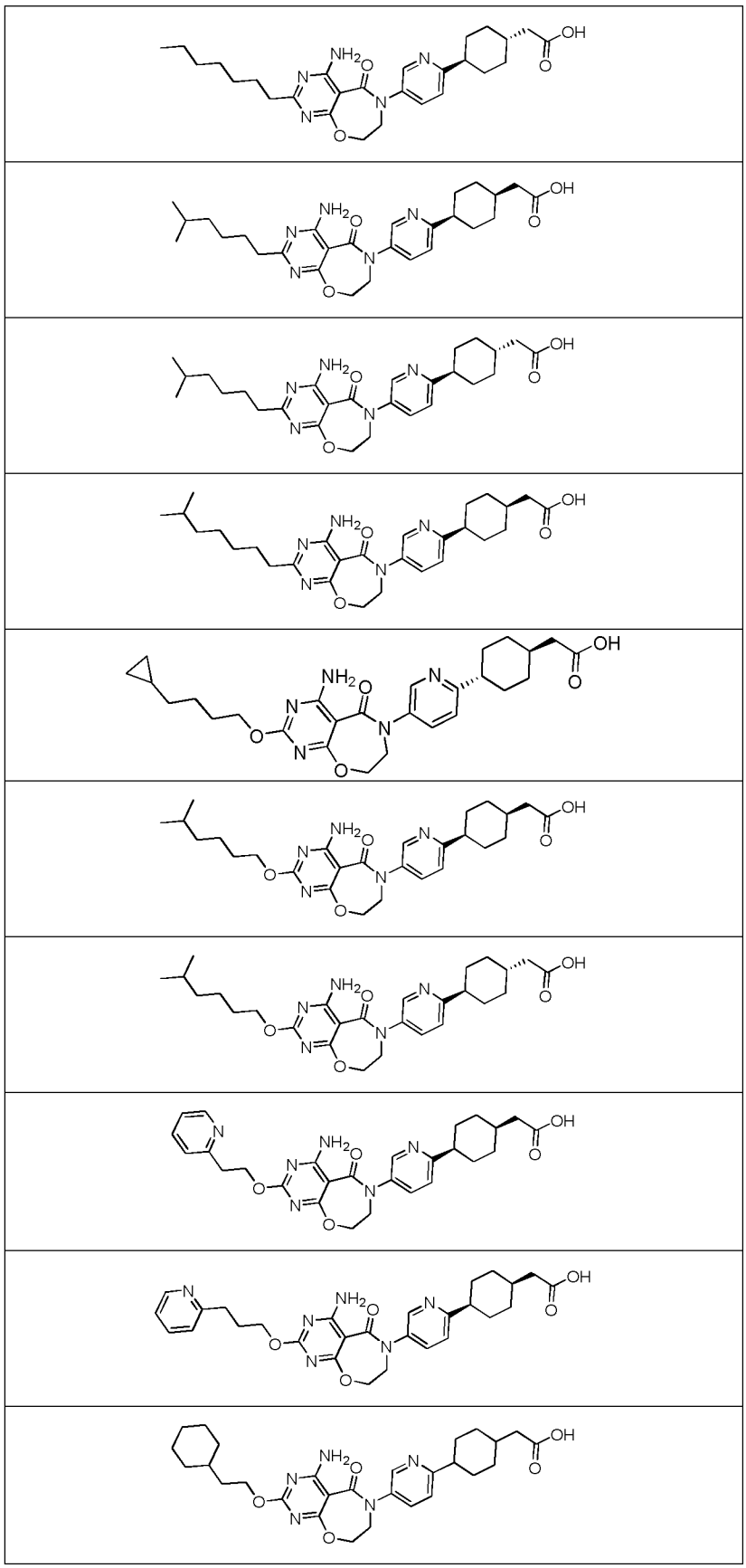
A is N or C, and ----- means a single or a double bond ; and

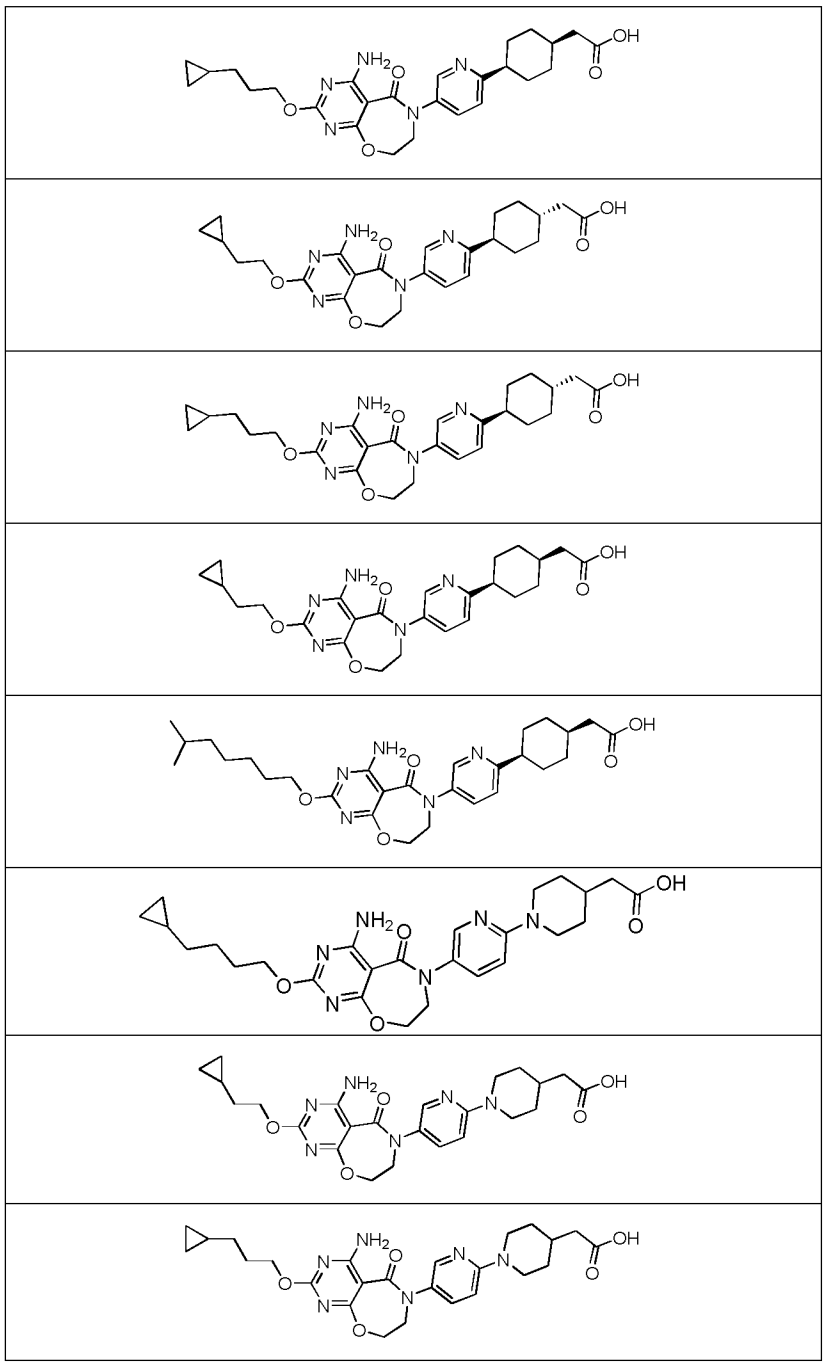
X is O or is not present.

Examples of the compounds described herein include, but are not limited to:

Structure
















Definitions

The term "halogen" includes “halogen”, fluorine, chlorine, bromine and iodine.

The term “C_1-C_{10}alkyl” encompasses straight alkyl having a carbon number of 5 to 10 and branched alkyl having a carbon number of 1 to 10. Specific examples thereof include propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-

methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, 1-ethyl-1-methylpropyl, and the like.

The term "halogen-substitutedC_1-C_{10} alkyl" encompasses C_1-C_{10}alkyl with the hydrogen atoms thereof being partially or completely substituted with halogen, examples thereof including fluoropentyl, difluoropentyl, trifluoropentyl, 6-fluorohexyl, 6,6-difluorohexyl, 6,5-difluorohexyl and the like.

The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine,

morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

The compounds of the present invention contain one or more asymmetric centers and can thus occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures, and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the X-ray crystallography of crystalline products or crystalline Intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

It will be understood that, as used herein, references to the compounds of the structural formulas described herein are meant to also include the pharmaceutically acceptable salts, and

also salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations.

Solvates, and in particular, the hydrates of the compounds of the structural formulas described herein are included in the present invention as well. Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

In the compounds of the formulas described herein, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of the formulas described herein. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic formula can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or Intermediates.

Methods of Treatment

Also encompassed by the present invention are methods of treating DGAT1-related diseases. The compounds described herein are effective in preventing or treating various DGAT1-related diseases, such as metabolic diseases such as obesity, diabetes, hormone secretion disorder, hyperlipemia, gout, fatty liver, and the like; circulatory diseases such as angina pectoris, acute/congestive cardiac insufficiency, myocardial infarction, coronary arteriosclerosis, hypertension, nephropathy, electrolyte abnormality, and the like; central and peripheral nervous system diseases such as bulimia, affective disorder, depression, anxiety, epilepsy, delirium, dementia, schizophrenia, attention deficit/hyperactivity disorder, dysmnesia,

somnipathy, cognitive impairment, dyskinesia, dysesthesia, dysosmia, morphine resistance, drug dependence, alcohol dependence, and the like; reproductive system diseases such as infertility, premature delivery, sexual dysfunction, and the like; and other conditions including digestive diseases, respiratory diseases, cancer, and chromatosis. The compound of the invention is especially useful as a preventive or a remedy for obesity, diabetes, fatty liver, bulimia, depression, or anxiety.

One aspect of the invention described herein provides a method for the treatment and control of obesity or metabolic syndrome, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound having the formulas described herein or a pharmaceutically acceptable salt thereof. For example, the compounds described herein are useful for treating or preventing obesity by administering to a subject in need thereof a composition comprising a compound of formula I.

Methods of treating or preventing obesity and conditions associated with obesity refer to the administration of the pharmaceutical formulations described herein to reduce or maintain the body weight of an obese subject or to reduce or maintain the body weight of an individual at risk of becoming obese. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject's body weight immediately before the administration of the compounds or combinations of the present invention. Another outcome of treatment may be preventing body weight, regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy and preventing weight gain from cessation of smoking. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. Yet another outcome of treatment may be decreasing the risk of developing diabetes in an overweight or obese subject. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate; and in weight reduction in patients in need thereof. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from weight loss.

Prevention of obesity and obesity-related disorders refers to the administration of the pharmaceutical formulations described herein to reduce or maintain the body weight of a subject at risk of obesity. One outcome of prevention may be reducing the body weight of a subject at risk of obesity relative to that subject's body weight immediately before the administration of the compounds or combinations of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, type 2 diabetes, polycystic ovary disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

Another aspect of the invention that is of interest relates to a method of treating hyperglycemia, diabetes or insulin resistance in a mammalian patient in need of such treatment which comprises administering to said patient a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to treat hyperglycemia, diabetes or insulin resistance.

More particularly, another aspect of the invention that is of interest relates to a method of treating type 2 diabetes in a mammalian patient in need of such treatment comprising administering to the patient a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to treat type 2 diabetes.

Yet another aspect of the invention that is of interest relates to a method of treating non-insulin dependent diabetes mellitus in a mammalian patient in need of such treatment comprising administering to the patient a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to treat non-insulin dependent diabetes mellitus.

The present invention is also directed to the use of a compound of structural formula I in the manufacture of a medicament for use in treating various DGAT1-related diseases, such as metabolic diseases such as obesity, diabetes, hormone secretion disorder, hyperlipemia, gout, fatty liver, and the like; circulatory diseases such as angina pectoris, acute/congestive cardiac insufficiency, myocardial infarction, coronary arteriosclerosis, hypertension, nephropathy, electrolyte abnormality, and the like; central and peripheral nervous system diseases such as bulimia, affective disorder, depression, anxiety, epilepsy, delirium, dementia, schizophrenia, attention deficit/hyperactivity disorder, dysmnesia, somnipathy, cognitive impairment, dyskinesia, dysesthesia, dysosmia, morphine resistance, drug dependence, alcohol dependence, and the like; reproductive system diseases such as infertility, premature delivery, sexual dysfunction, and the like; and other conditions including digestive diseases, respiratory diseases, cancer, and chromatosis. The compounds described herein are especially useful as a preventive or a remedy for obesity, diabetes, fatty liver, bulimia, depression, or anxiety.

For example, the present invention is directed to the use of a compound of structural formula I in the manufacture of a medicament for use in treating obesity, diabetes, hormone secretion disorder, hyperlipemia, gout and fatty liver.

Additionally, the present invention is directed to the use of a compound of structural formula I in the manufacture of a medicament for use in treating diabetes.

In an embodiment, the individual in need of treatment is a mammal. In another embodiment the individual is a human. In another embodiment, the individual is a dog or a cat. In another embodiment, the individual is a horse.

Pharmaceutical Compositions

Compounds of the invention may be administered orally or parenterally. As formulated into a dosage form suitable for the administration route, the compound of the invention can be used as a pharmaceutical composition for the prevention, treatment, or remedy of the above diseases.

In clinical use of the compound of the invention, usually, the compound is formulated into various preparations together with pharmaceutically acceptable additives according to the dosage form, and may then be administered. By "pharmaceutically acceptable" it is meant the additive, carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. As such additives, various additives ordinarily used in the field of pharmaceutical preparations are usable. Specific examples thereof include gelatin, lactose, sucrose, titanium oxide, starch, crystalline cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, corn starch, microcrystalline wax, white petrolatum, magnesium metasilicate aluminate, anhydrous calcium phosphate, citric acid, trisodium citrate, hydroxypropylcellulose, sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxyethylene, hardened castor oil, polyvinylpyrrolidone, magnesium stearate, light silicic acid anhydride, talc, vegetable oil, benzyl alcohol, gum arabic, propylene glycol, polyalkylene glycol, cyclodextrin, hydroxypropyl cyclodextrin, and the like.

Preparations to be formed with those additives include, for example, solid preparations such as tablets, capsules, granules, powders, suppositories; and liquid preparations such as syrups, elixirs, injections. These may be formulated according to conventional methods known in the field of pharmaceutical preparations. The liquid preparations may also be in such a form that may be dissolved or suspended in water or in any other suitable medium in their use. Especially for injections, if desired, the preparations may be dissolved or suspended in physiological saline or glucose liquid, and a buffer or a preservative may be optionally added thereto.

The pharmaceutical compositions may contain the compound of the invention in an amount of from 1 to 99.9 % by weight, preferably from 1 to 60 % by weight of the composition. The compositions may further contain any other therapeutically-effective compounds.

In case where the compounds of the invention are used for prevention or treatment for the above-mentioned diseases, the dose and the dosing frequency may be varied, depending on the sex, the age, the body weight and the disease condition of the patient and on the type and the range of the intended remedial effect. In general, when orally administered, the dose may be from 0.001 to 50 mg/kg of body weight/day, and it may be administered at a time or in several times. The dose is preferably from about 0.01 to about 25 mg/kg/day, more preferably from about 0.05 to about 10 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets or capsules containing from 0.01 mg to 1,000 mg, preferably 0.01, 0.05, 0.1, 0.2, 0.5, 1.0, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 500, 750, 850 and 1,000 milligrams of a compound described herein. This dosage regimen may be adjusted to provide the optimal therapeutic response.

Combination Therapy

The compounds of the present invention are further useful in methods for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other therapeutic agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, suppression or amelioration of diseases or conditions for which compounds of formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of formula I. When a compound of formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of formula I is preferred. However, the combination therapy may also include therapies in which the compound of formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the

present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of formula I.

Examples of other active ingredients that may be administered in combination with a compound of formula I and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

(1) dipeptidyl peptidase-IV (DPP-4) inhibitors;

(2) insulin sensitizers;

(3) insulin or insulin analogs;

(4) leptin and leptin derivatives and agonists;

(5) amylin and amylin analogs;

(6) sulfonylurea and non-sulfonylurea insulin secretagogues;

(7) α-glucosidase inhibitors;

(8) glucagon receptor antagonists;

(9) incretin mimetics;

(10) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors, (ii) bile acid sequestering agents, (iii) inhibitors of cholesterol absorption, and (iv) acyl CoA:cholesterol acyltransferase inhibitors, such as avasimibe;

(11) HDL-raising drugs;

(12) antiobesity compounds;

(13) agents intended for use in inflammatory conditions;

(14) antihypertensive agents, such as ACE, A-II receptor blockers, renin inhibitors, beta blockers and calcium channel blockers;

(15) glucokinase activators (GKAs);

(16) inhibitors of 11β-hydroxysteroid dehydrogenase type 1;

(17) inhibitors of cholesteryl ester transfer protein (CETP);

(18) inhibitors of fructose 1,6-bisphosphatase;

(19) inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2);

(20) AMP-activated Protein Kinase (AMPK) activators;

(21) agonists of the G-protein-coupled receptors: GPR-109, GPR-119, and GPR-40;

(22) SSTR3 antagonists;

(23) neuromedin U receptor agonists;

(24) inhibitors of stearoyl-coenzyme A delta-9 desaturase (SCD);

(25) GPR-105 antagonists;

(26) inhibitors of glucose uptake;

(27) inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2);

(28) inhibitors of fatty acid synthase;

(29) inhibitors of acetyl-CoA carboxylase-1 and 2 (ACC-1 and ACC-2);

(30) inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2);

(31) agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19, GPR131, and M-BAR); and

(32) bromocriptine mesylate and rapid-release formulations thereof.

In another aspect of the invention, a pharmaceutical composition is disclosed which comprises the above combinations of agents and a pharmaceutically acceptable carrier.

When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient.

Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

EXAMPLES

General Methods

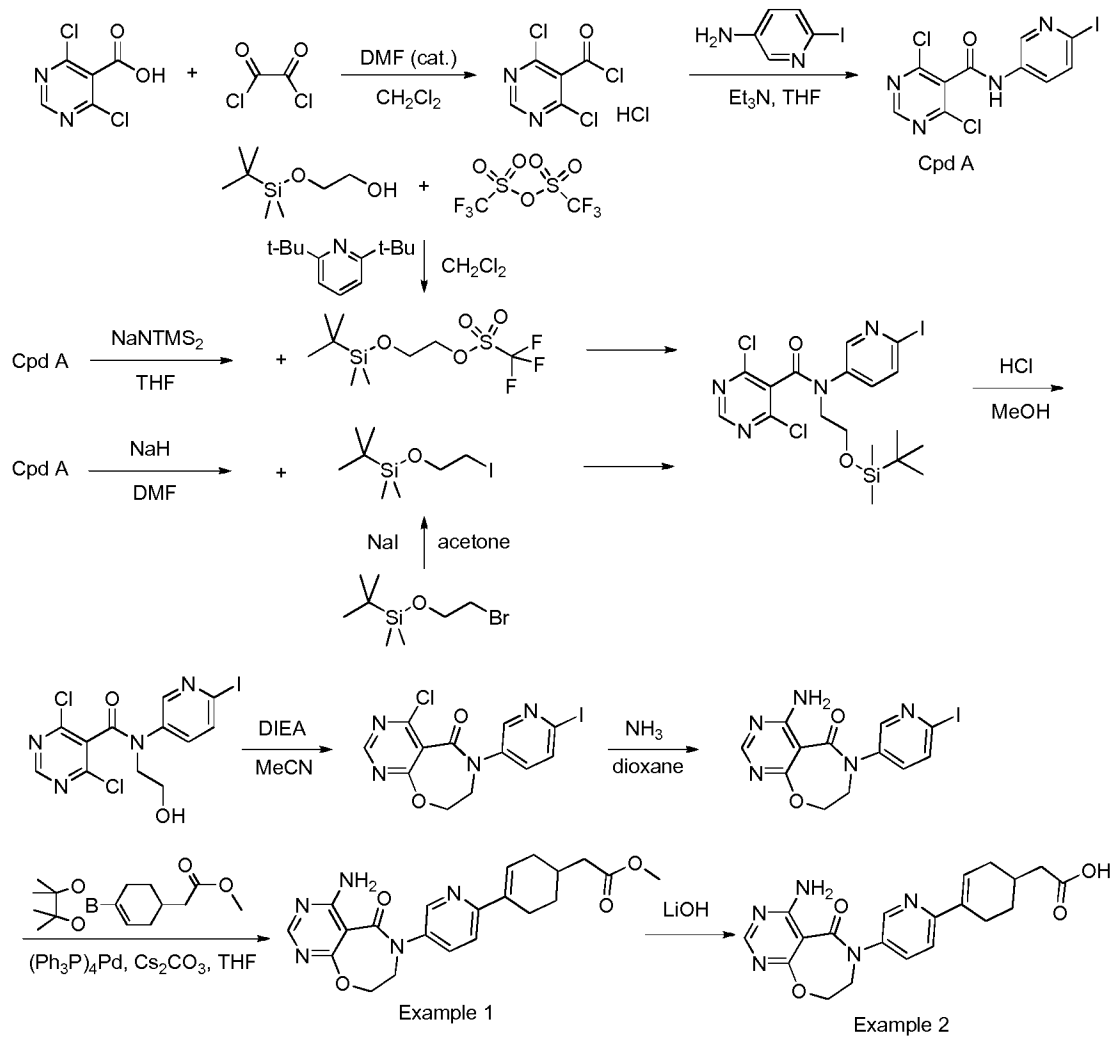
Reactions sensitive to moisture or air were performed under nitrogen using anhydrous solvents and reagents. The progress of reactions was determined by either analytical thin layer chromatography (TLC) performed with E. Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.25 mm or liquid chromatography-mass spectrum (LC-MS). Analytical HPLC/MS - Standard Method: Mass analysis was performed with electrospray ionization in positive ion detection mode. For HPLC/MS data, the three HPLC conditions used were as follows:

1) LC2 (Waters C18 XTerra™ 3.5 μm 2.1x20 mm column with gradient 10:90-98:2 v/v CH_3CN/H_2O + v 0.05 % TFA over 1.25 min then hold at 98:2 v/v CH_3CN/H_2O + v 0.05 % TFA for 0.75 min; flow rate 1.5 mL/min, UV wavelength 254 nm); and 2) LC4 (Waters C18 XTerra 3.5 μm 2.1x20 mm column with gradient 10:90-98:2 v/v CH_3CN/H_2O + v 0.05 % TFA over 3.25 min then hold at 98:2 v/v CH_3CN/H_2O + v 0.05 % TFA for 0.75 min; flow rate 1.5 mL/min, UV wavelength 254 nm); and 3) UPLC2 (Waters Acquity UPLC BEH 2.1X50mm, Solvent A: water with 0.1% NH_4OH, B: Acetonitrile with 0.1% NH_4OH. Gradient: B% = 5% to 95%, column temperature: 55°C, Flow 1 ml/min, 1 μl injection, MS detection: ESI+ (electrospray positive ion), 2 min run time).

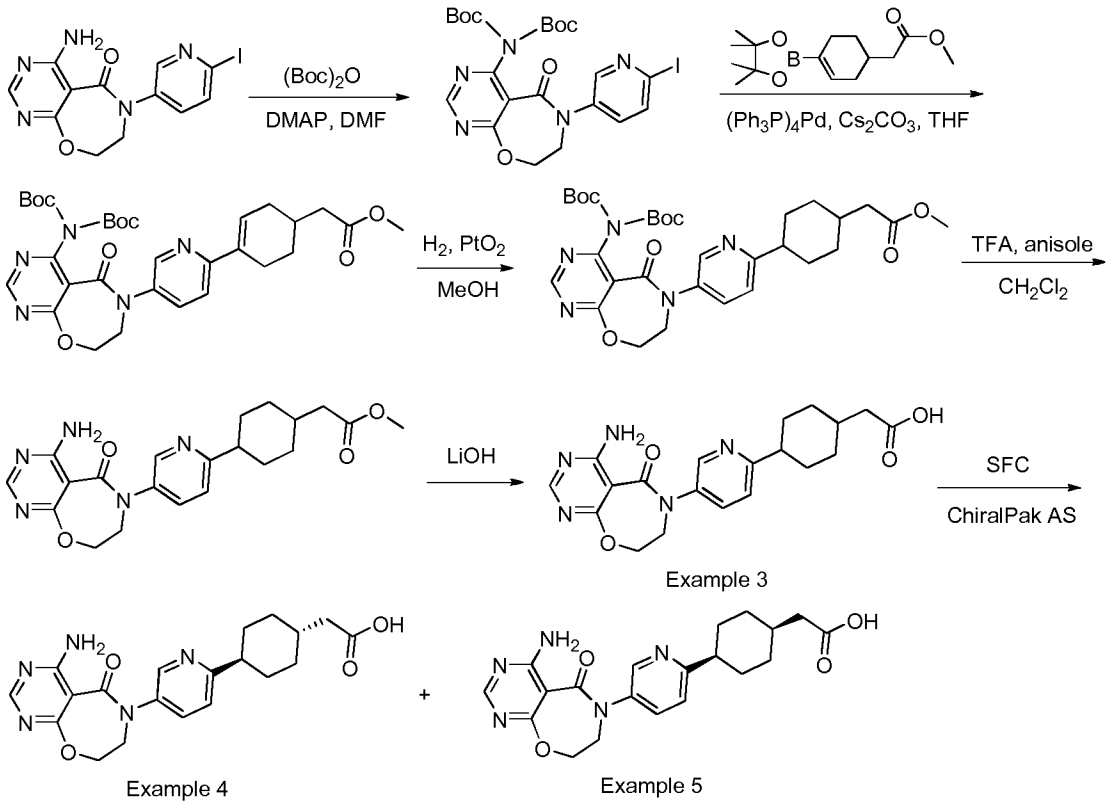
Preparative reverse phase high performance liquid chromatography (RP-HPLC) used for the purification of samples was performed using a Gilson™ RP-HPLC system with an Akzo-Nobel Kromasil™ 100-5C18 column (21.2 mm x 10 cm), 25 mL/ min gradient elution 10:90 to 100:0 CH_3CN/H_2O + v 0.05 % TFA over 12 min unless indicated otherwise. Concentration of solutions was carried out on a rotary evaporator under reduced pressure or by lyophilization. Flash chromatography was performed on silica gel using a commercial MPLC system.

The examples were prepared according the sequence depicted in Schemes 1-4.

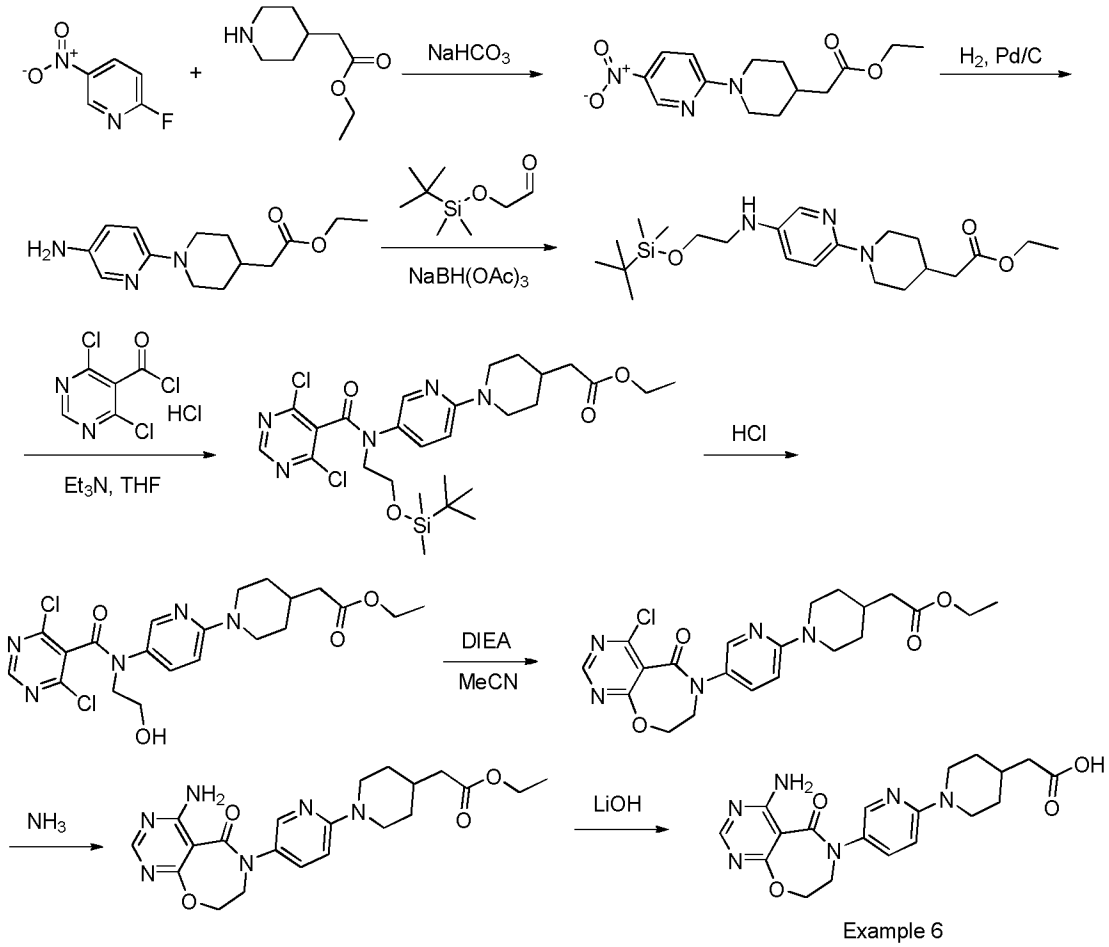
Scheme 1


DMF (cat.)
CH2Cl2
HCl
Et3N, THF
Cpd A
t-Bu
t-Bu
CH2Cl2
Cpd A
NaNTMS2
THF
Cpd A
NaH
DMF
HCl
MeOH
NaI
acetone
DIEA
MeCN
NH3
dioxane
(Ph3P)4Pd, Cs2CO3, THF
Example 1
LiOH
Example 2

Scheme 2

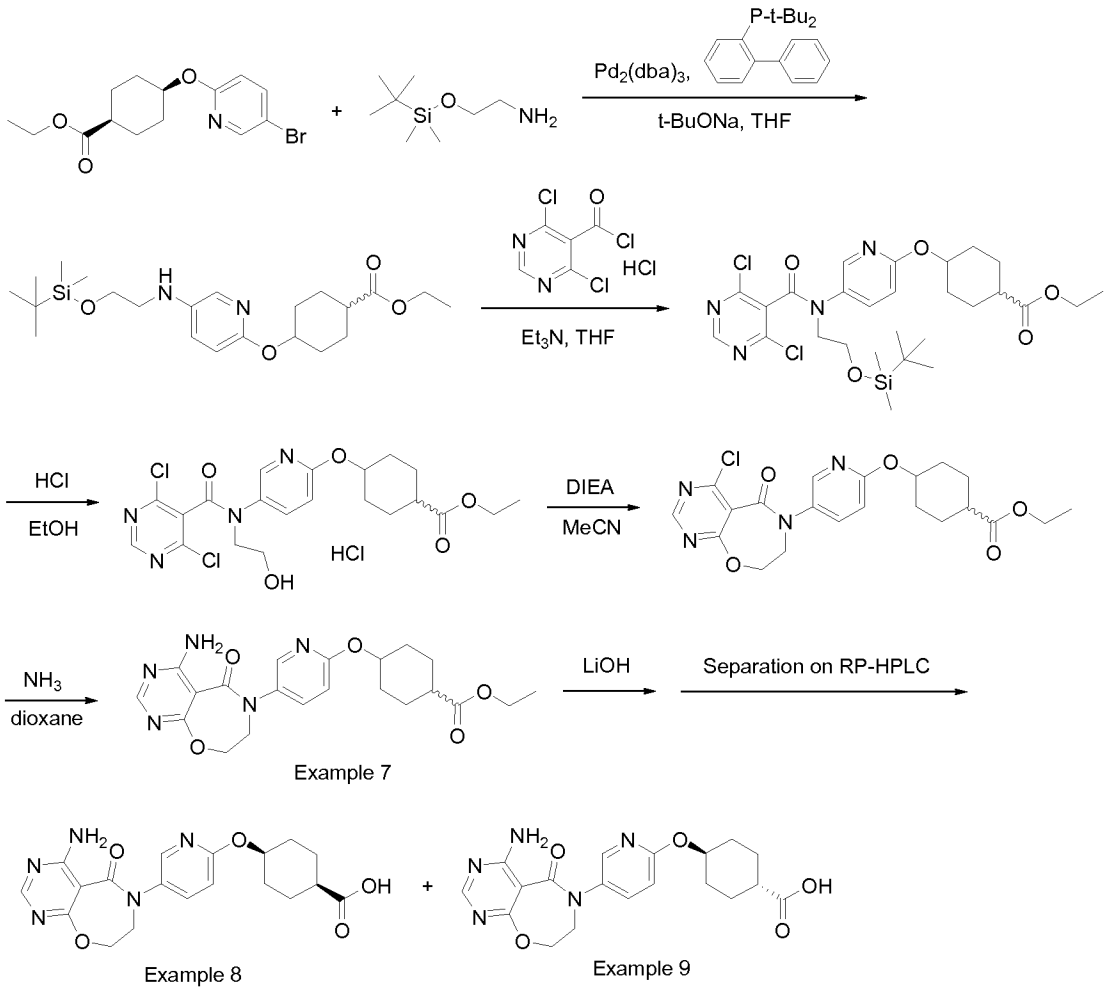

(Boc)2O
DMAP, DMF
(Ph3P)4Pd, Cs2CO3, THF
H2, PtO2
MeOH
TFA, anisole
CH2Cl2
LiOH
SFC
ChiralPak AS
Example 3
Example 4
Example 5

Scheme 3



Example 6

Scheme 4



General Methods: Reactions sensitive to moisture or air were performed under nitrogen using anhydrous solvents and reagents. The progress of reactions was determined by either analytical thin layer chromatography (TLC) performed with E. Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.25 mm or liquid chromatography-mass spectrum (LC-MS). Analytical HPLC conditions: Zorbax 3.5 □m SB-C18 column (4.6x75 mm) on a Shimadzu system running a 20~100% MeCN gradient in water with 0.1% TFA over 5 minutes and held at 100% MeCN for 2 minutes at a flow rate of 2.0 mL/min. Where specified, the MeCN gradient can be 0~100%. Mass analysis was performed with electrospray ionization in positive ion detection mode. For LC-MS data, the two HPLC conditions used were as follows:

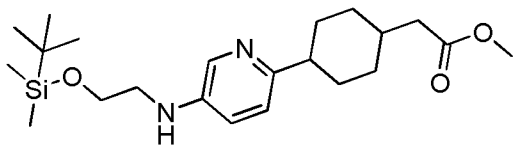
1) LC2 (Waters C18 XTerra□ 3.5 □m 2.1x20 mm column with gradient 10:90-98:2 v/v CH_3CN/H_2O + v 0.05 % TFA over 1.25 min then hold at 98:2 v/v CH_3CN/H_2O + v 0.05 % TFA for 0.75 min; flow rate 1.5 mL/min, UV wavelength 254 nm); and 2) LC4 (Waters C18

XTerra 3.5 □m 2.1x20 mm column with gradient 10:90-98:2 v/v CH_3CN/H_2O + v 0.05 % TFA over 3.25 min then hold at 98:2 v/v CH_3CN/H_2O + v 0.05 % TFA for 0.75 min; flow rate 1.5 mL/min, UV wavelength 254 nm).

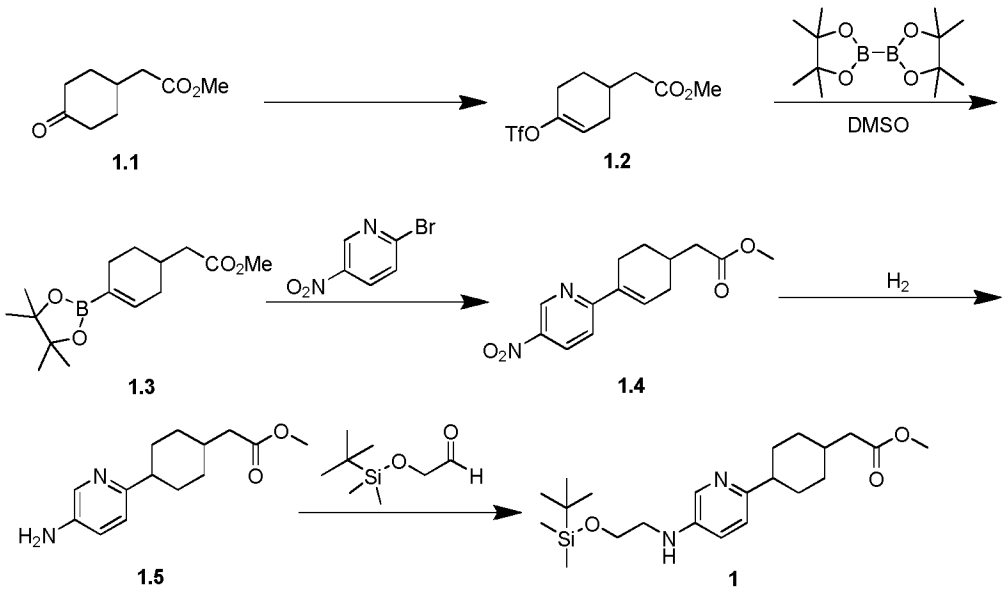
Preparative reverse phase high performance liquid chromatography (RP-HPLC) used for the purification of samples was performed using a Gilson□ RP-HPLC system with an Akzo-Nobel Kromasil□ 100-5C18 column (21.2 mm x 10 cm), 25 mL/ min gradient elution 10:90 to 100:0 CH_3CN/H_2O + v 0.05 % TFA over 12 min unless indicated otherwise. Concentration of solutions was carried out on a rotary evaporator under reduced pressure or by lyophilization. Flash chromatography was performed on silica gel using a commercial MPLC system.

Abbreviations: RT stands for room temperature; ACN is acetonitrile; aq is aqueous; Boc and BOC is *tert*-butoxycarbonyl; Celite™ is diatomaceous earth; CO_2 is carbon dioxide; DCM or CH_2Cl_2 is dichloromethane; dppf is 1,1" – bis(diphenylphosphino)ferrocene; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; DEA is diethylamine; DIPEA or DIEA is *N,N*-diisopropylethylamine; DMAP is 4-*N,N*-dimethylaminopyridine; DME is 1,2-dimethoxyethane; DMF is *N,N*-dimethyl-formamide; DMA is *N,N*-dimethylacetamide; DMSO is dimethyl sulfoxide; EDC is *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide; EtOH is ethyl alcohol; EtOAc is ethyl acetate; equiv is equivalent(s); ESI is electrospray ionization; Et_3N or TEA is triethylamine; g is grams; h or hr is hour(s); HCl is hydrochloric acid; HPLC is high-performance liquid chromatography; HPLC/MS or LC/MS is high-performance liquid chromatography mass spectroscopy; L is liter(s); mg is milligrams; ml and mL is milliliter; M is molar; mmol is millimole(s); Me is methyl; MeCN or ACN is acetonitrile; MeOH is methanol; min is minute(s); ms or MS is mass spectrum; MTBE is methyl-*tert*-butyl ether; μg is microgram(s); μL is microliter(s); N is normal; NMP is *N*-methyl-2-pyrrolidinone; NMR is nuclear magnetic resonance spectroscopy; NOE is nuclear Overhauser effect; RP or rp is reverse phase; RP-HPLC is reverse phase high-performance liquid chromatography; R_t is retention time; sat., sat'd., and sat is saturated; SFC is supercritical fluid chromatography; TFA is trifluoroacetic acid; THF is tetrahydrofuran; TLC is thin layer chromatography; and v/v is volume per volume (ratio).

Preparative Example 1



Methyl 2-(4-(5-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)pyridin-2-yl)cyclohexyl)acetate



Step 1: Methyl 2-(4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl)acetate (1.2)

A mixture of commercially available methyl 2-(4-oxocyclohexyl)acetate (5.09 g, 29.9 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (7.06 g, 34.4 mmol) in CH_2Cl_2 (100 ml) in a 250 mL round-bottom single-neck flask was cooled to 0°C under nitrogen and treated with triflic anhydride (5.30 ml, 31.4 mmol). The mixture was stirred at 0°C for 30 min then at RT for 20 h. The mixture was diluted with MTBE (50 mL), filtered through a pad of Celite, concentrated and filtered again with MTBE. The filtrate was concentrated and the residue was purified on Silica gel (0 to 100% EtOAc in heptane) to afford title compound as an oil. LC/MS (m/z): 302.72 ($M+H^+$), 2.07 min (LC4). Alternatively, the keto ester starting material, methyl (4-oxocyclohexyl)acetate, was obtained from commercially available methyl (4-hydroxyphenyl)acetate using a two-step sequence of hydrogenation (Rh/Al_2O_3) and oxidation (NaOCl).

Step 2: Methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)acetate (1.3)

A mixture of methyl 2-(4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl)acetate (11.00 g, 36.4 mmol) prepared as described in Step 1 above in DMSO (50 ml) was treated with potassium acetate (10.71 g, 109 mmol), $PdCl_2(dppf)$-CH_2Cl_2 complex (0.892 g, 1.092 mmol) and bis(pinacolato)diboron (10.17 g, 40.0 mmol). The mixture was sub-surface sparged with N_2 for 10 minutes, stirred at 60 °C (hot plate temp) for 6 h under N_2, cooled to RT and quenched with water (100 mL). The mixture was extracted with MTBE and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered through a pad of Celite/Florisil (1:1 v/v) and the filtrate was concentrated. Purification on Silica gel (0 to 50% EtOAc in heptane; fractions containing the product were identified by TLC 40% EtOAc in heptane with CAM staining) afforded title compound as light yellow clear oil, which solidified on standing in a freezer. LC/MS (m/z): 280.81 ($M+H^+$), 2.09 min (LC4).

Step 3: Methyl 2-(4-(5-nitropyridin-2-yl)cyclohex-3-en-1-yl)acetate (1.4)

Method A: Methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)acetate (1.0 g, 3.57 mmol) from Step 2 above and 2-bromo-5-nitropyridine (0.80 g, 3.93 mmol) were mixed in DME (10 ml), ethanol (7 ml), and 2.0 M aqueous solution of sodium carbonate (3.6 ml). The mixture was bubbled with nitrogen, followed by addition of tetrakis(triphenylphosphine)palladium (0.41 g, 0.36 mmol). After heating at 80°C in a sealed tube for 15 h, the mixture was concentrated. The resulting residue was diluted with ethyl acetate, and washed with water and brine, then dried over Na_2SO_4. The crude product was purified on a silica gel column using a gradient of 0-50% ethyl acetate in hexanes to give title compound as light brown solid. LC-MS (m/e): 277.18 ($M + H^+$), 1.73 min (LC4).

Method B: To a solution of methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)acetate (15.0 g, 53.5 mmol) and 2-bromo-5-nitropyridine (11.30 g, 55.7 mmol) in DMF (150 mL) was added a 2.0 M aqueous solution of sodium carbonate (53.5 ml, 107 mmol). The mixture was degassed and refilled with N_2 twice, then added $PdCl_2(dppf)$-CH_2Cl_2 adduct (2.19 g, 2.68 mmol), followed by degassing and refilling with N_2 twice again. After stirring at 80°C for 12 hours, the reaction mixture was quenched with EtOAc and washed with water. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The

resulting residue was purified by MPLC to give title compound. LC-MS (m/e): 277.13 ($M + H^+$), 1.18 min (LC2).

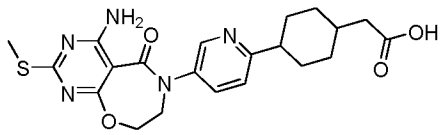
Step 4: Methyl 2-(4-(5-aminopyridin-2-yl)cyclohexyl)acetate (1.5)

A solution of methyl 2-(4-(5-nitropyridin-2-yl)cyclohex-3-en-1-yl)acetate (1.30 g, 4.71 mmol) from Step 3 above in methanol (30 ml) was hydrogenated over platinum oxide (0.107 g, 0.471 mmol) under a hydrogen balloon for 19 h. Then the catalyst was removed by filtration, and the solvent was removed under reduced pressure to give title compound as a mixture of cis- and trans- isomers, which was used directly without further purification. LC-MS: 249.22 ($M + H^+$), 0.46 and 0.60 min (LC4). It was discovered that using 9:1 mixture of MeOH/water can reduce side-product and the reaction can also be carried out in a Parr shaker at 40 psi of hydrogen at RT.

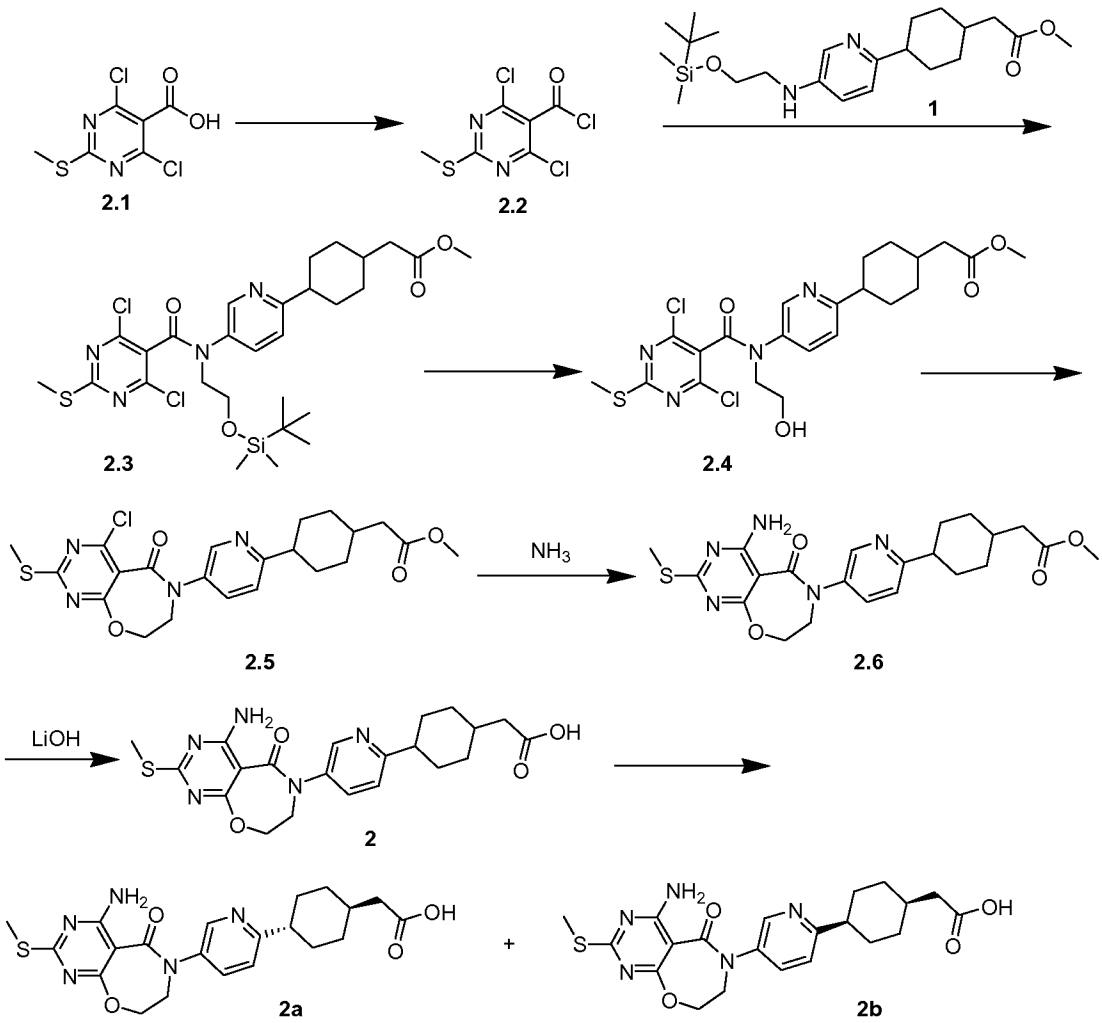
Step 5: Methyl 2-(4-(5-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)pyridin-2-yl)cyclohexyl)acetate (1)

Methyl 2-(4-(5-aminopyridin-2-yl)cyclohexyl)acetate (9.3 g, 37.5 mmol) and (*t*-butyldimethylsilyloxy)acetaldehyde (7.43 g, 38.4 mmol) were mixed in 1,2-dichloroethane (200 ml) with 1.00 g of 4A molecular sieves at 0°C. The mixture was stirred at RT for 1 h, then cooled to 0°C and followed by addition of sodium triacetoxyborohydride (10.32 g, 48.7 mmol) in several portions. After stirring at RT overnight, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and stirred for another 0.5 h, followed by extraction with EtOAc (2x). The combined organic layer was washed with brine and then dried over $MgSO_4$. The crude product was purified on MPLC using a gradient of 0-50% ethyl acetate in hexanes to give the title compound as clear oil. LC-MS (m/z): 407.3 ($M + H^+$), 1.93 min (LC4) and 1.14 min (LC2).

Preparative Example 2



2-(4-(5-(4-Amino-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid



Step 1: 4,6-Dichloro-2-(methylthio)pyrimidine-5-carbonyl chloride hydrochloride (2.2)

To a suspension of 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (2.45 g, 10.25 mmol) in CH_2Cl_2 (50 ml) was added oxalyl chloride (2.60 g, 20.50 mmol) at 0°C, followed by the addition of 0.024 mL of DMF. After stirring at RT overnight, solvent was removed to dryness under reduced pressure to give title compound as a brown solid, which was kept in freezer and used directly without further purification.

Step 2: Methyl 2-(4-(5-(N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,6-dichloro-2-(methylthio)pyrimidine-5-carboxamido)pyridin-2-yl)cyclohexyl)acetate (2.3)

To a suspension of 4,6-dichloro-2-(methylthio)pyrimidine-5-carbonyl chloride hydrochloride (0.564 g, 1.92 mmol) in THF (3.0 ml) at 0°C was added drop-wise a solution of methyl 2-(4-(5-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)pyridin-2-yl)cyclohexyl)acetate from Preparative Example 1 (0.39 g, 0.96 mmol) and DIEA (0.503 mL, 2.88 mmol) in THF (2.5 ml). The cooling bath was removed after 5 minutes. After stirring at RT overnight, solvent was removed

to dryness under reduced pressure. The residue was purified on a silica gel column using a gradient of 60-100% ethyl acetate in hexanes to give title compound as yellow oil. LC-MS (m/z): 627.12/629.06/631 ($M + H^+$), 2.51 min (LC4).

Step 3: Methyl 2-(4-(5-(4,6-dichloro-N-(2-hydroxyethyl)-2-(methylthio)pyrimidine-5-carboxamido)pyridin-2-yl)cyclohexyl)acetate (2.4)

Methyl 2-(4-(5-(N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,6-dichloro-2-(methylthio)pyrimidine-5-carboxamido)pyridin-2-yl)cyclohexyl)acetate from Step 2 above (14.13 g, 22.51 mmol) was dissolved in methanol (200 ml) and cooled in an ice-water bath, followed by drop-wise addition of concentrated aq. HCl (9.24 ml, 113 mmol). The mixture was stirred at RT for 2 hrs and concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc and washed with saturated solutions of $NaHCO_3$ and brine. The organic layer was separated, dried over $MgSO_4$, and concentrated to afford crude product as off-white foamy solid which was carried on to the next step without further purification. LC-MS (m/z): 513.1/515/517.1 ($M + H^+$), 1.12 min (LC2).

Step 4: Methyl (4-{5-[4-chloro-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl]pyridin-2-yl}cyclohexyl)acetate (2.5)

A mixture of methyl 2-(4-(5-(4,6-dichloro-N-(2-hydroxyethyl)-2-(methylthio)pyrimidine-5-carboxamido)pyridin-2-yl)cyclohexyl)acetate (23.3 g, 45.5 mmol) prepared as described in Step 3 above and DIEA (31.7 mL, 182 mmol) in acetonitrile (300 ml) was heated at 80°C overnight. After cooling, the reaction mixture was concentrated under vacuum, dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a semi-solid. MeOH (50 ml) was added to this residue and the resulting mixture stirred at 50°C for 15 minutes and then at RT for 20 minutes. The solid was filtered, washed with MeOH, and dried under vacuum to give the title compound as white solid. The mother liquid was concentrated and purified on a silica gel column using a gradient of 0~95% ethyl acetate in hexanes to give a second crop of the title compound as light yellow solid. LC-MS (m/z): 476.91/478.86 ($M + H^+$), 1.07 min (LC2).

Step 5: Methyl 2-(4-(5-(4-amino-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetate (2.6)

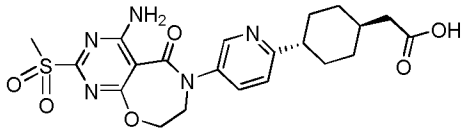
Methyl (4-{5-[4-chloro-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl]pyridin-2-yl}cyclohexyl)acetate (0.37 g, 0.78 mmol) from Step 4 and 0.5 M ammonia in dioxane (8.0 ml) were mixed in a sealed tube and heated at 50°C until no starting chloride was observed in LC-MS. The mixture was concentrated under vacuum and dissolved in ethyl acetate, washed with water, and concentrated to dryness. The resulting crude product was re-dissolved into mixture of acetonitrile and water and dried in a lyophilizer to give the title compound as light yellow solid. LC-MS (m/z): 458.02 ($M + H^+$), 1.31 min (LC4).

Step 6: 2-(4-(5-(4-Amino-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid (2)

The methyl 2-(4-(5-(4-amino-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetate (0.32 g, 0.69 mmol) from Step 5 above was dissolved in THF (4.0 ml) followed by addition of 0.5 M LiOH solution (4.2 ml). The mixture was stirred at 50°C for 2 hours; then concentrated to remove most solvent. The residue was dissolved in water (6 ml) and acidified with 1 N aq. HCl solution (2.0 ml) to give white precipitate. The solid was filtered, washed with water, and dried under vacuum to give Preparative Example 2 as a mixture of *trans*- and *cis*- isomers. LC-MS (m/z): 444.08 ($M + H^+$), 1.10 min (LC4).

The *trans*- and *cis*- mixture was then separated on SFC using a ChiralPak OJ column eluting with 40~60% MeOH in CO_2 containing 0.2% DEA to give *trans*-isomer and *cis*-isomer respectively as diethylamine salts. The *trans*-isomer DEA salt was then converted to free form **2a** by stirring in acetonitrile at RT overnight while the *cis*-isomer salt was dissolved in a minimum amount of 1,4-dioxane and water mixture (1:2) and acidified with 1 N HCl to pH 5 to precipitate neutral *cis*-isomer **2b**. **2a**: ^{1}H NMR (CD_3OD, 500 MHz) □ 8.48 (d, 2.3 Hz, 1H), 7.77 (dd, 8.5 & 2.3 Hz, 1H), 7.43 (d, 8.4 Hz, 1 H), 4.69 (t, 4.4 Hz, 2H), 4.08 (t, 4.5 Hz, 2H), 2.71~2.77 (m, 1H), 2.51 (s, 3H), 2.22 (d, 7.1 Hz, 2H), 1.98 (d, 12.1 Hz, 4H), 1.83~1.93 (m, 1H), 1.62~1.70 (m, 2H), 1.19~1.27 (m, 2H). **2b**: ^{1}H NMR (CD_3OD, 500 MHz) □ 8.50 (d, 2.4 Hz, 1H), 7.78 (dd, 8.4 & 2.5 Hz, 1H), 7.46 (d, 8.5 Hz, 1H), 4.70 (t, 4.5 Hz, 2H), 4.08 (t, 4.6 Hz, 2H), 2.82~2.89 (m, 1H), 2.51 (s, 3H), 2.46 (d, 7.5 Hz, 2H), 2.25~2.31 (m, 1H), 1.86~1.95 (m, 2H), 1.68~1.80 (m, 6H).

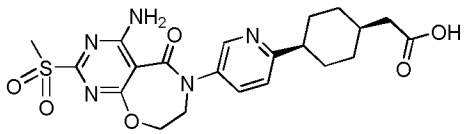
Preparative Example 3



2-(*Trans*-4-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid

To a suspension of *trans*-2-(4-(5-(4-amino-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid from Preparative Example **2a** (1.52 g, 3.43 mmol) in 1,4-dioxane (30 ml) was added drop-wise a solution of 4 M HCl in 1,4-dioxane (1.9 ml). The mixture was stirred for 15 minutes at RT and concentrated to dryness under vacuum. The resulting solid was treated with oxone (4.21 g, 6.85 mmol) and tetrabutylammonium hydrogen sulfate (0.12 g, 0.34 mmol) in DMA (25 ml). The reaction mixture was vigorously stirred at RT for 4 hr, and quickly poured into cold water (150 ml) with stirring. The resulting solution formed precipitates on standing at 4°C overnight. The mixture was filtered and the solid was washed with water and dried under vacuum to give Preparative Example 3. LC-MS: 1.11 min. (LC4), m/Z 476.08 ($M + H^+$). ^1H NMR (DMSO-d_6, 500 MHz) □ 12.0 (v br s, 1H), 8.54 (d, 2.4 Hz, 1H), 8.46 (br s, 1H), 8.06 (br s, 1H), 7.76 (dd, 8.4 & 2.3 Hz, 1H), 7.37 (d, 8.4 Hz, 1H), 4.74 (t, 4.3 Hz, 2H), 4.11 (t, 4.3 Hz, 2H), 3.27 (s, 3H), 2.63~2.70 (m, 1H), 2.16 (d, 7.1 Hz, 2H), 1.82~1.91 (m, 4H), 1.68~1.77 (m, 1H), 1.51~1.61 (m, 2H), 1.08~1.18 (m, 2H).

Preparative Example 4

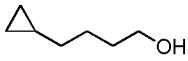


2-(*Cis*-4-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid

To a suspension of *cis*-2-(4-(5-(4-amino-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid from Preparative Example **2b** (1.18 g, 2.66 mmol) in 1,4-dioxane (20 ml) was added drop-wise a solution of 4 M HCl in 1,4-dioxane (1.36 ml). The mixture was stirred for 15 minutes at RT and was then concentrated to dryness under vacuum. The resulting solid was dissolved in DMA (20 ml) followed by the addition of oxone (3.34 g, 5.44 mmol) and tetrabutylammonium hydrogen sulfate (0.045 g, 0.13 mmol). After vigorously stirring at RT for 5 hrs, the reaction mixture was poured into cold

water (20 ml) and precipitated immediately and the precipitate was removed by filtration. The filtrate was adjusted to pH 5 by the addition of 1 N Na_2CO_3 solution. The resulting solution afforded a precipitate on standing at 4°C overnight. The mixture was filtered and the solid was washed with water and dried under vacuum to give Preparative Example 4. LC-MS: 1.04 min. (LC4), m/Z 476.07 ($M + H^+$). ^1H NMR (DMSO-d_6, 500 MHz) □ 11.97 (v br s, 1H), 8.56 (s, 1H), 8.46 (br s, 1 H), 8.07 (br s, 1H), 7.79 (d, 7.8 Hz, 1H), 7.42 (d, 8.1 Hz, 1H), 4.75 (t, 4.4 Hz, 2H), 4.12 (t, 4.3 Hz, 2H), 3.28 (s, 3H), 2.75~2.83 (m, 1H), 2.32 (d, 7.5 Hz, 2H), 2.10~2.17 (m, 1H), 1.79~1.86 (m, 2H), 1.59~1.69 (m, 4H), 1.51~1.59 (m, 2H).

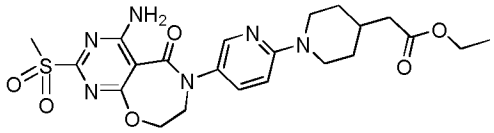
Preparative Example 5



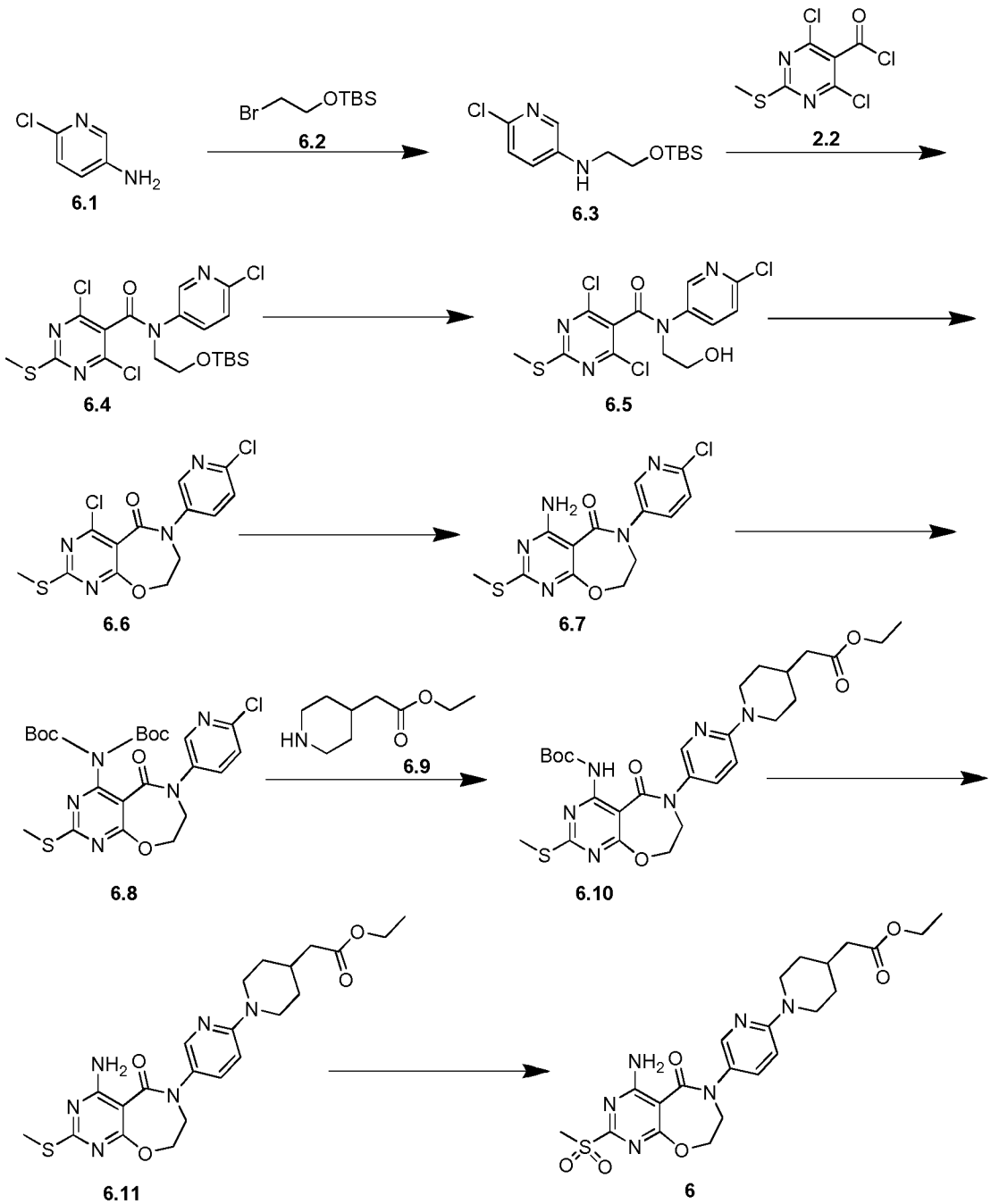
4-Cyclopropylbutan-1-ol

In a 1-L 3-necked round bottom flask, diethylzinc (341 mL, 341 mmol) in heptane was added to CH_2Cl_2 (749 ml) at 0 to -10°C in an ice-acetone bath, followed by addition of TFA (25.0 ml, 324 mmol) while keeping internal temperature <10°C. The reaction was stirred at 0°C for 30 min to give a white cloudy suspension, then was treated with diiodomethane (27.5 mL, 341 mmol) slowly for 30 minutes while keeping internal temperature <10°C. After the addition of diiodomethane, the reaction mixture was stirred at 0°C for 30 minutes, then treated with a solution of 5-hexen-1-ol (20.5 mL, 171 mmol) in CH_2Cl_2. The reaction mixture was allowed to warm up and stirred at RT and the progress of the reaction was monitored by NMR. The reaction was complete within 1.5 hr. The suspension turned clear and it was quenched with 6 N HCl. The mixture was extracted with MTBE and hexanes. The combined organic phase was washed with 2 N NaOH and brine, then dried over $MgSO_4$ and concentrated. The residue was purified on a silica gel column using a gradient of 0-40% EtOAc in hexanes to give title compound as clear oil. ^1H NMR ($CDCl_3$, 400 MHz) □ 3.68 (t, 6.6 Hz, 2H), 1.60~1.68 (m, 2H), 1.44~1.52 (m, 2H), 1.23~1.28 (m, 2H), 0.63~0.73 (m, 1H), 0.39~0.48 (m, 2H), -0.07~0.09 (m, 2H).

Preparative Example 6



Ethyl 2-(1-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetate



Step 1: *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-chloropyridin-3-amine (6.3)

6-Chloropyridine-3-amine (22.0 g, 171 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (49.1 g, 205 mmol) were dissolved in THF (500 ml), then treated with a suspension of NaH (8.21 g, 205 mmol, 60% oil dispersion) in hexanes. After stirring at 50 °C for 2 hours, the reaction mixture was quenched with water (100 ml) and extracted with MTBE (2x100 mL). The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated. The resulting crude product was purified on a silica gel column using a gradient of 0-20% EtOAc in hexanes to give the title compound. LC-MS (m/z): 287.16/289.14 ($M + H^+$), 2.28 min (LC4).

Step 2: *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4,6-dichloro-*N*-(5-chloropyridin-2-yl)-2-(methylthio)pyrimidine-5-carboxamide (6.4)

A solution of *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-chloropyridin-3-amine from Step 1 above (23.0 g, 80 mmol), DIEA (42 mL, 241 mmol) and catalytic amount of DMAP in CH_2Cl_2 (100 ml) was treated with a solution of 4,6-dichloro-2-(methylthio)pyrimidine-5-carbonyl chloride hydrochloride in CH_2Cl_2 (200 mL). This acid chloride was prepared using the procedure in Step 1 of Preparative Example 2 from 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (33.5 g, 140 mmol). After stirring at RT overnight, the reaction mixture was diluted with EtOAc (300 ml) and washed with saturated $NaHCO_3$ solution. The organic layer was separated, dried over Na_2SO_4, and concentrated. The resulting crude product was purified on silica gel using a gradient of 0-20% EtOAc in hexanes to afford the title compound as white solid after precipitation from a mixture of MTBE and hexanes. LC-MS (m/z): 507.08/509.09/511.09/513 ($M+H^+$), 2.64 min (LC4).

Step 3: 4,6-Dichloro-*N*-(5-chloropyridin-2-yl)-*N*-(2-hydroxyethyl)-2-(methylthio)pyrimidine-5-carboxamide (6.5)

A suspension of *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4,6-dichloro-*N*-(5-chloropyridin-2-yl)-2-(methylthio)pyrimidine-5-carboxamide from Step 2 above (37.0 g, 70.3 mmol) in MeCN (200 ml) was stirred vigorously to obtain a clear solution, followed by addition of 5 N HCl in isopropyl alcohol (42.2 ml, 211 mmol). After stirred at RT overnight, the solvent was removed under reduced pressure. The residue oil was dissolved in MeCN and concentrated to dryness three times to give title compound as yellowish foam. LC-MS (m/z): 393.01/395.00/396.99/399.0 ($M + H^+$), 1.57 min (LC4).

Step 4: 4-Chloro-6-(6-chloropyridin-3-yl)-2-(methylthio)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (6.6)

To a suspension of the crude product from Step 3 in MeCN (200 ml) was added DIEA (36.8 mL, 211 mmol). After heating at 80°C overnight, the mixture was cooled to RT, concentrated to ~80 mL under reduced pressure, filtered, and washed with MeCN to afford title compound as an off-white solid. LC-MS (m/z): 357.05/359/361.06 ($M + H^+$), 1.42 min (LC4).

Step 5: 4-Amino-6-(6-chloropyridin-3-yl)-2-(methylthio)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (6.7)

To a solution of 4-chloro-6-(6-chloropyridin-3-yl)-2-(methylthio)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (15.7 g, 44.0 mmol) from Step 4 above in CH_2Cl_2 (100 ml) was charged ammonia (25.1 mL, 176 mmol). The reaction mixture was warmed to 40 °C for 1 hr; then stirred at RT for 24 hr. The solvent was removed under reduced pressure and the resulting mixture was suspended in a mixture of MTBE and CH_2Cl_2 and filtered. The combined crude product was slurried with water, filtered, and dried in a vacuum oven to afford the title compound as white powder. LC-MS (m/z): 338.11/340.12 ($M + H^+$), 1.16 min (LC4). ^1H NMR (CD_3OD, 500 MHz) □ 8.43 (d, 2.8 Hz, 1H), 7.86 (dd, 8.5 & 2.8 Hz, 1H), 7.54 (d, 8.5 Hz, 1H), 4.68 (t, 4.6 Hz, 2H), 4.58 (br s, 2H), 4.08 (t, 4.6 Hz, 2H), 2.50 (s, 3H).

Step 6: 4-(Di-tert-butoxycarbonyl)amino-6-(6-chloropyridin-3-yl)-2-(methylthio)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (6.8)

4-Amino-6-(6-chloropyridin-3-yl)-2-(methylthio)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (0.700 g, 2.07 mmol) from Step 5 above and DMAP (0.063 g, 0.25 mmol) were mixed in DMF (10 ml), then treated with di-*tert*-butyl dicarbonate (1.36 g, 6.22 mmol). After stirring at RT overnight, the reaction mixture was diluted with EtOAc and washed with saturated solution of $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, and concentrated. The crude product was purified on silica gel using a gradient of 0~80% EtOAc in hexanes to afford the title compound as white solid. LC-MS (m/z): 538.06/540 ($M + H^+$), 2.17 min (LC4)

Step 7: Ethyl 2-(1-(5-(4-((tert-butoxycarbonyl)amino)-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetate (6.10)

A mixture of intermediate 6.8 (0.30 g, 0.56 mmol) and commercially available ethyl 2-(piperidin-4-yl)acetate (0.14 g, 0.84 mmol) in 1,4-dioxane (2.6 ml) was treated with 2-dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl (0.013 g, 0.028 mmol) and RuPhos indoline precatalyst (0.020 g, 0.028 mmol, {2-[2-(azanidyl-κ*N*)ethyl]phenyl-κC^1}{[2',6'-bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)-λ^5-phosphanyl}chloropalladium). The mixture was degassed by purging with nitrogen, followed by addition of sodium *tert*-butoxide (0.058 g, 0.59 mmol). After purging with nitrogen again, this mixture was heated at 90°C in a sealed tube for 16 hr. It was then cooled to RT and quenched with water. The mixture was extract with ethyl acetate and the combined organic layers were washed with water and brine, and dried over Na_2SO_4. The crude product was purified on silica gel using a gradient of 50~100% ethyl acetate in hexanes to give the title compound. LC-MS (m/e): 573.25 ($M + H^+$), 1.75 min (LC4).

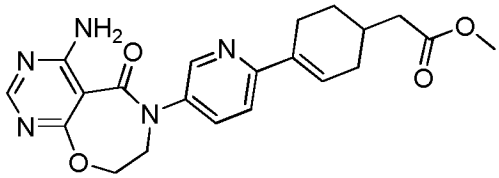
Step 8: Ethyl 2-(1-(5-(4-amino-2-(methylthio)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetate (6.11)

A solution of intermediate 6.10 (0.10 g, 0.18 mmol) and anisole (0.038 g, 0.35 mmol) in DCM (1.5 ml) was treated with TFA (0.15 ml, 1.95 mmol). After stirring at RT overnight, the volatiles were removed under vacuum to give the title compound as TFA salt, which was used directly in the subsequent step. LC-MS (m/e): 473.21 ($M + H^+$), 1.32 min (LC4).

Step 9: Ethyl 2-(1-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetate (6)

The intermediate 6.11 (0.12 g, 0.17 mmol) was dissolved in DMA (1.5 ml) followed by the addition of oxone (0.27 g, 0.44 mmol) and tetrabutylammonium hydrogen sulfate (0.003 g, 0.008 mmol). After vigorously stirring at RT overnight, the reaction mixture was quenched with a mixture of DMSO and water; and directly purified by RP-HPLC and lyophilization to afford Preparative Example 6. LC-MS (m/z): 505.3 ($M + H^+$), 1.17 min (LC4). ^1H NMR (CD_3OD, 500 MHz) □ 8.08 (d, 2.5 Hz, 1H), 7.96 (d, 9.3 Hz, 1H), 7.35 (d, 9.5 Hz, 1H), 4.79~4.81 (m, 2H), 4.21~4.24 (m, 2H), 4.15 (q, 7.0 Hz, 2H), 4.08~4.10 (m, 2H), 3.28 (s, 3H), 3.24~3.29 (m, 2H), 2.35 (d, 6.9 Hz, 2H), 2.14~2.23 (m, 1H), 1.96 (d, 13.3 Hz, 2H), 1.37~1.45 (m, 2H), 1.26 (t, 7.1 Hz, 3H).

Example 1



Methyl {4-[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohex-3-en-1-yl}acetate

Step 1. 4,6-Dichloropyrimidine-5-carbonyl chloride hydrochloride

Add oxalyl chloride (2.68 mL, 30.6 mmol) to a suspension of 4,6-dichloropyrimidine-5-carboxylic acid (1.97 g, 10.21 mmol) in 20 mL DCM at 0°C followed by one drop of DMF. Let this mixture warm to RT and stir overnight. After removing volatiles, the crude product was used in Step 2 below directly.

Step 2. 4,6-Dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide

Add a solution of 5-amino-2-iodopyridine (0.800 g, 3.45 mmol) and TEA (1.398 g, 1.93 mL, 13.82 mmol) in 5.0 mL THF drop-wise to a suspension of 4,6-dichloropyrimidine-5-carbonyl chloride hydrochloride (1.096 g, 4.42 mmol) from Step 1 above in 5.0 mL THF at 0°C. Stir at 0°C for 15 min and allow the reaction mixture to warm to RT over 2.5 hr. The residue after removal of volatiles was purified on silica gel column using 0~60% EtOAc gradient in hexanes to give the title compound. LC-MS: 1.73 min. (LC4, m/Z 395.0/396.9/398.9). HPLC 5.09 min. ^{1}H NMR ($CDCl_3$, 500 MHz) □ 8.90 (s, 1H), 8.48 (d, 2.7 Hz, 1H), 8.01 (dd, 2.8 & 8.6 Hz, 1H), 7.80 (d, 8.6 Hz, 1H), 7.76 (br s, 1H).

Step 3. *N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,6-dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide

Step 3-A. 2-{[*Tert*-butyl(dimethyl)silyl]oxy}ethyl trifluoromethanesulfonate

Added a solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}ethanol (134 mg, 0.760 mmol) and 2,6-di-tertbutylpyridine (152 mg, 0.795 mmol) in 0.5 mL DCM drop-wise to a solution of trifluomethanesulfonic anhydride (0.134 mL, 0.795 mmol) in 1.0 mL DCM at -20°C. After stirring at -20°C for 15 min., the reaction mixture was diluted with 2.0 mL hexanes and stirred vigorously at -78°C for 10 min. to give a white suspension. This mixture was filtered through a pad of anhydrous Na_2SO_4 into a pre-cooled (-70°C) flask and the solid was washed with 2 mL

hexanes. The combined filtrate and wash was transferred quickly into another flask via a cannula for use in Step 3-B directly.

Step 3-B. *N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,6-dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide

4,6-Dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide (200 mg, 0.506 mmol) from Step 2 above was dissolved in 1.0 mL THF and cooled to -23°C. A solution of NaHMDS (0.59 M, 0.90 mL, 0.532 mmol) in THF was added. After stirring at -20°C for 45 minutes, 2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl trifluoromethanesulfonate from Step 3-A above was added. This reaction mixture was stirred at -20°C, 0°C and RT for 15, 30, and 90 min., respectively, before being quenched with saturated ammonium chloride solution. The resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed with water and saturated brine, dried over anhydrous Na_2SO_4, solvents removed, and the residue purified on silica gel using 0~60% EtOAc gradient in hexanes to give title compound followed by recovered starting material. LC-MS: 2.66 min. (LC4, m/Z 553.0/555/57.1). ^{1}H NMR ($CDCl_3$, 500 MHz) □ 8.71 (s, 1H), 8.43 (d, 2.9 Hz, 1H), 7.67 (d, 8.2 Hz, 1H), 7.51 (dd, 2.8 & 8.3 Hz, 1H), 4.02~4.05 (m, 2H), 3.96~3.99 (m, 2H), 0.89 (s, 9H), 0.09 (s, 6H).

Step 3-alternative. *N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,6-dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamideStep 3-A-alternative. *Tert*-butyl(2-iodoethoxy)dimethylsilane

A solution of (2-bromoethoxy)(*tert*-butyl)dimethylsilane (500 mg, 0.45 mL, 2.09 mmol) and sodium iodide (470 mg, 3.14 mmol) in 5.0 mL acetone was heated at 70°C with stir overnight. After cooling, solids were removed by filtration and the solid was washed with EtOAc. The combine filtrate and wash was evaporated to give pure title compound. ^{1}H NMR ($CDCl_3$, 500 MHz) □ 3.85 (t, 6.9 Hz, 2H), 3.22 (t, 7.0 Hz, 2H), 0.93 (s, 9H), 0.11 (s, 6H).

Step 3-B-alternative. *N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,6-dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide

Add NaH (76 mg, 60% oil dispersion, 1.90 mmol) to a solution of 4,6-dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide (200 mg, 1.266 mmol) from Step 2 above in 2.50 mL DMF at -20°C. This mixture was stirred for 30 min. A solution of *tert*-butyl(2-iodoethoxy)dimethylsilane from Step 3-A-alternative above (725 mg, 2.53 mmol) in 1.5 mL DMF was added at -20°C. This reaction mixture was stirred at -20°C to 0°C for 30 minutes and

then it was heated at 40°C for 22 hrs. This reaction mixture was allowed to age over a weekend at RT before being quenched with saturated ammonium chloride solution. The resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed with water and saturated brine, dried over anhydrous Na_2SO_4, solvents removed, and the residue purified on silica gel using 0~70% EtOAc gradient in hexanes to give title compound followed by some recovered starting material. The title compound showed the same LC-MS and NMR as the material from Step 3-A above.

Step 4. 4,6-Ddichloro-*N*-(2-hydroxyethyl)-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide hydrochloride

To a solution of *N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,6-dichloro-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide (110 mg, 0.199 mmol) from Step 3 above in 2.5 mL MeOH was added 0.082 mL (0.994 mmol) of 37% HCl. After stirring at RT for 5 hrs, the solvent was removed on a rotary evaporator and the residue was lyophilized from MeCN/water to give the title compound. LC-MS: 1.43 min. (LC4, m/Z 438.9/440.9/443.0). ^{1}H NMR ($CDCl_3$, 500 MHz) □ 8.71 (s, 1H), 8.47 (d, 2.8 Hz, 1H), 7.69 (d, 8.4 Hz, 1H), 7.51 (dd, 2.9 & 8.4 Hz, 1H), 4.09 (t, 5.2 Hz, 2H), 3.99 (t, 5.2 Hz, 2H).

Step 5. 4-Chloro-6-(6-iodopyridin-3-yl)-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-5(6*H*)-one

A mixture of 4,6-dichloro-*N*-(2-hydroxyethyl)-*N*-(6-iodopyridin-3-yl)pyrimidine-5-carboxamide hydrochloride from Step 4 above (90 mg, 0.189 mmol) and DIEA (0.132 mL, 0.757 mmol) in 2 mL of acetonitrile was heated at 80°C for 15 hr. After the removal of volatiles, the residue was purified on silica gel column using 30~100% EtOAc gradient in hexanes to give the title compound. LC-MS: 1.32 min. (LC4, m/Z 403.0/404.9). HPLC 4.58 min. ^{1}H NMR ($CDCl_3$, 500 MHz) □ 8.80 (s, 1H), 8.43 (d, 2.7 Hz, 1H), 7.84 (d, 8.5 Hz, 1H), 7.50 (dd, 2.9 & 8.5 Hz, 1H), 4.77 (t, 4.9 Hz, 2H), 4.10 (t, 4.9 Hz, 2H).

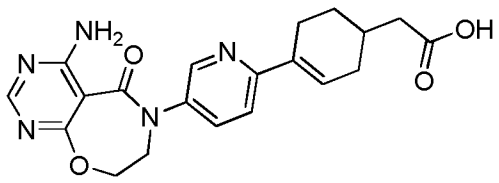
Step 6. 4-Amino-6-(6-iodopyridin-3-yl)-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-5(6*H*)-one

Add 3.25 mL 0.5 M ammonia in dioxane to 4-chloro-6-(6-iodopyridin-3-yl)-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-5(6*H*)-one from Step 5 above (131 mg, 0.325 mmol). This mixture was stirred at 50°C overnight. After removal of solvent, the crude product (containing ammonium chloride side-product) was used directly in the next step. LC-MS: 0.53 min. (LC4, m/Z 384.0). ^{1}H NMR (DMSO-d_6, 500 MHz) □ 8.47 (br s, 1H), 8.18 (br s, 1H), 7.92 (br d, 8.5 Hz, 1H), 7.61~7.67 (m, 3H), 4.62 (br, 2H), 4.03 (br, 2H).

Step 7. Methyl {4-[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohex-3-en-1-yl}acetate

Mix crude 4-amino-6-(6-iodopyridin-3-yl)-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-5(6*H*)-one from Step 6 above (50 mg, 0.115 mmol), methyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]acetate from Preparative Example 1 Step 2 (32.2 mg, 0.115 mmol), and cesium carbonate (56.2 mg, 0.173 mmol) in 0.8 mL THF. Purge with nitrogen and add tetrakis(triphenylphosphine)palladium (13.3 mg, 0.012 mmol). Purge with nitrogen for 2 minutes. This mixture was heated in a capped vial at 80°C for 17 hr. The solvent was removed and the residue was purified on RP-HPLC using 20~100% and 10~50% MeCN gradient in water containing 0.05% TFA to give title cpd. LC-MS: 1.32 min. (LC4, m/Z 410.3). HPLC 4.32 min. DGAT1 (human) IC_{50} 544 nM.

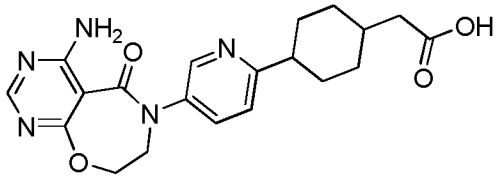
Example 2



{4-[5-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohex-3-en-1-yl}acetic acid

Add LiOH (0.5 M, 0.104 mL, 0.052 mmol) to a solution of methyl {4-[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohex-3-en-1-yl}acetate (9.1 mg, 0.017 mmol) from Step 7 Example 1 in 0.2 mL dioxane and heat the mixture at 50°C for 1 hr. This mixture was diluted with dioxane/water, acidified with TFA, and purified directly on RP-HPLC to give the title compound. LC-MS: 0.81 min. (LC4, m/Z 396.1. DGAT1 (human) IC_{50} 255 nM.

Example 3



Cis and trans-{4-[5-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohexyl}acetic acidStep 1. Di-*tert*-butyl [6-(6-iodopyridin-3-yl)-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-*f*][1,4]oxazepin-4-yl]imidodicarbonate

Stir a mixture of 4-amino-6-(6-iodopyridin-3-yl)-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-5(6*H*)-one (50 mg, 0.13 mmol) from Step 6, Example 1, di-t-butyl dicarbonate (0.091 mL, 0.391 mmol), and DMAP (3.2 mg, 0.026 mmol) in 0.5 mL DMF at RT overnight. Dilute the reaction mixture with 100 mL EtOAc, wash with saturated $NaHCO_3$, water, and saturated brine, dry with anhydrous Na_2SO_4 and concentrate by removal of solvents. The residue was purified on silica gel using 0~70% EtOAc gradient in hexanes to give the title compound. LC-MS: 1.92 min. (LC4, m/Z 584.1, 606.1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.84 (s, 1H), 8.43 (d, 2.3 Hz, 1H), 7.79 (d, 8.5 Hz, 1H), 7.48 (dd, 2.7 & 8.4 Hz, 1H), 4.72 (t, 5.1 Hz, 2H), 4.11 (t, 5.0 Hz, 2H), 1.50 (s, 18H).

Step 2. Methyl [4-(5-{4-[bis(*tert*-butoxycarbonyl)amino]-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl}pyridin-2-yl)cyclohex-3-en-1-yl]acetate

Mix di-*tert*-butyl [6-(6-iodopyridin-3-yl)-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-*f*][1,4]oxazepin-4-yl]imidodicarbonate from Step 1 above (63.8 mg, 0.109 mmol), methyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]acetate from Preparative Example 1 Step 2 (36.8 mg, 0.131 mmol), and cesium carbonate (53.4 mg, 0.164 mmol) in 1.0 mL THF. Purge with nitrogen and add tetrakis(triphenylphosphine)palladium (12.6 mg, 0.011 mmol). Purge with nitrogen for 2 minutes. This mixture was heated in a capped vial at 80°C for 15 hr. Following aqueous work-up using EtOAc, the residue was purified on silica gel using 0~90% EtOAc gradient in hexanes to give the title compound. LC-MS: 1.90 min. (LC4, m/Z 610.3).

Step 3. Cis- and trans-methyl [4-(5-{4-[bis(*tert*-butoxycarbonyl)amino]-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl}pyridin-2-yl)cyclohexyl]acetate

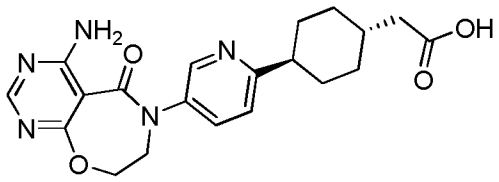
Dissolve methyl [4-(5-{4-[bis(*tert*-butoxycarbonyl)amino]-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl}pyridin-2-yl)cyclohex-3-en-1-yl]acetate from Step 2 above (20 mg, 0.033 mmol) in 1.0 mL methanol, purge with nitrogen, add 0.7 mg platinum oxide and hydrogenate using a hydrogen balloon for 105 minutes. At that time, LC-MS showed no starting material and mainly the desired product: 1.84 min. (LC4, m/Z 612.2). Filter to remove the catalyst and concentrate to give the title compound. This material was used directly in the next step.

Step 4. Cis- and trans-methyl {4-[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohexyl}acetate

Dissolve cis- and trans-methyl [4-(5-{4-[bis(*tert*-butoxycarbonyl)amino]-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl}pyridin-2-yl)cyclohexyl]acetate from Step 3 above (23 mg, 0.038 mmol) and anisole (8.1 mg, 0.082 μL) in 0.5 mL DCM and add TFA (0.049 μL). Let the mixture stir at RT overnight. After removal of solvents, the residue was purified on RP-HPLC using 0~40% MeCN gradient in water containing 0.05% TFA to give the title compounds. HPLC 1.64 and 1.75 min. LC-MS: 1.03 min. (LC4, m/Z 412.1) and 1.08 min. (m/Z 412.1).

Step 5. Cis- and trans-{4-[5-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohexyl}acetic acidDissolve cis- and trans-methyl {4-[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohexyl}acetate (10.7 mg, 0.020 mmol) in 0.25 mL dioxane and add a 0.5 M aqueous LiOH solution (0.244 mL, 0.122 mmol). After heating this mixture at 50°C for 3 hrs, this mixture was cooled, diluted with dioxane/water, acidified with TFA, and purified on RP-HPLC using 0~50% MeCN gradient in water containing 0.05% TFA to give the title compounds. HPLC 3.33 min. LC-MS: 0.47 min. (LC4, m/Z 398.1) and 0.54 min. (m/Z 398.1). DGAT1 (human) IC_{50} 157 nM.

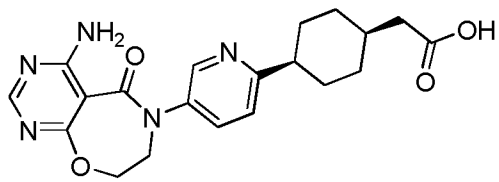
Example 4



Trans-{4-[5-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohexyl}acetic acid

The title compound was isolated as the fast-eluting isomer from SCF separation of the cis- and trans- mixture from Example 3 on a ChiralPak AS column using 25% MeOH (0.2% triethylamine) in CO_2. The triethylamine can be removed by re-purifying the separated isomer on RP-HPLC. LC-MS: 0.25 min. (LC4, m/Z 398.1). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.48 (s, 1H), 8.18 (s, 1H), 7.79 (d, 8.8 Hz, 1H), 7.44 (d, 8.8 Hz, 1H), 4.73~4.75 (m, 2H), 4.08~4.10 (m, 2H), 2.72~2.76 (m, 1H), 2.16 (d, 6.7 Hz, 2H), 1.98 (d, 11.6 Hz, 4H), 1.83~1.92 (m, 1H), 1.62~1.69 (m, 2H), 1.17~1.24 (m, 2H). The stereochemistry was assigned based on comparison of its NMR with those of the two isomers from Preparative Example 2. DGAT1 (human) IC_{50} 470 nM.

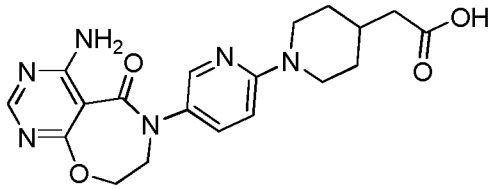
Example 5



Cis-{4-[5-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]cyclohexyl}acetic acid

The title compound was isolated as the slower-eluting isomer from SCF separation of the cis- and trans- mixture from Example 3 on a ChiralPak AS column using 25% MeOH (0.2% triethylamine) in CO_2. The triethylamine can be removed by re-purifying the separated isomer on RP-HPLC. LC-MS: 0.45 min. (LC4, m/Z 398.1). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.51 (s, 1H), 8.18 (s, 1H), 7.79 (d, 8.6 Hz, 1H), 7.49 (d, 8.6 Hz, 1H), 4.74~4.76 (m, 2H), 4.10~4.12 (m, 2H), 2.82~2.89 (m, 1H), 2.39 (d, 7.6 Hz, 2H), 2.25~2.31 (m, 1H), 1.88~1.96 (m, 2H), 1.70~1.79 (m, 6H). The stereochemistry was assigned based on comparison of its NMR with those of the two isomers from Preparative Example 2. DGAT1 (human) IC_{50} 288 nM.

Example 6



{1-[5-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]piperidin-4-yl}acetic acid

Step 1. Ethyl [1-(5-nitropyridin-2-yl)piperidin-4-yl]acetate

To a solution of 2-fluoro-5-nitropyridine (2.000 g, 14.08 mmol) and 2-(piperidine-4-yl)-acetic acid ethyl ester (2.410 g, 14.08 mmol) in 30 mL NMP was added sodium bicarbonate (3.5 g, 42.2 mmol). The reaction mixture was stirred at RT over night and was worked up using EtOAc extraction following addition of water. The crude product thus obtained was purified on silica gel using 0~50% gradient of EtOAc to give 3.98 g title compound as a bright yellow solid. LC-MS: 1.75 min. (LC4, m/Z 294.15). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.02 (d, 2.8 Hz, 1H), 8.18 (dd, 9.5 & 2.8 Hz, 1H), 6.56 (d, 9.6 Hz, 1H), 4.53 (br d, 12.0 Hz, 2H), 4.15 (q, 7.1 Hz, 2H), 3.01~3.06 (m, 2H), 2.28 (d, 7.1 Hz, 2H), 2.11~2.21 (m, 1H), 1.89 (d, 13.0 Hz, 2H), 1.27 (t, 7.1 Hz, 3H), 1.24~1.33 (m, 2H).

Step 2. Ethyl [1-(5-aminopyridin-2-yl)piperidin-4-yl]acetate

A mixture of ethyl [1-(5-nitropyridin-2-yl)piperidin-4-yl]acetate (2.00 g, 6.82 mmol) from Step 1 above and 0.363 g 10% Pd/C in 60 mL ethanol with 0.50 mL water was treated with hydrogen for 4 hrs. The mixture was filtered and concentrated to give the title compound as reddish oil. This crude product was used in the next step as is. LC-MS: 0.56 min. (LC4, m/Z 264.23). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, 2.8 Hz, 1H), 6.98 (dd, 8.9 & 2.9 Hz, 1H), 6.59 (d, 8.8 Hz, 1H), 4.14 (q, 7.1 Hz, 2H), 4.03 (br d, 12.7 Hz, 2H), 3.3 (v br s, 2H), 2.71~2.77 (m, 2H), 2.26 (d, 7.1 Hz, 2H), 1.95~2.05 (m, 1H), 1.80 (d, 12.8 Hz, 2H), 1.31~1.39 (m, 2H), 1.26 (t, 7.1 Hz, 3H).

Step 3. Ethyl [1-(5-{(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)[(4,6-dichloropyrimidin-5-yl)carbonyl]amino}pyridin-2-yl)piperidin-4-yl]acetate

Add crude ethyl [1-(5-aminopyridin-2-yl)piperidin-4-yl]acetate (1.59 g, 6.04 mmol) from Step 2 above and 100 mg 4A molecular sieve to a solution of (tert-butyldimethylsilyloxy)-acetaldehyde (1.406 g, 6.64 mmol) in 1,2-dichloroethane (30 ml). After stirring for 45 minutes at RT, sodium

triacetoxyborohydride (1.920 g, 9.06 mmol) was added and the mixture was stirred at RT overnight. The reaction was quenched by addition of 100 mL 1N NaOH solution. After stirring for 1 hr at RT, the layers were separated and the organic layer was washed with 1N NaOH, water, and brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified on silica gel using 0~50% gradient of EtOAc to give 1.35 g title compound as reddish oil. LC-MS: 1.92 min. (LC4, m/Z 422.23). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, 3.0 Hz, 1H), 6.95 (dd, 8.8 & 2.9 Hz, 1H), 6.62 (d, 8.8 Hz, 1H), 4.14 (q, 7.1 Hz, 2H), 4.02 (br d, 12.7 Hz, 2H), 3.79 (t, 5.3 Hz, 2H), 3.16 (t, 5.3 Hz, 2H), 2.71~2.77 (m, 2H), 2.26 (d, 7.1 Hz, 2H), 1.93~2.02 (m, 1H), 1.81 (d, 12.8 Hz, 2H), 1.31~1.41 (m, 2H), 1.27 (t, 7.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

Step 4. Ethyl [1-(5-{(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)[(4,6-dichloropyrimidin-5-yl)carbonyl]amino}pyridin-2-yl)piperidin-4-yl]acetate

A suspension of 4,6-dichloropyrimidine-5-carbonyl chloride hydrochloride (0.802 g, 3.24 mmol; see Step 1 Example 1) in 3 mL THF was added to a solution of ethyl [1-(5-{(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)[(4,6-dichloropyrimidin-5-yl)carbonyl]amino}pyridin-2-yl)piperidin-4-yl]acetate (1.20 g, 2.85 mmol) from Step 3 above and TEA (1.983 mL, 14.23 mmol) in 3 mL THF at 0°C. After stirring for 5 minutes, the cooling bath was removed and the mixture was stirred at RT for 3.5 hr. After evaporating THF under reduced pressure, the reaction mixture was diluted with EtOAc and washed with 5% $NaHCO_3$, water, and saturated brine; dried over anhydrous Na_2SO_4, and the resulting crude product purified on silica gel using a gradient of 0~40% EtOAc in hexanes to give 1.41 g title compound as gray solid. LC-MS: 2.27 min. (LC4, m/Z 596.16/98.07/600). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.61 (s, 1H), 8.13 (d, 2.8 Hz, 1H), 7.49 (dd, 9.2 & 2.8 Hz, 1H), 6.45 (d, 8.8 Hz, 1H), 4.20 (br d, 13.2 Hz, 2H), 4.14 (q, 7.2 Hz, 2H), 3.93~3.95 (m, 2H), 3.87~3.89 (m, 2H), 2.78~2.84 (m, 2H), 2.25 (d, 7.0 Hz, 2H), 1.96~2.06 (m, 1H), 1.79 (d, 11.6 Hz, 2H), 1.26 (t, 7.1 Hz, 3H), 1.19~1.27 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H).

Step 5. Ethyl [1-(5-{[(4,6-dichloropyrimidin-5-yl)carbonyl](2-hydroxyethyl)amino}pyridin-2-yl)piperidin-4-yl]acetate hydrochloride

Concentrated HCl (0.537 mL, 6.54 mmol) was added to a solution of ethyl [1-(5-{(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)[(4,6-dichloropyrimidin-5-yl)carbonyl]amino}pyridin-2-yl)piperidin-4-yl]acetate (1.30 g, 2.18 mmol) from Step 4 above in 19 mL ethanol. The mixture was stirred at RT for 4 hr and the solvent was removed under reduced pressure. The residue was re-dissolved in a mixture of acetonitrile and water and lyophilized to give 1.11 g title compound as powders. LC-MS: 1.32 min. (LC4, m/Z 482.02/483.98/486). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.75 (s, 1H), 8.15 (br s, 1H), 7.83 (d, 9.1 Hz, 1H), 6.95 (d, 9.3 Hz, 1H), 4.20 (br d, 13.1 Hz, 2H), 4.14 (q, 7.1 Hz, 2H), 3.97~4.99 (m, 2H), 3.82~3.85 (m, 2H), 2.97~3.04 (m, 2H), 2.29 (d, 7.1 Hz, 2H), 2.02~2.11 (m, 1H), 1.84 (d, 12.7 Hz, 2H), 1.24~1.32 (m, 2H), 1.26 (t, 7.1 Hz, 3H).

Step 6. Ethyl {1-[5-(4-chloro-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]piperidin-4-yl}acetate

To a solution of ethyl [1-(5-{[(4,6-dichloropyrimidin-5-yl)carbonyl](2-hydroxyethyl)amino}pyridin-2-yl)piperidin-4-yl]acetate hydrochloride (1.11 g, 2.14 mmol) from Step 5 above in acetonitrile (10 mL) was added DIEA (2.242 mL, 12.84 mmol) and the mixture was heated at 80°C overnight. Following removal of volatiles under reduced pressure and aqueous work-up using EtOAc extraction, the crude product was purified on silica gel using 50~100% EtOAc gradient to give 0.65 g title compound. LC-MS: 1.17 min. (LC4, m/Z 446.05/448.00). Analytical HPLC: single peak 2.46 min. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.76 (s, 1H), 8.15 (d, 2.8 Hz, 1H), 7.49 (dd, 9.1 & 2.8 Hz, 1H), 6.70 (d, 9.1 Hz, 1H), 4.74 (t, 4.9 Hz, 2H), 4.32 (br d, 12.9 Hz, 2H), 4.15 (q, 7.1 Hz, 2H), 3.98 (t, 4.9 Hz, 2H), 2.88~2.94 (m, 2H), 2.27 (d, 7.1 Hz, 2H), 2.04~2.12 (m, 1H), 1.82 (d, 12.7 Hz, 2H), 1.26~1.34 (m, 2H), 1.27 (t, 7.1 Hz, 3H).

Step 7. Ethyl {1-[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]piperidin-4-yl}acetate

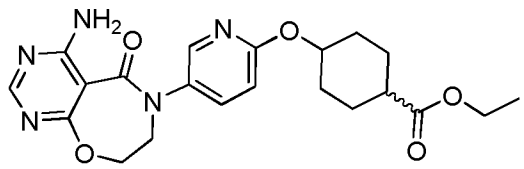
A solution of ammonia in dioxane (1.144 mL, 0.572 mmol) was added to ethyl {1-[5-(4-chloro-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]piperidin-4-yl}acetate (51 mg, 0.11 mmol) from Step 6 above and the mixture was heated at 50°C overnight. The solvent was removed under reduced pressure; the resulting residue was washed with water, re-

dissolved in water/acetonitrile, and lyophilized to give 49.4 mg title compound as off-white solid. LC-MS: 0.94 min. (LC4, m/Z 427.10). Analytical HPLC: 3.56 min. (0~100% MeCN gradient not the usual 20~100%).

Step 8. {1-[5-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]piperidin-4-yl}acetic acid, TFA salt

Aqueous solution of LiOH (0.345 mL, 0.345 mmol) was added to a solution of ethyl {1-[5-(4-chloro-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]piperidin-4-yl}acetate (49 mg, 0.115 mmol) from Step 7 above in 0.7 mL dioxane and the resulting mixture heated at 50°C 255 minutes. Another portion of 0.12 mL LiOH solution (0.12 mmol) was added and the mixture was heated at 35°C overnight. The reaction mixture was diluted with dioxane/water, acidified to pH ~4 with TFA, and purified on RP-HPLC using 0~35% MeCN gradient in water containing 0.05% (v/v) TFA. After lyophilization, the title compound was obtained as 30.3 mg solid. LC-MS: 0.21 min. (LC4, m/Z 399.14). Analytical HPLC: 3.15 min. (0~100% MeCN gradient not the usual 20~100%). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.34 (s, 1H), 8.09 (d, 2.1 Hz, 1H), 8.01 (dd, 9.8 & 2.4 Hz, 1H), 7.43 (d, 9.8 Hz, 1H), 4.90 (t, 2H; overlapping with residual water peak), 4.24 (d, 13.5 Hz, 2H), 4.17 (t, 4.3 Hz, 2H), 3.30~3.35 (m, 2H), 2.34 (d, 6.9 Hz, 2H), 2.15~2.24 (m, 1H), 2.01~2.03 (m, 2H), 1.41~1.48 (m, 2H). DGAT1 (human) IC_{50} 302 nM.

Example 7



Ethyl cis- and trans-4-{[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]oxy}cyclohexanecarboxylate

Step 1. Cis- and trans-ethyl 4-({5-[(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]pyridin-2-yl}oxy)cyclohexanecarboxylate

Add $Pd_2(dba)_3$ (0.070 g, 0.076 mmol) to a mixture of ethyl *cis*-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate (0.25 g, 0.762 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.160 g, 0.914 mmol), 2-(di-tert-butylphosphino)biphenyl (0.023 g, 0.076 mmol), and sodium tert-butoxide in THF (0.381 mL, 0.762 mmol). Flush with nitrogen for 5 minutes and the mixture in a capped vial was heated at 120°C with magnetic stir overnight. Filter the reaction mixture through a pad of Celite with EtOAc. The filtrate was washed with water and saturated

brine, dried over anhydrous sodium sulfate, and evaporated to remove solvents. The resulting crude product was purified on silica gel using 0~30% EtOAc gradient in hexanes to give 136.3 mg title compound as cis and trans mixture. LC-MS: 2.03 and 2.06 min. (LC4, m/Z 423.18). Analytical HPLC: 4.70 min. ^{1}H NMR ($CDCl_3$, 500 MHz) showed nearly 1:1 ratio of two isomers. A very similar mixture was obtained starting from *trans*-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate. When cesium carbonate was used as the base, only the cis-product was obtained starting from *cis*-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate, albeit in lower yield.

Step 2. Ethyl cis- and trans-4-[(5-{(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)[(4,6-dichloropyrimidin-5-yl)carbonyl]amino}pyridin-2-yl)oxy]cyclohexanecarboxylate

Add a suspension of 4,6-dichloropyrimidine-5-carbonyl chloride hydrochloride (0.245 g, 0.988 mmol) prepared as described in Step 1 Example 1 in 2.0 mL THF to a solution of cis- and trans-ethyl 4-({5-[(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]pyridin-2-yl}oxy)cyclohexanecarboxylate (0.22 g, 0.521 mmol) from Step 1 above and triethylamine (0.363 mL, 2.60 mmol) in 2.0 mL THF at 0°C and stir for 5 minutes. The cooling bath is then removed and the reaction mixture stirred at RT overnight. Remove some of the THF under reduced pressure and dilute the residual with EtOAc. Wash the mixture with 5% $NaHCO_3$, water, and saturated brine. Dry over anhydrous sodium sulfate. The crude product was purified on silica gel using 0~40% EtOAc gradient in hexanes to give 0.25 g title compound. LC-MS: 2.61 min. (LC4, m/Z 597.12/599/601). Analytical HPLC: 4.17 min. ^{1}H NMR ($CDCl_3$, 500 MHz) showed nearly 1:1 ratio of two isomers.

Step 3. Ethyl cis- and trans-4-[(5-{[(4,6-dichloropyrimidin-5-yl)carbonyl](2-hydroxyethyl)amino}pyridin-2-yl)oxy]cyclohexanecarboxylate

Concentrated hydrochloric acid (0.094 mL, 1.145 mmol) was added to a solution of ethyl cis- and trans-4-[(5-{(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)[(4,6-dichloropyrimidin-5-yl)carbonyl]amino}pyridin-2-yl)oxy]cyclohexanecarboxylate (228 mg, 0.382 mmol) from Step 2 above in 3.3 mL ethanol and the resulting mixture stirred at RT for 4 hrs. The solvent was removed and the residue was dried under vacuum to give the crude title compound, which was used in the next step without further purification. LC-MS: 1.75 min. (LC4, m/Z 483.00/485/487). Analytical HPLC: 4.02 min. ^{1}H NMR (CD_3OD, 500 MHz) showed nearly 1:1 ratio of two isomers.

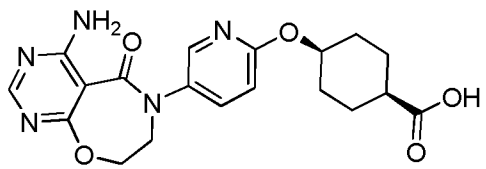
Step 4. Ethyl cis- and trans-4-{[5-(4-chloro-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]oxy}cyclohexanecarboxylate

A solution of ethyl cis- and trans-4-[(5-{[(4,6-dichloropyrimidin-5-yl)carbonyl](2-hydroxyethyl)amino}pyridin-2-yl)oxy]cyclohexanecarboxylate obtained from Step 3 above and DIEA (0.399 mL, 2.285 mmol) in 2.5 mL MeCN was stirred at 80°C overnight. After removal of solvent under reduced pressure the residue as purified on silica gel using 0~100% EtOAc gradient in hexanes to give 101 mg title compound. LC-MS: 1.71 and 1.73 min. (LC4, m/Z 447.05/449). Analytical HPLC: 4.01 min. ^{1}H NMR ($CDCl_3$, 500 MHz) showed nearly 1:1 ratio of two isomers.

Step 5. Cis- and trans-4-{[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]oxy}cyclohexanecarboxylate

Dissolve ethyl cis- and trans-4-{[5-(4-chloro-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]oxy}cyclohexanecarboxylate (98 mg, 0.219 mmol) from Step 4 above in ammonia solution in dioxane (2.193 mL, 1.096 mmol) and stir at 50°C overnight. The solvent was removed under reduced pressure and the residue was washed with water and lyophilized from MeCN/water. LC-MS: 1.46 and 1.49 min. (LC4, m/Z 428.08). Analytical HPLC: 3.41 min. ^{1}H NMR ($CDCl_3$, 500 MHz) showed nearly 1:1 ratio of two isomers. This product can be further purified on RP-HPLC using 20~90% MeCN gradient in water containing 0.05% TFA to give the title compound as a TFA salt. DGAT1 (human) IC_{50} 499 nM.

Example 8

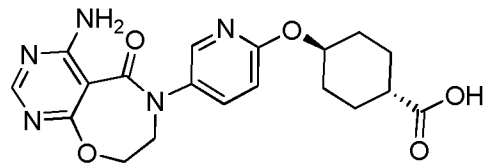


Cis-4-{[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]oxy}cyclohexanecarboxylic acid

An aqueous solution of LiOH (0.842 mL, 0421 mmol) was added to a solution of cis- and trans-4-{[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]oxy}cyclohexanecarboxylate (60 mg, 0.14 mmol) from Example 7 in 0.8 mL THF followed by 0.2 mL methanol. The mixture was stirred at RT for 3 hrs. Remove solvents under reduced

pressure. The TFA salt of the title compound was isolated as the fast-eluting isomer on RP-HPLC using 0~50% MeCN gradient in water containing 0.05% TFA. LC-MS: 1.05 min. (LC4, m/Z 400.11). Analytical HPLC: 3.49 min. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.2 (v br s, 1H), 8.21 (s, 1H), 8.15 (d, 2.8 Hz, 1H), 7.83 (br s, 2H), 7.72 (dd, 8.8 & 2.7 Hz, 1H), 6.85 (d, 8.8 Hz, 1H), 5.14 (br s, 1H), 4.64~4.66 (m, 2H), 3.97~3.99 (m, 2H), 2.35~2.41 (m, 1H), 1.64~1.87 (m, 8H). DGAT1 (human) IC_{50} 549 nM.

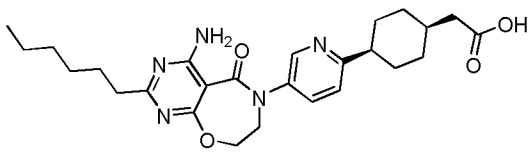
Example 9



Trans-4-{[5-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-*f*][1,4]oxazepin-6(5*H*)-yl)pyridin-2-yl]oxy}cyclohexanecarboxylic acid

The title compound was isolated as the slow-eluting isomer on RP-HPLC from the mixture in Example 8. LC-MS: 1.13 min. (LC4, m/Z 400.14). Analytical HPLC: 3.67 min. ^{1}H NMR (DMSO-d_6, 500 MHz) □ 12.05 (v br s, 1H), 8.17 (s, 1H), 8.13 (d, 2.7 Hz, 1H), 7.74 (br s, 2H), 7.68 (dd, 8.8 & 2.6 Hz, 1H), 6.60 (d, 8.7 Hz, 1H), 4.85~4.91 (m, 1H), 4.60~4.62 (m, 2H), 3.93~3.95 (m, 2H), 2.20~2.25 (m, 1H), 2.04~2.08 (m, 2H), 1.91~1.95 (m, 2H), 1.36~1.49 (m, 4H). DGAT1 (human) IC_{50} 808 nM.

Example 10

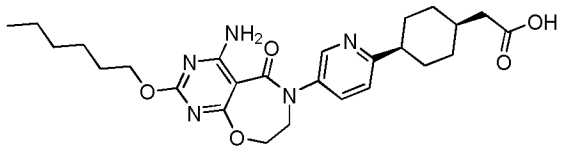


2-(*Cis*-4-(5-(4-amino-2-hexyl-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid

A solution of 2-(cis-4-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid from Preparative Example 4 (0.0137 g, 0.025 mmol) in THF (0.5 ml) was cooled to -78°C, followed by drop-wise addition of a 2.0 M solution of hexylmagnesium bromide solution in ether (0.125 ml, 0.25 mmol). After stirring at -78 °C for 1 hour, the mixture was concentrated to dryness and the resulting residue was then directly purified by RP-HPLC using 10~85% MeCN gradient to afford the title compound. LC-MS (m/z): 482.11 (M + H^+), 1.47 min (LC4). ^{1}H NMR (CD_3OD, 500 MHz) δ

8.63 (s, 1H), 7.96~8.00 (m, 1H), 7.63~7.65 (m, 1H), 4.93~4.95 (m, 2H), 4.24~4.26 (m, 2H), 2.89~2.96 (m, 1H), 2.71 (t, 7.6 Hz, 2H), 2.48 (d, 7.6 Hz, 2H), 2.27~2.34 (m, 1H), 1.86~1.96 (m, 2H), 1.69~1.84 (m, 8H), 1.35~1.46 (m, 6H), 0.94 (t, 7.0 Hz, 3H). DGAT1 (human) IC_{50} 363 nM.

Example 11

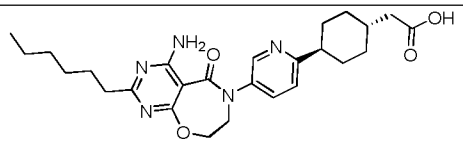
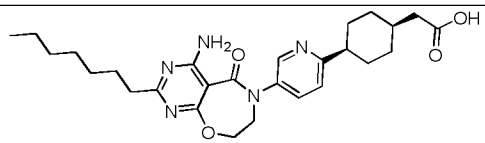
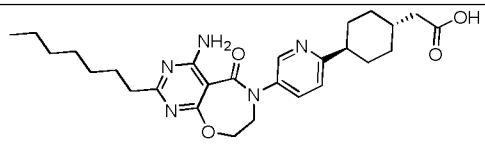
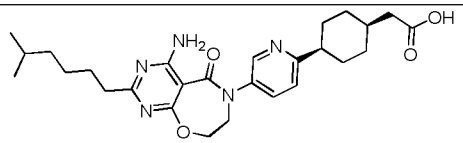
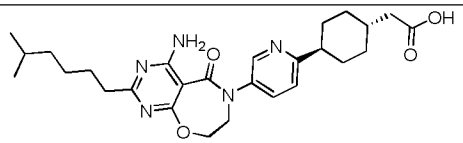
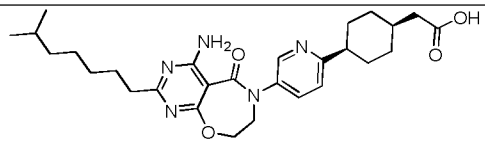


2-(*Cis*-4-(5-(4-amino-2-(hexyloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid

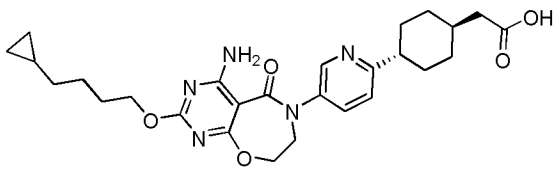
The title compound was isolated as a minor side-product from the reaction affording Example 10 above (see M. T. Goebel and C. S. Marvel *J. Amer. Chem. Soc.* **1933**, 55, 1693). LC-MS (m/z): 498.10 ($M + H^+$), 1.63 min (LC4). ^1H NMR (CD_3OD, 500 MHz) δ 8.75 (d, 2.2 Hz, 1H), 8.19 (dd, 8.6 & 2.2 Hz, 1H), 7.80 (d, 8.6 Hz, 1H), 4.76~4.78 (m, 2H), 4.38 (t, 6.6 Hz, 2H), 4.17~4.19 (m, 2H), 2.96~3.03 (m, 1H), 2.49 (d, 7.7 Hz, 2H), 2.28~2.36 (m, 1H), 1.72-1.96 (m, 10H), 1.44~1.51 (m, 2H), 1.35~1.40 (m, 4H), 0.94 (t, 7.0 Hz, 3H). DGAT1 (human) IC_{50} 73 nM.

The compounds in Table 1 were prepared according to the procedure described in Example 10, starting from the appropriate sulfone and Grignard reagent.

Table 1

Example	Structure	DGAT1 (human) IC_{50}, nM	MWt	LC-MS (M+H)	Rt (min)
12		717	481.6	482.14	1.47
13		67	495.63	496.14	1.60
14		86	495.63	496.14	1.59
15		129	495.63	496.16	1.57
16		132	495.63	496.08	1.57
17		18	509.65	510.31	1.72

Example 18

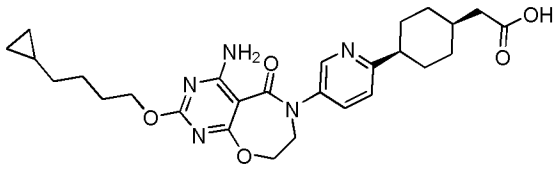


2-(*Trans*-4-(5-(4-amino-2-(4-cyclopropylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid

A mixture of 2-(trans-4-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid from Preparative Example 3 (0.10 g, 0.18 mmol) and 4-cyclopropylbutan-1-ol from Preparative Example 5 (0.13 g, 1.09 mmol) in

$CHCl_3$ (1.0 ml) was cooled to 0°C under nitrogen and treated with a solution of DBU (0.11 g, 0.73 mmol) in $CHCl_3$ (0.5 ml) by a syringe pump over 3.5 hours. After stirring at RT overnight, the solvent was removed under reduced pressure. The resulting residue was then dissolved in a mixture of DMSO and water, and directly purified by RP-HPLC using 10~70% MeCN gradient to afford the title compound as mono TFA salt following lyophilization. LC-MS (m/z): 510.20 ($M + H^+$), 1.70 min (LC4). ^1H NMR (CD_3OD, 500 MHz) δ 8.76 (d, 2.4 Hz, 1H), 8.23 (dd, 8.7 & 2.3 Hz, 1H), 7.80 (d, 8.7 Hz, 1H), 4.76~4.78 (m, 2H), 4.39 (t, 6.6 Hz, 2H), 4.17~4.19 (m, 2H), 2.89~2.95 (m, 1H), 2.28 (d, 7.0 Hz, 2H), 2.00~2.07 (m, 4H), 1.85~1.95 (m, 1H), 1.78~1.84 (m, 2H), 1.66~1.77 (m, 2H), 1.56~1.61 (m, 2H), 1.21~1.32 (m, 4H), 0.65~0.70 (m, 1H), 0.39~0.46 (m, 2H), 0.00~0.08 (m, 2H). DGAT1 (human) IC_{50} 35 nM.

Example 19

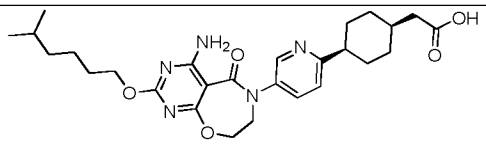
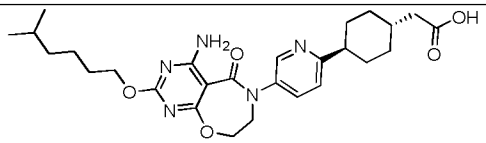
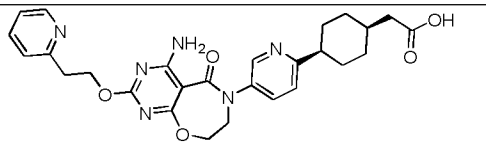
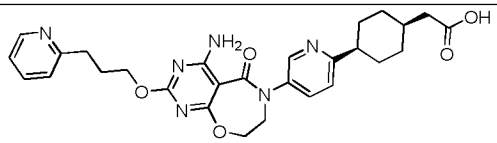
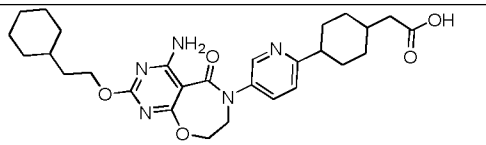
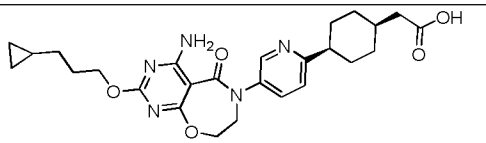
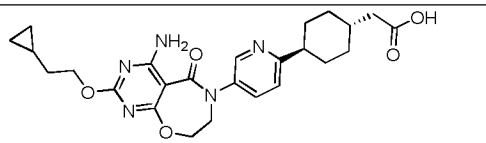
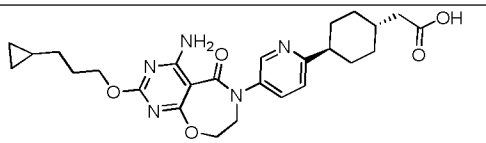


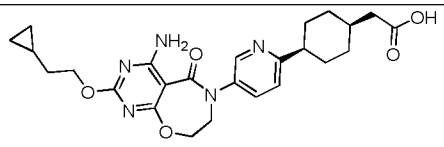
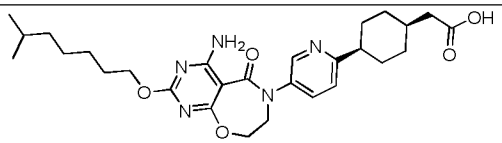
2-(*cis*-4-(5-(4-amino-2-(4-cyclopropylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid

A mixture of 2-(cis-4-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)cyclohexyl)acetic acid from Preparative Example 4 (0.47 g, 0.75 mmol) and 4-cyclopropylbutan-1-ol from Preparative Example 5 (0.62 g, 5.41 mmol) in CH_2Cl_2 (3.5 ml) was cooled to 0°C under nitrogen and treated with a solution of DBU (0.47 g, 4.08 mmol) in CH_2Cl_2 (1.0 ml) using a syringe pump over 3 hr. After stirring at RT overnight, the solvent was removed under reduced pressure. The resulting residue was then dissolved in a mixture of DMSO and water, and directly purified by RP-HPLC using 10~70% MeCN gradient to afford the title compound as mono TFA salt following lyophilization. LC-MS (m/z): 510.18 ($M + H^+$), 1.73 min (LC4). ^1H NMR (CD_3OD, 500 MHz) δ 8.76 (d, 2.4 Hz, 1H), 8.21 (dd, 8.7 & 2.5 Hz, 1H), 7.81 (d, 8.7 Hz, 1H), 4.76~4.78 (m, 2H), 4.39 (t, 6.6 Hz, 2H), 4.17~4.19 (m, 2H), 2.97~3.04 (m, 1H), 2.50 (d, 7.7 Hz, 2H), 2.28~2.36 (m, 1H), 1.72-1.96 (m, 10H), 1.52~1.62 (m, 2H), 1.27~1.32 (m, 2H), 0.68~0.74 (m, 1H), 0.38~0.48 (m, 2H), 0.00~0.08 (m, 2H). DGAT1 (human) IC_{50} 27 nM.

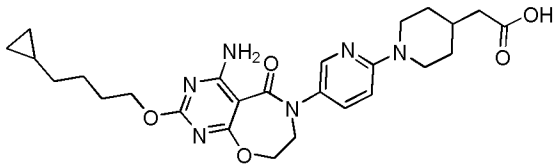
The compounds in Table 2 were prepared according to the methods described in Examples 18 and 19, starting from the appropriate sulfone and alcohol, except Examples 20 and Example 29 were obtained according to the methods described in Example 11 starting from the appropriate sulfone and Grignard reagent. Example 24 was prepared as described for Example 18 starting from the cis- and trans-sulfone mixture derived from Compound 2 of Preparative Example 2.

Table 2

Example	Structure	DGAT1 (human) IC_{50}, nM	MWt	LCMS (M+H)	Rt (min)
20		18	511.61	512.09	1.72
21		18	511.61	512.19	1.84
22		567	518.56	519.11	1.12
23		~2330	532.59	533.27	1.17
24		68	523.64	524.15	1.85
25		162	495.57	496.08	1.56
26		617	481.56	482.30	1.42
27		311	495.58	496.40	1.54

28		674	481.54	482.24	1.38
29		7.8	525.64	526.30	1.89

Example 30



2-(1-(5-(4-Amino-2-(4-cyclopropylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetic acid

Step 1: Ethyl 2-(1-(5-(4-amino-2-(4-cyclopropylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetate

A mixture of ethyl 2-(1-(5-(4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetate from Preparative Example 6 (0.020 g, 0.027 mmol) and 4-cyclopropylbutan-1-ol from Preparative Example 5 (0.025 g, 0.22 mmol) in $CHCl_3$ (0.3 ml) was cooled to 0°C under nitrogen and treated with DBU (0.012 g, 0.081 mmol). After stirring at RT overnight, the solvent was removed under reduced pressure. The resulting residue was then dissolved in a mixture of 1,4-dioxane and water, and directly purified by RP-HPLC using 10~100% MeCN gradient to afford the title compound. LC-MS (m/z): 539.36 ($M + H^+$), 1.75 min (LC4).

Step 2: 2-(1-(5-(4-Amino-2-(4-cyclopropylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetic acid

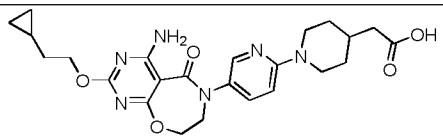
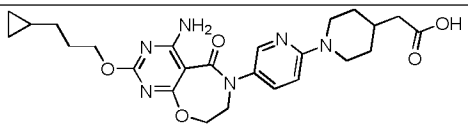
The ethyl 2-(1-(5-(4-amino-2-(4-cyclopropylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)pyridin-2-yl)piperidin-4-yl)acetate (0.010 g, 0.13 mmol) from Step 1 above was dissolved in THF (0.2 ml) and water (0.07 ml) followed by addition of 0.5 M LiOH solution (0.13 ml). After stirring at 40°C for 2 hours, the solvent was removed under reduced pressure. The resulting residue was then dissolved in a mixture of 1,4-dioxane and water, and directly purified by RP-HPLC using 10~80% MeCN gradient to afford the title compound. LC-MS (m/z): 511.32 ($M + H^+$), 1.55 min (LC4). ^1H NMR (CD_3OD, 500 MHz) δ 8.03 (d, 2.5 Hz,

1H), 7.93 (dd, 9.7 & 2.4 Hz, 1H), 7.35 (d, 9.8 Hz, 1 H), 4.72~4.73 (m, 2H), 4.36 (t, 6.6 Hz, 2H), 4.22 (br d, 13.2 Hz, 2H), 4.04~4.06 (m, 2H), 3.24~3.29 (m, 2H), 2.32 (d, 7.1 Hz, 2H), 2.12~2.21 (m, 1H), 1.98 (d, 10.7 Hz, 2H), 1.77~1.83 (m, 2H), 1.53~1.59 (m, 2H), 1.37~1.45 (m. 2H), 1.26~1.30 (m, 2H), 0.66~0.72 (m, 1H), 0.41~0.44 (m, 2H), 0.00~0.04 (m, 2H).

DGAT1 (human) IC_{50} 20 nM.

The compounds in Table 3 were prepared according to the methods described in Example 30, starting from Preparative Example 6 and the appropriate alcohol.

Table 3

Example	Structure	DGAT1 (human) IC_{50}, nM	MWt	LC-MS (M+H)	Rt (min)
31		809	482.53	483.24	1.25
32		185	496.56	497.27	1.41

DGAT1 CPM Assay

20uL substrate mixture of 300uM diolein, 40uM oleoyl-CoA, 10% ethanol and 1uL of the compound with different concentrations were delivered to a 384 well assay plate (Corning 3573) using a Tecan with TeMO module. Later 19uL of enzyme mixture of 1.05ug/ml human DGAT1 in buffer (200mM Tris, pH7, 200mM sucrose, 200mM MgCl2 + 20ug/ml NEM-treated BSA) was added via a Multidrop Combi using a microcassette. 20uL of 90uM CPM reagent in 90% ethanol was added after 1 hour incubation at room temperature. After 30 minutes at room temperature in dark, fluorescence measurement on Envision was carried out and IC50s were calculated.

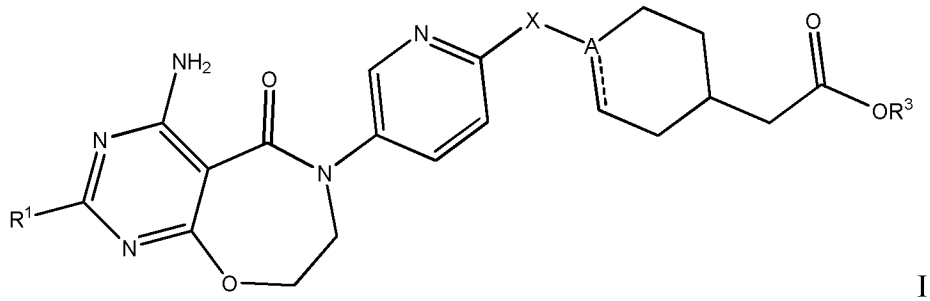
The compounds exemplified herein are believed to have a lower Cmax to trough ratio as compared to the Reference Examples. High Cmax to trough ratio is not a desirable feature of a drug. A higher ratio may lead to low therapeutic index due to potential Cmax related adverse events. It is also believed that the compounds exemplified herein show moderate metabolism in

vitro in hepatocyte incubations, which may impart multiple mechanism of excretion in vivo. Compounds found not to be metabolized by liver microsome or hepatocytes may indicate that they might be eliminated in vivo via excretion as intact drug, which may contribute to undesirably long pharmacodynamic half-life in vivo.

5

WHAT IS CLAIMED IS:

1. A compound of formula (I):



I

or pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from the group consisting of: hydrogen, C_1-C_{10} alkyl SO_2 , C_1-C_{10} alkyl S, C_1-C_{10} alkyl, and C_1-C_{10} alkoxy; wherein in the C_1-C_{10} alkyl may be unsubstituted or substituted with C_1-C_{10} alkyl, halogen, -OH, or $N(R^2)_2$; wherein each R^2 is independently selected from hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, or C(O) C_1-C_{10} alkyl;

R^3 is selected from the group consisting of: hydrogen and C_1-C_{10} alkyl; wherein in the C_1-C_{10} alkyl may be unsubstituted or substituted with C_1-C_{10} alkyl, halogen, -OH, or $N(R^2)_2$; wherein each R^2 is independently selected from hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, or C(O) C_1-C_{10} alkyl;

A is N or C, and ----- means a single or a double bond ; and

X is O or is not present.

2. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein R^1 is hydrogen.

3. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein R^1 is CH_3S.

4. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein R^1 is CH_3SO_2.

5. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein R^1 is C_1-C_{10} alkyl.

6. A compound of claim 5 or pharmaceutically acceptable salt thereof wherein R^1 is C_1-C_{10} branched alkyl.

7. A compound of claim 5 or pharmaceutically acceptable salt thereof wherein R^1 is C_1-C_{10} straight alkyl.

8. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein R^1 is C_1-C_{10} alkoxy.

9. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein R^3 is hydrogen.

10. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein R^3 is CH_3.

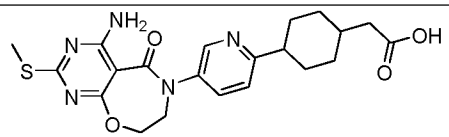
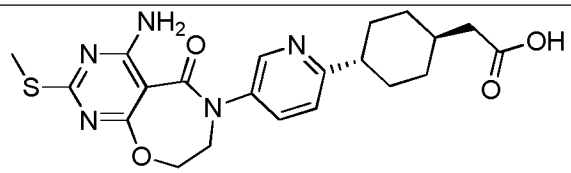
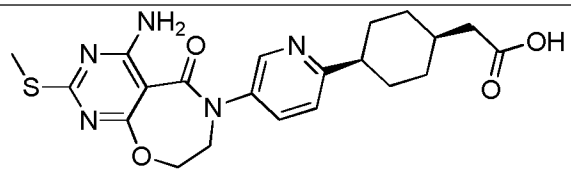
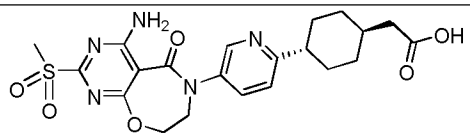
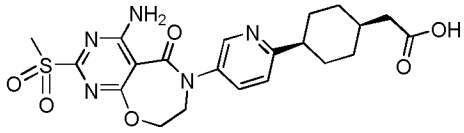
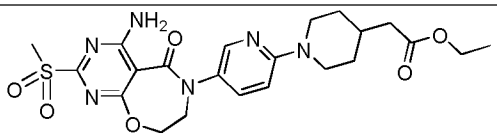
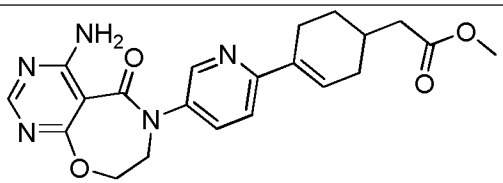
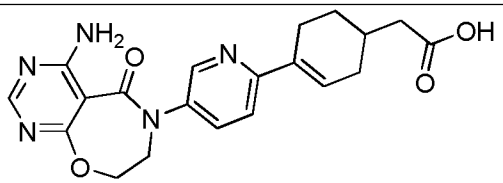
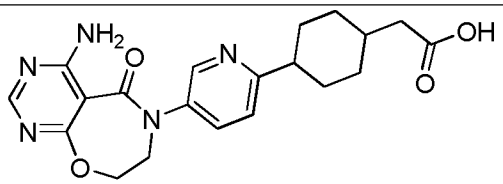
11. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein A is N.

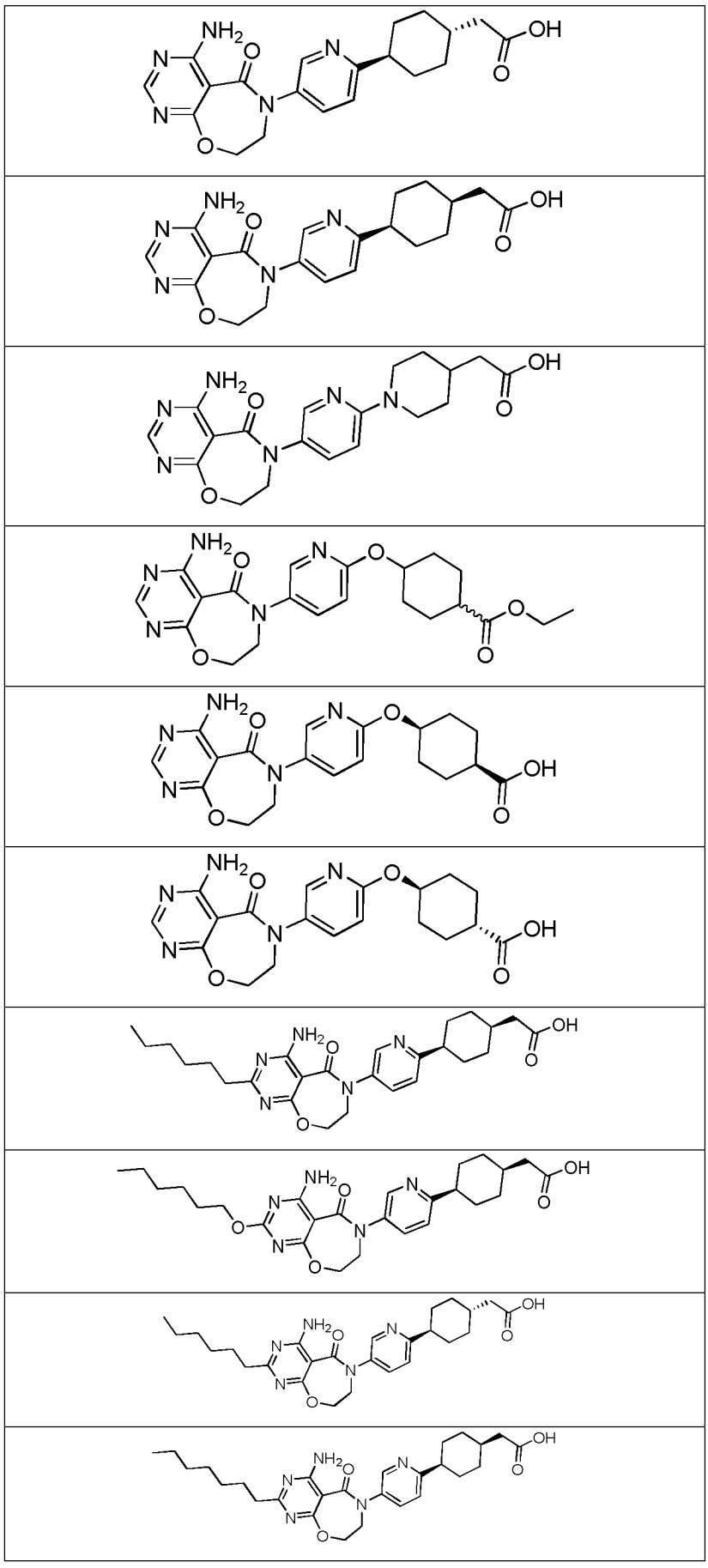
12. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein A is C.

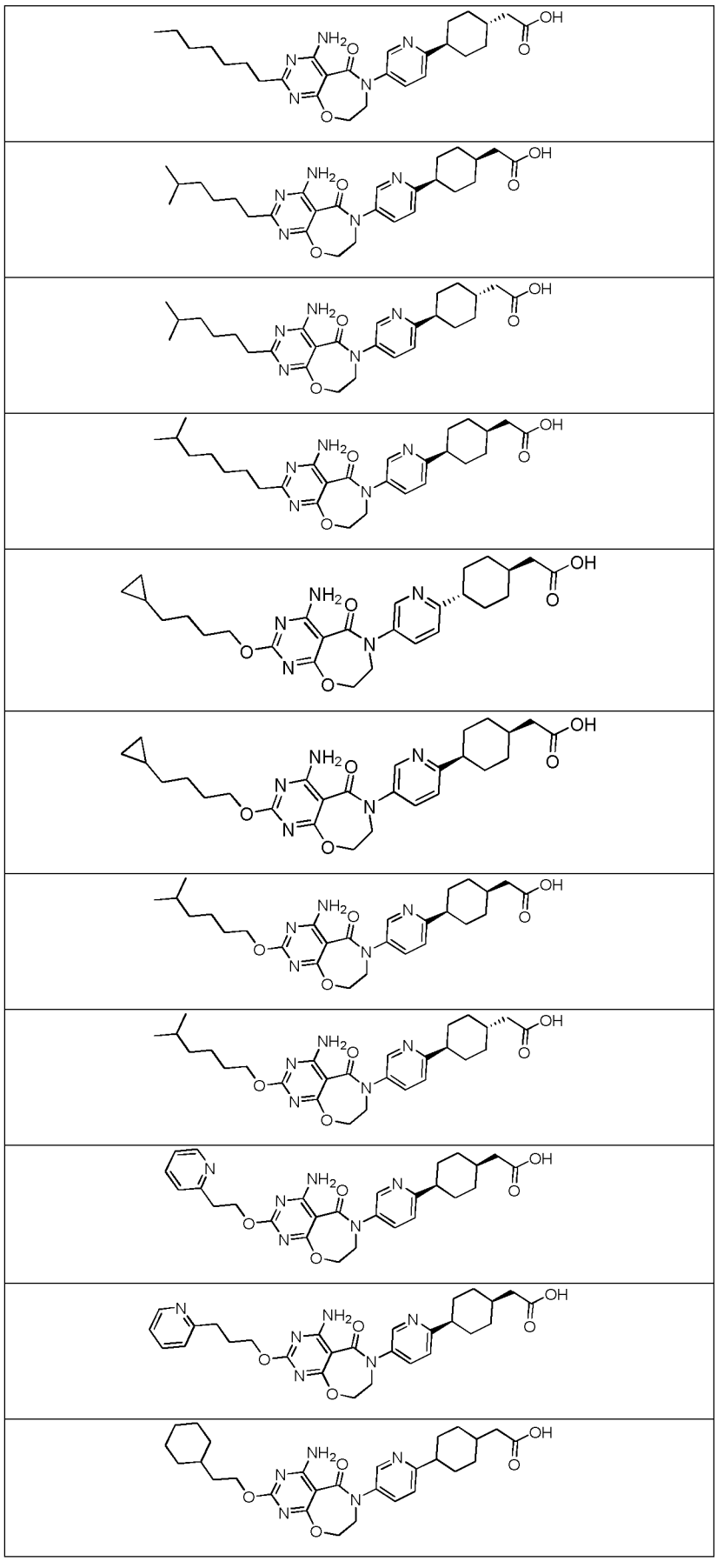
13. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein X is O.

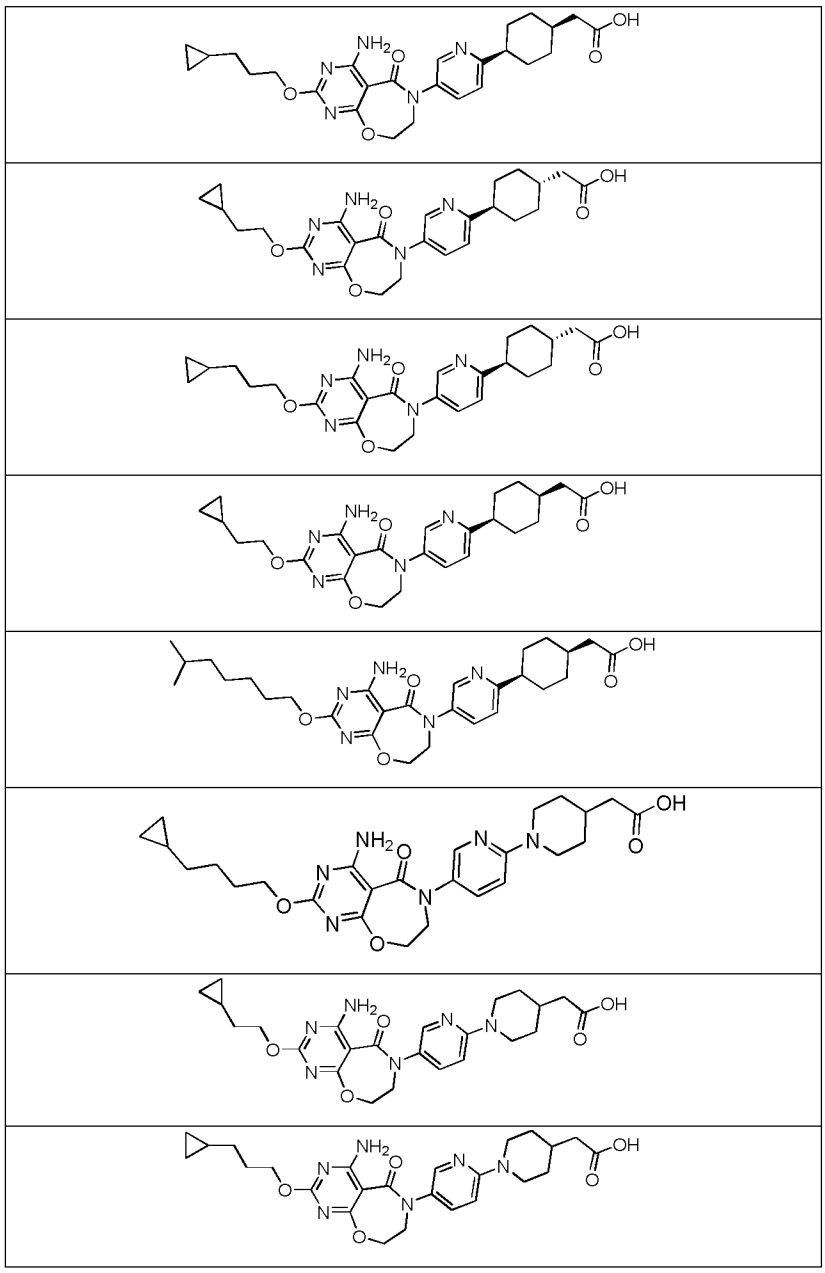
14. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein X is not present.

15. A compound or pharmaceutically acceptable salt thereof selected from the group consisting of:

Structure
















16. A pharmaceutical composition comprising a compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. Use of a compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating a condition selected from the group consisting of obesity and diabetes.

18. A method for the treatment of a condition selected from the group consisting of obesity and diabetes comprising administering to an individual a pharmaceutical composition comprising the pharmaceutical composition of claim 16.

19. The method of claim 18, wherein the individual is an animal.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/055056

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/04 A61K31/5383 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/016462 A2 (PFIZER PROD INC [US]; DOW ROBERT LEE [US]; MUNCHHOF MICHAEL JOHN [US]) 5 February 2009 (2009-02-05) page 24, line 10 - page 25, line 12	1-19
Y	WO 2012/112364 A1 (MERCK SHARP & DOHME [US]; GRAHAM THOMAS [US]; SHEN DONG-MING [US]; NAR) 23 August 2012 (2012-08-23) page 1, paragraph 1; claims 1,6,20-26 claim 1	1-19
Y	WO 2012/122075 A1 (MERCK SHARP & DOHME [US]; GRAHAM THOMAS H [US]; SHEN DONG-MING [US]; N) 13 September 2012 (2012-09-13) page 1, paragraph 1 claim 1	1-19

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2014	14/05/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fanni, Stefano

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/055056

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/009217 A1 (MERCK SHARP & DOHME [US]; CERNAK TIMOTHY A [US]; BALKOVEC JAMES M [US]) 19 January 2012 (2012-01-19) page 1, paragraph 1 claim 1	1-19
Y	WO 2012/015693 A1 (MERCK SHARP & DOHME [US]; LIU JIAN [US]; GUIADEEN DEODIAL [US]) 2 February 2012 (2012-02-02) page 1, paragraph 1 claim 1	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/055056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009016462 A2	05-02-2009	AR 067780 A1	21-10-2009
		AT 502948 T	15-04-2011
		AU 2008281545 A1	05-02-2009
		CA 2695291 A1	05-02-2009
		CN 101772504 A	07-07-2010
		CO 6251365 A2	21-02-2011
		CR 11223 A	04-02-2010
		DK 2185567 T3	16-05-2011
		DO P2010000046 A	31-03-2010
		EA 201000050 A1	30-08-2010
		EC SP109932 A	31-03-2010
		EP 2185567 A2	19-05-2010
		ES 2361716 T3	21-06-2011
		HN 2008001191 A	17-01-2012
		JP 4629808 B2	09-02-2011
		JP 2010535190 A	18-11-2010
		KR 20100032443 A	25-03-2010
		MA 31580 B1	02-08-2010
		PA 8791601 A1	16-12-2009
		PE 08972009 A1	06-08-2009
		PT 2185567 E	27-05-2011
		SI 2185567 T1	30-06-2011
		TW 200916471 A	16-04-2009
		US 2009036425 A1	05-02-2009
		US 2009137551 A1	28-05-2009
		WO 2009016462 A2	05-02-2009
WO 2012112364 A1	23-08-2012	NONE	
WO 2012122075 A1	13-09-2012	NONE	
WO 2012009217 A1	19-01-2012	AU 2011279509 A1	10-01-2013
		CA 2804970 A1	19-01-2012
		JP 2013531037 A	01-08-2013
		WO 2012009217 A1	19-01-2012
WO 2012015693 A1	02-02-2012	AU 2011282989 A1	10-01-2013
		CA 2805078 A1	02-02-2012
		WO 2012015693 A1	02-02-2012