Title: **INDOLE DERIVATIVES AND THEIR USE AS THYROID RECEPTOR LIGANDS**

Diagram:

![Diagram of Indole Derivatives](image)

**Partial agonist.**

**Abstract:** The invention provides compounds of formula (I) or pharmaceutically acceptable esters, amides, solvates or salts thereof, including salts of such esters or amides, and solvates of such esters, amides or salts, (I) wherein R1, R2, R3, R4, R5, R6, Y and W are as defined in the specification. The invention also provides the use of such compounds in the treatment or prophylaxis of a condition that may be treated with a thyroid receptor agonist or...
INDOLE DERIVATIVES AND THEIR USE AS THYROID RECEPTOR LIGANDS

Field of the invention
The present invention relates to compounds which are agonists or partial agonists of the thyroid receptor and the use of such compounds for therapeutic purposes.

Background of the invention
While the extensive role of thyroid hormones in regulating metabolism in humans is well recognized, the discovery and development of new specific drugs for improving the treatment of hyperthyroidism and hypothyroidism has been slow. This has also limited the development of thyroid agonists and antagonists for treatment of other important clinical indications, such as hypercholesterolemia, dyslipidemia, obesity, diabetes, atherosclerosis, cardiac diseases, and various endocrine disorders.

Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, metabolic rate, body temperature and mood, and influence blood levels of serum lipoproteins. Thus, in hypothyroidism there is weight gain, high levels of LDL cholesterol, and depression. In hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL cholesterol levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T₄) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or T₃) returns metabolic functions to normal and can easily be monitored with routine serum measurements of levels of thyroid-stimulating hormone (TSH), T₄ or T₃. However, replacement therapy, particularly in older individuals, may be restricted by certain detrimental effects from thyroid hormones.

In addition, some effects of thyroid hormones may be therapeutically useful in non-thyroid disorders if adverse effects can be minimized or eliminated. These potentially useful influences include for example, lowering of serum LDL levels, weight reduction, amelioration of depression and stimulation of bone formation. Prior attempts to utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in particular by cardiovascular toxicity.

Furthermore, useful thyroid agonist drugs should minimize the potential for undesired consequences due to locally induced hypothyroidism, i.e. sub-normal levels of thyroid hormone activity in certain
tissues or organs. This can arise because increased circulating thyroid hormone agonist concentrations may cause the pituitary to suppress the secretion of thyroid stimulating hormone (TSH), thereby reducing thyroid hormone synthesis by the thyroid gland (negative feedback control). Since endogenous thyroid hormone levels are reduced, localized hypothyroidism can result wherever the administered thyroid agonist drug fails to compensate for the reduction in endogenous hormone levels in specific tissues.

Development of specific and selective thyroid hormone receptor ligands, particularly agonists of the thyroid hormone receptor, is expected to lead to specific therapies for these common disorders, while avoiding the cardiovascular and other toxicity of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Tissue selectivity can also be achieved by selective regulation of thyroid hormone responsive genes in a tissue specific manner.

Accordingly, the compounds that are thyroid hormone receptor ligands, particularly selective agonists of the thyroid hormone receptor, are expected to demonstrate a utility for the treatment or prevention of diseases or disorders associated with thyroid hormone activity, for example: (1) hypercholesterolemia, dyslipidemia or any other lipid disorder manifested by an unbalance of blood or tissue lipid levels; (2) atherosclerosis; (3) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (4) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (5) obesity; (6) diabetes (7) depression; (8) osteoporosis (especially in combination with a bone resorption inhibitor); (9) goiter; (10) thyroid cancer; (11) cardiovascular disease or congestive heart failure; (12) glaucoma; and (13) skin disorders.

US 6,794,406 discloses certain novel indole derivatives useful for treating indications which can be treated using natural thyroid hormones, for example depression, goitre or cancer of the thyroid.

We have now found that certain novel 2,3-disubstituted indole derivatives have valuable therapeutic properties.

Summary of the invention
The present invention provides a compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt,
wherein:

5 \( R^1 \) is selected from \(-(\text{CH}_2)_n\text{-SO}_2\text{-R}^a\), \(-(\text{CH}_2)_n\text{-NH-SO}_2\text{-R}\), \(-(\text{CH}_2)_n\text{-SO}_2\text{-NH-R}^a\), \(-(\text{CH}_2)_n\text{-NH-CO-R}^a\), \(-(\text{CH}_2)_n\text{-CO-N(R)^b}\), \(-(\text{CH}_2)_n\text{-CO}_2\text{R}^a\), \(\text{C}_{6\text{-g}}\text{-alkyl}\), \(\text{C}_{2\text{-d}}\text{-alkenyl}\), \(\text{C}_{3\text{-e}}\text{ cycloalkyl-I-C}_{1\text{-f}}\text{-alkyl}\), \(\text{C}_{6\text{-i}}\text{-aryl}\), benzyl and \(\text{C}_{3\text{-j}}\text{-heterocyclyl}\), said alkyl, alkenyl or aikynyl optionally being substituted with 1, 2 or 3 groups each independently selected from halogen, hydroxy, \(\text{Cl}_{1\text{-q}}\text{-alkylthio}\), phenyl, or methoxy optionally substituted with 1, 2 or 3 halogen atoms; and said cycloalkyl, \(\text{Ce}_{1\text{-o}}\text{aryl}\), benzyl, \(\text{N(R)^b}_2\) or heterocyclyl optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, cyano, \(\text{C}_{1\text{-t}}\text{-alkyl}\), \(\text{C}_{2\text{-r}}\text{-alkenyl}\), \(\text{C}_{2\text{-s}}\text{-aikynyl}\), \(\text{N(R)^b}_2\), \(\text{haloCl}_{1\text{-q}}\text{-alkyl}\), \(\text{dihaloC}_M\text{-alkyl}\), \(\text{trihaloCl}_{1\text{-q}}\text{-alkyl}\) or \(\text{Cl}_{1\text{-r}}\text{-alkoxy}\) optionally substituted with 1, 2 or 3 halogen atoms, and wherein two of the 1, 2 or 3 groups may together with the atoms of the group to which they are attached form a 5-, 6- or 7-membered cyclic group optionally containing one or two heteroatoms selected from \(\text{O}\), \(\text{N}\) and \(\text{S}\);

each \( R^a \) is independently selected from hydrogen, \(\text{C}_{1\text{-t}}\text{-alkyl}\), \(\text{C}_{2\text{-r}}\text{-alkenyl}\), \(\text{C}_{2\text{-s}}\text{-aikynyl}\), fluoromethyl, difluoromethyl, or trifluoromethyl, benzyl, heterocyclyl and phenyl, said alkyl, alkenyl, aikynyl or phenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from \(\text{C}_{1\text{-t}}\text{-alkyl}\), halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

\( n \) is 0, 1, 2 or 3;

25 \( R^6 \) is selected from methyl, ethyl and n-propyl;

each \( R^2 \) is independently selected from halogen, mercapto, hydroxy, cyano, \(\text{C}_{1\text{-t}}\text{-alkoxy}\), \(\text{C}_{1\text{-t}}\text{-alkyl}\) and \(\text{N(R)^b}_2\), said alkyl or alkoxy groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;
each R\textsuperscript{b} is independently selected from a hydrogen atom and a C\textsubscript{1-4} alkyl group optionally substituted with 1, 2 or 3 groups independently selected from halogen, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

m is 0, 1 or 2;

Y is selected from oxygen, methylene, sulphur, SO, SO\textsubscript{2} and -N(R\textsuperscript{b});

R\textsuperscript{3} and R\textsuperscript{4} are independently selected from halogen, C\textsubscript{1-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, C\textsubscript{3} alkoxy, fluormethoxy, difluoromethoxy and trifluoromethoxy;

W is selected from C\textsubscript{1-3} alkenylene, C\textsubscript{2-3} alkenylene, C\textsubscript{2-3} alkenylene, N(R\textsuperscript{3})\textsubscript{2}-C\textsubscript{1-3} alkenylene, C(O)-C\textsubscript{1-3} alkenylene, S-C\textsubscript{1-3} alkenylene, O-C\textsubscript{1-3} alkenylene, C\textsubscript{1-3} alkenylene-O-C\textsubscript{1-3} alkenylene, C(O)NH-C\textsubscript{1-3} alkenylene, NHC(O)-C\textsubscript{1-3} alkenylene and C\textsubscript{1-3} alkenylene-C(O)NH-C\textsubscript{1-3} alkenylene, said alkenylene or alkenylene groups or portions of groups optionally being substituted with 1 or 2 groups selected from hydroxy, mercapto, amino, halo, C\textsubscript{1-3} alkyl, C\textsubscript{1-3} alkoxy, phenyl, C\textsubscript{1-3} alkyl substituted with phenyl, haloC\textsubscript{1-3} alkyl, dihaloC\textsubscript{1-3} alkyl, trihaloC\textsubscript{1-3} alkyl, haloC\textsubscript{1-3} alkoxy, dihaloC\textsubscript{1-3} alkoxy, trihaloC\textsubscript{1-3} alkoxy, and phenyl substituted with 1, 2 or 3 halogen atoms;

R\textsuperscript{5} is selected from hydrogen, hydroxy, Ci\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, fluoromethyl, difluoromethyl and trifluoromethyl;

R\textsuperscript{5} is selected from -CO\textsubscript{2}R\textsuperscript{6}, -PO(OR\textsuperscript{d})\textsubscript{2}, -PO(OR\textsuperscript{d})\textsubscript{2}NH\textsubscript{2}, -SO\textsubscript{2}OR\textsuperscript{d}, -COCO\textsubscript{2}H, -CONR\textsuperscript{d}OR\textsuperscript{d}, -SO\textsubscript{2}NHR\textsuperscript{d}, -NH\textsubscript{2}SO\textsubscript{2}R\textsuperscript{d}, -CONH\textsubscript{2}SO\textsubscript{2}R\textsuperscript{d}, and -SO\textsubscript{2}NHCOR\textsuperscript{d};

R\textsuperscript{d} is independently selected from hydrogen, Ci\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{3-7} heterocycl, C\textsubscript{5-10} aryl and C\textsubscript{5-10} aryly substituted with 1, 2 or 3 groups independently selected from amino, hydroxy, halogen or C\textsubscript{1-4} alkyl.

**Detailed description of the invention**

Preferably, R\textsuperscript{1} is selected from -(CH\textsubscript{2})\textsubscript{n}SO\textsubscript{2}R\textsuperscript{a}, -(CH\textsubscript{2})\textsubscript{n}NH-SO\textsubscript{2}R\textsuperscript{a}, -(CH\textsubscript{2})\textsubscript{n}SO\textsubscript{2}NH-R\textsuperscript{a}, -(CH\textsubscript{2})\textsubscript{n}NH-CO-R\textsuperscript{a}, -(CH\textsubscript{2})\textsubscript{n}CO\textsubscript{2}R\textsuperscript{a}, C\textsubscript{1-8} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{3-7} cycloalkyl, C\textsubscript{3-7} cycloalkyl-C\textsubscript{1-3} alkyl, phenyl, benzyl and C\textsubscript{3-7} heterocycl, said alkyl, alkenyl or alkynyl optionally being substituted with 1, 2 or 3 groups each independently selected from halogen, hydroxy, C\textsubscript{1-4} alkylthio, phenyl, or methoxy optionally substituted with 1, 2 or 3 halogen atoms; and said cycloalkyl, phenyl, benzyl, N(R\textsuperscript{a})\textsubscript{2} or heterocyclyl optionally being substituted with 1, 2 or 3 groups independently
selected from halogen, hydroxy, cyano, C<sub>M</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, N(R<sup>b</sup>)<sub>2</sub>, haloC<sub>i</sub>.<sub>4</sub> alkyl, dihaloC<sub>1</sub>-alkyl, trihaloC<sub>1</sub>-alkyl or methoxy optionally substituted with 1, 2 or 3 halogen atoms, and wherein two of the 1, 2 or 3 groups may together with the atoms of the group to which they are attached form a 5-, 6- or 7-membered cyclic group optionally containing one or two heteroatoms selected from O, N and S;

wherein each R<sup>i</sup> is independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl, benzyl, heterocyclyl and phenyl, said alkyl, alkenyl, alkynyl or phenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from Q<sub>4</sub> alkyl, halogen, hydroxy, methoxy, halomethoxy, difhalomethoxy, and trihalomethoxy;

R<sup>e</sup> is selected from C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl, benzyl, heterocyclyl and phenyl, said alkyl, alkenyl, alkynyl or phenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from C<sub>1-4</sub> alkyl, halogen, hydroxy, methoxy, halomethoxy, difhalomethoxy, and trihalomethoxy; and

n is 0, 1, 2 or 3.

Any alkyl, alkenyl or alkynyl group present in R<sup>i</sup> is preferably unsubstituted or substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, C<sub>1</sub>-alkylthio, phenyl, methoxy, halomethoxy, difhalomethoxy, and trihalomethoxy; and any cycloalkyl, phenyl, benzyl or heterocyclyl group is preferably unsubstituted or substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, C<sub>1</sub>-alkyl, haloC<sub>1</sub>-alkyl, dihaloC<sub>1</sub>-alkyl, tri haloC<sub>1</sub>-alkyl, methoxy, halomethoxy, difhalomethoxy, and trihalomethoxy. A substituted alkyl group R<sup>i</sup> may for example be a fluoromethyl, difluoromethyl or trifluoromethyl group.

Preferably, R<sup>i</sup> is selected from -(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-NH-SO<sub>2</sub>-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>-NH-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-NH-CO-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-CO-NH-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-CO-O-R<sup>a</sup>, C<sub>r</sub>-6 alkyl, C<sub>r</sub>-6 cycloalkyl, C<sub>r</sub>-6 cycloalkyl-C<sub>r</sub>-3 alky1, phenyl, benzyl and C<sub>3-7</sub> heterocyclyl; more preferably, R<sup>i</sup> is selected from -(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-NH-SO<sub>2</sub>-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>-NH-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-NH-CO-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-CO-NH-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-CO-O-R<sup>a</sup>, C<sub>r</sub>-6 alkyl, phenyl, benzyl and C<sub>3-7</sub> heterocyclyl; any alkyl, cycloalkyl, aryl or heterocyclyl group begin optionally substituted by one of the preferred substituents given above.

More preferably, R<sup>i</sup> is selected from -(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-NH-SO<sub>2</sub>-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>-NH-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-NH-CO-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-CO-NH-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-CO-O-R<sup>a</sup>, C<sub>r</sub>-6 alkyl, C<sub>r</sub>-6 cycloalkyl, C<sub>r</sub>-6 cycloalkyl-C<sub>r</sub>-3 alkyl, phenyl, benzyl and C<sub>3-7</sub> heterocyclyl; more preferably, R<sup>i</sup> is selected from -(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>-R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>-NH-
SO₂-R, -(CH₂)ₙ-SO₂-NH-R, -(CH₂)ₙ-NH-CO-R, C₆ alkyl, phenyl, benzyl and C₃-7 heterocyclyl;
any alkyl, cycloalkyl, aryl or heterocyclyl group begin optionally substituted by one of the preferred
substituents given above.

Preferably n is 0, 1 or 2. More preferably n is 0 or 1.

More preferably R¹ represents a C₁-₄ alkyl group, especially a methyl group; a phenyl group
optionally substituted by one or more substituents selected from halogen atoms and hydroxyl or
methoxy groups; a pyridyl group; or a CONHR² group.

Most preferably R¹ represents a C₂-₄ alkyl; a phenyl group optionally substituted by one or more
substituents selected from halogen atoms and hydroxyl or methoxy groups; a pyridyl group; a
CO₂Me group; or a CO₂Et group.

Where R¹ represents a phenyl group, the phenyl group is preferably substituted by one or two
substituents selected from halogen atoms and hydroxyl or methoxy groups. Preferred halogen
substituents for the phenyl group are bromo, chloro or fluoro, more preferably bromo or chloro.
Preferably, the phenyl group is substituted in the para or meta position with respect to the point of
attachment to the indole ring, more preferably the phenyl group is substituted in the para position.

Alternatively, where R¹ represents a phenyl group, the phenyl group may be substituted with two
groups which together with the atoms of the phenyl group to which they are attached form a 5-, or
6-membered cyclic group optionally containing one or two heteroatoms selected from O, N and S;
more preferably the two groups together with the atoms of the phenyl group to which they are
attached form a 5-, or 6-membered cyclic group, for example a 5-membered cyclic group,
containing one or two oxygen heteroatoms.

Preferably R² represents a C₁-₄ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzyl,
heterocyclyl or phenyl group being unsubstituted or substituted by C₁-₄ alkyl or halogen. More
preferably, R² represents an unsubstituted C₁-₄ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl
group, for example a methyl or ethyl group.

Preferably R² represents a C₁-₄ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzyl,
heterocyclyl or phenyl, group being unsubstituted or substituted by C₁-₄ alkyl or halogen. More
preferably, R² represents an unsubstituted C₆ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl
group, for example a methyl or ethyl group.
Preferably $R^4$ represents a methyl or ethyl group, especially an ethyl group.

Preferred substituents for an alkyl or alkoxy group $R^2$ are independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy.

Preferably m is 1 or, especially, 0.

Preferably, if present, each $R^2$ is independently selected from halogen, hydroxy, $C_{1,4}$ alkoxy, $C_{1,4}$ alkyl and $N(R^b)_2$, an alkyl or alkoxy group being unsubstituted or substituted by from 1 to 3 of the preferred substituents given above. More preferably, $R^2$ is selected from halogen, $C_{1,4}$ alkoxy and $C_{1,4}$ alkyl.

Preferably, $R^b$ is selected from hydrogen and $C_{1,4}$ alkyl or haloalkyl.

$R^3$ and $R^4$ are preferably independently selected from halogen, $C_{1,4}$ alkyl, fluoromethyl, difluoromethyl and trifluoromethyl. More preferably, $R^3$ and $R^4$ are independently selected from halogen, methyl, ethyl, propyl, fluoromethyl, difluoromethyl and trifluoromethyl, especially methyl or halogen. A halogen $R^3$ or $R^4$ is preferably selected from chlorine, bromine, and fluorine, especially chlorine and bromine. Preferably $R^3$ and $R^4$ represent the same group.

Preferably, $Y$ is methylene or oxygen, especially, oxygen.

An alkyne, alkenylene or alkynylene moiety present in $W$ is preferably unsubstituted or substituted by 1 or 2 groups selected from hydroxy, mercapto, amino, halo, $C_{1,3}$ alkyl, $C_{1,3}$ alkoxy, halo$C_{1,3}$ alkyl, dihalo$C_{1,3}$ alkyl, trihalo$C_{1,3}$ alkyl, halo$C_{1,3}$ alkoxy, dihalo$C_{1,3}$ alkoxy, and trihalo$C_{1,3}$ alkoxy. Preferred halo groups are chloro or fluoro, particularly fluoro.

$W$ is preferably selected from $C_{1,3}$ alkyne, $C_{2,3}$ alkenylene, $C_{2,3}$ alkynylene, $N(R^6)-C_{1,3}$ alkyne, $C(O)-C_{1,3}$ alkyne, $S-C_{1,3}$ alkyne, $O-C_{1,3}$ alkyne, $C_{1,3}$ alkyne-$O-C_{1,3}$ alkyne, $C(O)NH-C_{1,3}$ alkyne and $NHC(O)-C_{1,3}$ alkyne, said alkyne, alkenylene or alkynylene moiety being optionally substituted by 1 or 2 of the preferred substituents given above.

$R^c$ is preferably selected from hydrogen, $C_{1,2}$ alkyl, fluoromethyl, difluoromethyl and trifluoromethyl.
W is more preferably selected from C₃ alkylene, C₁₋₃ alkylene-O-C₁₋₃ alkylene, C₂₋₃ alkenylene, N(R⁺)-Cᵗ₂ alkylene, O-C₁₋₃ alkylene, C(O)NH-C₂ alkylene and NHC(O)-C₂ alkylene, said alkylene or alkenylene moiety optionally being substituted with a group selected from halo, C₂ alkyl, C₂ alkoxy, haloC₂ alkyl, dihaloC₁₋₂ alkyl, trihaloC₂ alkyl, haloC₂ alkoxy, dihaloC₁₋₂ alkoxy, and trihaloC₁₋₂ alkoxy.

Most preferably, W is selected from C₃ alkylene, O-C₂ alkylene, C(O)NH-C₂ alkylene and NHC(O)-C₂ alkylene, especially ethylene or C(O)NH-CH₂, in which the alkylene group (for example the ethylene group) is unsubstituted or, preferably, substituted with one or more halo groups, for example one or more fluoro groups (for example one fluoro group). Monohalo C₃ alkylene (for example fluoro C₁₋₃ alkylene) thus constitutes a preferred group W.

In another preferred embodiment, W is selected from C₃ alkylene, O-C₂ alkylene, and C(O)NH-C₁₋₃ alkylene, and monohalo C₁₋₃ alkylene. More preferably, W is selected from C₂ alkylene, 0-CH₂-C(O)NH-CH₂-, and monofluoro C₂ alkylene.

In another preferred embodiment, W is selected from C₃ alkylene, C₂₋₃ alkenylene, O-C₃ alkylene, C(O)NH-C₂ alkylene and NHC(O)-C₂ alkylene.

Preferably, R⁵ is selected from -CO₂R⁴, -SO₂OR⁴, -COCONH₂, -CONR⁴OR⁴, -SO₂NHR⁴, -NHSO₂R⁴, -CONHSO₂R⁴, and -SO₂NHCOR⁴.

R⁵ is more preferably selected from -CO₂R⁴, -SO₂OR⁴, -NHSO₂R⁴, -COCONH₂ and -CONR⁴OR⁴. Most preferably, R⁵ is -CO₂R⁴, or -SO₂OR⁴. Most particularly preferably, R⁵ is -CO₂R⁴, particularly -CO₂H.

R⁴ is preferably hydrogen, ethyl, methyl, phenyl or phenyl substituted with 1, 2 or 3 groups independently selected from amino, hydroxyl, halogen and methyl, particularly R⁴ is hydrogen.

Thus, in one preferred group of compounds of the invention, R¹ is selected from -(CH₂)ₙSO₂R³, -(CH₂)ₙNH-SO₂-R³, -(CH₂)ₙNH-SO₂-NH-R³, -(CH₂)ₙNH-CO-R³, -(CH₂)ₙ-C₀-NH-R³, C₆ alkyl, phenyl, benzyl and C₃₋₇ heterocyclyl; any alkyl group being optionally substituted by halogen, hydroxy, phenyl, benzyl, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy, and any cycloalkyl, phenyl, benzyl or heterocyclyl group being optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, C₃ alkyl, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy.
n is 0, 1 or 2, preferably 0 or 1;

R^a represents a C\textsubscript{1-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzyl, heterocyclyl or phenyl group being unsubstituted or substituted by C\textsubscript{1-4} alkyl or halogen.

R^6 represents a methyl, ethyl or n-propyl group;

m is 1 or 0;

if present, R^2 is selected from halogen, hydroxy, C\textsubscript{M} alkoxy, C\textsubscript{1-4} alkyl and N(R^b)\textsubscript{2}, an alkyl or alkoxy group being unsubstituted or substituted by from 1 to 3 substituents independently selected from halogen, hydroxy, C\textsubscript{1-4} alkylthio, halomethoxy, dihalomethoxy, and trihalomethoxy, and R^b being selected from hydrogen and C\textsubscript{1-4} alkyl or haloalkyl;

R^3 and R^4 are independently selected from halogen, C\textsubscript{1-4} alkyl, fluoromethyl, difluoromethyl and trifluoromethyl;

Y is methylene or, preferably, oxygen;

W is selected from C\textsubscript{i-3} alkyne, C\textsubscript{1-3} alkylene-O-C\textsubscript{i-3} alkylene, C\textsubscript{2-3} alkenylene, N(R^c)\textsubscript{2}C\textsubscript{i-2} alkenylene, 0-C\textsubscript{2} alkenylene, C(O)NH-C\textsubscript{2} alkenylene and NHC(O)C\textsubscript{2} alkenylene, said alkenylene or alkenylene moieties optionally being substituted with a group selected from halo, C\textsubscript{1-2} alkyl, C\textsubscript{1-2} alkoxy, haloC\textsubscript{1-2} alkyl, dihaloC\textsubscript{1-2} alkyl, trihaloC\textsubscript{1-2} alkyl, haloC\textsubscript{1-2} alkoxy, dihaloC\textsubscript{1-2} alkoxy, and trihaloC\textsubscript{1-2} alkoxy, and R^c being selected from hydrogen, C\textsubscript{1-2} alkyl, fluoromethyl, difluoromethyl and trifluoromethyl; and

R^5 is selected from -CO\textsubscript{2}H, -SO\textsubscript{2}OR\textsuperscript{d}, -NHSO\textsubscript{2}R\textsuperscript{i}, -CO\textsubscript{2}H and CONR\textsubscript{d}OR\textsuperscript{d} in which R\textsuperscript{d} is ethyl, methyl, phenyl and phenyl substituted with 1, 2 or 3 groups independently selected from amino, hydroxyl, halogen and methyl or hydrogen, particularly hydrogen.

In a further preferred group of compounds, R^1 represents a C\textsubscript{1-4} alkyl group, a phenyl group optionally substituted by one or more substituents selected from halogen atoms and hydroxy or methoxy groups, a pyridyl group, or a COOH group;

R^6 represents a methyl, ethyl or n-propyl group, especially a methyl or ethyl group;

m is 0.
Y represents oxygen;

R³ and R⁴ represent the same group selected from halogen, methyl, ethyl, propyl, fluoromethyl, difluoromethyl and trifluoromethyl, especially methyl or halogen;

W is selected from d⁻³ alkylene, O-C⁻₂ alkylene, C(0)NH-C⁻₂ alkylene and NHC(O)-C⁻₂ alkylene, especially ethylene or C(O)NH-CH⁻₂, in which the alkylene group (for example the ethylene group) is unsubstituted or, preferably, substituted with one or more halo groups, for example one or more fluoro groups (for example one fluoro group); and

R⁵ is selected from -SO₂OR⁴ in which R⁴ is ethyl, methyl or hydrogen, particularly hydrogen, or, preferably, -CO₂H.

In these preferred compounds, W is preferably monohalo C₁₋₃ alkylene (for example fluoro C₁₋₃ alkylene), C₋₀ alkylene, C₂₋₃ alkenylene, 0-C₋₀ alkylene, C(O)NH-C₋₂ alkylene orNHC(O)-C₋₂ alkylene, for example CONH-CH⁻₂, (CH₂)₂ or, especially, OCH₂ or CH₂.

The compounds of formula (I) may contain chiral (asymmetric) centres or the molecule as a whole may be chiral. The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are within the scope of the present invention.

Suitable salts according to the invention include those formed with organic or inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycollic, lactic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, for example those of potassium and sodium, alkaline earth metal salts, for example those of calcium and magnesium, and salts with organic bases, for example dicyclohexylamine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters and amides of the compounds of formula (I) may have an appropriate group, for example an acid group, converted to a d⁻³ alkyl, C₅₋₁₀ aryl, C₅₋₁₀ aryl-C₁₋₆ alkyl, or amino acid ester or amide. Pharmaceutically acceptable esters of the compounds of formula (I) may have an appropriate group, for example a hydroxy group, converted to a C₁₋₆ alkyl, C₅₋₁₀ aryl, or C₅₋₁₀ aryl-C₁₋₆ alkyl ester. Pharmaceutically acceptable amides and carbamates of the
compounds of formula (I) may have an appropriate group, for example an amino group, converted to a C6 alkyl, C5:16 aryl, C5:10 ary1-C1:6 alkyl, or amino acid ester or amide, or carbamate.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate".

As used herein, the term "alkyl" means both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, i-butyl, sec-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl groups. Among unbranched alkyl groups, there are preferred methyl, ethyl, n-propyl, iso-propyl, n-butyl groups. Among branched alkyl groups, there may be mentioned t-butyl, i-butyl, 1-ethylpropyl, 1-ethylbutyl, and 1-ethylpentyl groups.

As used herein, the term "alkoxy" means the group O-alkyl, where "alkyl" is used as described above. Examples of alkoxy groups include methoxy and ethoxy groups. Other examples include propoxy and butoxy. A particularly preferred alkoxy group is methoxy.

As used herein, the term "alkenyl" means both straight and branched chain unsaturated hydrocarbon groups with at least one carbon carbon double bond. Up to 5 carbon carbon double bonds may, for example, be present. Examples of alkenyl groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and dodecenyl. Preferred alkynyl groups include ethenyl, 1- propenyl and 2- propenyl.

As used herein, the term "alkynyl" means both straight and branched chain unsaturated hydrocarbon groups with at least one carbon carbon triple bond. Up to 5 carbon carbon triple bonds may, for example, be present. Examples of alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and dodecynyl. Preferred alkenyl groups include ethynyl 1- propynyl and 2- propynyl.

As used herein, the term "cycloalkyl" means a saturated group in a ring system. The cycloalkyl group can be monocyclic or bicyclic. A bicyclic group may, for example, be fused or bridged. Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl and cyclopentyl. Other examples of monocyclic cycloalkyl groups are cyclohexyl, cycloheptyl and cyclooctyl. Examples of bicyclic cycloalkyl groups include bicyclo [2.2.1]hept-2-yl. Preferably, the cycloalkyl group is monocyclic.
As used herein, the term "aryl" means a monocyclic or bicyclic aromatic carbocyclic group. Examples of aryl groups include phenyl and naphthyl. A naphthyl group may be attached through the 1 or the 2 position. In a bicyclic aromatic group, one of the rings may, for example, be partially saturated. Examples of such groups include indanyl and tetrahydronapthyl. Specifically, the term C₆₋₁₀ aryl is used herein to mean a group comprising from 6 to 10 carbon atoms in a monocyclic or bicyclic aromatic group. A particularly preferred C₆₋₁₀ aryl group is phenyl.

As used herein, the term "halogen" means fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are particularly preferred. In some embodiments, fluorine is especially preferred. In alternative embodiments, chlorine or bromine are especially preferred.

As used herein, the term "heterocyclyl" means an aromatic ("heteroaryl") or a non-aromatic ("heterocycloalkyl") cyclic group of carbon atoms wherein from one to three of the carbon atoms is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen or sulfur. A heterocyclyl group may, for example, be monocyclic or bicyclic. In a bicyclic heterocyclyl group there may be one or more heteroatoms in each ring, or only in one of the rings. A heteroatom is preferably O or N. Heterocyclyl groups containing a suitable nitrogen atom include the corresponding N-oxides. Examples of monocyclic heterocycloalkyl rings include aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and azepanyl.

Examples of bicyclic heterocyclyl rings in which one of the rings is non-aromatic include dihydrobenzofuranyl, indanyl, indolinyi, isoindolinyi, tetrahydroisoquinolinyi, tetrahydroquinolinyi and benzoazepanyl.

Examples of monocyclic heteroaryl groups include furanyl, thiienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl and pyrimidinyl; examples of bicyclic heteroaryl groups include quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, quinolinyi, benzofuranyi, indolinyi, benzothiazolyl, oxazolyl[4,5-b]pyridiyl, pyridopyrimidinyl, isoquinolinyi and benzodioxazole.

Examples of preferred heterocyclyl groups include piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrimidinyl and indolinyi.
As used herein the term "cycloalkylalkyl" means a group cycloalkyl-alkyl- attached through the alkyl group, "cycloalkyl" and "alkyl" being understood to have the meanings outlined above.

Numerous synthetic routes to the compounds of the present invention can be devised by any person skilled in the art and the possible synthetic routes described below are not limiting. Many methods exist in the literature for the synthesis of diaryl ethers, for example, two references directly apply to the synthesis of thyroid hormone analogs: Evans D. A. et al. Tetrahedron Lett., 39, 2937-2940, 1998 and Salamonczyk G. M. et al., Tetrahedron Lett., 38, 6965-6968, 1997.


Compounds of the invention wherein Y contains oxygen, sulphur or -N(R³)- may be prepared by a process which comprises reacting a compound of formula (II)

\[
\begin{array}{c}
\text{H} - Y \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^5 \\
\end{array}
\]

(II)

wherein W, R³, R⁴, and R⁵ are as defined above and Y is oxygen, sulphur or -N(R³)- with a compound of formula (III)

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^6 \\
\text{N} \\
\text{R}^2 \text{mZ} \\
\end{array}
\]

(III)

wherein R¹, R⁶, R² and m are as defined above and PG is hydrogen or a suitable protecting group, and Z is a suitable leaving group, optionally in the presence of a suitable base and optionally, in the presence of copper powder, followed optionally by removal of the protecting group, if present, and optionally by interconversion to another compound of the invention.
Suitable leaving groups Z include halogens and boron derivatives, for example a fluoride. Suitable bases include carbonates, alkylamines and alkali metal hydroxides, for example potassium carbonate, caesium carbonate, potassium hydroxide, sodium hydroxide, diisopropylamine and triethylamine. Other combinations of leaving groups and bases may be employed, as is known by the person skilled in the art. Optionally, one or more coupling reagents may be employed. The reaction mixture may be stirred at room temperature or heated until the starting materials have been consumed. The reaction may be carried out with protecting groups present and those protecting groups may be removed after the reaction. Suitable protecting groups are known to the person skilled in the art (see T. W. Greene, "Protective Groups in Organic Synthesis", 3rd Edition, New York, 1999).

The groups Y-H and Z could be switched, being the leaving group in the (II) fragment (the nucleophilic substituent, Z) and the electrophilic radical Y-H in the (III) fragment.

Preferred compounds of formula (II) include:
- Methyl 3-(3,5-Dibromo-4-hydroxy-phenyl)-propanoate
- Methyl (E)-3-(3,5-Dibromo-4-hydroxy-phenyl)-acrylate
- Methyl (3,5-Dibromo-4-hydroxy-phenoxy)-acetate
- Methyl 3-(3,5-Dibromo-4-hydroxy-phenyl)-2-fluoro-propanoate
- Methyl (3,5-Dibromo-4-hydroxy-benzoylamino)-acetate

Compounds of the invention wherein Y contains methylene may be prepared by a process which comprises reacting a compound of formula (IV)

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

wherein W, R₃, R⁴, and R⁵ are as defined above with a compound of formula (V)

\[
\begin{align*}
\text{(V)}
\end{align*}
\]
wherein \( R^1, R^6, R^2 \) and \( m \) are as defined above and \( PG \) is hydrogen or a suitable protecting group, and \( Z \) may for example be lithium or a Mg-halide, such as MgBr or MgCl. Alternatively, \( Z \) may be a derivative of Sn, Pd, B or Cu.

Other combinations to produce a nucleophilic attack to an aldehyde may be employed, as is known by the person skilled in the art. Optionally, one or more coupling reagents may be employed. The reaction mixture may be stirred at room temperature or heated until the starting materials have been consumed. The reaction may be carried out with protecting groups present and those protecting groups may be removed after the reaction. Suitable protecting groups are known to the person skilled in the art (see T. W. Greene, "Protective Groups in Organic Synthesis", 3rd Edition, New York, 1999).

The groups \(-CHO\) and \( Z \) could be switched, being the leaving group in the (IV) fragment (the metal substituent, \( Z \)) and the aldehyde in the (V) fragment.

Compounds of the invention wherein \( Y \) is oxygen, sulphur or \(-N(R^b)\)- may be prepared by reacting a compound of formula (II) in which \( Y \) is oxygen, sulphur or \(-N(R^b)\)- with a compound of formula (VI)

\[
\begin{align*}
\text{(VI)}
\end{align*}
\]

wherein \( R^2 \) and \( m \) are as defined above and \( Z \) is a suitable leaving group, optionally in the presence of a suitable base and optionally in the presence of copper powder, followed by reduction of the nitro group to an amino group and reaction of the resultant amine with a suitable reagent to form the bicyclic ring, followed optionally by interconversion to another compound in accordance with the invention.

Suitable leaving groups \( Z \) and various reaction conditions are as given above.

Preferred compounds of formula (VI) include:

1. Fluoro-4-nitro-benzene
2. Chloro-4-fluoro-1-nitro-benzene
The invention also provides a method for preparing a compound of the invention wherein Y is oxygen, NR², sulphur or methylene comprising reacting a compound of formula (VII)

![Chemical Structure](image)

or the corresponding hydrazine of formula (Vila) formed by reacting a compound of formula (VII) with sodium nitrate which is followed by reduction with a suitable reducing agent such as tin (II) chloride

![Chemical Structure](image)

wherein R², R³, R⁴, R⁵, W and m are as defined above with a compound of formula (VIII)

![Chemical Structure](image)

wherein R¹ and R⁶ are as defined above and X can be a halogen or a hydrogen, in the presence of a suitable acid or Lewis acid and followed optionally by interconversion to another compound of formula (I) wherein Y is oxygen, NR², sulphur or methylene.

Suitable acids for use in the reaction include acetic acid, toluenesulphonic acid and phosphorous trichloride.

Other acids may be employed, as is known by the person skilled in the art. The reaction mixture is stirred at room temperature or heated until the starting materials have been consumed. The reaction may be carried out with protecting groups present and those protecting groups may be removed after the reaction. Suitable protecting groups are known to the person skilled in the art (see T. W. Greene, "Protective Groups in Organic Synthesis", 3rd Edition, New York, 1999).

Preferred compounds of formula (VII) include:
Methyl 3-[4-(4-amino-phenoxy)-3,5-dibromo-phenyl]-propanoate
Methyl 3-[4-(4-amino-phenoxy)-3,5-dibromo-phenyl]-2-fluoro-propanoate
Methyl (E)-3-[4-(4-amino-phenoxy)-3,5-dibromo-phenyl]-acrylate
Methyl [4-(4-amino-phenoxy)-3,5-dibromo-phenoxy]-acetate
Methyl [4-(4-amino-phenoxy)-3,5-dibromo-benzoylamino]-acetate

Preferred compounds of formula (VIII) include:
3',4'-(methyleneedioxy)butyrophenone
4-chlorobutyrophenone
p-methoxyvalerophenone
p-methoxybutyrophenone
4-propionylpyredine
2,4'-dibromopropiophenone
3-Bromo-butan-2-one
2-Bromo-1-(4-methoxy-phenyl)-propan-1-one

Compounds of the invention wherein Y is oxygen, NR^b or sulphur may be prepared by a process which comprises reacting a compound of formula (IX)

![Chemical Structure](image)

(IX)

wherein R^3 and R^4 are as defined above and where substituent V represents nitro, aldehyde, cyano, carboxyl or derivatives of carboxyls and Z is a suitable leaving group, with a compound of formula (X)

![Chemical Structure](image)

(X)

wherein R^1, R^6, R^2 and m are as defined above, PG is hydrogen or a suitable protecting group, and Y is oxygen, sulphur or -N(R^b)-, optionally in the presence of a suitable base, and optionally, in the presence of copper powder, followed optionally by removal of the protecting group, if present, and
optionally by interconversion to another compound of the invention wherein $Y$ is oxygen, $NR^3$, or sulphur.

Preferred compounds of formula (IX) include:

5 (3,5-Dichloro-4-fluoro-benzoylamino)-acetic acid tert-butyl ester
2-Chloro-5-nitro-1,3-bis(trifluoromethyl)benzene

Preferred compounds of formula (X) include:

5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid methyl ester
5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester
5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid isopropylamide
5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid ethylamide
3-Ethyl-2-(4-methoxy-phenyl)-1H-indol-5-ol
3-Ethyl-2-oxazol-4-yl-1H-indol-5-ol

Especially preferred compounds of formula (X) include:

5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid methyl ester
5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester
5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid isopropylamide

Other suitable conditions and reagents suitable for use in the above reactions for the preparation of compounds of the invention or for the synthesis of intermediates suitable for preparing compounds of formula (I) are described in the following references:

Tet. Lett. 32 (38); 1991; 5035-5038
Organic Preparations and procedures int., 25 (6), 609-632

As mentioned above, the compounds of the invention have activity as thyroid receptor ligands. The compounds of the invention are agonists or partial agonists of the thyroid receptor. Compounds of the present invention possess activity as agonists of the thyroid receptor. They may thus be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, compounds of the present invention may be used in the treatment of diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a $T_3$ regulated gene.
The example compounds below are agonists or partial agonists of the thyroid receptor.

Clinical conditions for which an agonist or partial agonist is indicated include, but are not limited to, hypothyroidism; subclinical hyperthyroidism; non-toxic goiter; atherosclerosis; thyroid hormone replacement therapy (e.g., in the elderly); malignant tumor cells containing the thyroid receptor; papillary or follicular cancer; maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or age-related functional decline ("ARFD") in the elderly (e.g., sarcopenia); treatment of catabolic side effects of glucocorticoids; prevention and/or treatment of reduced bone mass, density or growth (e.g., osteoporosis and osteopenia); treatment of chronic fatigue syndrome (CFS); accelerating healing of complicated fractures (e.g. distraction osteogenesis); in joint replacement; eating disorders (e.g., anorexia); treatment of obesity and growth retardation associated with obesity; treatment of depression, nervousness, irritability and stress; treatment of reduced mental energy and low self-esteem (e.g., motivation/assertiveness); improvement of cognitive function (e.g., the treatment of dementia, including Alzheimer's disease and short term memory loss); treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g., associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure; protection against ventricular dysfunction or prevention of reperfusion events; treatment of hyperinsulinemia; stimulation of osteoblasts, bone remodeling and cartilage growth; regulation of food intake; treatment of insulin resistance, including NIDDM, in mammals (e.g., humans); treatment of insulin resistance in the heart; treatment of congestive heart failure; treatment of musculoskeletal impairment (e.g., in the elderly); improvement of the overall pulmonary function; skin disorders or diseases, such as dermal atrophy, glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical glucocorticoids, and the prevention of dermal atrophy induced by topical glucocorticoids (such as the simultaneous treatment with topical glucocorticoid or a pharmacological product including both glucocorticoid and a compound of the invention), the restoration/prevention of dermal atrophy induced by systemic treatment with glucocorticoids, restoration/prevention of atrophy in the respiratory system induced by local treatment with glucocorticoids, UV-induced dermal atrophy, dermal atrophy induced by aging (wrinkles, etc.), wound healing, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring. In addition, the conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome as detailed in Johannsson J. Clin. Endocrinol. Metab., 82, 727-34 (1997), may be treated employing the compounds of the invention. The term treatment includes, where appropriate, prophylactic treatment.
Accordingly, the compounds of the invention find application in the treatment or prophylaxis of the following: (1) hypercholesterolemia, dyslipidemia or any other lipid disorder manifested by an unbalance of blood or tissue lipid levels; (2) atherosclerosis; (3) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (4) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (5) obesity; (6) diabetes (7) depression; (8) osteoporosis (especially in combination with a bone resorption inhibitor); (9) goiter; (10) thyroid cancer; (11) cardiovascular disease or congestive heart failure; (12) glaucoma; and (13) skin disorders.

The compounds of the invention find special application in the treatment or prophylaxis of the following: (1) hypercholesterolemia, dyslipidemia or any other lipid disorder manifested by an unbalance of blood or tissue lipid levels; (2) atherosclerosis; (3) obesity; (4) diabetes.

The invention therefore provides a method for the treatment or prophylaxis of a condition that may be treated with a thyroid receptor agonist or partial agonist in a mammal, which comprises administering to the mammal a therapeutically effective amount of a compound of the invention. Clinical conditions mediated by a thyroid receptor that may be thus treated include those described above.

The invention also provides a compound of the invention for use as a medicament, for example for use in the treatment or prophylaxis of a condition that may be treated with a thyroid receptor agonist or partial agonist. Further, the invention provides the use of a compound of the invention for the manufacture of a medicament for the treatment or prophylaxis of a condition that may be treated with a thyroid receptor agonist or partial agonist. Clinical conditions mediated by a thyroid receptor that may be treated with a thyroid receptor agonist or partial agonist include those described above.

The amount of active ingredient which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered orally or via injection at a dose of from 0.05 to 500 mg/kg per day, preferably 0.05 to 100 mg/kg per day. The dose range for adult humans is generally from 5 mg to 35 g per day and preferably 5 mg to 2 g per day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for example units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.
While it is possible for the active ingredient to be administered alone, it is preferable for it to be present in a pharmaceutical formulation or composition. Accordingly, the invention provides a pharmaceutical composition comprising a compound according to the invention together with a pharmaceutically acceptable excipient.

The pharmaceutical formulations according to the invention include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered does pressurized aerosols), nebulizers or insufflaters, rectal and topical (including dermal, buccal, sublingual, and intraocular) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.
Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of the invention can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), male anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer’s solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.
Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers are typically solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug. Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerine or sucrose and acacia. Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

Whilst a compound of the invention may be used as the sole active ingredient in a medicament, it is also possible for the compound to be used in combination with one or more further active agents. Such further active agents may be further compounds according to the invention, or they may be different therapeutic agents, for example an anti-dyslipidemic agent or other pharmaceutically active material.

The compounds of the present invention may be employed in combination with one or more other modulators and/or ligands of the thyroid receptor or one or more other suitable therapeutic agents selected from the group consisting of cholesterol/lipid lowering agents, hypolipidemic agents, anti-atherosclerotic agents, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.

Examples of suitable hypolipidemic agents for use in combination with the compounds of the present invention include an acyl coenzyme A cholesterol acyltransferase (ACAT) inhibitor, a microsomal triglyceride transfer protein (MTP) inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, an ileal bile acid transporter (IBAT) inhibitor, any cholesterol absorption inhibitor, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, a squalene synthetase inhibitor, a bile acid sequestrant, a peroxisome proliferator-activator receptor (PPAR)-alpha agonist,
a peroxisome proliferator-activator receptor (PPAR)-delta agonist, any peroxisome proliferator-activator receptor (PPAR)-gamma/delta dual agonist, any peroxisome proliferator-activator receptor (PPAR)-alpha/delta dual agonist, a nicotinic acid or a derivative thereof, and a thiazolidinedione or a derivative thereof.

Examples of suitable hypolipidemic agents for use in combination with the compounds of the present invention also include ezetimibe, simvastatin, atorvastatin, rosuvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, fenofibrate, gemfibrozil and bezafibrate.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g., metformin or phenformin), glucosidase inhibitors (e.g., acarbose or miglitol), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, glipizide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone, enoglitazone, darglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, PPAR alpha/delta dual agonists, SGLT 1, 2 or 3 inhibitors, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), glucagon-like peptide-1 (GLP-I), glucocorticoid (GR) antagonist and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment, raloxifene, calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-I inhibitors.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), a serotonin (and dopamine) reuptake inhibitor, such as sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), other thyroid receptor beta drugs, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), CB-I (cannabinoid receptor) antagonists (see G. Colombo et al, "Appetite Suppression and Weight Loss After the Cannabinoid Antagonist SR 141716", Life Sciences, Vol 63, PL 113-1 17 (1998)) and/or an anorectic agent, such as dexamphetamine, phentermine, phenylpropanolamine or mazindol.
The compounds of the present invention may be combined with growth promoting agents, such as, but not limited to, TRH, diethylstilbestrol, theophylline, enkephalins, \( \text{E series prostaglandins} \), compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

The compounds of the invention may also be used in combination with growth hormone secretagogues such as GHRP-6, GHRP-I (as described in U.S. Patent No. 4,411,890 and publications WO 89/07110 and WO 89/07111), GHRP-2 (as described in WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677 (Merck), CP424391 (Pfizer) and B-HT920, or with growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-I and IGF-2, or with alpha-adrenergic agonists, such as clonidine or serotonin 5-HT\(_{\text{D}}\) agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as phystostigmine and pyridostigmine. A still further use of the disclosed compounds of the invention is in combination with parathyroid hormone, PTH(I-34) or bisphosphonates, such as MK-217 (alendronate).

Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel\(_{\text{R}}\), cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen\(_{\text{R}}\), Celebrex\(_{\text{R}}\), Vioxx\(_{\text{R}}\), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept\(_{\text{R}}\)), integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-I, tumor necrosis factor (TNF) antagonists (e.g., infliximab, ORI 384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., Zelmac\(_{\text{R}}\) and Maxi-K\(_{\text{R}}\) openers such as those disclosed in U.S. Patent No. 6,184,231 BI).

Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide,
methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, 
chlorthalidone, furosemide, musolimine, bumetanide, triamternene, amiloride, spironolactone), 
renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranolpril, 
cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-I receptor antagonists (e.g., 
losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds 
disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds 
disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual 
NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present 
invention include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds 
of the present invention include HMG-CoA reductase inhibitors, squalene synthetase inhibitors, 
fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipoxygenase inhibitors, an ileal 
Na\(^{+}\)/K\(^{+}\) acid cotransporter inhibitor, cholesterol absorption inhibitors, and cholesterol ester transfer 
protein inhibitors (e.g., CP-529414).

MTP inhibitors which may be employed herein in combination with one or more compounds of 
formula (I) include MTP inhibitors as disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 

The HMG CoA reductase inhibitors which may be employed in combination with one or more 
compounds of formula (I) include mevastatin and related compounds as disclosed in U.S. Patent No. 
3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, 
pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and 
related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Further HMG CoA 
reductase inhibitors which may be employed herein include fluvastatin, disclosed in U.S. Patent No. 
5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin 
disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pyrazole analogs of 
mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of 
mevalonolactone derivatives, as disclosed in PCT application WO 86/03488, 6-[2-(substituted-
pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof, as disclosed in U.S. Patent No. 4,647,576, 
Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs 
of mevalonolactone, as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propene-
phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole,
furan and thiophene derivatives, as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes, such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No.0,142,146 A2, as well as other known HMG CoA reductase inhibitors.


Bile acid sequestrants which may be used in combination with the compounds of the present invention include cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

ACAT inhibitors suitable for use in combination with compounds of the invention include ACAT inhibitors as described in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, CI-101 1 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfanyl-

Examples of suitable cholesterol absorption inhibitor for use in combination with the compounds of the invention include SCH48461 (Schering-Plough), as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

Examples of suitable ileal Na+/bile acid cotransporter inhibitors for use in combination with the compounds of the invention include compounds as disclosed in Drugs of the Future, 24, 425-430 (1999).

Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone, TRH diethylstibesterol, estrogens, β-agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E-series prostaglandins, retinoic acid and compounds as disclosed in U.S. Pat. No. 3,239,345, e.g., Zeranol®; U.S. Patent No. 4,036,979, e.g., Sulbenox® or peptides as disclosed in U.S. Pat. No. 4,411,890.

For the treatment of skin disorders or diseases as described above, the compounds of the present invention may be used alone or optionally in combination with a retinoid, such as tretinoin, or a vitamin D analog.

A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators, such as those disclosed in Edwards, J. P. et al., Bio. Med. Chem. Lett., 9, 1003-1008 (1999) and Hamann, L. G. et al., J. Med. Chem., 42, 210-212 (1999).
A further use of the compounds of this invention is in combination with steroidal or non-steroidal progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Where the compounds of the invention are utilized in combination with one or more other therapeutic agent(s), either concurrently or sequentially, the following combination ratios and dosage ranges are preferred:

When combined with a hypolipidemic agent, an antidepressant, a bone resorption inhibitor and/or an appetite suppressant, the compounds of the invention may be employed in a weight ratio to the additional agent within the range from about 500:1 to about 0.005:1, preferably from about 300:1 to about 0.01:1.

Where the antidiabetic agent is a biguanide, the compounds of the invention may be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 2:1.

The compounds of the invention may be employed in a weight ratio to a glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 50:1.

The compounds of the invention may be employed in a weight ratio to a sulfonylurea in the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The compounds of the invention may be employed in a weight ratio to a thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1. The thiazolidinedione may be employed in amounts within the range from about 0.01 to about 2000 mg/day, which may optionally be administered in single or divided doses of one to four times per day. Further, where the sulfonylurea and thiazolidinedione are to be administered orally in an amount of less than about 150 mg, these additional agents may be incorporated into a combined single tablet with a therapeutically effective amount of the compounds of the invention.
Metformin, or salt thereof, may be employed with the compounds of formula (I) in amounts within the range from about 500 to about 2000 mg per day, which may be administered in single or divided doses one to four times daily.

The compounds of the invention may be employed in a weight ratio to a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR-alpha/gamma dual agonist, an SGLT2 inhibitor and/or an aP2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1.

An MTP inhibitor may be administered orally with the compounds of the invention in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg, one to four times daily. A preferred oral dosage form, such as tablets or capsules, may contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, administered on a regimen of one to four times daily. For parenteral administration, the MTP inhibitor may be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg, administered on a regimen of one to four times daily.

A HMG CoA reductase inhibitor may be administered orally with the compounds of the invention within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg. A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

A squalene synthetase inhibitor may be administered with the compounds of the invention within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg. A preferred oral dosage form, such as tablets or capsules, will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The compounds of the invention as described above also find use, optionally in labelled form, as a diagnostic agent for the diagnosis of conditions associated with malfunction of the thyroid receptor. In particular, the compounds also find use, optionally in labelled form, as a diagnostic agent for the diagnosis of conditions that may be treated with a thyroid receptor agonist or partial agonist. For example, such a compound may be radioactively labelled.
The compounds of the invention also find use as a reference compound in methods of discovering other agonists or partial agonists of the thyroid receptor. Thus, the invention provides a method of discovering a ligand of the thyroid receptor which comprises use of a compound of the invention or a compound of the invention in labelled form, as a reference compound. For example, such a method may involve a competitive binding experiment in which binding of a compound of the invention to the thyroid receptor is reduced by the presence of a further compound which has thyroid receptor-binding characteristics, for example stronger thyroid receptor-binding characteristics than the reference compound in question.

Examples

The following Examples illustrate the invention.

**General experimental conditions**

Compounds were analyzed on HPLC-MS with alternating +/- API and equipped with different brands of 50 mm*2.1 mm, 5μ C8 columns. Elution was with 0.05% formic acid/acetonitrile or 0.05% ammonium acetate/acetonitrile.

MW calculated is an isotopic average and the "found mass" refers to the most abundant isotope detected in the LC-MS.

**Intermediate 1**

**Methyl 3-[(4-(4-aminophenoxy)-3,5-dibromophenyl]propanoate**

A solution of 7-fluoro nitrobenzene (210 mg, 1.5 mmol), methyl 3-(4-hydroxy-3,5-dibromophenyl) propanoate (500 mg, 1.5 mmol) and potassium carbonate (410 mg, 3 mmol) in dimethylsulfoxide (3 mL) was purged with nitrogen and heated at 130°C for 17 h. The mixture was diluted with ethylacetate and washed with sodium bicarbonate (sat), water and brine. The combined organic phases were evaporated on silica and purified by flash chromatography (heptane/ethyl acetate 10:0 to 5:5) to give methyl 3-[3,5-dibromo-4-(4-nitrophenoxy)phenyl] propanoate as a white solid (504 mg, yield: 74%).

To a stirred solution of methyl 3-[3,5-dibromo-4-(4-nitrophenoxy)phenyl]propanoate (505 mg, 1.1 mmol) in acetic acid (25 mL) and water (3 mL), iron powder (308 mg, 5.5 mmol) was added. The reaction mixture was stirred for 17 h at 20°C. Acetic acid was removed under vacuum and the residue was diluted with ethyl acetate (50 mL) and water (50 mL) and extracted with ethyl acetate
(2 x 5 mL). The combined ethyl acetate layers were washed with brine, dried over sodium sulphate and concentrated. The residue was purified by flash chromatography (dichloromethane/methanol 10:0 to 9:1) to afford the title compound (310 mg) in 72% yield (MW=429.1). LC/MS (ESI): m/z 430.4 (M+l).

Intermediate 2

[4-(4-Amino-phenoxy)-3,5-dichloro-phenyl]-acetic acid methyl ester

A stirred solution of 2,6-dichlorophenol (8.1 g, 50 mmol) in acetonitrile (40 mL) was cooled to 0°C and bromine (9.6 g) in acetonitrile (10 mL) was added dropwise. The red solution was stirred at 0°C for 2 h and a saturated aqueous solution of sodium sulphite was added until the red colour disappeared. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. Concentration of the combined organic phases gave a yellow oil, which was purified on a silica gel column (heptane/ethyl acetate, 10:1) to give 11.33 g of 4-Bromo-2,6-dichloro-phenol as a white solid. (Yield: 95.5%)

A stirred solution of 4-Bromo-2,6-dichloro-phenol (5.76 g, 20 mmol), 4-fluoronitrobenzene (2.82 g, 20 mmol), potassium carbonate (5.5 g, 48 mmol) and copper powder (128 mg, 2 mmol) in DMF (40 mL) was heated at 135°C for 45 h. The reaction was cooled to room temperature and concentrated. The residue was dissolved in ethyl acetate and washed twice with sodium hydroxide (2 M), twice with hydrochloric acid (1 M) and brine. After concentration of the organic phase, the residue was purified on a silica gel column (heptane: 100%) to give 5 g of 5-Bromo-1,3-dichloro-2-(4-nitrophenoxy)-benzene as white solid. (Yield: 69%).

To a solution of 5-Bromo-1,3-dichloro-2-(4-nitrophenoxy)-benzene (1.8 g, 5 mmol), Pd(Ph₃P)Cl₂ (80 mg, 0.1 mmol) and CuI (40 mg, 0.2 mmol) was added triethylamine (1 g, 10 mmol), followed by trimethylsilylacetylene (735 mg, 7.5 mmol). The reaction mixture was stirred under N₂ at 60°C for 1 h. The reaction mixture was cooled to room temperature, filtrated and concentrated. The residue was dissolved in ethyl acetate and the organic phase was washed twice with water and once with brine. After concentration of the organic phase, the residue was purified on column (heptane/ethyl acetate, 10:1) to give 1.8 g (94.9%) of [3,5-dichloro-4-(4-nitrophenoxy)-phenylethynyl]-trimethylsilane as a white solid.

Cyclohexene (3.4 g) was added dropwise to a solution of borane (IM in THF, 21 mL, 21 mmol) at 0°C. [3,5-Dichloro-4-(4-nitrophenoxy)-phenylethynyl]-trimethylsilane (2.4 g, 6 mmol) in THF was added dropwise at 0°C and the reaction mixture was stirred at this temperature for 2 h. A mixture of sodium hydroxide (17 mL, IM) and methanol (20 mL) was added dropwise at 0°C followed by dropwise addition of hydrogen peroxide (10 mL, 33%, 97 mmol) at the same temperature. The
mixture was stirred at 0°C for an additional hour and concentrated. The remaining aqueous solution was acidified with hydrochloric acid (IM) and extracted three times with ethyl acetate. Concentration of the organic phase gave a dark oil which was used in the next step without further purification. (4.87 g, crude)

The crude product above was dissolved in methanol (100 ml) and thionyl chloride (0.1 mL) was carefully added. The mixture was stirred at reflux for two hours. The reaction mixture was concentrated; water was added and extracted three times with ethyl acetate. Purification on column (silica, heptane/ethyl acetate, 10:1) gave 1.2 g of [3,5-Dichloro-4-(4-nitro phenoxy)-phenyl]-acetic acid methyl ester as white solid. (Yield: 56% of two steps)

To a solution of [3,5-dichloro-4-(4-nitro phenoxy)-phenyl]-acetic acid methyl ester in ethyl acetate was added platinum oxide monohydrate and the mixture was stirred vigorously under H2 atmospheres for 2 h. The suspension was filtered and the filtrate concentrated. The residue was purified on column (silica gel, petroleum ether/ethyl acetate, 4:1) to give 0.96 g of [4-(4-Aminophenoxy)-3,5-dichloro-phenyl]-acetic acid methyl ester as white solid. (Yield: 89.5%).

Intermediate 3

Methyl 3-[4-(4-aminophenoxy)-3,5-dichlorophenyl]propanoate

A solution of p-fluoro nitrobenzene (500 mg, 3.5 mmol), methyl 3-(4-hydroxy-3,5-dichlorophenyl) propanoate (500 mg, 2 mmol), copper (243 mg, 3.8 mmol) and potassium carbonate (630 mg, 4.5 mmol) in dimethylformamide (7 mL) was heated at 100°C for 3 h. The cooled reaction mixture was diluted with ethyl acetate and hydrochloric acid (IM) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were concentrated and filtered through a short flash chromatography column (heptane/ethyl acetate 10:0 to 5:5) to give methyl 3-[3,5-dichloro-4-(4-nitrophenoxy)phenyl] propanoate (600 mg, yield: 80%).

To a stirred solution of methyl 3-[3,5-dichloro-4-(4-nitrophenoxy)phenyl]propanoate (600 mg, 1.6 mmol) in ethanol (50 mL) and water (3 mL), tin dichloride (1.83 g, 8 mmol) was added. The reaction mixture was stirred for 17 h at 90°C. Ethanol was removed under vacuum and the residue was diluted with ethyl acetate (50 mL) and saturated solution of sodium carbonate (50 mL) and extracted with ethyl acetate (2 x 10 mL). The combined ethyl acetate layers were washed with brine, dried over sodium sulphate and concentrated. The residue was purified by flash chromatography (heptane/ethyl acetate 10:0 to 7:3) to afford the title compound (180 mg) in 35% yield.

Intermediate 4

Methyl 2-fluoro-3-[3,5-dibromo-4-(4-aminophenoxy)phenyl] propanoate
Sodium hydride (242 mg, 7.06 mmol, 70%) was dissolved in dry methanol (30 mL) with stirring. Methyl 2-hydroxy-3-(4-hydroxy-3,5-dibromophenyl) propanoate (2.5 g, 7.06 mmol) was added to the solution at room temperature and the solvent was evaporated off under reduced pressure to give the sodium phenolate as a white solid.

The phenolate and/or-dinitrobenzene (1.19 g, 7.06 mmol) were dissolved in dimethyl sulphoxide (25 mL). The reaction mixture was heated to 90 °C for 15 h under a calcium chloride guard tube. The reaction mixture was poured into ice-water (150 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic phases were washed with sodium hydroxide (50 mL, aqueous 1M) and brine and dried over sodium sulphate, filtrated and evaporated. The crude was purified by chromatography on silica gel (ethyl acetate/petroleum 1:9 to 2:8) to afford 1.39 g of methyl 2-hydroxy-3-[3,5-dibromo-4-(4-nitrophenoxy)phenyl] propanoate (43% yield).

A solution of methyl 2-hydroxy-3-[3,5-dibromo-4-(4-nitrophenoxy)phenyl] propanoate (1.39 g, 2.93 mmol) in dry dichloromethane (15 mL) was added dropwise to the solution of DAST (Et₂NSF₃) (0.5 g, 3.13 mmol) in dry dichloromethane (10 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 15 min and allowed to come to room temperature and poured into a mixture of ice and water. The organic layer was separated and the water was extracted with dichloromethane (2 x 60 mL). The combined organic layers were washed with brine and dried over sodium sulphate, filtrated and evaporated. Methyl 2-flouro-3-[3,5-dibromo-4-(4-nitrophenoxy)phenyl] propanoate (1.62 g) was pure enough to be used in the next step without further purification.

Pd/C (10%, 80 mg) was added to a solution of methyl 2-flouro-3-[3,5-dibromo-4-(4-nitrophenoxy)phenyl] propanoate (1.62 g) in methanol (150 mL). The reaction mixture was stirred under H₂ at room temperature until the starting material disappeared. The mixture was filtered through celite and the solvent evaporated under vacuum. The residue was purified by chromatography on silica gel (ethyl acetate/ heptane 2:8 to 3:7) to afford 1.15 g of methyl 2-flouro-3-[3,5-dibromo-4-(4-aminophenoxy)phenyl] propanoate as a yellow solid (80% yield for two steps).

**Intermediate 5**

(3,5-Dichloro-4-fluoro-benzoylamino)-acetic acid tert-butyl ester
3,5-Dichloro-4-fluoro-benzoic acid (1.036 g, 5 mmol), N,N-l-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochlorideethyl (1.319 g, 5 mmol), 1-hydroxybenzotriazole hydrate (1.048 mg, 8.5 mmol), and 1971 µL of triethylamine were stirred at 0°C in DMF (35 mL). Glycine tert-butyl ester hydrochloride (1.676 g, 10 mmol) was added and the reaction mixture was stirred at 0°C for 0.5 h. The reaction was allowed to reach room temperature and was stirred at room temperature for 65 h. The reaction was quenched with 5 mL of water and the solvents were removed by evaporation. To the remaining water phase, 200 mL of ethyl acetate was added. The organic layer was washed with brine (3 x 50 mL) and dried over Na₂SO₄. After evaporation, the residue was dissolved in 50 mL acetone, and 12 mL of ethyl acetate and 38 mL of heptane were added. After careful evaporation to remove acetone and cooling, the organic phase was filtered to remove formed precipitate. The precipitate was washed with 50 mL of mixture solvent (ethyl acetate/heptane 25:75). The combined organic phases were evaporated and the residue was purified with flash chromatography (ethyl acetate/heptane 40:60) to give 1.165 g of (3,5-dichloro-4-fluoro-benzyolamino)-acetic acid tert-butyl ester.

**Intermediate 6**

**Methyl [4-(aminophenoxy)-3,5-dibromophenoxy] acetate**

![Methyl [4-(aminophenoxy)-3,5-dibromophenoxy] acetate](attachment:image)

Sodium methoxide (2.2 g, 40 mmol) was added to a solution of 1,3-dibromo-5-fluoro-2-(4-nitrophenoxy)benzene (4 g, 10 mmol) in dimethylformamide (15 mL) at room temperature. The mixture was stirred at room temperature for 4 h. Water (20 mL) was added to the mixture and the product was extracted with ethyl acetate. The combined organic phases were washed consecutively with diluted hydrochloric acid and brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. This crude mixture was used immediately without further purification.

Boron trifluoride-methyl sulfide complex (IM, 12.8 mL, 12.8 mmol) was added dropwise to a stirred, chilled (dry ice-acetone bath) solution of crude 1,3-dibromo-5-methoxy-2-(4-nitrophenoxy)benzene (4.9 g, 12 mmol) in dichloromethane (150 mL). The mixture was allowed to warm up to room temperature and was stirred overnight. The reaction mixture was concentrated under vacuum, diluted with water, and extracted with ethyl acetate. The combined organic phases were washed with diluted hydrochloric acid, saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 20:1) to give 2.5 g (64.3%) of 3,5-dibromo-4-(4-nitrophenoxy)phenol as light yellow oil.
Ethyl bromoacetate (2.5 mL, 22 mmol) was added to a mixture of 3,5-dibromo-4-(4-nitrophenox)phenol (5.2 g, 13 mmol) and potassium carbonate (7.6 g, 54 mmol) in acetone (150 mL) at 0°C. After being stirred at ambient temperature for 4 h, the mixture was concentrated *in vacuo*. Ethyl acetate was added to the residue and the organic phase was washed with brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo* to give the crude mixture of ethyl [3,5-dibromo-4-(4-nitrophenox)phenox]acetate which was used without further purification.

To a solution of ethyl [3,5-dibromo-4-(4-nitrophenox)phenox]acetate (3.8 g, 8 mmol) in ethanol (150 mL), tin(II) chloride (9 g, 47 mmol) was added and the reaction mixture was stirred overnight at 80°C. After cooling to room temperature, the mixture was concentrated *in vacuo* and ethyl acetate and water were added to the residue. The organic phase was washed with sodium hydroxide (25% aqueous) and brine, dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 4:1 to 2:1) to give 1.2 g (64.3%) of methyl [4-(4-aminophenoxy)-3,5-dibromophenoxy]acetate.

**Intermediate 7**

4-(4-Amino-phenoxy)-3,5-dibromo-benzoic *acid methyl ester*

Bromine (5.75mL, 2.05eq) in glacial acetic acid (80mL) was added dropwise into a solution of p-cresol (5.9g, 54.6mmol) in acetic acid (12 mL) and water (33mL) with stirring and temperature control with a water-bath. The reaction solution was stirred for additional 0.5 h at room temperature and poured into water (200 mL). The precipitate was collected and purified by recrystallisation from ethyl acetate/heptane and 13.2g of 2,6-Dibromo-4-methyl-phenol was obtained (yield 91%). Sodium hydride (0.46g, 13.4mmol) was pre-washed with hexane and was carefully dissolved in methanol (anhydrous, 41 mL) 2,6-Dibromo-4-methyl-phenol (3.43g, 12mmol) was added to the basic solution, and the mixture was evaporated to obtain the sodium salt as a white solid. Anhydrous DMSO (18.5mL) and p-dinitrobenzene (1.90 g, 11.3 mmol) was mixed with the sodium salt, and heated at 90°C for 16 h. The reaction solution was poured into 500mL of water/ice, and extracted with diethyl ether (3X500 mL). The combined organic phases were washed with 5% aqueous sodium hydroxide (200 mL), water (200 mL), dried, filtrated and concentrated. The residue was purified on silica chromatograph to give 2.6 g of 1,3-dibromo-5-methyl-2-(4-nitro-phenoxy)-benzene. (Yield:59%).

1,3-Dibromo-5-methyl-2-(4-nitro-phenoxy)-benzene (2.60g, 6.7mmol) was dissolved in pyridine (30 mL) and water (12 mL), and heated to reflux. KMnO₄ (8.5 g, 53.8 mmol) was added in portions while the mixture was refluxed, and heated for additional 6 h. The reaction mixture was cooled to
ambient temperature and the solution was diluted with ethyl acetate and filtered with celite.

Concentration of the solution gave a sticky solid which was diluted with 2M HCl and extracted with ethyl acetate. The organic phase was concentrated and dissolved in 5% NaOH, which was washed with ether. The alkaline solution was acidified with cone. HCl and extracted with acetate. The combined organic phases were dried and concentrated to give 2.0 g of 3,5-Dibromo-4-(4-nitro-phenoxy)-benzoic acid. (Yield: 71%).

3,5-Dibromo-4-(4-nitro-phenoxy)-benzoic acid (1.1g) was refluxed in methanol (100 mL) with a catalytic amount of toluenesulfonic acid for 2 days to give 1.Og of 3,5-dibromo-4-(4-nitro-phenoxy)-benzoic acid methyl ester. (Yield: 85%).

3,5-Dibromo-4-(4-nitro-phenoxy)-benzoic acid methyl ester (900mg, 2.1 mmol) and PtO2 (60mg, O.1 eq.) were suspended in ethyl acetate (60 mL), and the reaction mixture was put under H2 atmospheres for 16 h. The reaction solution was filtered, concentrated and recrystallized from acetate/petroleum to obtain 630mg of 4-(4-amino-phenoxy)-3,5-dibromo-benzoic acid methyl ester (yield:75%)

General Procedure A for the preparation of examples 1-5, 19 and 20

To a solution of the appropriate aniline (e.g. methyl 3-[4-(4-aminophenoxy)-3,5-dichlorophenyl)acetate, intermediate 2) (2 eq.) in w-butanol (20 ml/mmol) was added the appropriate ketone (e.g. Β -bromo-2-butane) ( 1 eq.) and acetic acid (1.2 eq.). The mixture was heated to 130°C under positive pressure of nitrogen for 17 h. The solution was diluted with ethyl acetate, extracted with ethyl acetate and the combined organic phases washed with water and evaporated. The residue was purified by flash chromatography (dichloromethane /ethyl acetate 5:5). The obtained ester intermediate was dissolved in a 1:1 mixture of tetrahydrofuran and lithium hydroxide (1M) (20 mL/mmol) and stirred for 17 h at room temperature. The reaction mixture was acidified to pH 2 with hydrochloric acid (2M) and extracted with ethyl acetate. The combined organic phases were evaporated and purified by semi-preparative HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5μ) Mobile Phase: Solvent A. Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 2 min 80% of A then over 8 min to 5% of A) to yield the wanted product (e.g. 3,5-dibromo-4-[(2,3-dimethyl-1 H-indol-5-yl)oxy]phenyl)acetic acid).

General Procedure B for the preparation of examples 6-13 and 15

To a stirred solution of an appropriate aniline (e.g. methyl N-[4-(4-aminophenoxy)-3,5-dibromobenzoate ) in concentrated hydrochloric acid (20 mL/mmol) and acetic acid (4 mL/mmol) at 0°C, was added sodium nitrite (1.1 eq.). After 1 h stirring at 0°C, tin(II) chloride (2.5 eq.) in concentrated hydrochloric acid (4 mL/mmol) was added dropwise. After 1 h at 0°C, the yellow precipitate formed was filtered and washed with hydrochloric acid (2M) and water. The filtrate was dissolved in acetic acid (32 mL/mmol) and hydrochloric acid (4 μL/mmol) and the appropriate
ketone (e.g. 4-chlorobutyrophenone) (1.1 eq.) was added. The mixture was heated at 40°C for 1 h, followed by 17 h at 70°C. After evaporation of the acetic acid, the crude was dissolved in a 1:1 mixture of tetrahydrofuran and lithium hydroxide (IM) (20 mL/mmol) and stirred for 17 h. The mixture was acidified to pH 3 with hydrochloric acid (2M) and extracted with ethyl acetate. The combined organic phases were evaporated and purified by semi-preparative HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5μ) Mobile Phase: Solvent A. Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 2 min 80% of A then over 8 min to 5% of A) to give the wanted product (e.g. 3,5-dibromo-4-[(2-(4-methoxyphenyl)-3-methyl-lH-indol-5-yl)oxy]benzoic acid).

Example 14

N-(3,5-dibromo-4-[(2-(4-chlorophenyl)-3-ethyl-lH-indol-5-yl)oxy]benzoyl)glycine

3,5-Dibromo-4-[(2-(4-chlorophenyl)-3-ethyl-lH-indol-5-yl)oxy]benzoic acid (6 mg, 0.01 mmol) which was made utilising general procedure B from intermediate 7, glycine methyl ester (hydrochloride salt, 5 mg, 0.04mmol), 3-ethyl-l-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (5 mg, 0.03mmol) and 1-hydroxybenzotriazole hydrate (HOBr) (4 mg, 0.03 mmol) were dissolved in anhydrous dichloromethane (0.7 mL). After the addition of triethylamine (4 μL, 0.03 mmol), the reaction mixture was stirred overnight at room temperature. The solution was diluted with ethyl acetate, extracted (3 x 5 mL), washed with water and evaporated. The crude was filtered through a silica SPE column and eluted with dichloromethane. The obtained ester intermediate was dissolved in a 1:1 mixture of tetrahydrofuran and lithium hydroxide (IM) (20 mL/mmol) and stirred for 17 h. The reaction mixture was acidified to pH 3 with hydrochloric acid (2M) and extracted with ethyl acetate (3 x 10mL). The combined organic phases were evaporated and purified by semi-preparative HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5μ) Mobile Phase: Solvent A. Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 2 min 80% of A then over 8 min to 5% of A) giving N-(3,5-dibromo-4-[(2-(4-chlorophenyl)-3-ethyl-lH-indol-5-yl)oxy]benzoyl)glycine as a slightly yellow solid (yield 18%).

Example 16

To a stirred solution of the 5-Methoxy-3-methyl-lH-indole-2-carboxylic acid (42 mg, 0.125 mmol), made by basic hydrolysis from the commercially available 5-Methoxy-3-methyl-lH-indole-2-carboxylic acid ethyl ester (purchased from Zerenex Molecular Ltd, UK), in DMF (3 ml) was successively added 1-hydroxybenzotriazole hydrate (60 mg, 0.390mmol) and N,N-l-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloridethyl (75 mg, 0.390mmol) and isopropylamine (40 mg, 0.39 mmol) at 0°C. After being stirred for 1 h at 0°C the mixture was allowed to reach ambient temperature and was left stirring for 17 h. After filtration of the mixture, the filtrate was evaporated in vacuo. Purification on a silica SPE column (heptane:EtOAc 7:3) gave 5-methoxy-3-methyl-lH-indole-2-carboxylic acid.
isopropylamide as a solid. The indole was dissolved in dichloromethane (10 mL) which was cooled to 0 °C and put under nitrogen atmosphere. Boron trifluoride dimethyl sulphide complex (3 equivalents) was added. The organic phase was washed with water, brine, dried over Na₂SO₄, filrated and evaporated. The crude was utilised without further purification. The crude (30 mg) containing 5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid isopropylamide, 1,3-Dichloro-2-fluoro-5-nitro-benzene (22 mg, 0.1 mmol) and K₂CO₃ (28 mg, 0.17 mmol) was dissolved in DMSO (1.5 mL), purged with N₂ and stirred at 120 °C for 17 h. The mixture was diluted with EtOAc and washed with a saturated Na₂CO₃ solution, water, and brine. The organic phase were evaporated on silica and purified on a silica column (heptane: EtOAc, 7:3) to give 20 mg of 5-(2,6-dichloro-4-nitro-phenoxy)-3-methyl-1H-indole-2-carboxylic acid isopropylamide as a solid.

The biaryl indole was dissolved in a mixture of HOAc and H₂O (9:1, 5 mL) and Fe (27 mg) was added and the reaction was left stirring at ambient temperature for 3 h. The reaction was diluted with EtOAc and HCl (2M) was added. The organic phase was separated and the water phase extracted twice with EtOAc. The combined organic phases were washed with brine, dried with Na₂SO₄, filrated and evaporated. The evaporation gave 17 mg as a brown oil which was used without further purification.

To the crude (17 mg) containing 5-(4-amino-2,6-dichloro-phenoxy)-3-methyl-1H-indole-2-carboxylic acid isopropylamide, which was dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C, was added ethyl malonyl chloride (11 µL, 0.087 mmol) and pyridine (9 µL, 0.11 mmol). After 2.5 h at O°C the reaction was quenched by addition of HCl (3 mL, IM). After stirring for 10 min, additional CH₂Cl₂ (30 mL) and HCl (1 mL, 1 mL) was added. The organic layer was washed with HCl (IM), H₂O, brine and evaporated. The crude was dissolved in THF (5 ml) and LiOH (IM, 2 ml) and left overnight. The reaction mixture was acidified to pH 3 with HCl (2M). EtOAc was added and the organic phase was washed with brine, dried with Na₂SO₄, filrated and evaporated.

The ethyl ester was dissolved in THF (5 ml) and LiOH (IM, 2 ml) was added. The reaction was left stirring for 4 days at ambient temperature. HCl (2M) was added until pH 3 was reached. Extraction with EtOAc (2x20 ml), washed with brine, dried with Na₂SO₄ and evaporated. The crude was purified by semi-preparative HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5µ) Mobile Phase: Solvent A. Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 2 min 80% of A then over 8 min to 5% of A) giving 2.5 mg as a solid (yield: 4.1 %) LCMS.

**General Procedure C for the preparation of examples 17 and 18**

A solution of 5-Hydroxy-3-methyl-1H-indole-2-carboxylic acid methyl ester (21 mg, 0.1 mmol), (3,5-Dichloro-4-fluoro-benzoylamino)-acetie acid tert-butyl ester (Intermediate 5, 33 mg, 0.1 mmol) and K₂CO₃ (28 mg, 0.2 mmol) in DMF (2 mL) was purged with nitrogen and heated to 120 °C for 17 h.
Ethyl acetate (30 mL) was added and the organic layer was washed 3 times with brine, dried over Na₂SO₄ and evaporated. The residue was purified on a silica column (ethyl acetate/heptene 2:3), to give 3.1 mg of 5-[4-(tert-butoxycarbonylmethyl-carbamoyl)-6-dichloro-phenoxy]-methyl-1H-indole-2-carboxylic acid methyl ester.

5-[4-(tert-Butyoxycarbonylmethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-1H-indole-2-carboxylic acid methyl ester (31 mg, 0.36 mmol) was dissolved in 1,4-dioxane (2 mL), and NaOH (1 M, 3 mL) was added. The mixture stirred at room temperature for 17 h.

After evaporation of the solvent, the residue was purified by semi-preparative HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5μ) Mobile Phase: Solvent A. Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 2 min 80% of A then over 8 min to 5% of A) giving 13 mg of 5-[4-(carboxymethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-1H-indole-2-carboxylic acid methyl ester (yield 28.8%).

Example 21

2-Chloro-5-nitro-1,3-bis-trifluoromethyl-benzene (purchased from ACR GmbH & Co, 107 mg, 0.36 mmol) and K₂CO₃ (101 mg, 0.73 mmol) were added to a solution of 5-hydroxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester (80 mg, 0.36 mmol) in acetone (4 mL) under a positive pressure of nitrogen. The mixture was heated to 50°C and stirred for 4 hr until the starting materials had been consumed. Ethyl acetate (50 mL) was added and the organic layer was separated, washed with brine (3x30 mL), dried over Na₂SO₄, filtrated and evaporated. The residue was purified on a silica column (ethyl acetate/heptene 40:60) giving 162 mg of 3-methyl-5-[4-nitro-2,6-bis-trifluoromethyl-phenoxy]-1H-indole-2-carboxylic acid ethyl ester. (Yield: 93.2%).

To a solution of 3-methyl-5-[4-nitro-2,6-bis-trifluoromethyl-phenoxy]-1H-indole-2-carboxylic acid ethyl ester (162 mg, 0.34 mmol) in ethanol (50 mL), platinum oxide (7 mg, cat) was added. The mixture was evacuated and put under a positive pressure of hydrogen (4 psi) at room temperature for 6 hr. The reaction mixture was filtered via celite to remove catalyst, and evaporated to give 145 mg of crude product containing 5-[4-(amino-2,6-bis-trifluoromethyl-phenoxy)-3-methyl-1H-indole-2-carboxylic acid ethyl ester which was utilised without further purification. 70 mg of the crude mixture containing 5-[4-(amino-2,6-bis-trifluoromethyl-phenoxy)-3-methyl-1H-indole-2-carboxylic acid ethyl ester was dissolved with CH₂Cl₂ (10 mL) and methyl malonyl chloride (19 μL, 0.16 mmol) was added. The mixture was cooled to 0°C for 10 minutes and triethylamine (22 μL, 0.16 mmol) in CH₂Cl₂ (2 mL) was added with a syringe. After the addition the reaction mixture was stirred at 0°C for 3 h. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (2 mL). The organic phases were separated and evaporation gave 82 mg containing 5-[4-(2-methoxycarbonyl-acetamino)-2,6-bis-trifluoromethyl-phenoxy]-3-methyl-1H-indole-2-carboxylic acid ethyl ester, which was dissolved in 1,4-dioxane (2 mL), and NaOH (1 M, 3 mL) was added. The mixture stirred at room temperature for 17 h.
The pH was adjusted to 4-5 with HCl (IM) and the mixture was extracted with ethyl acetate (3x30 mL). The organic layer was washed with brine (2x20 mL), water (2x20 mL) and evaporated. Purification with semi-preparative HPLC (Zorbax CombiHT SB-C8 50x21.2 mm, 5µ) Mobile Phase: Solvent A. Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 2 min 80% of A then over 8 min to 5% of A) giving 5.1 mg of 5-[4-(2-Carboxy-acetylamino)-2,6-bis-trifluoromethyl-phenoxy]-3-methyl-lH-indole-2-carboxylic acid in an overall yield of 67.8 %.

The full chemical names of the compounds of Examples 1 to 21 are as follows, and the structures are summarized in the following Table:

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3,5-dichloro-4-{[2,3-dimethyl-lH-indol-5-yl]oxy}phenyl)acetic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
</tr>
<tr>
<td>(3,5-dichloro-4-{[2-(4-methoxyphenyl)-3-methyl-lH-indol-5-yl]oxy}phenyl)acetic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
</tr>
<tr>
<td>3-(3,5-dibromo-4-{[2-(4-methoxyphenyl)-3-methyl-lH-indol-5-yl]oxy}phenyl)propanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
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<tr>
<td>(3,5-dibromo-4-{[2-(4-methoxyphenyl)-3-methyl-lH-indol-5-yl]oxy}phenyl)acetic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
</tr>
<tr>
<td>3-{3,5-dibromo-4-{[2,3-dimethyl-lH-indol-5-yl]oxy}phenyl} propanoic acid</td>
<td><img src="image5.png" alt="Structure" /></td>
</tr>
<tr>
<td>(4-{[2-(4-bromophenyl)-3-methyl-lH-indol-5-yl]oxy}-3,5-dichlorophenyl)acetic acid</td>
<td><img src="image6.png" alt="Structure" /></td>
</tr>
<tr>
<td>(3,5-dichloro-4-{[2-(4-hydroxyphenyl)-3-methyl-lH-indol-5-yl]oxy}phenyl)acetic acid</td>
<td><img src="image7.png" alt="Structure" /></td>
</tr>
<tr>
<td>3-{[2-{(1,3-benzodioxol-5-yl)-3-ethyl-lH-indol-5-yl]oxy}-3,5-dichlorophenyl}propanoic acid</td>
<td><img src="image8.png" alt="Structure" /></td>
</tr>
<tr>
<td>3-{[2-{(1,3-benzodioxol-5-yl)-3-ethyl-lH-indol-5-yl]oxy}-3,5-dibromophenyl}propanoic acid</td>
<td><img src="image9.png" alt="Structure" /></td>
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<tr>
<td>3-{3,5-Dibromo-4{(3-methyl-2-pyridin-4-yI-1H-indol-5-yl)oxy}phenyl} propanoic acid</td>
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<tr>
<td>3-(3,5-dibromo-4-{[2-(4-methoxyphenyl)-3-ethyl-lH-indol-5-yl]oxy}phenyl)propanoic acid</td>
<td><img src="image11.png" alt="Structure" /></td>
</tr>
<tr>
<td>3-(3,5-dibromo-4-{[2-(4-chlorophenyl)-3-ethyl-lH-indol-5-yl]oxy}phenyl)propanoic acid</td>
<td><img src="image12.png" alt="Structure" /></td>
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<tr>
<td>3-(3,5-dibromo-4-{[2-(4-methoxyphenyl)-3-propyl-lH-indol-5-yl]oxy}phenyl)propanoic acid</td>
<td><img src="image13.png" alt="Structure" /></td>
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<tr>
<td>N^dibromo^l^-chlorophenylO-S-ethyl-lH-indol-5-yIoxJbenzoyOglycine</td>
<td><img src="image14.png" alt="Structure" /></td>
</tr>
<tr>
<td>3-{3,5-Dibromo-4{[3-ethyl-2-(4-methoxy-phenyl)-1H-indol-5-yl]oxy}phenyl}-2-fluoro-propionic acid</td>
<td><img src="image15.png" alt="Structure" /></td>
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<tr>
<td>N-[3,5-Dichloro-4-(2-isopropylcarbamoyl-3-methyl-lH-indol-5-yl)oxy]-malonamic acid</td>
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<tr>
<td>5-[4-(Carboxymethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-lH-indole-2-carboxylic acid methyl ester</td>
<td><img src="image17.png" alt="Structure" /></td>
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<tr>
<td>5-[4-(Carboxymethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-lH-indole-2-carboxylic acid ethyl ester</td>
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<tr>
<td>3-[3,5-Dichloro-4-(2,3-dimethyl-lH-indol-5-yl)oxy]-propionic acid</td>
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<tr>
<td>3-[3,5-Dichloro-4-{[2-(4-methoxy-phenyl)-3-methyl-lH-indol-5-yl]oxy}-phenyl]-propionic acid</td>
<td><img src="image20.png" alt="Structure" /></td>
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<tr>
<td>5-[4-(2-Carboxy-acetylamino)-2,6-bis-trifluoromethyl-phenoxy]-3-methyl-lH-indole-2-carboxylic acid</td>
<td><img src="image21.png" alt="Structure" /></td>
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<tr>
<td>Example</td>
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The following compounds are further Examples of the invention:

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<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td><img src="image" alt="Structure Image" /></td>
<td>3-{3,5-Dichloro-4-(3-ethyl-2-isoxazol-5-yl-1H-indol-5-yloxy)-phenyl}-propionic acid</td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Structure Image" /></td>
<td>3-{3,5-Dichloro-4-(2-cyclopropyl-3-ethyl-1H-indol-5-yloxy)-phenyl}-propionic acid</td>
</tr>
<tr>
<td>24</td>
<td><img src="image" alt="Structure Image" /></td>
<td>3-{3-Chloro-4-[2-(4-methoxy-phenyl)-3-methyl-1H-indol-5-yloxy]-5-trifluoromethyl-phenyl}-propionic acid</td>
</tr>
</tbody>
</table>
25. N-\{3,5-Dibromo-4-[3-ethyl-2-(4-methoxy-phenyl)-1H-indol-5-yloxy]-phenyl\}-malonic acid

26. N-\{4-[3-Ethyl-2-(4-methoxy-phenyl)-1H-indol-5-yloxy]-3,5-bis-trifluoromethyl-phenyl\}-malonic acid

27. N-\{3,5-Dichloro-4-[3-ethyl-2-(4-methoxy-phenyl)-1H-indol-5-yloxy]-phenyl\}-malonic acid

28. 3-[3,5-Dibromo-4-(2-ethylcarbamoyl-3-methyl-1H-indol-5-yloxy)-phenyl]-2-fluoro-propionic acid

29. 3-[3,5-Dichloro-4-(2-ethylcarbamoyl-3-methyl-1H-indol-5-yloxy)-phenyl]-2-fluoro-propionic acid

30. 3-[3-Chloro-4-(2-ethylcarbamoyl-3-methyl-1H-indol-5-yloxy)-5-trifluoromethyl-phenyl]-2-fluoro-propionic acid

31. 3-[4-(2-Benz[1,3]dioxol-5-yl-7-chloro-3-ethyl-1H-indol-5-yloxy)-3,5-dibromo-phenyl]-propionic acid
Procedures for the preparation of comparative examples

Comparative Example 1

To a solution of the aniline (Intermediate 3) in ethanol (5 ml), which completely dissolved after sonification, was added HCl (cone, 2.5 ml). The reaction mixture was cooled in an ice-bath and vigorously stirred. When the HCl salt was formed (precipitate) the reaction mixture was put in an EtOH/CO₂-ice bath and a solution of sodium nitrate (21 mg) in H₂O (1 ml) was added slowly and the reaction mixture was kept at -70 °C for 10 min. After the addition the flask was put in an ice bath for 0.5 h. A cooled solution of stannous chloride (198 mg) in HCl (1.5 ml) was added slowly. After 4 h at 0 °C a white precipitate was formed. Shaken between diethyl ether (3x50 ml) and a potassium hydroxide solution (25%).

The combined organic phases were dried over Na₂SO₄ and evaporated. The brown oil was dissolved in MeOH (10 ml), the 3-methyl-butyaldehyde and a catalytic amount OfH₂SO₄ was added. The flask was heated to 80 °C for 17 h. EtOAc and H₂O was added and the organic phase was washed with brine. The organic phase was dried over Na₂SO₄, filtration and evaporation, gave a brown oil which was purified on a silica column (Heptane:EtOAc, 9:1-8:2). The collected fractions were evaporated and gave 40 mg as a slightly yellow oil.

10 mg of the indole ester was dissolved in THF (1 ml). LiOH (1 ml, IM) was added. The reaction mixture was left at room temperature with stirring for 17 h. The reaction was acidified with HCl (2M) to pH-2 and extracted with CHCl₃. Separation with a phase separator and purification by preparative HPLC. Evaporation of the collected fractions gave 4 mg of 3-[3,5-dichloro-4-(3-isopropyl-1H-indol-5-ylmethyl)-phenyl]-propionic acid a white solid.

Comparative Example 2

3-[3,5-Dichloro-4-(3-isopropyl-1H-indol-5-ylmethyl)-phenyl]-propionic acid methyl ester (indole ester intermediate isolated prior to the final step in the synthesis of Comparative Example 1, 20 mg, 0.05 mmol) was dissolved in 3 mL ofCH₂Cl₂. NBS (9 mg, 0.05 mmol) was added and the reaction is left stirring under N₂-atmosphere at room temperature for 4 h. The crude was evaporated and put on a SPE silica column (Heptane EtOAc 9:1). Evaporation of the collected fractions gave 14 mg as brown oil that solidified. A solution containing 3-[4-(2-bromo-3-isopropyl-1H-indol-5-ylxyloxy)-3,5-dichloro-phenylj-propionic acid methyl ester (14 mg, 0.03 mmol) in DME (1 mL) was prepared and
treated with aqueous K$_2$CO$_3$ (13 mg in 0.5 mL H$_2$O) and phenyl boronic acid (14 mg, 0.09 mmol). The mixture was stirred at 60 °C for 6 h. The mixture was allowed to reach room temperature and then filtered through celite. The filtrate was diluted with EtOAc, washed with brine and dried. Concentration in vacuo afforded a residue which was dissolved in THF (2 mL) and LiOH (IM, ImL) and left stirring at room temperature for 17 h. After acidification to pH 3, the mixture was extracted with EtOAc, which was evaporated. Purification with semi-preparative HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5μ) Mobile Phase: Solvent A. Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 2 min 80% of A then over 8 min to 5% of A) giving 1.2 mg of 3-[3,5-Dichloro-4-[3-isopropyl-2-(4-methoxy-phenyl)-IH-indol-5-yloxy]-phenyl]-propionic acid as a white solid in an overall yield of 4.8%.

Comparative examples 3 and 4 correspond to examples 3 and 5 respectively of US 6,794,406 and may be synthesised according to the methods described in US 6,794,406.

<table>
<thead>
<tr>
<th>Comparative Example</th>
<th>R$^1$</th>
<th>R$^6$</th>
<th>X</th>
<th>W</th>
<th>Yield (%)</th>
<th>MW (calc)</th>
<th>M+1 (found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Iso-Pr</td>
<td>Cl</td>
<td>(CH$_2$)$_2$</td>
<td>17.3</td>
<td>392.3</td>
<td>392.2</td>
</tr>
<tr>
<td>2</td>
<td>p-OMe-Ph</td>
<td>Iso-Pr</td>
<td>Cl</td>
<td>(CH$_2$)$_2$</td>
<td>4.8</td>
<td>498.4</td>
<td>498.8</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Iso-Pr</td>
<td>Me</td>
<td>NH-CH$_2$ (Ethyl ester of acid)</td>
<td>9.5</td>
<td>380.5</td>
<td>381.5</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Iso-Pr</td>
<td>Me</td>
<td>NH-CH$_2$</td>
<td>5.1</td>
<td>352.4</td>
<td>353.8</td>
</tr>
</tbody>
</table>

**TR Competition binding assay with filter separation**

Compounds are tested for their ability to compete with the tracer $^{125}$I-T3 for binding to full length hTRα and hTRβ. Receptor extracts and tracer are diluted in assay buffer (17mM K$_2$HPO$_4$, 3mM KH$_2$PO$_4$, 400mM KCl, ImM MgCl$_2$, 0.5mM EDTA and 8.7% glycerol). $^{125}$I-T3 is diluted to a final concentration of 0.2nM and receptor is diluted to reach a final count in Trilux Microbeta of
approximately 100000 cpm. Compounds are typically serially diluted in DMSO from DMSO stock solutions of 10mM. To 96 well microtiter plates are 100µl tracer, 4µl test compound dilution series and 100µl receptor dilution added. The assay plates are incubated at +4°C over night (app. 16hrs incubation). Receptor bound and free tracer are separated over a glass fiber filter (FILTERMAT B, PerkinElmer) on a Tomtec Cellharvester with 18mM K₂HPO₄, 2mM KH₂PO₄, 0.5mM EDTA wash buffer. The filters are dried at 60°C for 1 hour and then merged with a scintillant wax (MELTILEX, PerkinElmer) on a Wallac Microsealer before measuring in a Trilux Microbeta. IC50s, the concentration test compound needed to decrease tracer binding by 50 percent, are generated via analysis of data in XLfit version 2.0 or later with a four parameter logistic model.

Compounds are considered to have activity as thyroid receptor-beta ligands if they have an IC₅₀ of 500nM or less. Preferred thyroid receptor-beta ligand compounds have an IC₅₀ of less than 100nM, especially less than 30 nM. Particularly preferred as thyroid receptor-beta ligands are those compounds having an IC₅₀ of 10nM or less.

Vector Constructs, Generation of Reporter Cell Lines (TRAF), and Assay Procedure.

The cDNAs encoding the full length human ThRa 1 and ThRB1 were cloned in the mammalian expression vector pMT-hGH. The pDR4-ALP reporter vector contains one copy of the direct repeat sequence AGGTCA nnnnAGGTCA, fused upstream of the core promoter sequences of the mouse mammary tumor virus long terminal repeat (MMTV), replacing the glucocorticoid response elements. The DR4-MMTV promoter fragment was then cloned in the 5' end of the cDNA encoding human placental alkaline phosphatase (ALP), followed in the 3'-end by the polyA-signal sequence of the human growth hormone gene. Chinese hamster ovary (CHO) K1 cells (ATCC No. CCL 61) were transfected in two steps, first with the receptor expression vectors pMT-hThR α1 and pMT-ThRB1, respectively, and the drug resistance vector pSV2-Neo, and in the second step, with the reporter vector pDR4-ALP and the drug resistance vector pJSV-Hyg. Individual drug resistant clones were isolated and selected based on T3 inducibility. One stable reporter cell clone each of CHO/hThR α1 and CHO/hThR β1 were chosen for further study in response to various thyroid hormone agonists.

Assay procedure:

CHO/hThR α1 and CHO/hThR β1 were seeded in growth medium (Coon's/F12, 10% L-3,5,3⁻ triiodothyronine and L-thyroxine depleted FCS, 2mM L-glutamine) in 96-well plates at 20 X 10³ cells per well. After 24 hour incubation at 37°C in humidified chambers, at 5% CO₂, conditioned medium was replaced by induction medium (OptiMEM, 2mM L-glutamine, 50µg/ml gentamycin) and cells were exposed to the test compounds at serial dilutions, at final DMSO concentration of 0.5%, or to serial dilution of T3 (positive control), to assess agonist activity of test compounds.
In order to examine antagonistic effect of test compounds, CHO/hThR αl and CHO/hThR β1 cells were exposed to serial dilution of the compounds in the presence of 1nM T3 (CHO/hThR αl) or 3nM T3 (CHO/hThR β1).

After 48 hours incubation at 37°C in humidified chambers at 5% CO₂ the level of alkaline phosphatase expressed and secreted into the cell culture medium was analyzed by chemiluminescence on MicroBeta Trilux.

Compounds are considered to be agonists of the thyroid receptor-beta ligands if they exhibit agonism of at least 50% and display no antagonism.

The assay procedures described above were carried out for the compounds of Examples 1-21 and Comparative Examples 1-4. Selected results for exemplary compounds are given in table below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>TR-β IC50 (nM)</th>
<th>β % agonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 10</td>
<td>2.77</td>
<td>79.73</td>
</tr>
<tr>
<td>Example 13</td>
<td>8.88</td>
<td>70.65</td>
</tr>
<tr>
<td>Example 3</td>
<td>7.16</td>
<td>97.50</td>
</tr>
<tr>
<td>Example 9</td>
<td>0.33</td>
<td>70.35</td>
</tr>
<tr>
<td>Example 8</td>
<td>2.5</td>
<td>76.93</td>
</tr>
<tr>
<td>Comparative Example 1</td>
<td>19.15</td>
<td>66.20</td>
</tr>
</tbody>
</table>
As shown in the Table above, introducing a substituent into the 2-position on the indole ring (Examples 10, 13, 3, 9, 8) leads to improved binding to the TR-β receptor and/or improved agonistic activity when compared to compounds lacking a substituent in the 2-position on the indole ring (Comparative Examples 1, 3, 4).

It is hypothesized that this improvement is due to the unexpected flexibility of the binding cavity in the thyroid hormone receptor ligand binding domain allowing the accommodation of ligands with surprisingly large R^1 substituents.
Claims

1. A compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt,

wherein:

R¹ is selected from -(CH₂)ₙ-SO₂-R⁴, -(CH₂)ₙ-NH-SO₂-R⁴, -(CH₂)ₙ-SO₂-NH-R⁴, -(CH₂)ₙ-NH-CO-R⁴,
-(CH₂)ₙ-CO-N(R)₂, -(CH₂)ₙ-CO₂-R⁴, C₈ alkyl, C₂₄ alkenyl, C₂₄ alkynyl, C₃₆ cycloalkyl, C₇₆ cycloalkyl-C₃₃ alkyl, C₆ io aryl, benzyl and C₃-7 heterocyclyl, said alkyl, alkenyl or alkynyl optionally being substituted with 1, 2 or 3 groups each independently selected from halogen, hydroxy, C₁₄alkylthio, phenyl, or methoxy optionally substituted with 1, 2 or 3 halogen atoms; and said cycloalkyl, C₆ io aryl, benzyl, N(R)₂ or heterocyclyl optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, cyano, C₁₄ alkyl, C₂₄ alkenyl, C₂₄ alkynyl, N(R)₂, haloC₁₄ alkyl, dihaloC₄ alkyl, trihaloC₄ alkyl or C₁₄alkoxy optionally substituted with 1, 2 or 3 halogen atoms, and wherein two of the 1, 2 or 3 groups may together with the atoms of the group to which they are attached form a 5-, 6- or 7-membered cyclic group optionally containing one or two heteroatoms selected from O, N and S;

each R⁴ is independently selected from hydrogen, C₄ alkyl, C₂₄ alkenyl, C₂₄ alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl, benzyl, heterocyclyl and phenyl, said alkyl, alkenyl, alkynyl or phenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from C₁₄ alkyl, halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

n is 0, 1, 2 or 3;

R⁶ is selected from methyl, ethyl and n-propyl;

each R² is independently selected from halogen, mercapto, hydroxy, cyano, C₁₄ alkoxy, C₁₄ alkyl and N(R)₂, said alkyl or alkoxy groups optionally being substituted with 1, 2 or 3 groups
independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

each R^b is independently selected from a hydrogen atom and a Q alkyl group optionally substituted with 1, 2 or 3 groups independently selected from halogen, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

m is 0, 1 or 2;

Y is selected from oxygen, methylene, sulphur, SO, SO_2 and -N(R^b)-;

R^3 and R^4 are independently selected from halogen, C_14 alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, C_14 alkoxy, fluoromethoxy, difluoromethoxy and trifluoromethoxy;

W is selected from C, 3 alkylene, C_2 alkylene, C_2 alkylene, N(R^4)-Ci, 3 alkylene, C(O)-C^i_3 alkylene, S-C, 3 alkylene, O-C, 3 alkylene, C, 3 alkylene-O-Ci, 3 alkylene, C(O)NH-Ci, 3 alkylene, NH(C)(O)-Ci, 3 alkylene and Ci, 3 alkylene-C(O)NH-Ci, 3 alkylene, said alkylene, alkenylene or alkynylene groups or portions of groups optionally being substituted with 1 or 2 groups selected from hydroxy, mercapto, amino, halo, C_1 alkyl, Ci alkyl, phenyl and Ci alkyl substituted with phenyl, haloC_1 alkyl, dihaloCi alkyl, trihaloC_1 alkyl, haloCi alkyl, dihaloC_1 alkyl, trihaloC_3 alkyl, and phenyl substituted with 1, 2 or 3 halogen atoms;

R^c is selected from hydrogen, hydroxy, C_14 alkyl, C_24 alkenyl, C_24 alkenyl, fluoromethyl, difluoromethyl and trifluoromethyl;

R^5 is selected from -CO_2R^d, -PO(OR)^d_2, -PO(OR)^d NH_2, -SO_2 OR^d, -COCO_2H, -CONR^d OR^d, -SO_2 NHR^d, -NH SO_2 R^d, -CONHSO_2 R^d, and -SO_2 NH COR^d;

each R^d is independently selected from hydrogen, C_14 alkyl, C_24 alkenyl, C_24 alkynyl, C_3 heterocycl, C_10 ary1 and C_5 ary1 substituted with 1, 2 or 3 groups independently selected from amino, hydroxy, halogen or Ci alkyl.

2. A compound as claimed in claim 1, wherein R^1 is selected from -(CH)2n SO_2 R^a, -(CH)2n NH SO_2 R^a, -(CH)2n SO_2 NH-R^a, -(CH)2n NH-CO-R^a, -(CH)2n C0 e, C_8 alkyl, C_24 alkenyl, C_24 alkynyl, C_3 cycloalkyl, C_3 cycloalkyl-C_1 alkyl, phenyl, benzyl and C_7 heterocycl, said alkyl, alkenyl or alkynyl optionally being substituted with 1, 2 or 3 groups each independently selected from halogen, hydroxy, C M alkylthio, phenyl, or methoxy optionally substituted with 1, 2 or 3
halogen atoms; and said cycloalkyl, phenyl, benzyl, N(R\(^a\)) or heterocyclyl optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, cyano, C\(_i\) alkyl, C\(_{2-4}\) alkenyl, C\(_{2-4}\) alkynyl, N(R\(^b\)) haloC\(_i\) alkyl, dihaloC\(_i\) alkyl, trihaloC\(_i\) alkyl or methoxy optionally substituted with 1, 2 or 3 halogen atoms, and wherein two of the 1, 2 or 3 groups may together with the atoms of the group to which they are attached form a 5-, 6- or 7-membered cyclic group optionally containing one or two heteroatoms selected from O, N and S; each R\(^a\) is independently selected from hydrogen, C\(_i\) alkyl, C\(_{2-4}\) alkenyl, C\(_{2-4}\) alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl, benzyl, heterocyclyl and phenyl, said alkyl, alkenyl, alkynyl or phenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from d \(_{2-4}\) alkyl, halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy; R\(^b\) is selected from C\(_i\) alkyl, C\(_{2-4}\) alkenyl, C\(_{2-4}\) alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl, benzyl, heterocyclyl and phenyl, said alkyl, alkenyl, alkynyl or phenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from C\(_i\) alkyl, halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy; and n is 0, 1, 2 or 3.

3. A compound as claimed in claim 2, wherein R\(^1\) is selected from a phenyl group optionally substituted by one, two or three substituents selected from halogen atoms and hydroxy or methoxy groups, and wherein two of the 1, 2 or 3 substituents may together with the atoms of the phenyl group to which they are attached form a 5-, 6- or 7-membered cyclic group optionally containing one or two heteroatoms selected from O, N and S; a pyridyl group; a CO\(_2\)Me group; or a CO\(_2\)Et group.

4. A compound as claimed in any of claims 1 to 3, wherein R\(^6\) is methyl or ethyl.

5. A compound as claimed in any of claims 1 to 4, wherein R\(^3\) and R\(^4\) are independently selected from halogen, C\(_{3-4}\) alkyl, fluoromethyl, difluoromethyl and trifluoromethyl.

6. A compound as claimed in any of claims 1 to 5, wherein W is selected from C\(_i\) alkylene, C\(_{2-3}\) alkenylene, C\(_{2-3}\) alkynylene, N(R\(^c\)) haloC\(_i\) alkylene, C(O)C\(_3\) alkylene, S-C\(_i\) alkylene, O-C\(_{1-3}\) alkylene, C\(_{1-3}\) alkylene-O-C\(_3\) alkylene, C(O)NH-C\(_{1-3}\) alkylene and NHC(O)-C\(_{1-3}\) alkylene, said alkylene, alkenylene or alkynylene moiety being optionally substituted by 1 or 2 groups selected...
from hydroxy, mercapto, amino, halo, C\textsubscript{1-3} alkyl, C\textsubscript{i-3} alkoxy, haloC\textsubscript{i-3} alkyl, dihaloC\textsubscript{i-3} alkyl, trihaloC\textsubscript{i} alkyl, haloC\textsubscript{i-3} alkoxy, dihaloC\textsubscript{i-3} alkoxy, and trihaloC\textsubscript{i-3} alkoxy.

7. A compound as claimed in claim 6, wherein W is selected from C\textsubscript{i-3} alkylene, O-C\textsubscript{1-2} alkylen, and C(O)NH-C\textsubscript{i-2} alkylen, and monohalo C\textsubscript{i-3} alkylene.

8. A compound as claimed in any of claims 1 to 7, wherein R\textsubscript{5} is selected from -CO\textsubscript{2}R\textsubscript{4}, -SO\textsubscript{2}OR\textsubscript{4}, -NHSO\textsubscript{2}R\textsubscript{4}, -CO\textsubscript{2}R\textsubscript{4} and CONR\textsubscript{d}OR\textsubscript{d}.

9. A compound as claimed in claim 1, wherein R\textsubscript{1} is selected from -(CH\textsubscript{2})\textsubscript{n}-SO\textsubscript{2}R\textsubscript{a}, -(CH\textsubscript{2})\textsubscript{n}-NH-SO\textsubscript{2}R\textsubscript{a}, -(CH\textsubscript{2})\textsubscript{n}-SO\textsubscript{2}-NH-R\textsubscript{a}, -(CH\textsubscript{2})\textsubscript{n}-NH-CO-R\textsubscript{a}, -(CH\textsubscript{2})\textsubscript{n}-CO-NH-R\textsubscript{a}, C\textsubscript{i-6} alkyl, phenyl, benzyl, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy, and any cycloalkyl, phenyl, benzyl or heterocycl group being optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, C\textsubscript{i-4} alkyl, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

\( n \) is 0, 1 or 2;

R\textsubscript{a} represents a C\textsubscript{i-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzyl, heterocyclyl or phenyl group being unsubstituted or substituted by C\textsubscript{i-4} alkyl or halogen.

R\textsubscript{6} represents a methyl, ethyl or n-propyl group;

m is 1 or 0;

if present, R\textsubscript{2} is selected from halogen, hydroxy, C\textsubscript{i-4} alkoxy, C\textsubscript{M} alkyl and N(R\textsubscript{b})\textsubscript{2}, an alkyl or alkoxy group being unsubstituted or substituted by from 1 to 3 substituents independently selected from halogen, hydroxy, C\textsubscript{i-4} alkylthio, halomethoxy, dihalomethoxy, and trihalomethoxy, and R\textsubscript{b} being selected from hydrogen and C\textsubscript{i-4} alkyl or haloalkyl;

R\textsubscript{3} and R\textsubscript{4} are independently selected from halogen, C\textsubscript{i-4} alkyl, fluoromethyl, difluoromethyl and trifluoromethyl;

Y is methylene or oxygen;
W is selected from C$_{1-3}$ alkenylene, C$_{1-3}$ alkenylene-O-C$_{1-3}$ alkenylene, C$_2$ alkenylene, C$_1$-3 alkylene-O-C$_{1-2}$ alkenylene, C$_2$-3 alkenylene, N(R,C$_{1}$)-C$_{1-2}$ alkylene, 0-C$_1$-2 alkylene, C(O)NH-C$_{1-2}$ alkenylene and NHC(O)-C$_{1-2}$ alkenylene, said alkenylene or alkenylene moieties optionally being substituted with a group selected from halo, C$_1$-2 alkyl, C$_{1-2}$ alkoxy, haloC$_{1-2}$ alkyl, dihaloC$_{1-2}$ alkyl, trihaloC$_{1-2}$ alkyl, haloC$_{1-2}$ alkoxy, dihaloC$_{1-2}$ alkoxy, and trihaloC$_{1-2}$ alkoxy, and R$^5$ being selected from hydrogen, C$_{1-2}$ alkyl, fluoromethyl, difluoromethyl and trifluoromethyl; and

R$^5$ is selected from -CO$_2$H, -SO$_2$OR$^d$, -NHSO$_2$R$^d$, -COC$_2$H and CONR$^d$OR$^d$ in which R$^d$ is ethyl, methyl, phenyl and phenyl substituted with 1, 2 or 3 groups independently selected from amino, hydroxyl, halogen and methyl or hydrogen, particularly hydrogen.

10. A compound as claimed in any of claims 1 to 9 for use as a medicament.

11. A compound as claimed in claim 10 for use in the treatment or prophylaxis of a condition that may be treated with a thyroid receptor agonist or partial agonist.

12. A method for the treatment or prophylaxis of a condition that may be treated with a thyroid receptor agonist or partial agonist in a mammal, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I) as defined in any of claims 1 to 9 or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt.

13. Use of a compound of formula (I) as defined in any of claims 1 to 9 or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt, for the manufacture of a medicament for the treatment or prophylaxis of a condition that may be treated with a thyroid receptor agonist or partial agonist.

14. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 9 or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and including a solvate of such an ester, amide or salt, and a pharmaceutically acceptable excipient.

15. A pharmaceutical composition as claimed in claim 14 further comprising an additional therapeutic agent selected from cholesterol/lipid lowering agents, hypolipidemic agents, antiatherosclerotic agents, anti-diabetic agents, anti-osteooporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive
agents, cardiac glycosides, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.

16. Use of a compound of formula (I) as defined in any of claims 1 to 9 in labelled form as a diagnostic agent for the diagnosis of conditions that may be treated with a thyroid receptor agonist or partial agonist.

17. Use of a compound of formula (I) as defined in any of claims 1 to 9 or a labelled form of such a compound as a reference compound in a method of identifying ligands for the thyroid hormone receptor.

18. A compound as claimed in claim 11, a method as claimed in claim 12, a use as claimed in claim 13, or a pharmaceutical composition as claimed in claim 14 or claim 15, wherein the condition that may be treated with a thyroid receptor agonist or partial agonist is selected from (1) hypercholesterolemia, dyslipidemia or any other lipid disorder manifested by an unbalance of blood or tissue lipid levels; (2) atherosclerosis; (3) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (4) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (5) obesity; (6) diabetes; (7) depression; (8) osteoporosis (especially in combination with a bone resorption inhibitor); (9) goiter; (10) thyroid cancer; (11) cardiovascular disease or congestive heart failure; (12) glaucoma; and (13) skin disorders.

19. A process for preparing a compound of formula (I) as defined in claim 1 wherein Y is oxygen, sulphur or -N(R^b)-, comprising reacting a compound of formula (II)

![Diagram](https://example.com/diagram.png)

wherein W, R^3, R^4, and R^5 are as defined in claim 1 and Y is oxygen, sulphur or -N(R^b)-, with a compound of formula (III)

![Diagram](https://example.com/diagram.png)
wherein \( R_1, R_6, R_2 \) and \( m \) are as defined in claim 1 and PG is hydrogen or a suitable protecting group, and \( Z \) is a suitable leaving group, optionally in the presence of a suitable base and optionally, in the presence of copper powder, followed optionally by removal of the protecting group, if present, and optionally by interconversion to another compound of formula (I) as defined in claim 1 wherein \( Y \) is oxygen, sulphur or \(-\text{N}(\text{R}_b)\)-.

20. A process for preparing a compound of formula (I) as defined in claim 1 wherein \( Y \) is methylene, comprising reacting a compound of formula (IV)

\[
\begin{array}{c}
\text{OHC} \\
\text{R}^4 \\
\text{R}^3 \\
\text{W} \\
\text{R}^5
\end{array}
\]

(IV)

wherein \( W, R^3, R^4, \) and \( R^5 \) are as defined in claim 1 with a compound of formula (V)

\[
\begin{array}{c}
\text{R}^1 \\
\text{PG} \\
\text{R}^6 \\
\text{(R}^2\text{)}_mZ
\end{array}
\]

(V)

wherein \( R_1, R_6, R_2 \) and \( m \) are as defined in claim 1 and PG is hydrogen or a suitable protecting group, and \( Z \) is lithium, MgBr, MgCl, or a derivative of Sn, Pd, B or Cu, followed optionally by removal of the protecting group, if present, and optionally by interconversion to another compound of formula (I) as defined in claim 1 wherein \( Y \) is methylene.

21. A process for preparing a compound of formula (I) as defined in claim 1 wherein \( Y \) is oxygen, sulphur or \(-\text{N}(\text{R}_b)\)-, comprising reacting a compound of formula (II) as defined in claim 19 in which \( Y \) is oxygen, sulphur or \(-\text{N}(\text{R}_b)\)-, with a compound of formula (VI)

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{Z} \\
\text{(R}^2\text{)}_m
\end{array}
\]

(VI)
wherein $R^2$ and $m$ are as defined in claim 1 and $Z$ is a suitable leaving group, optionally in the presence of a suitable base and optionally in the presence of copper powder, followed by reduction of the nitro group to an amino group and reaction of the resultant amine with a suitable reagent to form the bicyclic ring, followed optionally by interconversion to another compound of formula (I) as defined in claim 1 wherein $Y$ is oxygen, sulphur or $-N(R^b)$.

22. A process for preparing a compound of formula (I) as defined in claim 1 wherein $Y$ is oxygen, $NR^b$, sulphur or methylene, comprising reacting a compound of formula (VII)

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{Y} \\
\text{R}^3 \\
\text{R}^4 \\
\text{W} \\
\text{R}^5 \\
\end{array}
\]

(VII)

or the corresponding hydrazine of formula (Vila) formed by reacting a compound of formula (VII) with sodium nitrate which is followed by reduction with a suitable reducing agent

\[
\begin{array}{c}
\text{H}_2\text{N} \text{-NH} \\
\text{Y} \\
\text{R}^3 \\
\text{R}^4 \\
\text{W} \\
\text{R}^5 \\
\end{array}
\]

(Vila)

wherein $R^2$, $R^3$, $R^4$, $R^5$ $W$ and $m$ are as defined in claim 1 with a compound of formula (VIII)

\[
\begin{array}{c}
\text{X} \\
\text{R}^1 \\
\text{R}^6 \\
\end{array}
\]

(VIII)

wherein $R^1$ and $R^6$ are as defined in claim 1 and $X$ is hydrogen or a halogen, in the presence of a suitable acid or Lewis acid and followed optionally by interconversion to another compound of formula (I) as defined in claim 1 wherein $Y$ is oxygen, $NR^b$, sulphur or methylene.

23. A process for preparing a compound of formula (I) as defined in claim 1 wherein $Y$ is oxygen, $NR^b$ or sulphur, comprising reacting a compound of formula (IX)
wherein \( R^3 \) and \( R^4 \) are as defined in claim 1 and where substituent \( V \) represents nitro, aldehyde, cyano, carboxyl or derivatives of carboxyls and \( Z \) is a suitable leaving group, with a compound of formula (IX):

\[
\text{(IX)}
\]

wherein \( R^1 \), \( R^6 \), \( R^2 \) and \( m \) are as defined in claim 1, \( PG \) is hydrogen or a suitable protecting group, and \( Y \) is oxygen, sulphur or \(-N(R^b)^-\), optionally in the presence of a suitable base, and optionally, in the presence of copper powder, followed optionally by removal of the protecting group, if present, and optionally by interconversion to another compound of formula (I) as defined in claim 1 wherein \( Y \) is oxygen, \( NR^b \), or sulphur.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/EP2007/004623

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D209/08  C07D209/18  C07D209/20  C07D405/04  C07D413/04  
A61P5/14  A61K31/404

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<td>Y</td>
<td>WO 02/051805 A (BAYER AG [DE]; HANING HELMUT [US]; WOLTERING MICHAEL [DE]; SCHMIDT GUN) 4 July 2002 (2002-07-04) page 1, line 3 - page 2, line 21 page 63 - page 166; examples 1-703 claim 1</td>
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<td>Y</td>
<td>US 2003/114521 A1 (CHIANG YUAN-CHING PHOEBE [US] ET AL) 19 June 2003 (2003-06-19) page 1, column 1, paragraph 2 page 43, column 2; examples 10-10-7 claim 1</td>
<td>1-23</td>
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<td>X</td>
<td>Further documents are listed in the continuation of Box C</td>
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<td>See patent family annex</td>
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* 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

**Date of the actual completion of the international search**

26 September 2007

**Date of mailing of the international search report**

09/10/2007

**Name and mailing address of the ISA**

European Patent Office  P B 5818 Patentlaan 2  NL-2280 HV Rijswijk  Tel (+31-70) 340-2040, Tx 31651 epo nl,  Fax (+31-70) 340-3016

**Authorized officer**

Bissmire, Stewart

From PCT/IS/V21 0 (second sheet) (April 2005)
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<td>US 2003/078289 Al (ASPNES GARY E [US] ET Al) 24 April 2003 (2003-04-24) page 1, column 1, paragraph 2 example page 6, column 1, <strong>paragraph 101</strong> example page 6, column 2, paragraph 106 <strong>claim 1</strong></td>
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Continuation of Box II.1

Although claims 12 is 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.

Although claims 16 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos. 12, 16 because they relate to subject matter not required to be searched by this Authority, namely see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] 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

3. [ ] Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6(4)

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

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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