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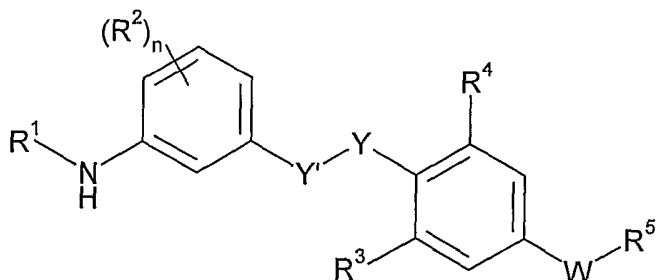
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(54) Title: NOVEL PHARMACEUTICAL COMPOSITIONS COMPRISING AGONISTS OF THE THYROID RECEPTOR



(57) Abstract: The invention provides compounds 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. The invention also provides the use of such compounds in the treatment or prophylaxis of a condition mediated by a thyroid receptor. Formula (I) wherein R¹, R², n, Y, Y', R³, R⁴, W and R⁵ are as defined in the specification.

NOVEL PHARMACEUTICAL COMPOSITIONS COMPRISING AGONISTS OF THE THYROID RECEPTOR

Field of the invention

The present invention relates to compounds which are agonists or partial agonists of the thyroid
5 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
10 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 and cardiac diseases.

Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these
15 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.

20 Thyroid hormones are currently used primarily as replacement therapy for patients with
hypothyroidism. Therapy with L-thyroxine returns metabolic functions to normal and can easily be
monitored with routine serum measurements of levels of thyroid-stimulating hormone (TSH),
thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T₄) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or
25 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
30 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.

35 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
5 endogenous hormone levels in specific tissues.

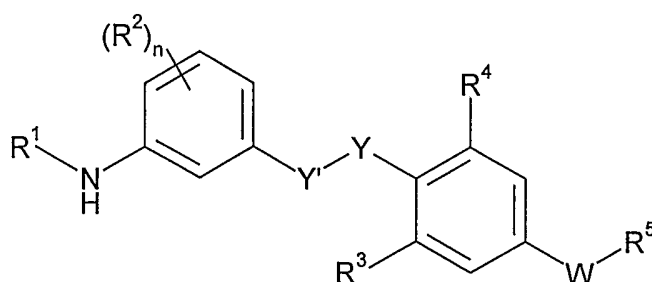
Development of specific and selective thyroid hormone receptor ligands, particularly agonists of the thyroid hormone receptor, is expected to lead to specific therapies for these common disorders, while avoiding the cardiovascular and other toxicity of native thyroid hormones. Tissue-selective
10 thyroid 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.

15 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
20 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.

25

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
30 ester, amide or salt,



wherein:

R¹ is selected from -SO₂R⁶, -SOR⁶ and -C(O)R⁶;

5

R⁶ is selected from C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₃ alkyl, phenyl and C₁₋₇ heterocyclyl, said alkyl, alkenyl or alkynyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy; said cycloalkyl, aryl or heterocyclyl groups or
10 portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, methoxy, halomethoxy, dihalomethoxy, trihalomethoxy, haloC₁₋₄ alkyl, dihaloC₁₋₄ alkyl, and trihaloC₁₋₄ alkyl;

Each R² is independently selected from halogen, mercapto, nitro, cyano, alkoxy, -CO₂R^c, -CONHR^c,
15 -CHO, -SO₂R⁶, -SO₂NHR⁶, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, NHR¹ and N(R¹)₂, said alkyl, alkenyl, alkynyl or alkoxy groups optionally being substituted with 1, 2 or 3 groups selected from halogen, hydroxy, methoxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, mercapto, nitro, cyano, halomethoxy, dihalomethoxy, and trihalomethoxy;

20 n is 0, 1, 2 or 3;

Y and Y' together are -C(R^a)=C(R^a)-,

or alternatively Y and Y' are independently selected from oxygen, sulphur and -CH(R^a)-, with the proviso that at least one of Y and Y' is -CH(R^a)- and the further proviso that when one of Y and Y'
25 is oxygen or sulphur, then R^a is hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^a is selected from hydrogen, halogen, hydroxy, mercapto, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy,
30 trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and thiotrifluoromethyl;

R^a is selected from hydrogen, halogen, mercapto, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and thiotrifluoromethyl;

35

R^3 and R^4 are independently selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4} alkoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

- 5 W is selected from C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, $N(R^b)$ - C_{1-3} alkylene, $C(O)$ - C_{1-3} alkylene, S - C_{1-3} alkylene, O - C_{1-3} alkylene, C_{1-3} alkylene- O - C_{1-3} alkylene, $C(O)NH$ - C_{1-3} alkylene and $NH(CO)$ - C_{0-3} 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_{1-3} 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;

R^b is selected from hydrogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy;

- 15 R^5 is selected from $-CO_2R^c$, $-PO(OR^c)_2$, $-PO(OR^c)NH_2$, $-SO_2OR^c$, $-COCO_2R^c$, $CONR^cOR^c$, $-SO_2NHR^c$, $-NHSO_2R^c$, $-CONHSO_2R^c$, and $-SO_2NHCOR^c$;

Each R^c is independently selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl;

- 20 $R^{c'}$ is selected from R^c , C_{5-10} aryl and C_{5-10} aryl substituted with 1, 2 or 3 groups independently selected from amino, hydroxy, halogen and C_{1-4} alkyl.

Compounds of the invention have surprisingly been found to be ligands of the thyroid receptor, in particular agonists or partial agonists of the thyroid receptor. The compounds accordingly have use
25 in the treatment or prophylaxis of conditions associated with thyroid receptor activity.

Detailed description of the invention

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
30 these are within the scope of the present invention.

Preferably, R^1 is selected from $-SO_2R^6$, and $-C(O)R^6$;

Preferably, R^6 is selected from C_{1-8} alkyl, C_{2-4} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-3} alkyl, phenyl and C_{3-7} heterocyclyl. Preferred substituents for said alkyl or alkenyl include groups
35 independently selected from halogen, methoxy or halomethoxy. Preferred substituents for said

cycloalkyl, aryl or heterocyclyl include halogen, methyl, ethyl, halomethoxy, dihalomethoxy, trihalomethoxy, halomethyl, dihalomethyl, and trihalomethyl.

5 More preferably, R⁶ is selected from C₁₋₅ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkyl, said alkyl or alkenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy and trihalomethoxy.

10 Most preferably, R⁶ is selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₄ cycloalkyl, C₃₋₆ cycloalkyl C₁₋₃ alkyl, unsubstituted phenyl, and C₃₋₅ heterocyclyl.

When R¹ is SO₂R⁶, R⁶ is preferably selected from phenyl, methyl, ethyl, propyl or 3,5 dimethyl isoxazole, for example methyl, ethyl and propyl. When R¹ is C(O)R⁶, R⁶ is preferably selected from methyl, ethyl, propyl, cyclobutyl, cyclopropyl, or i-propyl.

15 R² is preferably selected from halogen, C₁₋₂ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, nitro, cyano, C₁₋₂ alkoxy, haloC₁₋₂ alkyl, dihaloC₁₋₂ alkyl, and trihaloC₁₋₂ alkyl. More preferably, R² is selected from halogen, methyl, trifluoromethyl, difluoromethyl or fluoromethyl. When R² is a halogen, it is preferably selected from bromine, chlorine and fluorine, especially chlorine. Preferred locations for the R² group or groups are in the 2- or 5- position on the phenyl ring relative to the attachment point to the Y'-Y- of the remainder of the molecule.

20

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

25 Preferably, Y and Y' are independently selected from oxygen, sulphur or -CH(R^a)-, with the proviso that at least one of Y and Y' is -CH(R^a)- and the further proviso that when one of Y and Y' is oxygen or sulphur, then R^a is hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, fluoromethyl, difluoromethyl, trifluoromethyl. More preferably, Y is O or S, and Y' is CH(R^a). Most preferably, Y is O and Y' is CH(R^a).

30 In a second preferred embodiment, Y and Y' together are -C(R^a)=C(R^a)-.

In another preferred embodiment, Y and Y' together are -C(R^a)=C(R^a)-, or alternatively Y is O or S, and Y' is CH(R^a). In a further preferred embodiment Y and Y' together are -C(R^a)=C(R^a)-, or
35 alternatively Y is O and Y' is CH(R^a).

R^a is preferably selected from hydrogen, halogen, C₁₋₂ alkyl, fluoromethyl, difluoromethyl and trifluoromethyl. More preferably, R^a is selected from hydrogen, halogen, and C₁₋₂ alkyl. Most preferably, R^a is hydrogen.

5 R^{a'} is preferably selected from hydrogen, halogen, C₁₋₂ alkyl, fluoromethyl, difluoromethyl and trifluoromethyl. More preferably, R^{a'} is selected from hydrogen, halogen, and C₁₋₂ alkyl. Most preferably, R^{a'} is hydrogen.

10 R³ and R⁴ are preferably independently selected from halogen, C₁₋₄ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, and C₁₋₄ alkoxy. More preferably, R³ and R⁴ are independently selected from halogen, C₁₋₄ alkyl, fluoromethyl, difluoromethyl and trifluoromethyl. Most preferably, R³ and R⁴ are independently selected from halogen, methyl, fluoromethyl, difluoromethyl and trifluoromethyl. Amongst the halogens, there are preferred bromine, chlorine and fluorine, especially bromine and chlorine, in particular bromine.

15

R³ and R⁴ may simultaneously represent the same radical. Alternatively, R³ and R⁴ are different from each other.

20 W is preferably selected from C₁₋₃ alkylene, C₂₋₃ alkenylene, N(R^b)-C₁₋₂ alkylene, C(O)-C₁₋₂ alkylene, S-C₁₋₂ alkylene, O-C₁₋₂ alkylene, C(O)NH-C₀₋₂ alkylene or NH(CO)-C₁₋₂ alkylene, said alkylene or alkenylene groups or portions of groups optionally being substituted with a group selected from hydroxy, mercapto, amino, halo (preferably fluoro or chloro, particularly fluoro), C₁₋₂ alkyl, C₁₋₂ alkoxy, haloC₁₋₂ alkyl, dihaloC₁₋₂ alkyl, trihaloC₁₋₂ alkyl, haloC₁₋₂ alkoxy, dihaloC₁₋₂ alkoxy and trihaloC₁₋₂ alkoxy. More preferably, W is selected from C₁₋₃ alkylene, C₂₋₃ alkenylene, 25 O-C₁₋₃ alkylene, C₁₋₃ alkylene-O-C₁₋₃ alkylene, C(O)NH-C₁₋₂ alkylene and NH(CO)-C₁₋₂ alkylene. Most preferably, W is selected from C₁₋₃ alkylene, O-C₁₋₃ alkylene, C₁₋₃ alkylene-O-C₁₋₃ alkylene, C(O)-C₁₋₂ alkylene, C(O)NH-C₁₋₂ alkylene and NH(CO)-C₁₋₂ alkylene. Most particularly preferably, W is ethylene or C(O)NH-CH₂-. Preferably the alkylene group (for example the ethylene group) is substituted with one or more halo groups, for example one or more fluoro groups (for example one 30 fluoro group). Monohalo C₁₋₃ alkylene (for example fluoro C₁₋₃ alkylene) thus constitutes a preferred group W.

R^b is preferably selected from hydrogen, C₁₋₂ alkyl, fluoromethyl, difluoromethyl and trifluoromethyl;

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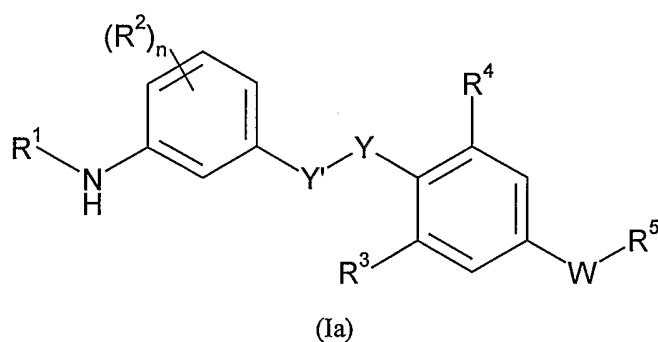
R^5 is preferably selected from $-\text{CO}_2R^c$, $-\text{PO}(\text{OR}^c)_2$, $-\text{SO}_2\text{OR}^c$, $-\text{COCO}_2R^c$, CONR^cOR^c and $-\text{NHSO}_2R^c$. More preferably, R^5 is $-\text{CO}_2R^c$, $-\text{PO}(\text{OR}^c)_2$ or $-\text{SO}_2\text{OR}^c$. Most preferably, R^5 is $-\text{CO}_2R^c$, particularly $-\text{CO}_2\text{H}$.

- 5 R^c is preferably hydrogen or C_{1-4} alkyl. More preferably, R^c is ethyl, methyl or hydrogen, particularly hydrogen.

R^d is preferably selected from R^c , phenyl and phenyl substituted with 1, 2 or 3 groups independently selected from amino, hydroxyl, halogen and methyl.

10

Accordingly, one preferred group of compounds of the invention includes compounds according to formula (Ia) or pharmaceutically acceptable esters, amides, solvates or salts thereof, including salts of such esters or amides, and solvates of such esters, amides or salts



15

wherein:

R^1 is selected from $-\text{SO}_2R^6$ and $-\text{C}(\text{O})R^6$;

20

R^6 is selected from C_{1-8} alkyl, C_{2-4} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, C_6 aryl and C_{3-7} heterocyclyl, said alkyl or alkenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy and trihalomethoxy; said cycloalkyl, aryl or heterocyclyl groups or portions of

25 groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, methyl, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

Each R^2 is independently selected from halogen, C_{1-2} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-2} alkoxy, halo C_{1-2} alkyl, dihalo C_{1-2} alkyl, and trihalo C_{1-2} alkyl;

30

n is 0, 1 or 2;

Y and Y' together are $-C(R^a)=C(R^a)-$,
or alternatively Y is O or S, and Y' is $CH(R^a)$;

5 R^a is selected from hydrogen, halogen, methyl, ethyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl and trifluoroethyl;

R^3 and R^4 are independently selected from halogen, C_{1-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4} alkoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio,
10 fluoromethylthio, difluoromethylthio and trifluoromethylthio;

W is selected from C_{1-3} alkylene, C_{1-3} alkylene-O- C_{1-3} alkylene, O- C_{1-3} alkylene, $C(O)-C_{1-2}$ alkylene, $C(O)NH-C_{1-2}$ alkylene and $NH(CO)-C_{1-2}$ alkylene; the alkylene group or portion of a group optionally being substituted with one or more halo groups.

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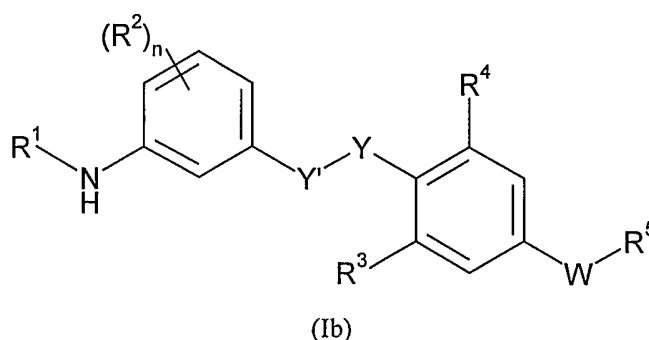
R^5 is selected from $-CO_2R^c$, $-PO(OR^c)_2$, $-SO_2OR^c$, $-COCO_2R^c$, $CONR^cOR^c$ and $-NHSO_2R^c$;

Each R^c is independently selected from hydrogen and C_{1-4} alkyl; and

20

R^c is selected from R^c , phenyl and phenyl substituted with amino, hydroxy, halogen and methyl.

A further preferred group of compounds of the invention includes compounds according to formula (Ib) or pharmaceutically acceptable esters, amides, solvates or salts thereof, including salts of such
25 esters or amides, and solvates of such esters, amides or salts,



30 wherein:

R^1 is selected from $-SO_2R^6$ and $-C(O)R^6$;

R⁶ is selected from C₁₋₅ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkyl, said alkyl or alkenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy and trihalomethoxy;

Each R² is independently selected from halogen, C₁₋₂ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₂ alkoxy, haloC₁₋₂ alkyl, dihaloC₁₋₂ alkyl, and trihaloC₁₋₂ alkyl;

n is 0, 1 or 2;

Y and Y' together are -C(R^a)=C(R^a)-, or alternatively Y is O, and Y' is CH(R^a);

R^a is selected from hydrogen, halogen, and C₁₋₂ alkyl;

R³ and R⁴ are independently selected from halogen, C₁₋₄ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, and C₁₋₄ alkoxy;

W is selected from C₁₋₃ alkylene, C₂₋₃ alkenylene, O-C₁₋₃ alkylene, C₁₋₃ alkylene-O-C₁₋₃ alkylene, C(O)NH-C₁₋₂ alkylene and NH(CO)-C₁₋₂ alkylene; the alkylene group or portion of a group optionally being substituted with one or more halo groups.

R⁵ is -CO₂R^c;

25

Each R^c is independently selected from hydrogen and C₁₋₄ alkyl.

Preferred compounds according to the invention include:

- 3-(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dichlorophenyl)propanoic acid
- 30 N-(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dibromobenzoyl)glycine
- 3-(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dibromophenyl)propanoic acid
- 3-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
- 3-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
- 3-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromophenyl)propanoic acid
- 35 3-(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dichlorophenyl)-2-fluoropropanoic acid
- 3-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dichlorophenyl)-2-fluoropropanoic acid
- 3-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dichlorophenyl)-2-fluoropropanoic acid

- 3-(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
3-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dichlorophenyl)acetic acid
N-(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dichlorobenzoyl)glycine
5 (4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dibromophenyl)acetic acid
(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dichlorophenyl)acetic acid
N-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dichlorobenzoyl)glycine
(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromophenyl)acetic acid
(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dichlorophenyl)acetic acid
10 N-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dichlorobenzoyl)glycine
(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromophenyl)acetic acid
3-[(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dichlorophenyl)amino]-3-oxopropanoic acid
acid
3-[(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dibromophenyl)amino]-3-oxopropanoic acid
15 oxopropanoic acid
3-[(4-{[3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy}-3,5-dimethylphenyl)amino]-3-oxopropanoic acid
3-[(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dichlorophenyl)amino]-3-oxopropanoic acid
3-[(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromophenyl)amino]-3-oxopropanoic acid
20 3-[(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dimethylphenyl)amino]-3-oxopropanoic acid
3-[(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dichlorophenyl)amino]-3-oxopropanoic acid
3-[(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromophenyl)amino]-3-oxopropanoic acid
3-[(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dimethylphenyl)amino]-3-oxopropanoic acid
(4-{[3-(acetylamino)benzyl]oxy}-3,5-dichlorophenyl)acetic acid
25 N-(4-{[3-(acetylamino)benzyl]oxy}-3,5-dichlorobenzoyl)glycine
(4-{[3-(acetylamino)benzyl]oxy}-3,5-dibromophenyl)acetic acid
3-(4-{[3-(acetylamino)-5-fluorobenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
N-(4-{[3-(acetylamino)-5-fluorobenzyl]oxy}-3,5-dibromobenzoyl)glycine
3-(4-{[3-(acetylamino)-5-fluorobenzyl]oxy}-3,5-dibromophenyl)propanoic acid
30 (4-{[3-(acetylamino)-5-fluorobenzyl]oxy}-3,5-dichlorophenyl)acetic acid
N-(4-{[3-(acetylamino)-5-fluorobenzyl]oxy}-3,5-dichlorobenzoyl)glycine
(4-{[3-(acetylamino)-5-fluorobenzyl]oxy}-3,5-dibromophenyl)acetic acid
3-(4-{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
N-(4-{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dibromobenzoyl)glycine
35 3-(4-{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dibromophenyl)propanoic acid
(4-{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dichlorophenyl)acetic acid
N-(4-{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dichlorobenzoyl)glycine

- (4-{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dibromophenyl)acetic acid
 3-(4-{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
 N-(4-{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dibromobenzoyl)glycine
 3-(4-{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dibromophenyl)propanoic acid
 5 (4-{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dichlorophenyl)acetic acid
 N-(4-{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dichlorobenzoyl)glycine
 (4-{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dibromophenyl)acetic acid
 3-(4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
 3-(4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dibromophenyl)propanoic acid
 10 (4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dibromophenyl)acetic acid
 N-(4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dichlorobenzoyl)glycine
 (4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dichlorophenyl)acetic acid
 3-(4-{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
 N-(4-{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dibromobenzoyl)glycine
 15 3-(4-{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dibromophenyl)propanoic acid
 (4-{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dichlorophenyl)acetic acid
 N-(4-{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dichlorobenzoyl)glycine
 (4-{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dibromophenyl)acetic acid
 3-(4-{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
 20 N-(4-{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dibromobenzoyl)glycine
 3-(4-{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dibromophenyl)propanoic acid
 (4-{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dichlorophenyl)acetic acid
 N-(4-{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dichlorobenzoyl)glycine
 (4-{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dibromophenyl)acetic acid
 25 3-(3,5-dichloro-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
 N-(3,5-dibromo-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}benzoyl)glycine
 3-(3,5-dibromo-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid
 N-(3,5-dibromo-4-{[3-chloro-5-(propionylamino)benzyl]oxy}benzoyl)glycine
 30 3-(3,5-dibromo-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid
 N-(3,5-dibromo-4-{[3-methyl-5-(propionylamino)benzyl]oxy}benzoyl)glycine
 3-(3,5-dibromo-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)-2-fluoropropanoic
 35 acid
 3-(3,5-dichloro-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)-2-fluoropropanoic acid
 3-(3,5-dichloro-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)-2-fluoropropanoic acid

- 3-(3,5-dibromo-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)-2-fluoropropanoic acid
- 3-(3,5-dibromo-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)-2-fluoropropanoic acid
- 3-(3,5-dibromo-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)-2-fluoropropanoic acid
- 5 (3,5-dichloro-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}benzoyl)glycine
- (3,5-dibromo-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)acetic acid
- (3,5-dichloro-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{[3-chloro-5-(propionylamino)benzyl]oxy}benzoyl)glycine
- 10 (3,5-dibromo-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
- (3,5-dichloro-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{[3-methyl-5-(propionylamino)benzyl]oxy}benzoyl)glycine
- (3,5-dibromo-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
- 3-[(3,5-dichloro-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)amino]-3-
- 15 oxopropanoic acid
- 3-[(3,5-dibromo-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(3,5-dimethyl-4-{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
- 20 3-[(3,5-dichloro-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(3,5-dibromo-4-{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(4-{[3-chloro-5-(propionylamino)benzyl]oxy}-3,5-dimethylphenyl)amino]-3-oxopropanoic acid
- 3-[(3,5-dichloro-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(3,5-dibromo-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
- 25 3-[(3,5-dimethyl-4-{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
- (3,5-dichloro-4-{[3-(propionylamino)benzyl]oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{[3-(propionylamino)benzyl]oxy}benzoyl)glycine
- (3,5-dibromo-4-{[3-(propionylamino)benzyl]oxy}phenyl)acetic acid
- 3-(3,5-dichloro-4-{[3-fluoro-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid
- 30 N-(3,5-dibromo-4-{[3-fluoro-5-(propionylamino)benzyl]oxy}benzoyl)glycine
- 3-(3,5-dibromo-4-{[3-fluoro-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid
- (3,5-dichloro-4-{[3-fluoro-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{[3-fluoro-5-(propionylamino)benzyl]oxy}benzoyl)glycine
- (3,5-dibromo-4-{[3-fluoro-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
- 35 3-(3,5-dichloro-4-{[3-cyano-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid
- N-(3,5-dibromo-4-{[3-cyano-5-(propionylamino)benzyl]oxy}benzoyl)glycine
- 3-(3,5-dibromo-4-{[3-cyano-5-(propionylamino)benzyl]oxy}phenyl)propanoic acid

- (3,5-dichloro-4-{[3-cyano-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{[3-cyano-5-(propionylamino)benzyl]oxy}benzoyl)glycine
(3,5-dibromo-4-{[3-cyano-5-(propionylamino)benzyl]oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{[2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
5 N-(3,5-dibromo-4-{[2-fluoro-3-(propionylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
(3,5-dichloro-4-{[2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{[2-fluoro-3-(propionylamino)benzyl]oxy}benzoyl)glycine
(3,5-dibromo-4-{[2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
10 3-(3,5-dichloro-4-{[2-chloro-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[2-chloro-3-(propionylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[2-chloro-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
(3,5-dibromo-4-{[2-chloro-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{[2-chloro-3-(propionylamino)benzyl]oxy}benzoyl)glycine
15 (3,5-dichloro-4-{[2-chloro-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
(3,5-dichloro-4-{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
20 N-(3,5-dichloro-4-{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}benzoyl)glycine
(3,5-dibromo-4-{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
25 (3,5-dichloro-4-{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}benzoyl)glycine
(3,5-dibromo-4-{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{[3-(isobutyrylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-(isobutyrylamino)-5-(trifluoromethyl)benzyl]oxy}benzoyl)glycine
30 3-(3,5-dibromo-4-{[3-(isobutyrylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(isobutyrylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-chloro-5-(isobutyrylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[3-chloro-5-(isobutyrylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-(isobutyrylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
35 N-(3,5-dibromo-4-{[3-(isobutyrylamino)-5-methylbenzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[3-(isobutyrylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid

- 3-(3,5-dichloro-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-fluoropropanoic acid
- 3-(3,5-dichloro-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)-2-fluoropropanoic acid
- 3-(3,5-dichloro-4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)-2-fluoropropanoic acid
- 5 3-(3,5-dibromo-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-fluoropropanoic acid
- 3-(3,5-dibromo-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)-2-fluoropropanoic acid
- 3-(3,5-dibromo-4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)-2-fluoropropanoic acid
- (3,5-dichloro-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)acetic acid
- 10 N-(3,5-dichloro-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}benzoyl)glycine
- (3,5-dibromo-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)acetic acid
- (3,5-dichloro-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
- (3,5-dibromo-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
- 15 (3,5-dichloro-4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}benzoyl)glycine
- (3,5-dibromo-4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)acetic acid
- 3-[(3,5-dichloro-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)amino]-3-oxopropanoic acid
- 20 3-[(3,5-dibromo-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}-3,5-dimethylphenyl)amino]-3-oxopropanoic acid
- 3-[(3,5-dichloro-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)amino]-3-oxopropanoic acid
- 25 3-[(3,5-dibromo-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}-3,5-dimethylphenyl)amino]-3-oxopropanoic acid
- 3-[(3,5-dichloro-4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(3,5-dibromo-4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)amino]-3-oxopropanoic acid
- 3-[(4-{{3-(isobutyrylamino)-5-methylbenzyl}oxy}-3,5-dimethylphenyl)amino]-3-oxopropanoic acid
- 30 (3,5-dichloro-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{{3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
- (3,5-dibromo-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
- 3-(3,5-dichloro-4-{{3-fluoro-5-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
- N-(3,5-dibromo-4-{{3-fluoro-5-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
- 35 3-(3,5-dibromo-4-{{3-fluoro-5-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
- (3,5-dichloro-4-{{3-fluoro-5-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
- N-(3,5-dichloro-4-{{3-fluoro-5-(isobutyrylamino)benzyl}oxy}benzoyl)glycine

- (3,5-dibromo-4-{{3-fluoro-5-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{{3-cyano-5-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{{3-cyano-5-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
3-(3,5-dibromo-4-{{3-cyano-5-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
5 (3,5-dichloro-4-{{3-cyano-5-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{{3-cyano-5-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
(3,5-dibromo-4-{{3-cyano-5-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{{2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{{2-fluoro-3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
10 3-(3,5-dibromo-4-{{2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
(3,5-dichloro-4-{{2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{{2-fluoro-3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
(3,5-dibromo-4-{{2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{{2-chloro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
15 N-(3,5-dibromo-4-{{2-chloro-3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
3-(3,5-dibromo-4-{{2-chloro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
(3,5-dibromo-4-{{2-chloro-3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{{2-chloro-3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
(3,5-dichloro-4-{{2-chloro-3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
20 3-(3,5-dichloro-4-{{2-fluoro-3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{{2-fluoro-3-(isobutyrylamino)-5-methylbenzyl}oxy}benzoyl)glycine
3-(3,5-dibromo-4-{{2-fluoro-3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)propanoic acid
(3,5-dichloro-4-{{2-fluoro-3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{{2-fluoro-3-(isobutyrylamino)-5-methylbenzyl}oxy}benzoyl)glycine
25 (3,5-dibromo-4-{{2-fluoro-3-(isobutyrylamino)-5-methylbenzyl}oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
3-(3,5-dibromo-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
(3,5-dichloro-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
30 N-(3,5-dichloro-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
(3,5-dibromo-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)acetic acid
3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dibromophenyl)propanoic acid
3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dichlorophenyl)propanoic acid
3-(4-{{3-(acetylamino)-4-methylbenzyl}oxy}-3,5-dibromophenyl)propanoic acid
35 3-(3,5-dibromo-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{{3-(butyrylamino)benzyl}oxy}phenyl)propanoic acid

- 3-(3,5-dibromo-4-{[3-(isobutyrylamino)benzyl]oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{[3-(isobutyrylamino)benzyl]oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{[3-(isobutyrylamino)-2-methylbenzyl]oxy}phenyl)propanoic acid
 3-[3,5-dibromo-4-({3-[(3-methylbutanoyl)amino]benzyl}oxy)phenyl]propanoic acid
 5 3-[3,5-dibromo-4-({3-[(2E)-but-2-enoylamino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclopropylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclobutylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclopentylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 N-(4-{[3-(acetylamino)benzyl]oxy}-3,5-dibromobenzoyl)glycine
 10 N-(3,5-dibromo-4-{[3-(propionylamino)benzyl]oxy}benzoyl)glycine
 N-(3,5-dibromo-4-{[3-(isobutyrylamino)benzyl]oxy}benzoyl)glycine
 3-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
 3-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromophenyl)propanoic acid
 N-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromobenzoyl)glycine
 15 N-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromobenzoyl)glycine
 N-(4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dibromobenzoyl)glycine
 3-(4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
 3-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromophenyl)butanoic acid
 20 and
 N-(3,5-dibromo-4-{[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}benzoyl)glycine
 3-[3,5-dichloro-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 25 3-(3,5-dichloro-4-{[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)-2-
 fluoropropanoic acid
 3-[3,5-dichloro-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 3-[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 3-(3,5-dibromo-4-{[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)-2-
 30 fluoropropanoic acid
 3-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic
 acid
 (3,5-dichloro-4-{[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)acetic acid
 N-(3,5-dichloro-4-{[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}benzoyl)glycine
 35 (3,5-dibromo-4-{[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)acetic acid
 [3,5-dichloro-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 N-[3,5-dichloro-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine

- [3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 [3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 3-[[3,5-dichloro-4-({3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy)phenyl]amino]-3-oxopropanoic acid
 5 3-[[3,5-dibromo-4-({3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy)phenyl]amino]-3-oxopropanoic acid
 3-[[3,5-dimethyl-4-({3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy)phenyl]amino]-3-oxopropanoic acid
 3-{{3,5-dichloro-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
 10 3-{{3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
 3-{{4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)-3,5-dimethylphenyl}amino}-3-oxopropanoic acid
 15 3-{{3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
 3-{{3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
 3-{{3,5-dimethyl-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
 20 [3,5-dichloro-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 N-[3,5-dichloro-4-({3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 [3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 3-[3,5-dichloro-4-({3-fluoro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 25 N-[3,5-dibromo-4-({3-fluoro-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 3-[3,5-dibromo-4-({3-fluoro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 [3,5-dichloro-4-({3-fluoro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 N-[3,5-dichloro-4-({3-fluoro-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 [3,5-dibromo-4-({3-fluoro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 30 3-[3,5-dichloro-4-({3-cyano-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 N-[3,5-dibromo-4-({3-cyano-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 3-[3,5-dibromo-4-({3-cyano-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 [3,5-dichloro-4-({3-cyano-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 N-[3,5-dichloro-4-({3-cyano-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 35 [3,5-dibromo-4-({3-cyano-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 3-[3,5-dichloro-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 N-[3,5-dibromo-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine

- 3-[3,5-dibromo-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
[3,5-dichloro-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
[3,5-dibromo-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- 5 3-[3,5-dichloro-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
[3,5-dichloro-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- 10 3-[3,5-dichloro-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
3-[3,5-dibromo-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
acid
[3,5-dichloro-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- 15 N-[3,5-dichloro-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
[3,5-dibromo-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
3-[3,5-dichloro-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
3-[3,5-dibromo-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
- 20 [3,5-dichloro-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
[3,5-dibromo-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
3-(3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}benzoyl)glycine
- 25 3-[3,5-dichloro-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)benzoyl]glycine
3-(3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-fluoropropanoic acid
- 30 3-[3,5-dichloro-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
3-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]-2-fluoropropanoic acid
3-(3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-fluoropropanoic acid
- 35 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]-2-fluoropropanoic acid
(3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)acetic acid
N-(3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}benzoyl)glycine

- (3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)acetic acid
 [3,5-dichloro-4-{{3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]acetic acid
 N-[3,5-dichloro-4-{{3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy}benzoyl]glycine
 [3,5-dibromo-4-{{3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]acetic acid
 5 [3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy}phenyl]acetic acid
 3-[(3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
 3-[(3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)amino]-3-oxopropanoic acid
 10 3-[[4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}-3,5-dimethylphenyl]amino]-3-oxopropanoic acid
 3-[[3,5-dichloro-4-{{3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]amino]-3-oxopropanoic acid
 3-[[3,5-dibromo-4-{{3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]amino]-3-oxopropanoic acid
 15 acid
 3-[[4-{{3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy}-3,5-dimethylphenyl]amino]-3-oxopropanoic acid
 3-[[3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy}phenyl]amino]-3-oxopropanoic acid
 20 3-[[3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy}phenyl]amino]-3-oxopropanoic acid
 3-[[4-{{3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy}-3,5-dimethylphenyl]amino]-3-oxopropanoic acid
 [3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]acetic acid
 25 N-[3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]benzyl}oxy}benzoyl]glycine
 [3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]acetic acid
 3-[3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy}phenyl]propanoic acid
 N-[3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy}benzoyl]glycine
 3-[3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy}phenyl]propanoic acid
 30 [3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy}phenyl]acetic acid
 N-[3,5-dichloro-4-{{3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy}benzoyl]glycine
 [3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy}phenyl]acetic acid
 3-[3,5-dichloro-4-{{3-cyano-5-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]propanoic acid
 N-[3,5-dibromo-4-{{3-cyano-5-[(ethylsulfonyl)amino]benzyl}oxy}benzoyl]glycine
 35 3-[3,5-dibromo-4-{{3-cyano-5-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]propanoic acid
 [3,5-dichloro-4-{{3-cyano-5-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]acetic acid
 N-[3,5-dichloro-4-{{3-cyano-5-[(ethylsulfonyl)amino]benzyl}oxy}benzoyl]glycine

- [3,5-dibromo-4-({3-cyano-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
3-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)benzoyl]glycine
3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]propanoic acid
5 [3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)benzoyl]glycine
[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]acetic acid
3-[3,5-dichloro-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
10 [3,5-dibromo-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
[3,5-dichloro-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
3-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)benzoyl]glycine
15 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl]propanoic acid
[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)benzoyl]glycine
[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl]acetic acid
3-[3,5-dichloro-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]propanoic acid
20 N-[3,5-dibromo-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)benzoyl]glycine
3-[3,5-dibromo-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]propanoic acid
[3,5-dichloro-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)benzoyl]glycine
[3,5-dibromo-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]acetic acid
25 3-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({4-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({2-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-(3,5-dibromo-4-{{3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic
acid
30 3-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-(3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic acid
3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-methylbenzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(propylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
35 3-[3,5-dibromo-4-({3-[(isopropylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(butylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(phenylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid

- 3-{3,5-dibromo-4-[(3-[(3,5-dimethylisoxazol-4-yl)sulfonyl]amino)benzyl]oxy}phenyl]propanoic acid
- 3-(3,5-dichloro-4-[(3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy})phenyl]propanoic acid
- 5 3-[3,5-dichloro-4-((3-[(methylsulfonyl)amino]benzyl)oxy)phenyl]propanoic acid
- N-[3,5-dibromo-4-((3-[(methylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- N-[3,5-dibromo-4-((3-[(ethylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- 3-[3,5-dibromo-4-((3-chloro-5-[(methylsulfonyl)amino]benzyl)oxy)phenyl]propanoic acid
- 3-[3,5-dibromo-4-((3-chloro-5-[(ethylsulfonyl)amino]benzyl)oxy)phenyl]propanoic acid
- 10 3-[3,5-dibromo-4-((3-[(ethylsulfonyl)amino]-5-methylbenzyl)oxy)phenyl]propanoic acid
- [3,5-dichloro-4-((3-[(ethylsulfonyl)amino]-5-methylbenzyl)oxy)phenyl]acetic acid
- [3,5-dichloro-4-((3-methyl-5-[(methylsulfonyl)amino]benzyl)oxy)phenyl]acetic acid
- N-[3,5-dichloro-4-((3-methyl-5-[(methylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- N-[3,5-dichloro-4-((3-[(ethylsulfonyl)amino]-5-methylbenzyl)oxy)benzoyl]glycine
- 15 N-[3,5-dibromo-4-((3-chloro-5-[(ethylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- N-[3,5-dibromo-4-((3-chloro-5-[(methylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- N-[3,5-dibromo-4-((2-chloro-3-[(methylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- N-[3,5-dibromo-4-((2,5-dichloro-3-[(methylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- 3-[3,5-dibromo-4-((2-chloro-3-[(ethylsulfonyl)amino]benzyl)oxy)phenyl]propanoic acid
- 20 3-[3,5-dibromo-4-((3-chloro-5-[(methylsulfonyl)amino]benzyl)oxy)phenyl]-2-fluoropropanoic acid
- 3-[3,5-dibromo-4-((2-chloro-3-[(methylsulfonyl)amino]benzyl)oxy)phenyl]-2-fluoropropanoic acid
- 3-[3,5-dibromo-4-((2,5-dichloro-3-[(methylsulfonyl)amino]benzyl)oxy)phenyl]-2-fluoropropanoic acid
- 3-[3,5-dibromo-4-((3-[(methylsulfonyl)amino]-5-methylbenzyl)oxy)phenyl]butanoic acid
- 25 N-[3,5-dibromo-4-((3-methyl-5-[(methylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
- {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-vinyl]-benzyloxy}-acetic acid
- {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-ethyl]-benzyloxy}-acetic acid
- 30 More preferred compounds according to the invention include:
- 3-(4-[(3-(acetylamino)-5-(trifluoromethyl)benzyl]oxy)-3,5-dichlorophenyl]propanoic acid
- 3-(4-[(3-(acetylamino)-5-chlorobenzyl]oxy)-3,5-dichlorophenyl]propanoic acid
- 3-(4-[(3-(acetylamino)-5-methylbenzyl]oxy)-3,5-dibromophenyl]propanoic acid
- 3-[(4-[(3-(acetylamino)-5-methylbenzyl]oxy)-3,5-dibromophenyl]amino]-3-oxopropanoic acid
- 35 (4-[(3-(acetylamino)benzyl]oxy)-3,5-dichlorophenyl]acetic acid
- N-(4-[(3-(acetylamino)benzyl]oxy)-3,5-dichlorobenzoyl]glycine
- (4-[(3-(acetylamino)benzyl]oxy)-3,5-dibromophenyl]acetic acid

- 3-(4-{{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dichlorophenyl})propanoic acid
N-(4-{{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dibromobenzoyl})glycine
3-(4-{{[3-(acetylamino)-5-cyanobenzyl]oxy}-3,5-dibromophenyl})propanoic acid
N-(4-{{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dibromobenzoyl})glycine
5 3-(4-{{[3-(acetylamino)-2-fluorobenzyl]oxy}-3,5-dibromophenyl})propanoic acid
3-(4-{{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dichlorophenyl})propanoic acid
3-(4-{{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dibromophenyl})propanoic acid
3-(4-{{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dichlorophenyl})propanoic acid
N-(4-{{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dibromobenzoyl})glycine
10 3-(4-{{[3-(acetylamino)-2-fluoro-5-methylbenzyl]oxy}-3,5-dibromophenyl})propanoic acid
3-(4-{{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dichlorophenyl})propanoic acid
N-(4-{{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dibromobenzoyl})glycine
3-(4-{{[3-(acetylamino)-5-chloro-2-fluorobenzyl]oxy}-3,5-dibromophenyl})propanoic acid
3-(3,5-dichloro-4-{{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl})propanoic acid
15 3-(3,5-dibromo-4-{{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl})propanoic acid
3-(3,5-dibromo-4-{{[3-methyl-5-(propionylamino)benzyl]oxy}phenyl})-2-fluoropropanoic acid
3-[(3,5-dibromo-4-{{[3-(propionylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl})amino]-3-oxopropanoic acid
3-[(3,5-dichloro-4-{{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl})amino]-3-oxopropanoic acid
20 3-[(3,5-dibromo-4-{{[3-chloro-5-(propionylamino)benzyl]oxy}phenyl})amino]-3-oxopropanoic acid
3-(3,5-dibromo-4-{{[2-chloro-3-(propionylamino)benzyl]oxy}phenyl})propanoic acid
N-(3,5-dibromo-4-{{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}benzoyl})glycine
3-(3,5-dibromo-4-{{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}phenyl})propanoic acid
(3,5-dibromo-4-{{[2-fluoro-5-methyl-3-(propionylamino)benzyl]oxy}phenyl})acetic acid
25 N-(3,5-dibromo-4-{{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}benzoyl})glycine
3-(3,5-dibromo-4-{{[5-chloro-2-fluoro-3-(propionylamino)benzyl]oxy}phenyl})propanoic acid
3-(3,5-dibromo-4-{{[3-(isobutyrylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl})propanoic acid
3-(3,5-dibromo-4-{{[3-chloro-5-(isobutyrylamino)benzyl]oxy}phenyl})propanoic acid
N-(3,5-dibromo-4-{{[3-(isobutyrylamino)-5-methylbenzyl]oxy}benzoyl})glycine
30 3-(3,5-dibromo-4-{{[3-(isobutyrylamino)-5-methylbenzyl]oxy}phenyl})propanoic acid
3-(3,5-dibromo-4-{{[3-(isobutyrylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl})-2-fluoropropanoic acid
3-(3,5-dibromo-4-{{[3-chloro-5-(isobutyrylamino)benzyl]oxy}phenyl})-2-fluoropropanoic acid
3-(3,5-dibromo-4-{{[3-(isobutyrylamino)-5-methylbenzyl]oxy}phenyl})-2-fluoropropanoic acid
35 3-[(3,5-dibromo-4-{{[3-chloro-5-(isobutyrylamino)benzyl]oxy}phenyl})amino]-3-oxopropanoic acid
3-[(3,5-dibromo-4-{{[3-(isobutyrylamino)-5-methylbenzyl]oxy}phenyl})amino]-3-oxopropanoic acid
3-(3,5-dibromo-4-{{[3-fluoro-5-(isobutyrylamino)benzyl]oxy}phenyl})propanoic acid

- 3-(3,5-dibromo-4-{{2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{2-chloro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dibromophenyl)propanoic acid
 5 3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dichlorophenyl)propanoic acid
 3-(4-{{3-(acetylamino)-4-methylbenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(butyrylamino)benzyl}oxy}phenyl)propanoic acid
 10 3-(3,5-dibromo-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(isobutyrylamino)-2-methylbenzyl}oxy}phenyl)propanoic acid
 3-[3,5-dibromo-4-({3-[(3-methylbutanoyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(2E)-but-2-enoylamino]benzyl}oxy)phenyl]propanoic acid
 15 3-[3,5-dibromo-4-({3-[(cyclopropylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclobutylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclopentylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 N-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dibromobenzoyl)glycine
 N-(3,5-dibromo-4-{{3-(propionylamino)benzyl}oxy}benzoyl)glycine
 20 N-(3,5-dibromo-4-{{3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
 3-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
 3-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 N-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromobenzoyl)glycine
 N-(4-{{3-(acetylamino)-5-methylbenzyl}oxy}-3,5-dibromobenzoyl)glycine
 25 N-(4-{{3-(acetylamino)-2-chlorobenzyl}oxy}-3,5-dibromobenzoyl)glycine
 3-(4-{{3-(acetylamino)-2-chlorobenzyl}oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
 3-(4-{{3-(acetylamino)-5-methylbenzyl}oxy}-3,5-dibromophenyl)butanoic acid
- and
- 30 N-(3,5-dibromo-4-{{3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}benzoyl)glycine
 3-[3,5-dichloro-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-(3,5-dichloro-4-{{3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-
 35 fluoropropanoic acid
 3-(3,5-dibromo-4-{{3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-
 fluoropropanoic acid

- 3-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
- 3-{{3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
- 5 3-{{3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
- 3-{{3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
- 3-[3,5-dibromo-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
- 10 [3,5-dichloro-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- N-[3,5-dichloro-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
- [3,5-dibromo-4-({2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- 3-[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
- N-[3,5-dibromo-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
- 15 3-[3,5-dibromo-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
- N-[3,5-dibromo-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
- 3-[3,5-dibromo-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
- N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)benzoyl]glycine
- 20 3-(3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-fluoropropanoic acid
- 3-[3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
- 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]-2-fluoropropanoic acid
- 3-{{3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl}amino}-3-oxopropanoic acid
- 25 acid
- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl}amino}-3-oxopropanoic acid
- [3,5-dichloro-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- N-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
- 30 [3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- 3-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy)phenyl]propanoic acid
- N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy)benzoyl]glycine
- 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy)phenyl]propanoic acid
- [3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy)phenyl]acetic acid
- 35 N-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy)benzoyl]glycine
- [3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy)phenyl]acetic acid
- 3-[3,5-dibromo-4-({3-cyano-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid

- N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)benzoyl]glycine
3-[3,5-dichloro-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
3-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl]propanoic acid
5 N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)benzoyl]glycine
3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl]propanoic acid
[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl]acetic acid
3-[3,5-dibromo-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
10 3-[3,5-dibromo-4-({4-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({2-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-(3,5-dibromo-4-[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
15 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-(3,5-dibromo-4-[3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-methylbenzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(propylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(isopropylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
20 3-[3,5-dibromo-4-({3-[(butylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(phenylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-{3,5-dibromo-4-[3-{{(3,5-dimethylisoxazol-4-yl)sulfonyl}amino}benzyl]oxy}phenyl]propanoic acid
3-(3,5-dichloro-4-[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy)phenyl]propanoic acid
25 acid
3-[3,5-dichloro-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
N-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
3-[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
30 3-[3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]propanoic acid
[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]acetic acid
[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
N-[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
35 N-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)benzoyl]glycine
N-[3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
N-[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine

- N-[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 N-[3,5-dibromo-4-({2,5-dichloro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 3-[3,5-dibromo-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 5 3-[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 3-[3,5-dibromo-4-({2,5-dichloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 acid
 3-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]butanoic acid
 N-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 10 {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-vinyl]-benzyloxy}-acetic acid
 {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-ethyl]-benzyloxy}-acetic acid

Most preferred compounds according to the invention include:

- 15 3-(4-{{3-(acetylamino)-5-(trifluoromethyl)benzyl}oxy}-3,5-dichlorophenyl)propanoic acid
 3-(4-{{3-(acetylamino)-5-methylbenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(4-{{3-(acetylamino)-2-chlorobenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(4-{{3-(acetylamino)-2-fluoro-5-methylbenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(4-{{3-(acetylamino)-5-chloro-2-fluorobenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 20 3-(3,5-dibromo-4-{{3-methyl-5-(propionylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-methyl-5-(propionylamino)benzyl}oxy}phenyl)-2-fluoropropanoic acid
 3-[(3,5-dibromo-4-{{3-(propionylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)amino]-3-oxopropanoic acid
 3-[(3,5-dibromo-4-{{3-chloro-5-(propionylamino)benzyl}oxy}phenyl)amino]-3-oxopropanoic acid
 25 3-(3,5-dibromo-4-{{2-chloro-3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{5-chloro-2-fluoro-3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(isobutyrylamino)-5-(trifluoromethyl)benzyl}oxy}phenyl)-2-fluoropropanoic acid
 30 acid
 3-[(3,5-dibromo-4-{{3-chloro-5-(isobutyrylamino)benzyl}oxy}phenyl)amino]-3-oxopropanoic acid
 3-(3,5-dibromo-4-{{5-chloro-2-fluoro-3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dichlorophenyl)propanoic acid
 35 3-(4-{{3-(acetylamino)-4-methylbenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid

- 3-(3,5-dibromo-4-{[3-(butyrylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(isobutyrylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-(isobutyrylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(isobutyrylamino)-2-methylbenzyl]oxy}phenyl)propanoic acid
5 3-[3,5-dibromo-4-({3-[(3-methylbutanoyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(2E)-but-2-enoylamino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(cyclopropylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(cyclobutylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-[3,5-dibromo-4-({3-[(cyclopentylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
10 N-(4-{[3-(acetylamino)benzyl]oxy}-3,5-dibromobenzoyl)glycine
N-(3,5-dibromo-4-{[3-(propionylamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(isobutyrylamino)benzyl]oxy}benzoyl)glycine
3-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
3-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromophenyl)propanoic acid
15 N-(4-{[3-(acetylamino)-5-chlorobenzyl]oxy}-3,5-dibromobenzoyl)glycine
N-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromobenzoyl)glycine
N-(4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dibromobenzoyl)glycine
3-(4-{[3-(acetylamino)-2-chlorobenzyl]oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
3-(4-{[3-(acetylamino)-5-methylbenzyl]oxy}-3,5-dibromophenyl)butanoic acid
20
and
3-[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-(3,5-dibromo-4-{[3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)-2-
fluoropropanoic acid
25 3-{[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]amino}-3-
oxopropanoic acid
3-[3,5-dibromo-4-({2-fluoro-5-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic
acid
N-[3,5-dibromo-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
30 3-[3,5-dibromo-4-({5-chloro-2-fluoro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
3-(3,5-dibromo-4-{[3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)-2-
fluoropropanoic acid
3-[3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]-2-fluoropropanoic acid
35 3-{[3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]amino}-3-oxopropanoic
acid

- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl}amino}-3-oxopropanoic acid
- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-fluorobenzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-fluoro-5-methylbenzyl}oxy)phenyl}propanoic acid
- 5 3-{{3,5-dibromo-4-({5-chloro-3-[(ethylsulfonyl)amino]-2-fluorobenzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({4-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({2-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy)phenyl}propanoic acid
- 10 acid
- 3-{{3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-methylbenzyl}oxy)phenyl}propanoic acid
- 15 3-{{3,5-dibromo-4-({3-[(propylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(isopropylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(butylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(phenylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-{{3,5-dimethylisoxazol-4-yl}sulfonyl}amino)benzyl}oxy}phenyl}propanoic acid
- 20 acid
- 3-{{3,5-dichloro-4-({3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dichloro-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- N-{{3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl}glycine
- 25 N-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl}glycine
- 3-{{3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid
- 3-{{3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl}propanoic acid
- [[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]acetic acid
- 30 [[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
- N-{{3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl}glycine
- N-{{3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)benzoyl}glycine
- N-{{3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl}glycine
- N-{{3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl}glycine
- 35 N-{{3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl}glycine
- N-{{3,5-dibromo-4-({2,5-dichloro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl}glycine
- 3-{{3,5-dibromo-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl}propanoic acid

- 3-[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 3-[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 3-[3,5-dibromo-4-({2,5-dichloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
- 5 3-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]butanoic acid
 N-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-vinyl]-benzyloxy}-acetic acid
 {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-ethyl]-benzyloxy}-acetic acid
- 10 In particular:
 3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dichlorophenyl)propanoic acid
 3-(4-{{3-(acetylamino)-4-methylbenzyl}oxy}-3,5-dibromophenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
- 15 3-(3,5-dichloro-4-{{3-(propionylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(butyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dichloro-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
 3-(3,5-dibromo-4-{{3-(isobutyrylamino)-2-methylbenzyl}oxy}phenyl)propanoic acid
- 20 3-[3,5-dibromo-4-({3-[(3-methylbutanoyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(2E)-but-2-enoylamino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclopropylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclobutylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(cyclopentylcarbonyl)amino]benzyl}oxy)phenyl]propanoic acid
- 25 N-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dibromobenzoyl)glycine
 N-(3,5-dibromo-4-{{3-(propionylamino)benzyl}oxy}benzoyl)glycine
 N-(3,5-dibromo-4-{{3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
 3-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
 3-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromophenyl)propanoic acid
- 30 N-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromobenzoyl)glycine
 N-(4-{{3-(acetylamino)-5-methylbenzyl}oxy}-3,5-dibromobenzoyl)glycine
 N-(4-{{3-(acetylamino)-2-chlorobenzyl}oxy}-3,5-dibromobenzoyl)glycine
 3-(4-{{3-(acetylamino)-2-chlorobenzyl}oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
 3-(4-{{3-(acetylamino)-5-methylbenzyl}oxy}-3,5-dibromophenyl)butanoic acid
- 35 and
 3-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({4-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid

- 3-[3,5-dibromo-4-({2-methyl-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-(3,5-dibromo-4-{{3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic acid
 3-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 5 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-(3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic acid
 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-2-methylbenzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(propylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(isopropylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 10 3-[3,5-dibromo-4-({3-[(butylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(phenylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-{{3,5-dibromo-4-[(3-{{(3,5-dimethylisoxazol-4-yl)sulfonyl}amino}benzyl}oxy]phenyl}propanoic acid
 3-(3,5-dichloro-4-{{3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic acid
 15 acid
 3-[3,5-dichloro-4-({3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 N-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 N-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 3-[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 20 3-[3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]propanoic acid
 [3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]acetic acid
 [3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]acetic acid
 N-[3,5-dichloro-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 25 N-[3,5-dichloro-4-({3-[(ethylsulfonyl)amino]-5-methylbenzyl}oxy)benzoyl]glycine
 N-[3,5-dibromo-4-({3-chloro-5-[(ethylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 N-[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 N-[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 N-[3,5-dibromo-4-({2,5-dichloro-3-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 30 3-[3,5-dibromo-4-({2-chloro-3-[(ethylsulfonyl)amino]benzyl}oxy)phenyl]propanoic acid
 3-[3,5-dibromo-4-({3-chloro-5-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 3-[3,5-dibromo-4-({2-chloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 3-[3,5-dibromo-4-({2,5-dichloro-3-[(methylsulfonyl)amino]benzyl}oxy)phenyl]-2-fluoropropanoic acid
 acid
 35 3-[3,5-dibromo-4-({3-[(methylsulfonyl)amino]-5-methylbenzyl}oxy)phenyl]butanoic acid
 N-[3,5-dibromo-4-({3-methyl-5-[(methylsulfonyl)amino]benzyl}oxy)benzoyl]glycine
 {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-vinyl]-benzyloxy}-acetic acid

{3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-ethyl]-benzyloxy}-acetic acid

The compounds names given above were generated in accordance with IUPAC by the ACD Labs/Name program, version 7.08 build 21 and with ISIS DRAW Autonom 2000.

5

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein a counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of the
10 compounds of formula (I) and their pharmaceutically acceptable salts, solvates and physiologically functional derivatives. According to the present invention, examples of physiologically functional derivatives include esters, amides, and carbamates; preferably esters and amides.

Suitable salts according to the invention include those formed with organic or inorganic acids or
15 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. Other acids such as oxalic, while not in themselves
20 pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutical acceptable acid addition salts. 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 e.g. primary, secondary or tertiary organic amines, for example dicyclohexylamine, and N-
25 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 C₁₋₆ alkyl, C₅₋₁₀ aryl, C₅₋₁₀ ar-C₁₋₆ alkyl, or amino acid ester or amide. Pharmaceutically acceptable amides and carbonates of the
30 compounds of formula (I) may have an appropriate group, for example an amino group, converted to a C₁₋₆ alkyl, C₅₋₁₀ aryl, C₅₋₁₀ aryl-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
35 crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate".

A compound which, upon administration to the recipient, is capable of being converted into a compound of formula (I) as described above or an active metabolite or residue thereof, is known as a "prodrug". A prodrug may, for example, be converted within the body, e. g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutical acceptable prodrugs are
5 described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series (1976); and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

10 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
15 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.

20 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 alkenyl groups include
25 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,
30 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.
35 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.

5 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 tetrahydronaphthyl. Specifically, the term C₅₋₁₀ aryl is used herein to mean a group comprising from 5 to 10 carbon atoms in a monocyclic or bicyclic aromatic group. A particularly preferred C₅₋₁₀ aryl group is phenyl.

10 As used herein, the term "halogen" means fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are particularly 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
15 is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen and 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,
20 azetidiny, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and azepanyl.

Examples of bicyclic heterocyclic rings in which one of the rings is non-aromatic include dihydrobenzofuranyl, indanyl, indolinyl, isoindolinyl, tetrahydroisoquinolinyl, tetrahydroquinolyl
25 and benzoazepanyl.

Examples of monocyclic heteroaryl groups include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl and pyrimidinyl; examples of bicyclic heteroaryl
30 groups include quinoxaliny, quinazoliny, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, quinolinyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridyl, pyridopyrimidinyl, isoquinolinyl and benzodioxazole.

Examples of preferred heterocyclyl groups include piperidinyl, tetrahydrofuranyl,
35 tetrahydropyranyl, pyridyl, pyrimidyl and indolyl.

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.

As mentioned above, the compounds of the invention have activity as thyroid receptor ligands. The compounds of the invention are preferably selective agonists or partial agonists of the thyroid receptor. Preferably compounds of the present invention possess activity as agonists of the thyroid receptor, preferably selective agonists of the thyroid receptor-beta. They may thus be used in the treatment of diseases or disorders associated with thyroid receptor activity, particularly diseases or disorders for which selective agonists of the thyroid receptor-beta are indicated. 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 T₃ regulated gene.

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.

The compounds of the invention find particular 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 especial 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 also provides a method for the treatment or prophylaxis of a condition in a mammal mediated by a thyroid receptor, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I) as defined above 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. Clinical conditions mediated by a thyroid receptor that may be treated by the method of the invention are those described above.

The invention also provides the use of a compound of formula (I) as defined above 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 mediated by a thyroid receptor. Clinical conditions mediated by a thyroid receptor that may be treated by the method of the invention are those described above.

Hereinafter, the term "active ingredient" means a compound of formula (I) as defined above, 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.

5 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 0.001 to 1500 mg/kg per day, preferably from 0.01 to 1500 mg/kg per day, more preferably from 0.1 to 1500 mg/kg per day, most preferably from 0.1 to 500
10 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.

15

While it is possible for the active ingredient to be administered alone, it is preferable for it to be present in a pharmaceutical formulation. Accordingly, the invention provides a pharmaceutical formulation comprising a compound of formula (I) as defined above or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a
20 solvate of such an ester, amide or salt, and 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
25 of metered dose pressurized aerosols), nebulizers or insufflators, 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
30 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.

35

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.

5 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
10 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
15 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
20 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 formula I can also be delivered through the oral cavity by sublingual
25 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
30 to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic 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.

35 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
5 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,
10 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
15 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 liquify and/or dissolve in the rectal cavity to release the drug.
20

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
25 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.

30 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.

35 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, a 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, glipyrizide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone, englitazone, 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-1), 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-1 inhibitors.

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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-1 (cannabinoid receptor) antagonists (see G. Colombo et al, "Appetite Suppression and Weight Loss After the Cannabinoid Antagonist SR 141716", Life Sciences, Vol 63, PL 113-117 (1998)) and/or an anorectic agent, such as dexamphetamine, phentermine, phenylpropanolamine or mazindol.

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The compounds of the present invention may be combined with growth promoting agents, such as, but not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, 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.

20

The compounds of the invention may also be used in combination with growth hormone secretagogues such as GHRP-6, GHRP-1 (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-1 and IGF-2, or with alpha-adrenergic agonists, such as clonidine or serotonin 5-HT_D agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as physostigmine and pyridostigmine. A still further use of the disclosed compounds of the invention is in combination with parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate).

25
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Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel®, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen®, Celebrex®, Vioxx®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®), integrin antagonists, alpha-4 beta-7

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integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), 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
5 the treatment of irritable bowel syndrome (e.g., Zelmac® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

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

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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, triamtrenene, amiloride, spironolactone),
15 renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 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
20 NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

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

30 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, lipooxygenase inhibitors, an ileal Na⁺/bile acid cotransporter inhibitor, cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

35

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.

5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Patent No. 5,962,440 all incorporated herein by reference.

The HMG CoA reductase inhibitors which may be employed in combination with one or more
5 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.
10 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,
15 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-propane-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,
20 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.

The squalene synthetase inhibitors which may be used in combination with the compounds of the
25 present invention include, but are not limited to, α -phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates, terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem.
30 Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, as well as other squalene synthetase inhibitors as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2,
35 1-40 (1996).

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 (Rhône-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche),
5 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,
10 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-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters",
15 Nicolosi et al, *Atherosclerosis* (Shannon, Ire). (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-diphenylimidazole ACAT inhibitor", Smith, C., et al, *Bioorg. Med. Chem. Lett.* (1996), 6(1), 47-50;
20 "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred A., *Inflammation: Mediators Pathways* (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, *Curr. Med. Chem.* (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, *Chemtracts: Org. Chem.* (1995), 8(6), 359-62.

30 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).

35 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.

5 Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone, TRH diethylstilbesterol, estrogens, β -agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E-series prostagladins, 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.

10 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
15 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. Let.*, 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 steriodal or non-steriodal
20 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
25 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:

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When combined with a hypolipidemic agent, an antidepressant, a bone resorption inhibitor and/or
an appetite suppressant, the compounds of formula I 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.

35

Where the antidiabetic agent is a biguanide, the compounds of formula I 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.

- 5 The compounds of formula I 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 formula I 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.

10

- The compounds of formula I 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 formula I.

15

- 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.

20

- The compounds of formula I 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.

25

- An MTP inhibitor may be administered orally with the compounds of formula I 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.

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A HMG CoA reductase inhibitor may be administered orally with the compounds of formula I 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
5 more preferably from about 10 to about 40 mg.

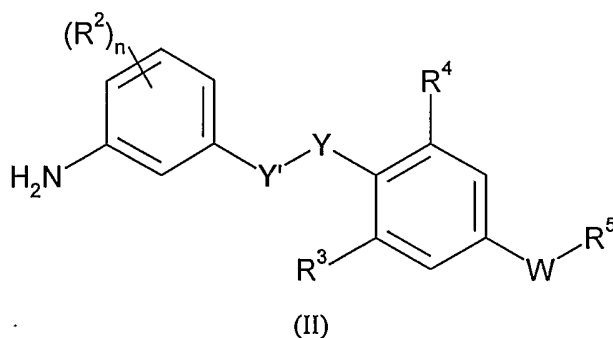
A squalene synthetase inhibitor may be administered with the compounds of formula I within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg. A preferred oral dosage form, such as tablets or capsules, will contain the squalene synthetase inhibitor
10 in an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

The compounds of formula (I) 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.
15 For example, such a compound may be radioactively labelled.

The compounds of formula (I) as described above, optionally in labelled form, also find use as a reference compound in methods of discovering other antagonists or partial antagonists of the thyroid receptor. Thus, the invention provides a method of discovering a ligand of the thyroid receptor
20 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 formula (I) 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 compound of formula (I) in question.

25

The invention also provides a method for preparing a compound in of formula (I) accordance with the invention as described above comprising a step of reacting
- a compound of formula (II)



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wherein R^2 , n , Y^1 , Y , R^3 , R^4 , W and R^5 are as defined above

- 5 - with a compound of formula R^1-L , wherein R^1 is as defined above and L is a suitable leaving group, optionally in the presence of a suitable base, followed optionally by interconversion to another compound in accordance with the invention.

Suitable leaving groups L include halogen, OR^c , $-SR^c$, C_{1-4} alkyl, C_{5-10} aryl or C_{5-10} aryl- C_{1-4} alkyl sulphonate esters, for example, a bromide, a methylsulfonyl or a toluenesulfonyl group. Particularly
10 preferred compounds R^1-L are acid chlorides (R^6COCl) and sulphonylchlorides (R^6SO_2Cl) ie reagents in which the leaving group L is Cl . Suitable bases include carbonates, alkylamines and alkali metal hydroxides, for example potassium carbonate, cesium carbonate, potassium hydroxide, sodium hydroxide diisopropylamine and triethylamine. Trimethylsilanoate may also be used. Other combinations of leaving groups and bases may be employed, as is known by the person skilled in
15 the art. Optionally, one or more coupling reagents may be employed. 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).

20

The invention will now be illustrated by the following Examples, which do not in any way limit the scope of the invention.

EXAMPLES

- 25 The following compounds illustrate compounds of the invention or, where appropriate, compounds for use in the invention.

DESCRIPTION 1

Methyl 3-(4-hydroxy-3,5-dibromophenyl) propionate

- 30 To a solution of 3-(4-hydroxyphenyl) propionate methyl ester (10 g, 55.5 mmol) in acetic acid (150 mL), bromine (19.5 g, 121.9 mmol) was added drop wise slowly. The reaction mixture was stirred for 5 h at room temperature and then evaporated and co-evaporated with ethyl acetate (2 x 200 mL). The residue was purified on silica gel column to give 17.0 g of the title compound (90.6% yield).

35 DESCRIPTION 2

Methyl 3-(4-hydroxy-3,5-dichlorophenyl) propionate

Methyl-3-(4-hydroxyphenyl) propionate (35.6 g, 0.198 mol) was dissolved in dichloromethane (200 mL). The reaction mixture was cooled to 4°C and sulfonyl chloride (120 mL, 1.42 mol) in diethyl ether (200 mL) was added drop wise to the reaction mixture over 1 h. After 3 h at room temperature the solvent was removed. The reaction mixture was dissolved in dichloromethane and washed with
5 water. The combined organic phases were dried over sodium sulphate, filtered and evaporated. The product was purified by flash chromatography (diethyl ether/heptane) to provide 16.6 g (34%) of the title compound.

DESCRIPTION 3

10 Methyl (3,5-dibromo-4-hydroxy-benzoylamino) acetate

3,5-Dibromo-4-hydroxybenzoic acid (5.1 g, 17.23 mmol) was refluxed in thionyl chloride (100 mL) for 6h. The reaction mixture was cooled and the excess thionyl chloride removed. The product was used in the next step without further purification.

Glycine methyl ester hydrochloride (4.33 g, 34.5 mmol) was dissolved in dichloromethane (430
15 mL) and triethyl amine (20 mL, 143.6 mmol). The acid chloride (17.23 mmol) was added in small portions. Stirring was continued overnight. The solvent was evaporated. The reaction mixture was dissolved in dichloromethane and washed with hydrochloric acid (0.1 M aqueous solution). The organic phase was dried over sodium sulphate, filtered and the solvent removed. A small amount of ethyl acetate was added and the mixture was filtered to give 4.21 g (88%) of almost pure compound.
20 The product was crystallized from heptanes/ethyl acetate to give 2.5 g of the title compound (52% yield) as a white powder.

DESCRIPTION 4

5-Trifluoromethyl-3-nitrobenzylbromide

25 5-Trifluoromethyl-3-nitrobenzoic acid (0.7g, 3.0 mmol) was dissolved in methanol and 10 drops of sulphuric acid (conc.) were added, and the reaction was stirred over night at reflux temperature. Methanol was removed and the residue re-dissolved in dichloromethane and washed with water. The solvent was dried (magnesium sulphate) and removed under vacuum to give 0.71 g of 5-trifluoromethyl-3-nitrobenzoate methyl ester.

30

To lithium aluminium hydride (0.32 g, 8.7 mmol) in tetrahydrofuran (8 mL) was carefully, and drop wise, added a solution of 5-trifluoromethyl-3-nitrobenzoate methyl ester in tetrahydrofuran (2 mL) and stirred at room temperature over night. The reaction was quenched with careful addition of water (20 mL) then acidified using hydrochloric acid (3 M) and finally extracted with diethylether
35 (3 x 50mL). The combined organic phases were dried (magnesium sulphate) and the solvent was removed under vacuum. The residue was purified on silica gel column (diethyl ether /heptane 1:3) to provide 0.35 g, (55%) of 5-trifluoromethyl-3-nitrobenzylalcohol.

5-Trifluoromethyl-3-nitrobenzylalcohol was dissolved in toluene (3 mL) and PBr₃ (0.1 mL) was added with a syringe and the reaction was stirred at room temperature over night. The reaction was filtered through a plug of silica which was washed with diethyl ether. The solvent was removed under vacuum to give 0.38 g (85% yield) of the title compound.

DESCRIPTION 5

5-Methyl-3-nitrobenzylbromide

10 5-Methyl-3-nitrotoluene (0.5 g, 3.3 mmol) and NBS (0.6 g, 3.3 mmol) were dissolved in CCl₄ and benzoylperoxide (10 mg) was added. The reaction was refluxed over night and then cooled to room temperature. The reaction mixture was filtered and the solvent evaporated after which the residue was dissolved in dichloromethane and filtered through a plug of silica. The obtained residue was a 2:1 mixture of the corresponding 5-methyl-3-nitrobenzylbromide and starting material. The yield
15 was calculated to 65%.

DESCRIPTION 6

5-Chloro-3-nitrobenzylbromide

20 5-Chloro-3-nitrotoluene (synthesized following *Journal of Medicinal Chemistry*, **2000**, 43, 4733) (0.33 g, 1.9 mmol) and NBS (0.34 g, 1.9 mmol) were dissolved in 9 mL of CCl₄ and 10 mg of benzoylperoxide were added. The reaction was refluxed over night and the cooled to room temperature. The reaction mixture was filtered and the solvent evaporated after which the residue was dissolved in dichloromethane and was filtered through a plug of silica. The solvent was again
25 evaporated to give 0.55 g crude product containing starting material the monobrominated and the dibrominated benzyl compound. Purification on silica (diethyl ether /heptane 9:1) gave 0.13 g (27% yield) of 5-chloro-3-nitrobenzylbromide.

DESCRIPTION 7

1,3-Dibromo-5-methyl-2-[(E)-2-(3-nitro-phenyl)-vinyl]-benzene

To 2,6-dibromo-4-methyl-benzaldehyde (prepared from literature procedure *JOC*, **2003**, 5384) (0.31 g, 1.28 mmol) in DMPU (13 mL) was added sodium hydride (0.083 g, 2.06 mmol) the mixture was stirred for 5 min. The (3-nitro-benzyl)-phosphonic acid dimethyl ester (0.47 g, 1.29 mmol),
35 (prepared from literature procedure *JMC*, **2004**, 2095) was added at 0°C and the reaction was stirred for 2 hours. Water and ethyl acetate was added, the organic phase collected and dried. The solvents

were distilled off and the product purified on silica (ethyl ether/ heptane 1:3) to give 0.45 g (88% yield) of 1,3-dibromo-5-methyl-2-[(E)-2-(3-nitro-phenyl)-vinyl]-benzene.

5 DESCRIPTION 8

{3,5-Dibromo-4-[(E)-2-(3-nitro-phenyl)-vinyl]-phenyl}-methanol

To 1,3-dibromo-5-methyl-2-[(E)-2-(3-nitro-phenyl)-vinyl]-benzene (Description 7, 0.070 g, 0.17 mmol) in CCl₄, 1 mL was added NBS, (0.030 g, 0.17 mmol) the mixture was stirred at reflux for 15h. Filtration throw silica with dichloromethane evaporation of solvents gave a crude product
10 which was dissolved in dioxane (3 mL) and potassium hydroxide (6 mL, aq., 2M) and refluxed overnight. Ethyl acetate was added to extract the product, which in turn was dried and evaporated to give a (3:1) mixture of starting material and {3,5-dibromo-4-[(E)-2-(3-nitro-phenyl)-vinyl]-phenyl}-methanol. The product was purified on silica (diethyl ether/ heptane, 1:1) to give 0.016 g (23% yield) of {3,5-dibromo-4-[(E)-2-(3-nitro-phenyl)-vinyl]-phenyl}-methanol.

15

DESCRIPTION 9

{3,5-Dibromo-4-[(E)-2-(3-nitro-phenyl)-vinyl]-benzyloxy}-acetic acid tert-butyl ester

To {3,5-dibromo-4-[(E)-2-(3-nitro-phenyl)-vinyl]-phenyl}-methanol (Description 8, 0.016g,
20 0.04mmol) in tetrahydrofuran (1 mL) was added sodium hydride (0.003 g, 0.08 mmol). The mixture was stirred 5 min, tert-butyl bromoacetate was added and the reaction was stirred for 15h. Ethyl acetate and water were added and the product was extracted, dried and evaporated. The residue was purified on silica (diethyl ester/ heptane, 1:3) to give 0.010g (60% yield) of {3,5-dibromo-4-[(E)-2-(3-nitro-phenyl)-vinyl]-benzyloxy}-acetic acid tert-butyl ester.

25

DESCRIPTION 10

{4-[(E)-2-(3-Amino-phenyl)-vinyl]-3,5-dibromo-benzyloxy}-acetic acid tert-butyl ester

30

To {3,5-dibromo-4-[(E)-2-(3-nitro-phenyl)-vinyl]-benzyloxy}-acetic acid tert-butyl ester (Description 10, 0.010 g, 0.02 mmol) in ethanol (1 mL) was added SnCl₂ (0.02 g, 0.1 mmol). The mixture was stirred at reflux for 2h. Ethyl acetate and saturated sodium carbonate were added and the product was extracted, dried and evaporated. The residue was purified on silica
5 (dichloromethane) to give 0.009 g (100% yield) of {4-[(E)-2-(3-amino-phenyl)-vinyl]-3,5-dibromo-benzyloxy}-acetic acid tert-butyl ester.

GENERAL PROCEDURE FOR THE PREPARATION OF THE ANILINES OF THE INVENTION

10 A mixture of the appropriate phenol (e.g. methyl 3-[3,5-dihalo-4-hydroxyphenyl] propionate) (1 eq.), the appropriate 3-nitrobenzylbromide (1 eq.) and potassium carbonate (5 eq.) in dry acetone (30 mL/mmol phenol) was heated to 56°C and stirred for 20 h. The reaction mixture was concentrated, diluted with ethyl acetate and washed with water. The organic phase was dried, evaporated and purified on a column (silica, 100% dichloromethane) to give the nitro derivative
15 (e.g. methyl 3-[3,5-dihalo-4-(3-nitrobenzyloxy)phenyl] propionate).

A mixture of the nitro derivative (e.g. methyl 3-[3,5-dihalo-4-(3-nitrobenzyloxy)phenyl] propionate) and tin(II)chloride dihydrate (5 eq.) in absolute ethanol (40 mL/mmol ester) was heated to 75°C for 4 h. The reaction mixture was quenched with sodium hydrogen carbonate aqueous solution
20 (saturated). The aqueous phase was extracted with ethyl acetate (3 x 40 mL) and the combined organic phases were washed with water and brine and dried over magnesium sulphate. After evaporation of the solvent, the residue was purified by flash chromatography (dichloromethane/diethylether 90:10) to yield the wanted amino derivative (e.g. methyl 3-[(3,5-dihalo-4-(3-aminobenzyloxy)phenyl] propionate).

25

Amides -

GENERAL PROCEDURE FOR THE PREPARATION OF EXAMPLES 1-25

METHOD A1

30 The appropriate acid chloride (R₆COCl) (2 eq.) was added to a dichloromethane solution of the appropriate aniline (e.g. methyl 3-[3,5-dihalo-4-(3-aminobenzyloxy)phenyl] propionate) (1 eq.) and triethylamine (1.5 eq.). The mixture was stirred at room temperature for 1-3 h. Water was added and the mixture was acidified with hydrochloric acid (1 M) and extracted with dichloromethane (3 x 25 mL). The organic phases were combined, the solvent was removed *in vacuo* and the residue was
35 purified by flash chromatography to provide the desired amide (e.g. methyl 3-[3,5-dihalo-4-(3-acetylamino-benzyloxy)phenyl] propionate).

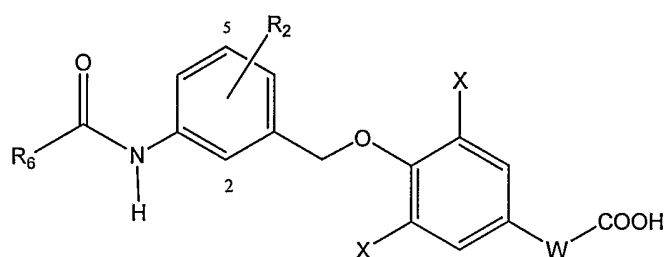
The amide (e.g. methyl 3-[3,5-dihalo-4-(3-acetylamino-benzyloxy)phenyl] propionate) was dissolved in dioxane (7 mL/mmol ester), sodium hydroxide (lithium hydroxide has also been used) (1 N in water, 5 eq.) was added and the mixture was stirred at room temperature over night. After acidification with hydrochloric acid (1 M) the product was extracted into ethyl acetate. The solvent was evaporated under vacuum to give the wanted acid (e.g. 3-[3,5-dihalo-4-(3-acetylamino-benzyloxy)phenyl] propionic acid).

METHOD A2

The appropriate acid chloride ($R_6\text{COCl}$) (1 eq) was dissolved in dichloromethane (2.5 mL/mmol), and added to a solution of the appropriate aniline (e.g. methyl 3-[3,5-dihalo-4-(3-acetylamino-benzyloxy)phenyl] propionate) (1 eq) in tetrahydrofuran (16 mL/mmol) containing Polystyrene bound diisopropylethyl amine (3.83 mmol/g, 6 eq). The mixtures were stirred over night at 50°C.

The resin was filtered off, and the dichloromethane / tetrahydrofuran solution was run through a short silica based amine column (Isolute, 1g, 0.6 mmol/g) to remove unreacted acid chloride. The column was rinsed with dichloromethane (2 ml), and the combined eluates were evaporated. The material was dissolved in tetrahydrofuran (0.5 ml) and lithium hydroxide (1 M, 1 ml) was added. The mixture was stirred over night at room temperature.

The reaction mixture was separated by semi-preparative-HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5 μ) Mobile Phase: Solvent A: Water with 0.5% formic acid; Solvent B: acetonitrile. Gradient: 20-100% acetonitrile gradient). Appropriate fractions were combined and evaporated to give the expected acid (e.g. 3-[3,5-dihalo-4-(3-acetylamino-benzyloxy)phenyl] propionic acid).



25

Example	R_6	R_2	X	W	Yield (%)	MW (calc)	M+1 (found)*	Method
1	Me	H	Br	(CH ₂) ₂	37	471.1	470.6 (M-1)	A1
2	Me	H	Cl	(CH ₂) ₂	18	382.2	380.0 (M-2)	A2
3	Me	4-Me	Br	(CH ₂) ₂	10	485.1	486.5	A2

4	Et	H	Br	(CH ₂) ₂	85	485.2	486.0	A2
5	Et	H	Cl	(CH ₂) ₂	17	396.2	394.3 (M-2)	A2
6	<i>n</i> -Pr	H	Br	(CH ₂) ₂	21	499.2	500.0	A2
7	<i>i</i> -Pr	H	Br	(CH ₂) ₂	56	499.0	500.0	A1
8	<i>i</i> -Pr	H	Cl	(CH ₂) ₂	40	410.2	410.1 (M)	A2
9	<i>i</i> -Pr	2-Me	Br	(CH ₂) ₂	52	513.2	514.1	A2
10	<i>i</i> -Bu	H	Br	(CH ₂) ₂	29	513.2	514.0	A2
11	<i>i</i> -Propenyl	H	Br	(CH ₂) ₂	17	497.2	498.0	A2
12	Cyclopropyl	H	Br	(CH ₂) ₂	18	497.2	498.0	A2
13	Cyclobutyl	H	Br	(CH ₂) ₂	50	511.2	512.0	A2
14	Cyclopentyl	H	Br	(CH ₂) ₂	45	525.2	526.0	A2
15	Me	5-Cl	Br	CH ₂ -CHF	31	523.6	522.2 (M-1)	A2
16	Me	2-Cl	Br	CH ₂ -CHF	96	523.6	522.5 (M-1)	A2
17	Me	5-Cl	Br	(CH ₂) ₂	37	505.6	504.2 (M-1)	A2
19	Me	H	Br	CONH-CH ₂	20	500.1	501.0	A2
20	Et	H	Br	CONH-CH ₂	20	514.1	515.0 (M-1)	A2
21	<i>i</i> -Pr	H	Br	CONH-CH ₂	16	528.2	529.0 (M-1)	A2
22	Me	2-Cl	Br	CONH-CH ₂	57	534.6	535 (M)	A2
23	Me	5-Cl	Br	CONH-CH ₂	61	534.6	535 (M)	A2
24	Me	5-Me	Br	CONH-CH ₂	50	514.2	515	A2
25	Me	5-Me	Br	(CH ₂) ₃	72	499.2	500	A2

*-Analyzed on HPLC-MS with alternating +/- API and equipped with different brands of 50 mm*2.1mm, 5 μ C8 columns. Eluted with 0.05% formic acid/ACN or 0.05% ammonium

5 acetate/ACN

*MW calc. (molecular weight) is an isotopic average and the "found mass" is referring to the most abundant isotope detected in the LC-MS. The "found mass" refers to M+1 unless specified otherwise.

5 Sulphonamides-

GENERAL PROCEDURE FOR THE PREPARATION OF EXAMPLES 26-60

METHOD B1

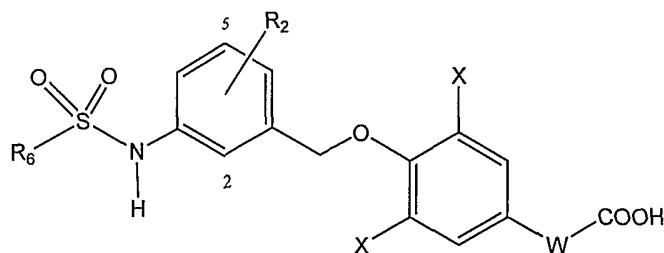
The dichloromethane solution of the appropriate aniline (e.g. methyl 3-(3,5-dihalo-4-(3-aminobenzyloxy)phenyl) propionate) (1 eq.) was treated with the appropriate sulphonylchloride (R_6SO_2Cl) (4 eq.) and pyridine (2.5 eq.). The mixture was stirred at 40°C for 2 h. Water was added and the mixture was acidified with hydrochloric acid (1 M) and extracted with dichloromethane (3 x 25 mL). The organic phases were combined, the solvent was removed under vacuum and the residue was purified by flash chromatography to provide the desired sulphonamide (e.g. methyl 3-[3,5-dihalo-4-(3-methanesulfonylamino-benzyloxy)phenyl] propionate).

The sulphonamide (e.g. methyl 3-[3,5-dihalo-4-(3-methanesulfonylamino-benzyloxy)phenyl] propionate) was dissolved in dioxane (7 mL/mmol ester), sodium hydroxide (lithium hydroxide has also been used) (1 N in water, 5 eq.) was added and the mixture was stirred at room temperature over night. After acidification with hydrochloric acid (1 N) the product was extracted into ethyl acetate. The solvent was evaporated under vacuum to yield the corresponding acid (e.g. 3-[3,5-dihalo-4-(3-methanesulfonylamino-benzyloxy)phenyl] propionic acid).

METHOD B2

The dichloromethane solution of the appropriate aniline (e.g. methyl 3-[3,5-dihalo-4-(3-methanesulfonylamino-benzyloxy)phenyl] propionate) (1 eq.) was treated with the appropriate sulphonylchloride (R_6SO_2Cl) (3 eq.) and pyridine (2.5 eq.). The mixture was stirred at 40°C for 4 h. The solvent was removed under vacuo and the residue was used in the next reaction without further purification.

The crude mixture was dissolved in tetrahydrofuran (6 mL/mmol ester), lithium hydroxide (1 N in water, 10 eq.) was added and the mixture was stirred at room temperature over night. The reaction mixture was acidified to pH=5 with hydrochloric acid (3 N). After filtration, the residue was purified by semi-preparative-HPLC (Zorbax CombiHT (SB-C8 50x21.2 mm, 5 μ) 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 expected acid (e.g. 3-[3,5-dihalo-4-(3-methanesulfonylamino-benzyloxy)phenyl] propionic acid).



Example	R ₆	R ₂	X	W	Yield (%)	MW (calc)	M (found)*	Method
26	Me	H	Br	(CH ₂) ₂	75	507.2	508.1 (M+1)	B1
27	Me	4-Me	Br	(CH ₂) ₂	18	521.2	520.4 (M-1)	B2
28	Me	2-Me	Br	(CH ₂) ₂	46	521.2	520.4 (M-1)	B1
29	Me	5-CF ₃	Br	(CH ₂) ₂	37	575.2	574.4 (M-1)	B1
30	Me	5-Me	Br	(CH ₂) ₂	59	521.2	520.4 (M-1)	B2
31	Et	H	Br	(CH ₂) ₂	41	521.2	520.1 (M-1)	B2
32	Et	2-Me	Br	(CH ₂) ₂	49	535.3	534.2 (M-1)	B2
33	Et	5-CF ₃	Br	(CH ₂) ₂	75	589.2	587.9 (M-1)	B2
34	<i>n</i> -Pr	H	Br	(CH ₂) ₂	57	535.2	534.2 (M-1)	B2
35	<i>i</i> -Pr	H	Br	(CH ₂) ₂	10	535.2	534.2 (M-1)	B2
36	<i>n</i> -Bu	H	Br	(CH ₂) ₂	53	549.3	548.3 (M-1)	B2
37	Ph	H	Br	(CH ₂) ₂	42	569.2	568.1 (M-1)	B2
38	2,5-Methylisoxazolyl	H	Br	(CH ₂) ₂	52	588.2	587.1 (M-1)	B2
39	Me	H	Cl	(CH ₂) ₂	67	418.3	416.6 (M-2)	B2
40	Et	H	Cl	(CH ₂) ₂	73	432.3	430.1 (M-2)	B2
41	Me	5-CF ₃	Cl	(CH ₂) ₂	37	486.3	484.4 (M-2)	B2

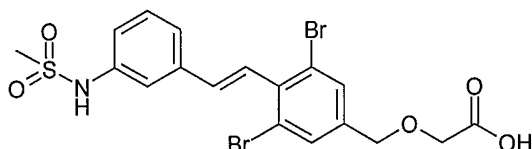
42	Me	H	Br	CONH-CH ₂	52	536.2	535.1 (M-1)	B2
43	Et	H	Br	CONH-CH ₂	62	550.2	549.5 (M-1)	B2
44	Me	5-Cl	Br	(CH ₂) ₂	67	418.3	416.6 (M-2)	B2
45	Et	5-Cl	Br	(CH ₂) ₂	24	461.3	459.3 (M-1)	B2
46	Et	5-Me	Br	(CH ₂) ₂	50	535.2	534.1 (M-1)	B2
47	Me	5-Me	Cl	CH ₂	10	418.3	416.3 (M-2)	B2
48	Et	5-Me	Cl	CH ₂	34	432.3	430.2 (M-2)	B2
49	Me	5-Me	Cl	CONH-CH ₂	18	461.3	459.3 (M-2)	B2
50	Et	5-Me	Cl	CONH-CH ₂	11	475.3	473.3 (M-2)	B2
51	Me	5-Cl	Br	CONH-CH ₂	48	570.6	571 (M)	B2
52	Et	5-Cl	Br	CONH-CH ₂	9	584.7	584.9 (M)	B2
53	Et	2-Cl	Br	(CH ₂) ₂	45	555.7	554.0 (M-1)	B2
54	Me	5-Cl	Br	CH ₂ -CHF	63	559.6	557.9 (M-2)	B1
55	Me	2-Cl	Br	CH ₂ -CHF	43	559.6	557.9 (M-1)	B2
56	Me	2,5-Cl	Br	CH ₂ -CHF	10	594.1	592.1 (M-2)	B2
57	Me	2,5-Cl	Br	CONH-CH ₂	6	605.1	603.2 (M-2)	B2
58	Me	2-Cl	Br	CONH-CH ₂	50	570.6	571.0 (M)	B2
59	Me	5-Me	Br	CONH-CH ₂	61	550.2	551.0 (M+1)	B2
60	Me	5-Me	Br	(CH ₂) ₃	75	535.2	534.0 (M-1)	B2

*-Analyzed on HPLC-MS with alternating +/- API and equipped with different brands of 50 mm*2.1mm, 5 μ C8 columns. Eluted with 0.05% formic acid/ACN or 0.05% ammonium acetate/ACN

*MW calc. (molecular weight) is an isotopic average and the "found mass" is referring to the most abundant isotope detected in the LC-MS. The "found mass" refers to M+1, M, M-1 or M-2 as stated below the respective masses in the column.

5 EXAMPLE 61

{3,5-Dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-vinyl]-benzyloxy}-acetic acid

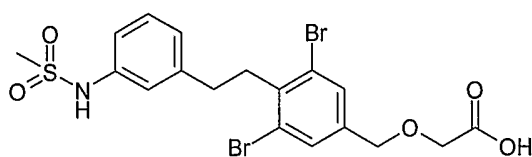


To {4-[(E)-2-(3-amino-phenyl)-vinyl]-3,5-dibromo-benzyloxy}-acetic acid tert-butyl ester
10 (Description 10, 0.015 g, 0.03 mmol) in dichloromethane (0.6 mL) was added methanesulfonyl
chloride, (9 μ L, 0.11 mmol) and pyridine (6 μ L, 0.07 mmol) the mixture was stirred at reflux for 2h.
Water and more dichloromethane added separated. Organic phase was dried and evaporated.

To the crude from above was added a mixture of dichloromethane /TFA (4:1) 1 mL and the mixture
15 was stirred at room temperature over night. The solvent was evaporated and the residue purified
using semi-preparative HPLC to yield {3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-
vinyl]-benzyloxy}-acetic acid (4.3mg, 27% yield two steps).

EXAMPLE 62

20 {3,5-Dibromo-4-[2-(3-methanesulfonylamino-phenyl)-ethyl]-benzyloxy}-acetic acid



To {4-[(E)-2-(3-amino-phenyl)-vinyl]-3,5-dibromo-benzyloxy}-acetic acid tert-butyl ester
(Description 10) in a round bottom flask was added a catalytic amount of Wilkinson catalyst (10
25 mol %). Nitrogen atmosphere was applied and degassed THF was added. The atmosphere was
changed to hydrogen and the reaction was allowed to stir over night. The reaction mixture was
filtered through silica and the solvent was evaporated. The crude reaction was dissolved in
dichloromethane containing 20 vol % trifluoroacetic acid, and stirred over night. Analysis of the
reaction mixture using LCMS showed the title compound {3,5-dibromo-4-[(E)-2-(3-
30 methanesulfonylamino-phenyl)-ethyl]-benzyloxy}-acetic acid.

Abbreviations:

NBS: N-Bromosuccinimide

ACN: acetonitrile

DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone

5 PBr₃: phosphorus tribromide

CCl₄: tetrachloromethane

Biological Assays

The utility of the compounds of the present invention can be evidenced by activity in at least one of
10 the assays below.

1. Binding to thyroid hormone receptors

The ability of compounds of the present invention to bind to thyroid hormone receptors was
demonstrated and evaluated by the present inventors using a selection of the protocols found in the
15 following scientific literature:

- 1) Barkhem, T.; Carlsson, B.; Simons, J.; Moeller, B.; Berkenstam, A.; Gustafsson, J.-Å.;
Nilsson, S. High level expression of functional full-length human thyroid hormone receptor
β₁ in insect cells using a recombinant baculovirus. *J. Steroid Biochem. Mol. Biol.*, **1991**, *38*,
20 667-75.
- 2) Carlsson, B.; Singh, B. N.; Temciuc, M.; Nilsson, S.; Li, Y.-L.; Mellin, C.; Malm, J.
Synthesis and preliminary characterization of a novel antiarrhythmic compound
(KB130015) with an improved toxicity profile compared with amiodarone. *J. Med. Chem.*,
25 **2002**, *45*, 623-630.
- 3) Liu Ye, Yi-Lin Li, Karin Mellström, Charlotta Mellin, Lars-Göran Bladh, Konrad Koehler,
Neeraj Garg, Ana Maria Garcia Collazo, Chris Litten, Bolette Husman, Karina Persson, Jan
Ljunggren, Gary Grover, Paul G. Sleph, Rocco George, Johan Malm: Thyroid Receptor
30 Ligands. 1. Agonist Ligands Selective for the Thyroid Receptor β₁. *J. Med. Chem.*, **2003**,
45, 1580-1588.

The literature above contain not only protocols for binding experiments to the TR-receptor, but also
vector constructs, generation of reporter cell lines and the corresponding assay procedures.

35

Compounds of the invention were found to exhibit binding affinities to the TR receptor in the range
of from 1 nM to 500 nM.

2. Lipid lowering effects in mice

The ability of a compound of the present invention to lower lipid levels in animals can be demonstrated and evaluated by those skilled in the art, using the following protocols:

5

Cholesterol fed C57BL/6J mice

Weanling C57BL/6J mice were placed on a special diet protocol (Purina chow supplemented with 1.5% cholesterol, 15% saturated fat and 0.5% cholic acid) for two weeks before administration of drugs. The animals were housed at room temperature, 12:12 light dark cycle, and free access to food and water. On the day of treatment all animals were weighed before drug was administered by intraperitoneal injection or by gavage. Compounds were administered once daily for 5-10 days, at different concentrations (nmol/kg body weight), in suitable vehicle. On the last day of treatment, food was removed from the cages and the animals were fasted for at least 4 hours before termination of the study. Blood for serum or plasma was collected, and different organs were dissected and immediately frozen for later analyses. Blood and tissue lipid analyses were consecutively executed using commercial and readily available kits for the determination.

10

15

Ob/ob mice

The value of ob/ob mouse is well documented and appreciated by the one skilled in the art for monitoring "Metabolic Syndrome X".

20

6-8 weeks old female ob/ob mice (i.e. leptin deficient mice) purchased from commercial supplier were used to characterize compounds binding to thyroid hormone receptors alpha (TR α) and beta (TR β). The animals were weighed and randomly divided into different study groups, and kept for a minimum of 5 days to adapt to the new environment (animal facility). The animals were housed at room temperature, 12:12 light dark cycle, and free access to food and water. On the day of treatment all animals were weighed before drug was administered by intraperitoneal injection or by gavage. Compounds were administered once daily for 5-10 days, at different concentrations (nmol/kg body weight), in suitable vehicle. On the last day of treatment, food was removed from the cages and the animals were fasted for at least 4 hours before termination of the study. Blood for serum or plasma was collected, and different organs were dissected and immediately frozen for later analyses. Blood and tissue lipid analyses were consecutively executed using commercial and readily available kits for the determination.

25

30

Other assays that may be used for the demonstration of the effectiveness of the compounds of the invention include those described in the following references:

35

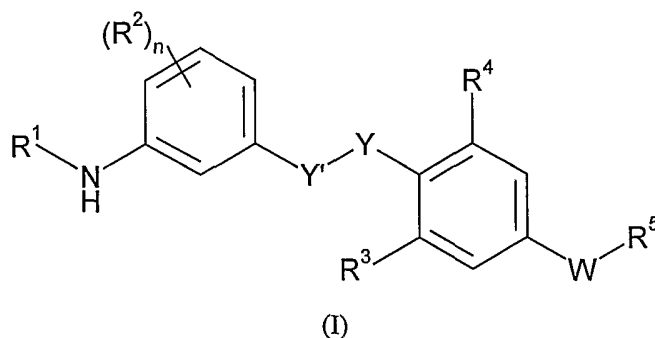
- 1) Liu Ye, Yi-Lin Li, Karin Mellström, Charlotta Mellin, Lars-Göran Bladh, Konrad Koehler, Neeraj Garg, Ana Maria Garcia Collazo, Chris Litten, Bolette Husman, Karina Persson, Jan Ljunggren, Gary Grover, Paul G. Sleph, Rocco George, Johan Malm: Thyroid Receptor Ligands. 1. Agonist Ligands Selective for the Thyroid Receptor β_1 . *J. Med. Chem.*, **2003**, 5 45, 1580-1588.
- 2) Liu Ye, Johan Malm, Yi-Lin Li, Lars-Göran Bladh, Karin Mellström, Paul G. Sleph, Mark A. Smith, Rocco George, Björn Vennström, Kasim Mookhtiar, Ryan Horvath, Jessica Speelman, John D. Baxter, Gary J. Grover: Selective Thyroid Hormone Receptor- β 10 Activation: A Strategy for Reduction of Weight, Cholesterol, and Lp(a) with Reduced Cardiovascular Liability. *PNAS*, **2003**, 100, 10067-10072.

Other assays to determine thyroid receptor mediated activity of the test compounds include assays that demonstrate modulation of endogenous TR mediated transcription in cell culture systems; 15 assays that demonstrate modulation of thyroid responsive tissue effects in rodents; assays for the identification of receptor surface conformation changes; and assays that demonstrate binding specificity to TR versus other nuclear receptors.

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,

5



10 wherein:

R^1 is selected from $-SO_2R^6$, $-SOR^6$ and $-C(O)R^6$;

R^6 is selected from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-3} alkyl, phenyl and C_{1-7} heterocyclyl, said alkyl, alkenyl or alkynyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy; said cycloalkyl, aryl or heterocyclyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, methoxy, halomethoxy, dihalomethoxy, trihalomethoxy, halo C_{1-4} alkyl, dihalo C_{1-4} alkyl and trihalo C_{1-4} alkyl;

20

Each R^2 is independently selected from halogen, mercapto, nitro, cyano, alkoxy, $-CO_2R^c$, $-CONHR^c$, $-CHO$, $-SO_2R^6$, $-SO_2NHR^6$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, NHR^1 and $N(R^1)_2$, said alkyl, alkenyl, alkynyl or alkoxy groups optionally being substituted with 1, 2 or 3 groups selected from halogen, hydroxy, methoxy, C_{1-4} alkoxy, C_{1-4} alkylthio, mercapto, nitro, cyano, halomethoxy, dihalomethoxy, and trihalomethoxy;

25

n is 0, 1, 2 or 3;

Y and Y' together are $-C(R^a)=C(R^a)-$,

30

or alternatively Y and Y' are independently selected from oxygen, sulphur and $-CH(R^a)-$, with the proviso that at least one of Y and Y' is $-CH(R^a)-$ and the further proviso that when one of Y and Y'

is oxygen or sulphur, then R^a is hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^a is selected from hydrogen, halogen, hydroxy, mercapto, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and thiotrifluoromethyl;

R^{a'} is selected from hydrogen, halogen, mercapto, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and thiotrifluoromethyl;

R³ and R⁴ are independently selected from halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, fluoromethyl, difluoromethyl, trifluoromethyl, C₁₋₄ alkoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

W is selected from C₁₋₃ alkylene, C₂₋₃ alkenylene, C₂₋₃ alkynylene, N(R^b)-C₁₋₃ alkylene, C(O)-C₁₋₃ alkylene, S-C₁₋₃ alkylene, O-C₁₋₃ alkylene, C₁₋₃ alkylene-O-C₁₋₃ alkylene, C(O)NH-C₁₋₃ alkylene and NH(CO)-C₀₋₃ 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, C₁₋₃ alkyl, C₁₋₃ alkoxy, haloC₁₋₃ alkyl, dihaloC₁₋₃ alkyl, trihaloC₁₋₃ alkyl, haloC₁₋₃ alkoxy, dihaloC₁₋₃ alkoxy and trihaloC₁₋₃ alkoxy;

R^b is selected from hydrogen, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R⁵ is selected from -CO₂R^c, -PO(OR^c)₂, -PO(OR^c)NH₂, -SO₂OR^c, -COCO₂R^c, CONR^cOR^c, -SO₂NHR^c, -NHSO₂R^c, -CONHSO₂R^c, and -SO₂NHCOR^c;

Each R^c is independently selected from hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl and C₂₋₄ alkynyl;

R^{c'} is selected from R^c, C₅₋₁₀ aryl and C₅₋₁₀ aryl substituted with 1, 2 or 3 groups independently selected from amino, hydroxy, halogen and C₁₋₄ alkyl.

2. A compound as claimed in claim 1 wherein R¹, R², n, R³, R⁴, and R⁵ are as defined in claim 1;

Y and Y' are independently selected from oxygen, sulphur or -CH(R^a)-, with the proviso that at least one of Y and Y' is -CH(R^a)- and the further proviso that when one of Y and Y' is oxygen or sulphur, then R^a is hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl; and

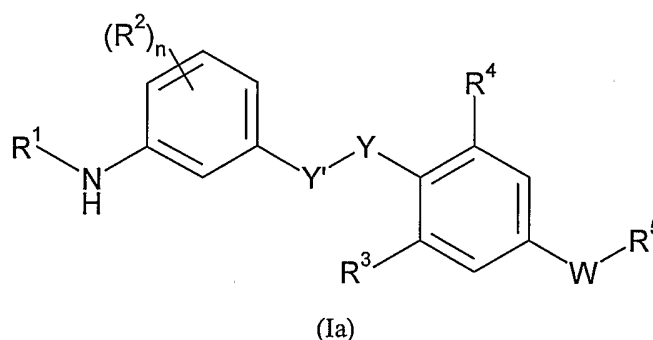
5

W is selected from C₁₋₃ alkylene, C₂₋₃ alkenylene, C₂₋₃ alkynylene, N(R^b)-C₁₋₃ alkylene, C(O)-C₁₋₃ alkylene, S-C₁₋₃ alkylene, O-C₁₋₃ alkylene, C(O)NH-C₁₋₃ alkylene and NH(CO)-C₀₋₃ 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, C₁₋₃ alkyl, C₁₋₃ alkoxy, haloC₁₋₃ alkyl, dihaloC₁₋₃ alkyl, trihaloC₁₋₃ alkyl, haloC₁₋₃ alkoxy, dihaloC₁₋₃ alkoxy and trihaloC₁₋₃ alkoxy.

10

3. A compound as claimed in claim 1 or claim 2 which is a compound according to formula (Ia) 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,

15



wherein:

20 R¹ is selected from -SO₂R⁶ and -C(O)R⁶;

R⁶ is selected from C₁₋₈ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkyl, phenyl and C₃₋₇ heterocyclyl, said alkyl or alkenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy and trihalomethoxy; said cycloalkyl, aryl or heterocyclyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, methyl, methoxy, halomethoxy, dihalomethoxy, and trihalomethoxy;

25

Each R² is independently selected from halogen, C₁₋₂ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₂ alkoxy, haloC₁₋₂ alkyl, dihaloC₁₋₂ alkyl, and trihaloC₁₋₂ alkyl;

30

n is 0, 1 or 2;

Y and Y' together are $-C(R^{a'})=C(R^a)-$,
or alternatively Y is O or S, and Y' is $CH(R^a)$;

5

R^a is selected from hydrogen, halogen, C_{1-2} alkyl, fluoromethyl, difluoromethyl and trifluoromethyl;

$R^{a'}$ is selected from hydrogen, halogen, and C_{1-2} alkyl;

10 R^3 and R^4 are independently selected from halogen, C_{1-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4} alkoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

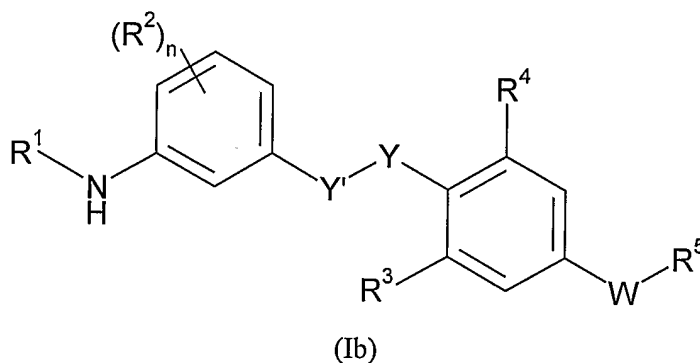
15 W is selected from C_{1-3} alkylene, C_{2-3} alkenylene, $O-C_{1-3}$ alkylene, C_{1-3} alkylene- $O-C_{1-3}$ alkylene, $C(O)-C_{1-2}$ alkylene, $C(O)NH-C_{1-2}$ alkylene and $NH(CO)-C_{1-2}$ alkylene; the alkylene group or portion of a group optionally being substituted with one or more halo groups.

R^5 is selected from $-CO_2R^c$, $-PO(OR^c)_2$, $-SO_2OR^c$, $-COCO_2R^c$, $CONR^cOR^c$ and $-NHSO_2R^c$;

20 Each R^c is independently selected from hydrogen and C_{1-4} alkyl; and

$R^{c'}$ is selected from R^c , phenyl and phenyl substituted with 1, 2 or 3 groups independently selected from amino, hydroxyl, halogen or methyl.

25 4. A compound as claimed in any of claims 1 to 3 which is a compound according to formula (Ib) 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,



30

wherein:

R¹ is selected from -SO₂R⁶ and -C(O)R⁶;

5 R⁶ is selected from C₁₋₅ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkyl, said alkyl or alkenyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected from halogen, hydroxy, methoxy, halomethoxy, dihalomethoxy and trihalomethoxy;

10 Each R² is independently selected from halogen, C₁₋₂ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₂ alkoxy, haloC₁₋₂ alkyl, dihaloC₁₋₂ alkyl, and trihaloC₁₋₂ alkyl;

n is 0, 1 or 2;

15 Y and Y' together are -C(R^a)=C(R^a)-,
or alternatively Y is O, and Y' is CH(R^a);

R^a is selected from hydrogen, halogen, and C₁₋₂ alkyl;

20 R^a is selected from hydrogen, halogen, and C₁₋₂ alkyl;

R³ and R⁴ are independently selected from halogen, C₁₋₄ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, and C₁₋₄ alkoxy;

25 W is selected from C₁₋₃ alkylene, C₂₋₃ alkenylene, O-C₁₋₃ alkylene, C₁₋₃ alkylene-O-C₁₋₃ alkylene, C(O)NH-C₁₋₂ alkylene and NH(CO)-C₁₋₂ alkylene; the alkylene group or portion of a group optionally being substituted with one or more halo groups.

R⁵ is -CO₂R^c;

30

Each R^c is independently selected from hydrogen and C₁₋₄ alkyl.

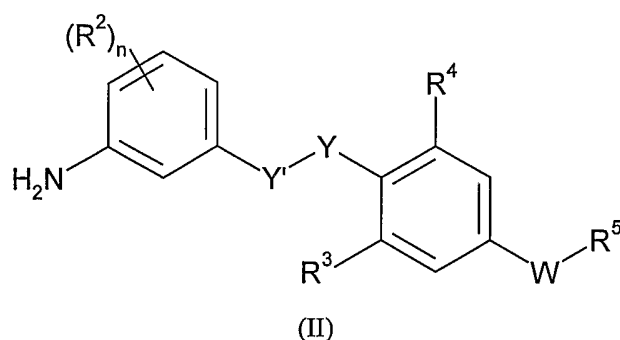
5. A compound as claimed in any of claims 1 to 4 for use as a medicament.

35 6. A compound as claimed in claim 5 for use in the treatment or prophylaxis of a condition associated with a disease or disorder associated with thyroid receptor activity.

7. A method for the treatment or prophylaxis of a disease or disorder associated with thyroid receptor activity in a mammal, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I) as defined in claim 1 or claim 2 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.
8. Use of a compound as defined in any of claims 1 to 4 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 disease or disorder associated with thyroid receptor activity.
9. A pharmaceutical formulation comprising a compound as defined in any of claims 1 to 4 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, and a pharmaceutically acceptable excipient.
10. A pharmaceutical formulation as claimed in claim 9 further comprising an additional therapeutic agent selected from 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.
11. Use of a compound as defined in any of claims 1 to 4 in labelled form as a diagnostic agent for the diagnosis of conditions condition associated with a disease or disorder associated with thyroid receptor activity.
12. A method of discovering a ligand of the thyroid hormone receptor which comprising use of a compound as defined in any of claims 1 to 4 or a compound as defined in any of claims 1 to 4 in labelled form, as a reference compound.
13. A compound as claimed in claim 6, a method as claimed in claim 7, a use as claimed in claim 8 or claim 11, or a pharmaceutical formulation as claimed in claim 9 or claim 10 wherein the condition associated with a disease or disorder associated with thyroid receptor activity 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.

- 5 14. A method for preparing a compound of formula (I) as described in claim 1 comprising a step of reacting
- a compound of formula (II)



10

wherein R^2 , n , Y' , Y , R^3 , R^4 , W and R^5 are as defined in claim 1

- 15 - with a compound of formula R^1-L , wherein R^1 is as defined in claim 1 and L is a suitable leaving group, optionally in the presence of a suitable base, followed optionally by interconversion to another compound as described in claim 1.

15. A pharmaceutical composition as claimed in claim 10 wherein the additional therapeutic agent is a hypolipidemic agent selected from the group consisting of an acyl coenzyme A cholesterol acyltransferase (ACAT) inhibitor, a microsomal triglyceride transfer protein (MTP) inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a 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, 25 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.

16. A pharmaceutical composition as claimed in claim 10 wherein the additional therapeutic agent is 30 a hypolipidemic agent selected from the group consisting of ezetimibe, simvastatin, atorvastatin,

rosuvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, fenofibrate, gemfibrozil and bezafibrate.

17. A pharmaceutical composition as claimed in claim 10 wherein the additional therapeutic agent is
5 an antidiabetic agent selected from the group consisting of a biguanide, a glucosidase inhibitor, a
meglitinide, a sulfonylurea, a thiazolidinedione, a peroxisome proliferator-activator receptor
(PPAR)-alpha agonist, a peroxisome proliferator-activator receptor (PPAR)-gamma agonist, a
peroxisome proliferator-activator receptor (PPAR) alpha/gamma dual agonist, a sodium glucose co-
10 transporter (SGLT) 1, 2 or 3 inhibitor, a glycogen phosphorylase inhibitor, an aP2 inhibitor, a
glucagon-like peptide-1 (GLP-1), a dipeptidyl peptidase IV inhibitor, a glucocorticoid (GR)
antagonist and insulin.

18. A pharmaceutical composition as claimed in claim 10 wherein the additional therapeutic agent is
an antidiabetic agent selected from the group consisting of metformin, glyburide, glimepiride,
15 glipyrizide, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, pioglitazone,
englitazone, darglitazone, rosiglitazone and insulin.

19. A pharmaceutical composition as claimed in claim 10 wherein the additional therapeutic agent is
an anti-obesity agent is selected from the group consisting of an aP2 inhibitor, a peroxisome
20 proliferator-activator receptor (PPAR) gamma antagonist, a peroxisome proliferator-activator
receptor (PPAR) delta agonist, a beta-3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake
inhibitor and an anorectic agent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003030

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/191 A61K31/18 C07D307/02 C07D311/14 C07D311/10
 C07D311/08 C07D235/02 C12Q1/68 G01N33/78

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K G01N

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, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/36365 A (KARO BIO AB; MALM, JOHAN; LITTEN, CHRIS; APELQVIST, THERESA; HEDFORS,) 25 May 2001 (2001-05-25)	1-10, 13, 14
Y	page 5, line 1 - page 12, line 3 page 30, paragraph 2 - page 34, paragraph 3; claims 1-43	11, 12, 15-19
Y	WO 03/094845 A (BRISTOL-MYERS SQUIBB COMPANY; ZHANG, MINSHENG; HANGELAND, JON; CARINGA) 20 November 2003 (2003-11-20) page 25, line 18 - page 36, line 36	15-19
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

5 August 2005

Date of mailing of the international search report

16/08/2005

Name and mailing address of the ISA

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Greif, G

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/EP2005/003030

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/059872 A (BAYER CORPORATION; DIXON, JULIE; BRENNAN, CATHERINE; DUMAS, JACQUES; H) 24 July 2003 (2003-07-24) page 1, line 16 - page 49, line 11; table 1 -----	1-5, 13
Y	LEESON P D ET AL: "Thyroid Hormone Analogues" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 31, no. 1, 1988, pages 37-54, XP002101081 ISSN: 0022-2623 the whole document -----	11, 12
Y	EP 1 148 054 A (PFIZER PRODUCTS INC) 24 October 2001 (2001-10-24) the whole document -----	1-10, 13-19
Y	WO 01/60784 A (BRISTOL-MYERS SQUIBB CO; FRIENDS, TODD, JASON; RYONO, DENNIS, E; ZHANG) 23 August 2001 (2001-08-23) the whole document -----	1-10, 13-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/003030

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0136365	A	25-05-2001	AU 2666901 A WO 0136365 A2	30-05-2001 25-05-2001
WO 03094845	A	20-11-2003	AU 2003225305 A1 WO 03094845 A2 US 2004039028 A1	11-11-2003 20-11-2003 26-02-2004
WO 03059872	A	24-07-2003	AU 2002364260 A1 WO 03059872 A1	30-07-2003 24-07-2003
EP 1148054	A	24-10-2001	BR 0101527 A CA 2344574 A1 EP 1148054 A1 JP 2002053564 A US 2002193268 A1 US 2004110951 A1 US 2001051645 A1	20-11-2001 21-10-2001 24-10-2001 19-02-2002 19-12-2002 10-06-2004 13-12-2001
WO 0160784	A	23-08-2001	AT 295348 T AU 3092901 A BR 0108134 A CA 2400486 A1 CN 1418185 A CZ 20022771 A3 DE 60110753 D1 EP 1257526 A1 HU 0301777 A2 JP 2004500382 T MX PA02007929 A NO 20023895 A NZ 520023 A PL 366149 A1 WO 0160784 A1 US 6800605 B1 US 2005032890 A1 ZA 200206072 A	15-05-2005 27-08-2001 30-09-2003 23-08-2001 14-05-2003 17-09-2003 16-06-2005 20-11-2002 29-09-2003 08-01-2004 10-02-2003 16-10-2002 28-05-2004 24-01-2005 23-08-2001 05-10-2004 10-02-2005 11-02-2004