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(54) **Title:** THIAZOLE AND OXAZOLE DERIVATIVES WHICH MODULATE PPAR ACTIVITY

(57) **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 hypercholesteremia 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 hypoglygemic 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.

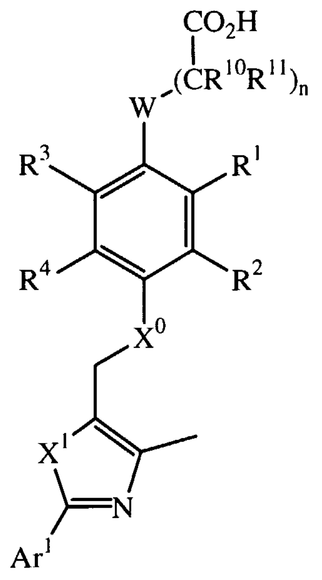
PPAR γ is associated with the development of non-insulin-dependent diabetes mellitus (NIDDM), hypertension, coronary artery disease, hyperlipidemia and certain malignancies. Finally, activation of PPAR β has been demonstrated to increase HDL levels. (Leibowitz, WO97/28149, Aug. 1997.) More recently, 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)

Antilipidemic and antidiabetic agents are still considered to have non-uniform effectiveness. The effectivieness of antidiabetic and antilipidemic 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 hepatoxicity. 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 antilipidemic 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:



I

or a pharmaceutically acceptable salt thereof,

where:

W is O, S, 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 a 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)$_p$alkyl, S(O)$_p$aryl, -$(CH_2)_mOR^7$, -$(CH_2)_mNR^8R^9$, -COR^7, -CO_2H, -CO_2R^7, or –NR^8R^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_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.

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 hypercholesteremia 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, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-OCF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NH_2$, $-NHC_1$-C_6 alkyl, –CONR'R", or $-N(C_1$-C_6alkyl$)_2$ where R' and R" are independently alkyl, akenyl, alkynyl, aryl, or joined together to form a 4 to 7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C_1-C_6 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, *tert*-butyl, n-pentyl, n-hexyl, and the like. Optionally, herein lower alkyl is referred to as "C_1-C_6alkyl."

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-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-methyl-3-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 3-heptenyl, l-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-heptynyl, l-octynyl, 1-nonynyl, 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 alkylene groups of this invention can be optionally substituted. The alkylene group can also be substituted with one or more of the substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NH_2$, $-NHC_1$-C_6 alkyl, –CONR'R", or

$-N(C_1-C_6alkyl)_2$ 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 (C_1-C_6 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, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-OCF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $-NH_2$, $-NHC_1-C_6$ alkyl, –CONR'R", or $-N(C_1-C_6alkyl)_2$ 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 (C_3-C_6 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 SO_2) 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, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2(C_1-C_6$ alkyl), $-NH_2$, $-NHC_1-C_6$ alkyl, –CONR'R", or $-N(C_1-C_6alkyl)_2$ 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 C_{1-6} alkyl. Examples of suitable monocyclic heterocycles include, but are not limited to substituted or unsubstituted thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazoiyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, piperidinyl, pyrrolidinyl, piperazinyl, azetidinyl, aziridinyl, morpholinyl, thietanyl, oxetaryl. Examples of monocyclic diheterocycles include, but are not limited to, 1-, 2-, 4-, or 5-imidazolyl, 1-, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 1, 3-, 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 indolizinyl, isoindolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 1-, 2-, 3-, 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, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NH_2$, $-NHC_1$-C_6 alkyl, –CONR'R", or $-N(C_1$-C_6alkyl$)_2$ 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, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-(CH_2)_{0-2}CF_3$, $-NH_2$, $-NHC_1$-C_6 alkyl, $-SO_2$alkyl, $-SO_2NH_2$, –CONR’R”, or $-N(C_1$-C_6alkyl$)_2$ 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, thienyl, 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.

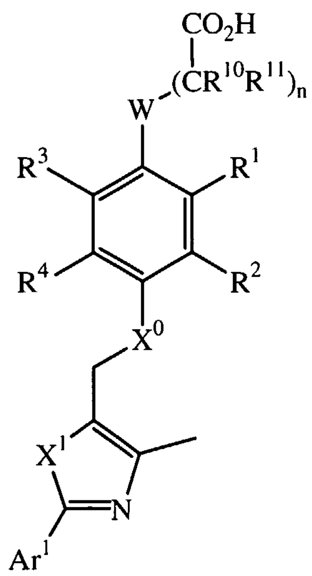
The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits.

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, palmitate, 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 "  " 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:



I

or a pharmaceutically acceptable salt thereof,

where:

W is O, S, 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 a unsubstituted or substituted aryl or heteroaryl;

R^1, R^2, R^3, and R^4 are independently hydrogen, lower alkyl, lower alkoxy, haloalkyl,$-O-(CH_2)_pCF_3$, halogen, nitro, cyano, -OH, -SH, $-CF_3$, $-S(O)_p$alkyl, $S(O)_p$aryl, $-(CH_2)_mOR^7$, $-(CH_2)_mNR^8R^9$, $-COR^7$, $-CO_2H$, $-CO_2R^7$, or $-NR^8R^9$;

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 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.

Examples of compounds of Formula I include those where W is O, Ar^1 is substituted aryl, and n is 1. For example compounds of Formula I where W is O, Ar^1 is substituted aryl, and n is 1 include those where Ar^1 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, $-(CH_2)_mNR^8R^9$, or $-(CH_2)_mOR^7$; 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

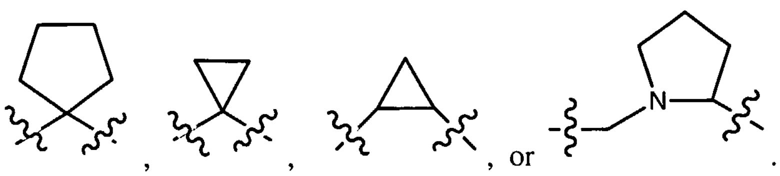
R^1	R^2	R^3	R^4
methyl	hydrogen	hydrogen	methyl
methyl	hydrogen	hydrogen	ethyl
methyl	hydrogen	hydrogen	iso-propyl
methyl	hydrogen	methyl	hydrogen
methyl	hydrogen	hydrogen	methoxy
hydrogen	methyl	methoxy	hydrogen
hydrogen	methyl	hydrogen	methyl
hydrogen	methoxy	hydrogen	methyl
hydrogen	methyl	iso-propyl	hydrogen
iso-propyl	hydrogen	iso-propyl	hydrogen
hydrogen	hydrogen	hydrogen	hydrogen
hydrogen	hydrogen	hydrogen	methoxy
methoxy	methoxy	hydrogen	hydrogen
hydrogen	methoxy	methoxy	hydrogen
methyl	hydrogen	hydrogen	$-NH-CO-CH_3$
methyl	hydrogen	hydrogen	fluoro
methyl	hydrogen	hydrogen	chloro
methyl	hydrogen	hydrogen	$-CH_2-O-CH_3$

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-$(CH_2)_pCF_3$, halogen, nitro, cyano, -OH, -SH, $-CF_3$, $-S(O)_p$alkyl, $S(O)_p$aryl, -$(CH_2)_mOR^7$, $-(CH_2)_mNR^8R^9$, $-COR^7$, $-CO_2H$, $-CO_2R^7$, or $-NR^8R^9$; R^7 is hydrogen, alkyl, alkenyl, alkynyl, or aryl; and R^8 and R^9 are independently hydrogen, alkyl, alkenyl, alkynyl, -COalkyl, -COaryl, cycloalkyl, $-CO_2$alkyl, $-CO_2$aryl, $-SO_2$alkyl, -SO_2aryl, 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, isopropoxy, n-propoxy, 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^5R^6, $-(CH_2)_p$-cycloalkylene, or $-(CH_2)_p$-heterocycloalkylene, R^5 and R^6 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^5R^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, -CF_3, -$(CH_2)_mOR^7$, or -$(CH_2)_mNR^8R^9$; 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)-OCH_3, or -NH-$COCH_3$.

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-ylmethylsulfanyl]-phenoxy}-acetic acid;

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

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

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

2-Methyl-2-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-propionic acid;

2-{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}-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-ylmethy lsulfanyl]-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-Methtyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{4-[4-Methtyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-phenyl-propionic acid;

3-{4-[4-Methtyl-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-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-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 (propyleneglycol, polyethyleneglycol, 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 micro-encapsulated 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, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols 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 metahydroxide, 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, polyethyleneglycol, 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.

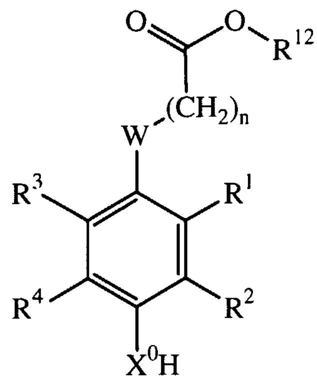
Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations,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

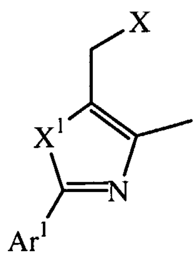
PREPARATION OF COMPOUNDS OF THE INVENTION

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:



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



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;

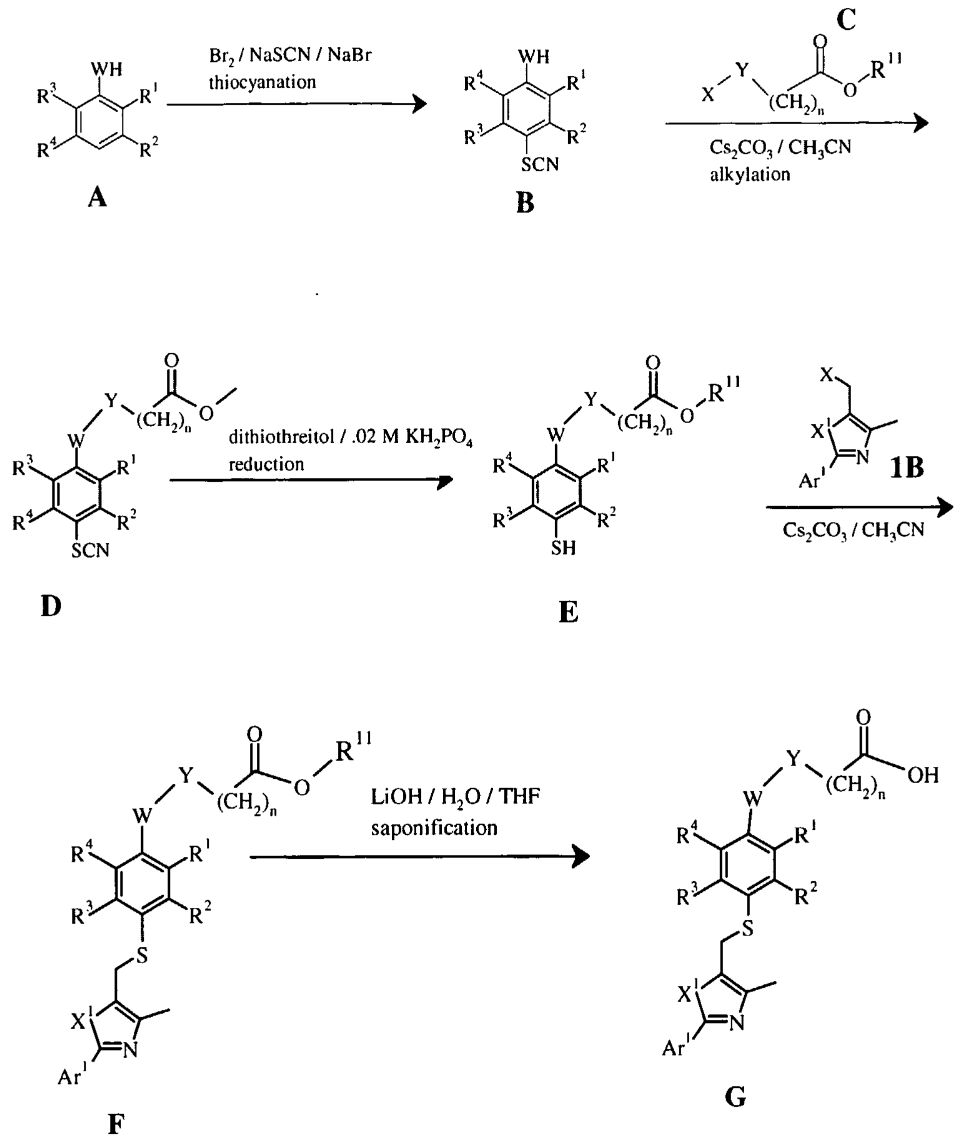
R^{12} is a lower alkyl; and

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.

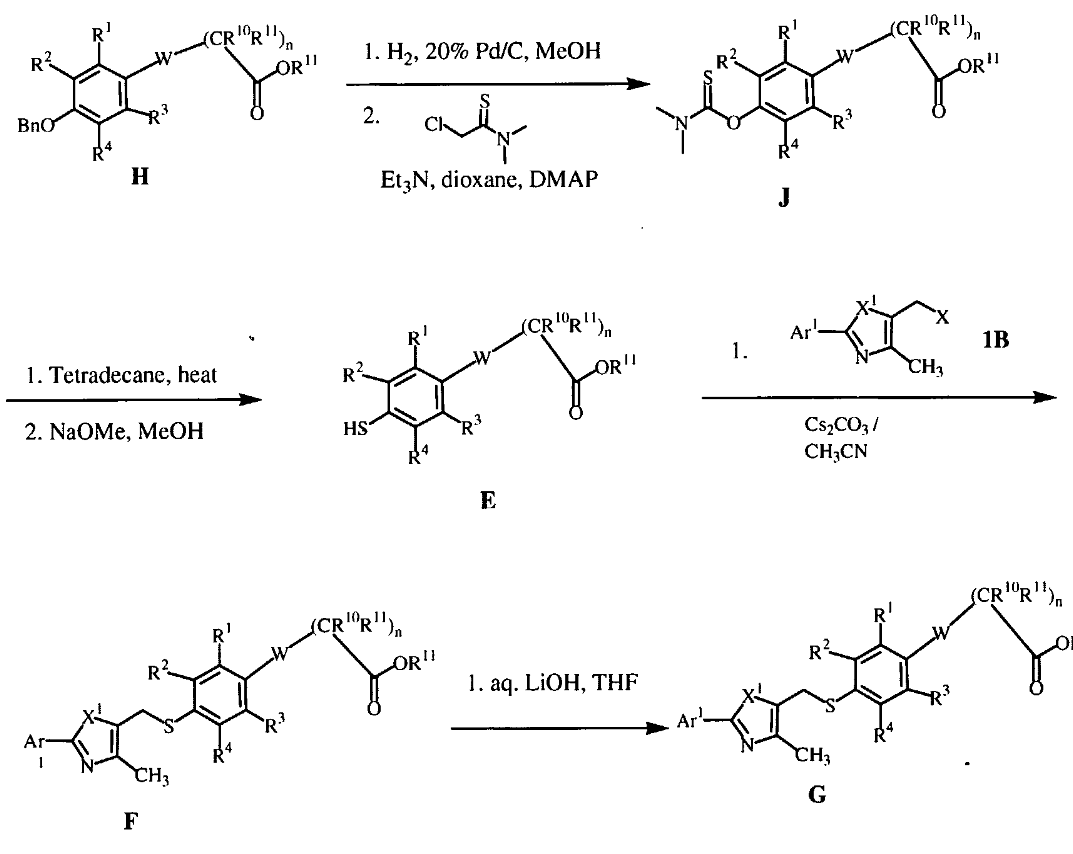
The compounds of Formula I can be prepared using the synthetic route outlined in Scheme 1 when W is O or S and X^0 is S. With reference to Scheme 1, compounds of the general formula **A** are thiocyanated with a mixture of bromine and sodium thiocyanate to give compounds of the general formula **B**. 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 **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 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.

Scheme 1



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 step1 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, 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.

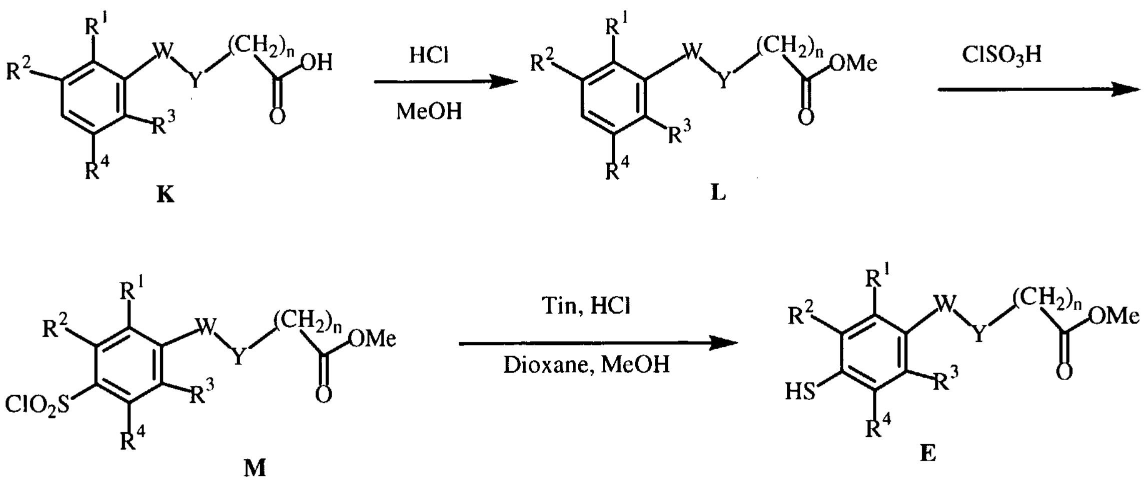
Scheme 2

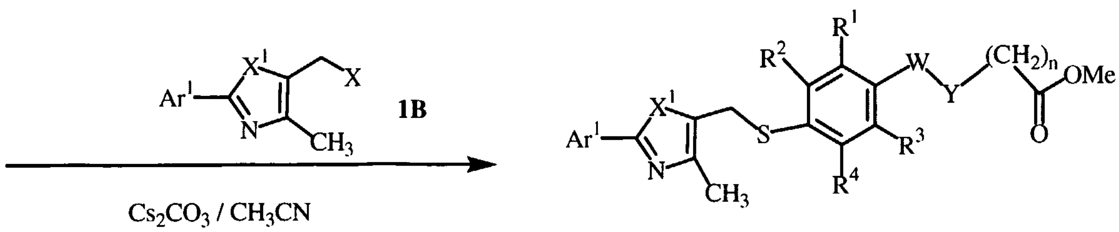


Finally, compounds of Formula I can be prepared using the synthetic route outlined in Scheme 3. With reference to Scheme 3, compounds of the general formula

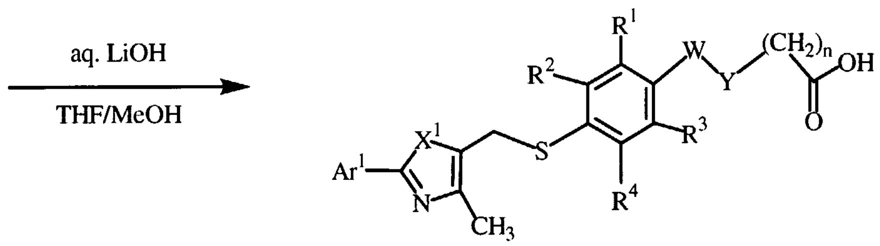
K are converted to the ester **L**. A useful method includes reacting compound **K** with an alcohol in the presence of an acid such as hydrochloric acid, although any compatible method for esterification may be used. Ester **L** is then reacted with cholorsulfonic acid to form compound **M**. Compound **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, 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.

Scheme 3





F

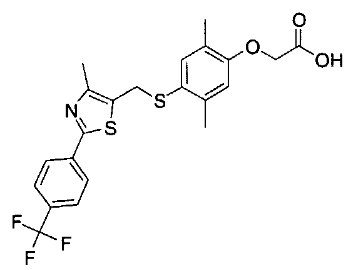


G

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

Example 1

<u>Synthesis of {2,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid (Compound 1)</u>



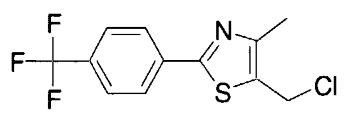
1

Preparation of [4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (compound 1A)

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. Recrystalisation from $CHCl_3$/hexanes gave the title compound (2.2 g, 85%). 400 MHz ^{1}H NMR (DMSO-d_6) 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).

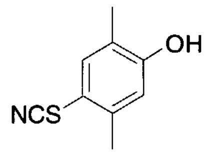
Preparation of 5-Chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (compound 1B)



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. $NaHCO_3$, 1 x brine, dried (Na_2SO_4) 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) δ 8.06 (d, 2H, J = 8.3 Hz), 7.80 (d, 2H, J = 8.3 Hz), 5.08 (s, 2H), 2.40 (s, 3H).

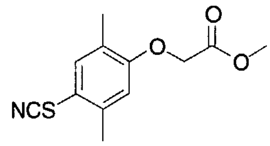
Preparation of 2,5-Dimethyl-4-thiocyanato-phenol (compound 1C)



1C

The title compound was prepared in a manner analogous to compound **3A**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

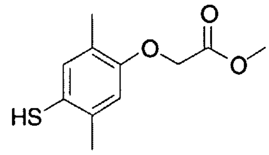
Preparation of (2,5-Dimethyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 1D)



1D

The title compound was prepared from compound 1C in a manner analogous to compound **3B**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

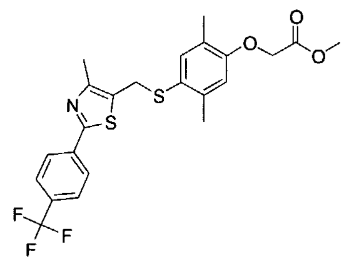
Preparation of (4-Mercapto-2,5-dimethyl-phenoxy)-acetic acid methyl ester (compound 1E)



1E

The title compound was prepared from compound 1D in a manner analogous to compound **3C**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

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



1F

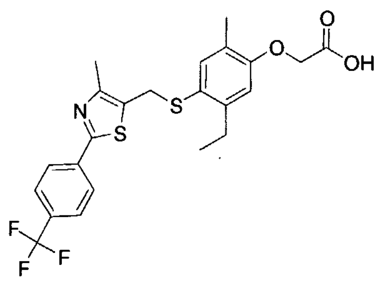
Compound **1E** (207 mg, 0.92 mmol) was dissolved in 5 ml anhydrous acetonitrile. Compound **1B** (294 mg, 1 mmol) was added followed by cesium carbonate (600 mg, 1.84 mmol). The reaction was stirred at ambient temperature for 2 hours, filtered and concentrated. Purification by flash column chromatography afforded the title compound. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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 recrystalized from chloroform/ hexanes. Mp 173-176 °C; IR (thin film) cm^{-1}: 2928, 1732, 1328, 1113; 400 MHz ^{1}H NMR (DMSO-d_6) δ 12.97 (s(br), 1H), 8.00 (d, 2H, J = 8 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 m/z 468 (M+1). Anal. Calc'd for $C_{22}H_{20}F_3NO_3S_2$ C, 56.52; H, 4.31; N, 3.00; found: C, 56.55; H, 4.31; N, 2.94.

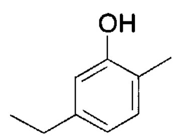
Example 2

<u>Synthesis of {5-Ethyl-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid (Compound 2)</u>



2

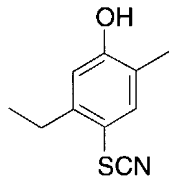
Preparation of 5-Ethyl-2-methyl-phenol (compound 2A)



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), $NaHSO_3$ (2 x 75mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was taken up in Et_2O and washed with sat. $NaHCO_3$(1 x 75 mL), dried (Na_2SO_4) and concentrated in vacuo to give 3.2 g of the crude product pure enough for subsequent use. 400 MHz ^{1}H NMR (DMSO-d_6) 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 K_2CO_3 (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 Et_2O and washed with 2 M HCL (1 x 50 mL), brine (1 x 50 mL), dried (Na_2SO_4) 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 ^{1}H NMR (DMSO-d_6) δ 400 MHz ^{1}H NMR (DMSO-d_6) 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).

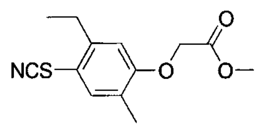
Preparation of 5-Ethyl-2-methyl-4-thiocyanato-phenol (compound 2B)



2B

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 recrytalisation from $CHCl_3$/hexanes, 0.8 g (29%) of the title compound as a single regioisomer. 400 MHz ^{1}H NMR (DMSO-d_6) 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).

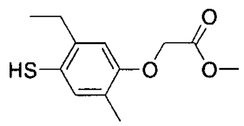
Preparation of (5-Ethyl-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 2C)



2C

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) δ 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).

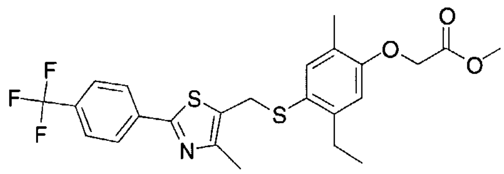
Preparation of (5-Ethyl-4-mercapto-2-methyl-phenoxy)-acetic acid methyl ester (compound 2D)



2D

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) δ 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)



2E

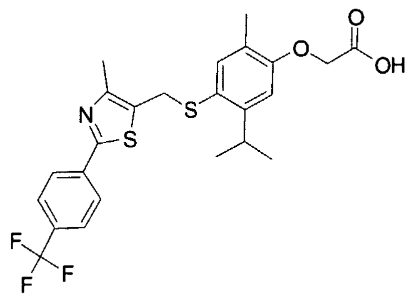
Compound **2D** and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound **1F** to provide, after purification by flash column chromatography (gradient elution: 100% hexanes to 30% EtOAc/hexanes), the title compound (0.24 g , 59%) as a yellow solid. IR (thin film) cm^{-1}: 1749, 1326; 400 MHz ^1H NMR (DMSO-d_6) 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 $C_{24}H_{24}F_3N_1O_3S_2$ 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 recrystalisation from $CHCl_3$/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-d_6) 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 $C_{24}H_{24}F_3N_1O_3S_2$ 0.5 H_2O C, 56.31; H, 4.73; N, 2.86; found: C, 56.53; H, 4.69; N, 2.68.

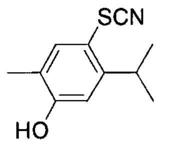
Example 3

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



3

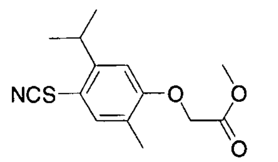
Preparation of 5-Isopropyl-2-methyl-4-thiocyanato-phenol (compound 3A)



3A

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 Na_2CO_3 (1 x 50 mL), brine (1 x 50 mL) dried (Na_2SO_4), 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 ^{1}H NMR (DMSO-d_6) 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).

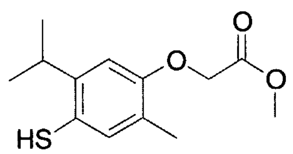
Preparation of (5-Isopropyl-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 3B)



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 (Na_2SO_4), 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-d_6) 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+).

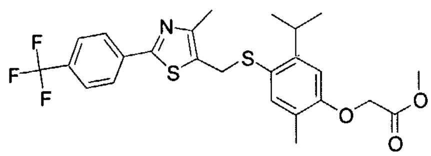
Preparation of (5-Isopropyl-4-mercapto-2-methyl-phenoxy)-acetic acid methyl ester (compound 3C)



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 KH_2PO_4 (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 (Na_2SO_4), 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 ^{1}H NMR (DMSO-d_6) 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)



3D

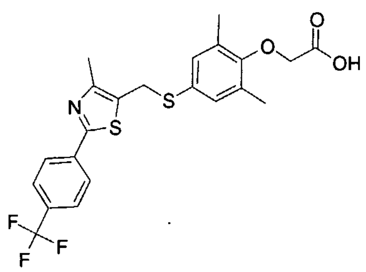
3C and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (compound **1B**) were coupled in a similar manner as described for compound **1F** to provide, after purification by flash column chromatography (gradient elution: 10% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound (0.66 g , 82%) as a yellow solid. IR (thin film) cm^{-1}: 2960, 1763, 1324; 400 MHz ^{1}H NMR (DMSO-d_6) 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 $C_{25}H_{26}F_3N_1O_3S_2$ 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 recrystalisation from $CHCl_3$/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 ^1H NMR (DMSO-d_6) δ 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+1); Anal. Calc'd for $C_{24}H_{24}F_3N_1O_3S_2$ 0.1 H_2O C, 57.96; H, 4.90; N, 2.82; found: C, 57.62; H, 4.82; N, 2.68.

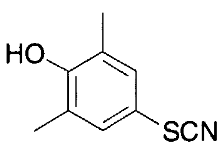
Example 4

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



4

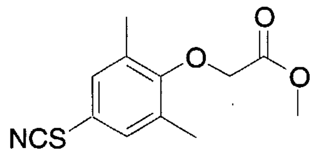
Preparation of 2,6-Dimethyl-4-thiocyanato-phenol (compound 4A)



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).

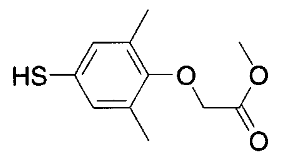
Preparation of (2,6-Dimethyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 4B)



4B

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).

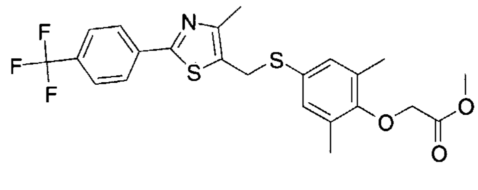
Preparation of (4-Mercapto-2,6-dimethyl-phenoxy)-acetic acid methyl ester (compound 4C)



4C

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)



4D

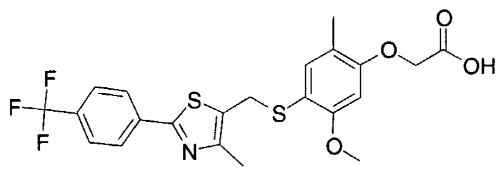
Compound **4C** and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound **1F** to provide, after purification by flash column chromatography (gradient elution: 10% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound (0.61 g , 57%) as a yellow solid. mp 104-105 °C;IR (thin film) cm^{-1}: 1754, 1325; 400 MHz ^{1}H NMR (DMSO-d_6) 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 $C_{23}H_{22}F_3N_1O_3S_2$ 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 recrystalisation from $CHCl_3$/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 ^{1}H NMR (DMSO-d_6) 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 $C_{22}H_{20}F_3N_1O_3S_2$ 0.2 H_2O C, 56.09; H, 4.36; N, 2.97; found: C, 55.79; H, 4.22; N, 2.94.

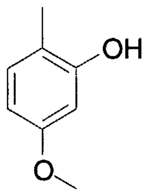
Example 5

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



5

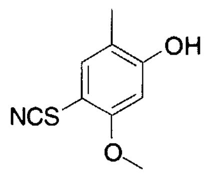
Preparation of 5-Methoxy-2-methyl-phenol (compound 5A)



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).

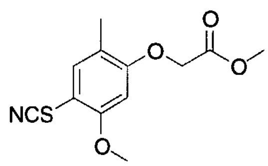
Preparation of 5-Methoxy-2-methyl-4-thiocyanato-phenol (compound 5B)



5B

Compound **5B** was prepared from compound **5A** in a manner analogous for example **3A**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

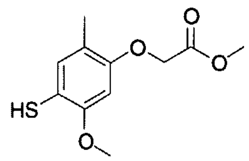
Preparation of (5-Methoxy-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 5C)



5C

Compound **5C** was prepared from compound **5B** in a manner analogous to compound **3B**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

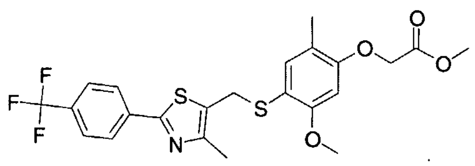
Preparation of (5-Methoxy-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 5D)



5D

Compound **5D** was prepared from compound **5C** in a manner analogous to compound **3C**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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)



5E

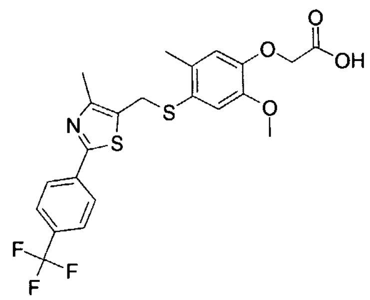
Compound **5E** was prepared from compound **5D** in a manner analogous to compound **3D**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.98 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, *J* = 8.4 Hz), 7.02 (s, 1H), 6.54 (s, 1H), 4.84 (s, 2H), 4.20 (s, 2H), 3.72 (s, 3H), 3.64 (s, 3H), 2.16 (s, 3H), 1.98 (s, 3H). ^{1}H NMR (DMSO-d_6) δ 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) δ 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 $C_{22}H_{20}F_3NO_4S_2$ C, 54.65; H, 4.17; N, 2.90; found: C, 54.68; H, 4.15; N, 2.84.

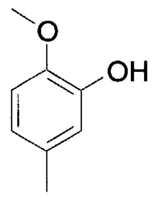
Example 6

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



6

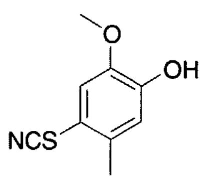
Preparation of 2-Methoxy-5-methyl-phenol (compound 6A)



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) δ 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).

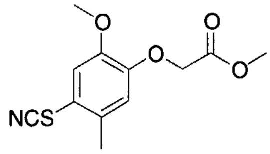
Preparation of 2-Methoxy-5-methyl-4-thiocyanato-phenol (compound 6B)



6B

The title compound was prepared from compound **6A** in a manner analogous to compound **3A**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

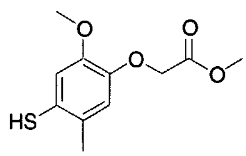
Preparation of (2-Methoxy-5-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 6C)



6C

The title compound was prepared from compound **6B** in a manner analogous to compound **3B**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

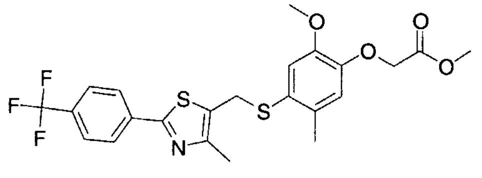
Preparation of (4-Mercapto-2-methoxy-5-methyl-phenoxy)-acetic acid methyl ester (compound 6D)



6D

The title compound was prepared from compound **6C** in a manner analogous to compound **3C**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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)



6E

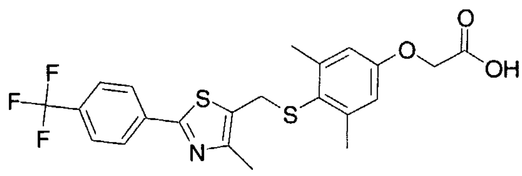
The title compound was prepared from compound **6D** in a manner analogous to compound **1F**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.99 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 8.4 Hz), 6.86 (s, 1H), 6.75 (s, 1H), 4.70 (s, 2H), 4.27 (s, 2H), 3.63 (s, 3H), 3.60 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H); MS *m/z* 498 (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) δ 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 $C_{22}H_{20}F_3NO_4S_2$ C, 54.65; H, 4.17; N, 2.90; found: C, 54.21; H, 4.03; N, 2.79.

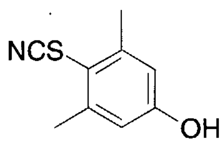
Example 7

<u>Preparation of {3,5-Dimethyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid (Compound 7)</u>



7

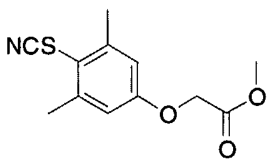
Preparation of 3,5-Dimethyl-4-thiocyanato-phenol (compound 7A)



7A

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

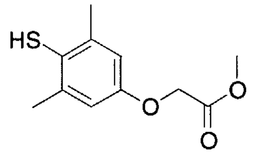
Preparation of (3,5-Dimethyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 7B)



7B

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) δ 6.63 (s, 2H), 4.72 (s, 2H), 3.62 (s, 3H), 2.08 (s, 6H).

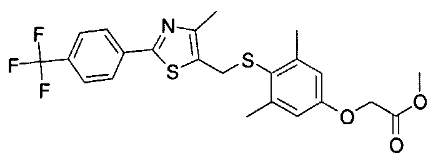
Preparation of (4-Mercapto-3,5-dimethyl-phenoxy)-acetic acid methyl ester (compound 7C)



7C

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) δ 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)



7D

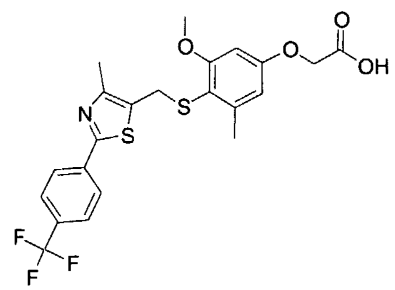
Compound **7C** and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound **1F** to provide, after purification by flash column chromatography (gradient elution: 10% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound (0.62 g , 79%) as a yellow solid. mp 113 °C; IR (thin film) cm^{-1}: 1739, 1325; 400 MHz ^1H NMR (DMSO-d_6) 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 $C_{23}H_{22}F_3N_1O_3S_2$ 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-ylmethylsulfanyl]-phenoxy}-acetic acid (Compound 7)

Compound **7D** was saponified in the same manner as described for compound **1F** to give, after recrystalisation from $CHCl_3$/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-d_6) 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 $C_{22}H_{20}F_3N_1O_3S_2$ C, 56.52; H, 4.31; N, 3.00; found: C, 56.19; H, 4.23; N, 2.91.

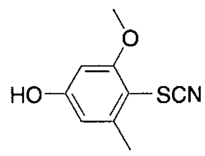
Example 8

<u>Synthesis of {3-Methoxy-5-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid (Compound 8)</u>



8

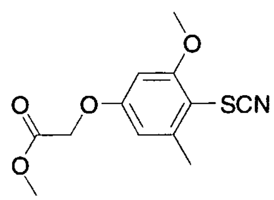
Preparation of 3-Methoxy-5-methyl-4-thiocyanato-phenol (compound 8A)



8A

Compound **8A** was prepared from 3-methoxy-5-methyl-phenol in a similar manner as described for compound **3A** to give, after recrystalisation from $CHCl_3$/hexanes, 1.9 g (13%) of the title compound. 400 MHz ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 6.39 (s, 2H), 3.79 (s, 3H), 2.35 (s, 3H); MS *m/z* 196 (M+1).

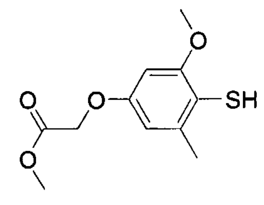
Preparation of (3-Methoxy-5-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 8B)



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) δ 6.60 (s, 2H), 4.84 (s, 2H), 3.85 (s, 3H), 3.66 (s, 3H), 2.40 (s, 3H); MS *m/z* 268 (M+1).

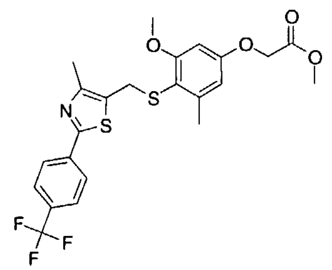
Preparation of (4-Mercapto-3-methoxy-5-methyl-phenoxy)-acetic acid methyl ester (compound 8C)



8C

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) δ 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)



8D

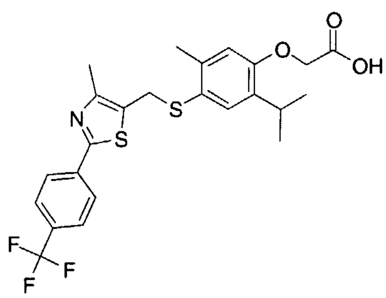
Compound **8C** and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole were coupled in a similar manner as described for compound **1F** to provide, after purification by flash column chromatography (gradient elution: 5% EtOAc/hexanes to 50% EtOAc/hexanes), the title compound (0.71 g, 69%) as a yellow solid. IR (thin film) cm^{-1}: 1766, 1325; 400 MHz ^{1}H NMR (DMSO-d_6) 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 $C_{23}H_{22}F_3N_1O_4S_2$ 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 recrystalisation from $CHCl_3$/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 ^{1}H NMR (DMSO-d_6) 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 $C_{22}H_{20}F_3N_1O_4S_2$ C, 54.65; H, 4.17; N, 2.90; found: C, 54.12; H, 4.06; N, 2.69.

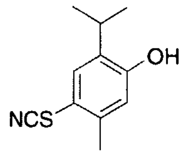
Example 9

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



9

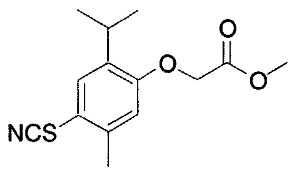
Preparation of 2-Isopropyl-5-methyl-4-thiocyanato-phenol (compound 9A)



9A

The title compound was prepared in a manner analogous to compound **3A**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

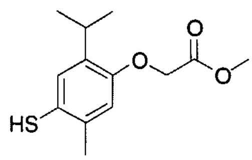
Preparation of (2-Isopropyl-5-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 9B)



9B

The title compound was prepared from compound **9A** in a manner analogous to compound **3B**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

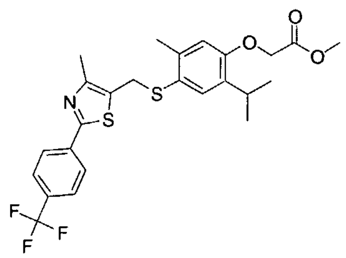
Preparation of (2-Isopropyl-4-mercapto-5-methyl-phenoxy)-acetic acid methyl ester (compound 9C)



9C

The title compound was prepared from compound **9B** in a manner analogous to compound **3C**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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)



9D

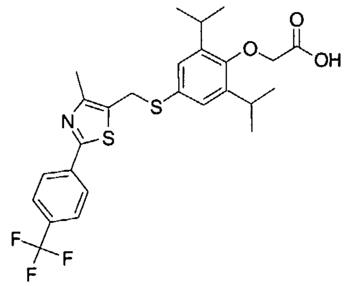
The title compound was prepared from compound **9C** in a manner analogous to example **1F**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.98 (d, 2H, J = 8 Hz), 7.76 (d, 2H, J = 8 Hz), 6.94 (s, 1H), 6.74 (s, 1H), 4.76 (s, 2H), 4.17 (s, 2H), 3.63 (s, 3H), 3.1 (m, 1H), 2.24 (s, 3H), 1.93 (s, 3H), .96 (d, 6H, J = 7.2 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) δ 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 $C_{24}H_{24}F_3NO_3S_2$ C, 58.17; H, 4.88; N, 2.83; found: C, 57.73; H, 4.62; N, 2.75.

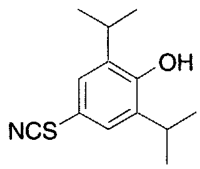
Example 10

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



10

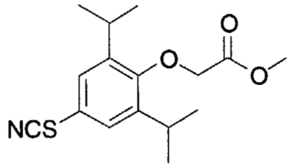
Preparation of 2,6-Diisopropyl-4-thiocyanato-phenol (compound 10A)



10A

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).

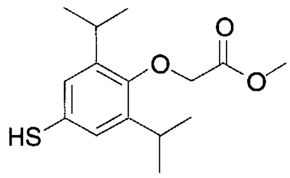
Preparation of (2,6-Diisopropyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (compound 10B)



10B

The title compound was prepared from compound **10A** in a manner analogous to compound **3B**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

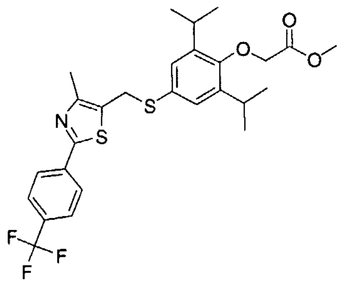
Preparation of (2,6-Diisopropyl-4-mercapto-phenoxy)-acetic acid methyl ester (compound 10C)



10C

The title compound was prepared from compound **10B** in a manner analogous to compound **3C**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

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



10D

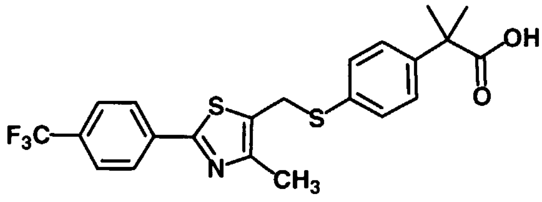
The title compound was prepared from compound **10C** in a manner analogous to compound **1F**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.97 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, 8.4 Hz), 7.00 (s, 2H), 4.3 (m, 4H), 3.66 (s, 3H), 3.13 (m, 2H), 2.04 (3H), 1.01 (d, 12H, J = 7.2 Hz); MS *m/z* 538 (M+1).

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-d_6) 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 $C_{26}H_{28}F_3NO_3S_2$ C, 59.64; H, 5.39; N, 2.67; found: C, 58.82; H, 5.54; N, 2.48.

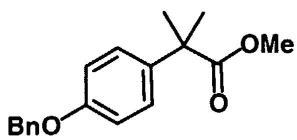
Example 11

<u>Synthesis of 2-Methyl-2-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-propionic acid (Compound 11)</u>



11

Preparation of 2-(4-Benzyloxy-phenyl)-2-methyl-propionic acid methyl ester (11A)



11A

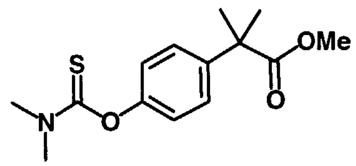
1). (4-Benzyloxy-phenyl)-acetic acid (10g, 41 mmol) was dissolved in MeOH (100 mL) and was then treated with H_2SO_4 (5 mL). The reaction mixture was refluxed overnight. MeOH was evaporated and the residue was diluted with water and ether. Layers were separated and the aqueous layer was extracted with ether (2x30mL). The combined organics were dried with $MgSO_4$ 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 $MgSO_4$ 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)



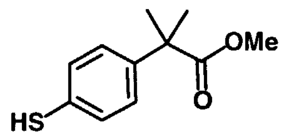
11B

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 Et_3N (1.04g, 10.3 mmol), DMAP (63mg, 0.52 mmol), and dimethyl thiocarbamoyl chloride (0.76g, 6.18 mmol). The reaction mixture was refluxed overnight. After cooling down to RT, the reaction mixture was diluted with EtOAc (100 mL) and H_2O (100 mL). Layers were separated and the aqueous layer was extracted with EtOAc (2x50mL). Combined organics was dried over $MgSO_4$ and condensed to give the desired product **11B** as a brown oil (1.61g, 100%)

MS: 282 $(M+1)^+$

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



11C

1). Compound **11B** (1.61g, 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 H_2O, dried over $MgSO_4$ and condensed to give the desired product as a tan solid (0.15g). More crystals (0.39g) were collected from the tetradecane solution that was first decanted. Total yield of the reaction was 34% (0.54g).

MS: 282 $(M+1)^+$

2). The above product (0.54g, 1.92 mmol) was immediately dissolved in MeOH (5 mL) and was treated with NaOMe (0.114g, 2.11mmol). 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 H_2O. Solvent was 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 pure product (0.22g, 24%) as a yellow oil.

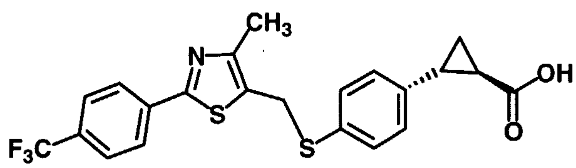
MS: 466 $(M+1)^+$

2). The above methyl ester (0.22g, 0.4 mmol) dissolved in THF (10 mL) and treated with $LiOH.H_2O$ (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 $MgSO_4$ 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.

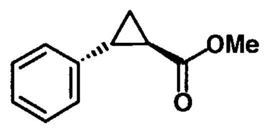
Example 12

Synthesis of 2-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclopropanecarboxylic acid (Compound 12)



12

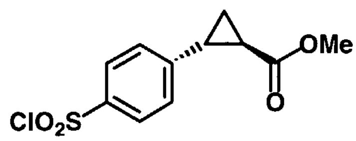
Preparation of 2-Phenyl-cyclopropanecarboxylic acid methyl ester (12A)



12A

2-Phenyl-cyclopropanecarboxylic acid (5g, 30.86 mmol) was dissolved in MeOH (100 mL) and was then treated with H_2SO_4 (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 $MgSO_4$ 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)

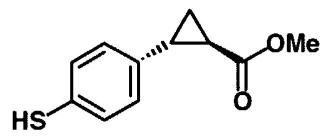


12B

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 (^{1}H, $CDCl_3$): δ 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)

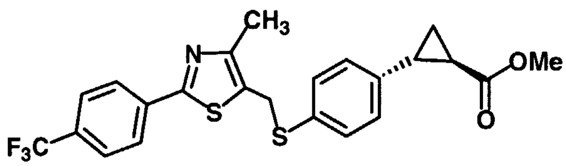


12C

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 CH_2Cl_2 (100 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (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

Compound **12C** (1.06g, 5.09 mmol) was dissolved in acetonitrile (80 mL) with the chloride **1B** (1.3g, 4.4 mmol) and Cs_2CO_3 (3.3g, 1.07 mmol). The reaction mixture was stirred at RT overnight. Ether (50 mL) and H_2O 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 $MgSO_4$ 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 $(M+1)^+$

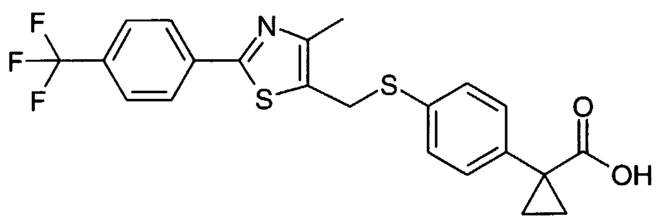
Preparation of 1-{4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclopropanecarboxylic acid (Compound 12)

To the solution of the above methyl ester, compound **12D** (0.38g, 0.82 mmol) in MeOH (7mL) and THF (7mL) was added $LiOH.H_2O$ (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 $MgSO_4$, 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 $(M+1)^+$.

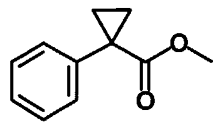
Example 13

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



13

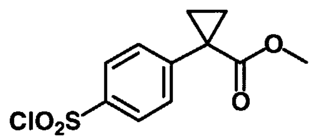
Preparation of 1-Phenyl-cyclopropanecarboxylic acid methyl ester (compound 13A)



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 $(M+1)^+$.

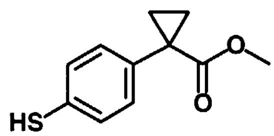
Preparation of 1-(4-Chlorosulfonyl-phenyl)-cyclopropanecarboxylic acid methyl ester (compound 13B)



13B

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

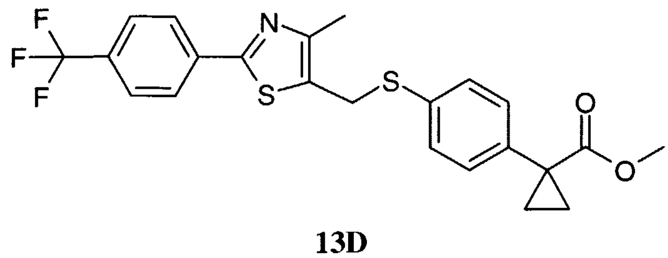
Preparation of 1-(4-Mercapto-phenyl)-cyclopropanecarboxylic acid methyl ester (compound 13C)



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):



13D

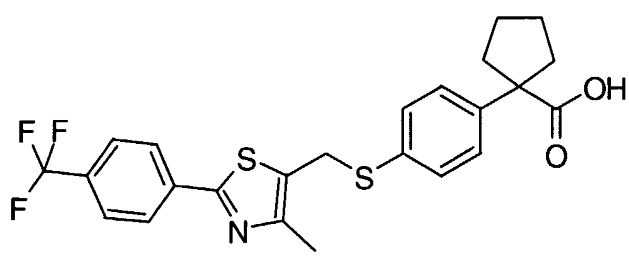
Compound **13D** was prepared analogously to compound **12D** using the crude product compound **13C**. Yield was 12% in 2 steps. MS for 15D: 464 $(M+1)^+$

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 $(M+1)^+$.

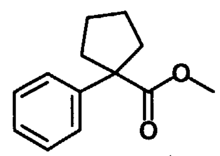
Example 14

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



14

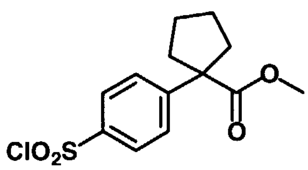
Preparation of 1-Phenyl-cyclopentanecarboxylic acid methyl ester (compound 14A)



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 $(M+1)^+$.

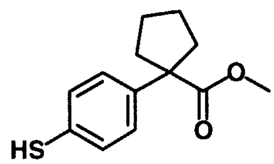
Preparation of 1-(4-Chlorosulfonyl-phenyl)-cyclopentanecarboxylic acid methyl ester (compound 14B)



14B

Compound **14B** was prepared analogously to compound **12B**. 50% yield. MS: 267 $(M\text{-}Cl)^+$:

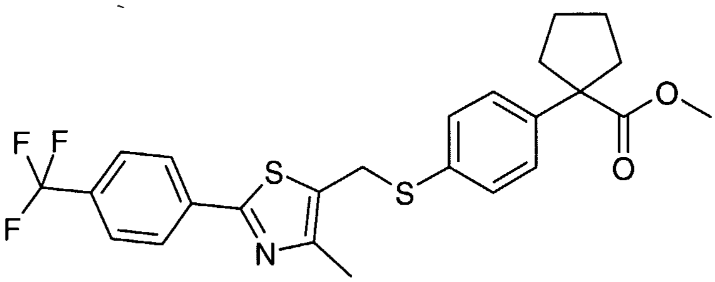
Preparation of 1-(4-Mercapto-phenyl)-cyclopentanecarboxylic acid methyl ester(compound 14C)



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)



14D

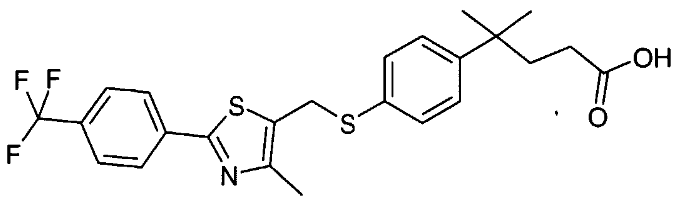
Compound **14D** was prepared analogously to compound **12D** using the crude product compound **14C**. Yield was 31% in 2 steps. MS for **14D**: 492 $(M+1)^+$

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 $(M+1)^+$.

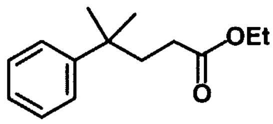
Example 15

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



15

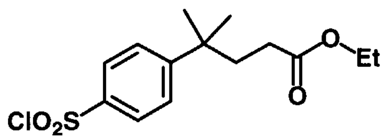
Preparation of 4-Methyl-4-phenyl-pentanoic acid methyl ester (compound 15A)



15A

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

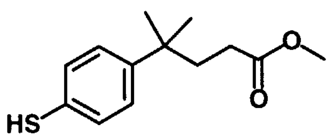
Preparation of 4-(4-Chlorosulfonyl-phenyl)-4-methyl-pentanoic acid ethyl ester(compound 15B)



15B

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

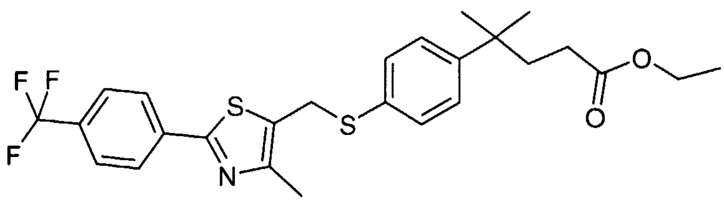
Preparation of 4-(4-Mercapto-phenyl)-4-methyl-pentanoic acid ethyl ester (compound 15C)



15C

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)



15D

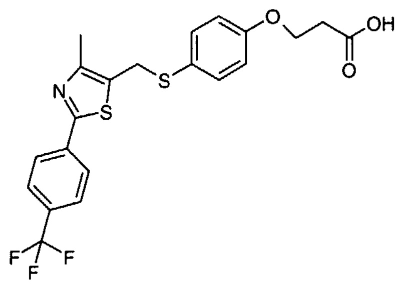
Compound **15D** was prepared analogously to compound **12D** using the crude product compound **15C**. Yield was 21% in 2 steps. MS for 17D: 508 $(M+1)^+$.

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 $(M+1)^+$.

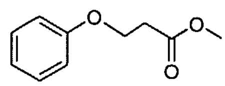
Example 16

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



16

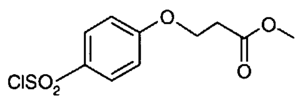
Preparation of 3-Phenoxy-propionic acid methyl ester (compound 16A)



16A

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

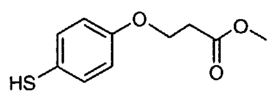
Preparation of 3-(4-Chlorosulfonyl-phenoxy)-propionic acid methyl ester (compound 16B)



16B

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

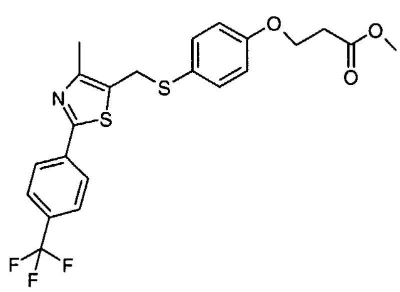
Preparation of 3-(4-Mercapto-phenoxy)-propionic acid methyl ester (compound 16C)



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)



16D

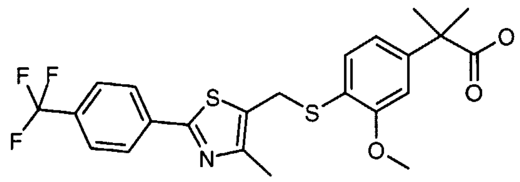
Compound **16D** was prepared analogously to compound **12D** using the crude product compound **16C**. Compound **16D** was prepared in 49% yield. MS: 211 $(M-1)^+$.

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 $(M+1)^+$.

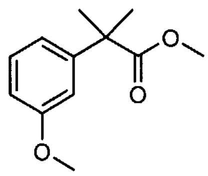
Example 17

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



17

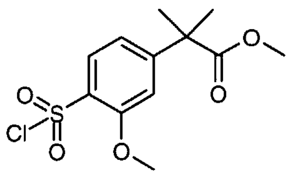
Preparation of 2-(3-Methoxy-phenyl)-2-methyl-propionic acid methyl ester (Compound 17A)



17A

17A was prepared analogously to compound **11A**. MS: 209 $(M+1)^+$.

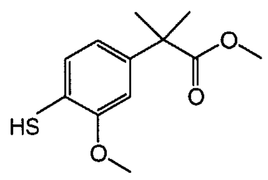
Preparation of 2-(4-Chlorosulfonyl-3-methoxy-phenyl)-2-methyl-propionic acid methyl ester (Compound 17B)



17B

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

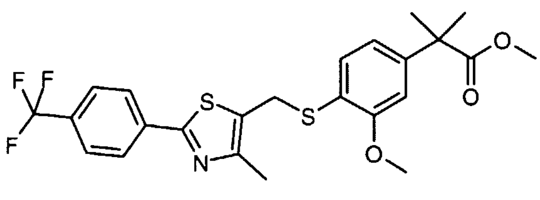
Preparation of 2-(4-Mercapto-3-methoxy-phenyl)-2-methyl-propionic acid methyl ester (Compound 17C)



17C

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-ylmethylsulfanyl]-2-methyl-propionic acid methyl ester (Compound 17D)



17D

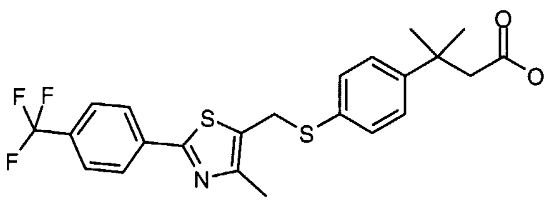
Compound **17D** was prepared analogously to compound **12D**. Yield was 12% after flash column purification. MS: 496 $(M+1)^+$.

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 $(M+1)^+$.

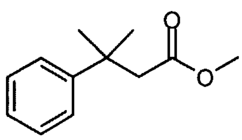
Example 18

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



18

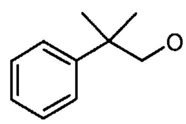
Preparation of 3-Methyl-3-phenyl-butyric acid methyl ester (Compound 18A



18A

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

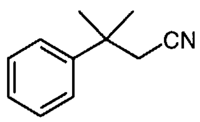
Preparation of 2-Methyl-2-phenyl-propan-1-ol (Compound 18B)



18B

18B was prepared analogously to compound **1A**. Quantitative yield. MS: 133 $(M-H_2O)^+$.

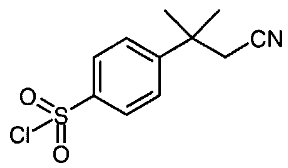
Preparation of 3-Methyl-3-phenyl-butyronitrile (Compound 18C)



18C

Methane sulfonyl chloride was added to a stirred solution of compound **18B** dissolved in CH_2Cl_2 and triethyl amine at 0°C. The mixture was stirred at RT for 4 hr. It was then diluted with CH_2Cl_2 and washed with 1 x sat. NH_4Cl, 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 $(M+1)^+$.

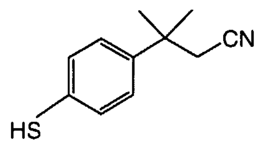
Preparation of 4-(2-Cyan-1, 1-dimethyl-ethyl)-benzenesulfonyl chloride (Compound 18D)



18D

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

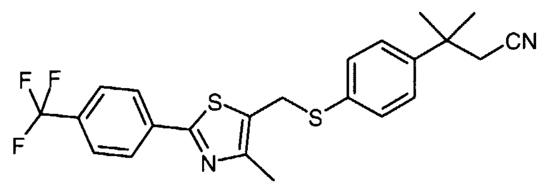
Preparation of 3-(4-Mercapto-phenyl)-3-methyl-butyronitrile (Compound 18E)



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)



18F

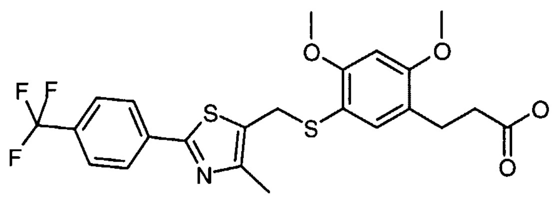
Compound **18F** was prepared analogously to compound **12D**. Yield was 20% after flash column purification. MS: 447 $(M+1)^+$.

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 $(M+1)^+$.

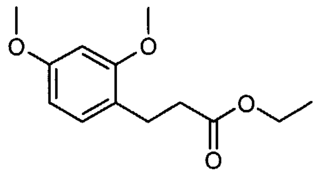
Example 19

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



19

Preparation of 3-(2,4-Dimethoxy-phenyl)-propionic acid ethyl ester(Compound 19A)

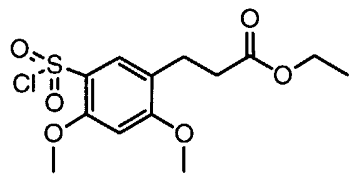


19A

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 $MgSO_4$ 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 $(M+1)^+$.

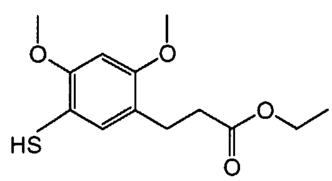
Preparation of 3-(5-Chlorosulfonyl-2,4-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 19B)



19B

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

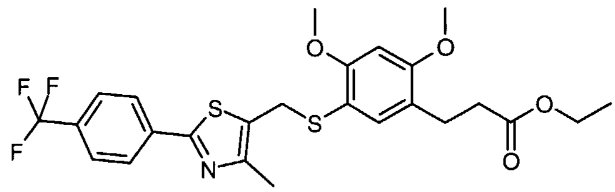
Preparation of 3-(5-Mercapto-2,4-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 19C)



19C

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)



19D

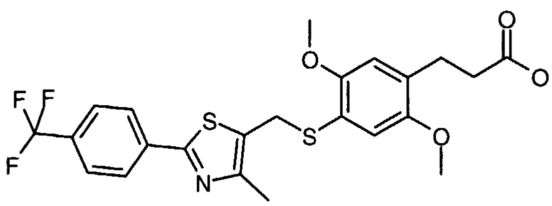
Compound **19D** was prepared analogously to compound **12D**. Yield was 45% after flash column purification. MS: 526 $(M+1)^+$.

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 $(M+1)^+$.

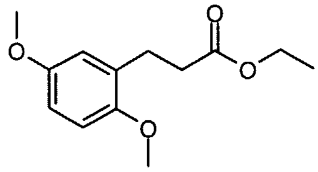
Example 20

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



20

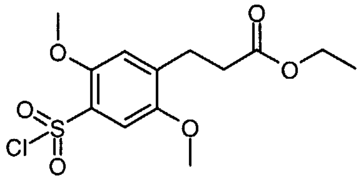
Preparation of 3-(2,5-Dimethoxy-phenyl)-propionic acid ethyl ester (Compound 20A)



20A

20A was prepared analogously to compound **19A**. 94% yield. MS: 239 $(M+1)^+$.

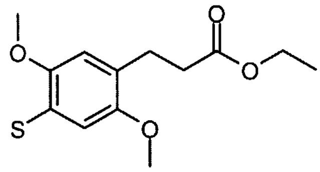
Preparation of 3-(4-Chlorosulfonyl-2,5-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 20B)



20B

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

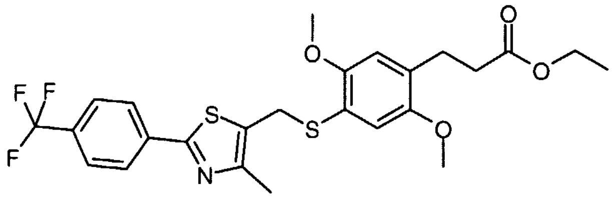
Preparation of 3-(4-Mercapto-2,5-dimethoxy-phenyl)-propionic acid ethyl ester (Compound 20C)



20C

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)



20D

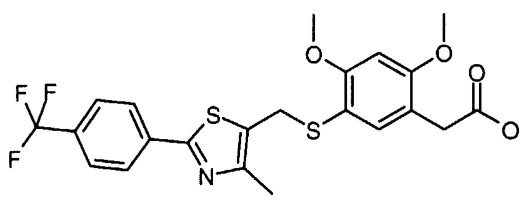
Compound **20D** was prepared analogously to compound **12D**. Yield was 26% after flash column purification. MS: 526 $(M+1)^+$.

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 $(M+1)^+$.

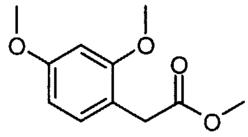
Example 21

<u>Synthesis of {2,4-Dimethoxy-5-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]}-acetic acid (Compound 21)</u>



21

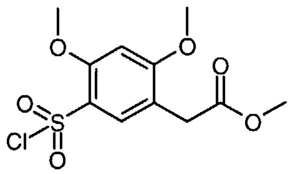
Preparation of (2,4-Dimethoxy-phenyl)-acetic acid methyl ester (Compound 21A)



21A

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

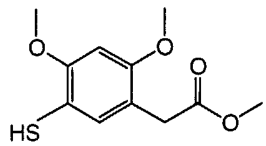
Preparation of (5-Chlorosulfonly-2, 4-dimethoxy-phenyl)-acetic acid methyl ester (Compound 21B)



21B

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

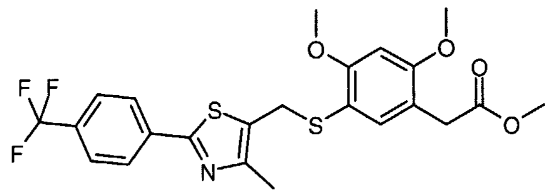
Preparation of (5-Mercapto-2, 4-dimethoxy-phenyl)-acetic acid methyl ester (Compound 21C)



21C

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)



21D

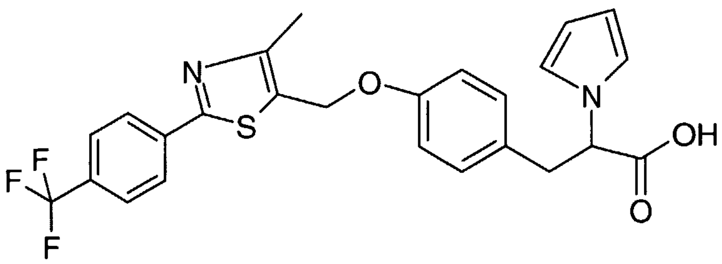
Compound **21D** was prepared analogously to compound **12D**. Yield was 25% after flash column purification. MS: 498 $(M+1)^+$.

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 $(M+1)^+$.

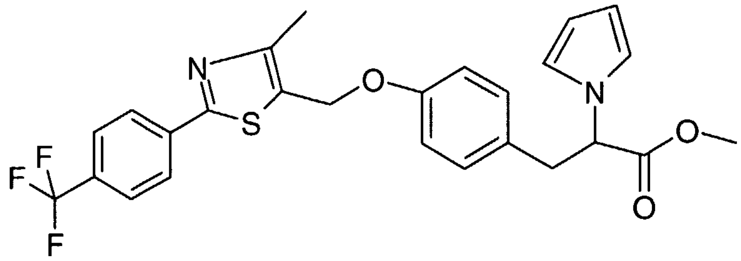
Example 22

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



22

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



22A

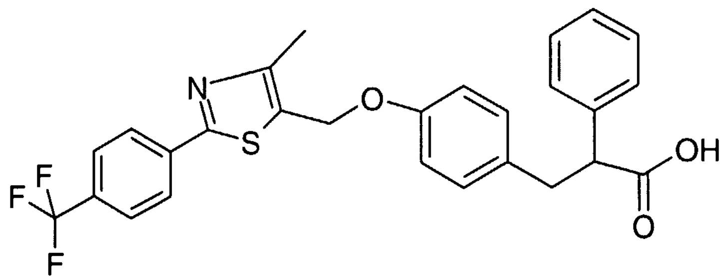
Compound **22A** was prepared according to the method of example **1F** utilizing 3-(4-hydroxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester. MS: 501 $(M+1)^+$.

Preparation of 3-{4-[4-Methtyl-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 $(M+1)^+$.

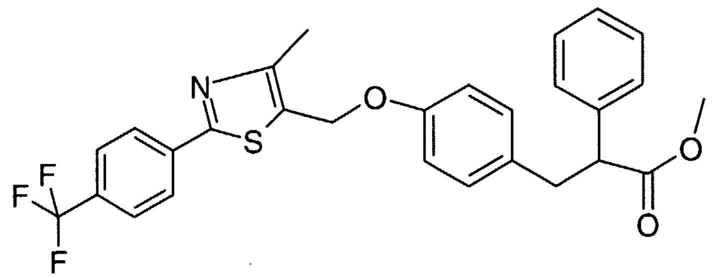
Example 23

<u>Synthesis of 3-{4-[4-Methtyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-phenyl-propionic acid (Compound 23)</u>



23

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



23A

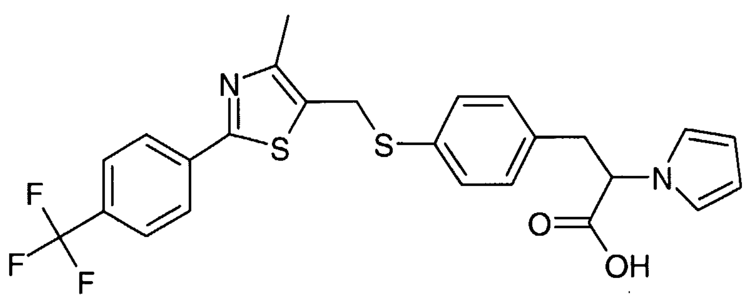
Compound **23A** was prepared according to the method of example **1F** utilizing 3-(4-hydroxy-phenyl)-2-phenylpropionic acid methyl ester. MS: 512 $(M+1)^+$.

Preparation of 3-{4-[4-Methtyl-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 $(M+1)^+$.

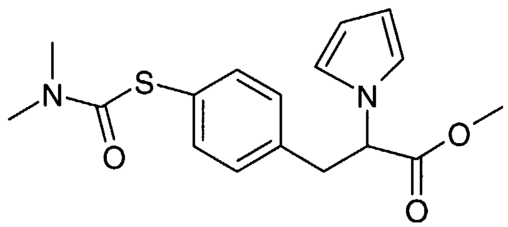
Example 24

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



24

Preparation of 3-(4-Dimethylcarbamoylsulfanyl-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (Compound 24A)



24A

3-(4-Hydroxy-phenyl)-2-phenylpropionic acid methyl ester, Et_3N, 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.

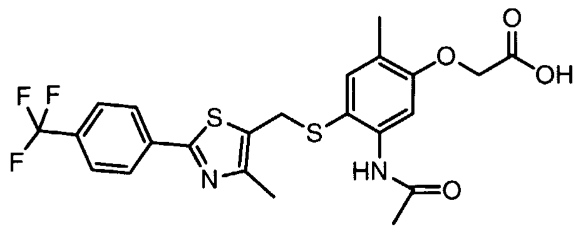
4-Dimethylthiocarbamoyloxy-phenyl-propionic acid methyl ester in THF was added drop wise into a refluxed solution of tetradecane, refluxed for another 3 hours. The solvent was decanted after cooling to room temperature, remaining oil washed several times with hexane. It was purified by flash column chromatography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

Preparation of 3-{4-[4-Methtyl-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 $(M+1)^+$.

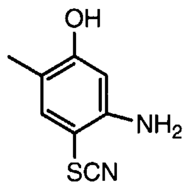
Example 25

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)



25

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



25A

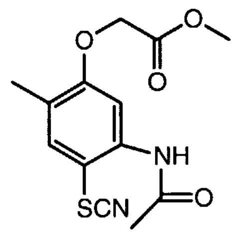
To a mixture of 5-amino-2-methylphenol, sodium thiocyanate and sodium bromide in anhydrous methanol, and bromine in methanol was added dropwise over 30 minutes and allowed to stir at 0 °C for 1 h. Saturated sodium bicarbonate was added to bring pH 7, and the crude product was extracted with ethyl acetate. 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}H NMR (DMSO-d_6) δ 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}H NMR (DMSO-d_6) δ 7.20 (s, 1H), 6.28 (s, 1H), 5.71 (s, 2H), 4.77 (s, 2H), 3.71 (s, 3H), 2.04 (s, 3H).

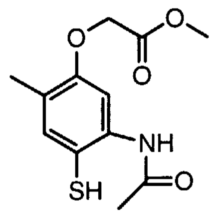
Preparation of methyl 2-[5-(acetylamino)-4-cyanothio-2-methylphenoxy]acetate (Compound 25C)



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}H NMR (DMSO-d_6) δ 7.55 (s, 1H), 6.81 (s, 1H), 4.90 (s, 2H), 3.70 (s, 3H), 2.23 (s, 3H), 2.07 (s, 3H).

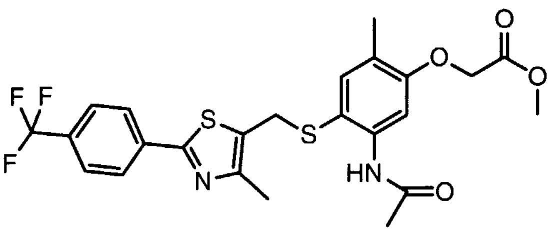
Preparation of methyl 2-[5-(acetylamino)-2-methyl-4-sulfanylphenoxy]acetate (Compound 25D)



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)}methylthio)phenoxy]acetate (Compound 25E)



25E

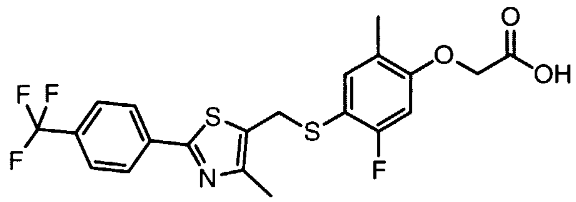
The title compound was prepared in the manner analogous to Example **1F** with the product from example **25D**, 5-(chloromethyl)-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole and cesium carbonate in anhydrous acetonitrile. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.92 (m, 3H), 7.68 (d, 2H), 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).

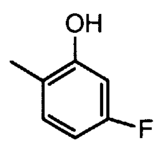
Example 26

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)



26

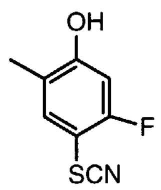
Preparation of 5-fluoro-2-methylphenol (compound 26A)



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).

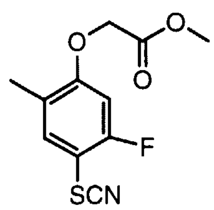
Preparation of (2-fluoro-4-hydroxy-5-methylphenyl)thiocarbonitrile (Compound 26B)



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).

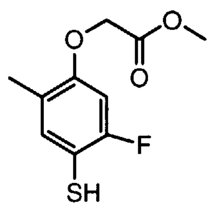
Preparation of methyl 2-(4-cyanothio-5-fluoro-2-methylphenoxy)acetate (Compound 26C)



26C

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 ($CDCl_3$) δ 7.40 (d, 1H), 6.55 (d, 1H), 4.68 (s, 2H), 3.85 (s, 3H), 2.26 (s, 3H).

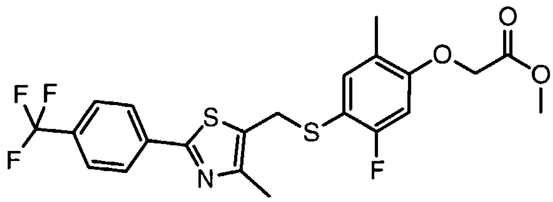
Preparation of methyl 2-(5-fluoro-2-methyl-4-sulfanylphenoxy)acetate (Compound 26D)



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) δ 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)



26E

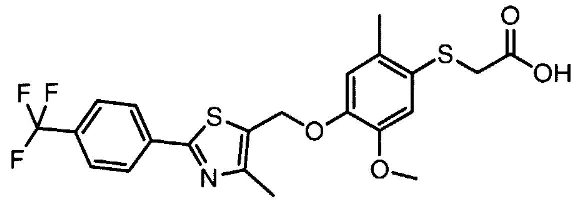
The title compound was prepared in the manner analogous to Example **1F** with the product from example **26D**, 5-(chloromethyl)-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole, and cesium carbonate in 15 ml of anhydrous acetonitrile. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2H), 7.65 (d, 2H), 7.12 (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)phenoxy]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).

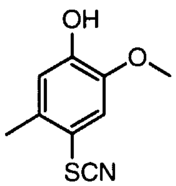
Example 27

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)



27

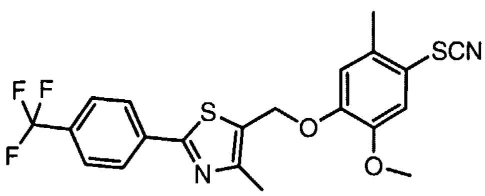
Preparation of (4-hydroxy-5-methoxy-2-methylphenyl)thiocarbonitrile (Compound 27A)



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) δ 9.78 (s, 1H), 7.20 (s, 1H), 6.82 (s, 1H), 3.79 (s, 3H), 2.32 (s, 3H).

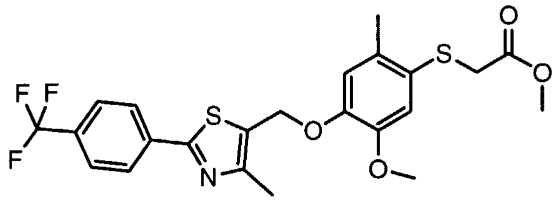
Preparation of [5-methoxy-2-methyl-4-({4-methyl-2-[4-(trifluoromethyl)phenyl](1,3-thiazol-5-yl)}methoxy)phenyl]thiocarbonitrile (Compound 27B)



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) δ 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)



27C

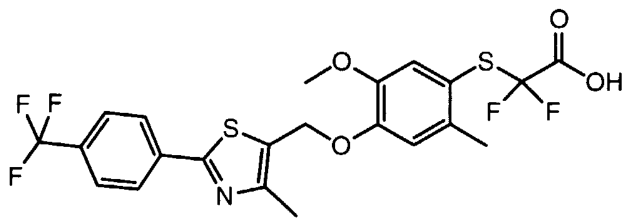
The product from example **27B**, and sodium sulfide in anhydrous methanol was refluxed for 2 h, then cooled and concentrated under reduced pressure. The residue was dissolved in anhydrous acetonitrile, methyl bromoacetate and cesium carbonate were added. The reaction mixture was heated at 60 °C for 2 h, then cooled and filtered through Celite®, concentrated, purified using normal phase chromatography. 400 MHz ^{1}H NMR ($CDCl_3$) δ 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).

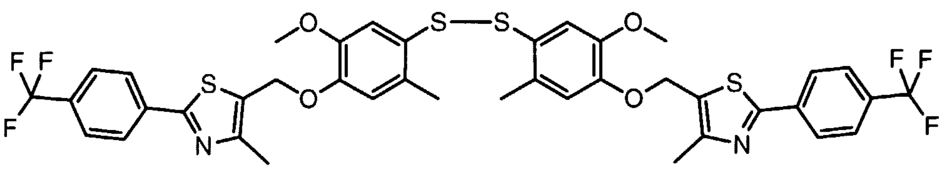
Example 28

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)



28

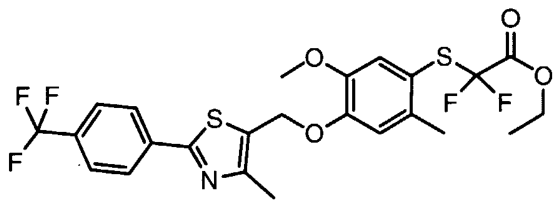
Preparation of 5-Methoxy-2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzene disulfide (compound 28A)



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) δ 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)



28B

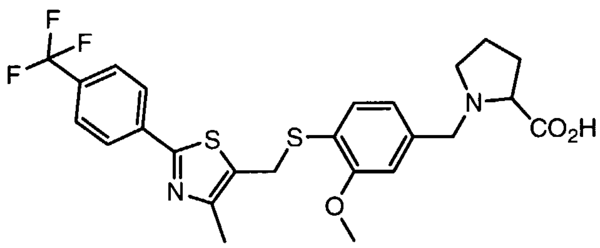
The mixture of the product from example **28A**, triphenylphospine, HCl in water and dioxane was heated at 60 °C for 12 h, then cooled to room temperature and concentrated in vacuo. The residue was dissolved in anhydrous acetonitrile, ethyl 2-bromo-2,2-difluoroacetate and cesium carbonate were added. 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 ($CDCl_3$) δ 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).

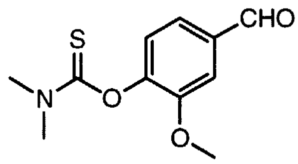
Example 29

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



29

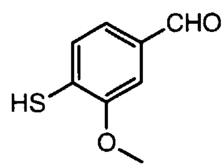
Preparation of Dimethylthiocarbamic acid O- (4-formyl-2methoxyphenyl) ester (compound 29A)



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 $C_{13}H_{15}NO_2$: Calc: C, 55.21%; H, 5.48%; N, 5.85%; Found: C, 55.17%; H, 5.42%; N, 5.92%.

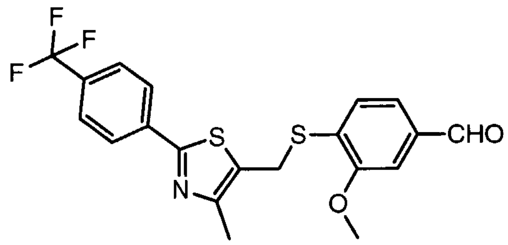
Preparation of 4-Mecapto-3-methoxybenzaldehyde (compound 29B)



29B

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, $CDCl_3$) δ 3.96 (s, 3H), 4.16 (s, 1H), 7.32-7.40 (m, 3H), 9.87 (s, 1H). MS: (m+1) 169.

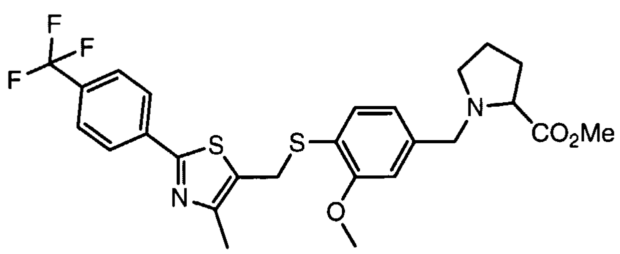
Preparation of 3-Methoxy-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsufanyl]benzaldehyde (compound 29C)



29C

To a solution of **29B** in acetonitrile, under nitrogen atmosphere, was added 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)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, $CDCl_3$) 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-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]benzyl}pyrrolidine-2-carboxylic acid methyl ester (compound 29 D)**



29D

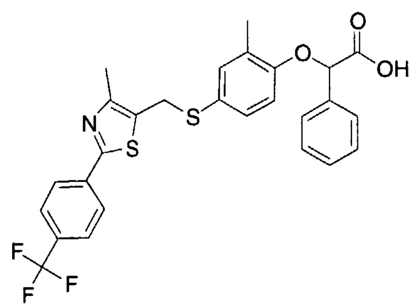
To a solution of **29C** in THF and N,N'-dimethylethyleneurea under nitrogen atmosphere was added DL-methylproline hydrochloride. The resulting mixture was stirred until clear , then glacial acetic acid was added dropwise followed by sodium triacetoxyborohydride in small portions over 30 min. The reaction 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, $CDCl_3$) 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 = 4,2H). MS: (m+1) 537.

Preparation of 1-[{3-Methoxy-4-[4-methyl-2(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]benzyl}pyrrolidine-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.

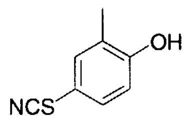
Example 30

<u>**Synthesis of ({2-Methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-phenyl-acetic acid (Compound 30)**</u>



30

Preparation of 4-thiocyanato-2-methyl-phenol (compound 30A)

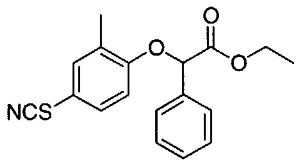


30A

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

400 MHz ^{1}H NMR (DMSO-d_6) δ 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).

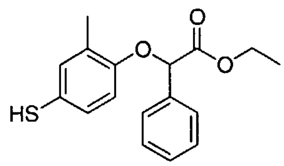
Preparation of (4-thiocyanato-2-methyl-phenoxy)-phenyl-acetic acid ethyl ester (Compound 30B)



30B

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.

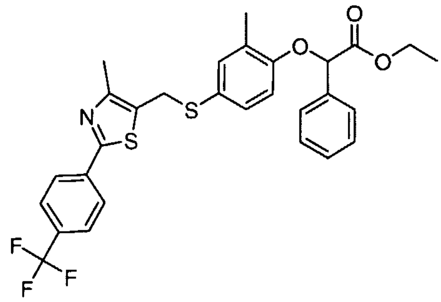
Preparation of (4-Mercapto-2-methyl-phenoxy)-phenyl-acetic acid ethyl ester (Compound 30C)



30C

The title compound was prepared in a manner analogous to compound **3C**. 400 MHz ^{1}H NMR (DMSO-d_6) δ 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)



30D

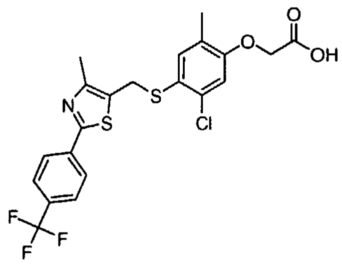
The title compound was prepared in a manner analogous to compound **1F**, using compound **30C** and **1B**. MS: (m+1) 558.

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 recrystalisation from $CHCl_3$/hexanes, the title compound as a solid. *m/z* = 530 (M+1).

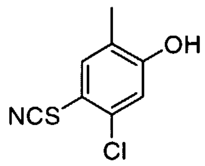
Example 31

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



31

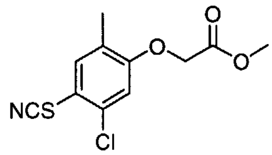
Preparation of 5-Chloro-2-methyl-4-thiocyanato-phenol (compound 31A)



31A

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

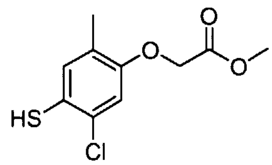
Preparation of (5-chloro-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (Compound 31B)



31B

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

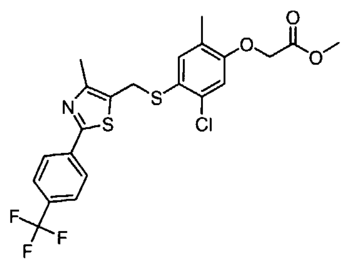
Preparation of (5-chloro-4-mercapto-2-methyl-phenoxy)-acetic acid methyl ester (Compound 31C)



31C

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)



31D

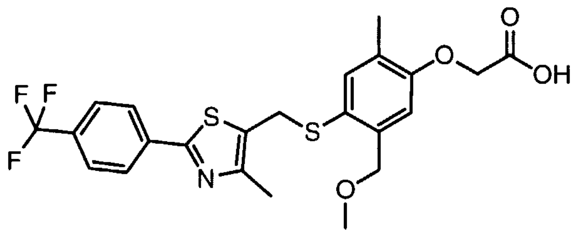
31C and 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (compound **1B**) were coupled in a similar manner as described for compound **1F** to provide, after purification by flash column chromatography (gradient elution: 5% EtOAc/hexanes to 35% EtOAc/hexanes), the title compound as a yellow 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 recrystalisation from $CHCl_3$/hexanes, the title compound as a solid. MS *m/z* 488 (M+1).

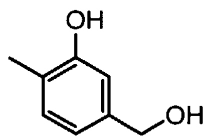
Example 32

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)



32

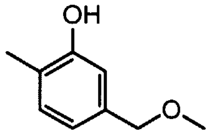
Preparation of 5-(hydroxymethyl)-2-methylphenol (Compound 32A)



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).

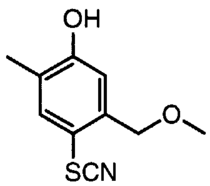
Preparation of 5-(methoxymethyl)-2-methylphenol (Compound 32B)



32B

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 (brs, 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).

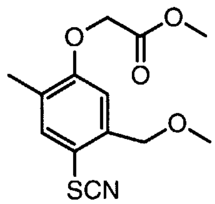
Preparation of 5-Methoxymethyl-2-methyl-4-thiocyanato-phenol (Compound 32C)



32C

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).

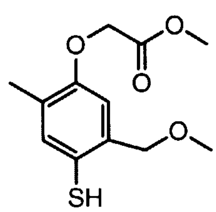
Preparation of (5-Methoxymethyl-2-methyl-4-thiocyanato-phenoxy)-acetic acid methyl ester (Compound 32D)



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).

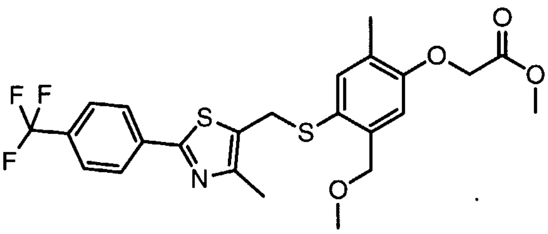
Preparation of methyl 2-[5-(methoxymethyl)-2-methyl-4-sulfanylphenoxy]acetate (Compound 32E)



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 ($CDCl_3$) δ 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)



32F

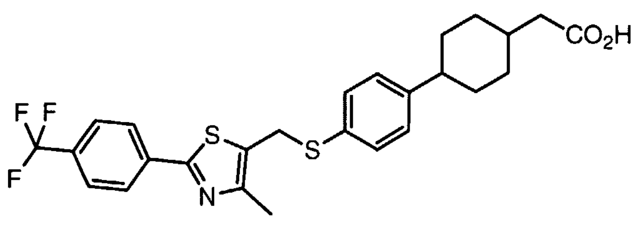
Compound 32E was dissolved in anhydrous acetonitrile, then 5-(chloromethyl)-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole was added followed by cesium carbonate. The mixture was stirred at room temperature for 2 h, then filtered through Celite®, concentrated, and purified using normal phase chromatography to afford the title product. 400 MHz ^{1}H NMR ($CDCl_3$) δ 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).

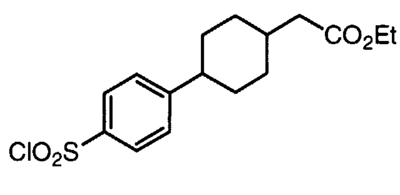
Example 33

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



33

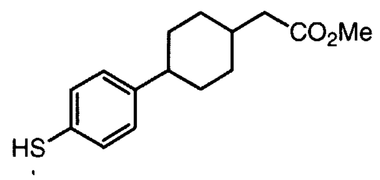
Preparation of [4-(4-Chlorosulfonyl-phenyl)-cyclohexyl]-acetic acid ethyl ester (compound 33A):



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 $(M+1)^+$

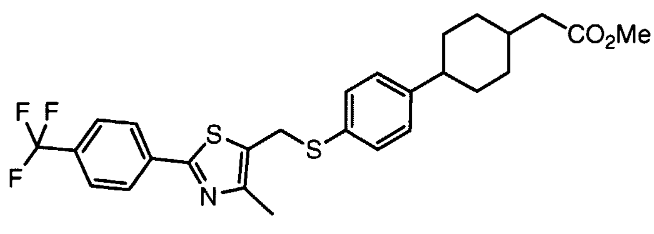
Preparation of [4-(4-Mercapto-phenyl)-cyclohexyl]-acetic acid methyl ester (Compound 33B):



33B

Compound **33A** was refluxed with tin powder in MeOH and 4M HCl/dioxane. After 3h, the reaction mixture was poured into ice with CH_2Cl_2. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. 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-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-cyclohexyl)-acetic acid methyl ester (Compound 33C):



33C

Compound **33B** (crude mixture from above) was dissolved in acetonitrile with chloride 5-chloromethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole and Cs_2CO_3.

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 $MgSO_4$ 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-[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 $LiOH.H_2O$. 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 $MgSO_4$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 $2.5x10^6$/dish and incubated overnight at 37C°/5% CO_2. 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 lucifease 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 the100 mm dishes and re-plated on 96 well plates. Cells were plated at $2.5x10^4$ cells per well in 150μl of media and 50μl of compound diluted by media was added. The test compounds added were in the range from 50μM to 50pM. After addition of compounds, the plates were incubated at 37C° 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 Bethold MicroLumat LB96P luminometer. EC_{50} 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 EC_{50} ("EC_{50}-β") data as well as the Hep G2-hAlpha EC_{50} ("EC_{50}-α") data of the compounds of the invention are presented in Table 2 below.

Table 2

Example	EC50-β nM	EC50-α nM
1	14.4	42
2	361.3	1227.5
3	1281.0	538
4	23.4	161
5	2.3	121
6	1235.0	1391
7	472.5	1338
8	45.3	840
9	891.3	5751.5
10	-	-
11	48.8	507.3
12	303.5	135
13	47.6	1098.2
14	6740.0	992
15	-	-
16	1953.2	1229
17	19.9	5.5
18	803.0	-
19	1124.0	1540
20	34.9	146
21	1246.5	442
22	-	-
23	-	-

Table 2 Continued

Example	EC50-β nM	EC50-α nM
24	2000000	2000000
25	2000000	-
26	.07	170.1
27	-	-
28	-	-
29	2000000	-
30	-	-
31	105.2	2047.4
32	649.0	625.1
33	2000000	-

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 levelswhich 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

Ingredient	Amount
compound of Formulas I-V	0.5 to 800 mg
sodium benzoate	5 mg
isotonic saline	1000 mL

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

Formulation 2

Ingredient	Amount
compound of Formulas I-V	0.5 to 800 mg
cellulose, microcrystalline	400 mg
stearic acid	5 mg
silicon dioxide	10 mg
sugar, confectionery	50 mg

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

Formulation 3

Ingredient	Amount
compound of Formulas I-V	0.5 to 800 mg
starch, dried	250 mg
magnesium stearate	10 mg

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

Formulation 4

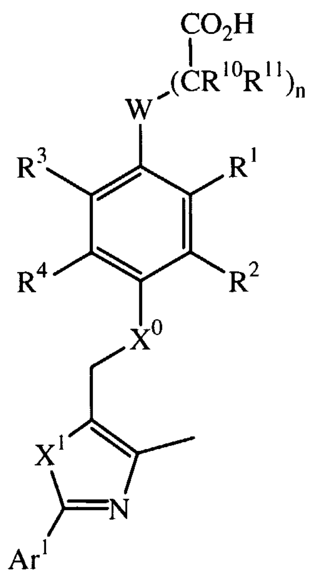
Ingredient	Amount % wt./(total wt.)
compound of Formulas I-V	1 to 50
Polyethylene glycol 1000	32 to 75
Polyethylene glycol 4000	16 to 25

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:



I

or a pharmaceutically acceptable salt thereof,

wherein:

W is O, S, 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 a unsubstituted or substituted aryl or heteroaryl;

R^1, R^2, R^3, and R^4 are independently alkyl, lower alkoxy, haloalkyl,-O-$(CH_2)_pCF_3$, halogen, nitro, cyano, -OH, -SH, $-CF_3$, $-S(O)_p$alkyl, $S(O)_p$aryl, -$(CH_2)_mOR^7$, $-(CH_2)_mNR^8R^9$, $-COR^7$, $-CO_2H$, $-CO_2R^7$, or $-NR^8R^9$;

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_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, -$(CH_2)_m NR^8R^9$, or -$(CH_2)_m OR^7$;

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, $-CF_3$, $-S(O)_p$alkyl, $S(O)_p$aryl, -$(CH_2)_mOR^7$, $-(CH_2)_mNR^8R^9$, $-COR^7$, $-CO_2H$, $-CO_2R^7$, 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, $-CO_2$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;

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;

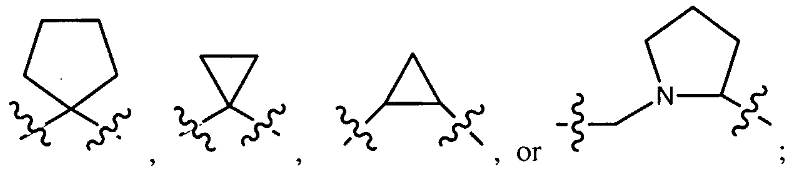
R^8 and R^9 are independently hydrogen, alkyl, or –COalkyl;

m is 0 to 5; and

n is 0.

6. A compound of claim 4, wherein

W is



, , , or ;

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^7 is independently hydrogen, or lower alkyl;

R^8 and R^9 are each independently hydrogen, or lower alkyl;

m is 0 to 5; and

n is 0.

7. A compound of claim1 or4, wherein:

R^2 and R^3 are hydrogen; and

R^1 and R^4 are lower alkyl or lower alkoxy.

8. A compound of claim1 or 4, wherein:

R^2 and R^3 are hydrogen;

R^1 is alkyl; and

R^4 is alkoxy.

9. A compound of claim1 or 4, wherein:

R^2 and R^3 are hydrogen;

R^1 is methyl, ethyl, isopropyl, n-propyl, t-butyl, n-butyl, or isobutyl; and

R^4 is methyoxy, ethoxy, isopropoxy, n-propoxy, t-butoxy, n-butoxy, or isobutoxy.

10. A compound selected from the group:

{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-ylmethylsulfanyl]-phenoxy}-acetic acid;

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

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

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

2-Methyl-2-{4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}-propionic acid;

2-{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}-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-ylmethy lsulfanyl]-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-Methtyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{4-[4-Methtyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-2-phenyl-propionic acid;

3-{4-[4-Methtyl-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-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenyl}cyclohexyl)-acetic acid; and
pharmaceutically acceptable salts thereof.

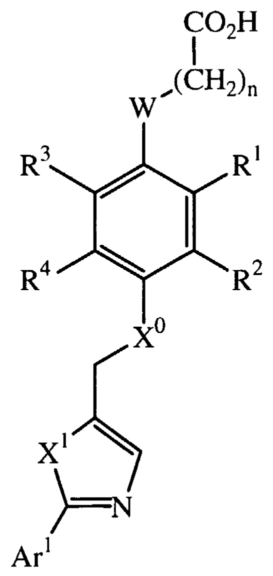
11. A pharmaceutical composition comprising a compound of claim 1, 4, or 10 and one or more pharmaceutically acceptable carriers, diluents, or excipients.

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.

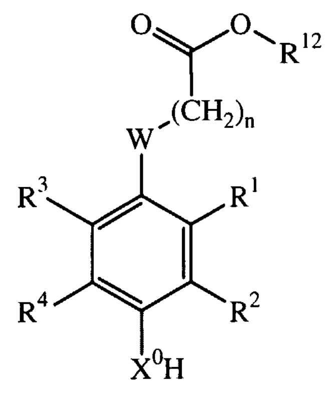
14. A method of treating, preventing or controlling atherosclerosis in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of claim 1, 4, or 10.

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

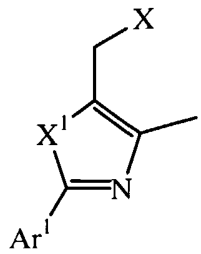


I,

the method comprising, reacting:



with:



wherein:

W is O, S, 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 a unsubstituted or substituted aryl or heteroaryl;

R^1, R^2, R^3, and R^4 are independently alkyl, lower alkoxy, haloalkyl,-O-$(CH_2)_pCF_3$, halogen, nitro, cyano, -OH, -SH, -CF_3, -$S(O)_p$alkyl, $S(O)_p$aryl, -$(CH_2)_mOR^7$, -$(CH_2)_mNR^8R^9$, -COR^7, -CO_2H, -CO_2R^7, or –NR^8R^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_2alkyl, -CO_2aryl, -SO_2alkyl, -SO_2aryl, 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

In[redacted]tional Application No
PCT/IB 03/00708

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/426 A61K31/427 C07D277/26 C07D277/24 C07D417/12

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

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 02 50047 A (SIERRA MICHAEL LAWRENCE ;GLAXO GROUP LTD (GB)) 27 June 2002 (2002-06-27) the whole document ---	1-15
P,Y	WO 02 092590 A (SIERRA MICHAEL LAWRENCE ;BESWICK PAUL JOHN (GB); RAMSDEN NIGEL GRA) 21 November 2002 (2002-11-21) the whole document ---	1-15
P,X	WO 02 062774 A (SIERRA MICHAEL LAWRENCE ;GOSMINI ROMAIN LUC MARIE (FR); GLAXO GROU) 15 August 2002 (2002-08-15) see examples and the general formula definitions ---	1-15
	-/--	

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"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 date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2003	09/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 00603 A (SIERRA MICHAEL LAWRENCE ;GELLIBERT FRANCOISE JEANNE (FR); GLAXO GR) 4 January 2001 (2001-01-04)	1,4,5, 11-15
Y	see general formula and examples (eg 1-8)	1-15

P,X	WO 02 100403 A (GONZALEZ-GARCIA MARIA ROSARIO ;GREEN JONATHAN EDWARD (US); WARSHAW) 19 December 2002 (2002-12-19)	1,4,5, 11-15
Y	see general formula, especially definitions of Y4, and examples (eg 3,6,9)	1-15

Y	EP 0 930 299 A (JAPAN TOBACCO INC) 21 July 1999 (1999-07-21) the whole document	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/00708

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 th epossibility 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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In[redacted]tional Application No
PCT/IB 03/00708

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WO 0250047 A	27-06-2002	AU 3327102 A	01-07-2002
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