Abstract:

Biaryl ethers in which one of the aromatic rings is fused to a cycloalkyl or heterocyclic ring, which is attached to a thiazolidinedione or oxazolidinedione ring, including pharmaceutically acceptable salts and prodrugs thereof, are agonists of G-protein coupled receptor 40 (GPR40) and are useful as therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, and of conditions that often occur with type 2 diabetes, including insulin resistance, obesity, and lipid disorders.

Title: ANTIDIABETIC BICYCLIC COMPOUNDS
THE INVENTION
ANTIDIABETIC BICYCLIC COMPOUNDS

FIELD OF THE INVENTION
The instant invention is concerned with biaryl ethers in which one of the aromatic rings
is fused to a cycloalkyl or heterocyclic ring, which is attached to a thiazohdinedione or oxazohdinedione
ring. The compounds are agonists of G-protein coupled receptor 40 (GPR40) and are useful as
therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, and of conditions that
are often associated with this disease, including insulin resistance, obesity, and lipid disorders.

BACKGROUND OF THE INVENTION
Diabetes is a disease derived from multiple causative factors and characterized by
elevated levels of plasma glucose (hyperglycemia) in the fasting state or after administration of glucose
during an oral glucose tolerance test. 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), insulin is still produced in the body. Patients having type 2 diabetes have a resistance
to the effects of insulin in stimulating glucose and lipid metabolism in the main insulin-sensitive tissues,
which are muscle, liver and adipose tissues. These patients often have normal levels of insulin, and may
have hyperinsulinemia (elevated plasma insulin levels), as they compensate for the reduced effectiveness
of insulin by secreting increased amounts of insulin. Insulin resistance is not primarily caused by a
diminished number of insulin receptors but rather by a post-insulin receptor binding defect that is not yet
completely understood. This lack of responsiveness to insulin results in insufficient insulin-mediated
activation of uptake, oxidation and storage of glucose in muscle, and inadequate insulin-mediated
repression of glycogen in adipose tissue and of glucose production and secretion in the liver.

Persistent or uncontrolled hyperglycemia that occurs with diabetes is associated with
increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both
directly and indirectly with obesity, hypertension, and alterations of the lipid, lipoprotein and
apolipoprotein metabolism, as well as other metabolic and hemodynamic disease. Patients with type 2
diabetes mellitus have a significantly increased risk of macrovascular and microvascular complications,
including atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension,
nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose homeostasis, lipid
metabolism, obesity, and hypertension are critically important in the clinical management and treatment
of diabetes mellitus.

Patients who have insulin resistance often have several symptoms that together are
referred to as syndrome X, or the metabolic syndrome. According to one widely used definition, a
patient having metabolic syndrome is characterized as having three or more symptoms selected from the

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The following group of five symptoms: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low high-density lipoprotein cholesterol (HDL); (4) high blood pressure; and (5) elevated fasting glucose, which may be in the range characteristic of Type 2 diabetes if the patient is also diabetic. Each of these symptoms is defined clinically in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670. Patients with metabolic syndrome, whether or not they have or develop overt diabetes mellitus, have an increased risk of developing the macrovascular and microvascular complications that occur with type 2 diabetes, such as atherosclerosis and coronary heart disease.

There are several available treatments for type 2 diabetes, each of which has its own limitations and potential risks. Physical exercise and a reduction in dietary intake of calories often dramatically improve the diabetic condition and are the usual recommended first-line treatment of type 2 diabetes and of pre-diabetic conditions associated with insulin resistance. Compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of fat and carbohydrates. Pharmacologic treatments have focused on three areas of pathophysiology: (1) Hepatic glucose production (biguanides), (2) insulin resistance (PPAR agonists), and (3) insulin secretion.

The biguanides are a class of drugs that are widely used to treat type 2 diabetes. The two best known biguanides, phenformin and metformin, cause some correction of hyperglycemia. The biguanides act primarily by inhibiting hepatic glucose production, and they also are believed to modestly improve insulin sensitivity. The biguanides can be used as monotherapy or in combination with other anti-diabetic drugs, such as insulin or an insulin secretagogues, without increasing the risk of hypoglycemia. However, phenformin and metformin can induce lactic acidosis and nausea/diarrhea. Metformin has a lower risk of side effects than phenformin and is widely prescribed for the treatment of Type 2 diabetes.

The ghtazones (i.e., 5-benzylthiazohdine-2,4-diones) are a newer class of compounds that can ameliorate hyperglycemia and other symptoms of type 2 diabetes. The ghtazones that are currently marketed (rosiglitazone and pioglitazone) are agonists of the peroxisome prohferator activated receptor (PPAR) gamma subtype. The PPAR-gamma agonists substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes, resulting in partial or complete correction of elevated plasma glucose levels without the occurrence of hypoglycemia. PPAR-gamma agonism is believed to be responsible for the improved insulin sensitization that is observed in human patients who are treated with the ghtazones. New PPAR agonists are currently being developed. Many of the newer PPAR compounds are agonists of one or more of the PPAR alpha, gamma and delta subtypes. Compounds that are agonists of both the PPAR alpha and PPAR gamma subtypes (PPAR alpha/gamma dual agonists) are promising because they reduce hyperglycemia and also improve lipid metabolism. The currently marketed PPAR gamma agonists are modestly effective in reducing plasma.
glucose and HemoglobinAlC. The currently marketed compounds do not greatly improve lipid metabolism and may actually have a negative effect on the lipid profile. Thus, the PPAR compounds represent an important advance in diabetic therapy, but further improvements are still needed.

Another widely used drug treatment involves the administration of insulin secretagogues, such as the sulfonylureas (e.g., tolbutamide and glipizide). These drugs increase the plasma level of insulin by stimulating the pancreatic β-cells to secrete more insulin. Insulin secretion in the pancreatic β-cell is under strict regulation by glucose and an array of metabolic, neural and hormonal signals. Glucose stimulates insulin production and secretion through its metabolism to generate ATP and other signaling molecules, whereas other extracellular signals act as potentiators or inhibitors of insulin secretion through GPCR's present on the plasma membrane. Sulfonylureas and related insulin secretagogues act by blocking the ATP-dependent K+ channel in β-cells, which causes depolarization of the cell and the opening of the voltage-dependent Ca2+ channels with stimulation of insulin release. This mechanism is non-glucose dependent, and hence insulin secretion can occur regardless of the ambient glucose levels. This can cause insulin secretion even if the glucose level is low, resulting in hypoglycemia, which can be fatal in severe cases. The administration of insulin secretagogues must therefore be carefully controlled. The insulin secretagogues are often used as a first-line drug treatment for Type 2 diabetes.

There has been a renewed focus on pancreatic islet-based insulin secretion that is controlled by glucose-dependent insulin secretion. This approach has the potential for stabilization and restoration of β-cell function. In this regard, several orphan G-protein coupled receptors (GPCR's) have recently been identified that are preferentially expressed in the β-cell and that are implicated in glucose stimulated insulin secretion (GSIS). GPR40 is a cell-surface GPCR that is highly expressed in human (and rodent) islets as well as in insulin-secreting cell lines. Several naturally-occurring medium to long-chain fatty acids (FA's) as well as synthetic compounds, including several members of the thiazolidinedione class of PPARγ agonists, have recently been identified as ligands for GPR40 (Itoh, Y. et al., Nature 422: 173 [2003], Bπscoe, CP. et al., J. Biol. Chem. 278: 11303 [2003], Kotarsky, K. et al., Biochem. Biophys. Res Comm 301: 406 [2003]. Under hyperglycemic conditions, GPR40 agonists are capable of augmenting the release of insulin from islet cells. The specificity of this response is suggested by results showing that the inhibition of GPR40 activity by siRNA attenuates FA-induced amplification of GSIS. These findings indicate that, in addition to the intracellular generation of hpid-deπvatives of FA's that are thought to promote insulin release, FA's (and other synthetic GPR40 agonists) may also act as extracellular ligands that bind to GPR40 in mediating FA-induced insulin secretion. There are several potential advantages of GPR40 as a potential target for the treatment of type 2 diabetes. First, since GPR40-mediated insulin secretion is glucose dependent, there is little or no πsk of hypoglycemia. Second, the limited tissue distribution of GPR40 (mainly in islets) suggests that there would be less chance for side effects associated with GPR40 activity in other tissues. Third, GPR40 agonists that are active in the islets may have the potential to restore or preserve islet function. This would be highly
advantageous, because long term diabetes therapy often leads to the gradual diminution of islet activity, so that after extended periods of treatment, it is often necessary to treat type 2 diabetic patients with daily insulin injections. By restoring or preserving islet function, GPR40 agonists may delay or prevent the diminution and loss of islet function in a type 2 diabetic patient.

SUMMARY OF THE INVENTION

The class of compounds described herein is a new class of GPR40 agonists. The compounds are useful in the treatment of diseases that are modulated by GPR40 agonists, including type 2 diabetes, hyperglycemia that may be associated with type 2 diabetes or pre-diabetic insulin resistance, and obesity.

The present invention is directed to a compound of formula I, or a pharmaceutically acceptable salt thereof, including individual diastereomers and enantiomers thereof, and mixtures of diastereomers and/or enantiomers thereof:

![Chemical structure](image)

In the compound of formula I, A is selected from the group consisting of -CH- and -N-;

B is selected from the group consisting of -S-, -O-, -NH-, and -CH2-;

W is selected from the group consisting of -CH2-, -CF2-, -O-, -C(=O)-, -NR6-, -S-, -S(O)-, and -S(O)2-;

Z is selected from the group consisting of -CH2- and -CH2CH2-;

or alternatively -W-Z- is selected from the group consisting of -N(R6)C(=O)- and -C(=O)N(R6)-, or -W-Z- represents two atoms that are connected to form one side of a 5-6-membered heteroaromatic πng having 1-3 heteroatoms independently selected from O, N and S, where the 5-membered heteroaromatic πng is optionally substituted with 1-3 groups independently selected from halogen, CH3, CF3, -OCH3, and -OCF3;

Heterocycle is a 5-6 membered saturated or partly saturated monocyclic heterocyclic πng having 1-3 heteroatoms independently selected from O, N and S;
Heteroaryl is a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from O, N and S:

R₁, R², R³ and R⁴ are each independently selected from the group consisting of H, halogen, -CN, -NO₂, -Q-Coalkyl, -OCi-C₆alkyl, -SQ-Coalkyl, -SR(O)₂Ci-C₆alkyl, -N(R⁵)(R⁶), -N(R⁶)C(=O)Ci-C₆alkyl, -N(R⁶)S(O)₂Ci-C₆alkyl, -S(O)₂N(R⁶)(R⁷), -C(=O)H, -C(=O)OH, -C(=O)OCi-C₆alkyl, -C(O)C i-C₆alkyl, -C(=O)N(R⁶)(R⁷), -C(O)Phenyl, -C(=O)Naphthyl, -C(=O)Heterocycle, Heterocycle, Heteroaryl, C₃-C₇-Cycloalkyl, Phenyl and Naphthyl;

wherein -C=C₆alkyl and the alkyl groups of -OCi-C₆alkyl, -SQ-C₆alkyl, -S(O)₂Ci-C₆alkyl, -N(R⁶)C(=O)Ci-C₆alkyl, -N(R⁶)S(O)₂Ci-C₆alkyl, -C(=O)OCi-C₆alkyl, and -C(=O)Ci-C₆alkyl are optionally substituted with 1-5 halogens and optionally substituted with 1-2 groups independently selected from -OH, -OCi-C₆alkyl which is optionally substituted with 1-5 halogens, -S(O)₂C(=O)-C₃alkyl which is optionally substituted with 1-5 halogens, -C(=O)Ci-C₆alkyl which is optionally substituted with 1-5 halogens, -OCi-C₆alkyl which is optionally substituted with 1-5 halogens, -NHC(=O)CH₃, -NHC(=O)OCi-C₆alkyl which is optionally substituted with 1-5 halogens, -NHS(O)₂CH₃, -N(R⁶)(R⁷)H, Heterocycle, Heteroaryl, C₃-C₇-Cycloalkyl, Phenyl, and Naphthyl;

wherein -C(=O)Phenyl, -C(=O)Naphthyl, -C(=O)Heterocycle, Heterocycle, Heteroaryl, C₃-C₇-Cycloalkyl, Phenyl and Naphthyl either as R₁, R₂, R₃, or R₄, or as substituents on R₁, R₂, R₃ and R₄ are optionally substituted with 1-4 substituents independently selected from halogen, -CF₃, -OCF₃, -CN, -NO₂, -OH, -Ci-C₆alkyl, -C(O)Ci-C₆alkyl, -S(O)₂Ci-C₆alkyl, and -OCi-C₆alkyl, wherein said -Ci-C₆alkyl, -OCi-C₆alkyl, -S(O)₂Ci-C₆alkyl, and -C(=O)Ci-C₆alkyl substituents are optionally substituted with 1-3 halogens;

wherein the pair of substituents R₁ and R₂ may together represent a bridging divalent 4-carbon chain -CH=CH-CH=CH-, forming a fused phenyl ring at the R₁ and R₂ positions, wherein said fused phenyl ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO₂, -Ci-C₆alkyl, -OCi-C₆alkyl, -SCI-C₆alkyl, -S(O)₂Ci-C₆alkyl, -CF₃, and -OCF₃; or alternatively the pair of substituents R₁ and R₂ may together represent a bridging divalent 3-atom chain selected from -CH=CHO-, -OCH=CH-, -CH=CH-S-, and -SCH=CH-, forming a fused furan or thiophene ring at the R₁ and R₂ positions, wherein said fused furan or thiophene ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO₂, -Q-C₃alkyl, -OCi-CSalkyl, -SCI-C₆alkyl, -S(O)₂Ci-C₆alkyl, -CF₃, and -OCF₃; and

Each R⁶ is independently selected from the group consisting of H and -C₃-C₆alkyl.

In the above description, the optional bridging groups as drawn that connect pairs of groups R₁ and R₂ are attached to the ring with the left-hand side of the structure attached where R₁ is attached and the right-hand side of the structure attached where R₂ is attached.
In the description above and in subsequent description below, alkyl, alkenyl, and alkynyl groups can each be linear or branched, unless otherwise defined.

5 DETAILED DESCRIPTION OF THE INVENTION

The invention has numerous embodiments, which are summarized below. The invention includes the specific compounds as shown, and also includes individual diastereomers, enantiomers, and epimers of the compounds, and mixtures of diastereomers and/or enantiomers thereof. The invention also includes pharmaceutically acceptable salts of the compounds, and pharmaceutical compositions comprising the compounds and a pharmaceutically acceptable carrier. The compounds are useful in treating insulin resistance, type 2 diabetes, and dyslipidemia that is associated with type 2 diabetes and insulin resistance.

Subgroups of the compounds of Formula I comprise compounds, including pharmaceutically acceptable salts thereof, in which R₁, R², R³, and R⁴ are independently selected from (I) H; (2) halogen; (3) -NO₂; (4) -CN; (5) C₁-C₄alkyl, which is optionally substituted with 1-5 halogens and optionally with 1-2 substituents independently selected from -OH, -C(=O)C₁-C₃alkyl, and -OC₁-C₃alkyl, where the C₁-C₃alkyl groups are optionally substituted with 1-3 halogens; (6) -OC₁-C₄alkyl, which is optionally substituted with 1-5 halogens and optionally with one -C(=O)C₁-C₃alkyl group; (7) -C(O)C₁-C₃alkyl, which is optionally substituted with 1-5 halogens; (8) -C(=0)H; (9) -C(=O)N(R₆)(R₆); (10) -S(O)₂N(R₆)(R₆); (11) -S(O)₂C₁-C₃alkyl; (12) -N(R₆)(R₆); (13) C₇Cycloalkyl; (14) Phenyl; and (15) Heterocycle, wherein C₃C₇Cycloalkyl, Phenyl, and Heterocycle are each optionally substituted with 1-3 substituents independently selected from halogen, -OH, -OC₁-C₃alkyl, CF₃, and -C(=O)C₁-C₃alkyl.

In subgroups of the compounds of Formula I, including pharmaceutically acceptable salts thereof, each R₆ is independently selected from H and CH₃.

In subgroups of the compounds of Formula I, including pharmaceutically acceptable salts thereof, R₁, R², R³, and R⁴ are each independently selected from H, halogen, C₁-C₃alkyl, CF₃, -OC₁-C₃alkyl, -OCF₃, -C(=0)H, -C(=0)N(R₆)(R₆), -S(O)₂N(R₆)(R₆), -C(=O)C₁-C₃alkyl, -CN, -NO₂, -S(O)₂C₁-C₃alkyl, and -N(R₆)(R₆).

In subgroups of the compounds of Formula I, including pharmaceutically acceptable salts thereof, R₁, R², R³, and R⁴ are each independently selected from H, F, Br, Cl, C₁-C₃alkyl, CF₃, -C(=0)NH₂, -S(O)₂NH₂, -C(=0)CH₃, -CN, -OCH₃, -OCF₃, and -NO₂.
In subgroups of the compounds of Formula I, including pharmaceutically acceptable salts thereof, the pair of ortho substituents \( R^1 \) and \( R^2 \) together represent a bridging divalent 4-carbon chain \(-\text{CH}=\text{CH}-\) forming a fused phenyl ring at the \( R^1 \) and \( R^2 \) positions, wherein the fused phenyl ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, \(-\text{N}^\theta_2\), -\text{Ci}-\text{C}3\text{alkyl}, -\text{O}\text{Ci}-\text{C}3\text{alkyl}, -\text{S}(\text{O})\text{Ci}-\text{C}3\text{alkyl}, \text{-CF3}, and \text{-OCF3}. In subgroups of the compounds of Formula I described immediately above, including pharmaceutically acceptable salts thereof, the fused phenyl ring at the \( R^1 \) and \( R^2 \) positions is optionally substituted with 1-2 substituents independently selected from halogen, -NO2, -\text{CH3}, -\text{CF3}, -\text{OCH3}, and -\text{OCF3}.

In subgroups of the compounds of Formula I, including pharmaceutically acceptable salts thereof, \( R^1 \) and \( R^2 \) together represent a bridging divalent group selected from \(-\text{CH}=\text{CHS}-\), -\text{SCH}=\text{CH}-, \(-\text{CH}=\text{CHO}-\), and \(-\text{OCH}=\text{CH}-\), forming a fused furan or thiophene at the \( R^1 \) and \( R^2 \) positions, wherein said fused furan or thiophene ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO2, -\text{Ci}-\text{C}3\text{alkyl}, -\text{O}\text{Ci}-\text{C}3\text{alkyl}, -\text{SCi}-\text{C}3\text{alkyl}, -\text{S}(\text{O})\text{Ci}-\text{C}3\text{alkyl}, \text{-CF3}, and \text{-OCF3}. In subgroups of the compounds of Formula I described immediately above, including pharmaceutically acceptable salts thereof, the fused furan or thiophene ring at the \( R^1 \) and \( R^2 \) positions is optionally substituted with 1-2 substituents independently selected from halogen, -NO2, -\text{CH3}, -\text{CF3}, -\text{OCH3}, and -\text{OCF3}.

In subgroups of the compounds of Formula I, including pharmaceutically acceptable salts thereof, \( A \) is \text{CH}- or \text{-N}\text{-}; and \( B \) is selected from -\text{O}- and -\text{S}-.

W is selected from the group consisting of \( \text{-CH2}- \), \( \text{-CF2}- \), \( \text{-O}- \), \( \text{-C(=0)}- \), \( \text{-NR6}- \), -\text{S}-, -\text{S(=O)}-, and -\text{S(O)}2-. and Z is selected from the group consisting of \( \text{-CH2}- \) and \( \text{-CH2CH2}- \).

W is selected from the group consisting of \( \text{-CH2}- \), \text{-O-}, and -\text{S}-; and Z is selected from the group consisting of \( \text{-CH2}- \) and \( \text{-CH2CH2}- \).

In a subgroup of the compound of Formula I, including pharmaceutically acceptable salts thereof, \( R^1, R^2, R^3 \), and \( R^4 \) are independently selected from (I) \text{H}; (2) halogen; (3) \text{-NO2}; (4) \text{-CN}; (5) \text{-Ci-C}4\text{alkyl}, which is optionally substituted with 1-5 halogens and optionally with 1-2 substituents independently selected from \text{-OH}, \text{-C(=O)}\text{Ci-C}3\text{alkyl}, and \text{-0Ci-C}3\text{alkyl}, where the \text{Ci-C}3\text{alkyl} groups.
are optionally substituted with 1-3 halogens; (6) -OCi-Ojalkyl, which is optionally substituted with 1-5 halogens and optionally with one -C(=O)Ci-C3alkyl group; (7) -C(=O)Ci-C3alkyl, which is optionally substituted with 1-5 halogens; (8) -C(=O)H; (9) -C(=O)N(R6)(R6); (10) -S(O)2N(R6)(R6); (11) -S(O)2Ci-C3alkyl; (12) -N(R6)(R6); (13) C3-C7Cycloalkyl; (14) Phenyl; and (15) Heterocycle,

wherein C3-C7Cycloalkyl, Phenyl, and Heterocycle are each optionally substituted with 1-3 substituents independently selected from halogen, -OH, -OCi-C3alkyl, CF3, and -C(=O)Ci-C3alkyl;

wherein the pair of substituents R1 and R2 may together represent a bridging divalent 4-carbon chain -CH=CH-CH=CH- or a bridging divalent 3-atom chain selected from -CH=CHO-, -OCH=CH-, -CH=CH-S-, and -SCH=CH-, forming a fused phenyl, furan or thiophene π ring at the R1 and R2 positions, wherein said fused phenyl, furan or thiophene π ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO2, -Ci-C3alkyl, -OCi-C3alkyl, -SCi-C3alkyl, -S(O)2Ci-C3alkyl, -CF3, and -OCF3;

Each R6 is independently selected from H and CH3;

W is selected from the group consisting of -CH2-, -O-, and -S-;

Z is selected from the group consisting of CH2- and CH2CH2-;

A is -CH- or N; and

B is selected from -S- and -O-

In subgroups of the compound of Formula 1, including pharmaceutically acceptable salts thereof, R1 is selected from the group consisting of H, CH3, and halogen.

In subgroups of the compound of Formula 1, including pharmaceutically acceptable salts thereof, R2 is selected from the group consisting of H, CH3, and halogen.

In subgroups of the compound of Formula 1, including pharmaceutically acceptable salts thereof, R1 and R2 together represent a bridging group selected from -CH=CH-CH=CH-, -CH=CHS-, -SCH=CH-, and -OCH=CH-, forming a fused phenyl, thiophene, or furan ring at the R1 and R2 positions, wherein said fused ring is optionally substituted with 1-2 substituents independently selected from halogen, CF3, -OCF3, -OCH3, -CN, -NO2, and Ci3alkyl.

In subgroups of the compound of Formula 1, including pharmaceutically acceptable salts thereof, R3 is selected from the group consisting of H, halogen, Ci3alkyl, -OCH3, -OCF3, CF3, -C(=O)NH2, -CN, and -NO2.

In subgroups of the compound of Formula 1, including pharmaceutically acceptable salts thereof, R4 is selected from the group consisting of H, halogen, CH3, CF3, and -S(O)2NH2.

In subgroups of the compound of Formula 1, including pharmaceutically acceptable salts thereof, W is selected from the group consisting of -CH2-, -O-, and -S-.

In subgroups of the compound of Formula 1, including pharmaceutically acceptable salts thereof, Z is selected from the group consisting of -CH2- and -CH2CH2-.
In subgroups of the compound of Formula I, including pharmaceutically acceptable salts thereof, A is -CH- or N; and B is selected from -S- and -O-.

Although the specific stereochemistries described above are preferred, all other stereoisomers, including diastereomers, enantiomers, epimers, and mixtures of these may also have utility in treating GPR40 mediated diseases. Inactive or less active diastereoisomers and enantiomers are useful for scientific studies relating to the receptor and the mechanism of activation.

Structures of specific compounds and synthetic methods for making the compounds are disclosed in the Examples. Some of the Examples are disclosed in tables in the specification, along with analytical information. These examples are readily made by one of ordinary skill in the art using the information disclosed herein. Where a stereochemical center is not defined (as for example, A in figure 1, where A is -CH-), the compound is a mixture of stereoisomers at that center. For such compounds, the individual stereoisomers, including enantiomers, diastereomers, and mixtures of these are also compounds of the invention. The compounds of the invention also include pharmaceutically acceptable salts.

The compounds of this invention may be used in pharmaceutical compositions comprising (a) the compound(s) or pharmaceutically acceptable salts thereof, and (b) a pharmaceutically acceptable carrier. The compounds of this invention may be used in pharmaceutical compositions that include one or more other active pharmaceutical ingredients. The compounds of this invention may also be used in pharmaceutical compositions in which the compound of Formula I or a pharmaceutically acceptable salt thereof is the only active ingredient.

A compound of Formula I, or a pharmaceutically acceptable salt thereof, may be used in the manufacture of a medicament for the treatment of type 2 diabetes mellitus in a human or other mammalian patient.

A method of treating type 2 diabetes comprises the administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound, to a patient in need of treatment. Other medical uses of the compounds of Formula I are described hereinafter.

**Definitions**

"Ac" is acetyl, which is CH3C(=O)-.

"Alkyl" means saturated carbon chains which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Other groups having the prefix "alk", such as alkoxy and alkanoyl, also may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, penty1, hexyl, heptyl, octyl, nonyl, and the like.
"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkyl" means a saturated carbocyclic ring, having a specified number of carbon atoms. The term may also be used to describe a carbocyclic ring fused to an aryl group. Examples of cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. Cycloalkenyl rings comprise a double bond in the ring.

"Aryl" is commonly used to refer to carbocyclic aromatic structures. The most common aryl groups are phenyl and naphthyl. Phenyl is generally the most preferred aryl group.

"Heterocycle" means a fully or partially saturated ring or πring system containing at least one heteroatom selected from N, S and O, wherein the number of heteroatoms and the πng size are defined herein. Examples of heterocycles include tetrahydrofuran, piperazme, pipeπdme, and morphohne.

"Heteroaryl" means an aromatic ring or two fused aromatic rings containing at least one ring heteroatom selected from N, O and S (including SO and SO2), as defined more specifically herein. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxazolyl, thiazolyl, imidazolyl, thiazolyl, furanyl, triazinyl, thienyl, pyridazinyl, pyrazynyl, benzoxazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl (including S-oxide and dioxide), fur(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, quinazolinyl, dibenzofuranyl, and the like.

"Halogen" includes fluorine, chlorine, bromine and iodine.

"Me" represents methyl.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, salts and/or dosage forms which are, using sound medical judgment, and following all applicable government regulations, safe and suitable for administration to a human being or an animal.

The term "composition," as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable earner.
The substituent "tetrazole" means a $2H$-tetrazol-5-yl substituent group and tautomers thereof.

**Optical Isomers - Diastereomers - Geometric Isomers - Tautomers**

Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates, racemic mixtures, single enantiomers, individual diastereomers, and mixtures of diastereomers and/or enantiomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I. Specifically, the compounds of the instant invention have at least one asymmetric center, which is on the π ring that is fused to the phenyl ring at the point where the heterocyclic ring is attached. There may also a second asymmetric center in the heterocyclic ring.

Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers, and it is intended that all of the possible optical isomers, stereoisomers, and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention (i.e. all possible combinations of the asymmetric centers as pure compounds or in mixtures).

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

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. An example is a ketone and its enol form, known as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of Formula I.

Compounds of Formula I having one or more asymmetric centers may be separated into diastereoisomers, enantiomers, and the like by methods well known in the art. Alternatively, enantiomers and other compounds with chiral centers may be synthesized by stereospecific synthesis using optically pure starting materials and/or reagents of known configuration.

**Salts**

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganese, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'.

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dibenzylethylenediamine, diethylamme, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morphohne, N-ethylpipεdme, glucamme, glucosamine, histidine, hydrabamine, lsopropylamme, lysine, methylglucamme, morphohne, piperazme, pipedme, polyamine resms, procaine, purines, theobromine, triethylamme, trimethylamme, Tπproplamine, tromethamme, and the like.

When the compound of the present invention is basic, or when it has a basic substituent group in its structure, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfomc, benzoic, camphorsulfonic, citric, ethanesulfonic, fumuzzy, gluconic, glutamic, hydrobromic, hydrochloric, lsethionic, lactic, maleic, malic, mandehc, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloriczc, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Metabolites - Prodrugs

Therapeutically active metabolites, where the metabolites themselves fall within the scope of the claimed invention, are also compounds of the current invention. Prodrugs, which are compounds that are converted to the claimed compounds as they are being administered to a patient or after they have been administered to a patient, are compounds of this invention. The claimed chemical structures of this application in some cases may themselves be prodrugs.

Utilities

Compounds of the present invention are potent agonists of the GPR40 receptor. The compounds of the invention, and pharmaceutically acceptable salts thereof, may be efficacious in the treatment of diseases that are modulated by GPR40 hands and agonists. Many of these diseases are summarized below.

One or more of the following diseases may be treated by the administration of a therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, to a patient in need of treatment. Also, the compounds of the invention may be used for the manufacture of a medicament for treating one or more of these diseases:

(1) non-insulin dependent diabetes melhtus (type 2 diabetes);
(2) hyperglycemia;
(3) the metabolic syndrome;
(4) obesity;
(5) hypercholesterolemia;
(6) hypertriglyceridemia (elevated levels of glycende-πch-hpoproteins);
mixed or diabetic dyslipidemia;
low HDL cholesterol;
high LDL cholesterol;
hyperapoB proteinemia; and
atherosclerosis.

Preferred uses of the compounds are for the treatment of one or more of the following diseases by administering a therapeutically effective amount to a patient in need of treatment. The compounds may be used for manufacturing a medicament for the treatment of one or more of these diseases:

Type 2 diabetes, and specifically hyperglycemia;
Metabolic syndrome;
Obesity; and
Hypercholesterolemia.

The compounds are expected to be effective in lowering glucose and lipids in diabetic patients and non-diabetic patients who have impaired glucose tolerance and/or are in a pre-diabetic condition. The compounds may ameliorate hyperinsulinemia, which often occurs in diabetic or pre-diabetic patients, by modulating the swings in the level of serum glucose that often occurs in these patients. The compounds may also be effective in treating or reducing insulin resistance. The compounds may be effective in treating or preventing gestational diabetes.

The compounds, compositions, and medicaments as described herein may also be effective in reducing the risks of adverse sequelae associated with metabolic syndrome, and in reducing the risk of developing atherosclerosis, delaying the onset of atherosclerosis, and/or reducing the risk of sequelae of atherosclerosis. Sequelae of atherosclerosis include angina, claudication, heart attack, stroke, and others.

By keeping hyperglycemia under control, the compounds may also be effective in delaying or preventing vascular restenosis and diabetic retinopathy.

The compounds of this invention may also have utility in improving or restoring /S-cell function, so that they may be useful in treating type 1 diabetes or in delaying or preventing a patient with type 2 diabetes from needing insulin therapy.

The compounds generally will be efficacious in treating one or more of the following diseases: (1) type 2 diabetes (also known as non-insulin dependent diabetes mellitus, or NIDDM), (2) hyperglycemia, (3) impaired glucose tolerance, (4) insulin resistance, (5) obesity, (6) lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) abdominal obesity, (16) retinopathy, (17) metabolic syndrome, (18) high blood pressure, and (19) insulin resistance.
One aspect of the invention provides a method for the treatment and control of mixed or diabetic dyslipidemia, hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, and/or hypertriglyceridemia, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound having formula I. The compound may be used alone or advantageously may be administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor such as lovastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, piropatstatin, itavastatin, or ZD-4522. The compound may also be used advantageously in combination with other lipid lowering drugs such as cholesterol absorption inhibitors (for example statin esters, sterol glycosides such as tiqueside, and azetidinones such as ezetimibe), ACAT inhibitors (such as avasimibe), CETP inhibitors (for example torcetrapib), niacin and niacin receptor agonists, bile acid sequestrants, microsomal triglyceride transport inhibitors, and bile acid reuptake inhibitors. These combination treatments may be effective for the treatment or control of one or more related conditions selected from the group consisting of hypercholesterolemia, atherosclerosis, hyperlipidemia, hypertriglyceridemia, dyslipidemia, high LDL, and low HDL.

Administration and Dose Ranges

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating or controlling diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of Formula I are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 1 milligram to about 500 milligrams. For a particularly potent compound, the dosage for an adult human may be as low as 0.1 mg. The dosage regimen may be adjusted within this range or even outside of this range to provide the optimal therapeutic response.

Oral administration will usually be carried out using tablets or capsules. Examples of doses in tablets and capsules are 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, and 500 mg. Other oral forms may also have the same or similar dosages.
Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I or a pharmaceutically acceptable salt as an active ingredient, as well as a pharmaceutically acceptable earner and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids. A pharmaceutical composition may also comprise a prodrug, or a pharmaceutically acceptable salt thereof, if a prodrug is administered.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The earner may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions, or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, algmic acid; a lubricant such as magnesium stearate; and a sweetening
agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

In some instances, depending on the solubility of the compound or salt being administered, it may be advantageous to formulate the compound or salt as a solution in an oil such as a triglyceride of one or more medium chain fatty acids, a lipophilic solvent such as trAceTM, a hydrophilic solvent (e.g. propylene glycol), or a mixture of two or more of these, also optionally including one or more ionic or nonionic surfactants, such as sodium lauryl sulfate, polysorbate 80, polyethoxylated triglycerides, and mono and/or diglycerides of one or more medium chain fatty acids. Solutions containing surfactants (especially 2 or more surfactants) will form emulsions or microemulsions on contact with water. The compound may also be formulated in a water soluble polymer in which it has been dispersed as an amorphous phase by such methods as hot melt extrusion and spray drying, such polymers including HPMCAS, HPMCS, and polyvmlyprrindonones.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syrangiability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Combination Therapy

Compounds of Formula I may be used in combination with other drugs that may also be useful in the treatment or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. In the treatment of patients who have type 2 diabetes, insulin resistance, obesity, metabolic syndrome, and co-morbidities that accompany these diseases, more than one drug is commonly administered. The compounds of this invention may generally be administered to a patient who is already taking one or more other drugs for these conditions.
When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy also includes therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules.

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

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

(a) PPAR gamma agonists and partial agonists, including both ghtazones and non-ghtazones (e.g. troghtazone, pioghtazone, enghtazone, MCC-555, rosiglitazone, balaghtazone, netoghtazone, T-131, LY-300512, and LY-818;
(b) biguanides such as metformin and phenformin;
(c) protein tyrosine phosphatase- IB (PTP-IB) inhibitors;
(d) dipeptidyl peptidase IV (DP-FV) inhibitors, such as sitagptin, saxaghptin, and vildaghptin;
(e) insulin or insulin mimetics;
(f) sulfonylureas such as tolbutamide, glimepi\(\pi\)de, glipizide, and related materials;
(g) \(\alpha\)-glucosidase inhibitors (such as acarbose);
(h) agents which improve a patient's lipid profile, such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, \(\pi\)vastatin, itavastatin, ZD-4522 and other statins), (\(\pi\)) bile acid sequestrants (cholesteryamine, colestipol, and dialkylammonalkyl derivatives of a cross-linked dextran), (in) niacin receptor agonists, nicotymyl alcohol, nicotinic acid, or a salt thereof, (iv) PPAR\(\alpha\) agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) cholesterol absorption inhibitors, such as for example ezetimibe, (vi) acyl CoA:cholesterol acyltransferase (ACAT) inhibitors, such as avasimibe, (\(\pi\)) CETP inhibitors, such as torcetrapib, and (vin) phenolic anti-oxidants, such as probucol;

(i) PPAR\(\alpha\)/\(\gamma\) dual agonists, such as muraghtazar, tesaghtazar, farghtazar, and JT-501;
(j) PPAR\(\delta\) agonists such as those disclosed in WO97/28149;
(k) antiobesity compounds such as fenfluramine, dexfenfluramine, phentiramine, subitramine, orhatstat, neuropeptide Y5 inhibitors, Mc4r agonists, cannabinoid receptor 1 (CB-1) antagonists/inverse agonists, and \(\beta3\) adrenergic receptor agonists;

(m) agents intended for use in inflammatory conditions such as aspin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 selective inhibitors;
(n) glucagon receptor antagonists;
(o) GLP-I,
(P) GIP-I,
(q) GLP-I analogs, such as exendins, for example exenatide (Byetta), and
(r) Hydroxysterol dehydrogenase-1 (HSD-I) inhibitors.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Non-limiting examples include combinations of compounds having Formula I with two or more active compounds selected from biguanides, sulfonylureas, HMG-CoA reductase inhibitors, other PPAR agonists, PTP-IB inhibitors, DP-IV inhibitors, and anti-obesity compounds.

BIOLOGICAL ASSAYS

Generation of GPR40-Expressing Cells

Human and mouse GPR40 stable cell-lines were generated in CHO cells stably expressing NFAT BLA (Beta-lactamase). A human GPR40 stable cell-line was generated in HEK cells stably expressing the aequorin expressing reporter. The expression plasmids were transfected using lipofectamine (Life Technologies) following manufacturer's instructions. Stable cell-lines were generated following drug selection.

FLIPR Assays

FLIPR (Fluorescence Imaging Plate Reader, Molecular Devices) assays were performed to measure agonist-induced calcium mobilization of the stable clones. For the FLIPR assay, one day before assay, GPR40/CHO NFAT BLA cells were seeded into black-wall-clear-bottom 384-well plates (Costar) at 1.4 x 10^4 cells / 20 µl medium / well. The cells were incubated with 20 µl / well of the assay buffer (HBSS, 0.1% BSA, 20 mM HEPES, 2.5 mM probenecid, pH 7.4) containing 8µM fluo-4,AM, 0.08 % pluronic acid at room temperature for 100 minutes. Fluorescence output was measured using FLIPR. Compounds were dissolved in DMSO and diluted to desired concentrations with assay buffer 13.3 µl/well of compound solution was added.

EC50 activities were measured for the compounds using both the human and mouse GPR40 cell lines. The activities for the compounds herein are as follows: human FLIPR EC50: 0.033 to 40 µM; mouse FLIPR EC50: 0.051 to 40 µM. The preferred compounds have an EC50 <10 µM.

Inositol Phosphate Turnover Assay

The assay is performed in 96-well format. HEK cells stably expressing human GPR40 are plated to be 60-80% confluent within 72 hours. After 72 hours, the plates are aspirated and the cells washed with inositol-free DMEM (ICN). The wash media is replaced with 150µL of 3H-inositol labeling media (inositol-free media containing 0.4% human albumin or 0.4% mouse albumin, 1X pen/strep...
antibiotics, glutamme, 25mM HEPES to which is added 3H-myo-inositol NEN #NET1 14A lmCi/mL, 25Ci/mmol diluted 1:150 in loading media with a final specific radioactivity of 1UCI/150UL). Alternatively, the human and mouse albumin can be added after the overnight labeling step before the addition of LiCl.

The assay is typically run the next day after 18 hours labeling. On the day of the assay, 5uL of 30OmM LiCl is added to all wells and incubated at 37 degrees for 20 mins. 0.75uL of 200X compounds are added and incubated with the cells for 60 minutes at 37 degrees. The media is then aspirated off and the assay terminated with the addition of 60uL 10mM formic acid. The cells are lysed for 60 mms at room temperature. 15-30uL of lysate is mixed with 70uL/img YSi SPA beads (Amersham) in clear bottom Isoplates. The plates are shaken for 2 hours at room temperature. Beads are allowed to settle and the plates are counted in the Wallac Microbeta.

**In Vivo Studies**

Male C57BL/6N mice (7-12 weeks of age) are housed 10 per cage and given access to normal diet rodent chow and water ad libitum. Mice are randomly assigned to treatment groups and fasted 4 to 6 hours. Baseline blood glucose concentrations are determined by glucometer from tail nick blood. Animals are then treated orally with vehicle (0.25% methylcellulose) or test compound. Blood glucose concentration is measured at a set time point after treatment (t = 0 mm) and mice are then intraperitoneally-challenged with dextrose (2 g/kg). One group of vehicle-treated mice is challenged with saline as a negative control. Blood glucose levels are determined from tail bleeds taken at 20, 40, 60 minutes after dextrose challenge. The blood glucose excursion profile from t = 0 to t = 60 mm is used to integrate an area under the curve (AUC) for each treatment. Percent inhibition values for each treatment are generated from the AUC data normalized to the saline-challenged controls.

**EXAMPLES**

The following Examples are provided to illustrate the invention and are not to be construed as limiting the invention in any manner. The scope of the invention is defined by the appended claims.

Methods for preparing the compounds of this invention are illustrated in the following Examples. Syntheses of several Intermediates that are used for making the exemplified compounds are also provided. Starting materials are either commercially available or made by known procedures in the literature or as illustrated. The present invention further provides processes for the preparation of compounds of formula I as defined above.
To a cooled (-78 °C) solution of ethyl [(lS)-5-methoxy-2,3-dihydro-1H-mden-1-yl]acetate (2.34 g, 10 mmol), prepared according to a published procedure (WO 2004001 1446), in 20 mL of anhydrous THF was added a solution of sodium bis(trimethylsilyl)amide (1.0 M, 12 mL, 12 mmol) dropwise. The mixture was stirred at -78 °C for 30 min, then a neat solution of πmethylsilyl chloride (1.4 mL, 11 mmol) was added dropwise. The reaction was stirred for an additional 10 min., solid NBS (2.0 g, 11 mmol) was added in one portion, the reaction was warmed to RT for one hour, quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, evaporated to afford a crude oil which was used in the next step without further purification.

The crude product (3.70 g) from step A was treated with thiourea (0.76 g, 10 mmol) and sodium acetate (0.82 g, 10 mmol) in 50 mL of ethanol. The mixture was refluxed for 13 h, cooled at RT. After addition of 20 mL of ether and 20 mL of hexane, the resulting solid was collected by filtration and washing with hexane. The desired product was obtained as off white solid. LC-MS: calc. for C13H14N2O2S: 262; Found: 263 (M+H). 1H NMR (400 MHz, CD3OD) δ 7.11, 6.90 (dd, J = 8.1, 8.3 Hz, ratio = 2:1, IH), 6.58-6.76 (m, 2H), 5.03, 4.66 (dd, J = 3.0, 2.8 Hz, ratio = 2:1, IH), 3.95 (m, IH), 3.70 (s, 3H), 2.92 (m, 2H), 2.42, 2.05, 1.82, 1.70 (m, 2H).
The product from step B was mixed with 50 mL of 2N aq. HCl and 50 mL of ethanol. The mixture was refluxed overnight (monitored by LC-MS until a complete conversion was observed). After removal of ethanol under vacuum, the residue was extracted with ethyl acetate, dried over anhydrous sodium sulfate, evaporated and dried under high vacuum to afford a yellow solid. LC-MS: calc. for C13H13NO3S: 263

Found: 264 (M+H).

1H NMR (400 MHz, CD3OD) δ 7.10, 6.96 (dd, J = 8.3, 8.4 Hz, ratio = 3:1, IH), 6.60-6.80 (m, 2H), 5.11, 4.76 (dd, J = 3.7, 4.1 Hz ratio = 3:1, IH), 4.0 (s, IH), 3.72 (s, 3H), 3.0-2.7 (m, 2H), 2.40, 2.08, 1.90 (mmm, 2H).

Step D

To a stirred, cool (-78 °C) solution of the product (1.40 g, 5.3 mmol) from step C in 10 mL of dichloromethane was added a solution of boron tribromide in dichloromethane (1.0 M, 15 mL, 15 mmol). The reaction was then warmed to RT for 30 min., then quenched with ice-water. The product was extracted with ethyl acetate twice. The organic phase was washed with water twice, dried over anhydrous sodium sulfate, and evaporated. The residue was dried under high vacuum to afford a light brown solid which could be used in next step without further purification. LC-MS: calc. for C12H11NO3S: 249

Found: 250 (M+H).

1H NMR (400 MHz, CD3OD) δ 7.0, 6.9 (dd, J = 8.2, 8.2 Hz, ratio = 3:1, IH), 6.50-6.62 (m, 2H), 5.08, 4.71 (dd, J = 3.8, 4.2 Hz ratio = 3:1, IH), 3.90 (m, IH), 3.72 (s, 3H), 2.92-2.70 (m, 2H), 2.38, 2.06, 1.86 (mmm, 2H).

INTERMEDIATE 2

To a stirred solution of the racemic [6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid (69.4 g, prepared according to a published procedure (WO 2004001 1446) in 1500 mL of acetone was added 38.7
mL of (S)-alpha-methylbenzylamine in one portion. The mixture was stirred at RT for 30 min, then 1500 mL of hexane was added. The mixture was stirred for one hour. The resulting solid was removed by filtration and washing with hexane/acetone (4:1 v/v), and was then dried in air to give the first batch of solid. The combined mother liquids were stored at 0-5 °C overnight, the resulting solid was collected by filtration to give a second batch of solid. The two batches of the salt were combined, dissolved in warm acetone (500 mL). 750 mL of hexane was added, and the mixture was stirred at RT for one hour. The resulting solid was collected by filtration, washed with hexane/acetone (4:1), and dried in air to give off-white crystals of (R,S)-salt.

Step B

All mother liquids from the above step A were combined and condensed to give a light brown solid. 3N aq. HCl was added to adjust pH <3, stirred with ethyl acetate (500 mL), and separated. The organic phase was washed with 3N aq. HCl, dried over sodium sulfate, filtered and evaporated to afford a light brown solid (32 g, 145 mmol, S-πched acid). This solid was dissolved in 500 mL of acetone, (R)-(+)alpha-methylbenzylamine (16.6 mL, 145 mmol) was added, the mixture was refluxed until all the solid dissolved, and was then cooled to RT. The resulting precipitate was collected by filtration and washing with acetone to afford a white solid salt (S,R). The (S)-absolute configuration of the acid was confirmed by X-ray crystallography of the amide formed by treatment of the above salt with EDAC.

Step C

The (S,R) salt from the above step B (23.2 g) was stirred for one hour with 200 mL of 3N HCl and 200 mL of ethyl acetate. The organic phase was separated and washed with 3N aq. HCl (2 x 100 mL), dried over sodium sulfate, filtered and evaporated to give the desired (S)-acid as a light brown solid.
The (S)-acid from the above step D (14 g) was dissolved in 150 mL of ethanol, and 19 mL of trimethylsilyl chloride was added. The mixture was stirred at RT overnight, and was then evaporated and mixed with ethyl acetate (100 mL). The organic phase was washed with water and saturated aq. sodium hydrogen carbonate, dried over sodium sulfate, and purified on FC (Silica gel, 20% ethyl acetate/hexane) to give the desired (S)-ester as a colorless oil. IH NMR (400 MHz, CDCl3) δ 7.04 (d, J = 7.7 Hz, 1H), 6.67 (m, 1H), 6.60 (m, 1H), 4.14 (m, 2H), 3.74 (bs, 3H), 3.26 (m, 1H), 2.80-2.40 (m, 4H), 1.90-1.60 (m, 4H), 1.24 (m, 3H).

Step E

To a cooled (-78 °C) solution of ethyl [(lS)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl] acetate (7.45 g, 30 mmol), from the above step D, in 50 mL of anhydrous THF was added a solution of sodium bis(tπmethylsilyl)amide (1.0 M, 36 mL, 36 mmol) dropwise. The mixture was stirred at -78 °C for 30 min, then a neat solution of trimethylsilyl chloride (4.22 mL, 33 mmol) was added dropwise. The reaction was stirred for additional 10 min. Solid NBS (5.87 g, 33 mmol) was added in one portion. The reaction was warmed to RT during one hour, quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to afford a crude oil which was used in the next step without further purification.

Step F

The crude product from the above step E was treated with thiourea (2.28 g, 30 mmol) and sodium acetate (2.46 g, 30 mmol) in 50 mL of ethanol. The mixture was refluxed for 13 h, cooled at RT. After addition of 20 mL of ether and 20 mL of hexane, the resulting solid was collected by filtration and washing with hexane. The desired product was obtained as an off white solid. LC-MS: calc. for C14H16N2O2S: 276; Found: 277 (M+H).
The product from the above step F was mixed with 50 mL of 4N aq. HCl and 50 mL of ethanol. The
mixture was refluxed overnight (monitored by LC-MS until a complete conversion was observed). After
removal of ethanol under vacuum, the residue was extracted with ethyl acetate, dried over anhydrous
sodium sulfate, evaporated, and dried under high vacuum to afford a yellow solid. LC-MS: calc. for
C14H15NO3S: 277 Found: 278 (M+H).

Step H

To a stirred, cool (-78 °C) solution of the product from the above step G (5.2 g, 18.7 mmol) in 50 mL of
dichloromethane was added a solution of boron trifluoride in dichloromethane (1.0 M, 57 mL, 57 mmol).
The reaction was then warmed to RT for 30 min. and quenched with ice-water. The product was
extracted with ethyl acetate twice. The organic phase was washed with water twice, dried with
anhydrous sodium sulfate, and evaporated. The residue was dried under high vacuum to afford a light
brown solid which could be used in next step without further purification. LC-MS: calc. for
C13H13NO3S: 263 Found: 264 (M+H).

INTERMEDIATE 3

The (R,S) salt (24.5 g) from step A of the synthesis of Intermediate 2 was stirred for one hour with 200
mL of 3N HCl and 200 mL of ethyl acetate. The organic phase was separated and washed with 3N aq.
HCl (2 x 100 mL), dried over sodium sulfate, filtered, and evaporated to give the desired (R)-acid as a
light brown solid.
Step B

![Chemical structure](image)

The (R)-acid from the above step A (15.6 g) was dissolved in 150 mL of ethanol followed by addition of 19 mL of trimethylsilyl chloride. The mixture was stirred at RT overnight, evaporated and mixed with ethyl acetate (100 mL). The organic phase was washed with water and saturated aq. sodium hydrogen carbonate, dried over sodium sulfate, and purified on FC (Silica gel, 5% ethyl acetate/hexane) to give the desired (R)-ester as a colorless oil.

Step C

![Chemical structure](image)

To a cooled (-78 °C) solution of ethyl [(IR)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl] acetate (7.45 g, 30 mmol), from the above step B, in 50 mL of anhydrous THF was added a solution of sodium bis(trimethylsilyl)amide (1.0 M, 36 mL, 36 mmol) dropwise. The mixture was stirred at -78 °C for 30 mm. A neat solution of trimethylsilyl chloride (4.22 mL, 33 mmol) was added dropwise. The reaction was stirred for an additional 10 min., and solid NBS (5.87 g, 33 mmol) was added in one portion. The reaction was warmed to RT during one hour, quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to afford a crude oil which was used in the next step without further purification.

Step D

![Chemical structure](image)

The crude product from the above step C was treated with thiourea (2.28 g, 30 mmol) and sodium acetate (2.46 g, 30 mmol) in 50 mL of ethanol. The mixture was refluxed for 13 h, and cooled to RT. After addition of 20 mL of ether and 20 mL of hexane, the resulting solid was collected by filtration and washed with hexane. The desired product was obtained as an off white solid. LC-MS: calc. for C14H16N2O2S: 276; Found: 277 (M+H).
Step E

The product from the above step D was mixed with 50 mL of 4 N aq. HCl and 50 mL of ethanol. The mixture was refluxed overnight (monitored by LC-MS until a complete conversion was observed). After removal of ethanol under vacuum, the residue was extracted with ethyl acetate, dried over anhydrous sodium sulfate, and evaporated and dried under high vacuum to afford a yellow solid. LC-MS: calc. for C14H15NO3S: 277 Found: 278 (M+H).

Step F

To a stirred, cool (-78 °C) solution of the product from the above step E (4.02 g, 14.5 mmol) in 50 mL of dichloromethane was added a solution of boron tribromide in dichloromethane (1.0 M, 30 mL, 30 mmol). The reaction was then warmed to RT for 30 min., and quenched with ice-water. The product was extracted with ethyl acetate twice. The organic phase was washed with water twice, dried with anhydrous sodium sulfate, and evaporated. The residue was dried under high vacuum to afford a light brown solid which could be used in the next step without further purification. LC-MS: calc. for C13H13NO3S: 263 Found: 264 (M+H).

INTEMEDEIATE 4

Step A

To 6-hydroxyl-2, 3-dihydrobenzofuran-3-one (30 g, 200 mmol) in DMF (600 mL) was added K2CO3 (220 mmol, 30.4 g) followed by BnBr (200 mmol, 24 mL). After stirring at room temperature for 3
hours, the reaction mixture was partitioned between methyl t-butyl ether (MTBE, 500 mL) and water (IL). The aqueous layer was separated and further extracted with MTBE (2 x 500 mL). The organic layers were combined, washed with water (500 mL), Brine (500 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo to give 6 as the product yellow solid. LC-MS for C15H13O3 [M+H]: calculated 241, found 241.

Step B

To a suspension of NaH (60% in mineral oil, 381 mmol, 15.2 g) in anhydrous THF (900 mL) was added triethyl phosphonoacetate (381 mmol, 76 mL) dropwise in an ice bath. After addition, the reaction was stirred at room temperature for 20 minutes until a clear solution was obtained. A solution of the ketone (45.7 g, 190 mmol) from Step A in THF (100 mL) was then added to the reaction. The reaction was stirred overnight at room temperature and then quenched with 0.1N HCl (1 L). The aqueous layer was separated and extracted with EtOAc (2 x 500 mL). The organic layers were combined, washed with water (500 mL), then Brine (500 mL), then dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% to 30% EtOAc/hexanes) to give the product as a yellow solid. LC-MS for C19Hl9O4 [M+H]: calculated 311.1, found 311.3.

Step C

To a solution of the unsaturated ester (6.6 g, 21.3 mmol) from Step B in ethanol (75 mL) and EtOAc (75 mL) was added 10% Pd/C (2 g). The mixture was hydrogenated in a Parr-shaker at 50 psi for 2 hours. The mixture was then filtered through celite. The filtrate was concentrated in vacuo to give the product as a red oil. LC-MS for C12H15O4 [M+H]: calculated 223, found 223.

Step D

To a solution of the acid (2 g, 9 mmol) from Step C in DMF (15 mL) and acetone (60 mL) was added K2CO3 (11 mmol, 1.5 g) followed by BnBr (11 mmol, 1.3 mL). The reaction was stirred overnight at
room temperature and then concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (200 mL). The aqueous layer was separated and further extracted with EtOAc (2 x 100 mL). The organic layers were combined, washed with water (100 mL), then Brine (100 mL), then dried with anhydrous Na2SO4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (0% to 15% EtOAc/hexanes) to give the product as an oil. 1H NMR (500 MHz, CDC13) δ 7.50-7.30 (m, 5H), 7.06 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 6.50 (bs, 1H), 5.0 (s, 2H), 4.8 (t, J = 8.9 Hz, 1H), 4.30 (dd, J = 6.1, 8.9 Hz, 1H), 4.2 (q, J = 7.1 Hz, 2H), 4.85 (m, 1H), 2.75 (dd, J = 5.5, 16.5 Hz, 1H), 2.58 (dd, J = 9.1, 16.2 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H). LC-MS for C19H21O4 [M+H]: calculated 313.4, found 313.2.

**Step E**

![Image](image.png)

To a flame-dried flask was added anhydrous THF (30 mL) followed by NaHMDS (7.5 mmol, 7.5 mL of 1 M THF solution). After cooling to -78 °C, a solution of the ester (2.0 g, 6.3 mmol) from Step D in THF (10 mL) was added to the reaction slowly. After addition, the reaction was stirred at -78 °C for 15 minutes before TMSCl (7.2 mL of 1 M solution in THF, 7.2 mmol) was added. After another 30 minutes at -78 °C, NBS (6.9 mmol, 1.2 g) was added in one portion. The reaction was allowed to warm up to 0 °C over 2 hours before being quenched with 0.1 N HCl (200 mL). The aqueous layer was separated and further extracted with EtOAc (2 x 100 mL). The organic layers were combined, washed with water (100 mL), then Brine (100 mL), then dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (0% to 18% EtOAc/hexanes) to give 2.3 g of oil. This oil was then dissolved in ethanol (40 mL), and thiourea (7.0 mmol, 0.54 g) and NaOAc (12 mmol, 0.96 g) were added. The reaction was refluxed for 24 hours and then cooled back to room temperature. The suspension was then filtered. The solid was further washed with cold EtOH (4 mL) and dried in air to give the product as a white solid. LC-MS for C18H17N2O3S [M+H]: calculated 341.1, found 341.1.

**Step F**

![Image](image.png)

A suspension of the cyclic product (1.5 g, 4.4 mmol) from Step E in EtOH (20 mL) and 6 N HCl (4 mL) was refluxed overnight. The reaction was then concentrated *in vacuo*. The residue was purified by silica
gel flash chromatography (0% to 50% EtOAc/hexanes) to give the desired TZD as a mixture of diastereomers. LC-MS for C18H16NO4S [M+H]: calculated 342.1, found 342.1.

**Step G**

To a suspension of the methoxy TZD (300 mg, 0.88 mmol) from Step F in EtOH (20 mL) was added 4 N HCl in dioxane (500 µL and 10% Pd/C (500 mg). The reaction was hydrogenated at 1 atm for 2 hours to give a completed reaction. The mixture was then filtered through celite. The filtrate was concentrated in vacuo to give INTERMEDIATE 4 as a yellow solid. LC-MS for C11H10NO4S [M+H]: calculated 252.0, found 252.1.

**INTERMEDIATE 5**

To a cooled (-78 °C) solution of ethyl [(1S)-5-methoxy-2,3-dihydro-IH-inden-l-yl]acetate (2.34 g, 10 mmol), prepared according to a published procedure (WO 20040011446), in 20 mL of anhydrous THF was added a solution of sodium bis(trimethylsilyl)amide (1.0 M, 12 mL, 12 mmol) dropwise. The mixture was stirred at -78 °C for 30 min, then a neat solution of trimethylsilyl chloride (1.4 mL, 11 mmol) was added dropwise. The reaction was stirred for an additional 30 min., then the reaction vessel was gradually warmed to room temperature. Solvent was then removed in vacuo (roto-evaporation) and then ca. 75 mL of pentane was added to the residue. Rapid filtration and removal of solvent in vacuo yielded crude alkyl trimethyl ketene acetal.

**Step B**
A pre-cooled (ice-methanol) stirred solution of 2.35 g (77% purity, 10 mmol) of MCPBA in 100 mL of dry hexane under an atmosphere of nitrogen was treated with a solution containing 10 mmol of the above acetal from Step A in 100 mL of dry hexane. After addition was complete (ca. 5 min), the resulting slurry was stirred for 30 min at room temperature. The reaction mixture was then treated with 1.2 g (10 mmol) of triethylammonium fluoride with stirring, which continued for 30 min after addition was completed. The mixture was then filtered, and the filtrate was diluted with 100 mL of ethyl acetate. The solution was then washed sequentially with 200 mL of 5% aqueous hydrochloric acid and 2 x 200 mL of 5% aqueous sodium carbonate. The organic layer was then dried using anhydrous sodium sulfate. Filtration and solvent removal in vacuo gave crude hydroxyl ester. The pure compound was then obtained on Combi-Flash (5-10% ethyl acetate/hexane). LC-MS for C14H18O4: calculated 250, found 251 [M+H].

IH NMR (400 MHz, CDC13) (major isomer) δ 7.2 (d, 1H), 6.72 (s, 1H), 6.05 (d, 1H), 4.28 (d, 1H), 4.18 (m, 2H), 3.68 (s, 1H), 3.52 (m, 1H), 2.90 (m, 1H), 2.72 (m, 1H), 2.10 (m, 2H), 1.22 (t, 3H).

Step C

The hydroxyl ester obtained from Step B was mixed with 4N ammonia-methanol (50 mL) and stirred overnight, then was evaporated, and the residue was mixed with 5 mL of ethyl acetate and 20 mL of hexane. The resulting white powder was filtered and washed with hexane, dried under high vacuum to give the pure product as single isomer. LC-MS for C12H15NO3: calculated 221, found 222 [M+H]. IH NMR (400 MHz, CDC13) δ 7.12 (d, J = 8.1 Hz, 1H), 6.77 (m, 2H), 6.55 (bs, 1H), 5.53 (bs, 1H), 4.54 (s, 1H), 3.76 (s, 3H), 2.82 (m, 2H), 2.12 (m, 1H), 2.00 (m, 1H), 1.98 (m, 1H).

Step D

The hydroxy amide from Step C (280 mg, 1.267 mmol) and diethyl carbonate (747 mg, 6.335 mmol) were mixed with sodium methoxide (345 mg, 6.335 mmol) and ethanol (10 mL). The mixture was refluxed for 1.5 h, then evaporated. The residue was acidified with 3N aq. HCl, extracted with ethyl acetate, dried over sodium sulfate, evaporated and purified on Comb-Flash (5-30% ethyl acetate/hexane) to give the product. LC-MS calculated for C13H13NO4 [M+H] calculated: 247; Found: [M+H]. IH NMR (400 MHz, CDC13) (major isomer) δ 7.17 (d, J = 8.0 Hz, 1H), 6.75 (m, 2H), 5.10 (s, 1H), 3.75 (s, 3H), 3.00 (m, 1H), 2.84 (m, 1H), 2.22 (m, 2H), 2.04 (m, 1H). Major/minor ≈ 6:1.

Step E

- 30 -
To a stirred, cool (-78 °C) solution of the product from the above step D (100 mg, 0.4 mmol) in 5 mL of dichloromethane was added a solution of boron tribromide in dichloromethane (1.0 M, 1.0 mL, 1.0 mmol). The reaction was warmed to RT for 50 min., then quenched with ice-water. The product was extracted with ethyl acetate twice. The organic phase was washed with water twice, dried with anhydrous sodium sulfate, and evaporated. The residue was dried under high vacuum to afford INTERMEDIATE 5 which could be used in next step without further purification. LC-MS: calc. for C12H11NO4: 233 Found: 234 (M+H).

INTERMEDIATE 6

Step A

To a dried 3-neck 2 L round bottom was added freshly azeotroped 7-(benzyloxy)chroman-4-one (287 g, 1.13 mol, synthesized according to J. Med. Chem. 1998, 41, 1172-1 184) and 2 L of anhydrous THF (no inhibitor). Zinc (124.9 g, 1.92 mol) and CuI (10.7 g, 56.5 mmol) were then quickly added to the reaction solution. After refluxing for 30 minutes under N2 atmosphere, 81 mL of ethyl bromoacetate (1/2 of total needed, F.W. 167.01, d 1.506, 0.7 mol) was added dropwise to the refluxing mixture. Heat was then turned off and the reaction was stirred at ambient temperature for 4-5 h. Another 81 mL of ethyl bromoacetate (F.W. 167.01, d 1.506, 0.7 mol) was then added dropwise and the reaction was stirred without heating until the reaction temperature returned to ambient temperature. Solids were removed by vacuum filtration through celite and the filtrate was concentrated to ~800 mL by rotary evaporation, which was poured into 1 L of IN HCl (aq) with 1000 g of ice, and stirred vigorously for 30 min. The mixture was extracted with EtOAc (1 x 2 L, 2 x 1 L). The combined organic layers were washed with
H₂O (1 x 3 L), Brine (1 x 2 L), dried over Na₂SO₄, and concentrated in vacuo. The crude compound was used without further purification.

Step B

\[
\text{\begin{align*}
\text{BnO} & \quad \text{COOEt} \quad & \quad \text{LiOH} \quad & \quad \text{THF/MeOH/H₂O} \quad & \quad \text{BnO} & \quad \text{COOH} \\
\text{BnO} & \quad \text{COOEt} \quad & \quad \text{LiOH} \quad & \quad \text{THF/MeOH/H₂O} \quad & \quad \text{BnO} & \quad \text{COOH}
\end{align*}}
\]

To a solution of crude product (-356 g, 1.1 mol) from step A in THF/MeOH/H₂O (2:2:1, 2.5 L) was added LiOKH₂O (92.4 g, M.W. 41.96, 2.2 mol). The reaction was stirred at ambient temperature overnight. The organic solvents were removed \textit{in vacuo} and the residue was diluted with water to 3 L in volume. This aqueous solution was washed with diethyl ether (2 x 500 mL) and the aqueous layer was then acidified to pH=1 with 10 N HCl (aq). The solid was isolated by vacuum filtration, washed with EtOAc and dried under vacuum. The filtrate was extracted with EtOAc (2 x 500 mL). The combined organics were washed with brine (400 mL) and concentrated \textit{in vacuo}. All solids were combined, triturated with minimal EtOAc, and dried under high vacuum to give a mixture of two isomers.

Step C

A solution of product from step B (20 g, 67.6 mmol) in anhydrous methanol (800 mL) was degassed by bubbling through N₂ for 1 hour. (R)-BINAP RuCl₂ (1.11 g, F.W. 794.65, 1.4 mmol) and 950 µL of freshly degassed trimethylamine (F.W. 101.19, d 0.72, 6.76 mmol) were quickly added under N₂ atmosphere. The mixture was hydrogenated under H₂ (50 psi) for 4 days. The mixture was then filtered and the filtrate was concentrated \textit{in vacuo}. The residue was purified by column chromatography to give the desired product (70% ee) and recovered starting material. The product was dissolved in minimal EtOAc (~20 mL) and petroleum ether (~20 mL) and re-crystallized to give chiral acid (~95%ee).

Step D
A solution of chiral acid from step C (6.5 g, 21.8 mmol) in 100 mL of 6 N HCl/EtOH, was stirred at RT for 5 hour. The reaction was then concentrated in vacuo to give the desired chiral ester. IH NMR (400 MHz, CDC13) δ 7.5 - 7.25 (m, 5 H), 7.0 (d, J = 10 Hz, IH), 6.55 (m, 1 H), 6.44 (s, 1 H), 5.01 (s, 2 H), 4.20 - 4.12 (m, 4 H), 3.34 - 3.28 (m, 1 H), 2.78 - 2.73 (m, 1 H), 2.51 - 2.45 (m, 1 H), 2.18 - 2.10 (m, 1 H), 1.85 - 1.78 (m, IH), 1.30 - 1.24 (m, 3 H).

Step E

To a solution of chiral ester from step D (7.3 g, 22.4 mmol) in anhydrous THF (100 mL) was added NaHMDS (2.0 M THF, 14.6 mL, 29.2 mmol) at -78 °C. After addition, the reaction was stirred at -78 °C for 30 minutes before TMSCl (2.0 M THF, 13.5 mL, 26.9 mmol) was added. After the addition of TMSCl, the reaction was stirred for another 30 minutes and NBS (4.4 g, 24.7 mmol) was added in one portion. The reaction was allowed to warm up to 0 °C over 2-3 hours. The reaction was partitioned between 0.1 N HCl aq (200 mL) and ethyl acetate (200 mL). The organic layer was washed with 0.1 N HCl aq (1 x 200 mL). The aqueous layers were combined and back-extracted with EtOAc (1 x 100 mL). The organic layers were combined and washed with Brine (2 x 100 mL), dried over Na₂SO₄ and concentrated in vacuo to give the desired product. This crude material was used without further purification.

Step F

To the crude material from step E (~20 mmol) in 100 mL of EtOH was added thiourea (M.W. 76.12, 1.979 g, 26 mmol) and sodium acetate (M.W. 82.03, 3.281 g, 40 mmol). The reaction was refluxed overnight. The organic solvent was removed in vacuo and the residue was partitioned between 50 mL of 6 N HCl (aq) and 50 mL of EtOAc. The organic layer was further extracted with 6 N HCl (aq) (2 x 25 mL). The aqueous layers were combined and further washed with EtOAc (1 x 10 mL). The aqueous layer was separated and EtOH (50 mL) was added to the aqueous solution. This solution was refluxed for 24 hours and then cooled to room temperature. The reaction was diluted with water (400 mL) and extracted with EtOAc (1 x 400 mL, 2 x 200 mL). The organic layers were combined and washed with...
Bπne (1 x 100 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica, 0-20% EtOAc/CH₂Cl₂) to afford the desired INTERMEDIATE 6. LC-MS negative[M-H]: calc. for C₁₂H₁₀N₂O₄S: 264 Found: 264.

The INTERMEDIATE 7 was prepared according to the same procedures as in the preparation of INTERMEDIATE 5 by replacing ethyl [(lS)-5-methoxy-2,3-dihydro-1H-inden-1-yl]acetate with the product of Step D in INTERMEDIATE 2. LC-MS for C₁₃H₁₃N₂O₄: calculated 247.1, found 246.1 [M-H].

Step A

This material was prepared according to the procedure used in the Steps A - E in the preparation of INTERMEDIATE 6, using 7-methoxythiochroman-4-one (prepared according to the procedure used in Tetrahedron, 1970, 26(10), 2353-2363) as the starting material. This crude material was used without further purification.
INTERMEDIATE 8 was prepared from material obtained in the above Step A using a similar procedure to that used in Steps B-D in the preparation of INTERMEDIATE 1. LC-MS for C₈HnNO₃S₂: calculated 281.02, found 280 [M-H].

![Example 1](image1)

INTERMEDIATE 2 (52.6 mg, 0.2 mmol) was combined with 4-chloroquinoline (39 mg, 0.24 mmol) and Cs₂CO₃ (156 mg, 0.48 mmol) in 1 riiL of N,N-dimethylformamide. The reaction mixture was stirred at 110 °C for 6 hours, then was poured into water and acidified with 2N aq. HCl to pH <2. The resulting solid precipitate was extracted with ethyl acetate and the combined organic layers were washed with water followed by brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. Purification by preparative thin layer chromatography (silica, 6% methanol in dichloromethane) gave the product. LC-MS calc. for C₂₂H₁₈N₂O₃S: 390; Found 391 (M+H).

EXAMPLES 2-45

The following examples in Table 1 were prepared following a procedure similar to the one used in the preparation of EXAMPLE 1. These are readily prepared by one of skill in the art of synthetic organic chemistry or medicinal chemistry using the information provided herein.

Table 1

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To a stirred solution of 5-hydroxy-1-indanone (296.3 mg, 2 mmol) in 3 mL of DMF was added 4-chloro-7-(trifluoromethyl)quinoline (473.2 mg, 2 mmol) and cesium carbonate (977.4 mg, 3 mmol). The reaction mixture was heated at 80 °C for 16 hours. After cooling to room temperature, it was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography using ethyl acetate/hexanes as the eluant (10 - 70%). LC-MS LC-MS calc. for C19H12F3NO2: 343; Found: 344 (M+H).
To a stirred solution of (R)-2-methyl-CBS-oxazaborohdine (1 M in toluene, 57 µL, 5.68 mmol) in 3 mL of dichloromethane at -20 °C was added slowly borane-methyl sulfide complex (1 M in dichloromethane, 1.14 mL, 1.136 mmol). Then the ketone obtained in Step A (195 mg, 0.568 mmol) in 3 mL of dichloromethane was added at -20 °C over 3 h. The reaction mixture was stored in the freezer (-15 °C) over night. The reaction was quenched with methanol, and heated at 70 °C for 1 hour before concentration under reduced pressure. The residue was purified with preparative TLC (40% EtOAC/hexane) to give the desired product. LC-MS calc. for C19H14F3NO2: 345; Found: 346 (M+H).

**Step C**

To a stirred solution of the product obtained in Step B (90.0 mg, 0.261 mmol) in 1 mL of THF was added 1,2,4-oxadiazohdme-3,5-dione (26.6 mg, 0.261 mmol), triphenylphosphine (102.7 mg, 0.392 mmol) and dπsopropyl azo-dicarboxylate (50.6 µL, 0.261 mmol). The reaction mixture was treated in a microwave reactor at 80 °C for 2 mm before being concentrated under reduced pressure. The residue was purified with preparative TLC (8% MeOH/CH₂Cl₂ plus 0.5% HOAc) to give the desired product. LC-MS calc. for C21H14F3N3O4: 429; Found: 430 (M+H).
Example 47 was prepared following a procedure similar to the one used in the preparation of Example 46, replacing 4-chloro-7-(trifluoromethyl)quinoline with 4,7-dichloroquinoline. LC-MS calc. for C20H14ClN3O4: 395; Found: 396 (M+H).
WHAT IS CLAIMED IS:

1. A compound of formula I, or a pharmaceutically acceptable salt thereof:

\[
\begin{array}{c}
R^1 \quad R^2 \\
N \quad O \\
R^3 \quad R^4
\end{array}
\]

wherein A is selected from the group consisting of -CH- and -N-;

B is selected from the group consisting of -S-, -O-, -NH-, and -CH2-;

W is selected from the group consisting of -CH2-, -CF2-, -O-, -C(=O)-, -NR.6-, -S-, -S(O)-, and -S(O)2-;

Z is selected from the group consisting of -CH2- and -CH2CH2-;

or alternatively -W-Z- is selected from the group consisting of -N(R6)C(=O)- and -C(=O)(R6)-, or -W-Z- represents two atoms that are connected to form one side of a 5-6-membered heteroaromatic ring having 1-3 heteroatoms independently selected from O, N and S, where the 5-membered heteroaromatic ring is optionally substituted with 1-3 groups independently selected from halogen, CH3, CF3, -OCH3, and -OCF3;

Heterocycle is a 5-6 membered saturated or partly saturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from O, N and S;

Heteroaryl is a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from O, N and S;

R1, R2, R3 and R4 are each independently selected from the group consisting of H, halogen, -CN, -NO2, -Q-Coalkyl, -0Ci-C6alkyl, -SCi-C6alkyl, -S(O)2Ci-C6alkyl, -N(R6)(R6), -N(R6)C(=O)C 1-C6alkyl, -N(R6)S(O)2C 1-C6alkyl, -S(O)2N(R6)(R6), -C(=O)H, -C(O)OH, -C(=O)O Ci-C6alkyl, -C(=O)O Ci-C6alkyl, -C(=O)O Ci-C6alkyl, -C(=O)N(R6)(R6), -C(=O)Phenyl, -C(=O)Naphthyl, -C(=O)Heterocycle, Heterocycle, Heteroaryl, C3-C7-Cycloalkyl, Phenyl and Naphthyl;
wherein -Ci-C6alkyl and the alkyl groups of -O Ci-C6alkyl, -SCi-C6alkyl,
-S(O)2Ci-C6alkyl, -N(R6)C(=O)Ci-C6alkyl, -C(O)OCi-C6alkyl, and
-C(O)C i-Cgalkyl are optionally substituted with 1-5 halogens and optionally substituted with 1-2
groups independently selected from -OH, -0C]-C3alkyl which is optionally substituted with 1-5 halogens,
-S(O)2Ci-C3alkyl which is optionally substituted with 1-5 halogens, -C(=0)Ci-C3alkyl which is
optionally substituted with 1-5 halogens, -0C(=0)Ci-C6alkyl which is optionally substituted with 1-5 halogens,
-NHC(=0)CH3, -NHC(=0)0Ci-C6alkyl which is optionally substituted with 1-5 halogens,
-NHS(O)2CH3, -N(R6XR6), Heterocycle, Heteroaryl, C3-C7-Cycloalkyl, Phenyl, and Naphthyl;
wherein -C(=0)Phenyl, -C(=O)Naphthyl, -C(=O)Heterocycle, Heterocycle, Heteroaryl, C3-C7-Cycloalkyl, Phenyl and Naphthyl either as R1, R2, R3, or R4, or as substituents on R1, R2, R3 and
R4 are optionally substituted with 1-4 substituents independently selected from halogen, -CF3, -OCF3, -CN,
-N02, -OH, -Ci-C3alkyl, -C(=0)Ci-C3alkyl, -S(O)2Ci-C3alkyl, and -0Ci-C3alkyl,
wherein said -Ci-C3alkyl, -0Ci-C3alkyl, -S(O)2Ci-C3alkyl, and -C(=0)Ci-C3alkyl substituents are
optionally substituted with 1-3 halogens;
wherein the pair of substituents R1 and R2 may together represent a bridging divalent 4-carbon chain
,C3-C7-CHO, -0CH=CH-, -CH=CH-CH=CH-, forming a fused phenyl ring at the R1 and R2 positions, wherein said
fused phenyl ring is optionally substituted with 1-3 substituents independently selected from halogen,
-OH, -CN, -NO2, -Ci-C3alkyl, -0Ci-C3alkyl, -SCI-C3alkyl, -S(O)2Ci-C3alkyl, -CF3, and -OCF3;
or alternatively the pair of substituents R1 and R2 may together represent a bridging
divalent 3-atom chain selected from -CH=CHO-, -0CH=CH-, -CH=CH-S-, and -SCH=CH-, forming a fused
furan or thiophene ring at the R1 and R2 positions, wherein said fused furan or thiophene ring is
optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO2, -Q-
-C3alkyl, -0Ci-C3alkyl, -SCI-C3alkyl, -S(O)2Ci-C3alkyl, -CF3, and -OCF3, and
Each R6 is independently selected from the group consisting of H and -Ci-C6alkyl.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof,
wherein R1, R2, R3, and R4 are independently selected from (1) H; (2) halogen; (3) -NO2; (4) -CN;
(5) Ci-C4alkyl, which is optionally substituted with 1-5 halogens and optionally with 1-2 substituents
independently selected with 1-3 halogens; (6) -0Ci-C4alkyl, which is optionally substituted with 1-5 halogens and optionally with one -C(=0)Ci-C3 alkyl group; (7) -C(=0)Ci-C3alkyl, which is optionally
substituted with 1-5 halogens; (8) -C(O)H; (9) -C(O)N(R6)(R6); (10) -S(O)2N(R6)(R6); (11)
-S(O)2Ci-C3alkyl; (12) -N(R6)(R6); (13) C3-C7-Cycloalkyl; (14) Phenyl; and (15) Heterocycle;
wherein C3-C7-Cycloalkyl, Phenyl, and Heterocycle are each optionally substituted with 1-3 substituents
independently selected from halogen, -OH, -0Ci-C3alkyl, CF3, and -C(O)C i-C3alkyl; and
Each R6 is independently selected from H and CH3.
3. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R₁, R₂, R₃, and R⁴ are each independently selected from H, halogen, Ci-C₃alkyl, CF₃, -O-Ci-C₃alkyl, -OCF₃, -C(=O)H, -C(=O)N(R⁶)(R⁶), -S(O)2N(R⁶)(R⁶), -C(=O)Ci-C₃alkyl, -CN, -NO₂, -S(O)2Ci-C₃alkyl, and -N(R⁶)(R⁶); and

Each R⁶ is independently selected from H and CH₃.

4. The compound of Claim 3, or a pharmaceutically acceptable salt thereof, wherein R₁, R₂, R₃, and R⁴ are each independently selected from H, F, Br, Cl, Ci-C₃alkyl, CF₃, -C(O)NH₂, -S(O)2NH₂, -C(=O)CH₃, -CN, -OCH₃, -OCF₃, and -NO₂.

5. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the pair of ortho substituents R₁ and R₂ together represent a bridging divalent 4-carbon chain -CH=CH-CH=CH-, forming a fused phenyl ring at the R₁ and R₂ positions, wherein the fused phenyl ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO₂, -Ci-C₃alkyl, -OCl-C₃alkyl, -SCI-C₃alkyl, -S(O)2Ci-C₃alkyl, -CF₃, and -OCF₃.

6. The compound of Claim 5, or a pharmaceutically acceptable salt thereof, wherein the fused phenyl ring at the R₁ and R₂ positions is optionally substituted with 1-2 substituents independently selected from halogen, -NO₂, -CH₃, -CF₃, -OCH₃, and -OCF₃.

7. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R₁ and R₂ together represent a bridging divalent group selected from -CH=CH-, -SCH=CH-, -CH=CHO-, and -OCH=CH-, forming a fused furan or thiophene at the R₁ and R₂ positions, wherein said fused furan or thiophene ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO₂, -Ci-C₃alkyl, -OQ^alkyl, -SCI-Csalkyl, -S(O)2Ci-C₃alkyl, -CF₃, and -OCF₃.

8. The compound of Claim 7, or a pharmaceutically acceptable salt thereof, wherein the fused furan or thiophene ring at the R₁ and R₂ positions is optionally substituted with 1-2 substituents independently selected from halogen, -NO₂, -CH₃, -CF₃, -OCH₃, and -OCF₃.

9. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein A is CH- or -N-; and

B is selected from -O- and -S-.

10. The compound of Claim 1, or a pharmaceutically acceptable salt thereof,
wherein W is selected from the group consisting of -CH2-, -CF2-, -O-, -C(=O)-, -NR6-, -S-, -S(O)-, and -S(0)2S and

Z is selected from the group consisting of -CH2- and -CH2CH2-.

11. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein W is selected from the group consisting of -CH2-, -O-, and -S; and

Z is selected from the group consisting of -CH2- and -CH2CH2-.

12. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R1, R2, R3, and R4 are independently selected from (1) H; (2) halogen; (3) -NO2; (4) -CN; (5) -Ci-C4alkyl, which is optionally substituted with 1-5 halogens and optionally with 1-2 substituents independently selected from -OH, -C(=O)Ci-C3alkyl, and -OCiX^alkyl, where the Q-C3alkyl groups are optionally substituted with 1-3 halogens; (6) -OCi-C4alkyl, which is optionally substituted with 1-5 halogens and optionally with one -C(=O)Ci-C3alkyl group; (7) -C(=O)Ci-C3alkyl, which is optionally substituted with 1-5 halogens; (8) -C(=O)H; (9) -C(=O)N(R6)(R6); (10) -S(O)2N(R6)(R6); (11) -S(O)2Ci-C3alkyl, (12) -N(R6)(R6); (13) C3.C7Cycloalkyl; (14) Phenyl; and (15) Heterocycle, wherein C3.C7Cycloalkyl, Phenyl, and Heterocycle are each optionally substituted with 1-3 substituents independently selected from halogen, -OH, -OCi-C3alkyl, CF3, and -C(=O)Ci-C3alkyl;

wherein the pair of substituents R1 and R2 may together represent a bridging divalent 4-carbon chain -CH=CH-CH=CH- or a bridging divalent 3-atom chain selected from -CH=CHO-, -OCH=CH-, -CH=CH-S-, and -SCH=CH-, forming a fused phenyl, furan or thiophene ring at the R1 and R2 positions, wherein said fused phenyl, furan or thiophene ring is optionally substituted with 1-3 substituents independently selected from halogen, -OH, -CN, -NO2, -Ci-C3alkyl, -0Ci-C3alkyl, -SCi-C3alkyl, -S(O)2Ci-C3alkyl, -CF3, and -OCF3;

Each R6 is independently selected from H and CH3;

W is selected from the group consisting of -CH2-, -O-, and -S-;

Z is selected from the group consisting of -CH2- and -CH2CH2-;

A is -CH- or N; and

B is selected from -S- and -O-.

13. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein R1, R2, R3, and R4 are each independently selected from H, F, Br, Cl, Ci-C3alkyl, CF3, -C(=O)NH2, -S(O)2NH2, -C(=O)CH3, -CN, -OCH3, -CN, -OCF3, and -NO2.
14. The compound of Claim 13, or a pharmaceutically acceptable salt thereof, wherein

R₁ is selected from the group consisting of H, CH₃, and halogen;

R₂ is selected from the group consisting of H, CH₃, and halogen;

or alternatively R₁ and R₂ together represent a bridging group selected from

-CH-CH-CH=CH-, -CH=CHS-, -SCH=CH-, and -OCH=CH-, forming a fused phenyl, thiophene, or furan ring at the R₁ and R₂ positions, wherein said fused ring is optionally substituted with 1-2 substituents independently selected from halogen, CF₃, -OCF₃, -OCH₃, -CN, -NO₂, and Ci-3alkyl;

R³ is selected from the group consisting of H, halogen, Ci₃alkyl, -OCH₃, -OCF₃, CF₃, -C(=O)NH₂, -CN, and-NO₂;

R⁴ is selected from the group consisting of H, halogen, CH₃, CF₃, and -S(O)₂NH₂;

W is selected from the group consisting of -CH₂-, -O-, and -S-;

Z is selected from the group consisting of -CH₂- and -CH₂CH₂-;

A is -CH- or N; and

B is selected from -S- and -O-.

The compound of Claim 14, which is selected from the group consisting of the compounds below, or a pharmaceutically acceptable salt thereof:

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</table>
16. A pharmaceutical composition comprising the compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. The use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Type 2 diabetes mellitus.
18. A method of treating type 2 diabetes mellitus in a patient in need of treatment comprising the administration to the patient of a therapeutically effective amount of the compound of formula I, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising

(1) the compound of Claim 1 or a pharmaceutically acceptable salt thereof;
(2) one or more compounds selected from the group consisting of:
   (a) PPAR gamma agonists and partial agonists;
   (b) biguanides;
   (c) protein tyrosine phosphatase-IB (PTP-IB) inhibitors;
   (d) dipeptidyl peptidase IV (DP-IV) inhibitors;
   (e) insulin or an insulin mimetic;
   (f) sulfonylureas;
   (g) alpha-glucosidase inhibitors;
   (h) agents which improve a patient's lipid profile, said agents being selected from the group consisting of:
      (i) HMG-CoA reductase inhibitors, (n) bile acid sequestrants, (in) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPARα agonists, (v) cholesterol absorption inhibitors, (vi) acyl CoA:cholesterol acyltransferase (ACAT) inhibitors, (vii) CETP inhibitors, and (via) phenolic anti-oxidants;
      (i) PPARα/γ dual agonists,
      (j) PPARδ agonists,
      (k) antiobesity compounds,
      (l) ileal bile acid transporter inhibitors;
      (m) anti-inflammatory agents;
      (n) glucagon receptor antagonists;
   (o) GLP-I,
   (p) GIP-I;
   (q) GLP-I analogs; and
   (r) HSD-I inhibitors; and
(3) a pharmaceutically acceptable carrier.