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- (71) **Applicant (for all designated States except US):** **MERCK SHARP & DOHME CORP.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** **GRAHAM, Thomas, H.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **SHEN, Dong-Ming** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **NARGUND, Ravi, P.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **DEVITA, Robert, J.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **YU, Yang** [CN/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LIU, Wensheng** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

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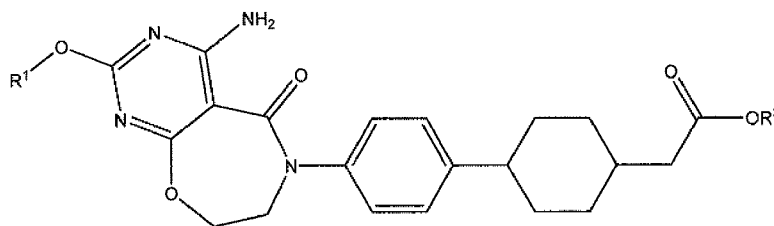
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(54) **Title:** LACTAM DERIVATIVES AS DGAT-1 INHIBITORS



I

(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.

## LACTAM DERIVATIVES AS DGAT-1 INHIBITORS

## TECHNICAL FIELD

The present invention is directed to lactam 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.

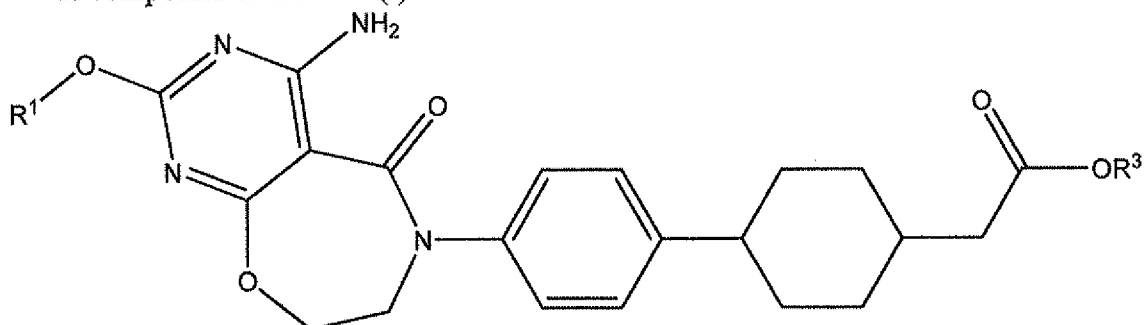
In the body there are two TG synthesis pathways, a glycerol phosphate pathway, which is present in most organs and causes *de novo* TG synthesis, and a monoacylglycerol pathway, which is involved principally in absorption of aliphatic acid from the small intestine. Diacylglycerol acyltransferases (DGATs, 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 postprandial 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, lipodosis, hypertension, fatty liver, arteriosclerosis, cerebrovascular disorder, coronary artery disease and metabolic syndrome.

## SUMMARY OF THE INVENTION

A compound of formula (I):



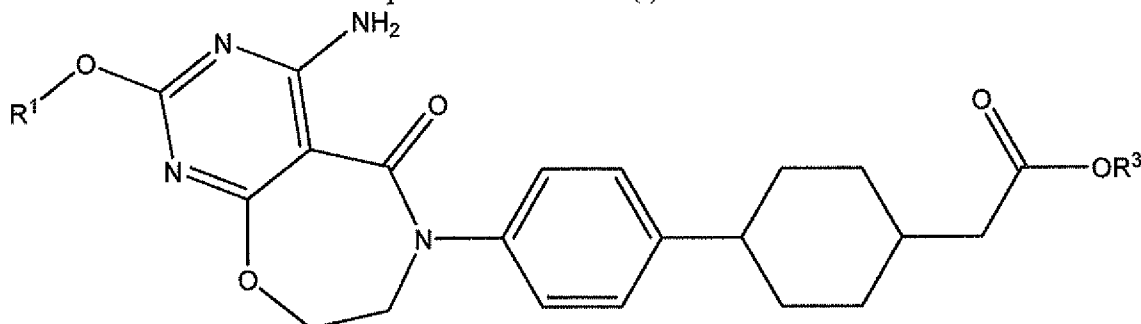
I

or pharmaceutically acceptable salts thereof, wherein  $R^1$  and  $R^3$  are further described below. The compounds described herein are DGAT-1 inhibitors, which are useful in the treatment of type 2 diabetes mellitus, obesity, lipodosis, 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):



I

or pharmaceutically acceptable salts thereof, wherein  $R^1$  is selected from the group consisting of:  
hydrogen;

$C_5$ - $C_{10}$ alkyl, wherein the  $C_5$ - $C_{10}$ alkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of  $C_1$ - $C_6$ alkoxy and -OH;

halogen-substituted  $C_1$ - $C_{10}$ alkyl;

$-(CH_2)_mO(CH_2)_nCH_3$ , wherein  $-(CH_2)_mO(CH_2)_nCH_3$  is unsubstituted or substituted with at least one  $C_1$ - $C_6$ alkyl, and wherein m and n are independently selected from the group consisting of 1, 2, 3 or 4; and

$-(CH_2)_pR^2$ , wherein the  $-(CH_2)_pR^2$  is unsubstituted or substituted with one or more substituents selected from the group consisting of  $C_1$ - $C_6$ alkyl, halogen, - $NH_2$ , phenyl,  $C_1$ -

C<sub>6</sub>alkoxy and -OC<sub>3</sub>-C<sub>6</sub>cycloalkyl, wherein R<sup>2</sup> is aryl, heteroaryl, cycloalkyl or heterocycloalkyl, and wherein p is 0, 1, 2, 3 or 4; and

R<sup>3</sup> is independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>6</sub>alkyl.

In one embodiment of the compounds described herein, R<sup>1</sup> is hydrogen.

5 In another embodiment of the compounds described herein, R<sup>1</sup> is C<sub>5</sub>-C<sub>10</sub>alkyl, wherein the C<sub>5</sub>-C<sub>10</sub>alkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>alkoxy and -OH.

In certain embodiments of the compounds described herein R<sup>1</sup> is C<sub>5</sub>-C<sub>10</sub>alkyl. In certain embodiments R<sup>1</sup> is C<sub>5</sub>-C<sub>9</sub>alkyl. In other embodiments R<sup>1</sup> is C<sub>6</sub>-C<sub>10</sub>alkyl. In still other  
10 embodiments R<sup>1</sup> is C<sub>6</sub>-C<sub>9</sub>alkyl. In any of the embodiments described herein the alkyl can be branched or straight.

In one embodiment R<sup>1</sup> is C<sub>5</sub>alkyl such as, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1,2-dimethylpropyl and 1-ethylpropyl. In another embodiment R<sup>1</sup> is C<sub>6</sub>alkyl, such as n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 3,3-dimethylbutyl,  
15 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In still another embodiment, R<sup>1</sup> is C<sub>7</sub>alkyl, such as n-heptyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3-ethylpentyl, 2-ethylpentyl, 1-ethylpentyl and 4,4-dimethylpentyl. In yet another embodiment R<sup>1</sup> is C<sub>8</sub>alkyl such as, n-octyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 4-ethylhexyl, 3-ethylhexyl, 2-ethylhexyl, 1-ethylhexyl, 4,4-dimethylhexyl and 5,5-dimethylhexyl. In another  
20 embodiment R<sup>1</sup> is C<sub>9</sub>alkyl such as, n-nonyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 5-ethylheptyl, 4-ethylheptyl, 3-ethylheptyl, 2-ethylheptyl, 1-ethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl and 6,6-dimethylheptyl. In another embodiment R<sup>1</sup> is C<sub>10</sub>alkyl such as, n-decyl, 1-methylnonyl, 2-methylnonyl, 3-methylnonyl, 4-methylnonyl, 5-methylnonyl, 6-methylnonyl, 1-ethyloctyl, 4,4-dimethyloctyl, 5,5-dimethyloctyl, 6,6-dimethyloctyl and 7,7-dimethyloctyl.

In any of the alkyl embodiments described herein, the alkyl can be unsubstituted or substituted with one or more substituents selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>alkoxy and  
30 -OH. In certain embodiments, the alkyl is unsubstituted. In other embodiments the alkyl is substituted with one or more C<sub>1</sub>-C<sub>6</sub>alkoxy. Suitable alkoxys include methoxy, ethoxy, butoxy and propoxy. In certain embodiments, R<sup>1</sup> is C<sub>5</sub>-C<sub>10</sub>alkyl, wherein C<sub>5</sub>-C<sub>10</sub>alkyl is substituted with methoxy. In another embodiment, when R<sup>1</sup> is C<sub>5</sub>-C<sub>10</sub>alkyl the alkyl is substituted with -OH.

In certain embodiments of the compounds described herein, R<sup>1</sup> is halogen-substituted C<sub>1</sub>-  
35 C<sub>10</sub>alkyl. Suitable halogen-substituted alkyls include fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoropropyl, trifluorobutyl, fluoropentyl, difluoropentyl, trifluoropentyl, fluoroethyl, difluoroethyl, difluoroethyl.

In certain embodiments of the compounds described herein,  $R^1$  is  $-(CH_2)_mO(CH_2)_nCH_3$ , wherein  $-(CH_2)_mO(CH_2)_nCH_3$  is unsubstituted or substituted with at least one  $C_1$ - $C_6$ alkyl, and wherein  $m$  is selected from the group consisting of 1, 2, 3 or 4 and  $n$  is selected from the group consisting of 0, 1, 2, 3 or 4.

When  $R^1$  is  $-(CH_2)_mO(CH_2)_nCH_3$ ,  $m$  is selected from the group consisting of 1, 2, 3 or 4. In one embodiment,  $m$  is 1. In another embodiment,  $m$  is 2. In still another embodiment,  $m$  is 3. In yet another embodiment,  $m$  is 4. Additionally, when  $R^1$  is  $-(CH_2)_mO(CH_2)_nCH_3$ ,  $n$  is selected from the group consisting of 0, 1, 2, 3 or 4. In one embodiment,  $n$  is 0. In one embodiment,  $n$  is 1. In another embodiment,  $n$  is 2. In still another embodiment,  $n$  is 3. In yet another embodiment,  $n$  is 4.

In certain embodiments of the compounds described herein, when  $R^1$  is  $-(CH_2)_mO(CH_2)_nCH_3$ , wherein  $-(CH_2)_mO(CH_2)_nCH_3$  is unsubstituted or substituted with at least one  $C_1$ - $C_6$ alkyl. In one embodiment,  $-(CH_2)_mO(CH_2)_nCH_3$  is unsubstituted. In another embodiment,  $-(CH_2)_mO(CH_2)_nCH_3$  is substituted with at least one  $C_1$ - $C_6$ alkyl. Suitable alkyls include, methyl, ethyl, propyl, butyl, pentyl and hexyl. In certain embodiments,  $R^1$  is  $-(CH_2)_2O(CH_2)CH(CH_3)_2$ . In other embodiments,  $R^1$  is  $-(CH_2)_3OCH(CH_3)_2$ . In another embodiment,  $R^1$  is  $-(CH_2)_2O(CH_2)_2OCH_3$ .

In certain embodiments of the compounds described herein,  $R^1$  is  $-(CH_2)_pR^2$ , wherein the  $-(CH_2)_pR^2$  is unsubstituted or substituted with  $C_1$ - $C_6$ alkyl, halogen,  $-NH_2$ , phenyl,  $C_1$ - $C_6$ alkoxy or  $-OC_1$ - $C_6$ cycloalkyl, wherein  $R^2$  is aryl, heteroaryl, cycloalkyl or heterocycloalkyl, and wherein  $p$  is 0, 1, 2, 3 or 4.

In certain embodiments of the compounds described herein  $p$  is 0. In other embodiments,  $p$  is 1. In still other embodiments,  $p$  is 2. In yet other embodiments,  $p$  is 3. In another embodiment of the compounds described herein,  $p$  is 4. In other embodiments,  $p$  is 0, 1 or 2. In other embodiments,  $p$  is 0, 1, 2 or 3. In still other embodiments,  $p$  is 1, 2, 3 or 4.

In certain embodiments of the compounds described herein,  $R^1$  is  $-(CH_2)_pR^2$ , wherein  $R^2$  is aryl. Suitable aryls include phenyl, naphthyl and tolyl. In certain embodiments  $R^2$  is phenyl. In other embodiments,  $R^2$  is fluorophenyl

In certain embodiments of the compounds described herein,  $R^1$  is  $-(CH_2)_pR^2$ , wherein  $R^2$  is heteroaryl. Suitable heteroaryls include 5- or 6-membered monocyclic or 8- to 14-membered polycyclic heteroaromatic cyclic groups containing at least one, preferably from 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom as a part of the ring-constitutive members. Suitable examples include a pyridinyl group, a pyrimidinyl group, a pyridazinyl group, a pyrazyl group, a pyrazolyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, an oxazolyl group, an isoxazolyl group, an oxadiazolyl group, a thiazolyl group, an isothiazolyl group, a thiadiazolyl group, a tetrazolyl group, a pyridazinyl group, a pyrazinyl group, a furyl group, a thienyl group, an indolyl group, a benzofuranyl group, a benzothienyl

group, a benzimidazolyl group, a benzoxazolyl group, a benzisoxazolyl group, a benzothiazolyl group, a benzisothiazolyl group, an indazolyl group, a purinyl group, a quinolyl group, an isoquinolyl group, a phthalazinyl group, a naphthyridinyl group, a quinoxalinyl group, a quinazolinyl group, a cinnolinyl group, a pteridinyl group, a pyrido[3,2-b]pyridyl group. In certain embodiments  $R^2$  is a pyrimidinyl group, a pyridinyl group, a pyrazyl group, a thiazolyl group or an oxazolyl group.

In certain embodiments of the compounds described herein,  $R^1$  is  $-(CH_2)_pR^2$ , wherein  $R^2$  is cycloalkyl. Suitable cycloalkyls include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, a cyclononyl group, a cyclodecyl group, a bicyclohexyl group and an adamantyl group. In certain embodiments  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In other embodiments,  $R^1$  is  $-(CH_2)cyclopropyl$ ,  $-(CH_2)_2cyclopropyl$ ,  $-(CH_2)_3cyclopropyl$  or  $-(CH_2)_4cyclopropyl$ . In still other embodiments,  $R^1$  is  $-(CH_2)cyclobutyl$ ,  $-(CH_2)_2cyclobutyl$ , cyclopentyl,  $-(CH_2)cyclopentyl$ ,  $-(CH_2)_2cyclopentyl$ ,  $-(CH_2)_3cyclopentyl$ ,  $-(CH_2)cyclohexyl$  or  $-(CH_2)_2cyclohexyl$ .

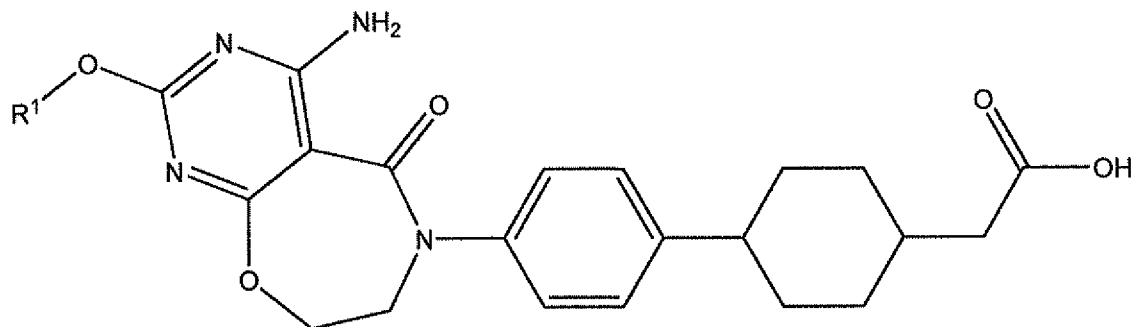
In certain embodiments of the compounds described herein,  $R^1$  is  $-(CH_2)_pR^2$ , wherein  $R^2$  is cycloheteroalkyl. Suitable cycloheteroalkyls include an aziridine ring, oxolan ring, pyrrolidine ring, piperidine ring, tetrahydropyran ring, tetrahydrofuran ring, oxodihydropyridinyl ring, dioxane ring and morpholine ring. In certain embodiments  $R^2$  is pyrrolidine or piperidine. In other embodiments,  $R^2$  is tetrahydrofuran, dioxane or morpholine.

In certain embodiments of the compounds described herein,  $-(CH_2)_pR^2$  is unsubstituted. In other embodiments,  $-(CH_2)_pR^2$  is substituted with one or more substituents selected from the group consisting of  $C_1$ - $C_6$ alkyl, halogen,  $-NH_2$ , phenyl,  $C_1$ - $C_6$ alkoxy or  $-OC_1$ - $C_6$ cycloalkyl. In one embodiment,  $-(CH_2)_pR^2$  is substituted with one or more  $C_1$ - $C_6$ alkyls. Suitable  $C_1$ - $C_6$ alkyls include methyl, ethyl, butyl, propyl and hexyl. In another embodiment,  $-(CH_2)_pR^2$  is substituted with one or more halogens. Suitable halogens include fluorine, chlorine, bromine and iodine. In yet another embodiment,  $-(CH_2)_pR^2$  is substituted with one or more phenyl group. In still another embodiment,  $-(CH_2)_pR^2$  is substituted with one or more  $C_1$ - $C_6$ alkoxy. Suitable alkoxy include methoxy, ethoxy, butoxy and propoxy. In yet another embodiment,  $-(CH_2)_pR^2$  is substituted with one or more  $-OC_3$ - $C_6$ cycloalkyl. Suitable  $-OC_3$ - $C_6$ cycloalkyl include  $-O$ cyclopropyl,  $-O$ cyclobutyl,  $-O$ cyclopentyl and  $-O$ cyclohexyl. In one embodiment,  $-(CH_2)_pR^2$  is substituted with one or more  $-NH_2$ .

In certain embodiments of the compounds described herein,  $R^1$  is  $-(CH_2)_pR^2$ , wherein  $-(CH_2)_p$  is substituted with one or more substituents selected from the group consisting of  $C_1$ - $C_6$ alkyl, halogen or  $C_1$ - $C_6$ alkoxy. In one embodiment,  $-(CH_2)_p$  is substituted with one or more  $C_1$ - $C_6$ alkyls. Suitable  $C_1$ - $C_6$ alkyls include methyl, ethyl, butyl, propyl and hexyl. In another embodiment,  $-(CH_2)_p$  is substituted with one or more halogens. Suitable halogens include fluorine, chlorine, bromine and iodine. In yet another embodiment,  $-(CH_2)_p$  is substituted with

one or more C<sub>1</sub>-C<sub>6</sub>alkoxy. Suitable alkoxy include methoxy, ethoxy, butoxy and propoxy.

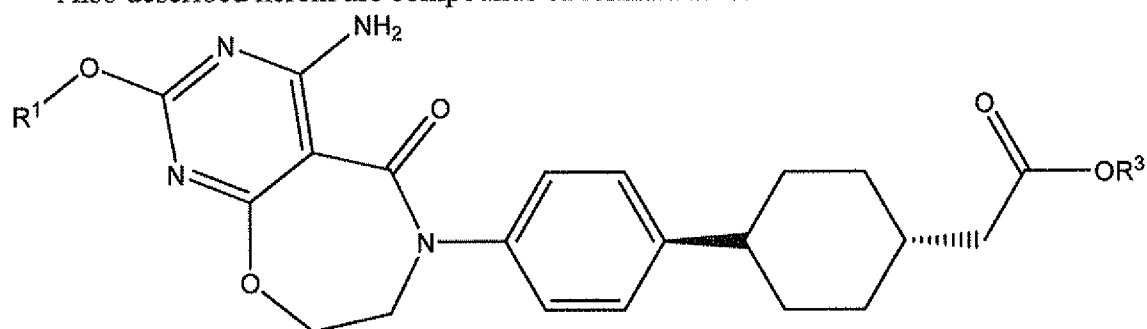
In certain embodiments of the compounds described here, R<sup>3</sup> is independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>6</sub>alkyl. In certain embodiments, R<sup>3</sup> is hydrogen, as shown in formula Ia:



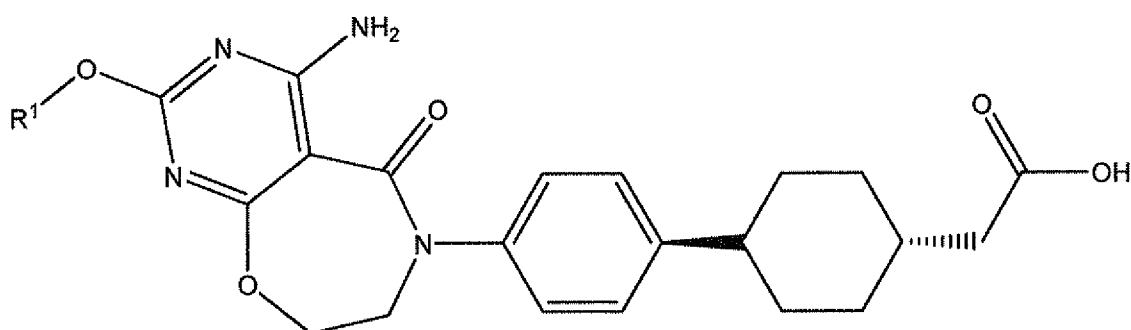
Ia

In other embodiments, R<sup>3</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl. Suitable C<sub>1</sub>-C<sub>6</sub>alkyl include methyl, ethyl, propyl, butyl, pentyl and hexyl.

Also described herein are compounds of formula Ib and Ic:



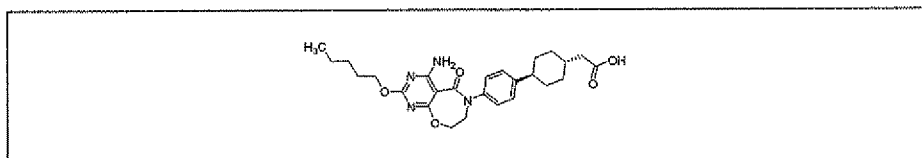
Ib



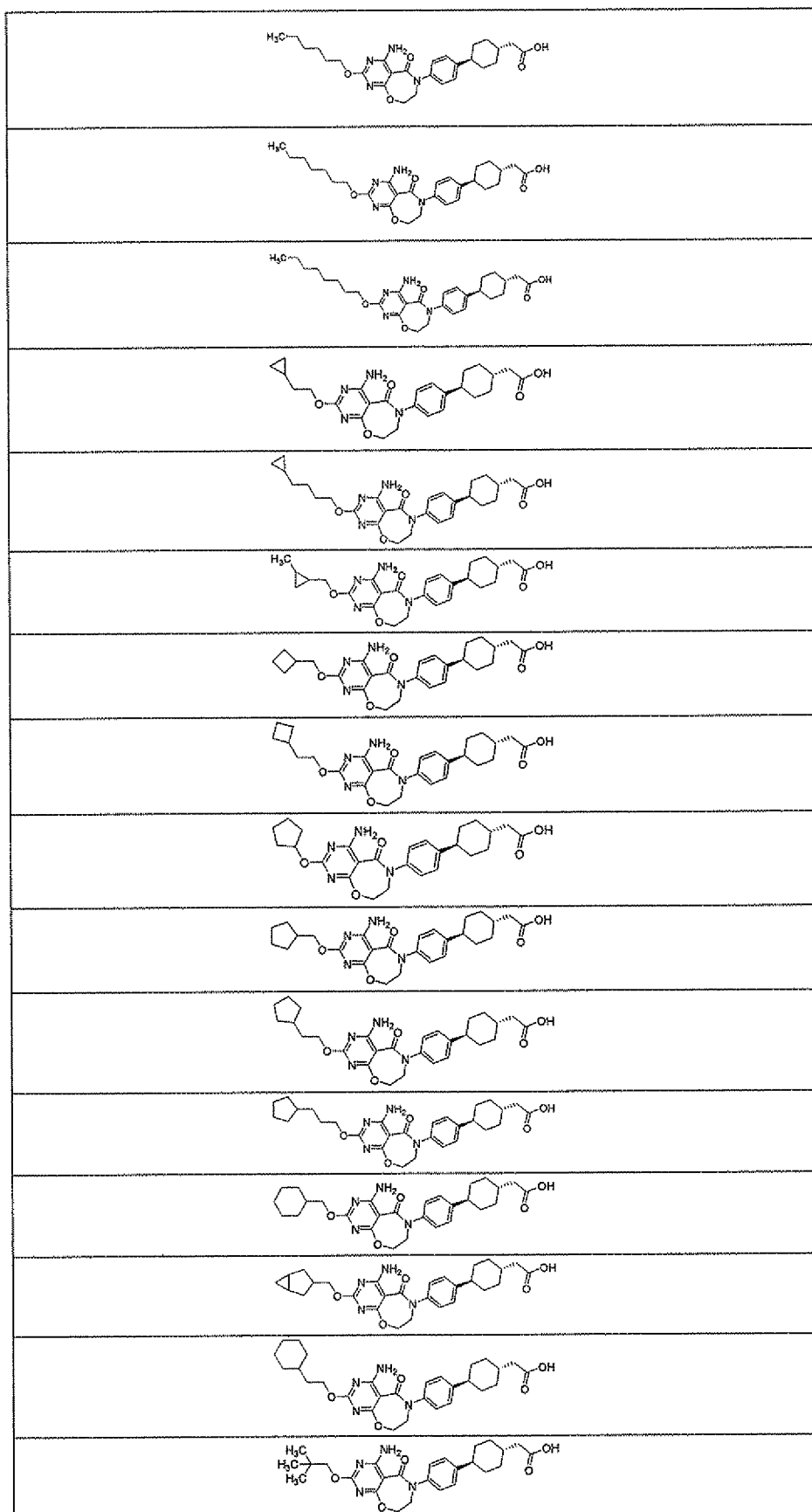
Ic

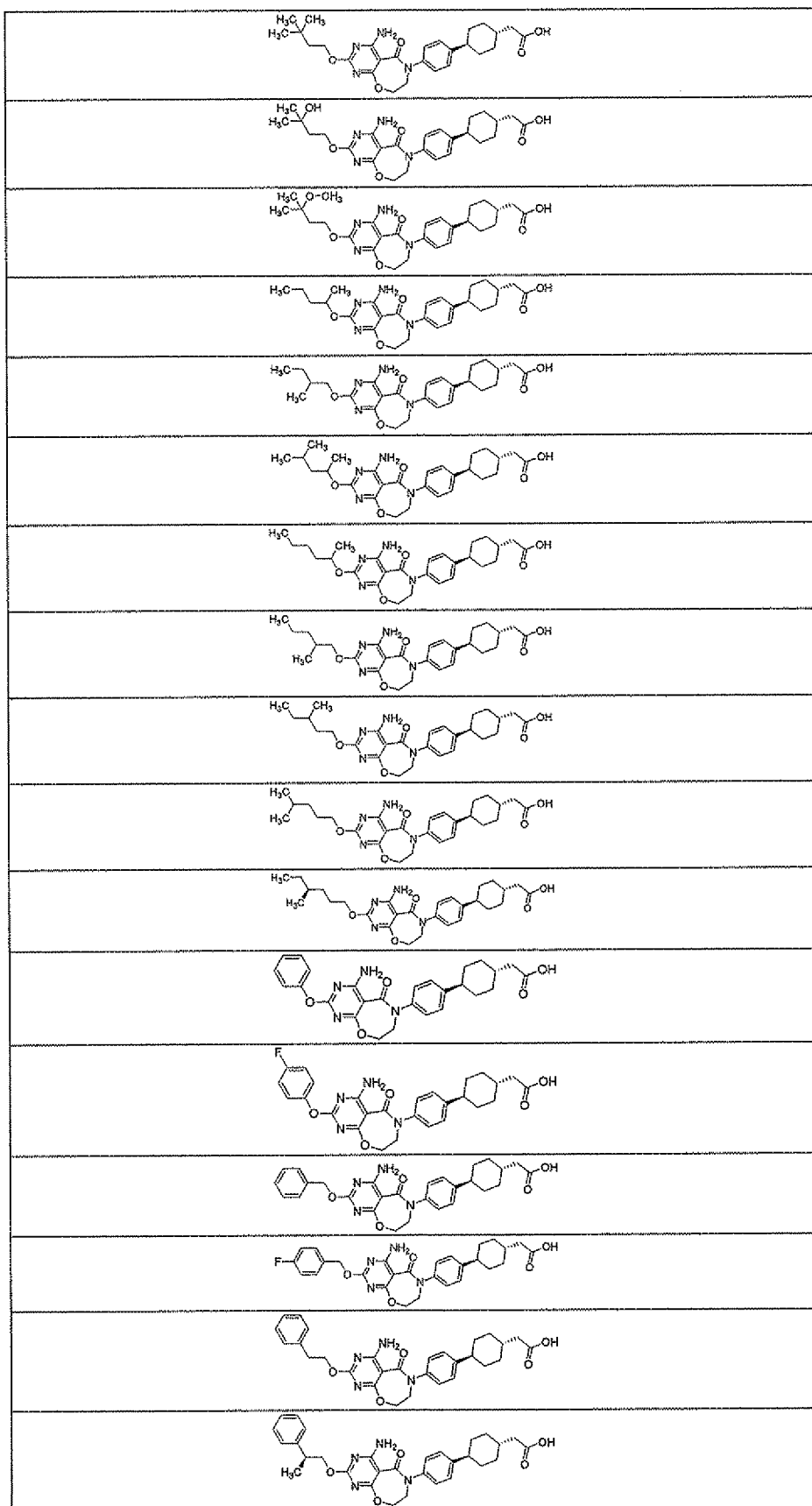
wherein R<sup>1</sup> and R<sup>3</sup> are described above.

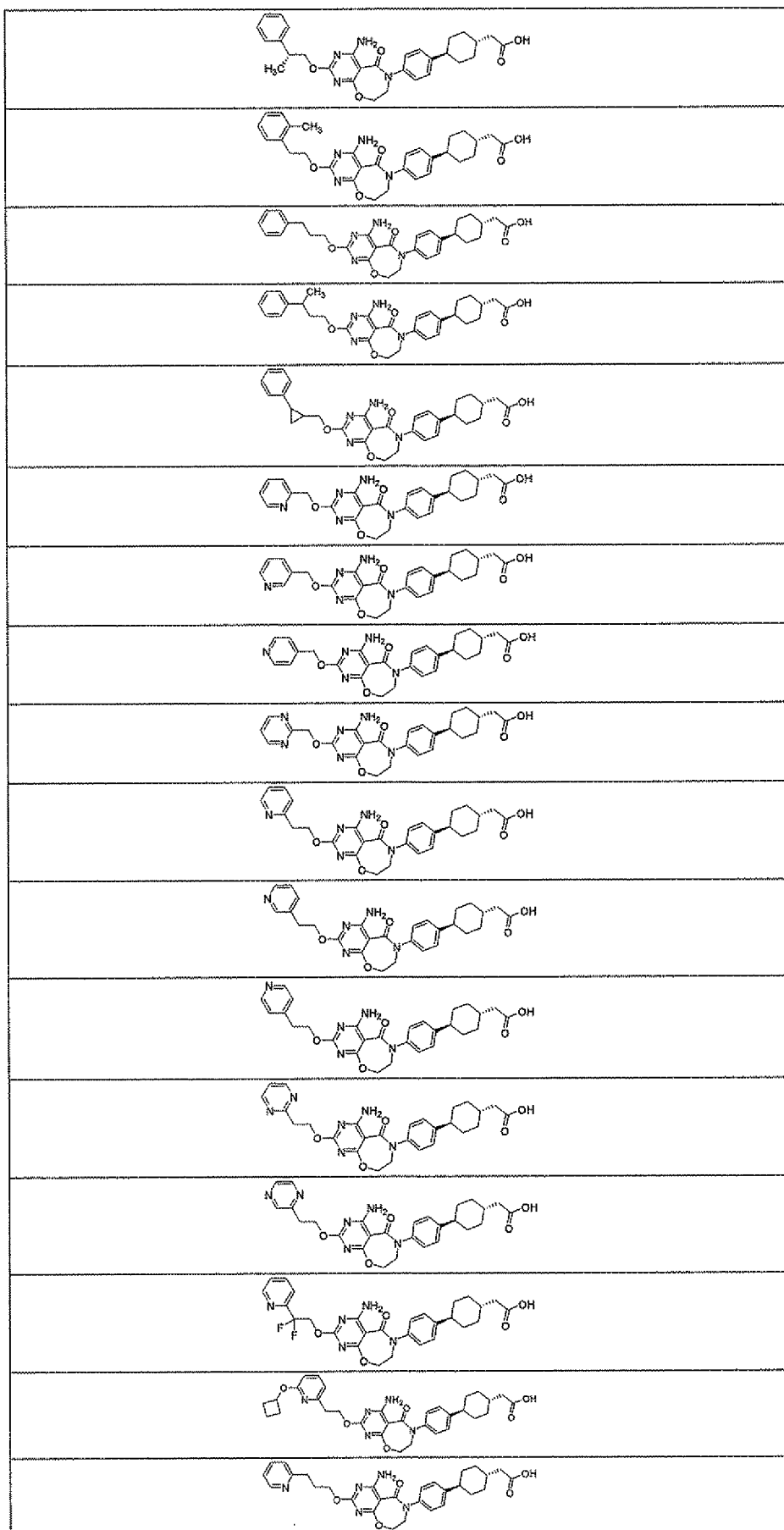
Examples of the compounds described herein include, but are not limited to:

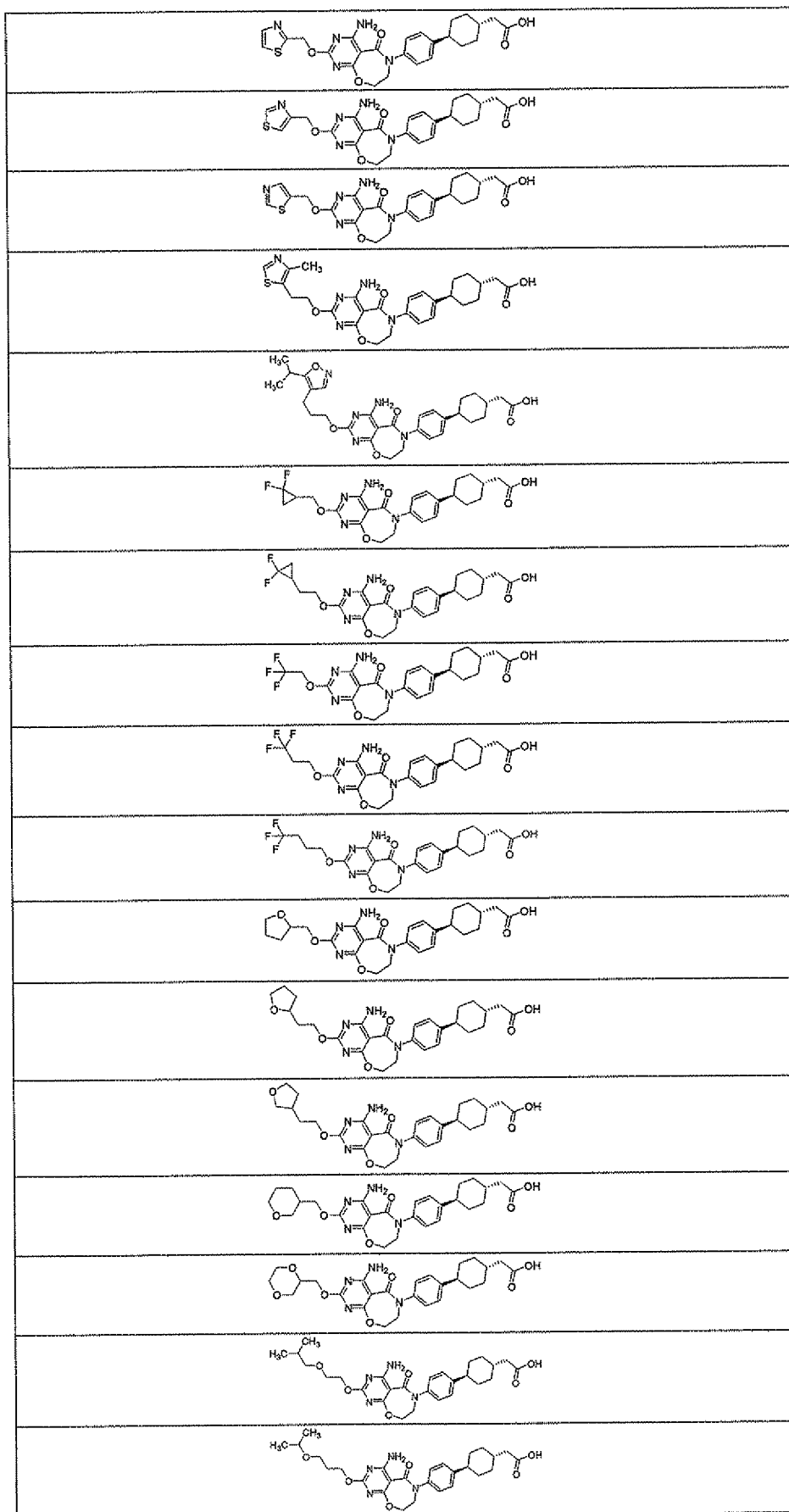


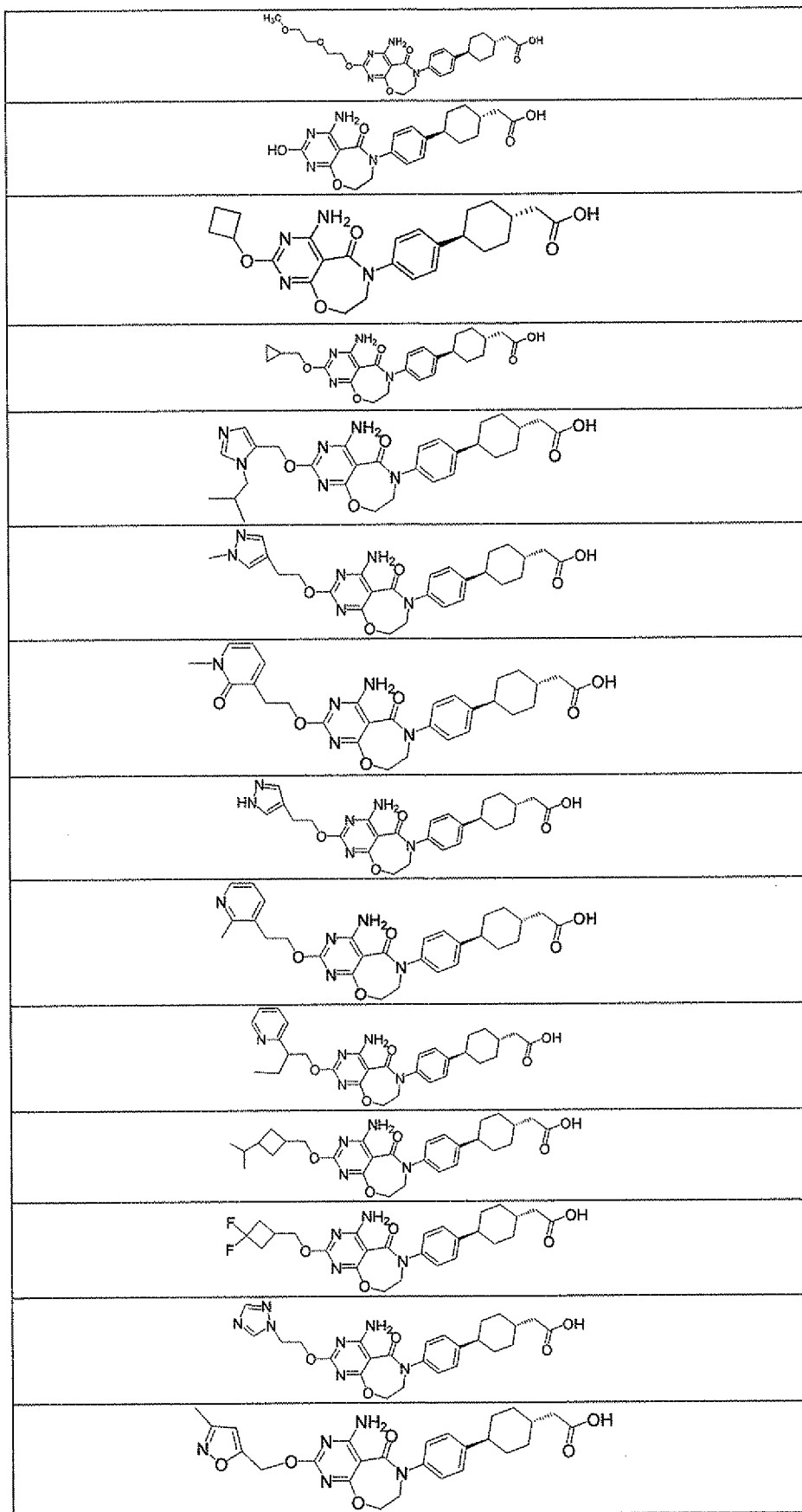


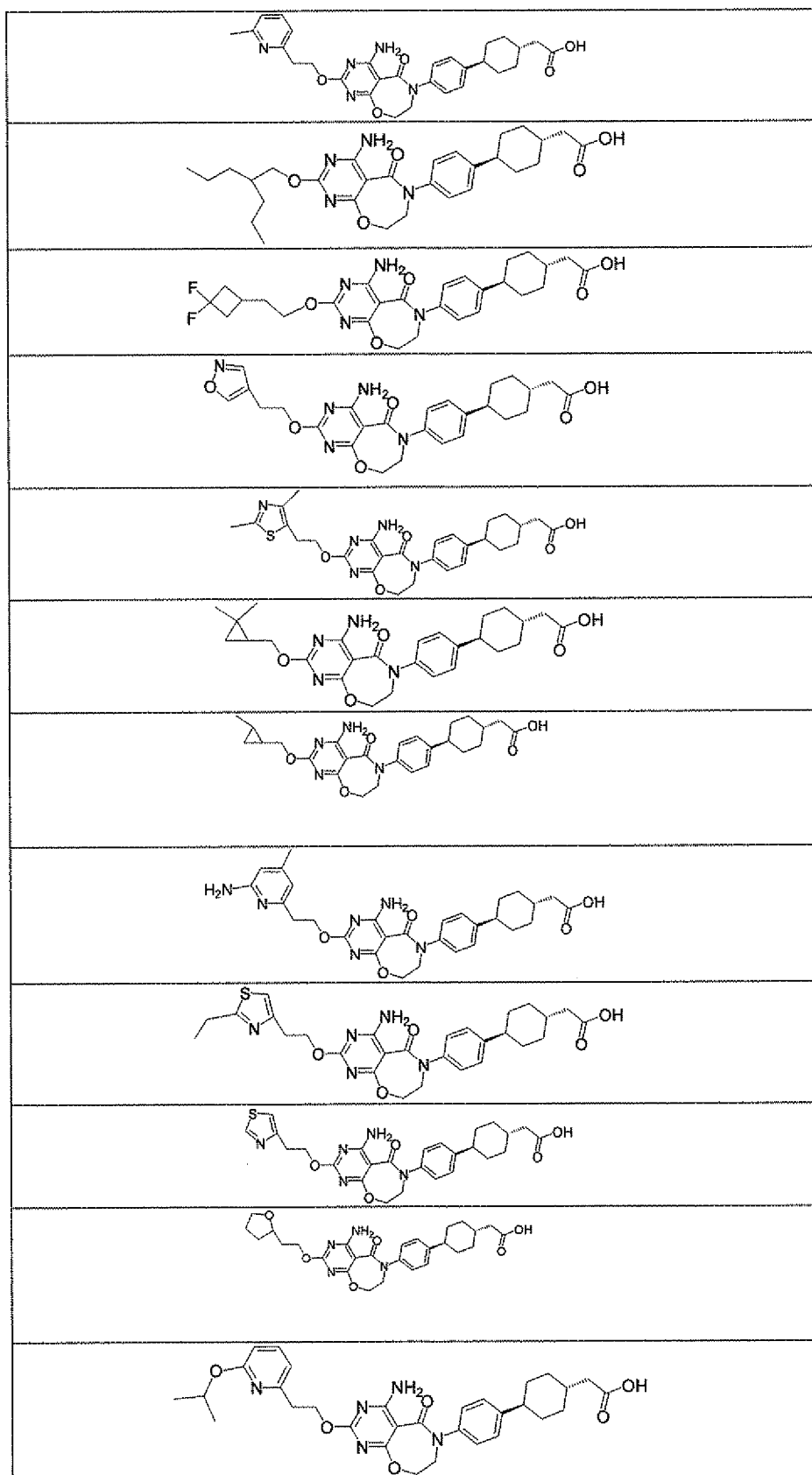


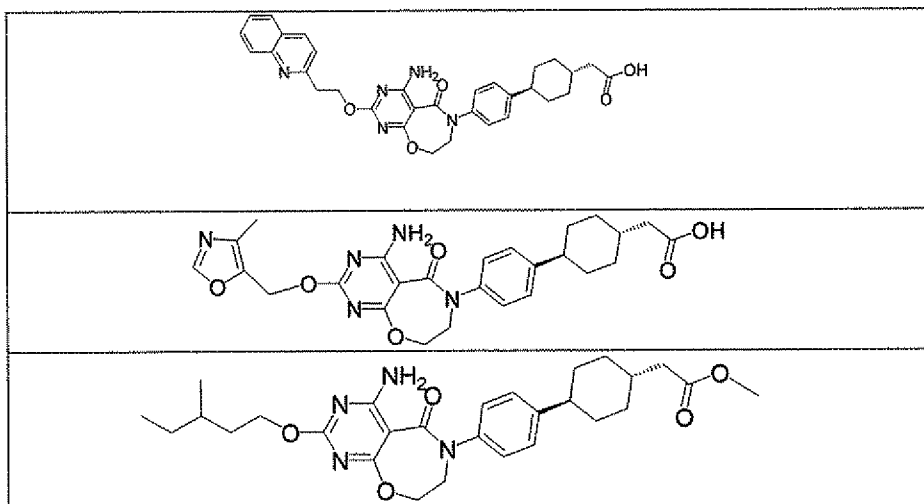












### Definitions

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

The term "C<sub>5</sub>-C<sub>10</sub>alkyl" encompasses straight alkyl having a carbon number of 5 to 10 and branched alkyl having a carbon number of 5 to 10. Specific examples thereof include 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 terms "-OC<sub>1</sub>-C<sub>6</sub>alkyl" or "C<sub>1</sub>-C<sub>6</sub>alkoxy" refers to an alkyl group having 1 to 6 carbons linked to oxygen, also known as an alkoxy group. Examples include methoxy, ethoxy, butoxy and propoxy.

The term "halogen-substituted C<sub>1</sub>-C<sub>10</sub> alkyl" encompasses C<sub>1</sub>-C<sub>10</sub>alkyl with the hydrogen atoms thereof being partially or completely substituted with halogen, examples thereof including fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,3-difluorobutyl and the like.

Examples of "aryl" include phenyl, naphthyl, tolyl, and the like.

The term "heteroaryl" includes a 5- or 6-membered monocyclic or 8- to 14-membered polycyclic heteroaromatic cyclic group containing at least one, preferably from 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom as a part of the ring-constitutive members; and concretely, for example, it includes a pyridinyl group, a pyrimidinyl group, a pyridazinyl group, a pyrazyl group, a pyrazolyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, an oxazolyl group, an isoxazolyl group, an oxadiazolyl group, a thiazolyl group, an isothiazolyl group, a thiadiazolyl group, a tetrazolyl group, a pyridazinyl group, a pyrazinyl group, a furyl group, a thienyl group, an indolyl group, a benzofuranyl group, a benzothienyl group, a benzimidazolyl group, a benzoxazolyl group, a benzisoxazolyl group, a benzothiazolyl group, a benzisothiazolyl group, an indazolyl group, a purinyl group, a quinolyl

group, an isoquinolyl group, a phthalazinyl group, a naphthyridinyl group, a quinoxalinyl group, a quinazolinyl group, a cinnolinyl group, a pteridinyl group, a pyrido[3,2-b]pyridyl group and the like.

The term "cycloalkyl" includes a monocyclic or polycyclic, saturated or partially-unsaturated carbocyclic group having from 3 to 10, preferably from 3 to 8 carbon atoms, concretely, for example, a cyclopropyl group, a cyclobutenyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, a cyclononyl group, a cyclodecyl group, a bicyclohexyl group, an adamantyl group and the like.

The term "cycloheteroalkyl" includes an aziridine ring, oxolan ring, pyrrolidine ring, piperidine ring, tetrahydropyran ring, tetrahydrofuran ring, dioxane ring, morpholine ring 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, glycolylarsanilate, 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.

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

      Some of the compounds described herein contain substituted cycloalkanes having cis-and trans-isomers, and unless specified otherwise, are meant to include both cis- and trans-geometric isomers.

10       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.

15       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  
20       often the formation of salts using an enantiomerically pure acid or base. The diastereomeric 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.

25       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  
30       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.

35       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 ( $^1\text{H}$ ) and deuterium ( $^2\text{H}$ ). 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, dysmnnesia, 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, Ia, Ib or Ic.

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, Ia, Ib or Ic 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, dysmnnesia, 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, Ia, Ib or Ic 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, Ia, Ib or Ic in the manufacture of a medicament for use in treating diabetes.

#### 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, Ia, Ib or Ic 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, Ia, Ib or Ic. When a compound of formula I, Ia, Ib or Ic 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, Ia, Ib or Ic is preferred. However, the combination therapy may also include therapies in which the compound of formula I, Ia, Ib or Ic 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, Ia, Ib or Ic.

Examples of other active ingredients that may be administered in combination with a compound of formula I, Ia, Ib or Ic 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, including (i) PPAR $\gamma$  agonists, such as the glitazones (e.g. pioglitazone, rosiglitazone, netoglitazone, rivoglitazone, and balaglitazone) and other PPAR ligands, including (1) PPAR $\alpha/\gamma$  dual agonists, such as muraglitazar, aleglitazar, sodelglitazar, and naveglitazar, (2) PPAR $\alpha$  agonists, such as fenofibric acid derivatives (gemfibrozil, clofibrate, ciprofibrate, fenofibrate and bezafibrate), (3) selective PPAR $\gamma$  modulators (SPPAR $\gamma$ M's), such as those disclosed in WO 02/060388, WO 02/08188, WO 2004/019869, WO 2004/020409, WO 2004/020408, and WO 2004/066963, and (4) PPAR $\gamma$  partial agonists; (ii) biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin hydrochloride, and extended-release formulations thereof, such as Glumetza®, Fortamet®, and GlucophageXR®; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(3) insulin or insulin analogs, such as insulin lispro, insulin detemir, insulin glargine, insulin glulisine, and inhalable formulations of each thereof;

(4) leptin and leptin derivatives and agonists;

(5) amylin and amylin analogs, such as pramlintide;

(6) sulfonylurea and non-sulfonylurea insulin secretagogues, such as tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, and meglitinides, such as nateglinide and repaglinide;

(7)  $\alpha$ -glucosidase inhibitors (such as acarbose, voglibose and miglitol);

(8) glucagon receptor antagonists, such as those disclosed in WO 98/04528, WO 99/01423, WO 00/39088, and WO 00/69810;

(9) incretin mimetics, such as GLP-1, GLP-1 analogs, derivatives, and mimetics; and GLP-1 receptor agonists, such as exenatide, liraglutide, taspoglutide, AVE0010, CJC-1131, and BIM-51077, including intranasal, transdermal, and once-weekly formulations thereof;

(10) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin), (ii) bile acid sequestering agents (such as cholestyramine, colestimide, colesevelam hydrochloride, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran, (iii) inhibitors of cholesterol absorption, such as ezetimibe, and (iv) acyl CoA:cholesterol acyltransferase inhibitors, such as avasimibe;

(11) HDL-raising drugs, such as niacin or a salt thereof and extended-release versions thereof; MK-524A, which is a combination of niacin extended-release and the DP-1 antagonist MK-524; and nicotinic acid receptor agonists;

(12) antiobesity compounds;

(13) agents intended for use in inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and selective cyclooxygenase-2 (COX-2) inhibitors;

(14) antihypertensive agents, such as ACE inhibitors (such as enalapril, lisinopril, ramipril, captopril, quinapril, and tandolapril), A-II receptor blockers (such as losartan, candesartan, irbesartan, olmesartan medoxomil, valsartan, telmisartan, and eprosartan), renin inhibitors (such as aliskiren), beta blockers (such as and calcium channel blockers (such as;

(15) glucokinase activators (GKAs), such as LY2599506;

(16) inhibitors of 11 $\beta$ -hydroxysteroid dehydrogenase type 1, such as those disclosed in U.S. Patent No. 6,730,690; WO 03/104207; and WO 04/058741;

(17) inhibitors of cholesteryl ester transfer protein (CETP), such as torcetrapib and MK-0859;

(18) inhibitors of fructose 1,6-bisphosphatase, such as those disclosed in U.S. Patent Nos. 6,054,587; 6,110,903; 6,284,748; 6,399,782; and 6,489,476;

(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, such as those disclosed in WO 2009/011836;

(23) neuromedin U receptor agonists, such as those disclosed in WO2009/042053, including, but not limited to, neuromedin S (NMS);

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

(25) GPR-105 antagonists, such as those disclosed in WO 2009/000087;

(26) inhibitors of glucose uptake, such as sodium-glucose transporter (SGLT) inhibitors and its various isoforms, such as SGLT-1; SGLT-2, such as dapagliflozin, canagliflozin and remogliflozin and those described in WO2010/023594 such as PF-04971729; and SGLT-3;

(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.

Dipeptidyl peptidase-IV (DPP-4) inhibitors that can be used in combination with compounds of formula I, Ia, Ib or Ic include, but are not limited to, sitagliptin (disclosed in US Patent No. 6,699,871), vildagliptin, saxagliptin, alogliptin, denagliptin, carmegliptin, dutogliptin, melogliptin, linagliptin, and pharmaceutically acceptable salts thereof, and fixed-dose combinations of these compounds with metformin hydrochloride, pioglitazone, rosiglitazone, simvastatin, atorvastatin, or a sulfonylurea.

Other dipeptidyl peptidase-IV (DPP-4) inhibitors that can be used in combination with compounds of formula I, Ia, Ib or Ic include, but are not limited to:

(2*R*,3*S*,5*R*)-5-(1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine;

(2*R*,3*S*,5*R*)-5-(1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)-2-(2,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-3-amine;

(2*R*,3*S*,5*R*)-2-(2,5-difluorophenyl)tetrahydro-5-(4,6-dihydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)tetrahydro-2*H*-pyran-3-amine;

(3*R*)-4-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-hexahydro-3-methyl-2*H*-1,4-diazepin-2-one;

4-[(3*R*)-3-amino-4-(2,5-difluorophenyl)butanoyl]hexahydro-1-methyl-2*H*-1,4-diazepin-2-one hydrochloride; and

(3*R*)-4-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-hexahydro-3-(2,2,2-trifluoroethyl)-2*H*-1,4-diazepin-2-one; and

pharmaceutically acceptable salts thereof.

Antiobesity compounds that can be combined with compounds of formula I, Ia, Ib or Ic include topiramate; zonisamide; naltrexone; phentermine; bupropion; the combination of bupropion and naltrexone; the combination of bupropion and zonisamide; the combination of topiramate and phentermine; fenfluramine; dexfenfluramine; sibutramine; lipase inhibitors, such as orlistat and cetilistat; melanocortin receptor agonists, in particular, melanocortin-4 receptor agonists; CCK-1 agonists; melanin-concentrating hormone (MCH) receptor antagonists; neuropeptide Y<sub>1</sub> or Y<sub>5</sub> antagonists (such as MK-0557); CB1 receptor inverse agonists and antagonists (such as rimonabant and taranabant);  $\beta_3$  adrenergic receptor agonists; ghrelin antagonists; bombesin receptor agonists (such as bombesin receptor subtype-3 agonists); and 5-hydroxytryptamine-2c (5-HT<sub>2c</sub>) agonists, such as



lorcaserin. For a review of anti-obesity compounds that can be combined with compounds of the present invention, see S. Chaki et al., "Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity," *Expert Opin. Ther. Patents*, 11: 1677-1692 (2001); D. Spanswick and K. Lee, "Emerging antiobesity drugs," *Expert Opin. Emerging Drugs*, 8: 217-237 (2003); J.A. Fernandez-Lopez, et al., "Pharmacological Approaches for the Treatment of Obesity," *Drugs*, 62: 915-944 (2002); and K.M. Gadde, et al., "Combination pharmaceutical therapies for obesity," *Exp. Opin. Pharmacother.*, 10: 921-925 (2009).

Glucagon receptor antagonists that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:

- 10 *N*-[4-((1*S*)-1-{3-(3,5-dichlorophenyl)-5-[6-(trifluoromethoxy)-2-naphthyl]-1*H*-pyrazol-1-yl}ethyl)benzoyl]-β-alanine;  
*N*-[4-((1*R*)-1-{3-(3,5-dichlorophenyl)-5-[6-(trifluoromethoxy)-2-naphthyl]-1*H*-pyrazol-1-yl}ethyl)benzoyl]-β-alanine;  
*N*-(4-{1-[3-(2,5-dichlorophenyl)-5-(6-methoxy-2-naphthyl)-1*H*-pyrazol-1-yl]ethyl}benzoyl)-β-  
15 alanine;  
*N*-(4-{(1*S*)-1-[3-(3,5-dichlorophenyl)-5-(6-methoxy-2-naphthyl)-1*H*-pyrazol-1-yl]ethyl}benzoyl)-β-alanine;  
*N*-(4-{(1*S*)-1-[(*R*)-(4-chlorophenyl)(7-fluoro-5-methyl-1*H*-indol-3-yl)methyl]butyl}benzoyl)-β-alanine; and  
20 *N*-(4-{(1*S*)-1-[(4-chlorophenyl)(6-chloro-8-methylquinolin-4-yl)methyl]butyl}benzoyl)-β-alanine; and  
pharmaceutically acceptable salts thereof.

Inhibitors of stearoyl-coenzyme A delta-9 desaturase (SCD) that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:

- 25 [5-(5-{4-[2-(trifluoromethyl)phenoxy]piperidin-1-yl}-1,3,4-thiadiazol-2-yl)-2*H*-tetrazol-2-yl]acetic acid;  
(2'-{4-[2-(trifluoromethyl)phenoxy]piperidin-1-yl}-2,5'-bi-1,3-thiazol-4-yl)acetic acid;  
(5-{3-[4-(2-bromo-5-fluorophenoxy)piperidin-1-yl]isoxazol-5-yl}-2*H*-tetrazol-2-yl)acetic acid;  
(3-{3-[4-(2-bromo-5-fluorophenoxy)piperidin-1-yl]-1,2,4-oxadiazol-5-yl}-1*H*-pyrrol-1-yl)acetic  
30 acid;  
(5-{5-[4-(2-bromo-5-fluorophenoxy)piperidin-1-yl]pyrazin-2-yl}-2*H*-tetrazol-2-yl)acetic acid;  
and  
(5-{2-[4-(5-bromo-2-chlorophenoxy)piperidin-1-yl]pyrimidin-5-yl}-2*H*-tetrazol-2-yl)acetic acid;  
and pharmaceutically acceptable salts thereof.

- 35 Glucokinase activators that can be used in combination with the compounds of formula I, Ia, Ib or Ic, but are not limited to:

3-(6-ethanesulfonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;  
 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulfonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;  
 5 5-(1-hydroxymethyl-propoxy)-3-(6-methanesulfonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;  
 3-(6-methanesulfonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;  
 5-isopropoxy-3-(6-methanesulfonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;  
 10 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulfonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;  
 3-({4-[2-(dimethylamino)ethoxy]phenyl}thio)-N-(3-methyl-1,2,4-thiadiazol-5-yl)-6-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]pyridine-2-carboxamide;  
 3-({4-[(1-methylazetidin-3-yl)oxy]phenyl}thio)-N-(3-methyl-1,2,4-thiadiazol-5-yl)-6-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]pyridine-2-carboxamide;  
 15 N-(3-methyl-1,2,4-thiadiazol-5-yl)-6-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]-3-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]thio}pyridine-2-carboxamide; and  
 3-[(4-{2-[(2R)-2-methylpyrrolidin-1-yl]ethoxy}phenyl)thio]-N-(3-methyl-1,2,4-thiadiazol-5-yl)-6-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]pyridine-2-carboxamide; and pharmaceutically acceptable salts thereof.

Agonists of the GPR-119 receptor that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:

*rac-cis* 5-chloro-2-{4-[2-(2-{[5-(methylsulfonyl)pyridin-2-yl]oxy}ethyl)cyclopropyl]piperidin-1-yl}pyrimidine;

25 5-chloro-2-{4-[(1R,2S)-2-(2-{[5-(methylsulfonyl)pyridin-2-yl]oxy}ethyl)cyclopropyl]piperidin-1-yl}pyrimidine;

*rac cis*-5-chloro-2-[4-(2-{2-[4-(methylsulfonyl)phenoxy]ethyl}cyclopropyl)piperidin-1-yl]pyrimidine;

5-chloro-2-[4-((1S,2R)-2-{2-[4-(methylsulfonyl)phenoxy]ethyl}cyclopropyl)piperidin-1-yl]pyrimidine;

30 5-chloro-2-[4-((1R,2S)-2-{2-[4-(methylsulfonyl)phenoxy]ethyl}cyclopropyl)piperidin-1-yl]pyrimidine;

*rac cis*-5-chloro-2-[4-(2-{2-[3-(methylsulfonyl)phenoxy]ethyl}cyclopropyl)piperidin-1-yl]pyrimidine; and

35 *rac cis* -5-chloro-2-[4-(2-{2-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]ethyl}cyclopropyl)piperidin-1-yl]pyrimidine; and pharmaceutically acceptable salts thereof.

Selective PPAR $\gamma$  modulators (SPPAR $\gamma$ M's) that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:

(2*S*)-2-({6-chloro-3-[6-(4-chlorophenoxy)-2-propylpyridin-3-yl]-1,2-benzisoxazol-5-yl}oxy)propanoic acid;

5 (2*S*)-2-({6-chloro-3-[6-(4-fluorophenoxy)-2-propylpyridin-3-yl]-1,2-benzisoxazol-5-yl}oxy)propanoic acid;

(2*S*)-2-{{6-chloro-3-(6-phenoxy-2-propylpyridin-3-yl)-1,2-benzisoxazol-5-yl}oxy}propanoic acid;

10 (2*R*)-2-({6-chloro-3-[6-(4-chlorophenoxy)-2-propylpyridin-3-yl]-1,2-benzisoxazol-5-yl}oxy)propanoic acid;

(2*R*)-2-{3-[3-(4-methoxy)benzoyl-2-methyl-6-(trifluoromethoxy)-1*H*-indol-1-yl]phenoxy}butanoic acid;

(2*S*)-2-{3-[3-(4-methoxy)benzoyl-2-methyl-6-(trifluoromethoxy)-1*H*-indol-1-yl]phenoxy}butanoic acid;

15 2-{3-[3-(4-methoxy)benzoyl-2-methyl-6-(trifluoromethoxy)-1*H*-indol-1-yl]phenoxy}-2-methylpropanoic acid; and

(2*R*)-2-{3-[3-(4-chloro)benzoyl-2-methyl-6-(trifluoromethoxy)-1*H*-indol-1-yl]phenoxy}propanoic acid; and pharmaceutically acceptable salts thereof.

20 Inhibitors of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:

3-[1-(4-chlorophenyl)-*trans*-3-fluorocyclobutyl]-4,5-dicyclopropyl-*r*-4*H*-1,2,4-triazole; 3-[1-(4-chlorophenyl)-*trans*-3-fluorocyclobutyl]-4-cyclopropyl-5-(1-methylcyclopropyl)-*r*-4*H*-1,2,4-triazole;

25 3-[1-(4-chlorophenyl)-*trans*-3-fluorocyclobutyl]-4-methyl-5-[2-(trifluoromethoxy)phenyl]-*r*-4*H*-1,2,4-triazole;

3-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole;

3-{4-[3-(ethylsulfonyl)propyl]bicyclo[2.2.2]oct-1-yl}-4-methyl-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole;

30 4-methyl-3-{4-[4-(methylsulfonyl)phenyl]bicyclo[2.2.2]oct-1-yl}-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole;

3-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-5-(3,3,3-trifluoropropyl)-1,2,4-oxadiazole;

3-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-5-(3,3,3-trifluoroethyl)-1,2,4-oxadiazole;

35 5-(3,3-difluorocyclobutyl)-3-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-1,2,4-oxadiazole;

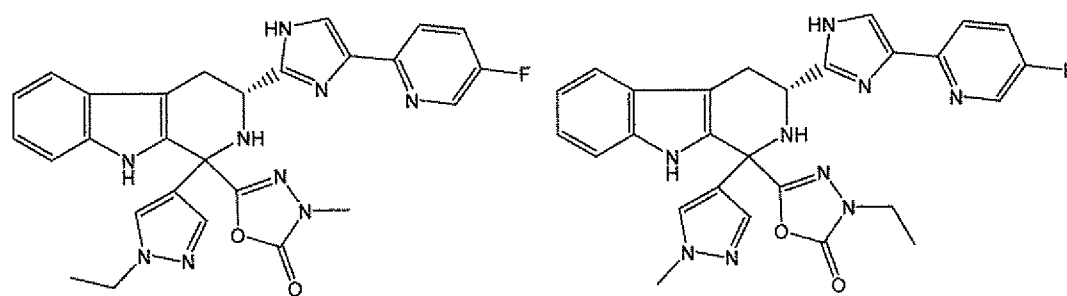
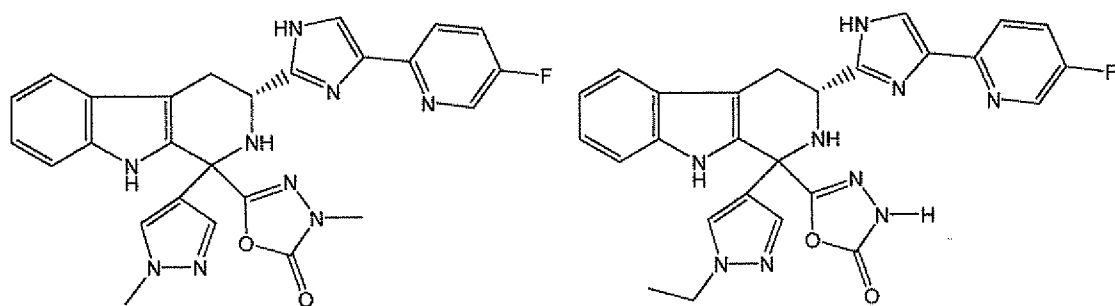
5-(1-fluoro-1-methylethyl)-3-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-1,2,4-oxadiazole;

2-(1,1-difluoroethyl)-5-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-1,3,4-oxadiazole;

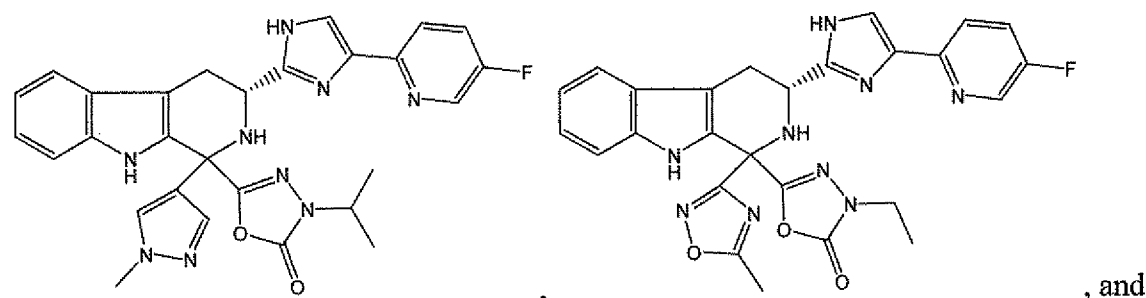
5 2-(3,3-difluorocyclobutyl)-5-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-1,3,4-oxadiazole; and

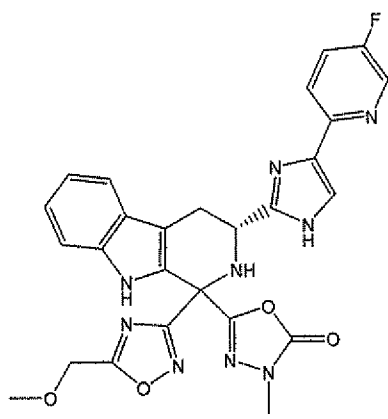
5-(1,1-difluoroethyl)-3-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-1,2,4-oxadiazole; and pharmaceutically acceptable salts thereof.

10 Somatostatin subtype receptor 3 (SSTR3) antagonists that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:



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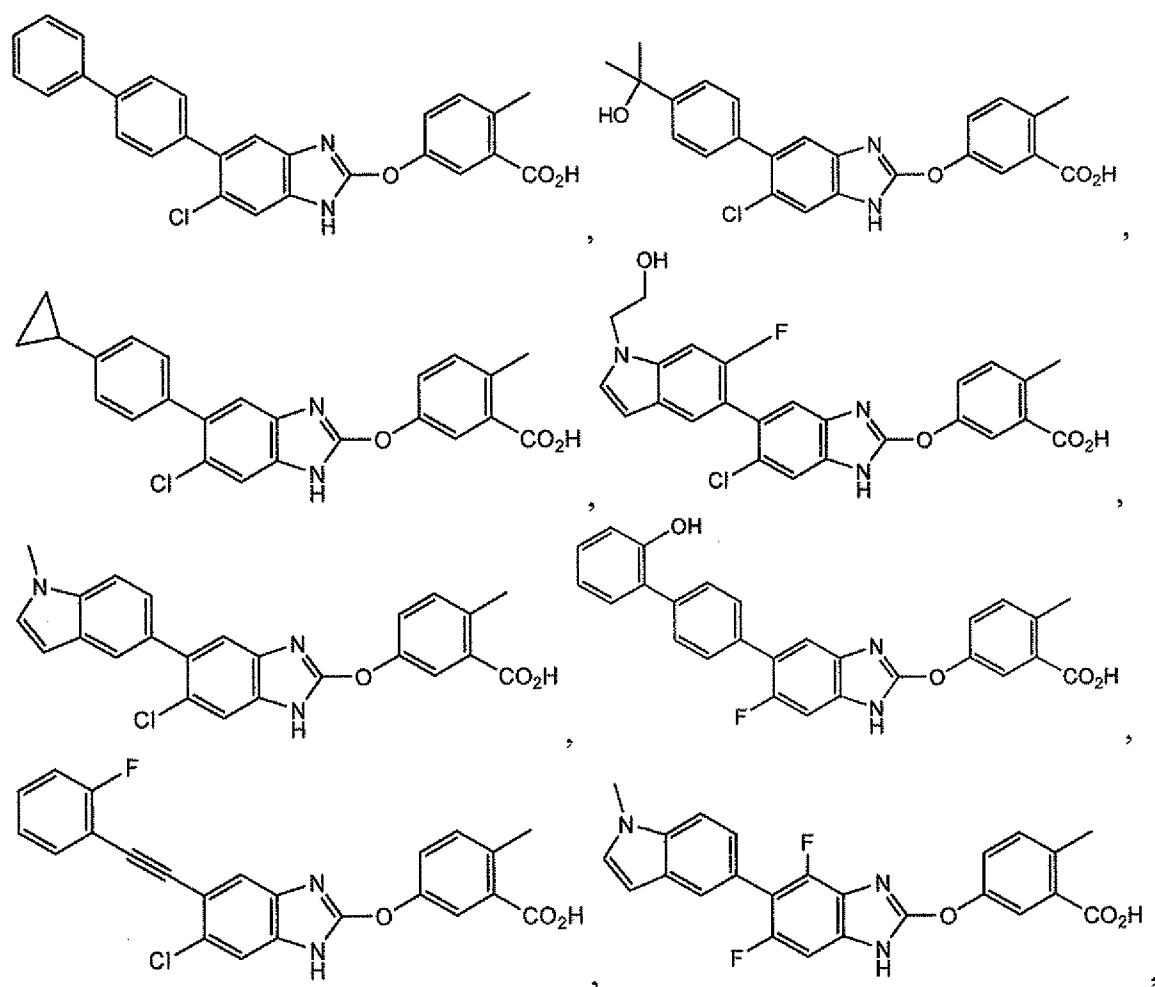


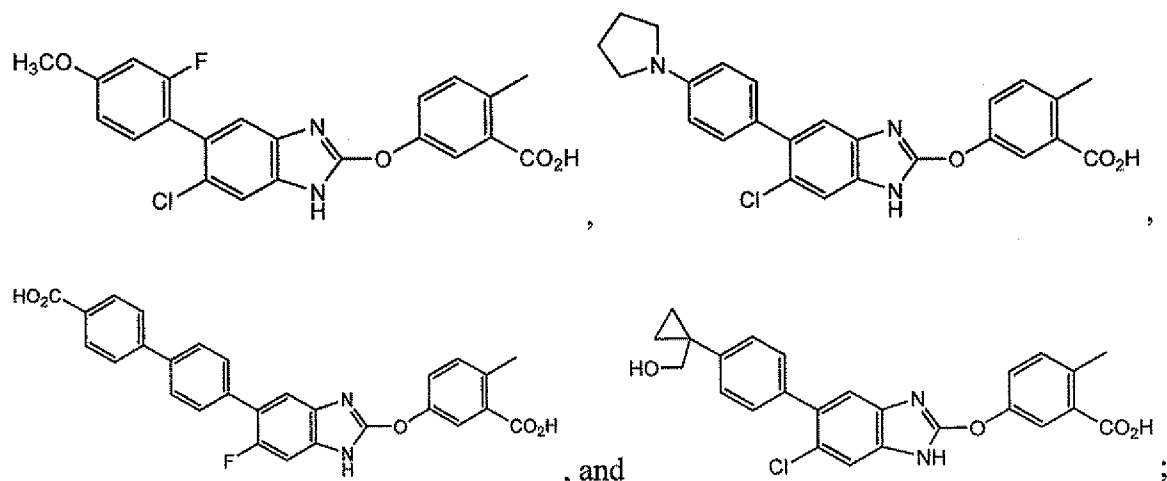


and pharmaceutically acceptable salts thereof.

AMP-activated Protein Kinase (AMPK) activators that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:

5





5 and pharmaceutically acceptable salts thereof.

Inhibitors of acetyl-CoA carboxylase-1 and 2 (ACC-1 and ACC-2) that can be used in combination with the compounds of formula I, Ia, Ib or Ic include, but are not limited to:

3-{1'-[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl}benzoic acid;

10 5-{1'-[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl}nicotinic acid;

1'-[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one;

1'-[(1-cyclopropyl-4-ethoxy-3-methyl-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-

15 yl)spiro[chroman-2,4'-piperidin]-4-one; and

5-{1'-[(1-cyclopropyl-4-methoxy-3-methyl-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl}nicotinic acid; and

pharmaceutically acceptable salts thereof.

20 In another aspect of the invention, a pharmaceutical composition is disclosed which comprises one or more of the following agents:

(a) a compound of structural formula I, Ia, Ib or Ic;

(b) one or more compounds selected from the group consisting of:

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

(2) insulin sensitizers, including (i) PPAR $\gamma$  agonists, such as the glitazones (e.g.

25 pioglitazone, rosiglitazone, netoglitazone, rivoglitazone, and balaglitazone) and other PPAR ligands, including (1) PPAR $\alpha/\gamma$  dual agonists, such as muraglitazar, aleglitazar, sodelglitazar, and naveglitazar,

(2) PPAR $\alpha$  agonists, such as fenofibric acid derivatives (gemfibrozil, clofibrate, ciprofibrate, fenofibrate and bezafibrate), (3) selective PPAR $\gamma$  modulators (SPPAR $\gamma$ M's), and (4) PPAR $\gamma$  partial agonists; (ii)

biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin

hydrochloride, and extended-release formulations thereof, such as Glumetza®, Fortamet®, and GlucophageXR®; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(3) sulfonylurea and non-sulfonylurea insulin secretagogues, such as tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, and meglitinides, such as nateglinide and repaglinide;

(4)  $\alpha$ -glucosidase inhibitors (such as acarbose, voglibose and miglitol);

(5) glucagon receptor antagonists;

(6) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin),

(ii) bile acid sequestering agents (such as cholestyramine, colestimide, colesevelam hydrochloride, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran, (iii) inhibitors of cholesterol absorption, such as ezetimibe, and (iv) acyl CoA:cholesterol acyltransferase inhibitors, such as avasimibe;

(7) HDL-raising drugs, such as niacin or a salt thereof and extended-release versions thereof; MK-524A, which is a combination of niacin extended-release and the DP-1 antagonist MK-524; and nicotinic acid receptor agonists;

(8) antiobesity compounds;

(9) agents intended for use in inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and selective cyclooxygenase-2 (COX-2) inhibitors;

(10) antihypertensive agents, such as ACE inhibitors (such as enalapril, lisinopril, ramipril, captopril, quinapril, and tandolapril), A-II receptor blockers (such as losartan, candesartan, irbesartan, olmesartan medoxomil, valsartan, telmisartan, and eprosartan), renin inhibitors (such as aliskiren), beta blockers (such as and calcium channel blockers (such as;

(11) glucokinase activators (GKAs), such as LY2599506;

(12) inhibitors of  $11\beta$ -hydroxysteroid dehydrogenase type 1;

(13) inhibitors of cholesteryl ester transfer protein (CETP), such as torcetrapib and MK-0859;

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

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

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

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

(18) SSTR3 antagonists;

(19) neuromedin U receptor agonists, including, but not limited to, neuromedin S (NMS);

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

(21) GPR-105 antagonists;

(22) inhibitors of glucose uptake, such as sodium-glucose transporter (SGLT) inhibitors and its various isoforms, such as SGLT-1; SGLT-2, such as dapagliflozin, canagliflozin and remogliflozin and those described in WO2010/023594 such as PF-04971729; and SGLT-3;

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

(24) inhibitors of fatty acid synthase;

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

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

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

(28) bromocriptine mesylate and rapid-release formulations thereof; and  
(c) 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:

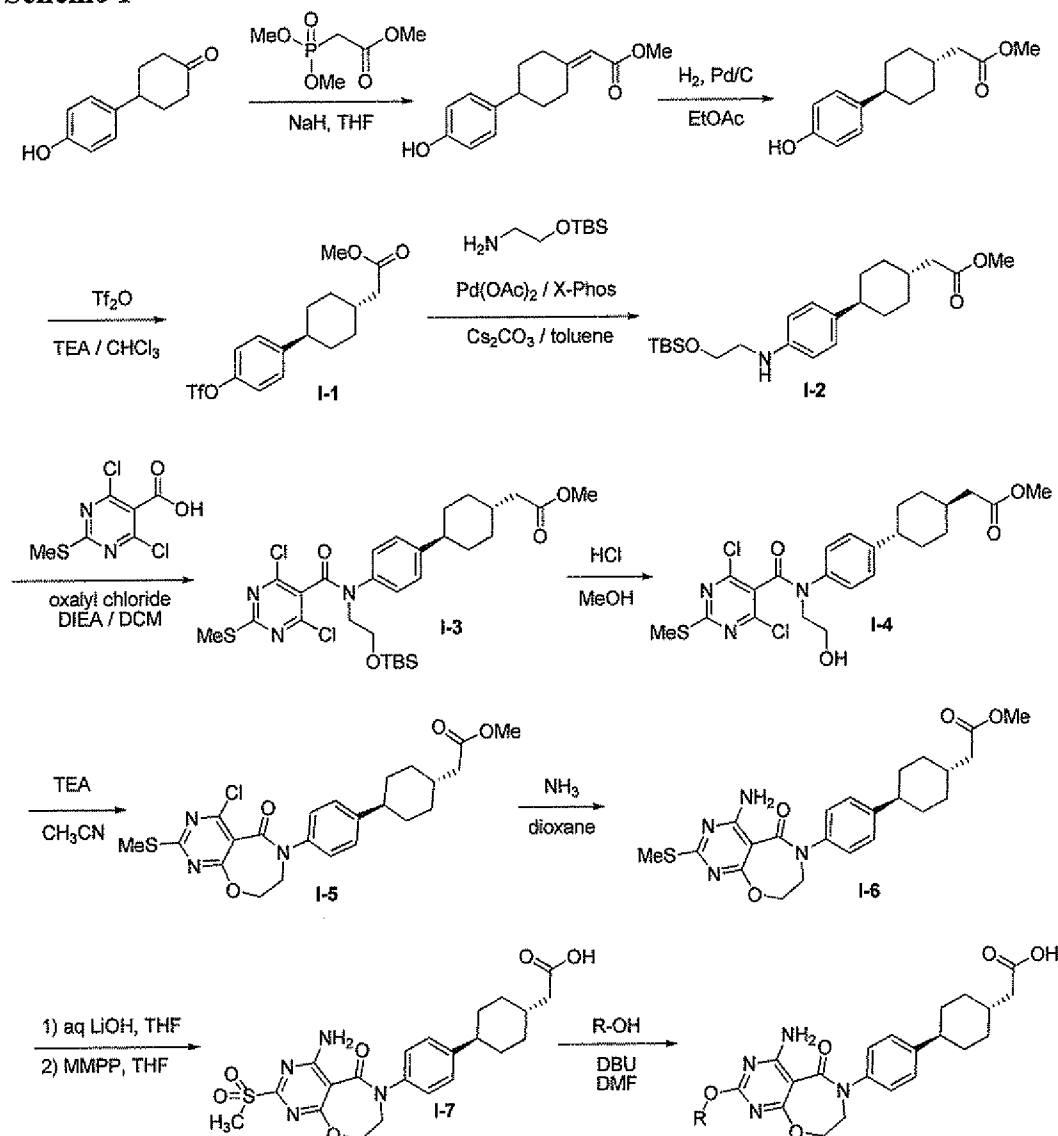
1) LC2 (Waters C18 XTerra™ 3.5 µm 2.1x20 mm column with gradient 10:90-98:2 v/v CH<sub>3</sub>CN/H<sub>2</sub>O + v 0.05 % TFA over 1.25 min then hold at 98:2 v/v CH<sub>3</sub>CN/H<sub>2</sub>O + v 0.05 % TFA

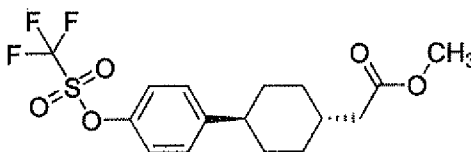


for 0.75 min; flow rate 1.5 mL/min, UV wavelength 254 nm); and 2) LC4 (Waters C18 XTerra 3.5  $\mu$ m 2.1x20 mm column with gradient 10:90-98:2 v/v CH<sub>3</sub>CN/H<sub>2</sub>O + v 0.05 % TFA over 3.25 min then hold at 98:2 v/v CH<sub>3</sub>CN/H<sub>2</sub>O + v 0.05 % TFA for 0.75 min; flow rate 1.5 mL/min, UV wavelength 254 nm); and 3) Waters Acquity UPLC BEH 2.1X50mm, Solvent A: water with 0.1% NH<sub>4</sub>OH, B: Acetonitrile with 0.1% NH<sub>4</sub>OH. Gradient: B% = 5% to 95%, column temperature: 55°C, Flow 1 ml/min, 1  $\mu$ l injection, MS detection: ESI+ (electrospray positive ion), 2 minute 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<sub>3</sub>CN/H<sub>2</sub>O + 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.

### Scheme 1



**Intermediate 1**Methyl [trans-4-(4-((trifluoromethyl)sulfonyl)oxy)phenyl]cyclohexyl]acetate

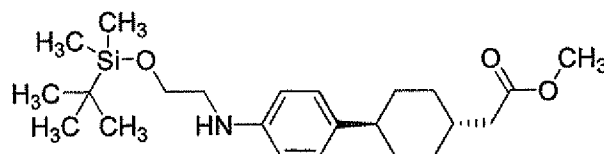
Step A: methyl [4-(4-hydroxyphenyl)cyclohexylidene]acetate. A 2 L 4-neck round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was charged with a solution of sodium hydride (60% in mineral oil, 42.5 g, 1.1 mol, 1.0 equiv) in tetrahydrofuran (500 mL). This was followed by the addition of a solution of 4-(4-hydroxyphenyl)cyclohexanone (200 g, 1.05 mol, 1.00 equiv) in tetrahydrofuran (1000 mL) dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at room temperature. The resulting solution was assigned as solution A. Into a 5 L 4-neck round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of sodium hydride (63 g, 1.7 equiv, 60%) in tetrahydrofuran (1000 mL). This was followed by the addition of a solution of methyl 2-(dimethoxyphosphoryl)acetate (229.7 g 1.2 equiv) in tetrahydrofuran (1500 mL) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at room temperature. To this reaction mixture was added solution A dropwise with stirring. The resulting solution was stirred for 1 h at room temperature, then quenched by the addition of water/ice. The resulting solution was extracted with 3x500 mL of ethyl acetate. The combined organic layers were washed with brine (1 L), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by recrystallization from ether to afford the title compound as a white solid.

Step B: methyl [trans-4-(4-hydroxyphenyl)cyclohexyl]acetate. The product from step A (200 g, 812 mmol, 1.00 equiv) and Pd/C (20 g) in ethyl acetate (2500 mL) was stirred overnight at room temperature under a hydrogen atmosphere. The solid was filtered out. The filtrate was concentrated under vacuum. The crude product was re-crystallized from ethyl acetate/hexane in the ratio of 1:1 to afford the title compound as a white solid.

Step C: methyl [trans-4-(4-((trifluoromethyl)sulfonyl)oxy)phenyl]cyclohexyl]acetate. A 250-mL 4-neck round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was charged with a solution of the product from step B (7.16 g, 28.9 mmol, 1.00 equiv) in chloroform (60 mL) and triethylamine (4.37 g, 43.2 mmol, 1.50 equiv). A solution of trifluoromethanesulfonic anhydride (9.76 g, 34.6 mmol, 1.20 equiv) in chloroform (10 mL) was added dropwise with stirring at 0 °C. The resulting solution was stirred for 1 h at 0°C, quenched

with 100 mL of water/ice. The resulting mixture was washed with aqueous sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by chromatography on silica gel (1:10 ethyl acetate/petroleum ether) to afford the title compound as a white solid. HPLC/MS: 381.01 (M+H); R<sub>t</sub> 1.31 min (LC2).

### Intermediate 2

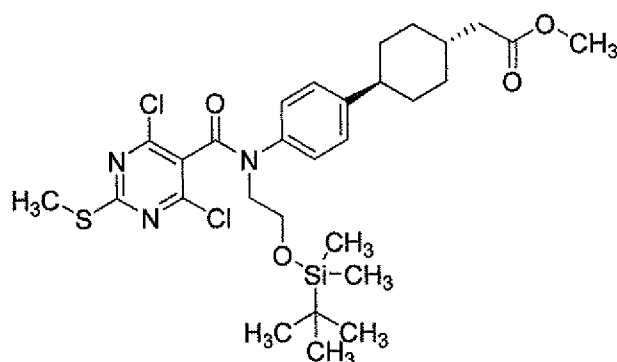


Methyl (trans-4-{4-[(2-{tert-butyl(dimethyl)silyl}oxy)ethyl]amino}phenyl)cyclohexyl)acetate.

Into a 1000-mL sealed tube, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of Intermediate 1 (100 g, 263.16 mmol, 1.00 equiv) in toluene (500 mL), 2-(tert-butyl(dimethyl)silyloxy)ethanamine (55.3 g, 316.00 mmol, 1.20 equiv), Cs<sub>2</sub>CO<sub>3</sub> (85.7 g, 1.00 equiv), Pd(OAc)<sub>2</sub> (5.9 g, 0.10 equiv) and X-Phos (12.6 g, 0.10 equiv). The resulting solution was stirred overnight at 116 °C. The resulting mixture was cooled and concentrated under vacuum.

The residue was purified by chromatography on silica gel (1:30 ethyl acetate/petroleum ether) to afford the title compound as a yellow oil. HPLC/MS: 406.34 (M+H); R<sub>t</sub> 3.81 min (LC4).

### Intermediate 3

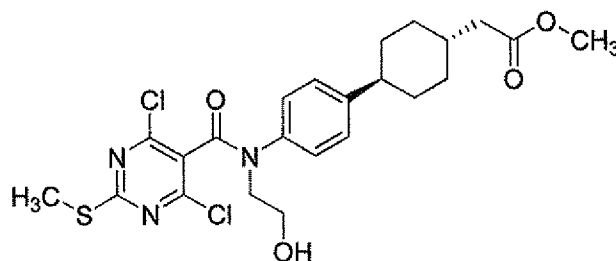


Methyl (trans-4-{4-[(2-{tert-butyl(dimethyl)silyl}oxy)ethyl]([4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]carbonyl)amino}phenyl)cyclohexyl)acetate.

A 50-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was charged with a solution of 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (700 mg, 2.93 mmol, 1.50 equiv) and N,N-dimethylformamide (1 drop) in dichloromethane (10 mL). The solution was treated with oxalyl chloride (750 mg, 5.91 mmol, 3.00 equiv)

dropwise with stirring, stirred for 2 h at room temperature and then treated with a solution of Intermediate 2 (800 mg, 1.97 mmol, 1.00 equiv) in dichloromethane (10 mL) and DIEA (2 mL) dropwise with stirring at 0°C. The resulting solution was stirred for an additional 1 h at room temperature, concentrated under vacuum and the residue was purified by chromatography on silica gel (1:10 ethyl acetate/petroleum ether) to afford the title compound as a colorless oil. HPLC/MS: 626.31 (M+H); R<sub>t</sub> 4.78 min (LC4).

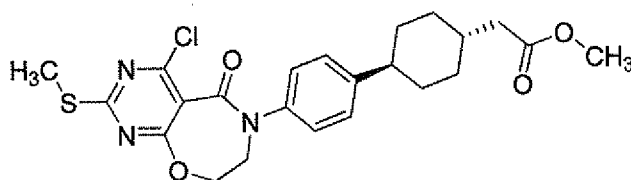
#### Intermediate 4



- 10 Methyl (trans-4-{4-[[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]carbonyl}(2-hydroxyethyl)amino]phenyl}cyclohexyl)acetate.

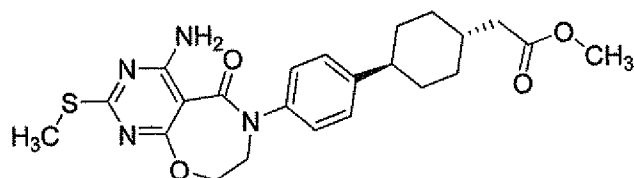
A 2-L round-bottom flask was charged with a solution of Intermediate 3 (80 g, 128.00 mmol, 1.00 equiv) in methanol (800 mL) and HCl (36%, 10 mL). The resulting solution was stirred for 1 h at room temperature, then concentrated under vacuum. The residue was dissolved in 500 mL of EtOAc and washed with 500 mL of aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound as a yellow oil. HPLC/MS: 512.19 (M+H); R<sub>t</sub> 3.65 min (LC4).

#### Intermediate 5



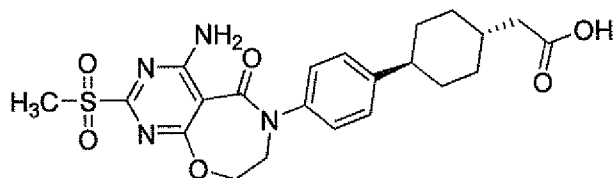
- 20 Methyl (trans-4-{4-[4-chloro-2-(methylsulfanyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetate.

A 1-L round-bottom flask was charged with a solution of Intermediate 4 (60 g, 117.19 mmol, 1.00 equiv) and triethylamine (80 mL) in acetonitrile (600 mL). The resulting solution was stirred for 5 h at 80°C, cooled to room temperature with a water/ice bath and concentrated under vacuum. The residue was diluted with 500 mL of DCM and washed with 1x500 mL of H<sub>2</sub>O. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by recrystallization from methanol to afford the title compound as a white solid. HPLC/MS: 476.20 (M+H); R<sub>t</sub> 3.69 min (LC4).

**Intermediate 6**

Methyl (trans-4-{4-[4-amino-2-(methylsulfanyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetate.

A 2 L 3-neck round-bottom flask was charged with Intermediate 5 (40 g, 84.2 mmol, 1.00 equiv) and a 1 M solution of  $\text{NH}_3$  in 1,4-dioxane (1200 mL, 1200 mmol, 14 equiv). The resulting solution was stirred overnight at room temperature, concentrated under vacuum. The residue was diluted with 500 mL of dichloromethane, washed with 500 mL of water and 500 mL of brine. The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. Purification by recrystallization from methanol afforded the title compound as a white solid. HPLC/MS: 457.30 (M+H);  $R_t$  3.38 min (LC4).

**Intermediate 7**

(trans-4-{4-[4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid.

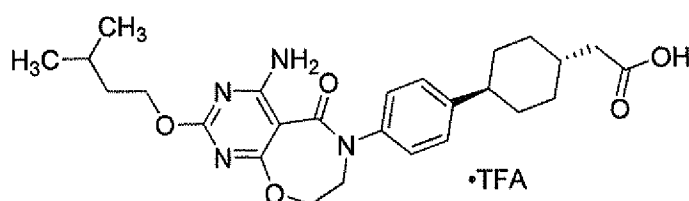
Step A: (trans-4-{4-[4-amino-2-(methylsulfanyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid.

A 250 mL single neck round bottom flask was charged with Intermediate 6 (5.45 g, 11.9 mmol) and THF (60 mL). The mixture was treated with a 2 M aqueous lithium hydroxide solution (29.8 mL, 59.7 mmol), warmed to 55 °C for 16 h, cooled to rt and partitioned between 2 M aq HCl (300 mL) and dichloromethane (400 mL). The aqueous phase was washed with dichloromethane (2 x 150 mL) and the combined organic layers were washed with water (4x150 mL) and then concentrated under reduced pressure to afford the title compound as a crude residue which was used without further purification. HPLC/MS: 443.16 (M+H);  $R_t$  1.111-5 min (LC2).

Step B: (trans-4-{4-[4-amino-2-(methylsulfonyl)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid.

The product from step A (5.28 g, 11.9 mmol) in THF (100 ml) was treated with magnesium bis(monoperoxyphthalate) hexahydrate (8.88 g, 18.0 mmol) was slowly added portionwise to the suspension. The reaction mixture was stirred for 16 h and concentrated under reduced pressure. The residue was dissolved in DMSO (50 mL) and the solution was poured into water (500 mL) with vigorous stirring. The resulting precipitate was collected by vacuum filtration and the filter cake was washed with water (500 ml) and dried under vacuum to afford the title compound as a colorless solid. HPLC/MS: 474.99 (M+H);  $R_t$  1.05 min (LC2).

### Example 1



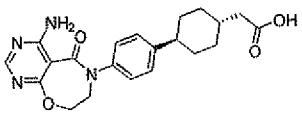
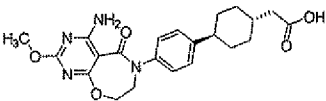
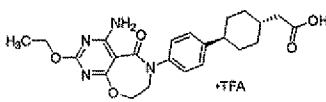
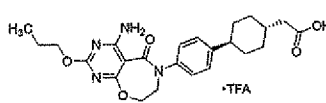
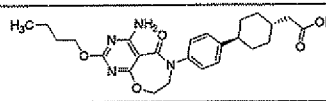
(trans-4-{4-[4-Amino-2-(3-methylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetate salt.

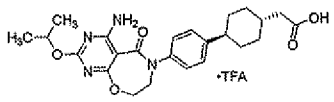
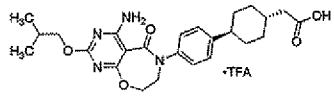
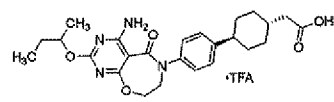
An 8 mL vial was charged with Intermediate 7 (250 mg, 0.527 mmol), isoamyl alcohol (0.574 ml, 5.27 mmol) and DMF (2 ml). The mixture was treated at rt with 1,8-diazabicyclo[5.4.0]undec-7-ene

(0.397 ml, 2.63 mmol), stirred at rt for 18 h and then quenched with glacial AcOH (0.5 mL). Direct purification by RP-HPLC (C18, 30% to 90% ACN/ water+0.05% TFA over 10 min, 25 mL/min, UV 254 nm) afforded the title compound. HPLC/MS: 483.08 (M+H);  $R_t$  1.92 min (LC4); human DGAT1  $IC_{50}$  = 14 nM

All the Reference Examples and Examples in Table 1 and 2 below were prepared using procedures outlined in Scheme 1, except for Reference Example 1, which was synthesized following the procedure from WO2009016462.

Table 1. Reference Examples

| Reference Example Number                                                                                                                                                    | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| <b>Reference Example 1</b><br>{trans-4-[4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)phenyl]cyclohexyl}acetic acid                                     |    | 396.18            | 397.14 (M+H)<br>1.46 min (LC4)                      | 26                                |
| <b>Reference Example 2</b><br>{trans-4-[4-(4-amino-2-methoxy-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)phenyl]cyclohexyl}acetic acid                           |    | 426.19            | 427.18 (M+H);<br>1.05 min (LC2)                     | 22                                |
| <b>Reference Example 3</b><br>{trans-4-[4-(4-amino-2-ethoxy-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)phenyl]cyclohexyl}acetic acid trifluoroacetic acid salt  |  | 440.21            | 441.43 (M+H);<br>0.48 min (UPLC2)                   | 54                                |
| <b>Reference Example 4</b><br>{trans-4-[4-(4-amino-5-oxo-2-propoxy-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)phenyl]cyclohexyl}acetic acid trifluoroacetic acid salt |  | 454.22            | 455.44 (M+H);<br>0.53 min (UPLC2)                   | 193                               |
| <b>Reference Example 9</b><br>{trans-4-[4-(4-amino-2-                                                                                                                       |  | 468.24            | 469.20 (M+H);                                       | 44                                |

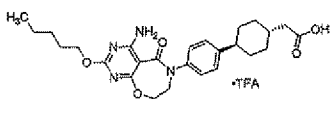
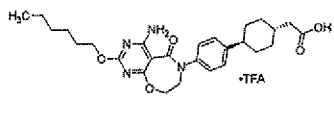
| Reference Example Number                                                                                                                                                               | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| butoxy-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl]cyclohexyl}acetic acid                                                                                            |                                                                                     |                   | 1.14 min (LC2)                                      |                                   |
| <b>Reference Example 10</b><br>(trans-4-{4-[4-amino-5-oxo-2-(propan-2-yloxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetic acid salt  |    | 454.22            | 455.01 (M+H);<br>1.66 min (LC4)                     | 2660                              |
| <b>Reference Example 11</b><br>(trans-4-{4-[4-amino-2-(2-methylpropoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetic acid salt |  | 468.24            | 469.49 (M+H);<br>0.56 min (UPLC2)                   | 470                               |
| <b>Reference Example 12</b><br>(trans-4-{4-[4-amino-2-(butan-2-yloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetic acid salt   |  | 468.24            | 469.48 (M+H);<br>0.57 min (UPLC2)                   | 101                               |

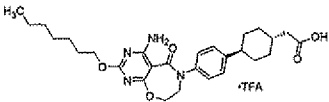
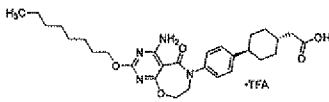
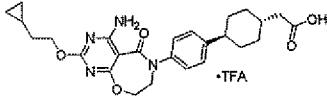


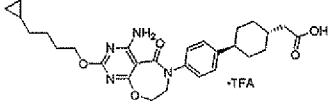
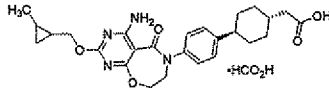
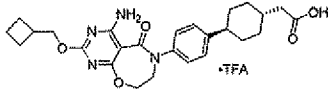
| Reference Example Number | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|--------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| acid salt                |           |                   |                                                     |                                   |

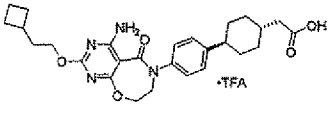
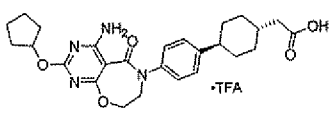
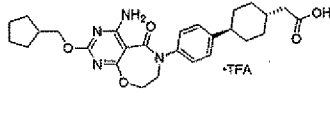
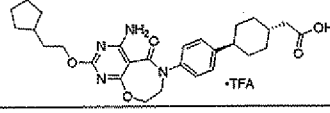
- The following Examples 2-101 were synthesized from the relevant intermediates using procedures adapted from those described in general Scheme 1 and Example 1. Examples 100 and 101 were prepared as shown in Scheme 1 by excluding the aqueous LiOH saponification step (i.e. step 1 in the conversion of I-6 to I-7). Examples 95 and 96, where R-OH is equal to 2-(tetrahydrofuran-2-yl)ethanol, the enantiomers of 2-(tetrahydrofuran-2-yl)ethyl benzoate were separated using chiral HPLC (AD column, 30x250mm, 70ml/min, 5% IPA/hexanes, 230nm). Subsequent saponification (potassium trimethylsilanoate in THF) afforded the single enantiomers which were used in the conversion of I-7 to examples 95 and 96.

Table 2. Examples 2-101

| Example Number                                                                                                                                                        | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| <b>Example 2</b><br>(trans-4-{4-[4-amino-5-oxo-2-(pentyloxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetic acid salt |  | 482.25            | 483.18 (M+H); 1.92 min (LC4)                        | 16                                |
| <b>Example 3</b><br>(trans-4-{4-[4-amino-2-(hexyloxy)-5-oxo-                                                                                                          |  | 496.27            | 497.12 (M+H); 1.19 min                              | 4                                 |

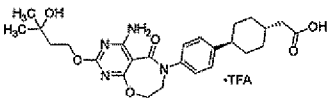
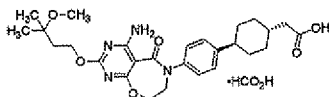
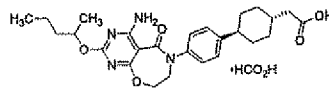
| Example Number                                                                                                                                                         | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| 7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt                                                              |                                                                                     |                   | (LC2)                                               |                                   |
| <b>Example 4</b><br>(trans-4-{4-[4-amino-2-(heptyloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |   | 510.28            | 511.15 (M+H); 2.14 min (LC4)                        | 2                                 |
| <b>Example 5</b><br>(trans-4-{4-[4-amino-2-(octyloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt  |  | 524.30            | 525.13 (M+H); 2.24 min (LC4)                        | 2                                 |
| <b>Example 6</b><br>(trans-4-{4-[4-amino-2-(2-cyclopropylethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)                             |  | 480.24            | 481.08 (M+H); 1.85 min (LC4)                        | 19                                |

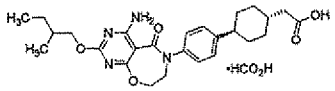
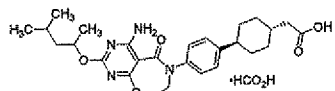
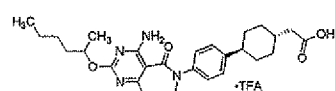
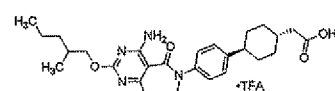
| Example Number                                                                                                                                                                   | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| acetic acid<br>trifluoroacetic acid salt                                                                                                                                         |                                                                                     |                   |                                                     |                                   |
| <b>Example 7</b><br>(trans-4-{4-[4-amino-2-(4-cyclopropylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |    | 508.27            | 509.07 (M+H);<br>2.02 min (LC4)                     | 3                                 |
| <b>Example 8</b><br>[trans-4-(4-{4-amino-2-[(2-methylcyclopropyl)methoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt |  | 480.24            | 481.02 (M+H);<br>1.85 (LC4)                         | 26                                |
| <b>Example 9</b><br>(trans-4-{4-[4-amino-2-(cyclobutylmethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt   |  | 480.24            | 481.08 (M+H);<br>2.00 min (LC4)                     | 31                                |

| Example Number                                                                                                                                                                  | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| <b>Example 10</b><br>(trans-4-{4-[4-amino-2-(2-cyclobutylethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetic acid salt |    | 494.25            | 495.16 (M+H); 1.98 min (LC4)                        | 10                                |
| <b>Example 11</b><br>(trans-4-{4-[4-amino-2-(cyclopentyloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetic acid salt     |  | 480.24            | 481.50 (M+H); 0.58 min (UPLC2)                      | 168                               |
| <b>Example 12</b><br>(trans-4-{4-[4-amino-2-(cyclopentylmethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid trifluoroacetic acid salt |  | 494.25            | 495.04 (M+H); 1.93 min (LC4)                        | 11                                |
| <b>Example 13</b><br>(trans-4-{4-[4-amino-                                                                                                                                      |  | 508.27            | 509.10 (M+H);                                       | 4                                 |

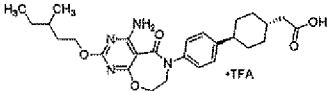
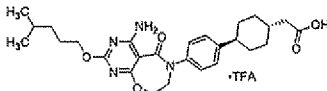
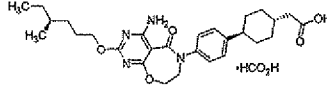
| Example Number                                                                                                                                                            | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| 2-(2-cyclopentylethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt                                   |           |                   | 2.06 min (LC4)                                      |                                   |
| <b>Example 14</b><br>(trans-4-{4-[4-amino-2-(3-cyclopentylpropoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt |           | 522.28            | 523.08 (M+H); 2.16 min (LC4)                        | 3                                 |
| <b>Example 15</b><br>(trans-4-{4-[4-amino-2-(cyclohexylmethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt    |           | 508.27            | 509.07 (M+H); 2.04 min (LC4)                        | 14                                |
| <b>Example 16</b><br>(trans-4-{4-[4-amino-2-(bicyclo[3.1.0]hex-3-ylmethoxy)-5-oxo-                                                                                        |           | 506.25            | 507.13 (M+H); 2.11 min (LC4)                        | 9                                 |

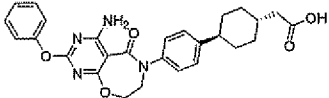
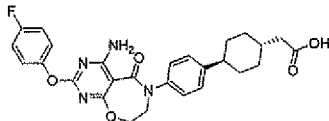
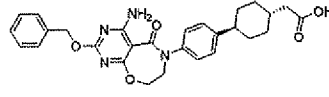
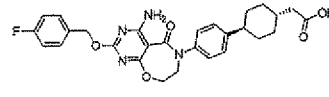
| Example Number                                                                                                                                                          | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| 7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt                                                               |           |                   |                                                     |                                   |
| <b>Example 17</b><br>(trans-4-{4-[4-amino-2-(2-cyclohexylethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt |           | 522.28            | 523.19 (M+H);<br>1.26 min (LC2)                     | 5                                 |
| <b>Example 18</b><br>(trans-4-{4-[4-amino-2-(2,2-dimethylpropoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid                 |           | 482.25            | 483.2 (M+H);<br>1.16 (LC2)                          | 136                               |
| <b>Example 19</b><br>(trans-4-{4-[4-amino-2-(3,3-dimethylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid                  |           | 496.27            | 497.12 (M+H);<br>1.18 min (LC2)                     | 14                                |

| Example Number                                                                                                                                                                         | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt                                                                                                                            |                                                                                     |                   |                                                     |                                   |
| <b>Example 20</b><br>(trans-4-{4-[4-amino-2-(3-hydroxy-3-methylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |    | 498.25            | 499.05 (M+H); 1.59 min (LC4)                        | 334                               |
| <b>Example 21</b><br>(trans-4-{4-[4-amino-2-(3-methoxy-3-methylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt          |  | 512.26            | 513.09 (M+H); 1.10 min (LC2)                        | 317                               |
| <b>Example 22</b><br>(trans-4-{4-[4-amino-5-oxo-2-(pentan-2-yloxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt                    |  | 482.25            | 483.05 (M+H); 1.88 min (LC4)                        | 146                               |

| Example Number                                                                                                                                                                 | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| <b>Example 23</b><br>(trans-4-{4-[4-amino-2-(2-methylbutoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt            |    | 482.25            | 483.06 (M+H); 1.91 min (LC4)                        | 38                                |
| <b>Example 24</b><br>[trans-4-(4-{4-amino-2-[(4-methylpentan-2-yl)oxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)] acetic acid formic acid salt |  | 496.27            | 497.07 (M+H); 1.96 min (LC4)                        | 111                               |
| <b>Example 25</b><br>(trans-4-{4-[4-amino-2-(hexan-2-yloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt    |  | 496.27            | 497.11 (M+H); 1.98 min (LC4)                        | 91                                |
| <b>Example 26</b><br>[trans-4-(4-{4-amino-2-[(2-methylpentyl)oxy]-5-oxo-7,8-                                                                                                   |  | 496.27            | 497.14 (M+H); 2.03 min (LC4)                        | 12                                |



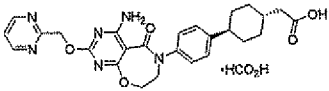
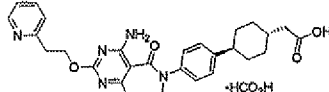
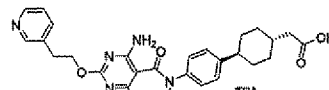
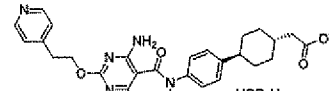
| Example Number                                                                                                                                                                    | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt                                                                             |                                                                                     |                   |                                                     |                                   |
| <b>Example 27</b><br>[trans-4-(4-{4-amino-2-[(3-methylpentyl)oxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt |    | 496.27            | 497.08 (M+H); 2.02 min (LC4)                        | 4                                 |
| <b>Example 28</b><br>[trans-4-(4-{4-amino-2-[(4-methylpentyl)oxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt |  | 496.27            | 497.14 (M+H); 2.03 min (LC4)                        | 4                                 |
| <b>Example 29</b><br>(trans-4-{4-[4-amino-2-[[[(4S)-4-methylhexyl]oxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-                                                       |  | 510.28            | 511.09 (M+H); 2.12 min (LC4)                        | 4                                 |

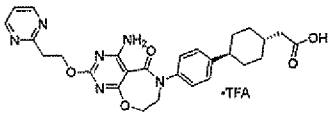
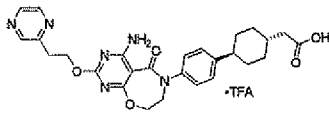
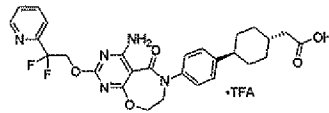
| Example Number                                                                                                                                      | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| yl]phenyl}cyclohexyl) acetic acid formic acid salt                                                                                                  |                                                                                     |                   |                                                     |                                   |
| <b>Example 30</b><br>{trans-4-[4-(4-amino-5-oxo-2-phenoxy-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)phenyl]cyclohexyl} acetic acid           |    | 488.21            | 489.27 (M+H);<br>3.18 min (LC4)                     | 323                               |
| <b>Example 31</b><br>(trans-4-{4-[4-amino-2-(4-fluorophenoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid |  | 506.20            | 507.16 (M+H);<br>1.14 min (LC2)                     | 220                               |
| <b>Example 32</b><br>(trans-4-{4-[4-amino-2-(benzyloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid       |  | 502.22            | 503.17 (M+H);<br>1.16 min (LC2)                     | 52                                |
| <b>Example 33</b><br>[trans-4-(4-{4-amino-2-[(4-fluorobenzyl)oxy]-5-oxo-7,8-dihydropyrimido[5,4-                                                    |  | 520.21            | 521.45 (M+H);<br>0.60 min (UPLC2)                   | 30                                |

| Example Number                                                                                                                                                                         | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| f[1,4]oxazepin-6(5H)-yl}phenyl}cyclohexyl] acetic acid                                                                                                                                 |           |                   |                                                     |                                   |
| <b>Example 34</b><br>(trans-4-{4-[4-amino-5-oxo-2-(2-phenylethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid                                     |           | 516.24            | 517.19 (M+H); 1.15 min (LC2)                        | 30                                |
| <b>Example 35</b><br>(trans-4-{4-[4-amino-5-oxo-2-{[(2S)-2-phenylpropyl]oxy}-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |           | 530.25            | 531.12 (M+H); 2.02 min (LC4)                        | 22                                |
| <b>Example 36</b><br>(trans-4-{4-[4-amino-5-oxo-2-{[(2R)-2-phenylpropyl]oxy}-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |           | 530.25            | 531.10 (M+H); 2.02 min (LC4)                        | 33                                |

| Example Number                                                                                                                                                                   | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| <b>Example 37</b><br>[trans-4-(4-{4-amino-2-[2-(2-methylphenyl)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt     |           | 530.25            | 531.05 (M+H); 2.02 min (LC4)                        | 10                                |
| <b>Example 38</b><br>(trans-4-{4-[4-amino-5-oxo-2-(3-phenylpropoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid formic acid salt              |           | 530.25            | 531.07 (M+H); 1.16 min (LC2)                        | 7                                 |
| <b>Example 39</b><br>(trans-4-{4-[4-amino-5-oxo-2-(3-phenylbutoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid formic acid salt               |           | 544.27            | 545.07 (M+H); 1.16 min (LC2)                        | 18                                |
| <b>Example 40</b><br>[trans-4-(4-{4-amino-5-oxo-2-[(2-phenylcyclopropyl)methoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt |           | 542.25            | 543.53 (M+H); 0.67 min (UPLC2)                      | 10                                |

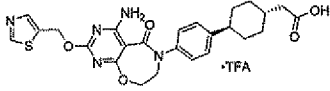
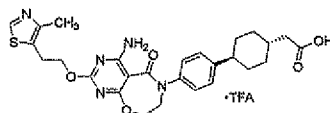
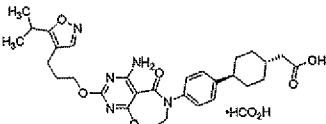
| Example Number                                                                                                                                                                    | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| hoxyl]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt                                                                  |           |                   |                                                     |                                   |
| <b>Example 41</b><br>(trans-4-{4-[4-amino-5-oxo-2-(pyridin-2-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |           | 503.22            | 504.47 (M+H); 0.49 min (UPLC2)                      | 95                                |
| <b>Example 42</b><br>(trans-4-{4-[4-amino-5-oxo-2-(pyridin-3-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |           | 503.22            | 504.46 (M+H); 0.48 min (UPLC2)                      | 2020                              |
| <b>Example 43</b><br>(trans-4-{4-[4-amino-5-oxo-2-(pyridin-4-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid                           |           | 503.22            | 504.70 (M+H); 0.48 min (UPLC2)                      | 7230                              |

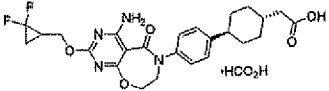
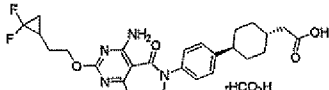
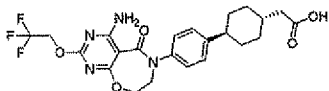
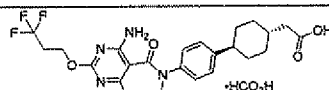
| Example Number                                                                                                                                                                      | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| trifluoroacetic acid salt                                                                                                                                                           |                                                                                     |                   |                                                     |                                   |
| <b>Example 44</b><br>(cis-4-{4-[4-amino-5-oxo-2-(pyrimidin-2-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid formic acid salt             |    | 504.21            | 505.07 (M+H); 1.05 min (LC2)                        | 366                               |
| <b>Example 45</b><br>[trans-4-(4-{4-amino-5-oxo-2-[2-(pyridin-2-yl)ethoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt          |  | 517.23            | 518.04 (M+H); 1.41 min (LC4)                        | 47                                |
| <b>Example 46</b><br>[trans-4-(4-{4-amino-5-oxo-2-[2-(pyridin-3-yl)ethoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid trifluoroacetic acid salt |  | 517.23            | 518.12 (M+H); 1.49 min (LC4)                        | 1160                              |
| <b>Example 47</b><br>[trans-4-(4-{4-amino-5-oxo-2-[2-(pyridin-4-yl)ethoxy]-7,8-                                                                                                     |  | 517.23            | 518.13 (M+H); 1.01 min (LC2)                        | 1340                              |

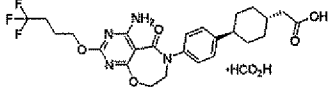
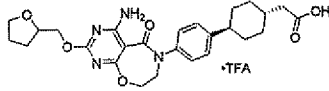
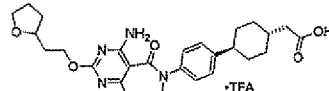
| Example Number                                                                                                                                                                         | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid formic acid salt                                                                                           |                                                                                     |                   |                                                     |                                   |
| <b>Example 48</b><br>[trans-4-(4-{4-amino-5-oxo-2-[2-(pyrimidin-2-yl)ethoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt |    | 518.23            | 519.13 (M+H); 1.68 min (LC4)                        | 1930                              |
| <b>Example 49</b><br>[trans-4-(4-{4-amino-5-oxo-2-[2-(pyrazin-2-yl)ethoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt   |  | 518.23            | 519.11 (M+H); 1.71 min (LC4)                        | 356                               |
| <b>Example 50</b><br>[trans-4-(4-{4-amino-2-[2,2-difluoro-2-(pyridin-2-yl)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid                |  | 553.21            | 554.11 (M+H); 1.97 min (LC4)                        | 101                               |

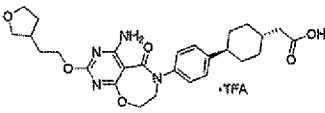
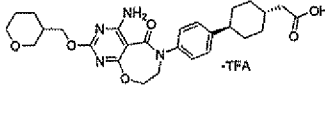
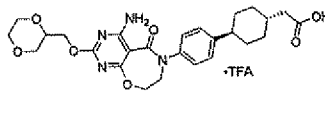
| Example Number                                                                                                                                                                              | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| trifluoroacetic acid salt                                                                                                                                                                   |           |                   |                                                     |                                   |
| <b>Example 51</b><br>(trans-4-{4-[4-amino-2-{2-[6-(cyclobutyloxy)pyridin-2-yl]ethoxy}-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid formic acid salt |           | 587.27            | 588.18 (M+H); 1.18 min (LC2)                        | 25                                |
| <b>Example 52</b><br>[trans-4-(4-{4-amino-5-oxo-2-[3-(pyridin-2-yl)propoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt                 |           | 531.25            | 532.03 (M+H); 1.44 min (LC4)                        | 138                               |
| <b>Example 53</b><br>(trans-4-{4-[4-amino-5-oxo-2-(1,3-thiazol-2-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid                                  |           | 509.17            | 510.38 (M+H); 0.49 min (UPLC2)                      | 135                               |
| <b>Example 54</b><br>(trans-4-{4-[4-amino-5-oxo-2-(1,3-thiazol-4-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid                                  |           | 509.17            | 510.38 (M+H); 0.48 min                              | 146                               |

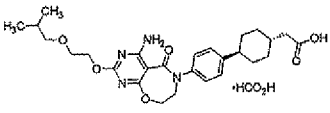
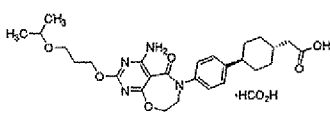
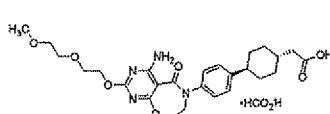
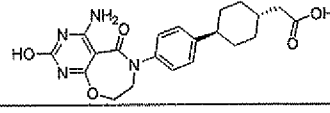


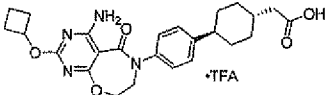
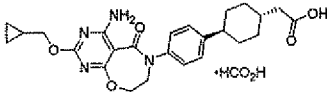
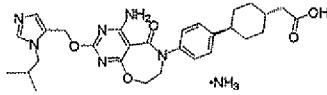
| Example Number                                                                                                                                                                                     | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl} cyclohexyl) acetic acid                                                                                                        |                                                                                     |                   | (UPLC2)                                             |                                   |
| <b>Example 55</b><br>(trans-4-{4-[4-amino-5-oxo-2-(1,3-thiazol-5-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl} cyclohexyl) acetic acid trifluoroacetic acid salt             |    | 509.17            | 510.42 (M+H); 0.48 min (UPLC2)                      | 4170                              |
| <b>Example 56</b><br>[trans-4-(4-{4-amino-2-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl} cyclohexyl) acetic acid trifluoroacetic acid salt |  | 537.20            | 538.11 (M+H); 1.69 min (LC4)                        | 452                               |
| <b>Example 57</b><br>(trans-4-{4-[4-amino-5-oxo-2-{3-[5-(propan-2-yl)isoxazol-4-yl]propoxy}-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl} cyclohexyl)                                   |  | 563.27            | 564.17 (M+H); 1.17 min (LC2)                        | 36                                |

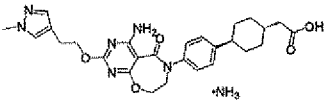
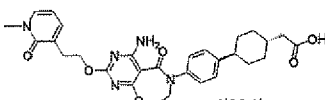
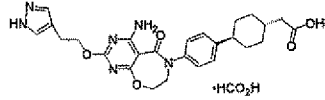
| Example Number                                                                                                                                                                        | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| acetic acid formic acid salt                                                                                                                                                          |                                                                                     |                   |                                                     |                                   |
| <b>Example 58</b><br>[trans-4-(4-{4-amino-2-[(2,2-difluorocyclopropyl)methoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt  |    | 502.20            | 503.02 (M+H); 1.09 min (LC2)                        | 178                               |
| <b>Example 59</b><br>[trans-4-(4-{4-amino-2-[2-(2,2-difluorocyclopropyl)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt |  | 516.22            | 517.07 (M+H); 1.15 min (LC2)                        | 65                                |
| <b>Example 60</b><br>(trans-4-{4-[4-amino-5-oxo-2-(2,2,2-trifluoroethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl)acetic acid                              |  | 494.18            | 495.11 (M+H); 1.15 min (LC2)                        | 193                               |
| <b>Example 61</b><br>(trans-4-{4-[4-amino-                                                                                                                                            |  | 508.19            | 509.08 (M+H);                                       | 290                               |

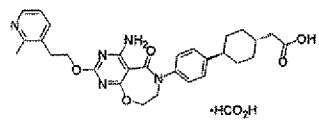
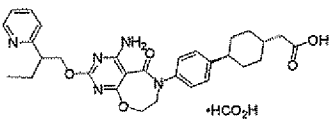
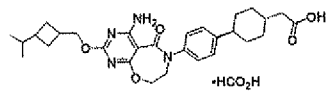
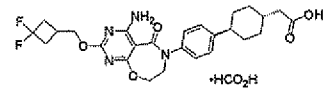
| Example Number                                                                                                                                                                            | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| 5-oxo-2-(3,3,3-trifluoropropoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt                                                         |                                                                                     |                   | 1.14 min (LC2)                                      |                                   |
| <b>Example 62</b><br>(cis-4-{4-[4-amino-5-oxo-2-(4,4,4-trifluorobutoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt                  |   | 522.21            | 523.04 (M+H);<br>1.14 min (LC2)                     | 52                                |
| <b>Example 63</b><br>(trans-4-{4-[4-amino-5-oxo-2-(tetrahydrofuran-2-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |  | 496.23            | 497.11 (M+H);<br>1.77 min (LC4)                     | 236                               |
| <b>Example 64</b><br>[trans-4-(4-{4-amino-5-oxo-2-[2-(tetrahydrofuran-2-yl)ethoxy]-7,8-dihydropyrimido[5,4-                                                                               |  | 510.25            | 511.14 (M+H);<br>1.83 min (LC4)                     | 52                                |

| Example Number                                                                                                                                                                                | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt                                                                                                             |                                                                                     |                   |                                                     |                                   |
| <b>Example 65</b><br>[trans-4-(4-{4-amino-5-oxo-2-[2-(tetrahydrofuran-3-yl)ethoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl] acetic acid trifluoroacetic acid salt  |    | 510.25            | 511.14 (M+H); 1.79 min (LC4)                        | 752                               |
| <b>Example 66</b><br>(trans-4-{4-[4-amino-5-oxo-2-(tetrahydro-2H-pyran-3-ylmethoxy)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |  | 510.25            | 511.13 (M+H); 1.83 min (LC4)                        | 301                               |
| <b>Example 67</b><br>(trans-4-{4-[4-amino-2-(1,4-dioxan-2-ylmethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid                                    |  | 512.23            | 513.09 (M+H); 1.71 min (LC4)                        | 1340                              |

| Example Number                                                                                                                                                                | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| trifluoroacetic acid salt                                                                                                                                                     |                                                                                     |                   |                                                     |                                   |
| <b>Example 68</b><br>[trans-4-(4-{4-amino-2-[2-(2-methylpropoxy)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt |    | 512.26            | 513.07 (M+H); 1.87 min (LC4)                        | 27                                |
| <b>Example 69</b><br>[trans-4-(4-{4-amino-5-oxo-2-[3-(propan-2-yloxy)propoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt |  | 512.26            | 513.07 (M+H); 1.80 min (LC4)                        | 109                               |
| <b>Example 70</b><br>[trans-4-(4-{4-amino-2-[2-(2-methoxyethoxy)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetic acid formic acid salt |  | 514.24            | 515.12 (M+H); 1.08 min (LC2)                        | 198                               |
| <b>Example 71</b><br>{trans-4-[4-(4-amino-                                                                                                                                    |  | 412.17            | 413.24 (M+H);                                       | 3630                              |

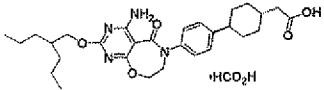
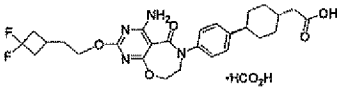
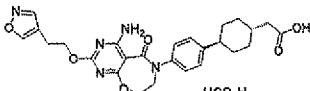
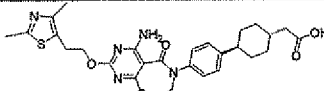
| Example Number                                                                                                                                                              | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| 2-hydroxy-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl]cyclohexyl} acetic acid                                                                             |                                                                                     |                   | 2.14 min (LC4)                                      |                                   |
| <b>Example 72</b><br>(trans-4-{4-[4-amino-2-(cyclobutyloxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid trifluoroacetic acid salt |    | 466.22            | 467.45 (M+H); 0.55 min (UPLC2)                      | 305                               |
| <b>Example 73</b><br>(trans-4-{4-[4-amino-2-(cyclopropylmethoxy)-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl) acetic acid formic acid salt     |  | 466.22            | 467.09 (M+H); 1.11 min (LC2)                        | 134                               |
| <b>Example 74</b><br>Ammonium (trans-4-{4-[4-amino-2-{[1-(2-methylpropyl)-1H-imidazol-5-yl]methoxy}-5-oxo-7,8-dihydropyrimido[5,4-                                          |  | 548.27            | 549.15 (M+H); 1.62 min (LC4)                        | ~6146                             |

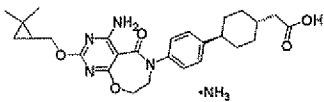
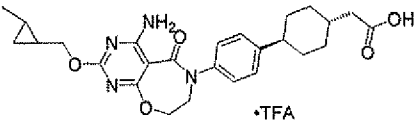
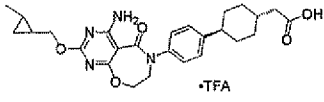
| Example Number                                                                                                                                                                                       | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| f][1,4]oxazepin-6(5H)-yl]phenyl}cyclohexyl]acetate                                                                                                                                                   |                                                                                     |                   |                                                     |                                   |
| <b>Example 75</b><br>Ammonium [trans-4-(4-{4-amino-2-[2-(1-methyl-1H-pyrazol-4-yl)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl)cyclohexyl]acetate                           |    | 520.24            | 521.14 (M+H); 1.73 min (LC4)                        | ~1849                             |
| <b>Example 76</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)ethoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate |  | 547.24            | 548.11 (M+H); 1.1 min (LC4)                         | 683                               |
| <b>Example 77</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-[2-(1H-pyrazol-4-yl)ethoxy]-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate                        |  | 506.23            | 507.09 (M+H); 1.07 min (LC4)                        | 2432                              |

| Example Number                                                                                                                                                                         | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| <b>Example 78</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[2-(2-methylpyridin-3-yl)ethoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate     |    | 531.25            | 532.15 (M+H); 1.03 min (LC4)                        | 817                               |
| <b>Example 79</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-[2-(pyridin-2-yl)butoxy]-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate             |  | 545.26            | 546.14 (M+H); 1.08 min (LC4)                        | 264                               |
| <b>Example 80</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-{[3-(propan-2-yl)cyclobutyl]methoxy}-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate |  | 522.28            | 523.16 (M+H); 1.24 min (LC4)                        | 3.7                               |
| <b>Example 81</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-{[3-(propan-2-yl)cyclobutyl]methoxy}-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate |  | 516.22            | 517.08 (M+H); 1.15 min (LC4)                        | 159                               |

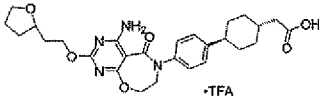
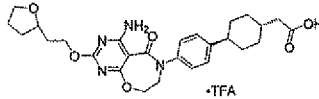
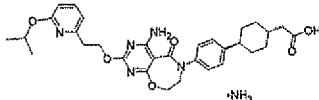


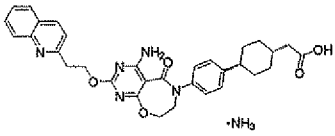
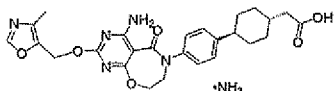
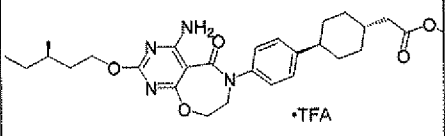
| Example Number                                                                                                                                                                      | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| xyl]phenyl}-2-[(3,3-difluorocyclobutyl)methoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate                                                                  |           |                   |                                                     |                                   |
| <b>Example 82</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-[2-(1H-1,2,4-triazol-1-yl)ethoxy]-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate |           | 507.22            | 508.08 (M+H); 1.05 min (LC4)                        | 1875                              |
| <b>Example 83</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[(3-methylisoxazol-5-yl)methoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate  |           | 507.21            | 508.08 (M+H); 1.13 min (LC4)                        | 170                               |
| <b>Example 84</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[2-(6-methylpyridin-2-yl)ethoxy]-5-oxo-5,6,7,8-                                                      |           | 531.25            | 532.16 (M+H); 1.02 min (LC4)                        | 110                               |

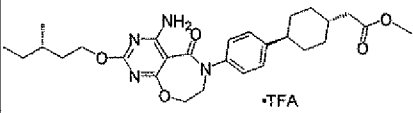
| Example Number                                                                                                                                                                       | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate                                                                                                                                 |                                                                                     |                   |                                                     |                                   |
| <b>Example 85</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-[(2-propylpentyl)oxy]-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate              |    | 524.30            | 525.18 (M+H); 1.25 min (LC4)                        | 8.7                               |
| <b>Example 86</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[2-(3,3-difluorocyclobutyl)ethoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate |  | 530.23            | 531.11 (M+H); 1.16 min (LC4)                        | 81                                |
| <b>Example 87</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[2-(isoxazol-4-yl)ethoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate          |  | 507.21            | 508.08 (M+H); 1.12 min (LC4)                        | 628                               |
| <b>Example 88</b><br>Ammonium [trans-4-(4-                                                                                                                                           |  | 551.22            | 552.09 (M+H); 1.04                                  | 590                               |

| Example Number                                                                                                                                                                                                                        | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| {4-Amino-2-[2-(2,4-dimethyl-1,3-thiazol-5-yl)ethoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetate                                                                                                 |                                                                                     |                   | min (LC4)                                           |                                   |
| <b>Example 89</b><br>Ammonium [trans-4-(4-{4-Amino-2-[(2,2-dimethylcyclopropyl)methoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl}phenyl)cyclohexyl]acetate                                                              |   | 494.25            | 495.11 (M+H); 1.2 min (LC4)                         | 25                                |
| <b>Example 90</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[(2-methylcyclopropyl)methoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium trifluoroacetate; enantiomer A (c/t mixture on cyclopropane) |  | 480.24            | 481.02 (M+H); 1.83 min (LC4)                        | 27                                |
| <b>Example 91</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[(2-                                                                                                                                                   |  | 480.24            | 481.02 (M+H); 1.83 min (LC4)                        | 49                                |

| Example Number                                                                                                                                                                             | Structure | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------|-----------------------------------------------------|-----------------------------------|
| methylcyclopropyl)methoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium trifluoroacetate; enantiomer B (c/t mixture on cyclopropane)                                         |           |                   |                                                     |                                   |
| <b>Example 92</b><br>4-Amino-2-[2-(6-Amino-4-methylpyridin-2-yl)ethoxy]-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate |           | 546.26            | 547.04 (M+H); 1.49 min (LC4)                        | 951                               |
| <b>Example 93</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[2-(2-ethyl-1,3-thiazol-4-yl)ethoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate     |           | 551.22            | 552.01 (M+H); 1.79 min (LC4)                        | 40                                |
| <b>Example 94</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-2-[2-(2-ethyl-1,3-thiazol-4-yl)ethoxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate     |           | 523.19            | 523.97 (M+H); 1.71 min (LC4)                        | 52                                |

| Example Number                                                                                                                                                                                               | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| xyl]phenyl}-5-oxo-2-[2-(1,3-thiazol-4-yl)ethoxy]-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium formate                                                                                                |                                                                                     |                   |                                                     |                                   |
| <b>Example 95</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-[2-(tetrahydrofuran-2-yl)ethoxy]-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium trifluoroacetate;<br>Enantiomer A |   | 510.25            | 511.05 (M+H); 1.77 min (LC4)                        | 56                                |
| <b>Example 96</b><br>4-Amino-6-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}-5-oxo-2-[2-(tetrahydrofuran-2-yl)ethoxy]-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium trifluoroacetate;<br>Enantiomer B |  | 510.25            | 510.99 (M+H); 1.73 min (LC4)                        | 70                                |
| <b>Example 97</b><br>Ammonium (trans-4-{4-[4-amino-5-oxo-2-{2-[6-(propan-2-yloxy)pyridin-2-yl]ethoxy}-7,8-dihydropyrimido[5,4-                                                                               |  | 575.27            | 576.06 (M+H); 1.92 min (LC4)                        | 37                                |

| Example Number                                                                                                                                                                           | Structure                                                                           | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| f[[1,4]oxazepin-6(5H)-yl]phenyl)cyclohexyl]acetate                                                                                                                                       |                                                                                     |                   |                                                     |                                   |
| <b>Example 98</b><br>Ammonium [trans-4-(4-{4-amino-5-oxo-2-[2-(quinolin-2-yl)ethoxy]-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl)cyclohexyl]acetate                          |    | 567.25            | 568.04 (M+H); 1.6 min (LC4)                         | 101                               |
| <b>Example 99</b><br>Ammonium [trans-4-(4-{4-amino-2-[(4-methyl-1,3-oxazol-5-yl)methoxy]-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl]phenyl)cyclohexyl]acetate                |  | 507.21            | 508.00 (M+H); 1.76 min (LC4)                        | 3245                              |
| <b>Example 100</b><br>4-Amino-6-{4-[trans-4-(2-methoxy-2-oxoethyl)cyclohexyl]phenyl}-2-[(3-methylpentyl)oxy]-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium trifluoroacetate |  | 510.28            | 511.05 (M+H); 2.35 min (LC4)                        | 120                               |

| Example Number                                                                                                                                                                               | Structure                                                                         | Calc'd exact mass | Parent ion m/z (ESI-MS); R <sub>t</sub> (LC method) | human DGAT1 IC <sub>50</sub> (nM) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------|-----------------------------------------------------|-----------------------------------|
| <b>Example 101</b><br>4-Amino-6-{4-[trans-4-(2-methoxy-2-oxoethyl)cyclohexyl]phenyl}-2-[(3S)-3-methylpentyl]oxy}-5-oxo-5,6,7,8-tetrahydropyrimido[5,4-f][1,4]oxazepin-3-ium trifluoroacetate |  | 510.28            | 511.08 (M+H); 2.36 min (LC4)                        | 119                               |

#### DGAT1 CPM Assay

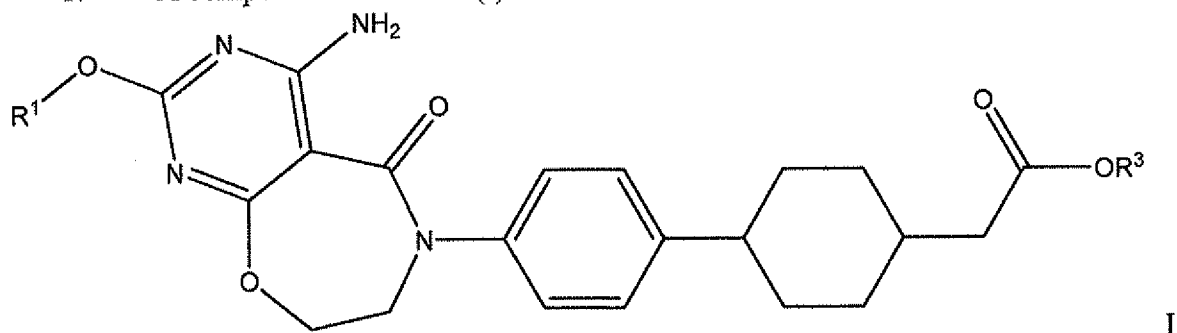
20uL substrate mixture of 300uM diolein, 40uM oleoyl-CoA, 10% ethanol and 1uL of the compound with different concentrations were delivered to a 384 well assay plate (Corning 3573) using a Tecan with TeMO module. Later 19uL of enzyme mixture of 1.05ug/ml human DGAT1 in buffer (200mM Tris, pH7, 200mM sucrose, 200mM MgCl<sub>2</sub> + 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 IC<sub>50</sub>s were calculated.

#### Hepatocyte Stability

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.

## WHAT IS CLAIMED IS:

1. A compound of formula (I):



- 5 or pharmaceutically acceptable salts thereof, wherein  $R^1$  is selected from the group consisting of:  
 hydrogen;  
 $C_5$ - $C_{10}$ alkyl, wherein the  $C_5$ - $C_{10}$ alkyl is unsubstituted or substituted with one or more  
 substituents selected from the group consisting of  $C_1$ - $C_6$ alkoxy and -OH;  
 halogen-substituted  $C_1$ - $C_{10}$ alkyl;  
 10  $-(CH_2)_mO(CH_2)_nCH_3$ , wherein  $-(CH_2)_mO(CH_2)_nCH_3$  is unsubstituted or substituted with  
 at least one  $C_1$ - $C_6$ alkyl, and wherein  $m$  is selected from the group consisting of 1, 2, 3 or 4 and  $n$   
 is selected from the group consisting of 0, 1, 2, 3 or 4; and  
 $-(CH_2)_pR^2$ , wherein the  $-(CH_2)_pR^2$  is unsubstituted or substituted with one or more  
 substituents selected from the group consisting of  $C_1$ - $C_6$ alkyl, halogen, - $NH_2$ , phenyl,  $C_1$ -  
 15  $C_6$ alkoxy and - $OC_1$ - $C_6$ cycloalkyl, wherein  $R^2$  is aryl, heteroaryl, cycloalkyl or heterocycloalkyl,  
 and wherein  $p$  is 0, 1, 2, 3 or 4; and  
 $R^3$  is selected from the group consisting of hydrogen and  $C_1$ - $C_6$ alkyl.

- 20 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  
 $C_5$ - $C_{10}$  alkyl.

- 25 4. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein  $R^1$  is  
 $C_5$ - $C_{10}$  straight alkyl.

5. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein  $R^1$  is  
 $C_5$ - $C_{10}$  branched alkyl.

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

7. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein  $-(CH_2)_pR^2$  is  $-(CH_2)_p$ phenyl.

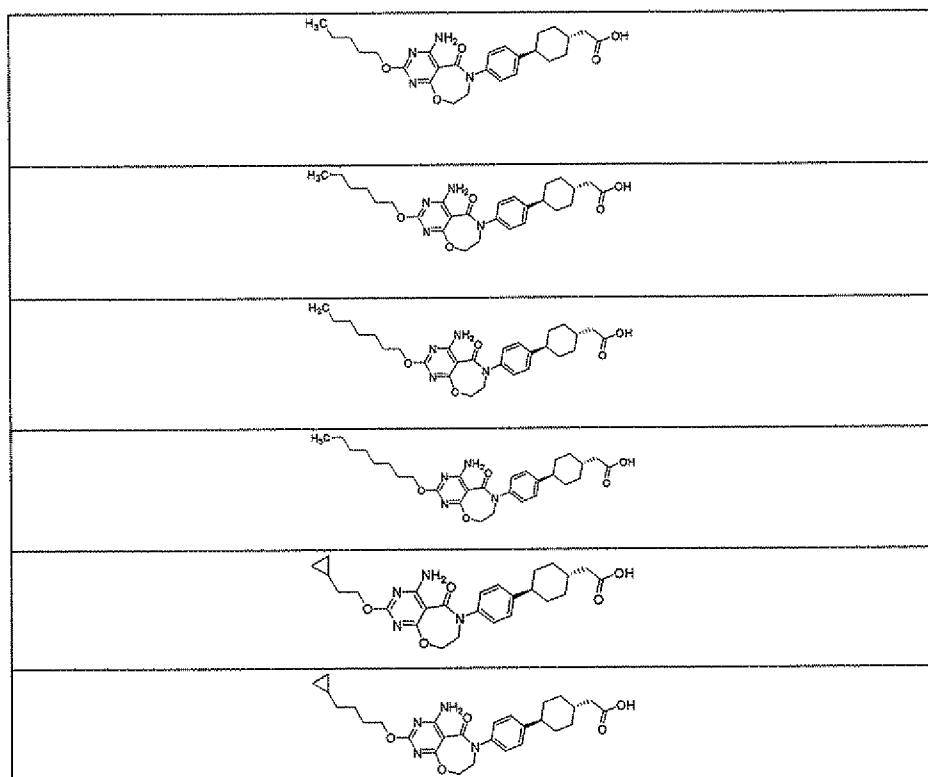
8. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein  $-(CH_2)_pR^2$  is  $-(CH_2)_p$ heteroaryl.

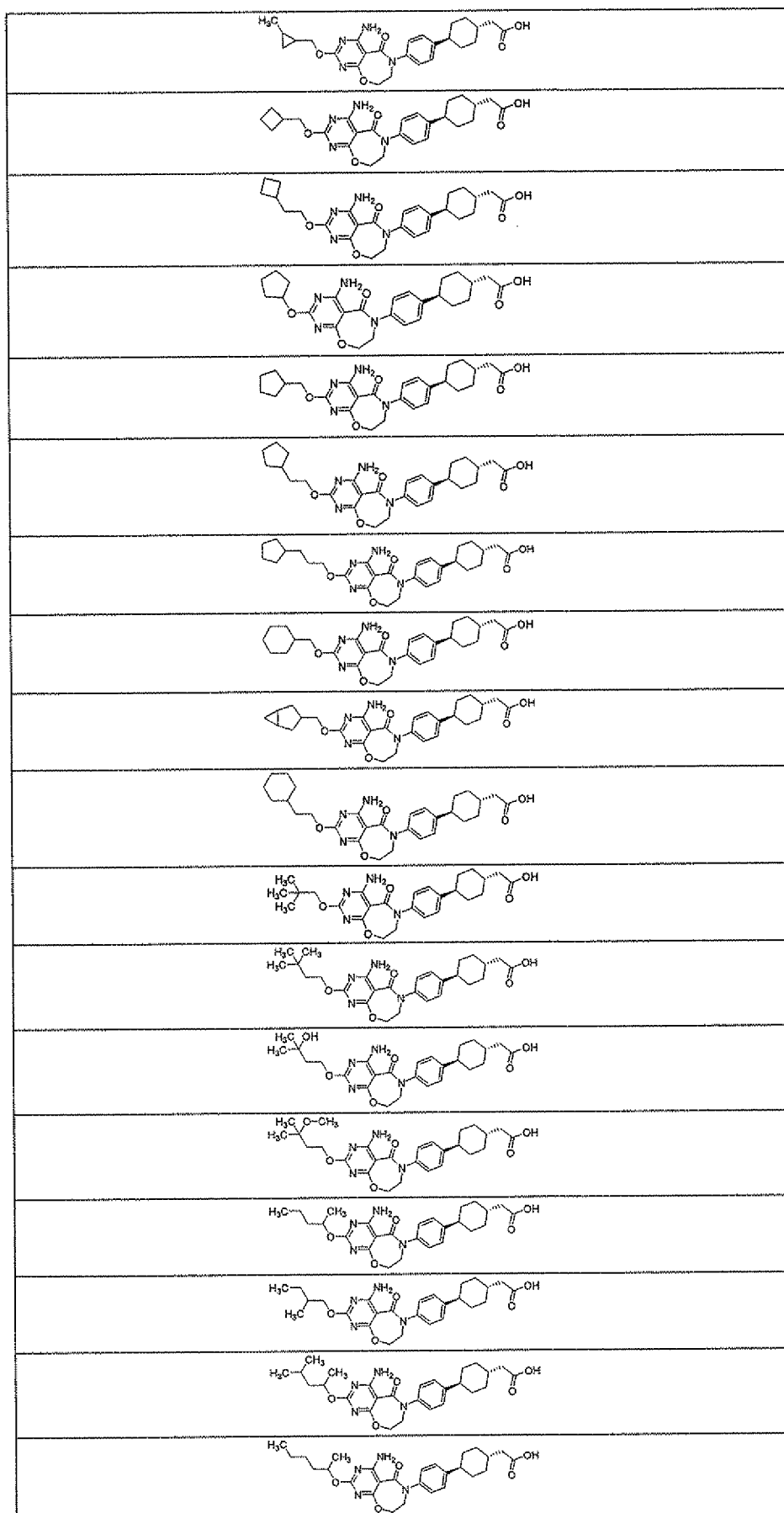
9. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein  $-(CH_2)_pR^2$  is  $-(CH_2)_p$ cycloalkyl.

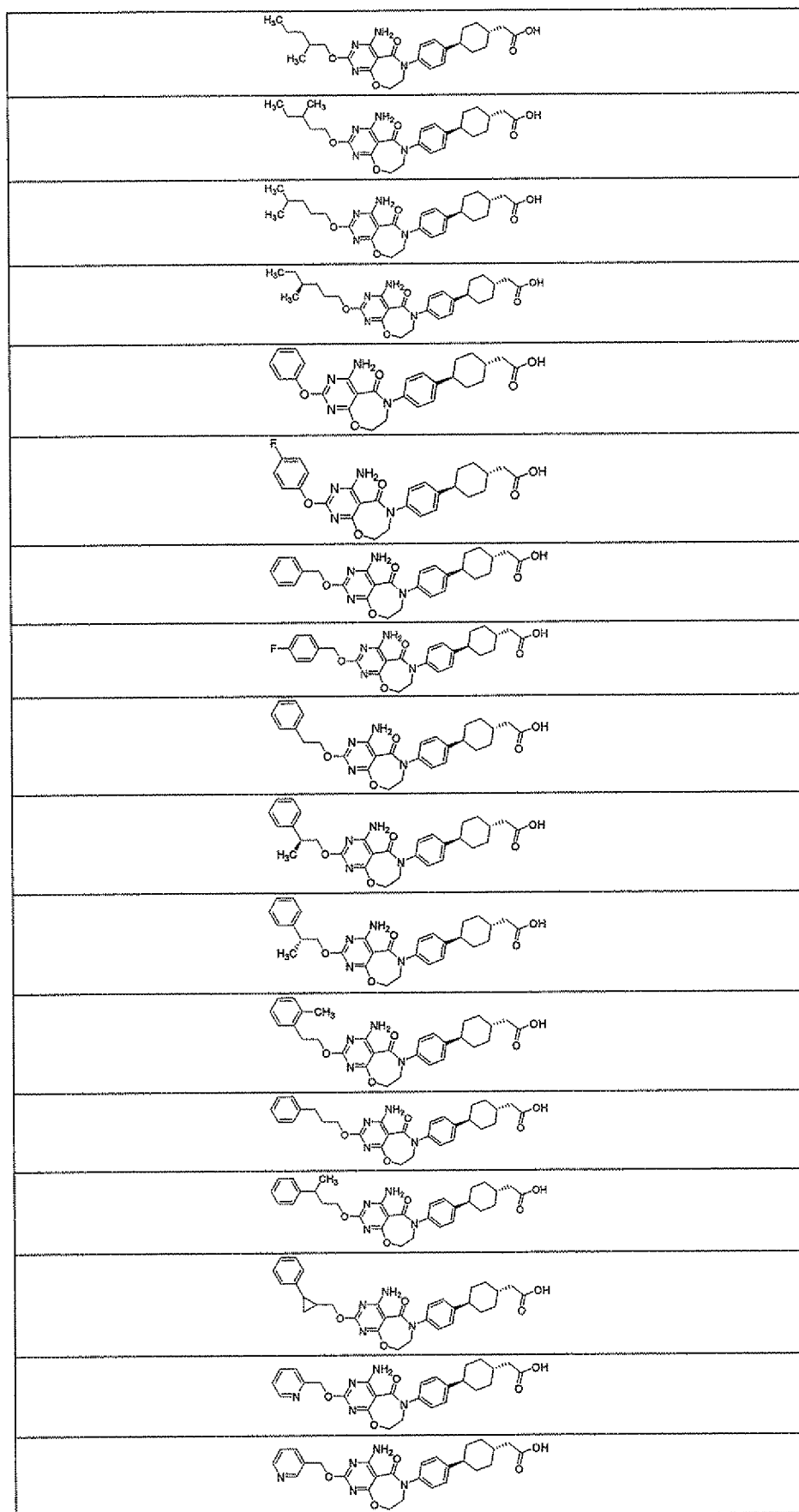
10. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein  $-(CH_2)_pR^2$  is  $-(CH_2)_p$ heterocycloalkyl.

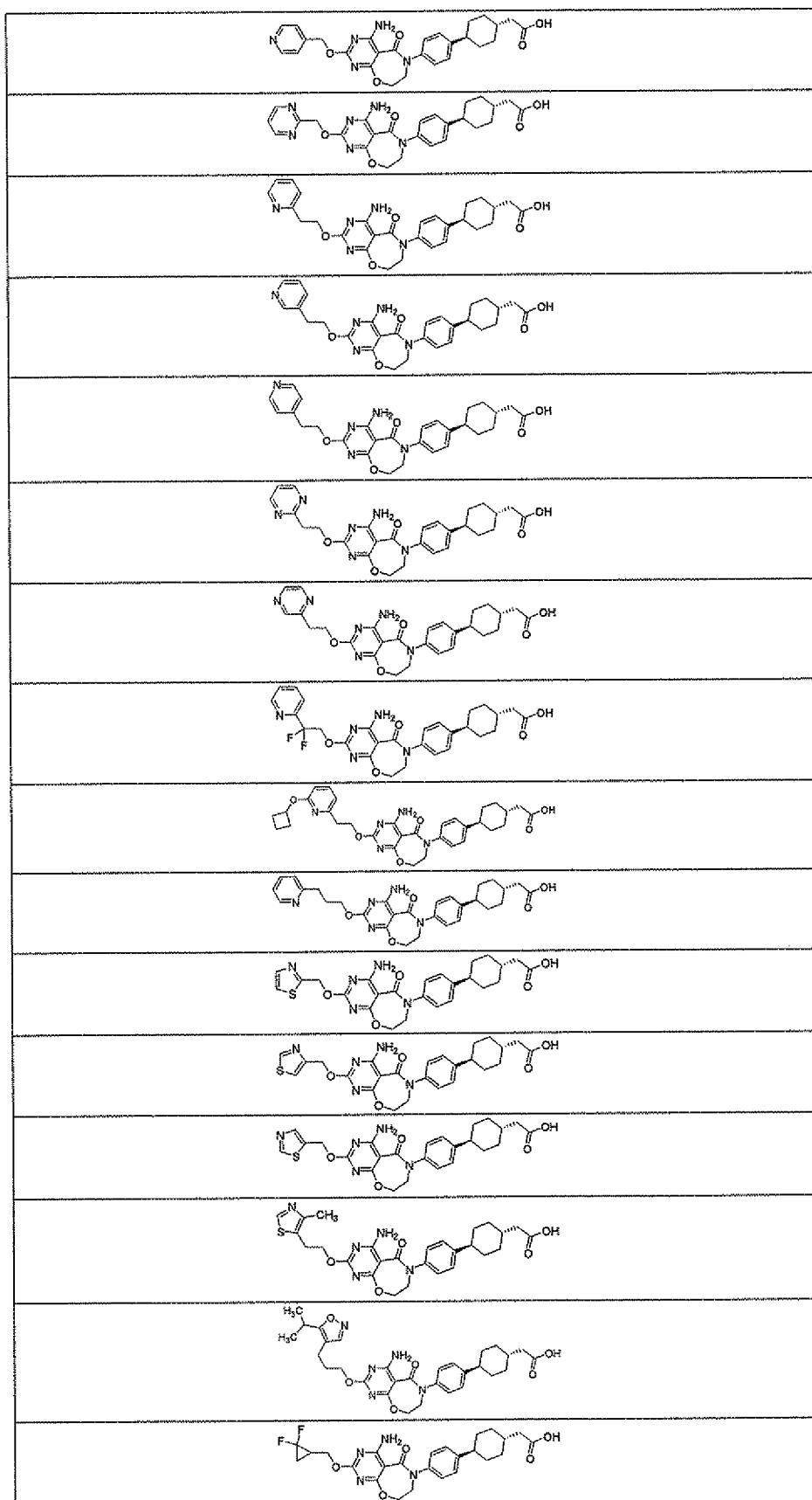
11. A compound of claim 1 or pharmaceutically acceptable salt thereof wherein  $R^1$  is  $-(CH_2)_mO(CH_2)_nCH_3$ .

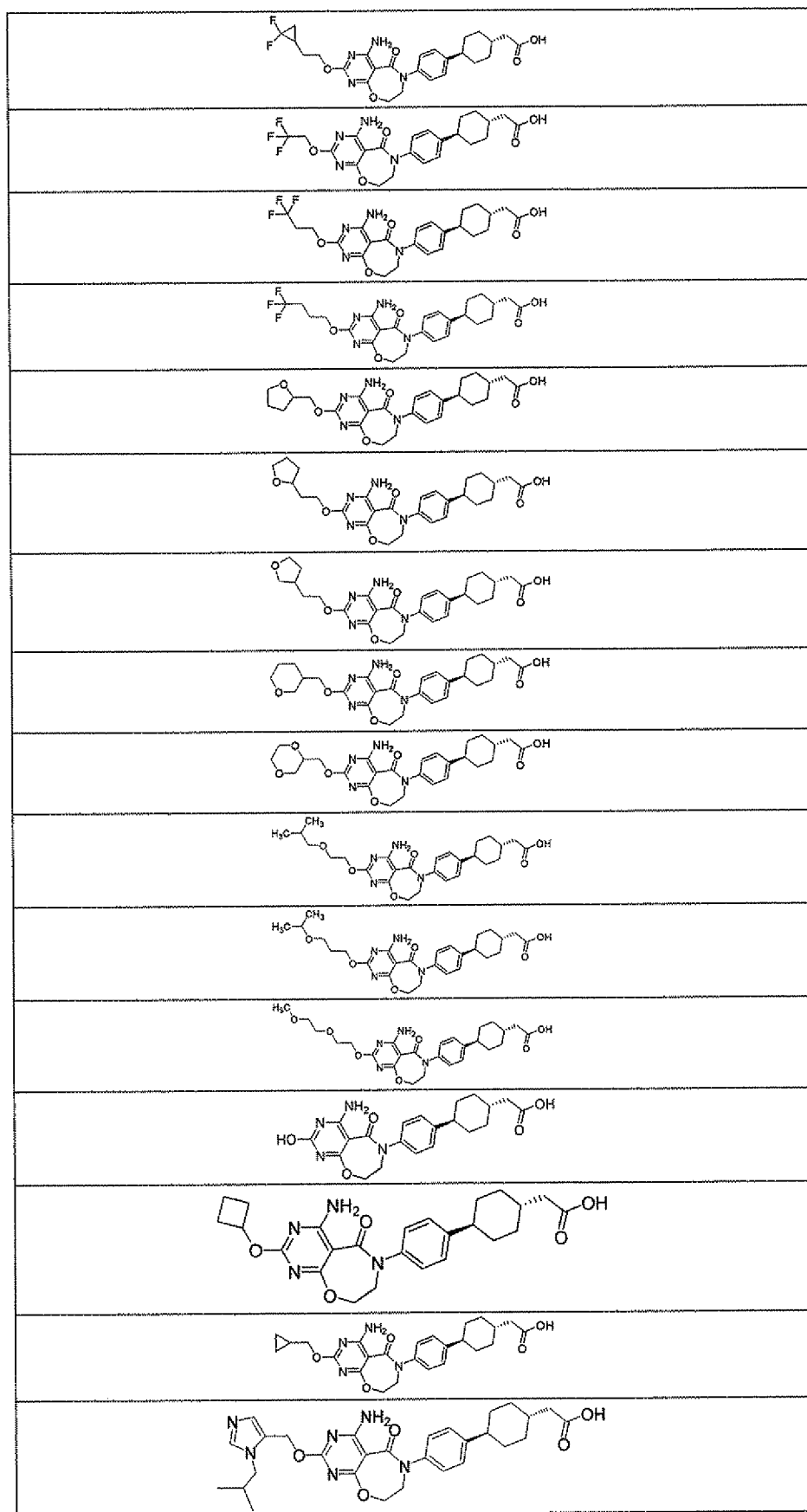
12. A compound or pharmaceutically acceptable salt thereof selected from the group consisting of:

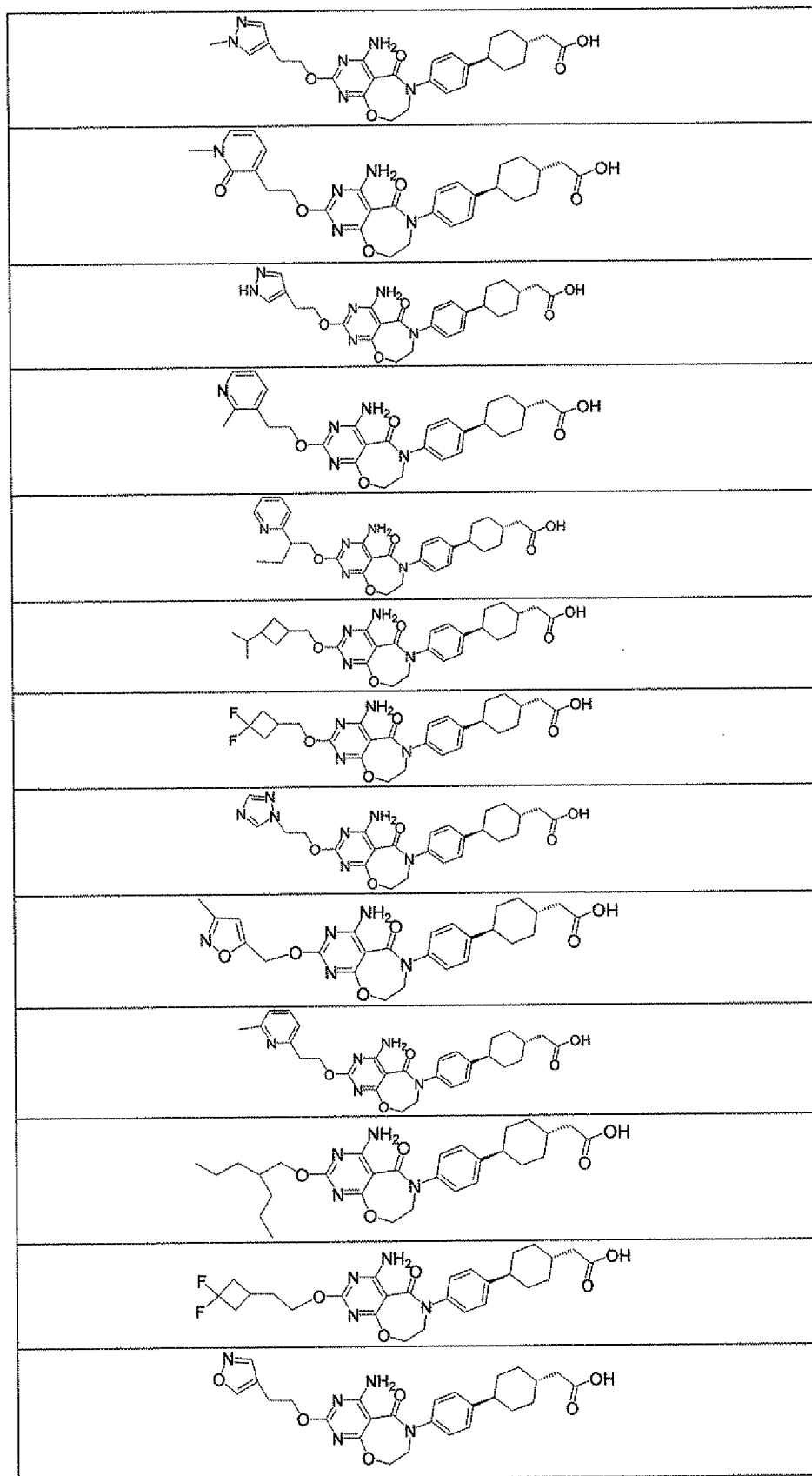


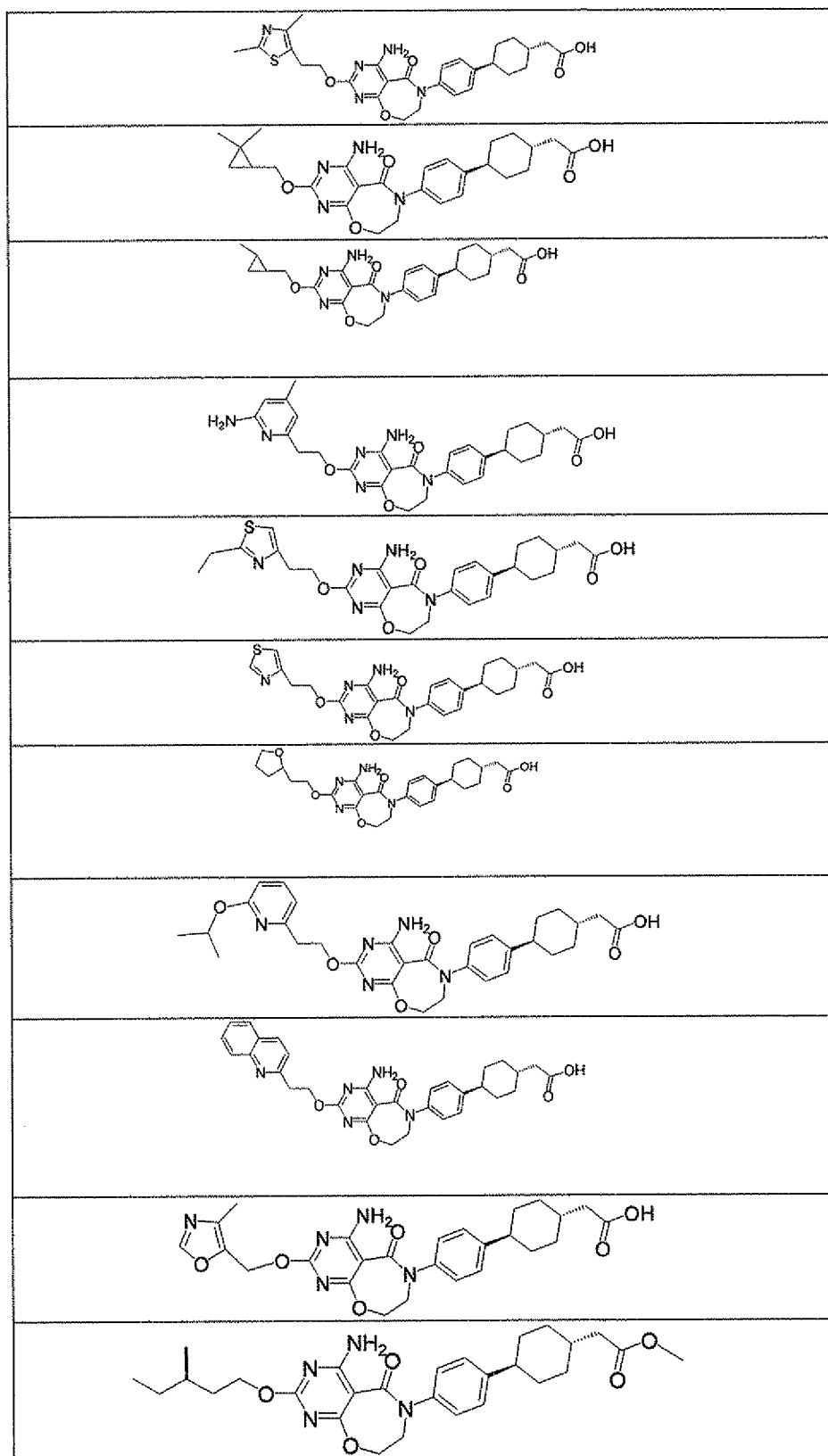












13. A pharmaceutical composition comprising a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

14. Use of a compound of any one of claims 1-12, 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.

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15. 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 compound of any one of claims 1-12.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/27655

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/00; A61K 31/00 (2012.01)

USPC - 514/211.05

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)

USPC - 514/211.05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
USPC - 514/211.01; 514/211.09; 514/211.14 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: DGAT-1 inhibitors, dihydropyrimido[5,4-f][1,4]oxazepin, 4-amino, 5-oxo, phenyl cyclohexyl, acetic acid, acetate, treating, type 2 diabetes, obesity, DGAT1, inhibition, diabetes mellitus, DGAT1 gene, ACAT, similarity, manufacture, medicaments, ACAT receptor, QSAR, HTS, combinatorial library. INTERNET s

## 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 (DOW et al.) 05 February 2009 (05.02.2009) pg 2, ln 9 - pg 3, ln 27; pg 10, ln 1-17                                                                                                                                                                                                                                     | 1-15                  |
| Y         | WO 2007/141538 A1 (BIRCH et al.) 13 December 2007 (13.12.2007) pg 1, ln 3-13, 21-24; pg 2, ln 30 - pg 4, ln 13; pg 38, ln 9-14                                                                                                                                                                                                            | 1-15                  |
| Y         | LABUTE et al. A Probabilistic Approach to High Throughput Drug Discovery. Combinatorial Chemistry & High Throughput Screening, 2002, Vol 5, pp 135-145; Abstract; pg 142-144<br>Downloaded at <a href="http://www.benthamscience.com/cchts/samples/cchts5-2/0005A.pdf">http://www.benthamscience.com/cchts/samples/cchts5-2/0005A.pdf</a> | 1-15                  |

☐ Further documents are listed in the continuation of Box C.

## \* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

30 May 2012 (30.05.2012)

Date of mailing of the international search report

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Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

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