Title: THIAZOLE AND OXAZOLE DERIVATIVES WHICH MODULATE PPAR ACTIVITY

Abstract: This invention discloses compounds that alter PPAR activity. The invention also discloses pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable compositions comprising the compounds or their salts, and methods of using them as therapeutic agents for treating or preventing hyperlipidemia and hypercholesterolemia in a mammal. The present invention also discloses methods for making the disclosed compounds.
THIAZOLE AND OXAZOLE DERIVATIVES WHICH MODULATE PPAR ACTIVITY

FIELD OF THE INVENTION

The present invention relates to compounds and pharmaceutical formulations that can be used to treat conditions mediated by nuclear hormone receptors, more specifically, to compounds and pharmaceutical formulations that modulate PPAR activity.

BACKGROUND OF THE INVENTION

Hypercholesterolemia, hyperlipidemia, and diabetes are well recognized risk factors in the onset of atherosclerosis and coronary heart disease.

Hypercholesterolemia and hyperlipidemia are characterized by excessively high levels of blood cholesterol and lipids. The blood cholesterol pool is generally dependent on dietary uptake of cholesterol from the intestine and biosynthesis of cholesterol throughout the body, especially the liver. The majority of cholesterol in plasma is carried on apolipoprotein B-containing lipoproteins, such as low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL). The risk of coronary artery disease in man increases when LDL and VLDL levels increase. Conversely, high levels of cholesterol carried in high-density lipoproteins (HDL) is protective against coronary artery disease (Am. J. Med., 1977;62:707-714).

The statins represent perhaps the most important class of lipid-lowering drugs. These compounds inhibit HMG-CoA reductase which is implicated in the rate-limiting step in cellular cholesterol biosynthesis. Representative statins include atorvastatin, lovastatin, pravastatin, and simvastatin. The effectiveness of these compounds depends on LDL receptor regulation. Other important antilipidemia drugs
include fibrates such as gemfibril and clofibrate, bile acid sequestrants such as cholestyramine and colestipol, probucol, and nicotinic acid analogs.

To date, a number of oral antidiabetic agents have been developed. The most commonly used hypoglycemic drugs are the sulfonylureas. Sulfonylureas are generally used to stimulate insulin. The biguanide metformin is generally used to improve insulin sensitivity and to decrease hepatic glucose output. Acarbose is used to limit postprandial hyperglycemia. Thiazolidine 2,4 diones are used to enhance insulin action without increasing insulin secretion.

Peroxisome Proliferator Activation Receptors (PPAR) are implicated in a number of biological processes and disease states including hypercholesterolemia, hyperlipidemia, and diabetes. PPARs are members of the nuclear receptor superfamily of transcription factors that includes steroid, thyroid, and vitamin D receptors. They play a role in controlling expression of proteins that regulate lipid metabolism. Furthermore, the PPARs are activated by fatty acids and fatty acid metabolites. There are three PPAR subtypes PPAR α, PPAR β (also referred to as PPAR δ), and PPAR γ. Each receptor shows a different pattern of tissue expression, and differences in activation by structurally diverse compounds. PPAR γ, for instance, is expressed most abundantly in adipose tissue and at lower levels in skeletal muscle, heart, liver, intestine, kidney, vascular endothelial and smooth muscle cells as well as macrophages. PPAR receptors are associated with regulation of insulin sensitivity and blood glucose levels, macrophage differentiation, inflammatory response, and cell differentiation. Accordingly, PPARs have been associated with obesity, diabetes, carcinogenesis, hyperplasia, atherosclerosis, hyperlipidemia, and hypercholesterolemia.

In addition, PPARα agonists lower plasma triglycerides and LDL cholesterol and are therefore useful in treating hypertriglyceridemia, hyperlipidemia and obesity.
PPAR γ is associated with the development of non-insulin-dependent diabetes mellitus (NIDDM), hypertension, coronary artery disease, hyperlipidemia and certain malignancies. Finally, activation of PPAR β has been demonstrated to increase HDL levels. (Leibowitz, WO97/28149, Aug. 1997.) More recently, a PPAR β selective agonist was reported to have shown a dose-related increase in serum HDL-C and decrease in LDL-C and VLDL-TG in insulin-resistant middle aged rhesus monkeys. (W. R. Oliver et al., PNAS, v. 98, pp. 5306-5311, 2001)

Antiligemide and antidiabetic agents are still considered to have non-uniform effectiveness. The effectivness of antidiabetic and antiligemide therapies is limited, in part because of poor patient compliance due to unacceptable side effects. These side effects include diarrhea and gastrointestinal discomfort, and in the case of antidiabetics, edema, hypoglycemia and hepatotoxicity. Furthermore, each type of drug does not work equally well in all patients.

For the reasons set forth above, there is a need for novel antiligemide and antidiabetic agents that can be used alone or in combination. Furthermore, activation of PPARβ alone or in combination with the simultaneous activation of PPAR α and/or PPAR γ may be desirable in formulating a treatment for hyperlipidemia in which HDL is increased and LDL lowered.

SUMMARY OF THE INVENTION

The present invention provides compounds capable of modulating PPAR activity. Compounds of the present invention are described by Formula I:
or a pharmaceutically acceptable salt thereof,

where:

W is O, S, CR₄R₆, -(CH₂)ₜ-cycloalkylene, or -(CH₂)ₜ-heterocycloalkylene;
X⁰ and X¹ are independently O or S;
Ar¹ is a unsubstituted or substituted aryl or heteroaryl;
R¹, R², R³, and R⁴ are hydrogen, lower alkyl, lower alkoxy, haloalkyl,-O-
(CH₂)ₜCF₃, halogen, nitro, cyano, -OH, -SH, -CF₃, -S(O)ₜalkyl, S(O)ₜaryl, -
(CH₂)ₜOR₇, -(CH₂)ₜNR₈R₉, -COR₇, -CO₂H, -CO₂R₇, or -NR₈R₉;
R⁵ and R⁶ are independently hydrogen, alkyl, alkenyl, alkynyl, or aryl, or
joined together to form a 3 to 7 member cycloalkyl or cycloalkenyl;
R⁷ is independently hydrogen, alkyl, alkenyl, alkynyl, or aryl;
R⁸ and R⁹ are each independently hydrogen, alkyl, alkenyl, alkynyl, -COalkyl,
-COaryl, cycloalkyl, -CO₂alkyl, -CO₂aryl, -SO₂alkyl, -SO₂aryl, or joined together to
form a 4 to 7 member ring having 1 to 3 heteroatoms;
R¹⁰ and R¹¹ are independently hydrogen, halo, aryl, or hereroaryl;
m is 0 to 5;
n is 0 to 5; and
p is 0 to 2;
with the following provisos:
that when W is O, n = 1, and R¹ is hydrogen, \( R² \) and \( R⁴ \) are not hydrogen or
\[ R² \] and \[ R³ \] are not hydrogen;
that when W is O, n = 1, and R² is hydrogen, \( R¹ \) and \( R³ \) are not hydrogen or
\[ R¹ \] and \( R⁴ \) are not hydrogen;
that when W is O, n = 1, and R³ is hydrogen, \( R¹ \) and \( R⁴ \) are not hydrogen or
\[ R² \] and \( R⁴ \) are not hydrogen; and
that when W is O, n = 1, and R⁴ is hydrogen, \( R¹ \) and \( R³ \) are not hydrogen or
\[ R² \] and \( R³ \) are not hydrogen.

In one embodiment of the present invention a pharmaceutical composition
comprising a compound of Formula I and one or more pharmaceutically acceptable
carriers, diluents, or excipients is provided.

In one embodiment of the present invention a method of treating, preventing
or controlling hypercholesterolemia and hyperlipidemia in a mammal is provided. The
method comprises administering to the mammal in need thereof a therapeutically
effective amount of the compounds of the present invention.

In another embodiment of the present invention a method for treating,
preventing, or controlling obesity is provided.

In another embodiment of the present invention a method for treating,
preventing, or controlling hyperglycemia is provided.

In another embodiment of the present invention a method for treating,
preventing, or controlling atherosclerosis is provided.

In another embodiment of the present invention a method for treating,
preventing, or controlling hypertriglyceridemia is provided.

In another embodiment of the present invention a method for treating,
preventing, or controlling hyperinsulinemia is provided.
In another embodiment of the present invention a method for treating, preventing, or controlling diabetes is provided.

For each disease state treatable, preventable, or controllable by the method of the present invention, a therapeutically effective amount of the compounds of the present invention are administered to the mammal in need thereof.

In yet another embodiment of the present invention, a method for preparing compounds of Formula I is provided.

**DETAILED DESCRIPTION OF THE INVENTION**

The following definitions are used, unless otherwise described: alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to.

The term "alkyl" as used herein refers to a straight or branched hydrocarbon of from 1 to 11 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like. The alkyl group can also be substituted with one or more of the substituents selected from lower alkoxy, lower thioalkoxy, -O(CH₂)ₙCF₃, halogen, nitro, cyano, =O, =S, -OH, -SH, -CF₃, -OCF₃, -CO₂H, -CO₂C₁-C₆ alkyl, -NH₂, -NH-C₁-C₆ alkyl, -CONR'R", or -N(C₁-C₆alkyl)₂ where R’ and R” are independently alkyl, alkenyl, alkynyl, aryl, or joined together to form a 4 to 7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C₁-C₆ alkyl).

The term "lower alkyl" as used herein refers to a subset of alkyl which means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl,
**- 7 -**

**tert-butyl, n-pentyl, n-hexyl, and the like. Optionally, herein lower alkyl is referred to as “C₁-C₆ alkyl.”**

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl, trifluoromethyl, or 1,1,1-trifluoroethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorine atoms.

The term “alkenyl” means a straight or branched unsaturated hydrocarbon radical having from 2 to 12 carbon atoms and includes, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butynyl, 2-butynyl, 1-pentenyl, 2-pentenyl, 3-methyl-3-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 3-heptenyl, 1-octenyl, 1-nonenyl, 1-decenyl, 1-undecenyl, 1-dodecenyl, and the like.

The term “alkynyl” means a straight or branched hydrocarbon radical having from 2 to 12 carbon atoms having at least one triple bond and includes, for example, 1-propynyl, 1-butynyl, 3-butynyl, 1-pentynyl, 3-pentynyl, 3-methyl-3-butynyl, 1-hexynyl, 3-hexynyl, 3-heptynyll, 1-octynyl, 1-nonynyll, 1-decynyl, 1-undecynyl, 1-dodecynyl, and the like.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2- dimethylpropylene, and the like. The alkyne groups of this invention can be optionally substituted. The alkyne group can also be substituted with one or more of the substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, -O(CH₂)ₐ CF₃, halogen, nitro, cyano, =O, =S, -OH, -SH, -CF₃, -CO₂H, -CO₂C₁-C₆ alkyl, -NH₂, -NHC₁-C₆ alkyl, -CONR’R”, or
-N(C₁-C₆alkyl)₂ where R' and R" are independently alkyl, akenyl, alkynyl, aryl, or joined together to form a 4 to 7 member ring. Useful alkylene groups have from 1 to 6 carbon atoms (C₁-C₆ alkylene).

The term "cycloalkylene" as used herein refers to a divalent group derived from a cyclic saturated hydrocarbon having from 3 to 8 carbon atoms by the removal of two hydrogen atoms. The cycloalkylene groups of this invention can be optionally substituted. The cycloalkylene group can also be substituted with one or more of the substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, -O(CH₂)ₙCF₃, halogen, nitro, cyano, =O, =S, -OH, -SH, -OCF₃, -CO₂H, -CO₂C₁-C₆ alkyl, -NH₂, -NHC₁-C₆ alkyl, -CONR’R”, or -N(C₁-C₆alkyl)₂ where R’ and R” are independently alkyl, akenyl, alkynyl, aryl, or joined together to form a 4 to 7 member ring. Useful cycloalkylene groups have from 3 to 6 carbon atoms (C₃-C₆ alkyl).

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

The term “heteroatom” as used herein represents oxygen, nitrogen, or sulfur (O, N, or S) as well as sulfoxyl or sulfonyl (SO or SO₂) unless otherwise indicated.

The term “heterocycloalkylene” as used herein, refers to a cycloalkylene group that includes one or more heteroatoms such as oxygen, sulfur, or nitrogen.

The term “hydrocarbon chain” as used herein refers to a straight hydrocarbon of from 2 to 6 carbon atoms. The hydrocarbon chain is optionally substituted with one or more substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, -O(CH₂)ₙCF₃, halogen, nitro, cyano, =O, =S, -OH, -SH, -CF₃, -CO₂H, -CO₂(C₁-C₆ alkyl), -NH₂, -NHC₁-C₆ alkyl, -CONR’R”, or -N(C₁-C₆alkyl)₂ where R’ and R” are independently alkyl, akenyl, alkynyl, aryl, or joined together to form a 4 to 7 member ring.
The term “heterocycle” means a saturated or unsaturated mono- or polycyclic (i.e. bicyclic) ring incorporating one or more (i.e. 1-4) heteroatoms selected from N, O, and S. It is understood that a heterocycle is optionally substituted with -OH, -O(alkyl), SH, S(alkyl), amine, halogen, acid, ester, amide, amidine, alkyl ketone, aldehyde, nitrile, fluoroalkyl, nitro, sulphone, sulfoxide or C4-6 alkyl. Examples of suitable monocyclic heterocycles include, but are not limited to substituted or unsubstituted thiienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazoil, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, piperidinyl, pyrrolidinyl, piperazinyl, azetidinyl, aziridinyl, morpholinyl, thietanyl, oxetanyl. Examples of monocyclic diheterocycles include, but are not limited to, 1-2, 3-4, or 5-imidazolyl, 1-, 3-, 4-, or 5-pyrazolyl, 2-, 3-, 4-, or 5-thiazolyl, 1-, 3-, 4-, or 5-isothiazolyl, 1-, 3-, or 5-oxazolyl, 2-, 4-, or 5-oxazolyl, 1-, 3-, or 5-isoxazolyl, 2-, 3-, 4-, or 5-triazolyl, 1-, 2-, or 3-tetrazolyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 1- or 2-piperazinyl, 2-, 3-, or 4-morpholinyl. Examples of suitable bicyclic heterocycles include, but are not limited to indolizyl, isoindolyl, benzfuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-indolizinyl, 1-, 2-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzothienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 1-, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, and 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl.

The term “hydrocarbon-heteroatom chain” as used herein refers to a hydrocarbon chain wherein one or more carbon atoms are replaced with a heteroatom. The hydrocarbon-heteroatom chain is optionally substituted with one or more substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, -OH, -O(CH₂)₂CF₃, halogen, nitro, cyano, =O, =S, -NH₂, -NHC₆H₅ alkyl, -CONR'R", or -N(C₆H₅alkyl)₂ where R' and R" are independently alkyl, akenyl, alkynyl, aryl, or joined together to form a 4 to 7 member ring.
The term "heteroalkylene" as used herein, refers to an alkylene radical as defined above that includes one or more heteroatoms such as oxygen, sulfur, or nitrogen (with valence completed by hydrogen or oxygen) in the carbon chain or terminating the carbon chain.

The terms “lower alkoxy” and “lower thioalkoxy” as used herein refers to O-alkyl or S-alkyl of from 1 to 6 carbon atoms as defined above for “lower alkyl.”

The term “aryl” as used herein refers to an aromatic ring which is unsubstituted or optionally substituted by 1 to 4 substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, halogen, nitro, cyano -OH, -SH, -CF₃, -CO₂H, -CO₂C₁-C₆ alkyl, -(CH₂)₀₂CF₃, -NH₂, -NHC₁-C₆ alkyl, -SO₂alkyl, -SO₂NH₂, – CONR’R”, or -N(C₁-C₆alkyl)₂ where R’ and R” are independently alkyl, akenyl, alkynyl, aryl, or joined together to form a 4 to 7 member ring. Examples include, but are not limited to, phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-chloro-3-methylphenyl, 2-chloro-4-methylphenyl, 2-chloro-5-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-2-methylphenyl, 4-chloro-3-methylphenyl, 5-chloro-2-methylphenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethylphenyl, 3,4-dimethylphenyl, and the like.

The term “heteroaryl” means an aromatic ring containing one or more heteroatoms. The heteroaryl is optionally substituted with one or more groups enumerated for aryl. Examples of heteroaryl include, but are not limited to, thienny, furanyl, pyrrolyl, pyridyl, pyrimidyl, imidazoyl, pyrazinyl, oxazolyl, thiazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, isoquinolinyl, and quinazolinyl, and the like.
The term "cycloalkenyl" means a cycloalkyl group having one or more carbon-carbon double. Example includes cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclobutadiene, cyclopentadiene, and the like.

The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits.

A "therapeutically effective amount" is an amount of a compound of the present invention that when administered to a patient ameliorates a symptom of dyslipidemia, non-insulin dependent diabetes mellitus, obesity, hyperglycemia, hypercholesteremia, hyperlipidemia, atherosclerosis, hypertriglyceridemia, or hyperinsulinemia.

The term "a pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic base or acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free form with a suitable organic or inorganic base or acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmiate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. These also include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S.M., et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19, which is incorporated herein by reference.) The free base form may be regenerated
by contacting the salt form with a base. While the free base may differ from the salt form in terms of physical properties, such as solubility, the salts are equivalent to their respective free bases for the purposes of the present invention.

The symbol "\( \equiv \equiv \equiv \)" indicates a point of attachment.

The present invention provides compounds capable of modulating PPAR activity. Compounds of the present invention are described by Formula I:

\[
\begin{align*}
\text{CO}_2\text{H} \\
\text{W} \left( \text{CR}^{10R^{11}} \right)_n \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^1 \\
\text{R}^2 \\
\text{X}^0 \\
\text{X}^1 \\
\text{Ar}^1
\end{align*}
\]

or a pharmaceutically acceptable salt thereof,

where:

W is O, S, CR\(^5\)R\(^6\), -(CH\(_2\))\(_p\)cycloalkylene, or -(CH\(_2\))\(_p\)heterocycloalkylene;

X\(^0\) and X\(^1\) are independently O or S;

Ar\(^1\) is a unsubstituted or substituted aryl or heteroaryl;

R\(^1\), R\(^2\), R\(^3\), and R\(^4\) are independently hydrogen, lower alkyl, lower alkoxy, haloalkyl, -O-(CH\(_2\))\(_p\)CF\(_3\), halogen, nitro, cyano, -OH, -SH, -CF\(_3\), -S(O)\(_p\)alkyl, S(O)\(_p\)aryl, -(CH\(_2\))\(_m\)OR\(^2\), -(CH\(_2\))\(_m\)NR\(^8\)R\(^9\), -COR\(^2\), -CO\(_2\)H, -CO\(_2\)R\(^7\), or -NR\(^8\)R\(^9\);
R⁵ and R⁶ are independently hydrogen, alkyl, alkenyl, alkynyl, or aryl, or joined together to form a 3 to 7 member cycloalkyl or cycloalkenyl;

R⁷ is independently hydrogen, alkyl, alkenyl, alkynyl, or aryl;

R⁸ and R⁹ are independently hydrogen, alkyl, alkenyl, alkynyl, -COalkyl, -COaryl, cycloalkyl, -CO₂alkyl, -CO₂aryl, -SO₂alkyl, -SO₂aryl, or joined together to form a 4 to 7 member ring having 1 to 3 heteroatoms;

R¹⁰ and R¹¹ are independently hydrogen, halo, aryl, or hereroaryl;

m is 0 to 5;

n is 0 to 5; and

p is 0 to 2;

with the following provisos:

that when W is O, n = 1, and R¹ is hydrogen, R² and R⁴ are not hydrogen or R² and R³ are not hydrogen;

that when W is O, n = 1, and R² is hydrogen, R¹ and R³ are not hydrogen or R¹ and R⁴ are not hydrogen;

that when W is O, n = 1, and R³ is hydrogen, R¹ and R⁴ are not hydrogen or R² and R⁴ are not hydrogen; and

that when W is O, n = 1, and R⁴ is hydrogen, R¹ and R³ are not hydrogen or R² and R³ are not hydrogen.

Examples of compounds of Formula I include those where W is O, Ar¹ is substituted aryl, and n is 1. For example compounds of Formula I where W is O, Ar¹ is substituted aryl, and n is 1 include those where Ar¹ is 4-trifluoromethylphenyl.
Other examples of compounds of Formula I include those where $R^1$, $R^2$, $R^3$, and $R^4$ are independently hydrogen, lower alkyl, lower alkoxy, -(CH$_2$)$_n$NR$^8$R$^9$, or -(CH$_2$)$_n$OR$^7$ ; where $R^7$ is alkyl, $R^8$ and $R^9$ are independently hydrogen, alkyl, or COalkyl. For example such compounds include those compounds where $R^1$, $R^2$, $R^3$, and $R^4$ are the following combinations shown in Table 1 below, provided that $R^1$, $R^2$, $R^3$, and $R^4$ are not each hydrogen when W is O.

Table 1

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$R^4$</th>
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<tbody>
<tr>
<td>methyl</td>
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<td>hydrogen</td>
<td>chloro</td>
</tr>
<tr>
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<td>hydrogen</td>
<td>-CH$_2$-O-CH$_3$</td>
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</table>
Other examples of compounds of Formula I also include those where \( R^2 \) is hydrogen; \( R^1 \), \( R^3 \), and \( R^4 \) are independently lower alkyl, lower alkoxy, haloalkyl, -O-(CH\(_2\))\(_p\)CF\(_3\), halogen, nitro, cyano, -OH, -SH, -CF\(_3\), -S(O)\(_p\)alkyl, S(O)\(_p\)aryl, -(CH\(_2\))\(_m\)OR\(_7\), -(CH\(_2\))\(_m\)NR\(_p\)R\(_9\), -COR\(_7\), -CO\(_2\)H, -CO\(_2\)R\(_7\), or -NR\(_p\)R\(_9\); \( R^7 \) is hydrogen, alkyl, alkenyl, alkynyl, or aryl; and \( R^8 \) and \( R^9 \) are independently hydrogen, alkyl, alkenyl, alkynyl, -COalkyl, -Oaryl, cycloalkyl, -CO\(_2\)alkyl, -CO\(_2\)aryl, -SO\(_2\)alkyl, -SO\(_2\)aryl, or joined together to form a 4 to 7 member ring having 1 to 3 heteroatoms.

Additional examples of compounds of Formula I also include those where \( R^2 \) and \( R^3 \) are both hydrogen. For example compounds of Formula I where \( R^2 \) and \( R^3 \) are hydrogen include those where \( R^2 \) and \( R^3 \) are hydrogen, and \( R^1 \) and \( R^4 \) are lower alkyl, such as methyl, ethyl, isopropyl, n-propyl, t-butyl, n-butyl, and isobutyl, or lower alkoxy, such as methoxy, ethoxy, isopropyloxy, n-propyloxy, t-butoxy, n-butoxy, and isobutoxy. More specific examples of compounds of Formula I where \( R^2 \) and \( R^3 \) are hydrogen include those where \( R^2 \) and \( R^3 \) are hydrogen, \( R^1 \) is lower alkyl, and \( R^4 \) is lower alkoxy.

Other examples of compounds of Formula I include those where \( R^{10} \) and \( R^{11} \) are independently fluorine, phenyl or pyrrolyl;

Additional examples of compounds of Formula I include those where \( W \) is CR\(_5\)R\(_6\), -(CH\(_2\))\(_p\)-cycloalkylene, or -(CH\(_2\))\(_p\)-heterocycloalkylene, \( R^3 \) and \( R^5 \) are joined together to form a 3 to 7 member cycloalkyl or cycloalkenyl ring, and \( p \) is 0 to 2. For example, compounds of Formula I where \( W \) is CR\(_5\)R\(_6\), -(CH\(_2\))\(_p\)-cycloalkylene, or -(CH\(_2\))\(_p\)-heterocycloalkylene include those where \( W \) is
Other examples, compounds of Formula I where \( W \) is \( CR^5R^6, -(CH_2)_p- \)-cycloalkylene, or \(-(CH_2)_p-\)-heterocycloalkylene include those where \( X^0 \) and \( X^1 \) are S.

Additional examples, compounds of Formula I where \( W \) is \( CR^5R^6, -(CH_2)_p- \) cycloalkylene, or \(-(CH_2)_p-\)-heterocycloalkylene include those where \( Ar^1 \) is 4-trifluoromethylphenyl.

Further examples, compounds of Formula I where \( W \) is \( CR^5R^6, -(CH_2)_p- \)-cycloalkylene, or \(-(CH_2)_p-\)-heterocycloalkylene include those where \( R^1, R^2, R^3, \) and \( R^4 \) are independently hydrogen, lower alkyl, lower alkoxy, halogen, -CF3, \(-(CH_2)_m OR^7, \) or \(-(CH_2)_m NR^8 R^9, R^7 \) is hydrogen, or alkyl; and \( R^8 \) and \( R^9 \) are independently hydrogen, alkyl, or \( -COalkyl \). Such compounds include those where \( R^1, R^2, R^3, \) and \( R^4 \) are independently hydrogen, methyl, ethyl, isopropyl, n-propyl, t-butyl, n-butyl, or isobutyl, methoxy, ethoxy, isopropoxy, n-propoxy, t-butoxy, n-butoxy, isobutoxy, \( (CH_2)_2 OC\mathcal{H}_3, \) or \(-NH-CO\mathcal{H}_3, \).

Examples of compounds of Formula I include

\{2,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid;\}

\{5-Ethyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid;\}

\{5-Isopropyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid;\}

\{2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid;\}

\{5-Methoxy-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid;\}

\{2-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid;\}
{3,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-
yl methylsulfanyl]-phenoxy}-acetic acid;
{3-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-
yl methylsulfanyl]-phenoxy}-acetic acid;
{2-Isopropyl-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-
yl methylsulfanyl]-phenoxy}-acetic acid
{2,6-Diisopropyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-
yl methylsulfanyl]-phenoxy}-acetic acid;
2-Methyl-2-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-
yl methylsulfanyl]-phenyl]-propionic acid;
2-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-cyclopropanecarboxylic acid;
1-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-cyclopropanecarboxylic acid;
1-[4-[4-Methyl-2-(4-trifluoromethyl -phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-cyclopentane carboxylic acid;
4-Methyl-4-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-pentanoic acid;
3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenoxy]-propionic acid;
2-[3-Methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-2-methyl-propionic acid;
3-Methyl-3-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-butyric acid;
3-[2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-propionic acid;
3-[2,5-Dimethoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl methylsulfanyl]-phenyl]-propionic acid;
{2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]}-acetic acid;
3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y1methoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y1methoxy]-phenyl}-2-phenyl-propionic acid;
3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y1methylsulfanyl]-phenyl}-2-pyrrol-1-yl-propionic acid;
2-[5-(acetylamino)-2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)])methylthio)phenoxy]acetic acid;
2-[5-fluoro-2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)])methylthio)phenoxy]acetic acid;
2-[5-methoxy-2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)])methoxy)phenylthio]acetic acid;
2,2-difluoro-2-[5-methoxy-2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)])methoxy)phenylthio]acetic acid;
1-[(3-Methoxy-4-[4-methyl-2(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]benzyl)pyrrolidine-2-carboxylic acid;
{(2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy)-phenyl-acetic acid;
{5-Chloro-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid;
2-[5-(methoxymethyl)-2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)])methylthio)phenoxy]acetic acid;
(4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y1methylsulfanyl]-phenyl)cyclohexyl)-acetic acid; and
pharmaceutically acceptable salts thereof.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention
includes all diastereomeric, enantiomeric, and epimeric forms as well as the
appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods
known in the art as, for example, the separation of stereoisomers by chiral
chromatographic columns. Additionally, the compounds of the present invention may
exist as geometric isomers. The present invention includes all cis, trans, syn, anti,
entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

In some situations, compounds may exist as tautomers. All tautomers are
included within Formula I and are provided by this invention.

In addition, the compounds of the present invention can exist in unsolvated as
well as solvated forms with pharmaceutically acceptable solvents such as water,
ethanol, and the like. In general, the solvated forms are considered equivalent to the
unsolvated forms for the purposes of the present invention.

The present invention includes all pharmaceutically acceptable, non-toxic
esters of the compounds of Formula I. Such esters include C_1-C_6 alkyl esters wherein
the alkyl group is a straight or branched chain. Acceptable esters also include
C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl.
C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention
may be prepared according to conventional methods.

The compounds of the present invention are suitable to be administered to a
patient for the treatment, control, or prevention of non-insulin dependent diabetes
mellitus, hypercholesteremia, hyperlipidemia, obesity, hyperglycemia,
hyperlipidemia, atherosclerosis, hypertriglyceridemia, and hyperinsulinemia.
Accordingly, the compounds may be administered to a patient alone or as part of a
composition that contains other components such as excipients, diluents, and carriers,
all of which are well-known in the art. The compositions can be administered to
humans and/or animals either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example,
agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and
sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metaphosphate, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 2,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of
about 0.01 to about 10 mg per kilogram of body weight per day is preferable. However, the specific dosage used can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

PREPARATION OF COMPOUNDS OF THE INVENTION

The present invention contains compounds that can be synthesized in a number of ways familiar to one skilled in organic synthesis. The compounds disclosed herein can be synthesized according to the methods described below and in the examples, along with methods typically utilized by a synthetic chemist, and combinations or variations of those methods, which are generally known to one skilled in the art of synthetic chemistry. The synthetic route of compounds in the present invention is not limited to the methods outlined below. It is assumed one skilled in the art will be able to use the schemes outlined below to synthesize compounds claimed in this invention. Individual compounds may require manipulation of the conditions in order to accommodate various functional groups. A variety of protecting groups generally known to one skilled in the art may be required. Purification, if necessary, can be accomplished on a silica gel column eluted with the appropriate organic solvent system. Also, reverse phase HPLC or recrystallization may be employed.
The compounds or Formula I can be prepared by reacting:

![Chemical structure](attachment://structure.png)

in a solvent in the presence of a base such as cesium carbonate, with the aryl halide:

![Chemical structure](attachment://halide.png)

wherein:

- $W$, $Y$, $n$, $R^1$, $R^2$, $R^3$, $R^4$, $X^0$, $X^1$ and $Ar^1$ are the same as defined above for Formula I;
- $R^{12}$ is a lower alkyl; and
- $X$ is a halogen.

The resulting ester is then converted to the compounds of Formula I by various methods known in the art for the conversion of esters to acids, such as via hydrolysis for example. Useful aryl halides include, for example, 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole.

The compounds of Formula I can be prepared using the synthetic route outlined in Scheme 1 when $W$ is O or S and $X^0$ is S. With reference to Scheme 1, compounds of the general formula A are thiocyanated with a mixture of bromine and sodium thiocyanate to give compounds of the general formula B. Compounds of the
general formula B are then alkylated with the haloester C to give compounds of the general formula D. A useful haloester C is the corresponding bromoester. Compounds of the general formula E are then prepared by reduction of D with dithiothreitol in methanol. Compounds of the general formula E are then alkylated with the halide compound IB to form compound F. Suitable halide compounds IB include, for example, 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole. Compounds of the general formula F are then saponified with LiOH in THF to give the final compound G. W, Y, R^1, R^2, R^3, and R^4 are the same as defined above for Formula I above; X is a halogen. Compound G corresponds to compounds described by Formula I above when X^0 is S.
Alternatively, compounds of Formula I can be prepared using the synthetic route outlined in Scheme 2 when $X^0$ is S. With reference to Scheme 2, compounds of the general formula H are debenzylated and then reacted with 2-chloro-$N,N$-dimethyl-thioacetamide to form compound J. A useful method for step 1 is reaction with hydrogen gas in the presence of carbon activated palladium. Compound J is
then heated followed by saponification to form compound E. Compounds of the
general formula E are then alkylated with the halide compound 1B to form compound
F. Suitable halide compounds 1B include, for example, 5-chloromethyl-4-methyl-2-
(4-trifluoromethyl-phenyl)-thiazole. Compounds of the general formula F are then
saponified with LiOH in the THF to give the final compound G. W, Y, R₁, R², R³,
and R⁴ are the same as defined above for Formula I above; X is a halogen.
Compound G corresponds to compounds described by Formula I above when X⁰ is S.

Scheme 2

![Chemical structure diagram]

1. H₂, 20% Pd/C, MeOH
2. Et₃N, dioxane, DMAP

1. Tetradecane, heat
2. NaOMe, MeOH

Finally, compounds of Formula I can be prepared using the synthetic route
outlined in Scheme 3. With reference to Scheme 3, compounds of the general formula
K are converted to the ester L. A useful method includes reacting compound K with an alcohol in the presence of an acid such as hydrochloric acid, although any compatible method for esterification may be used. Ester L is then reacted with chloirorsulfonic acid to form compound M. Compound M is then reduced to form compound E. Compounds of the general formula E are then alkylated with the halide compound 1B to form compound F. Suitable halide compounds 1B include, for example, 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole.

Compounds of the general formula F are then saponified with LiOH in the THF to give the final compound G. W, Y, R₁, R₂, R₃, and R₄ are the same as defined above for Formula I above; X is a halogen. Compound G corresponds to compounds described by Formula I above when X₀ is S.

Scheme 3
The following non-limiting descriptions also demonstrate methods for the synthesis of compounds of Formula I.

**Example 1**

**Synthesis of [2,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 1)**
Preparation of [4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (compound 1A)

![Chemical Structure 1A]

A solution of 4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester (3.0 g, 9.5 mmol) in 25 mL THF at 0 °C was treated portionwise with lithium aluminum hydride (0.4 g, 10.5 mmol). After 4 hours, the reaction mixture was carefully quenched with water, followed by the addition of 10 mL 6N NaOH. The reaction mixture was then extracted with EtOAc, dried, and concentrated in vacuo. Recrystallisation from CHCl₃/hexanes gave the title compound (2.2 g, 85%). 400 MHz ¹H NMR (DMSO-ᵈ) δ 8.03 (d, 2H, J = 8.3 Hz), 7.78 (d, 2H, J = 8.3 Hz), 5.66 (s(br), 1H), 4.62 (s, 2H), 2.31 (s, 3H).

Preparation of 5-Chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (compound 1B)

![Chemical Structure 1B]

Methanesulfonyl chloride (1.0 mL, 12.9 mmol) was added to a stirred solution of [4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (2.2 g, 8.1 mmol) and triethylamine (2.2 mL, 16.1 mmol) in 25 mL THF at 0 °C. After 3 hours, the reaction mixture was diluted with dichloromethane, washed with 1 x sat. NaHCO₃, 1 x brine, dried (Na₂SO₄) and the solvent removed in vacuo to give 2.0 g (84%) of the title
compound pure enough for subsequent use. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 8.06 (d, 2H, $J = 8.3$ Hz), 7.80 (d, 2H, $J = 8.3$ Hz), 5.08 (s, 2H), 2.40 (s, 3H).

**Preparation of 2,5-Dimethyl-4-thiocyanato-phenol (compound 1C)**

![Structure of 1C]

The title compound was prepared in a manner analogous to compound 3A. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 10.0 (s, 1H), 7.35 (s, 1H), 6.73 (s, 1H), 2.3 (s, 3H), 2.04 (s, 3H); MS m/z 180 (m+1).

**Preparation of (2,5-Dimethyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 1D)**

![Structure of 1D]

The title compound was prepared from compound 1C in a manner analogous to compound 3B. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.07 (s, 1H), 6.50 (s, 1H), 4.56 (s, 2H), 3.76 (s, 3H), (s, 1H), 2.26 (s, 3H), 2.17 (s, 3H); MS m/z 252 (m+1).

**Preparation of (4-Mercapto-2,5-dimethyl-phenoxy)-acetic acid methyl ester (compound 1E)**

![Structure of 1E]
The title compound was prepared from compound 1D in a manner analogous to compound 3C. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.07 (s, 1H), 6.50 (s, 1H), 4.56 (s, 2H), 3.76 (s, 3H), 3.07 (s, 1H), 2.26 (s, 3H), 2.17 (s, 3H); MS m/z 227 (M+1).

5 Preparation of [2,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 1F)

![Chemical Structure]

1F

Compound 1E (207 mg, 0.92 mmol) was dissolved in 5 ml anhydrous acetonitrile. Compound 1B (294 mg, 1 mmol) was added followed by cesium carbonate (600 mg, 1.84 mmol). The reaction was stirred at ambient temperature for 2 hours, filtered and concentrated. Purification by flash column chromatography afforded the title compound. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 8.00 (d, 2H, J = 8 Hz), 7.76 (d, 2H, J = 8.4 Hz), 7.15 (s, 1H), 6.72 (s, 1H), 4.76 (s, 2H), 4.22 (s, 2H), 2.17 (s, 3H), 3.63 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H). MS m/z 482 (M+1).

Preparation of [2,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 1)

Compound 1F (360 mg, 0.75 mmol), dissolved in 5 ml THF and 1 ml water, was treated with lithium hydroxide monohydrate (95 mg, 2.25 mmol); stirring at room temperature for 1 hour. The reaction mixture was then acidified to about pH 3 with 2 N HCl. The reaction was then extracted into ethyl acetate (2x20 ml). The organic extracts were washed with brine, dried over anhydrous sodium sulfate, decanted, and
concentrated. The title compound was then recrystallized from chloroform/hexanes. Mp 173-176 °C; IR (thin film) cm⁻¹: 2928, 1732, 1328, 1113; 400 MHz ¹H NMR (DMSO-\textit{d}_6) δ 12.97 (s(br), 1H), 8.00 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 8.4 Hz), 7.15 (s, 1H), 6.69 (s, 1H), 4.63 (s, 2H), 4.22 (s, 2H), 2.17 (s, 3H), 2.09 (s, 3H), 6.00 (s, 2H), 2.04 (s, 3H); MS \textit{m/z} 468 (M+1). Anal. Calc’d for C_{22}H_{20}F_{3}NO_{3}S_{2} C, 56.52; H, 4.31; N, 3.00; found: C, 56.55; H, 4.31; N, 2.94.

Example 2

**Synthesis of [5-Ethyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 2)**

![Chemical structure of Compound 2]

**Preparation of 5-Ethyl-2-methyl-phenol (compound 2A)**

![Chemical structure of Compound 2A]

A 3:1 mixture of 1-(5-ethyl-2-methyl-phenyl)-ethanone and 1-(2-ethyl-5-methyl-phenyl)-ethanone (J. Chem. Soc., 152, 1123) (3.6 g, 22 mmol), m-chloroperbenzoic acid (8.4 g, 29 mmol), and p-toluenesulfonic acid (0.5 g, 2.6 mmol) in 100 mL
dichloromethane was heated at reflux for 20 hours. The reaction was then cooled and washed with KI(aq.) (2 x 75 mL), NaHSO₃ (2 x 75mL), dried (Na₂SO₄) and concentrated in vacuo. The resulting residue was taken up in Et₂O and washed with sat. NaHCO₃(1 x 75 mL), dried (Na₂SO₄) and concentrated in vacuo to give 3.2 g of the crude product pure enough for subsequent use. 400 MHz ¹H NMR (DMSO-d₆) δ 7.11 (d, 2H, J = 7.8 Hz), 6.96 (d, 2 H, J = 7.8 Hz), 6.83 (s, 1H), 6.80 (s, 1H), 2.51 (q, 2H, J = 7.6 Hz), 2.37 (q, 2H, J = 7.6 Hz), 2.23 (s, 6H), 2.01 (s, 6H), 1.10 (t, 3H, J = 7.6 Hz), 1.08 (t, 3H, J = 7.6 Hz). The crude product was then dissolved in MeOH (75 mL) and K₂CO₃ (2.5 g, 18 mmol) was added followed by stirring for 15 minutes. The reaction mixture was then filtered, the filtrate collected and concentrated in vacuo.

The residue was taken up in Et₂O and washed with 2 M HCL (1 x 50 mL), brine (1 x 50 mL), dried (Na₂SO₄) and the solvent removed in vacuo to give the title compound and its regioisomer as a 3:1 mixture pure enough for subsequent use. 400 MHz ¹H NMR (DMSO-d₆) δ 400 MHz ¹H NMR (DMSO-d₆) δ 6.87 (d, 1H, J = 7.3 Hz (title compound)), 6.85 (d, 1H, J = 7.3 Hz), 6.54 (s, 1H(title compound)), 6.46 (d, 2H, J = 7.3 Hz), 2.44 (m, 4H), 2.37, 2.00 (s, 6H), 1.06 (m, 6H).

**Preparation of 5-Ethyl-2-methyl-4-thiocyanato-phenol (compound 2B)**

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    OH
   /   \
5-SCN
  /    \
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**2B** was prepared from 2A in a similar manner as described for compound 3A to give, after purification by flash column chromatography (gradient elution: 100% hexanes to 20% EtOAc/hexane) and then recrystalisation from CHCl₃/hexanes, 0.8 g (29%) of the title compound as a single regioisomer. 400 MHz ¹H NMR (DMSO-d₆) δ 7.36 (s,
1H), 6.77 (s, 1H), 2.67 (q, 2H, J = 7.4 Hz), 2.05 (s, 3H), 1.13 (t, 3H, J = 7.4 Hz); MS m/z 194 (M+1).

Preparation of (5-Ethyl-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 2C)

2C was prepared from 2B in a similar manner as described for compound 3B to give 1.1 g (95%) of the title compound pure enough for subsequent use. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.46 (s, 1H), 6.90 (s, 1H), 4.87 (s, 2H), 3.65 (s, 3H), 2.72 (q, 2H, J = 7.5 Hz), 2.13 (s, 3H), 1.14 (t, 3H, J = 7.5 Hz).

Preparation of (5-Ethyl-4-mercapto-2-methyl-phenoxy)-acetic acid methyl ester (compound 2D)

2D was prepared from 2C in a similar manner as described for compound 3C to give, after purification by flash column chromatography (gradient elution: 100% hexanes to 30% EtOAc/hexanes), 0.3 g (32%) of the title compound. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.09 (s, 1H), 6.72 (s, 1H), 4.81 (s, 2H), 3.64 (s, 3H), 2.55 (q, 2H, J = 7.5 Hz), 2.05 (s, 3H), 0.99 (t, 3H, J = 7.5 Hz); MS m/z 241 (M+1).
Preparation of [5-Ethyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 2E)

Compound 2D and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound 1F to provide, after purification by flash column chromatography (gradient elution: 100% hexanes to 30% EtOAc/hexanes), the title compound (0.24 g, 59%) as a yellow solid. IR (thin film) cm⁻¹: 1749, 1326; 400 MHz ¹H NMR (DMSO-δ6) δ 7.98 (d, 2H, J = 8.0 Hz), 7.76 (d, 2H, J = 8.0 Hz), 7.19 (s, 1H), 6.68 (s, 1H), 4.77 (s, 2H), 4.24 (s, 2H), 3.63 (s, 3H), 2.54 (q, 2H, J = 7.6 Hz), 2.09 (s, 3H), 2.06 (s, 3H), 0.97 (t, 3H, J = 7.6 Hz); MS m/z 496 (M+1); Anal. Calc'd for C₂₄H₂₄F₃N₁O₃S₂ C, 58.17; H, 4.88; N, 2.83; found: C, 58.19; H, 4.80; N, 2.76.

Preparation of [5-Ethyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 2)

Compound 2E was saponified in the same manner as described for compound 1 to give, after recrystallisation from CHCl₃/hexanes, the title compound (0.12 g, 96%) as a pale yellow solid. mp 169-171 °C; IR (thin film) cm⁻¹: 1736, 1325; 400 MHz ¹H NMR (DMSO-δ6) δ 7.98 (d, 2H, J = 8.0 Hz), 7.76 (d, 2H, J = 8.0 Hz), 7.17 (s, 1H), 6.66 (s, 1H), 4.65 (s, 2H), 4.23 (s, 2H), 2.54 (q, 2H, J = 7.6 Hz), 2.09 (s, 3H), 2.05 (s, 3H), 0.97 (t, 3H, J = 7.6 Hz); MS m/z 482 (M+1); Anal. Calc’d for C₂₄H₂₄F₃N₁O₃S₂ 0.5 H₂O C, 56.31; H, 4.73; N, 2.86; found: C, 56.53; H, 4.69; N, 2.68.
Example 3

**Synthesis of 5-Isopropyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl-phenoxy]-acetic acid (Compound 3)**

![Chemical Structure](image)

**Preparation of 5-Isopropyl-2-methyl-4-thiocyanato-phenol (compound 3A)**

![Chemical Structure](image)

A rapidly stirred solution of 5-isopropyl-2-methyl-phenol (10 g, 67 mmol), sodium thiocyanate (15.6 g, 214 mmol), and sodium bromide (6.8 g, 66 mmol) in 40 mL MeOH at 0 °C was treated with bromine in 40 mL MeOH by dropwise addition over 30 minutes. After completion of the bromine addition, the reaction mixture was heated at 50 °C for 45 minutes. The reaction mixture was then cooled and concentrated in vacuo to about 20 mL. The resulting residue was taken up in EtOAc and filtered. The filtrate was collected and washed with saturated Na₂CO₃ (1 x 50 mL), brine (1 x 50 mL) dried (Na₂SO₄), and the solvent removed in vacuo.

Purification by flash column chromatography (gradient elution: 5% EtOAc/hexanes to 35% EtOAc/hexanes to 55% EtOAc/hexanes) gave the title compound (7.9 g, 57%) as a yellow solid. mp 72-75 °C; 400 MHz ³¹H NMR (DMSO-d₆) δ 10.0 (s, 1H),
7.37 (s, 1H), 6.81 (s, 1H), 3.31 (m, 1H), 2.04 (s, 3H), 1.14 (d, 6H, J = 6.8 Hz); MS m/z 208 (M+1).

Preparation of (5-Isopropyl-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 3B)

A solution of 5-isopropyl-2-methyl-4-thiocyanato-phenol (3.0 g, 14 mmol), methyl bromoacetate (0.90 g, 15.4 mmol), and cesium carbonate (6.8 g, 21 mmol) in 50 mL acetonitrile was heated at 60 °C for 3 hours. PS-Trisamine scavenger resin was then added to the warmed solution followed by an additional 30 minutes heating. The reaction mixture was then cooled and filtered. The filtrate was collected, diluted with 100 mL ether, washed with brine (1 x 50 mL), dried (Na₂SO₄), and the solvent removed in vacuo to give 3.8 g (94%) of the title compound as an orange solid, pure enough for subsequent use. mp 67-69 °C; 400 MHz ¹H NMR (DMSO-d₆) δ 7.46 (s, 1H), 6.88 (s, 1H), 4.91 (s, 2H), 3.65 (s, 3H), 3.31 (m, 1H), 2.13 (s, 3H), 1.16 (d, 6H, J = 6.8 Hz); MS m/z 279 (M+).

Preparation of (5-Isopropyl-4-mercapto-2-methyl-phenoxy)-acetic acid methyl ester (compound 3C)
A solution of (5-isopropyl-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (3g, 10.7 mmol), dithiothreitol (2.1 g, 13.9 mmol), and KH₂PO₄ (5 mL of a .02M solution) in 40 mL MeOH was heated at reflux for 1 hour after which time thin-layer chromatography (33% EtOAc hexanes) indicated the reaction to be complete. The reaction was cooled and concentrated in vacuo to about 10 mL. The resulting residue was diluted with 100 mL ether and washed with brine (2 x 50 mL), dried (Na₂SO₄), and the solvent removed in vacuo. Purification by flash column chromatography (gradient elution: 5% EtOAc/hexanes to 25% EtOAc/hexanes to 55% EtOAc/hexanes) gave the title compound (2.0 g, 72%) as a yellow oil. 400 MHz ¹H NMR (DMSO-d₆) δ 7.10 (s, 1H), 6.64 (s, 1H), 4.75 (s, 2H), 3.63 (s, 3H), 3.02 (septet, 1H, J = 6.8 Hz), 2.05 (s, 3H), 1.08 (d, 6H, J = 6.8 Hz); MS m/z 255 (M+1).

Preparation of [5-Isopropyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl-phenoxy]-acetic acid methyl ester (compound 3D)

3C and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (compound 1B) were coupled in a similar manner as described for compound 1F to provide, after purification by flash column chromatography (gradient elution: 10% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound (0.66 g, 82%) as a yellow solid. IR (thin film) cm⁻¹: 2960, 1763, 1324; 400 MHz ¹H NMR (DMSO-d₆) δ 7.97 (d, 2H, J = 8.1 Hz), 7.76 (d, 2H, J = 8.1 Hz), 7.23 (s, 1H), 6.64 (s, 1H), 4.80 (s, 2H), 4.21 (s, 2H), 3.61 (s, 3H), 3.31 (m, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.08 (d, 6H, J = 6.8 Hz); MS m/z 510 (M+1); Anal. Calc'd for C₂₅H₂₆F₃N₁O₃S₂ C, 58.92; H, 5.14; N, 2.75; found: C, 58.50; H, 5.39; N, 2.66.
Preparation of \{5-Isopropyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy\}-acetic acid (Compound 3)

3D was saponified in the same manner as described for compound 1 to give, after recrystallisation from CHCl₃/hexanes, the title compound (0.24 g, 71%) as a white solid. mp 132-134 °C; IR (thin film) cm⁻¹: 1744, 1325; 400 MHz \(^1\)H NMR (DMSO-d₆) \(\delta\) 7.97 (d, 2H, \(J = 8.3\) Hz), 7.76 (d, 2H, \(J = 8.3\) Hz), 7.22 (s, 1H), 6.64 (s, 1H), 4.67 (s, 2H), 4.20 (s, 2H), 3.31 (m, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 0.93 (d, 6H, \(J = 6.8\) Hz); MS \(m/z\) 496 (M⁺); Anal. Calc’d for C₂₂H₂₄F₃N₁O₃S₂ 0.1 H₂O C, 57.96; H, 4.90; N, 2.82; found: C, 57.62; H, 4.82; N, 2.68.

Example 4

Synthesis of \{2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy\}-acetic acid (Compound 4)

Preparation of 2,6-Dimethyl-4-thiocyanato-phenol (compound 4A)
Compound 4A was prepared from 2,6-dimethylphenol in a similar manner as described for compound 3A. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 8.96 (s, 1H), 7.22 (s, 2H), 2.13 (s, 6H).

5  Preparation of (2,6-Dimethyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 4B)

![Chemical Structure 4B]

10  Compound 4B was prepared from compound 4A in a similar manner as described for compound 3B to give 2.5 g (46%) of the title compound pure enough for subsequent use. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 7.11 (s, 2H), 4.41 (s, 2H), 3.63 (s, 3H), 2.14 (s, 6H).

15  Preparation of (4-Mercapto-2,6-dimethyl-phenoxy)-acetic acid methyl ester (compound 4C)

![Chemical Structure 4C]

20  Compound 4C was prepared from compound 4B in a similar manner as described for compound 3C to give, after purification by flash column chromatography (gradient elution: 100% hexanes to 30% EtOAc/hexanes), 1.8 g (82%) of the title compound. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 6.90 (s, 2H), 5.51 (s, 1H), 4.39 (s, 2H), 3.66 (s, 3H), 2.10 (s, 6H); MS m/z 225 (M-1).
Preparation of [2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 4D)

![Chemical Structure](image)

**4D**

Compound 4C and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound 1F to provide, after purification by flash column chromatography (gradient elution: 10% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound (0.61 g, 57%) as a yellow solid. mp 104-105 °C; IR (thin film) cm⁻¹: 1754, 1325; 400 MHz ¹H NMR (DMSO-d₆) δ 7.99 (d, 2H, J = 8.3 Hz), 7.76 (d, 2H, J = 8.3 Hz), 7.02 (s, 2H), 4.41 (s, 2H), 4.37 (s, 2H), 3.65 (s, 3H), 2.23 (s, 3H), 2.10 (s, 6H); MS m/z 482 (M+1); Anal. Calc’d for C₂₃H₂₃F₃N₁O₃S₂ C, 57.37; H, 4.60; N, 2.91; found: C, 57.43; H, 4.55; N, 2.94.

Preparation of [2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 4)

Compound 4D was saponified in the same manner as described for compound 1 to give, after recrystallisation from CHCl₃/hexanes, the title compound (0.29 g, 86%) as a pale yellow solid. mp 157-158 °C; IR (thin film) cm⁻¹: 1738, 1326; 400 MHz ¹H NMR (DMSO-d₆) δ 7.99 (d, 2H, J = 8.3 Hz), 7.76 (d, 2H, J = 8.3 Hz), 7.02 (s, 2H), 4.36 (s, 2H), 4.29 (s, 2H), 2.22 (s, 3H), 2.12 (s, 6H); MS m/z 468 (M+1); Anal. Calc’d for C₂₃H₂₀F₃N₁O₃S₂ 0.2 H₂O C, 56.09; H, 4.36; N, 2.97; found: C, 55.79; H, 4.22; N, 2.94.
Example 5

Synthesis of [5-Methoxy-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl-phenoxy]-acetic acid (Compound 5)

Preparation of 5-Methoxy-2-methyl-phenol (compound 5A)

2-Hydroxy-4-methoxy-benzaldehyde (3 g, 19.7 mmol), ammonium formate (6.2 g, 99 mmol) and palladium/carbon (900 mg @ 10%) were added to 26 ml glacial acetic acid and heated at 110 °C for 1 h. The reaction was cooled, filtered, and diluted with water (100 ml). The crude product was extracted with chloroform (3x50 ml), washed with water, brine, and dried over anhydrous sodium sulfate. The resulting solution was concentrated and used for the next step without further purification. MS m/z 139 (M+1).
Preparation of 5-Methoxy-2-methyl-4-thiocyanato-phenol (compound 5B)

![Chemical Structure](image)

5B

Compound 5B was prepared from compound 5A in a manner analogous for example 3A. 400 MHz $^1$H NMR (DMSO-$_d_6$) $\delta$ 10.13 (s, 1H), 7.25 (s, 1H), 6.54 (s, 1H), 3.77 (s, 3H), 2.0 (s, 3H). MS $m/z$ 196 (M+1).

Preparation of (5-Methoxy-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 5C)

![Chemical Structure](image)

5C

Compound 5C was prepared from compound 5B in a manner analogous to compound 3B. 400 MHz $^1$H NMR (DMSO-$_d_6$) $\delta$ 7.33 (s, 1H), 6.72 (s, 1H), 4.93 (s, 2H), 3.84 (s, 3H), 3.66 (s, 3H), 2.09 (s, 3H); MS $m/z$ 268 (M+1).

Preparation of (5-Methoxy-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 5D)

![Chemical Structure](image)

5D
Compound 5D was prepared from compound 5C in a manner analogous to compound 3C. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.02 (s, 1H), 6.54 (s, 1H), 4.79 (s, 2H), 4.41 (s, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 2.02 (s, 3H); MS m/z 243 (M+1).

Preparation of [5-Methoxy-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 5E)

![Chemical Structure]

Compound 5E was prepared from compound 5D in a manner analogous to compound 3D. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.98 (d, 2H, $J = 8.4$ Hz), 7.76 (d, 2H, $J = 8.4$ Hz), 7.02 (s, 1H), 6.54 (s, 1H), 4.84 (s, 2H), 4.20 (s, 2H), 3.72 (s, 3H), 3.64 (s, 3H), 2.16 (s, 3H), 1.98 (s, 3H). $^1$H NMR (DMSO-$d_6$) $\delta$ MS m/z 498 (M+1).

Preparation of [5-Methoxy-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 5)

Compound 5 was prepared from compound 5E in a manner analogous to compound 1. mp 211-213 °C; IR (thin film) cm$^{-1}$: 2936, 1719, 1328, 1111; 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 12.96 (s(br), 1H), 7.98 (d, 2H, $J = 8.4$ Hz), 7.76 (d, 2H, $J = 8.4$ Hz), 7.02 (d, 1H, $J = 0.4$ Hz), 6.53 (s, 1H), 4.71 (s, 2H), 4.20 (s, 2H), 3.73 (s, 3H), 2.16 (s, 3H), 1.98 (s, 3H); MS m/z 484 (M+1). Anal. Calc’d for C$_{22}$H$_{20}$F$_3$NO$_4$S$_2$: C, 54.65; H, 4.17; N, 2.90; found: C, 54.68; H, 4.15; N, 2.84.
Example 6

Synthesis of (2-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl-phenoxy]-acetic acid (Compound 6)

Preparation of 2-Methoxy-5-methyl-phenol (compound 6A)

The title compound was prepared from 3-hydroxy-4-methoxy-benzaldehyde in a manner analogous to compound 5A. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 8.73 (s, 1H), 6.71 (d, 1H, $J = 8.1$ Hz), 6.53 (s, 1H), 6.48 (d, 1H, $J = 8.1$ Hz), 3.65 (s, 3H), 2.10 (s, 3H); MS m/z 139 (M+1).

Preparation of 2-Methoxy-5-methyl-4-thiocyanato-phenol (compound 6B)
The title compound was prepared from compound 6A in a manner analogous to compound 3A. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 9.7 (s(br), 1H), 7.15 (s, 1H), 6.78 (1H), 3.73 (s, 3H), 2.3 (s, 3H); MS m/z 196 (M+1).

Preparation of (2-Methoxy-5-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 6C)

![Image](NCS.png)

6C

The title compound was prepared from compound 6B in a manner analogous to compound 3B. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.22 (1H), 6.97 (s, 1H), 4.81 (s, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 2.34 (s, 3H); MS m/z 268 (M+1).

Preparation of (4-Mercapto-2-methoxy-5-methyl-phenoxy)-acetic acid methyl ester (compound 6D)

![Image](HS.png)

6D

The title compound was prepared from compound 6C in a manner analogous to compound 3C. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 6.96 (s, 1H), 6.71 (s, 1H), 4.88 (s, 1H), 4.65 (s, 2H), 3.67 (s, 3H), 3.63 (s, 3H), 2.08 (s, 3H); MS m/z 243 (M+1).
Preparation of [2-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 6E)

The title compound was prepared from compound 6D in a manner analogous to compound 1F. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.99 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 8.4 Hz), 6.86 (s, 1H), 6.75 (s, 1H), 4.70 (s, 2H), 4.27 (s, 2H), 3.63 (s, 3H), 3.60 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H); MS m/z 498 (M+1).

Preparation of [2-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 6)

The title compound was prepared from compound 6E in a manner analogous to compound 1. mp 165-167 °C; IR (thin film) cm$^{-1}$: 2904, 1747, 1504, 1326; 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 12.91 (s(br), 1H), 7.99 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 8.4 Hz), 6.85 (s, 1H), 6.72 (s, 1H), 4.59 (s, 2H), 4.27 (s, 2H), 3.60 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H); MS m/z 484 (M+1).  Anal. Calc'd for C$_{22}$H$_{20}$F$_3$NO$_4$S$_2$: C, 54.65; H, 4.17; N, 2.90; found: C, 54.21; H, 4.03; N, 2.79.
Example 7

Preparation of [3,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 7)

\[
\begin{align*}
\text{F} & \text{F} \\
& \text{F} \\
& \text{S} \\
& \text{S} \\
\text{N} & \text{O} \\
\text{C} & \text{O} \\
7
\end{align*}
\]

Preparation of 3,5-Dimethyl-4-thiocyanato-phenol (compound 7A)

\[
\begin{align*}
\text{NCS} & \text{OH} \\
7A
\end{align*}
\]

7A was prepared from 3,5-dimethylphenol in a similar manner as described for compound 3A. 400 MHz \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 9.61 (s, 1H), 6.64 (s, 2H), 2.04 (s, 6H).

Preparation of (3,5-Dimethyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 7B)

\[
\begin{align*}
\text{NCS} & \text{O} \\
\text{O} & \text{O} \\
7B
\end{align*}
\]
Compound 7B was prepared from compound 7A in a similar manner as described for compound 3B to give 2.0 g (95%) of the title compound pure enough for subsequent use. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 6.63 (s, 2H), 4.72 (s, 2H), 3.62 (s, 3H), 2.08 (s, 6H).

5

Preparation of (4-Mercapto-3,5-dimethyl-phenoxy)-acetic acid methyl ester (compound 7C)

![Chemical Structure of 7C](image)

Compound 7C was prepared from compound 7B in a similar manner as described for compound 3C to give, after purification by flash column chromatography (gradient elution: 100% hexanes to 30% EtOAc/hexanes), 0.38 g (21%) of the title compound. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 6.66 (s, 2H), 4.68 (s, 2H), 4.20 (s, 1H), 3.63 (s, 3H), 2.23 (s, 6H).

Preparation of {3,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid methyl ester (compound 7D)

![Chemical Structure of 7D](image)

Compound 7C and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound 1F to provide, after
purification by flash column chromatography (gradient elution: 10% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound (0.62 g, 79%) as a yellow solid. mp 113 °C; IR (thin film) cm⁻¹: 1739, 1325; 400 MHz ¹H NMR (DMSO-d₆) δ 7.99 (d, 2H, J = 8.3 Hz), 7.76 (d, 2H, J = 8.3 Hz), 6.69 (s, 2H), 4.73 (s, 2H), 4.04 (s, 2H), 3.63 (s, 3H), 2.25 (s, 3H), 1.94 (s, 3H); MS m/z 482 (M+1); Anal. Calc’d for C₂₃H₂₂F₃N₁O₅S₂ C, 57.37; H, 4.60; N, 2.91; found: C, 57.22; H, 4.55; N, 2.78.

Preparation of [3,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyisulfanyl]-phenoxy]-acetic acid (Compound 7)

Compound 7D was saponified in the same manner as described for compound 1F to give, after recrystalisation from CHCl₃/hexanes, the title compound (0.22 g, 76%) as a pale yellow solid. mp 184-185 °C; IR (thin film) cm⁻¹: 1746, 1320; 400 MHz ¹H NMR (DMSO-d₆) δ 7.99 (d, 2H, J = 8.3 Hz), 7.76 (d, 2H, J = 8.3 Hz), 6.67 (s, 2H), 4.61 (s, 2H), 4.04 (s, 2H), 2.25 (s, 6H), 1.94 (s, 3H); MS m/z 468 (M+1); Anal. Calc’d for C₂₂H₂₀F₃N₁O₅S₂ C, 56.52; H, 4.31; N, 3.00; found: C, 56.19; H, 4.23; N, 2.91.

Example 8

**Synthesis of [3-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyisulfanyl]-phenoxy]-acetic acid (Compound 8)**

![Chemical Structure](image)
Preparation of 3-Methoxy-5-methyl-4-thiocyanato-phenol (compound 8A)

\[
\begin{array}{c}
\text{HO} \\
\text{SCN} \\
\end{array}
\]

\[8A\]

Compound 8A was prepared from 3-methoxy-5-methyl-phenol in a similar manner as described for compound 3A to give, after recrystallisation from CHCl₃/hexanes, 1.9 g (13%) of the title compound. 400 MHz \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 10.14 (s, 1H), 6.39 (s, 2H), 3.79 (s, 3H), 2.35 (s, 3H); MS \(m/\ell\) 196 (M+1).

Preparation of (3-Methoxy-5-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 8B)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{SCN} \\
\end{array}
\]

\[8B\]

Compound 8B was prepared from compound 8A in a similar manner as described for compound 3B to give 2.2 g (87%) of the title compound pure, enough for subsequent use. 400 MHz \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 6.60 (s, 2H), 4.84 (s, 2H), 3.85 (s, 3H), 3.66 (s, 3H), 2.40 (s, 3H); MS \(m/\ell\) 268 (M+1).
Preparation of (4-Mercapto-3-methoxy-5-methyl-phenoxy)-acetic acid methyl ester (compound 8C)

![Chemical Structure](image)

Compound 8C was prepared from compound 8B in a similar manner as described for compound 3C to give, after purification by flash column chromatography (gradient elution: 5% EtOAc/hexanes to 50% EtOAc/hexanes), the title compound (0.82 g, 45%) as a white solid. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 6.46 (s, 1H), 6.42 (s, 1H), 4.71 (s, 2H), 4.24 (s, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 2.16 (s, 3H); MS m/z 243 (M+1).

Preparation of [3-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 8D)

![Chemical Structure](image)

Compound 8C and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound 1F to provide, after purification by flash column chromatography (gradient elution: 5% EtOAc/hexanes to 50% EtOAc/hexanes), the title compound (0.71 g, 69%) as a yellow solid. IR (thin
film) cm⁻¹: 1766, 1325; 400 MHz ¹H NMR (DMSO-d₆) δ 7.97 (d, 2H, J = 8.1 Hz), 7.75 (d, 2H, J = 8.1 Hz), 6.42 (s, 1H), 6.37 (s, 1H), 4.75 (s, 2H), 4.09 (s, 2H), 3.74 (s, 3H), 3.63 (s, 3H), 2.12 (s, 3H), 2.01 (s, 3H); MS m/z 498 (M+1); Anal. Calc’d for C₂₃H₂₂F₃N₁O₄S₂ C, 55.52; H, 4.46; N, 2.82; found: C, 55.30; H, 4.44; N, 2.73.

Preparation of [3-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 8)

Compound 8D was saponified in the same manner as described for compound 1F to give, after recrystallisation from CHCl₃/hexanes, the title compound (0.14 g, 49%) as a pale yellow solid. mp 164-165 °C; IR (thin film) cm⁻¹: 1726, 1323; 400 MHz ¹H NMR (DMSO-d₆) δ 7.97 (d, 2H, J = 8.1 Hz), 7.75 (d, 2H, J = 8.1 Hz), 6.41 (s, 1H), 6.35 (s, 1H), 4.62 (s, 2H), 4.08 (s, 2H), 3.73 (s, 3H), 2.12 (s, 3H), 2.01 (s, 3H); MS m/z 484 (M+1); Anal. Calc’d for C₂₂H₂₀F₃N₁O₄S₂ C, 54.65; H, 4.17; N, 2.90; found: C, 54.12; H, 4.06; N, 2.69.

Example 9

Synthesis of [2-Isopropyl-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 9)
Preparation of 2-Isopropyl-5-methyl-4-thiocyanato-phenol (compound 9A)

\[
\text{9A}
\]

The title compound was prepared in a manner analogous to compound 3A. 400 MHz \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 8.9 (s(br), 1H), 7.37 (s, 1H), 6.86 (s, 1H), 3.23 (m, 1H), 2.38 (s, 3H), 1.12 (d, 6H, \(J = 7.1\) Hz); MS m/z 208 (M+1).

Preparation of (2-Isopropyl-5-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 9B)

\[
\text{9B}
\]

The title compound was prepared from compound 9A in a manner analogous to compound 3B. 400 MHz \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 7.41 (s, 1H), 6.86 (s, 1H), 4.86 (s, 2H), 3.65 (s, 3H), 3.20 (m, 1H), 2.38 (s, 3H), 1.1 (d, 6H, \(J = 7.2\) Hz); MS m/z 280 (M+1).

Preparation of (2-Isopropyl-4-mercapto-5-methyl-phenoxy)-acetic acid methyl ester (compound 9C)

\[
\text{9C}
\]
The title compound was prepared from compound 9B in a manner analogous to compound 3C. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.37 (s, 1H), 6.86 (s, 1H), 5.0 (s, 1H), 4.85 (s, 2H), 3.68 (s, 3H), 3.23 (m, 1H), 2.28 (s, 3H), 1.12 (d, 6H, $J = 6.8$ Hz); MS m/z 255 (M+1).

Preparation of [2-Isopropyl-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 9D)

The title compound was prepared from compound 9C in a manner analogous to example 1F. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.98 (d, 2H, $J = 8$ Hz), 7.76 (d, 2H, $J = 8$ Hz), 6.94 (s, 1H), 6.74 (s, 1H), 4.76 (s, 2H), 4.17 (s, 2H), 3.63 (s, 3H), 3.1 (m, 1H), 2.24 (s, 3H), 1.93 (s, 3H), .96 (d, 6H, $J = 7.2$ Hz); MS m/z 510 (M+1).

Preparation of [2-Isopropyl-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 9)

The title compound was prepared from compound 9D in a manner analogous to compound 1. mp 168-171 °C; IR (thin film) cm$^{-1}$: 2956, 2583, 1749, 1326; 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 12.94 (s(br), 1H), 8.00 (d, 2H, $J = 8.4$ Hz), 7.78 (d, 2H, $J = 8.4$ Hz), 6.95 (s, 1H), 6.74 (s, 1H), 4.66 (s, 2H), 4.18 (s, 2H), 3.11 (m, 1H), 2.27 (s,
3H), 1.95 (s, 3H), 0.98 (d, 6H, J = 7.2 Hz); MS m/z 496 (M+1). Anal. Calc'd for C_{24}H_{24}F_{3}NO_{3}S_{2}, C 58.17; H, 4.88; N, 2.83; found: C, 57.73; H, 4.62; N, 2.75.

**Example 10**

5 **Synthesis of [2,6-Diisopropyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 10)**

![Chemical Structure](image)

10 **Preparation of 2,6-Diisopropyl-4-thiocyanato-phenol (compound 10A)**

![Chemical Structure](image)

The title compound was prepared in a manner analogous to compound 3A. 400 MHz \(^1\)H NMR (DMSO-\(d_6\)) \(δ\) 8.8 (s, 1H), 7.22 (s, 2H), 3.25 (m, 2H), 1.1 (d, 12H, J = 7.2 Hz); MS m/z 236 (M+1).

**Preparation of (2,6-Diisopropyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 10B)**

![Chemical Structure](image)
The title compound was prepared from compound 10A in a manner analogous to compound 3B. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.37 (s, 2H), 4.44 (s, 2H), 3.68 (s, 3H), 3.23 (m, 2H), 1.12 (d, 12H, $J = 6.8$ Hz); MS $m/z$ 308 (M+1).

5 Preparation of (2,6-Diisopropyl-4-mercapto-phenoxy)-acetic acid methyl ester (compound 10C)

10 The title compound was prepared from compound 10B in a manner analogous to compound 3C. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.37 (s, 2H), 4.88 (s, 1H) 4.49 (s, 2H), 3.7 (s, 3H), 3.23 (m, 2H), 1.12 (d, 12H, $J = 6.8$ Hz); MS $m/z$ 283 (M+1).

15 Preparation of[2,6-Diisopropyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (compound 10D)

20 The title compound was prepared from compound 10C in a manner analogous to compound 1F. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.97 (d, 2H, $J = 8.4$ Hz), 7.76 (d,
2H, 8.4 Hz), 7.00 (s, 2H), 4.3 (m, 4H), 3.66 (s, 3H), 3.13 (m, 2H), 2.04 (3H), 1.01 (d, 12H, J = 7.2 Hz); MS m/z 538 (M+1).

Preparation of [2,6-Diisopropyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 10)

The title compound was prepared from compound 10D in a manner analogous to compound 1. mp 161-163 °C; IR (thin film) cm⁻¹: 2966, 1739, 1438, 1323; 400 MHz ¹H NMR (DMSO-d₆) δ 12.93 (s(br), 1H), 7.8 (d, 2H, J = 8 Hz), 7.76 (d, 2H, J = 8 Hz), 7.00 (s, 2H), 4.32 (s, 2H), 4.2 (s, 2H), 3.12 (m, 2H), 2.03 (s, 3H), 1.01 (d, 12H, J = 7.2 Hz); MS m/z 524 (M+1). Anal. Calc’d for C₂₅H₂₈F₃NO₅S₂ C, 59.64; H, 5.39; N, 2.67; found: C, 58.82; H, 5.54; N, 2.48.

Example 11

Synthesis of 2-Methyl-2-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid (Compound 11)

Preparation of 2-(4-Benzylxy-phenyl)-2-methyl-propionic acid methyl ester (11A)
1. (4-Benzyloxy-phenyl)-acetic acid (10g, 41 mmol) was dissolved in MeOH (100 mL) and was then treated with H₂SO₄ (5 mL). The reaction mixture was refluxed overnight. MeOH was evaporated and the residue was diluted with water and ether. Layers were separated and the aqueous layer was extracted with ether (2x30mL). The combined organics were dried with MgSO₄ and condensed to afford the product (10.24g, 97%) as white crystals. MS: 257 (M+1)⁺

2. To a suspension of NaH (2.34g, 58.5 mmol) in THF (150 mL) was added a solution of the above ester (5.0g, 19.8 mmol) in THF (50 mL) followed by dropwise addition of methyl iodide (6.65g, 47 mmol). The mixture was stirred at RT overnight. Water (100 mL) was added and the layers were separated. The aqueous layer was extracted with ether (2x50mL). The combined organics was dried with MgSO₄ and evaporated to give a yellow solid as the desired product 11A (4.37g, 79%). MS: 285 (M+1)⁺

**Preparation of 2-(4-Dimethylthiocarbamoyloxy-phenyl)-2-methyl-propionic acid methyl ester (compound 11B)**

![Chemical Structure](image)

1. Compound 11A (2.08g, 7.31 mmol) was dissolved in MeOH (50 mL) and was subjected to hydrogenation conditions catalyzed by 20% Pd/C. After 17 h, the reaction mixture was filtered and the filtrate was evaporated to give the desired product as a white solid (1.85g, 100%)

2. The phenol compound obtained from above (1.0g, 5.15 mmol) was dissolved in dioxane (10 mL) followed by addition of Et₃N (1.04g, 10.3 mmol), DMAP (63mg,
0.52 mmol), and dimethyl thiocarbamoyl chloride (0.76 g, 6.18 mmol). The reaction mixture was refluxed overnight. After cooling down to RT, the reaction mixture was diluted with EtOAc (100 mL) and H₂O (100 mL). Layers were separated and the aqueous layer was extracted with EtOAc (2x50 mL). Combined organics was dried over MgSO₄ and condensed to give the desired product 11B as a brown oil (1.61 g, 100%).

MS: 282 (M+1)

Preparation 2-(4-Mercapto-phenyl)-2-methyl-propionic acid methyl ester (compound 11C)

![Diagram of 11C]

1). Compound 11B (1.61 g, 5.15 mmol) in tetradecane (20 mL) was heated to reflux overnight. After cooling down to RT, solvent was decanted out and the residue was washed with hexane. It was then taken up to EtOAc (100 mL) and washed with H₂O, dried over MgSO₄ and condensed to give the desired product as a tan solid (0.15 g). More crystals (0.39 g) were collected from the tetradecane solution that was first decanted. Total yield of the reaction was 34% (0.54 g).

MS: 282 (M+1)

2). The above product (0.54 g, 1.92 mmol) was immediately dissolved in MeOH (5 mL) and was treated with NaOMe (0.114 g, 2.11 mmol). The reaction mixture was heated to reflux overnight and MS indicated the presence of the desired product 11C. The reaction was cooled to RT and used for next step without purification.

MS: 209 (M-1)
Preparation 2-Methyl-2-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid (Compound 11)

1). To the above mixture was added a solution of the chloride 1B (0.25g, 0.86 mmol) in MeOH (10 mL) and the resulting solution was heated to reflux overnight. MeOH was then removed via rotavap and the residue was dissolved in EtOAc (50mL) and washed with H₂O. Solvent was dried over MgSO₄ and condensed to give the crude product as an oil. It was purified by silica gel chromatography eluted with 10% EtOAc/Hexanes to afford the pure product (0.22g, 24%) as a yellow oil.

MS: 466 (M+1)⁺

2). The above methyl ester (0.22g, 0.4 mmol) dissolved in THF (10 mL) and treated with LiOH·H₂O (0.1g, 2 mmol). After reflux overnight, the reaction mixture was cooled to RT and neutralized with aq. HCl (1N). Solvent was removed and the solid was filtered off and washed with EtOAc. The filtrate was dried over MgSO₄ and condensed to give the desired product compound 11 as a yellow solid (0.17g, 96%).

MS: 452 (M+1)⁺, CHN: Calc’d: C 58.52, H 4.46, N 3.10; Found: C 58.65, H 4.33, N 3.04.

Example 12

Synthesis of 2-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-cyclopropanecarboxylic acid (Compound 12)
Preparation of 2-Phenyl-cyclopropanecarboxylic acid methyl ester (12A)

\[
\begin{align*}
\text{12A}
\end{align*}
\]

2-Phenyl-cyclopropanecarboxylic acid (5g, 30.86 mmol) was dissolved in MeOH (100 mL) and was then treated with H₂SO₄ (2 mL). The reaction mixture was refluxed overnight. MeOH was evaporated and the residue was diluted with water and ether. Layers were separated and the aqueous layer was extracted with ether (2x30mL). The combined organics were dried with MgSO₄ and condensed to afford the product compound 12A (5.3g, 97%) as white crystals. MS: 177 (M+1)⁺

Preparation of 2-(4-Chlorosulfonyl-phenyl)-cyclopropanecarboxylic acid methyl ester (compound 12B)

\[
\begin{align*}
\text{12B}
\end{align*}
\]

Chlorosulfonic acid (10 mL) was cooled to 0°C. Then compound 12A (2.0g, 11.36 mmol) was added over 30 min. The mixture was stirred at RT for 3h and was poured into ice (100g). The cloudy solution was extracted with ether (2x100mL). The extracts were dried with magnesium sulfate and concentrated to give a brown oil which was passed through a short pad of silica gel to afford the desired product 12B (2.96g, 95%) as white plates.
NMR (1H, CDCl3): 6 7.95 (2H, m), 7.29 (2H, m), 3.74 (3H, s), 2.68 (1H, m), 2.03 (1H, m), 1.78 (1H, m), 1.41 (1H, m).

**Preparation of 2-(4-Mercapto-phenyl)-cyclopropanecarboxylic acid methyl ester (compound 12C)**

![12C](image)

The above product **12B** was refluxed with tin powder (4.4g, 37.7 mmol) in MeOH (10 mL) and 4M HCl/dioxane (10 mL). After 3h, the reaction mixture was poured into ice with CH₂Cl₂ (100 mL). The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (2x50mL). The combined organic layers were dried with magnesium sulfate, filtered and evaporated to give the thiol compound **12C** as a yellow oil (1.06g, 70%).

MS: 207 (M-1)⁺

**Preparation of 2-[4-(4-Methyl-2-p-tolyl-thiazol-5-ylsulfanyl)-phenyl]-cyclopropanecarboxylic acid methyl ester (compound 12D)**

![12D](image)

Compound **12C** (1.06g, 5.09 mmol) was dissolved in acetonitrile (80 mL) with the chloride **1B** (1.3g, 4.4 mmol) and Cs₂CO₃ (3.3g, 1.07 mmol). The reaction mixture was stirred at RT overnight. Ether (50 mL) and H₂O were added and stirring was continued for another 5 min. The layers were separated and the aqueous layer was
extracted with ether (2x100 mL). The combined organics was dried over MgSO₄ and concentrated to an oil. The crude product was purified by column chromatography eluted with EtOAc and hexanes to give the desired product, compound 12D as a thick yellow oil (1.1g, 47%).

MS: 464 (M+1)<sup>+</sup>

Preparation of 1-[(4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-cyclopropanecarboxylic acid (Compound 12)

To the solution of the above methyl ester, compound 12D (0.38g, 0.82 mmol) in MeOH (7mL) and THF (7mL) was added LiOH.H₂O (69mg, 1.64 mmol). After refluxing overnight, the solution was cooled to RT and solvents were removed by rotavap. The residue was dissolved in water and neutralized with 1N HCl. The cloudy solution was extracted with EtOAc (3x50 mL) and the extracts were dried with MgSO₄, and concentrated. The crude product was purified by chromatography to afford a yellow solid, which was further washed with ether to yield the desired product as yellowish crystals (116mg, 31%).

MS: 450 (M+1)<sup>+</sup>.

Example 13

Synthesis of 1-[(4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-cyclopropanecarboxylic acid (Compound 13)
Preparation of 1-Phenyl-cyclopropanecarboxylic acid methyl ester (compound 13A)

Compound 13A was made following the procedure in Example 12A, by replacing 2-Phenyl-cyclopropanecarboxylic acid with compound 1-Phenyl-cyclopropanecarboxylic acid. Compound 13A was prepared in quantitative yield. MS: 177 (M+1)^+. 

Preparation of 1-(4-Chlorosulfonyl-phenyl)-cyclopropanecarboxylic acid methyl ester (compound 13B)

Compound 13B was prepared analogously to compound 12B. 57% yield. MS: 239 (M-Cl)^+. 

Preparation of 1-(4-Mercapto-phenyl)-cyclopropanecarboxylic acid methyl ester (compound 13C)

Compound 13C was prepared analogously to compound 12C.
Preparation of 1-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclopropanecarboxylic acid methyl ester (compound 13D):

5

Compound 13D was prepared analogously to compound 12D using the crude product compound 13C. Yield was 12% in 2 steps. MS for 15D: 464 (M+1)^+

Preparation of 1-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclopropanecarboxylic acid (Compound 13):

Compound 13 was prepared analogously to compound 12. Compound 13 was prepared in 54% yield. MS: 450 (M+1)^+

Example 14

Synthesis of 1-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclopentanecarboxylic acid (Compound 14)

25
Preparation of 1-Phenyl-cyclopentanecarboxylic acid methyl ester (compound 14A)

Compound 14A was made following the procedure in Example 12A, by replacing 2-Phenyl-cyclopropanecarboxylic acid with 1-Phenyl-cyclopentanecarboxylic acid. Compound 14A was prepared in quantitative yield. MS: 205 (M+1)^+.

Preparation of 1-(4-Chlorosulfonyl-phenyl)-cyclopentanecarboxylic acid methyl ester (compound 14B)

Compound 14B was prepared analogously to compound 12B. 50% yield. MS: 267 (M-Cl)^+.

Preparation of 1-(4-Mercapto-phenyl)-cyclopentanecarboxylic acid methyl ester (compound 14C)
Compound 14C was prepared analogously to compound 12C.

**Preparation of 1-(4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl)-cyclopentanecarboxylic acid methyl ester (compound 14D)**

![Compound 14D](image)

Compound 14D was prepared analogously to compound 12D using the crude product compound 14C. Yield was 31% in 2 steps. MS for 14D: 492 (M+1)^+.

**Preparation of 1-(4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl)-cyclopentanecarboxylic acid (Compound 14)**

Compound 14 was prepared analogously to compound 12 in 80% yield. MS: 478 (M+1)^+.

**Example 15**

**Synthesis of 4-Methyl-4-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-pentanoic acid (Compound 15)**

![Compound 15](image)
Preparation of 4-Methyl-4-phenyl-pentanoic acid methyl ester (compound 15A)

![15A](image)

Compound 15A was prepared by hydrogenation of the corresponding crotonate catalyzed by Pd/C (10%) in 93% yield. MS: 221 (M+1)^+.

Preparation of 4-(4-Chlorosulfonyl-phenyl)-4-methyl-pentanoic acid ethyl ester (compound 15B)

![15B](image)

Compound 15B was prepared analogously to compound 12B in 85% yield. MS: 283 (M-Cl)^+.

Preparation of 4-(4-Mercapto-phenyl)-4-methyl-pentanoic acid ethyl ester (compound 15C)

![15C](image)

Compound 15C was prepared analogously to compound 12C.
Preparation of 4-Methyl-4-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-pentanoic acid ethyl ester (compound 15D)

Compound 15D was prepared analogously to compound 12D using the crude product compound 15C. Yield was 21% in 2 steps. MS for 17D: 508 (M+1)⁺.

Preparation of 4-Methyl-4-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-pentanoic acid (Compound 15)

Compound 15 was prepared analogously to compound 12. Compound 15 was prepared in 38% yield. MS: 480 (M+1)⁺.

Example 16

Synthesis of 3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-propionic acid (Compound 16)
Preparation of 3-Phenoxy-propionic acid methyl ester (compound 16A)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array} \\
16A
\]

Compound 16A is commercially available from Aldrich of Milwaukee, Wisconsin.

Preparation of 3-(4-Chlorosulfonyl-phenoxy)-propionic acid methyl ester (compound 16B)

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array} \\
16B
\]

Compound 16B was prepared analogously to compound 12B. 69% yield.

Preparation of 3-(4-Mercapto-phenoxy)-propionic acid methyl ester (compound 16C)

\[
\begin{array}{c}
\text{S} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array} \\
16C
\]

Compound 16C was prepared analogously to compound 12C.

Preparation of 3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-propionic acid methyl ester (compound 16D)

\[
\begin{array}{c}
\text{S} \\
\text{N} \\
\text{F} \\
\text{F} \\
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array} \\
16D
\]
Compound 16D was prepared analogously to compound 12D using the crude product compound 16C. Compound 16D was prepared in 49% yield. MS: 211 (M-1)^+.

Synthesis of 3-(4-(4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl)-phenoxy)-propionic acid (Compound 16)

Compound 16 was prepared by treating the ester with concentrated HBr in 17% yield. MS: 454 (M+1)^+.

Example 17

Synthesis of 2-(3-Methoxy-4-(4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl)-phenyl)-2-methyl-propionic acid (Compound 17)

Preparation of 2-(3-Methoxy-phenyl)-2-methyl-propionic acid methyl ester (Compound 17A)

17A was prepared analogously to compound 11A. MS: 209 (M+1)^+. 
Preparation of 2-(4-Chlorosulfonyl-3-methoxy-phenyl)-2-methyl-propionic acid methyl ester (Compound 17B)

17B was prepared analogously to compound 12B. 39% yield. MS: 271 (M-Cl)^+.

Preparation of 2-(4-Mercapto-3-methoxy-phenyl)-2-methyl-propionic acid methyl ester (Compound 17C)

17C was prepared analogously to compound 12C. Used as unpurified oil. MS: 239 (M-1)^+.

Preparation of 2-{3-Methoxy-4-[methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethysulfanyl]-2-methyl-propionic acid methyl ester (Compound 17D)
Compound 17D was prepared analogously to compound 12D. Yield was 12% after flash column purification. MS: 496 (M+1)$^+$.  

**Preparation of 2-{3-Methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-2-methyl-propionic acid (Compound 17)**

Compound 17 was prepared analogously to compound 12. Compound 17 was prepared in 50% yield. MS: 482 (M+1)$^+$.  

**Example 18**

**Synthesis of 3-Methyl-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-butyric acid (Compound 18)**

![Chemical structure of 18]

**Preparation of 3-Methyl-3-phenyl-butyric acid methyl ester (Compound 18A)**

![Chemical structure of 18A]

18A was prepared analogously to compound 11A. 96% yield. MS: 179 (M+1)$^+$.  

**Preparation of 2-Methyl-2-phenyl-propan-1-ol (Compound 18B)**

![Chemical structure of 18B]

18B was prepared analogously to compound 1A. Quantitative yield. MS: 133 (M-H$_2$O)$^+$. 
Preparation of 3-Methyl-3-phenyl-butyronitrile (Compound 18C)

![Chemical Structure of 18C]

Methane sulfonyl chloride was added to a stirred solution of compound 18B dissolved in CH$_2$Cl$_2$ and triethyl amine at 0°C. The mixture was stirred at RT for 4 hr. It was then diluted with CH$_2$Cl$_2$ and washed with 1 x sat. NH$_4$Cl, 1 x brine, dried (MgSO$_4$) and the solvent removed in vacuo to give 2.68 g (88%) of the methanesulfonated compound.

The methanesulfonated intermediate obtained from above was dissolved in DMSO and added with sodium cyanide. The mixture was heated at 100°C overnight. After cooling down to RT, the reaction mixture was diluted with water and layered with ether. The layers were separated and the aqueous layer extracted with ether. The combined organics were dried over MgSO$_4$ and condensed to give the crude product as an oil. It was purified by silica gel chromatography eluted with 10% EtOAc/Hexanes to afford the desired compound 18C as a clear oil (0.26 g, 26%). MS: 160 (M+1)$^+$.  

Preparation of 4-(2-Cyan-1, 1-dimethyl-ethyl)-benzenesulfonyl chloride (Compound 18D)

![Chemical Structure of 18D]

18D was prepared analogously to compound 12B. 71% yield. MS: 222 (M-Cl)$^+$.  

Preparation of 3-(4-Mercapto-phenyl)-3-methyl-butyronitrile (Compound 18E)

![Chemical Structure of 18E]
18E was prepared analogously to compound 12C. 92% yield. MS: 252 (M+1)^+.

Preparation of 3-Methyl-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-butyronitrile (Compound 18F)

![Chemical Structure 18F]

Compound 18F was prepared analogously to compound 12D. Yield was 20% after flash column purification. MS: 447 (M+1)^+.

Preparation of 3-Methyl-3-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-butyric acid (Compound 18)

Compound 18F stirred in 2-methoxy ethanol was added with 30% NaOH solution. The mixture was heated at reflux overnight. The solvent was removed in vacuo to give the crude product as a dark oil. It was purified by silica gel chromatography eluted with 15% EtOAc/Hexanes to afford the desired compound 18 as a yellow solid (0.014 g, 8%). MS: 466 (M+1)^+.

Example 19

Synthesis of 3-{2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-propionic acid (Compound 19)

![Chemical Structure 19]
Preparation of 3-(2,4-Dimethoxy-phenyl)-propionic acid ethyl ester (Compound 19A)

2,4-Dimethoxybenzaldehyde in THF was added to a stirred solution of sodium hydride and triethyl phosphonoacetate in THF at 0°C. After 15 min., water was added and the mixture was stirred at RT for 2 hr. The layers were separated and the aqueous layer was extracted with ether. The combined organics was dried with MgSO₄ and evaporated to a yellow oil in quantitative yield. MS: 237 (M+1)^+.

Compound 19A was then prepared by hydrogenation of the unsaturated oil catalyzed by Pd/C (10%) in 88% yield. MS: 239 (M+1)^+.

Preparation of 3-(5-Chlorosulfonyl-2,4-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 19B)

19B was prepared analogously to compound 12B. 52% yield. MS: 301 (M-Cl)^+.

Preparation of 3-(5-Mercapto-2,4-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 19C)
19C was prepared analogously to compound 12C. Used as unpurified oil. MS: 271 (M+1)+.

**Preparation of 3-[2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid ethyl ester (Compound 19D)**

![Chemical Structure 19D](image)

Compound 19D was prepared analogously to compound 12D. Yield was 45% after flash column purification. MS: 526 (M+1)+.

**Preparation of 3-[2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid (Compound 19)**

Compound 19 was prepared analogously to compound 12. Compound 19 was prepared in 54% yield. MS: 498 (M+1)+.

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**Example 20**

**Synthesis of 3-[2,5-Dimethoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid (Compound 20)**

![Chemical Structure 20](image)

**Preparation of 3-(2,5-Dimethoxy-phenyl)-propionic acid ethyl ester (Compound 20A)**
20A was prepared analogously to compound 19A. 94% yield. MS: 239 (M+1)^+.

Preparation of 3-(4-Chlorosulfonyl-2,5-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 20B)

20B was prepared analogously to compound 12B. 88% yield. MS: 301 (M-Cl)^+.

Preparation of 3-(4-Mercapto-2,5-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 20C)

20C was prepared analogously to compound 12C. Used as unpurified oil. MS: 271 (M+1)^+.
Preparation of 3-[2,5-Dimethoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid ethyl ester (Compound 20D)

![Chemical Structure](image)

Compound 20D was prepared analogously to compound 12D. Yield was 26% after flash column purification. MS: 526 (M+1)^+. 

Preparation of 3-[2,5-Dimethoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid (Compound 20)

Compound 20 was prepared analogously to compound 12. Compound 20 was prepared in 98% yield. MS: 498 (M+1)^+.

Example 21

Synthesis of 2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfany]-acetic acid (Compound 21)

![Chemical Structure](image)
Preparation of (2,4-Dimethoxy-phenyl)-acetic acid methyl ester (Compound 21A)

![21A](image)

21A was prepared analogously to compound 12A. Quantitative yield. MS: 211 (M+1)^+. 

Preparation of (5-Chlorosulfonyl-2, 4-dimethoxy-phenyl)-acetic acid methyl ester (Compound 21B)

![21B](image)

21B was prepared analogously to compound 12B. 83% yield. MS: 307 (M+1)^+. 

Preparation of (5-Mercapto-2, 4-dimethoxy-phenyl)-acetic acid methyl ester (Compound 21C)

![21C](image)

21C was prepared analogously to compound 12C. Used as unpurified oil. MS: 243 (M+1)^+. 


Preparation of [2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-acetic acid methyl ester (Compound 21D)

Compound 21D was prepared analogously to compound 12D. Yield was 25% after flash column purification. MS: 498 (M+1)^+.  

Preparation of [2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-acetic acid (Compound 21)

Compound 21 was prepared analogously to compound 12. Compound 21 was prepared in 82% yield. MS: 484 (M+1)^+.  

Example 22

Synthesis of 3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid (Compound 22)
Preparation of 3-{4-[4-Methy1-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (Compound 22A)

![Chemical Structure](image)

5

Compound 22A was prepared according to the method of example 1F utilizing 3-(4-hydroxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester. MS: 501 (M+1)

Preparation of 3-{4-[4-Methy1-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid (Compound 22)

Compound 22 was prepared according to the method of example 1 utilizing compound 22A. MS: 487 (M+1)

Example 23

**Synthesis of 3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-phenyl-propionic acid (Compound 23)**

![Chemical Structure](image)

23
Preparation of 3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-phenyl-propionic acid methyl ester (Compound 23A)

Compound 23A was prepared according to the method of example 1F utilizing 3-(4-hydroxy-phenyl)-2-phenylpropionic acid methyl ester. MS: 512 (M+1)^+.

Preparation of 3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-phenyl-propionic acid (Compound 23)

Compound 23 was prepared according to the method of example 1 utilizing compound 23A. MS: 498 (M+1)^+.

Example 24

Synthesis of 3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl-phenyl]-2-pyrrol-1-yl-propionic acid (Compound 24)
Preparation of 3-(4-Dimethylcarbamoylsulfanyl-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (Compound 24A)

3-(4-Hydroxy-phenyl)-2-phenylpropionic acid methyl ester, Et₃N, 4-dimethylamino-pyridine and dimethyl thiocarbamoyl chloride in dioxane was refluxed for 16h. After removing most of solvent, the mixture was partition between ethyl acetate and water. The organic layer was separated, washed with water, dried, filtered and evaporated to afford 4-dimethylthiocarbamoyloxy-phenyl-propionic acid methyl ester, was used in the next step without further purification.

4-Dimethylthiocarbamoyloxy-phenyl-propionic acid methyl ester in THF was added drop wise into a refluxed solution of tetradecane, refluxed for another 3 hours. The solvent was decanted after cooling to room temperature, remaining oil washed several times with hexane. It was purified by flash column chromatography to afford compound 24A. MS: 333(M+1)⁺.

Preparation of 3-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-2-pyrrol-1-yl-propionic acid (Compound 24)

A solution of compound 24A in MeOH and NaOH was refluxed for 5 h. Then the 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol was added and the mixture was refluxed for another hour. The solvent was removed and the crude
product was purified by flash column chromatography to afford the compound 24. MS: 503 (M+1)⁺.

Example 25

5 Synthesis of 2-[(5-(acetylamino)-2-methyl-4-((4-methyl-2-(4-(trifluoromethyl)phenyl)[1,3-thiazol-5-yl])methylthio)phenoxy]acetic acid (Compound 25)

![Chemical Structure of Compound 25]

Preparation of (2-amino-4-hydroxy-5-methylphenyl)thiocarbonitrile (Compound 25 A)

![Chemical Structure of Compound 25 A]

To a mixture of 5-amino-2-methylphenol, sodium thiocyanate and sodium bromide in anhydrous methanol, and bromine in methanol was added dropwise over 30 minutes and allowed to stir at 0 °C for 1 h. Saturated sodium bicarbonate was added to bring pH 7, and the crude product was extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulfate, concentrated, and purified using normal phase chromatography to afford the title product. 400 MHz
\(^1\text{H NMR (DMSO-d}_6\) \delta 9.72 (s, 1H), 7.10 (s, 1H), 6.30 (s, 1H), 5.59 (s, 2H), 1.98 (s, 3H).}

**Preparation of methyl 2-(3-amino-4-cyanothio-6-methylphenoxy)acetate (Compound 25B)**

The title compound was prepared in the manner analogous to Example 3B with the product from example 25A methyl bromoacetate and cesium carbonate in acetonitrile. 400 MHz \(^1\text{H NMR (DMSO-d}_6\) \delta 7.20 (s, 1H), 6.28 (s, 1H), 5.71 (s, 2H), 4.77 (s, 2H), 3.71 (s, 3H), 2.04 (s, 3H).

**Preparation of methyl 2-[5-(acetylamino)-4-cyanothio-2-methylphenoxy]acetate (Compound 25C)**

![Chemical Structure](image)

25C

A mixture of the product from example 25B and acetic anhydride in pyridine was stirred at ambient temperature overnight, then ethyl acetate was added, washed with water, brine, dried over anhydrous sodium sulfate, concentrated to give 25C. 400 MHz \(^1\text{H NMR (DMSO-d}_6\) \delta 7.55 (s, 1H), 6.81 (s, 1H), 4.90 (s, 2H), 3.70 (s, 3H), 2.23 (s, 3H), 2.07 (s, 3H).

**Preparation of methyl 2-[5-(acetylamino)-2-methyl-4-sulfanylphenoxy]acetate (Compound 25D)**
A mixture of the product from example 25C, dithiothreitol and 0.2M potassium in methanol was refluxed for 1 h. After cooling, ethyl acetate was added, washed with water, brine, dried over anhydrous sodium sulfate, concentrated, and purified using normal phase chromatography to afford the title product. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 9.26 (s, 1H), 7.25 (s, 1H), 7.20 (s, 1H), 4.81 (s, 2H), 3.71 (s, 3H), 2.12 (s, 3H), 1.95 (s, 3H).

**Preparation of methyl 2-[5-(acetylamino)-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)]methy1thio)phenoxy]acetate (Compound 25E)**

The title compound was prepared in the manner analogous to Example 1F with the product from example 25D, 5-(chloromethyl)-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole and cesium carbonate in anhydrous acetonitrile. 400 MHz $^1$H NMR (CDCl$_3$) δ 8.25 (s, 1H), 7.92 (m, 3H), 7.68 (d, 2H), 4.70 (s, 2H), 4.00 (s, 2H), 3.81 (s, 3H), 2.20 (s, 3H), 2.12 (s, 3H), 2.02 (s,3H). MS m/z 524.83 (M+1).
Preparation of 2-\{5-(acetylamino)-2-methyl-4-\{(4-methyl-2-\{4-(trifluoromethyl)phenyl\}(1,3-thiazol-5-yl))methylthio\}phenoxy\}acetic acid (Compound 25)

The title compound was prepared in the manner analogous to Example 1 with the product from example 25E and lithium hydroxide monohydrate in tetrahydrofuran/water mixture (10:1). MS m/z 510.75 (M+1).

Example 26

Synthesis of 2-\{5-fluoro-2-methyl-4-\{(4-methyl-2-\{4-(trifluoromethyl)phenyl\}(1,3-thiazol-5-yl))methylthio\}phenoxy\}acetic acid (Compound 26)

Preparation of 5-fluoro-2-methylphenol (compound 26A)
A mixture of 5-fluoro-2-methylphenylamine in concentrated sulfuric acid and water was heated until a clear solution was obtained, then cooled to 0 °C, a solution of sodium nitrite in water was added dropwise over 15 minutes, then poured into boiled saturated copper sulfate solution and heated for 15 minutes, cooled and extracted with ethyl acetate washed with water, brine, dried over anhydrous sodium sulfate, and concentrated to give 26A in good purity. 400 MHz $^1$H NMR (CDCl$_3$) δ 7.05 (t, 1H), 6.56 (m, 2H), 4.92 (s, 1H), 2.19 (s, 3H).

**Preparation of (2-fluoro-4-hydroxy-5-methylphenyl)thiocarbonitrile (Compound 26B)**

![Chemical Structure](image)

26B

The title compound was prepared in the manner analogous to Example 3A with the product from example 26A sodium thiocyanate, sodium bromide and bromine in anhydrous methanol. 400 MHz $^1$H NMR (CDCl$_3$) δ 7.35 (d, 1H), 6.67 (d, 1H), 5.41 (s, 1H), 2.22 (s, 3H).

**Preparation of methyl 2-(4-cyanothio-5-fluoro-2-methylphenoxy)acetate (Compound 26C)**

![Chemical Structure](image)
The title compound was prepared in the manner analogous to Example 3B with the product from example 26B, methyl bromoacetate, and cesium carbonate in anhydrous acetonitrile. 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.40 (d, 1H), 6.55 (d, 1H), 4.68 (s, 2H), 3.85 (s, 3H), 2.26 (s, 3H).

**Preparation of methyl 2-(5-fluoro-2-methyl-4-sulfanylphenoxy)acetate**

(Compound 26D)

The title compound was prepared in the manner analogous to Example 3C with the product from example 26C, dithiothreitol and 0.2M potassium dihydrogenphosphate in anhydrous methanol. 400 MHz $^1$H NMR (DMSO-d$_6$) $\delta$ 7.21 (d, 1H), 6.88 (d, 1H) 5.10 (s, 1H), 4.84 (s, 2H), 3.69 (s, 3H), 2.10 (s, 3H).

**Preparation of methyl 2-[5-fluoro-2-methyl-4-((4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl)]methylthio)phenoxy]acetate**

(Compound 26E)
The title compound was prepared in the manner analogous to Example 1F with the product from example 26D, 5-(chloromethyl)-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole, and cesium carbonate in 15 ml of anhydrous acetonitrile. 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.98 (d, 2H), 7.65 (d, 2H), 7.12 (d, 1H), 6.47 (d, 1H), 4.63 (s, 2H), 4.12 (s, 2H), 3.81 (s, 3H), 2.25 (s, 3H), 2.13 (s, 3H).

Preparation of 2-[5-fluoro-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl)]methylthio]phenoxo]acetic acid (Compound 26)

The title compound was prepared in the manner analogous to Example 1 with the product from example 26E, and lithium hydroxide monohydrate in tetrahydrofuran/water mixture (10:1). MS m/z 471.72(M+1).

Example 27

Synthesis of 2-[5-methoxy-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl)]methoxy]phenylthio]acetic acid (Compound 27)
Preparation of (4-hydroxy-5-methoxy-2-methylphenyl)thiocarbonitrile
(Compound 27A)

The title compound was prepared in the manner analogous to Example 6B with 2-methoxy-5-methylphenol, sodium thiocyanate, sodium bromide, and bromine in methanol. 400 MHz $^1$H NMR (DMSO-d$_6$) $\delta$ 9.78 (s, 1H), 7.20 (s, 1H), 6.82 (s, 1H), 3.79 (s, 3H), 2.32 (s, 3H).

Preparation of [5-methoxy-2-methyl-4-((4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl])methoxy)phenyl]thiocarbonitrile
(Compound 27B)
The title compound was prepared in the manner analogous to Example 1F with the product from example 27A, 5-(chloromethyl)-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole, and cesium carbonate in anhydrous acetonitrile. 400 MHz $^1$H NMR (DMSO-d$_6$) $\delta$ 8.14 (d, 2H), 7.85 (d, 2H), 7.29 (s, 1H), 7.25 (s, 1H), 5.40 (s, 2H), 3.80 (s, 3H), 2.50 (s, 3H), 2.47 (s, 3H).

**Preparation of methyl 2-[5-methoxy-2-methyl-4-(4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)methoxy)phenylthio]acetate (Compound 27C)**

The product from example 27B, and sodium sulfide in anhydrous methanol was refluxed for 2 h, then cooled and concentrated under reduced pressure. The residue was dissolved in anhydrous acetonitrile, methyl bromoacetate and cesium carbonate were added. The reaction mixture was heated at 60 °C for 2 h, then cooled and filtered through Celite®, concentrated, purified using normal phase chromatography. 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.04 (d, 2H), 7.70 (d, 2H), 7.08 (s, 1H), 6.82 (s, 1H), 5.23 (s, 2H), 3.88 (s, 3H), 3.70 (s, 3H), 3.52 (s, 2H), 2.50 (s, 3H), 2.39 (s, 3H). MS m/z 498 (M+1).
Preparation of 2-[5-methoxy-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)]phenyl)[1,3-thiazol-5-yl)]methoxy]phenylthio]acetic acid (Compound 27)

The title compound was prepared in the manner analogous to Example 1 with the product from example 27C, and lithium hydroxide monohydrate in tetrahydrofuran/water mixture (10:1). MS m/z 483.87 (M+1).

Example 28

Synthesis of 2,2-difluoro-2-[5-methoxy-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)]phenyl)[1,3-thiazol-5-yl)]methoxy]phenylthio]acetic acid (Compound 28)

Preparation of 5-Methoxy-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzene disulfide (compound 28A)
The title compound was prepared from compound 27B and 0.2 M potassium dihydrogenphosphate in methanol in the manner analogous to Example 3C. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 8.13 (d, 4H), 7.88 (d, 4H), 7.10 (s, 2H), 6.98 (s, 2H), 5.38 (s, 4H), 3.70 (s, 6H), 2.50 (s, 6H), 2.25 (s, 6H).

Preparation of ethyl 2,2-difluoro-2-[5-methoxy-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl)]methoxy)phenylthio]acetate (Compound 28B)

![Chemical Structure](attachment:image.png)

28B

The mixture of the product from example 28A, triphenylphospine, HCl in water and dioxane was heated at 60 °C for 12 h, then cooled to room temperature and concentrated in vacuo. The residue was dissolved in anhydrous acetonitrile, ethyl 2-bromo-2,2-difluoroacetate and cesium carbonate were added. The reaction mixture was stirred at room temperature for 2 h, then filtered through Celite®. The filtrate was concentrated, and purified using normal phase chromatography to afford the title product. 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.03 (d, 2H), 7.68 (d, 2H), 7.15 (s, 1H), 6.90 (s, 1H), 5.29 (s, 2H), 4.25 (q, 2H), 3.88 (s, 3H), 2.55 (s, 3H), 2.44 (s, 3H), 1.29 (t, 3H).
Preparation of 2,2-difluoro-2-[5-methoxy-2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl)]methoxy)phenylthio]acetic acid (Compound 28)

The product from example 28B was dissolved in a mixture of methanol and water, then treated with sodium hydroxide. After stirring at 70 °C for 1 h, the reaction mixture was cooled to room temperature, and acidified to pH 3 with 1 N HCl. The white precipitate was collected by filtration, washed subsequently with water and hexanes, and dried in vacuo to afford the title product. MS m/z 520 (M+1).

Example 29

Synthesis of 1-[3-Methoxy-4-[4-methyl-2(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]benzyl]pyrrolidine-2-carboxylic acid (Compound 29)

Preparation of Dimethylthiocarbamic acid O- (4-formyl-2methoxyphenyl) ester (compound 29A)
To a solution of vanillin in Dioxane, under nitrogen atmosphere, was added dimethylthiocarbonyl chloride, triethylamine, and DMAP. The resulting mixture was warmed to reflux and refluxed 16h, then diluted with water and extracted with EtOAc. The combined extracts were washed with water and brine, and the organic phase dried over sodium sulfate then concentrated. The residue was purified by recrystallization in MeOH and water to give 29A as a white solid. (mp 126-127°C) Analyzed for C13H15NO2: Calc: C, 55.21%; H, 5.48%; N, 5.85%; Found: C, 55.17%; H, 5.42%; N, 5.92%.

Preparation of 4-Mecapto-3-methoxybenzaldehyde (compound 29B)

![Chemical Structure](image)

Compound 29A was heated to 230-240°C under nitrogen atmosphere for 1h, then cooled to room temperature. The residue was dissolved in methano, placed under nitrogen atmosphere, and solution of 50% aqueous sodium hydroxide in water was added. The resulting mixture was refluxed for 16h, cooled to room temperature, acidified with 2N HCL and extracted with EtOAc. The combined extracts were washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, 10% EtOAc/Hexane) to give 29B as a yellow oil. NMR (400MHz, CDCl3) δ 3.96 (s, 3H), 4.16 (s, 1H), 7.32-7.40 (m, 3H), 9.87 (s, 1H). MS: (m+1) 169.
Preparation of 3-Methoxy-4-[4-methyl-2-(4-trifluoromethyl)phenyl]thiazol-5-ylmethylsulfanyl]benzaldehyde (compound 29C)

![Formula Image]

To a solution of 29B in acetonitrile, under nitrogen atmosphere, was added 5-chloromethyl-4-methyl-2-(4-trifluoromethyl)phenyl]thiazole followed by cesium carbonate. The resulting mixture was stirred 16h, diluted with water. The precipitate was collected by filtration, dried, dissolved in ethyl ether, and filtered. The filtrate was concentrated under vacuum and the residue purified by flash chromatography (silica gel, 20% EtOAc/Hexane to give 29C as a yellow solid. NMR (400Mhz, CDCl₃) δ 2.55 (s, 3H), 3.92 (s, 3H), 4.74 (s, 2H), 7.46-7.50 (m, 1H), 7.68-7.72 (m, 3H), 8.08-8.11 (m, 2H), 8.20-8.23 (m, 1H), 9.89 (s, 1H). MS: (m+1) 424.

Preparation of 1-[3-Methoxy-4-[4-methyl-2-(4-trifluoromethyl)phenyl]thiazol-5-ylmethylsulfanyl]benzyl]pyrrolidine-2-carboxylic acid methyl ester (compound 29D)

![Formula Image]
To a solution of 29C in THF and N,N’-dimethylethyleneurea under nitrogen atmosphere was added DL-methylproline hydrochloride. The resulting mixture was stirred until clear, then glacial acetic acid was added dropwise followed by sodium triacetoxborohydride in small portions over 30 min. The reaction mixture was stirred 16h, quenched with water, and extracted with EtOAc. The combined extracts were washed with brine. The organic phase was dried over magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, 20% EtOAc/Hexane) to give 29D as a yellow solid. NMR (400Mhz, CDCl3) δ 2.03-2.20 (m, 2H), 2.22- 2.40 (m, 2H) 2.51 (s, 3H), 2.62-2.80 (m, 1H) 3.38-3.45 (m, 1H) 3.79 (s, 3H), 4.02-4.18 (m, 2H) 4.80 (s, 2H), 6.68-6.71 (m, 1/2H), 6.88-6.91 (m, 1/2H), 7.18 (d, J = 7Hz, 1/2H), 7.43 (d, J = 7Hz, 1/2H) 7.63-7.69 (m, 3H), 8.00 (d, J = 4.2Hz). MS: (m+1) 537.

Preparation of 1-[3-Methoxy-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]benzyl]pyrroolidine-2-carboxylic acid (Compound 29)

To a solution of 29D in methanol was added lithium hydroxide monohydrate. The resulting mixture was warmed to reflux and refluxed for 16h, then neutralized with 1N aqueous HCl and diluted with water. The precipitate was collected, air dried, then triturated in EtOAc to give 29 as a white solid. MS: (m+1) 523.

Example 30

Synthesis of ((2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy)-phenyl-acetic acid (Compound 30)
Preparation of 4-thiocyanato-2-methyl-phenol (compound 30A)

\[
\text{OH} \\
\text{NCS} \\
\text{30A}
\]

5

The title compound was prepared in a manner analogous to compound 3A.

400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 10.1 (s, 1H), 7.36 (s, 1H), 7.30 (d, 1H, $J=8.1$ Hz), 6.77 (d, 1H, $J=8.1$ Hz), 2.08 (s, 3H).

Preparation of (4-thiocyanato-2-methyl-phenoxy)-phenyl-acetic acid ethyl ester
(Compound 30B)

\[
\text{30B}
\]

15

The title compound was prepared in a manner analogous to compound 3B by reacting copound 30A with bromo-phenyl-acetic acid ethyl ester. MS: (m+1) 328.

Preparation of (4-Mercapto-2-methyl-phenoxy)-phenyl-acetic acid ethyl ester
(Compound 30C)

\[
\text{30C}
\]

25

The title compound was prepared in a manner analogous to compound 3C. 400 MHz $^1$H NMR (DMSO-$d_6$) $\delta$ 7.51 (d, 2H, $J=8.5$ Hz), 7.35 (m, 3H), 7.07 (s, 1H), 6.99 (d, 1H, $J=10.5$ Hz), 6.76 (d, 1H, $J=10.5$ Hz), 5.90 (s, 1H), 5.03 (s, 1H), 4.04 (m, 2H), 2.15 (s, 3H), 1.04 (t, 3H, $J=7.3$ Hz).
Preparation of [2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-phenyl-acetic acid ethyl ester (Compound 30D)

The title compound was prepared in a manner analogous to compound 1F, using compound 30C and 1B. MS: (m+1) 558.

Preparation of ([2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-phenyl-acetic acid (Compound 30)

30D was saponified in the same manner as described for compound 1F to give, after recrystallisation from CHCl3/hexanes, the title compound as a solid. m/z = 530 (M+1).

Example 31

Synthesis of [5-Chloro-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 31)
Preparation of 5-Chloro-2-methyl-4-thiocyanato-phenol (compound 31A)

31A

5

The title compound was prepared from 5-chloro-2-methyl-phenol in a manner analogous to compound 3A. MS m/z 199 (M+).

Preparation of (5-chloro-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (Compound 31B)

31B

10

The title compound was prepared from compound 31A in a manner analogous to compound 3B. MS m/z 245 (M-CN).

Preparation of (5-chloro-4-mercapto-2-methyl-phenoxy)-acetic acid methyl ester (Compound 31C)

31C

20

The title compound was prepared from compound 31B in a manner analogous to compound 3C. MS m/z 245 (M-1).
Preparation of [5-Chloro-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid methyl ester (Compound 31D)

31C and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (compound 1B) were coupled in a similar manner as described for compound 1F to provide, after purification by flash column chromatography (gradient elution: 5% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound as a yellow solid. MS m/z 502 (M+1).

Preparation of [5-Chloro-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-acetic acid (Compound 31)

31D was saponified in the same manner as described for compound 1F to give, after recrystallisation from CHCl₃/hexanes, the title compound as a solid. MS m/z 488 (M+1).

- 105 -
Example 32

Synthesis of 2-{5-(methoxymethyl)-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl)]methylthio]phenoxy}acetic acid (Compound 32)

Preparation of 5-(hydroxymethyl)-2-methylphenol (Compound 32A)

To 3-hydroxy-4-methylbenzoic acid in THF was added borane/THF complex (1.0 M solution) slowly at 0 °C under nitrogen. After completion of addition, the mixture was allowed to warm to room temperature, then heated at 70 °C for 2 h, cooled to room temperature again, 1 N HCl (150 ml) was added slowly and stirred at room temperature. The reaction mixture was concentrated in vacuo, then ethyl acetate was added, washed with brine, dried over sodium sulfate, and concentrated to give 32A in good purity. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 9.19 (s, 1H), 6.98 (d, 1H), 6.77 (s, 1H), 6.62 (d, 1H), 5.03 (t, 1H), 4.39 (d, 2H), 2.08 (s, 3H).
Preparation of 5-(methoxymethyl)-2-methylphenol (Compound 32B)

![Chemical Structure of 32B]

5

To a stirred solution of 32A in methanol was added concentrated sulfuric acid slowly at room temperature. The mixture was refluxed overnight. After cooling, pH was adjusted to 3 ~ 4 with 2 N sodium hydroxide and concentrated, then ethyl acetate was added, washed with brine, dried over sodium sulfate, and concentrated to give 32B in good purity. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 9.23 (burs, 1H), 7.00 (d, 1H), 6.76 (s, 1H), 6.62 (d, 1H), 4.29 (s, 2H), 3.23 (s, 3H), 2.10 (s, 3H).

Preparation of 5-Methoxymethyl-2-methyl-4-thiocyanato-phenol (Compound 32C)

![Chemical Structure of 32C]

15

To a stirred solution of the product from example 32B, sodium thiocyanate, and sodium bromide in methanol at 0 °C was added a solution of bromine in methanol dropwise. After the completion of the bromine addition, the reaction mixture was stirred at room temperature for 1 h, then concentrated in vacuo. The resulting residue was taken up in ethyl acetate, washed with saturated sodium bicarbonate solution, brine, dried over sodium sulfate, concentrated, and purified using normal phase
chromatography to afford the title product. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 10.18 (brs, 1H), 7.46 (s, 1H), 6.99 (s, 1H), 4.48 (s, 2H), 3.32 (s, 3H), 2.17 (s, 3H).

**Preparation of (5-Methoxymethyl-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (Compound 32D)**

![Chemical Structure 32D]

The mixture of the product from example 32C, methyl bromoacetate, and cesium carbonate in anhydrous acetonitrile was heated at 60 °C for 2 h. After cooling, the reaction mixture was filtered through Celite®. The filtrate was diluted with diethyl ether, washed with brine, dried over sodium sulfate, and concentrated to give 32D. 400 MHz $^1$H NMR (DMSO-$d_6$) δ 7.58 (s, 1H), 7.06 (s, 1H), 4.96 (s, 2H), 4.50 (s, 2H), 3.74 (s, 3H), 3.32 (s, 3H), 2.22 (s, 3H).

**Preparation of methyl 2-[5-(methoxymethyl)-2-methyl-4-sulfanylphenoxy]acetate (Compound 32E)**

![Chemical Structure 32E]
A solution of the product from example 32D, dithiothreitol, and 0.2 M potassium dihydrogenphosphate in methanol was refluxed for 1 h under nitrogen, then cooled and concentrated in vacuo. The resulting residue was taken up in diethyl ether, and washed with brine, dried over sodium sulfate, concentrated, and purified using normal phase chromatography to afford the title product. 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.17 (s, 1H), 6.75 (s, 1H), 4.63 (s, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.45 (s, 1H), 3.40 (s, 3H), 2.22 (s, 3H).

Preparation of methyl 2-[5-(methoxymethyl)-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl))methylthio]phenoxy]acetate (Compound 32F)

![Chemical Structure of 32F]

Compound 32E was dissolved in anhydrous acetonitrile, then 5-(chloromethyl)-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole was added followed by cesium carbonate. The mixture was stirred at room temperature for 2 h, then filtered through Celite®, concentrated, and purified using normal phase chromatography to afford the title product. 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.98 (d, 2H), 7.65 (d, 2H), 7.21 (s, 1H), 6.80 (s, 1H), 4.69 (s, 2H), 4.48 (s, 2H), 4.11 (s, 2H), 3.80 (s, 3H), 3.37 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H).
Preparation of 2-[5-(methoxymethyl)-2-methyl-4-[[4-methyl-2-[4-(trifluoromethyl)phenyl][1,3-thiazol-5-yl)]methylthio]phenoxy]acetic acid (Compound 32)

The title compound was prepared in the manner analogous to Example 1 with the product from example 32F and lithium hydroxide monohydrate) in THF and water. MS m/z 498 (M+1).

Example 33

Synthesis of (4-[[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-cyclohexyl)-acetic acid (Compound 33):

Preparation of [4-(4-Chlorosulfonyl-phenyl)-cyclohexyl]-acetic acid ethyl ester (compound 33A):

Compound 33A was prepared as follows. Chlorosulfonic acid was cooled to 0 °C. Then (4-Phenyl-cyclohexyl)-acetic acid ethyl ester was added over 30 min. The
mixture was stirred at RT for 3h and was poured into ice (100g). The cloudy solution was extracted with ether (2x50mL). The extracts were dried with magnesium sulfate and concentrated to give a brown oil which was passed through a short pad of silica gel to afford the desired product. MS 345 (M+1)⁺

Preparation of [4-(4-Mercapto-phenyl)-cyclohexyl]-acetic acid methyl ester (Compound 33B):

![Chemical Structure](image)

33B

Compound 33A was refluxed with tin powder in MeOH and 4M HCl/dioxane. After 3h, the reaction mixture was poured into ice with CH₂Cl₂. The phases were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with magnesium sulfate, filtered and evaporated to give the crude thiol. The ethyl ester was completely transesterified to the methyl ester. MS 263 (M-1)⁺

Preparation of (4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl)-cyclohexyl]-acetic acid methyl ester (Compound 33C):

![Chemical Structure](image)

33C

Compound 33B (crude mixture from above) was dissolved in acetonitrile with chloride 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole and Cs₂CO₃.
The reaction mixture was stirred at RT overnight. Ether and water were added and stirring was continued for another 5 min. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over MgSO₄ and concentrated to an oil. The crude product was purified by column chromatography eluted with EtOAc and hexanes to give the desired product. MS 520 (M+1)⁺

**Preparation of (4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-cyclohexyl)-acetic acid (Compound 33):**

To a solution of 33C in MeOH and THF was added LiOH.H₂O. After refluxing overnight, the solution was cooled to RT and solvents were removed. The residue was dissolved in water and neutralized with 1N HCl. The cloudy solution was extracted with EtOAc and the extracts were dried with MgSO₄ and concentrated. The crude product was purified by chromatography to afford the desired product. MS 506 (M+1)⁺

**BIOLOGICAL ASSAYS**

The compounds of the present invention have demonstrated PPAR modulating activity in the standard assays commonly employed by those skilled in the art. Accordingly, such compounds and formulations comprising such compounds are useful for treating, preventing or controlling hypercholesterolemia and hyperlipidemia.

**A. Selectivity Measurements**

**1. Test A. Transient transfections assay using the HepG2 hepatoma cell line.**

HepG2 cells were transiently transfected with an expression plasmids encoding hPPARα, hPPARβ or mPPARγ chimeric receptors and a reporter
containing the yeast upstream activating sequence (UAS) upstream of the viral E1B promoter controlling a luciferase reporter gene. In addition, the plasmid pRSVβ-gal was used to control for transfection efficiency. HepG2 cells were grown in DMEM supplemented with 10% FBS and 1μM non-essential amino acid. On the first day, cells were split into 100mm dishes at 2.5x10⁶/dish and incubated overnight at 37°C/5% CO₂. On the second day the cells were transiently transfected with plasmid DNA encoding a chimeric receptor, the luciferase reporter gene; and β-gal. For each 100 mm dish, 15μg of lucifase reporter (PG5E1b) DNA, 15μg of Gal4-PPAR chimeric receptor DNA, and 1.5μg of β-gal plasmid DNA were mixed with 1.4ml of opti-MEM in the tube. 28μl of LipoFectamine-2000 reagent was added to 1.4ml of opti-MEM in the tube, and incubate for 5 min at RT. The diluted LipoFectamine-2000 reagent was combined with the DNA mixture, and incubate for 20 min at RT. After fresh medium was added to each100mm dish of cells, 2.8ml of Lipofectamine2000-DNA mixture was added dropwise to the 100mm dish containing 14ml of medium, and incubate 37°C overnight. On day three cells were trypsinized off the 100 mm dishes and re-plated on 96 well plates. Cells were plated at 2.5x10⁴ cells per well in 150μl of media and 50μl of compound diluted by media was added. The test compounds added were in the range of 50μM to 50pM. After addition of compounds, the plates were incubated at 37°C for 24 hours. Subsequently cells were washed with once with 100μl of PBS, lysed, and processed for measuring luciferase and β-gal activity using Dual-Light luciferase kit from Tropix®, according to the manufacturer’s recommendations, on an EG&G Bethesda MicroLumat LB96P luminometer. EC₅₀ values were obtained using the GraphPad Prism™ program. Surprisingly, the compounds of the present invention exhibit activity for both PPARα and PPARβ. Accordingly, the compounds of the present invention should find considerable therapeutic applications for hypercholesterolemia and hyperlipidemia. The Hep G2-hBeta EC₅₀ ("EC₅₀,β") data as well as the Hep G2-hAlpha EC₅₀ ("EC₅₀,α") data of the compounds of the invention are presented in Table 2 below.
Table 2

<table>
<thead>
<tr>
<th>Example</th>
<th>EC50-β nM</th>
<th>EC50-α nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.4</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>361.3</td>
<td>1227.5</td>
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<td>3</td>
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<td>538</td>
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<td>4</td>
<td>23.4</td>
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<td>2.3</td>
<td>121</td>
</tr>
<tr>
<td>6</td>
<td>1235.0</td>
<td>1391</td>
</tr>
<tr>
<td>7</td>
<td>472.5</td>
<td>1338</td>
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<td>8</td>
<td>45.3</td>
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<td>891.3</td>
<td>5751.5</td>
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<tr>
<td>10</td>
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<td>-</td>
</tr>
<tr>
<td>11</td>
<td>48.8</td>
<td>507.3</td>
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<td>-</td>
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<td>21</td>
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<td>442</td>
</tr>
<tr>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2 Continued

<table>
<thead>
<tr>
<th>Example</th>
<th>EC50-β nM</th>
<th>EC50-α nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>2000000</td>
<td>2000000</td>
</tr>
<tr>
<td>25</td>
<td>2000000</td>
<td>-</td>
</tr>
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<td>26</td>
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<td>27</td>
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<tr>
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<td>-</td>
</tr>
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<td>31</td>
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<tr>
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<td>625.1</td>
</tr>
<tr>
<td>33</td>
<td>2000000</td>
<td>-</td>
</tr>
</tbody>
</table>

B. Effect of PPAR-beta compounds on lipid and human apoprotein A1 concentrations in the hApoA1 transgenic mouse

Mice, transgenic for human apoA1, were purchased from Jackson laboratories. All animals were allowed normal chow (Ralston-Purina) and water ad libitum in temperature controlled rooms, under a 12-h light, 12-h dark cycle beginning with lights on at 6 AM. During the treatment phase of the study the mice were dosed daily between 6 and 9 AM by oral gavage using a suspension vehicle of 1.5% carboxymethylcellulose plus 0.2 percent Tween-20 (CMC/Tween) containing the specified compounds. Control animals received vehicle alone. Vehicle volume represented 0.25 percent of body weight. Under anesthesia, tail blood was obtained weekly in the morning at the indicated days of study. At termination, tissue samples (liver, intestine, fat, and muscle) were taken to study effects on genes effecting lipid metabolism. Each of the compounds of the present invention that were tested effected a significant increase in HDL over the values observe for the control animals. Furthermore, these compounds resulted in triglyceride levels which were lower than
observed in controls. The compounds of the present invention exhibited a 61 to 123 mg/dL increase in HDL compared to a 44 mg/dL increase for the controls at the end of the study (day 16). Similarly, compounds of the present invention exhibited an increase on average for the HDL to (LDL + VLDL) ratio. This ratio was 14 to 18.3 at the beginning of the study. At the end of the study this ratio was found to be from 11.9 to 83.9. (Controls dropped from 15.5 to 11.9)

FORMULATIONS

The compounds of the present invention can be administered alone or in combination with one or more therapeutic agents. These include, for example, other agents for treating, preventing or controlling hypercholesteremia, hyperlipidemia, obesity, hyperglycemia, hypercholesteremia, hyperlipidemia, atherosclerosis, hypertriglyceridemia, and hyperinsulinemia.

The compounds are thus well suited to formulation for convenient administration to mammals for the prevention and treatment of such disorders.

The following examples further illustrate typical formulations provided by the invention.

**Formulation 1**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of Formulas I-V</td>
<td>0.5 to 800 mg</td>
</tr>
<tr>
<td>sodium benzoate</td>
<td>5 mg</td>
</tr>
<tr>
<td>isotonic saline</td>
<td>1000 mL</td>
</tr>
</tbody>
</table>

The above ingredients are mixed and dissolved in the saline for IV administration to a patient.
Formulation 2

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of Formulas I-V</td>
<td>0.5 to 800 mg</td>
</tr>
<tr>
<td>cellulose, microcrystalline</td>
<td>400 mg</td>
</tr>
<tr>
<td>stearic acid</td>
<td>5 mg</td>
</tr>
<tr>
<td>silicon dioxide</td>
<td>10 mg</td>
</tr>
<tr>
<td>sugar, confectionery</td>
<td>50 mg</td>
</tr>
</tbody>
</table>

The ingredients are blended to uniformity and pressed into a tablet that is well suited for oral administration to a patient.

Formulation 3

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of Formulas I-V</td>
<td>0.5 to 800 mg</td>
</tr>
<tr>
<td>starch, dried</td>
<td>250 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

The ingredients are combined and milled to afford material suitable for filling hard gelatin capsules administered to a patient.

Formulation 4

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>% wt./(total wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of Formulas I-V</td>
<td>1 to 50</td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol 1000</td>
<td>32 to 75</td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol 4000</td>
<td>16 to 25</td>
<td></td>
</tr>
</tbody>
</table>

The ingredients are combined via melting and then poured into molds containing 2.5 g total weight.
While embodiments of the invention have been illustrated and described, it is not intended that these embodiments illustrate and describe all possible forms of the invention. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from the spirit and scope of the invention.
What is claimed is:

1. A compound having Formula I:

\[
\begin{align*}
\text{W} & \quad \text{O, S, CR}^5\text{R}^6, -(\text{CH}_2)_p\text{-cycloalkylene, or -(CH}_2)_p\text{-heterocycloalkylene;} \\
\text{X}^0 \text{ and } \text{X}^1 & \text{ are independently O or S;} \\
\text{Ar}^1 & \text{ is a unsubstituted or substituted aryl or heteroaryl;} \\
\text{R}^1, \text{R}^2, \text{R}^3, \text{ and R}^4 & \text{ are independently alkyl, lower alkoxy, haloalkyl, -O-(CH}_2)_p\text{CF}_3, \text{ halogen, nitro, cyano, -OH, -SH, -CF}_3, -\text{S(O)}_p\text{alkyl, S(O)}_p\text{aryl, -} \\
(\text{CH}_2)_m\text{OR}^7, -(\text{CH}_2)_m\text{NR}^8\text{R}^9, -\text{COR}^7, -\text{CO}_2\text{H, -CO}_2\text{R}^7, \text{ or -NR}^8\text{R}^9; \\
\text{R}^5 \text{ and R}^6 & \text{ are independently hydrogen, alkyl, alkenyl, alkynyl, or aryl, or joined together to form a 3 to 7 member cycloalkyl or cycloalkenyl;} \\
\text{R}^7 & \text{ is independently hydrogen, alkyl, alkenyl, alkynyl, or aryl;}
\end{align*}
\]
R^8 and R^9 are each independently hydrogen, alkyl, alkenyl, alkynyl, -COalkyl, -COaryl, cycloalkyl, -CO_2alkyl, -CO_2aryl, -SO_2alkyl, -SO_2aryl, or joined together to form a 4 to 7 member ring having 1 to 3 heteroatoms; R^{10} and R^{11} are independently hydrogen, halo, aryl, or hereroaryl;

m is 0 to 5;

n is 0 to 5; and

p is 0 to 2;

with the following provisos:

that when W is O, n = 1, and R^1 is hydrogen, R^2 and R^4 are not hydrogen or R^2 and R^3 are not hydrogen;

that when W is O, n = 1, and R^2 is hydrogen, R^1 and R^3 are not hydrogen or R^1 and R^4 are not hydrogen;

that when W is O, n = 1, and R^3 is hydrogen, R^1 and R^4 are not hydrogen or R^2 and R^4 are not hydrogen; and

that when W is O, n = 1, and R^4 is hydrogen, R^1 and R^3 are not hydrogen or R^2 and R^3 are not hydrogen.

2. A compound of claim 1, wherein W is O, Ar^1 is 4-trifluoromethylphenyl, and n is 1.

3. A compound of claim 1, wherein W is O;

X^0 and X^1 are S;

Ar^1 is 4-trifluoromethylphenyl;

R^1, R^2, R^3, and R^4 are hydrogen, lower alkyl, lower alkoxy, -(CH_2)_mNR^8R^9, or -(CH_2)_mOR^7;

R^7 is alkyl;

R^8 and R^9 are independently hydrogen, alkyl, or -COalkyl;

R^{10} and R^{11} are hydrogen;
m is 0 to 5; and
n is 1.

4. A compound of claim 1, wherein

W is CR^5R^6, -(CH_2)_p-cycloalkylene, or -(CH_2)_p-heterocycloalkylene;
X^0 and X^1 are independently O or S;
Ar^1 is unsubstituted or substituted aryl or heteroaryl;
R^1, R^2, R^3, and R^4 are hydrogen, lower alkyl, lower alkoxy, haloalkyl, -O-(CH_2)_pCF_3, halogen, nitro, cyano, -OH, -SH, -CF_3, -S(O)Palkyl, S(O)paryl, -

(CH_2)_mOR^7, -(CH_2)_mNR^8R^9, -COR^7, -COO_R, -CO_2R^7, or -NR^8R^9;

R^5 and R^6 are joined together to form a 3 to 7 member cycloalkyl or
cycloalkenyl;
R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, or aryl;
R^8 and R^9 are independently hydrogen, alkyl, alkenyl, alkynyl, -COalkyl, -

COaryl, cycloalkyl, -CO_2alkyl, -CO_2aryl, -SO_2alkyl, -SO_2aryl, or joined together to
form a 4 to 7 member ring having 1 to 3 heteroatoms;
m is 0 to 5;
n is 0 to 5; and
p is 0 to 2.

5. A compound of claim 4, wherein

W is CR^5R^6, cycloalkylene or -(CH_2)-heterocycloalkylene;
X^0 and X^1 are S;
Ar^1 is 4-trifluoromethylphenyl;
R^1, R^2, R^3, and R^4 are hydrogen, lower alkyl, lower alkoxy, halogen, -CF_3, -

(CH_2)_mOR^7, or -(CH_2)_mNR^8R^9;

R^5 and R^6 are joined together to form a 3 to 7 member cycloalkyl ring;
R^7 is hydrogen, or alkyl;
R^8 and R^9 are independently hydrogen, alkyl, or -COalkyl;
m is 0 to 5; and
n is 0.

6. A compound of claim 4, wherein

5

\( \text{W is} \)

\[ \text{X}^0 \text{ and } \text{X}^1 \text{ are S;} \]
\( \text{Ar}^1 \text{ is 4-trifluoromethylphenyl;} \)
\( \text{R}^1, \text{R}^2, \text{R}^3, \text{and } \text{R}^4 \text{ are hydrogen, lower alkyl, lower alkoxy, halogen, -CF}_3, -\)

10 \( \text{(CH}_2)_n\text{OR}^7, \text{ or } \text{(CH}_2)_m\text{NR}^8\text{R}^9; \)
\( \text{R}^7 \text{ is independently hydrogen, or lower alkyl;} \)
\( \text{R}^8 \text{ and } \text{R}^9 \text{ are each independently hydrogen, or lower alkyl;} \)
\( m \text{ is 0 to 5; and} \)
\( n \text{ is 0.} \)

7. A compound of claim 1 or 4, wherein:
\( \text{R}^2 \text{ and } \text{R}^3 \text{ are hydrogen; and} \)
\( \text{R}^1 \text{ and } \text{R}^4 \text{ are lower alkyl or lower alkoxy.} \)

8. A compound of claim 1 or 4, wherein:
\( \text{R}^2 \text{ and } \text{R}^3 \text{ are hydrogen;} \)
\( \text{R}^1 \text{ is alkyl; and} \)
\( \text{R}^4 \text{ is alkoxy.} \)

9. A compound of claim 1 or 4, wherein:
\( \text{R}^2 \text{ and } \text{R}^3 \text{ are hydrogen;} \)
\( \text{R}^1 \text{ is methyl, ethyl, isopropyl, n-propyl, t-butyl, n-butyl, or isobutyl; and} \)
R is methoxy, ethoxy, isopropoxy, n-propoxy, t-butoxy, n-butoxy, or isobutoxy.

10. A compound selected from the group:

5  {2,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{5-Ethyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{5-Isopropyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{2,6-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{5-Methoxy-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{2-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{3,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{3-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{2-Isopropyl-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid
{2,6-Diisopropyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenoxy]-acetic acid;
{2-Methyl-2-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenyl}-propionic acid;
{2-[4-[Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-y]methylsulfanyl]-phenyl}-cyclopropanecarboxylic acid;
1-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclopropanecarboxylic acid;
1-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclopentanecarboxylic acid;

4-Methyl-4-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyIsulfanyl]-phenyl]-pentanoic acid;
3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy]-propionic acid;
2-[3-Methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-2-methyl-propionic acid;
3-Methyl-3-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-butyric acid;
3-[2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid;

3-[2,5-Dimethoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-propionic acid;
{2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl] acetic acid;
3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid;
3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid;
3-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl]-2-pyrrol-1-yl-propionic acid;

2-[5-(acetylamino)-2-methyl-4-((4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl))methylthio)phenoxy]acetic acid;
2-[5-fluoro-2-methyl-4-((4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl))methylthio)phenoxy]acetic acid;
2-[(5-methoxy-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)]methoxy)phenylthio)acetic acid;
2,2-difluoro-2-[(5-methoxy-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)]methoxy)phenylthio)acetic acid;
1-[(3-Methoxy-4-[4-methyl-2(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]benzyl)pyrrolidine-2-carboxylic acid;
(2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy)-phenyl-acetic acid;
{5-Chloro-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid;
2-[5-(methoxymethyl)-2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)]methylthio)phenoxy]acetic acid;
(4-[(4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}cyclohexyl)-acetic acid; and

pharmacologically acceptable salts thereof.

11. A pharmaceutical composition comprising a compound of claim 1, 4, or 10 and one or more pharmacologically acceptable carriers, diluents, or excipients.

12. A method of treating, preventing or controlling hyperlipidemia in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of claim 1, 4, or 10.

13. A method of treating, preventing or controlling hypercholesteremia in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of claim 1, 4, or 10.
14. A method of treating, preventing or controlling atherosclerosis in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of claim 1, 4, or 10.

5 15. A method of making a compound having Formula I:

![Chemical Structure](image)

the method comprising, reacting:

![Chemical Structure](image)

with:
wherein:

- W is O, S, CR\textsuperscript{5}R\textsuperscript{6}, -(CH\textsubscript{2})\textsubscript{p}cycloalkylene, or -(CH\textsubscript{2})\textsubscript{p}heterocycloalkylene;
- \(X^0\) and \(X^1\) are independently O or S;
- \(\text{Ar}^1\) is a unsubstituted or substituted aryl or heteroaryl;
- \(R^1\), \(R^2\), \(R^3\), and \(R^4\) are independently alkyl, lower alkoxy, haloalkyl, O-(CH\textsubscript{2})\textsubscript{p}CF\textsubscript{3}, halogen, nitro, cyano, -OH, -SH, -CF\textsubscript{3}, -S(O)\textsubscript{p}alkyl, S(O)\textsubscript{p}aryl, -(CH\textsubscript{2})\textsubscript{m}OR\textsuperscript{7}, -(CH\textsubscript{2})\textsubscript{m}NR\textsuperscript{8}R\textsuperscript{9}, -COR\textsuperscript{7}, -CO\textsubscript{2}H, -CO\textsubscript{2}R\textsuperscript{7}, or -NR\textsuperscript{8}R\textsuperscript{9};
- \(R^5\) and \(R^6\) are independently hydrogen, alkyl, alkenyl, alkynyl, or aryl, or joined together to form a 3 to 7 member cycloalkyl or cycloalkenyl;
- \(R^7\) is independently hydrogen, alkyl, alkenyl, alkynyl, or aryl;
- \(R^8\) and \(R^9\) are each independently hydrogen, alkyl, alkenyl, alkynyl, -COalkyl, -COaryl, cycloalkyl, -CO\textsubscript{2}alkyl, -CO\textsubscript{2}aryl, -SO\textsubscript{2}alkyl, -SO\textsubscript{2}aryl, or joined together to form a 4 to 7 member ring having 1 to 3 heteroatoms;
- \(R^{12}\) is a lower alkyl;
- \(X\) is a halogen;
- \(m\) is 0 to 5;
- \(n\) is 0 to 5; and
- \(p\) is 0 to 2;

with the following provisos:

that when W is O, \(n = 1\), \(Y\) is absent, and \(R^1\) is hydrogen, \(R^2\) and \(R^4\) are not hydrogen or \(R^2\) and \(R^3\) are not hydrogen;

that when W is O, \(n = 1\), \(Y\) is absent, and \(R^2\) is hydrogen, \(R^1\) and \(R^3\) are not hydrogen or \(R^1\) and \(R^4\) are not hydrogen;
that when $W$ is $O$, $n = 1$, $Y$ is absent, and $R^3$ is hydrogen, $R^1$ and $R^4$ are not hydrogen or $R^2$ and $R^4$ are not hydrogen; and

that when $W$ is $O$, $n = 1$, $Y$ is absent, and $R^4$ is hydrogen, $R^1$ and $R^3$ are not hydrogen or $R^2$ and $R^3$ are not hydrogen.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

- IPC 7 C07D A61K

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

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

- EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 02 50047 A (SIERRA MICHAEL LAWRENCE; GLAXO GROUP LTD (GB)) 27 June 2002 (2002-06-27) the whole document ---</td>
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</table>

**X** Further documents are listed in the continuation of box C.  
**X** Patent family members are listed in annex.

**A** document defining the general state of the art which is not considered to be of particular relevance

**E** earlier document but published on or after the international filing date

**L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

**&** document member of the same patent family

Date of the actual completion of the international search

| 30 April 2003 |

Date of mailing of the international search report

| 09/05/2003 |

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL--2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016

Authorized officer

Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)
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<td>WO 01 00603 A (SIERRA MICHAEL LAWRENCE; GELLIBERT FRANCOISE JEANNE (FR); GLAXO GR) 4 January 2001 (2001-01-04)</td>
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INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 12-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:  
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   Although the definition of R1-R4 in claim 1 does not include H, this is considered to be an error, given the definitions in the description and the dependent claims and provisos, and thus the possibility of H for R1-R4 has been searched.

3. [ ] Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
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<td>01-11-2001</td>
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<td>19-04-1999</td>
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