

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:

☒ **Patente de invención** ☐ **Patente de Modelo de Utilidad**

☐ **Capítulo I.** ☒ **Capítulo II.**

2) SOLICITANTE
(71)

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2. BRISTOL-MYERS SQUIBB
COMPANY
Dirección: 1. Novum, SE-141 57
Huddinge SUECIA
2.P.O Box 4000, Princeton, NJ 08543-
4000 ESTADOS UNIDOS
Nacionalidad o domicilio: 1. SUECIA.
2. ESTADOS UNIDOS
Lugar de constitución: 1.SUECIA
2.ESTADOS UNIDOS DE AMERICA

Teléfono: **Fax:**
E. Mail:

IDENTIFICACIÓN

C.C. ☐ **NIT:** ☒

C.E. ☐ **OTRO** ☐

NÚMERO **Cual** _____

3) REPRESENTANTE
O APODERADO

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IDENTIFICACIÓN

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TP: 20824 CSJ

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Nacionalidad o Domicilio: 1. SUECO; 2 SUECO; 3. SUECO;
4.SUECO; 5. ESTADOUNIDENSE.

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SUPERINDUSTRIA Y COMERCIO
 Radicacion : 05001416 00000000 Folios: 320
 Fecha (AMD): 2005-01-11 15:49:00
 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 4 - 96,047
 FECHA : DICIEMBRE 13 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	37353687	13/12/2004	3,250,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL ASUNTO No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03001416 00000000 Folios: 320
Fecha (AMD): 2005-01-11 15:49:20
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

CERTIFICACION DE EXCEDENTE : 05 - 251
FECHA : ENERO 3 DE 2005

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE NODET Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	37333690	03/01/2005	392,500.00

CONCEPTO

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	21,000.00
		TOTAL :	\$ 21,000.00

SOM: VEINTIUNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIBENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

10)

ANEX S

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros
 1. Petitorio PCT
 2. Informe de Búsqueda Internacional y documentos citados en ella
 3. Petitorio de solicitud de Examen Preliminar Internacional
 4. Traducción de anexos de examen preliminar

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA: _____

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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
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For two-letter codes and other abbreviations, refer to the "Guid-
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WO 2004/007430 A2

(54) Title: NOVEL COMPOUNDS

(57) Abstract: This invention relates to novel compounds, which are thyroid receptor ligands, and to methods of preparing such compounds. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T₃ regulated gene, wherein a compound as described herein is admin-
istered in a therapeutically effective amount.

5

NOVEL COMPOUNDS**FIELD OF THE INVENTION**

10 This invention relates to novel compounds which are thyroid receptor ligands, and to methods of preparing such compounds and to methods for using such compounds such as in the regulation of metabolism.

15

BACKGROUND OF THE INVENTION

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

Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, metabolic rate, body temperature and
25 mood, and influence blood levels of serum low density lipoprotein (LDL). 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 levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

30

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
35 triiodothyronine (3,5,3'-triiodo-L-thyronine, or T₃). However, replacement therapy, particularly in older individuals, may be restricted by certain detrimental effects from thyroid hormones.

5

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 weight reduction, lowering of serum LDL levels, amelioration of depression and stimulation of bone formation. Prior attempts to utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in particular by cardiovascular toxicity.

Furthermore, useful thyroid agonist drugs should minimize the potential for undesired consequences due to locally induced hypothyroidism, i.e. sub-normal levels of thyroid hormone activity in certain tissues or organs. This can arise because increased circulating thyroid hormone agonist concentrations may cause the pituitary to suppress the secretion of thyroid stimulating hormone (TSH), thereby reducing thyroid hormone synthesis by the thyroid gland (negative feedback control). Since endogenous thyroid hormone levels are reduced, localized hypothyroidism can result wherever the administered thyroid agonist drug fails to compensate for the reduction in endogenous hormone levels in specific tissues. For example, if the thyroid agonist drug does not penetrate the blood-brain barrier, the effects of TSH suppression can lead to CNS hypothyroidism and associated risks such as depression.

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

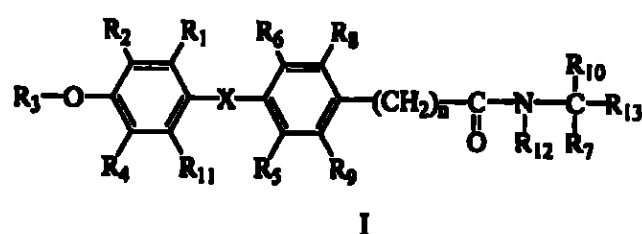
Accordingly, the discovery of compounds that are thyroid hormone receptor ligands, particularly selective agonists of the thyroid hormone receptor, may demonstrate a utility for the treatment or prevention of diseases or disorders associated with thyroid hormone activity, for example: (1) replacement therapy in elderly subjects with hypothyroidism

5 who are at risk for cardiovascular complications; (2) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (3) obesity; (4) hypercholesterolemia due to elevations of plasma LDL levels; (5) depression; and (6) osteoporosis in combination with a bone resorption inhibitor.

10

SUMMARY OF THE INVENTION

15 In accordance with the illustrative embodiments and demonstrating features of the present invention, compounds are provided which are thyroid receptor ligands, and have the general formula I:



20 or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from a group consisting of hydrogen, halogen, and C₁ to C₆ alkyl;

25 R₂ is selected from the group consisting of halogen, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, C₄ to C₇ cycloalkenyl, C₃ to C₇ cycloalkoxy, SO₂(NR₁₄R₁₅), N(R₁₆)SO₂R₁₇, SR₁₇, SOR₁₇, SO₂R₁₇, COR₁₆, and CR₁₈(OR₁₆)R₁₉; or R₂ is hydrogen when R₄ is alkyl and R₁ is halogen;

R₃ is selected from the group consisting of hydrogen, alkyl, benzyl, aroyl, and alkanoyl;

30

R₄ is halogen, cyano or alkyl;

5

R₅ and R₆ are independently selected from hydrogen, halogen; cyano, C₁₋₄ alkyl, C₃ to C₆ cycloalkyl; where at least one of R₅ and R₆ is not hydrogen;

10

R₇ and R₁₀ are independently selected from hydrogen, halogen, aryl and alkyl, and R₇ and R₁₀ may be joined so as to comprise a chain of 2 to 6 methylene groups to form a ring of 3 to 7-membered in size;

15

R₈ and R₉ are each independently selected from the group consisting of hydrogen, halogen, alkoxy, hydroxy (OH), cyano, and alkyl;

provided that not more than one of R₂, R₄, R₈ and R₉ are hydrogen;

R₁₁ is hydrogen, halogen or alkyl;

20

R₁₂ is hydrogen or alkyl;

R₁₃ is carboxylic acid (COOH) or esters thereof, phosphonic and phosphinic acid or esters thereof, sulfonic acid, tetrazole, hydroxamic acid, thiazolidinedione, acylsulfonamide, or other carboxylic acid surrogates known in the art;

25

R₁₄ and R₁₅ for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, and R₁₄ and R₁₅ may be joined so as to comprise a chain of 3 to 6 methylene groups to form a ring of 4 to 7-membered in size;

30

R₁₆ is selected from a group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;

- 5 R_{17} is selected from a group consisting of alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;

R_{18} and R_{19} for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;

10

n is an integer of 0, 1 or 2;

X is selected from: $-O-$, $-CH_2-$, $-CF_2-$, $-Se-$, $-NH-$, $-S-$, $-SO-$, $-SO_2-$ and $-CO-$;

- 15 The definition of formula I above includes all prodrugs, stereoisomers and pharmaceutically acceptable salts of formula I.

The compounds of formula I are thyroid hormone receptor ligands and include compounds which are, for example, selective agonists, partial agonists, antagonists or
20 partial antagonists of the thyroid receptor. Preferably, the compounds of formula I possess activity as agonists of the thyroid receptor, and may be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, the compounds of formula I may be used in the treatment of diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T_3
25 regulated gene, such as obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, skin disorders or diseases and congestive heart failure.

The present invention provides for compounds of formula I, pharmaceutical compositions
30 employing such compounds and for methods of using such compounds. In particular, the present invention provides for a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, alone or in combination with a pharmaceutically acceptable carrier.

5

Further, in accordance with the present invention, a method is provided for preventing, inhibiting or treating the progression or onset of diseases or disorders associated with the thyroid receptor, such as the diseases or disorders defined above and hereinafter, wherein a therapeutically effective amount of a compound of formula I is administered to a mammalian, e.g., human patient in need of treatment.

10

The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s) active in the therapeutic areas described herein.

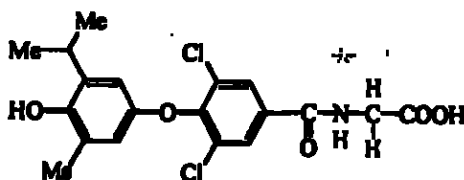
15

In addition, a method is provided for preventing, inhibiting or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I and another compound of the invention and/or another type of therapeutic agent, is administered to a mammalian patient in need of treatment.

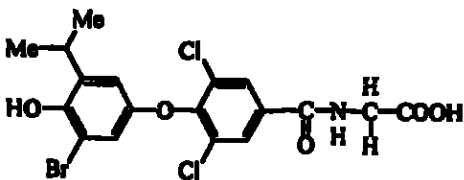
20

Compounds of the invention include, but are not limited to, the following:

N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine (E1);

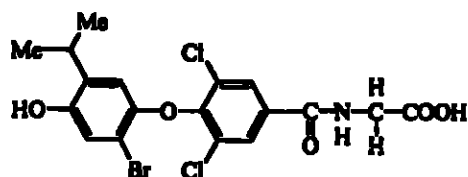


25 N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E2);

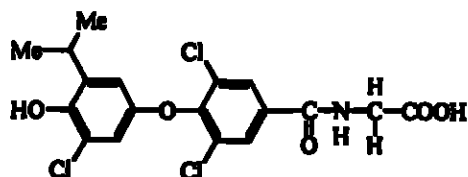


N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E3);

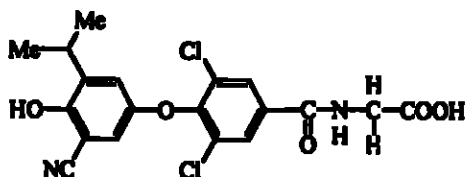
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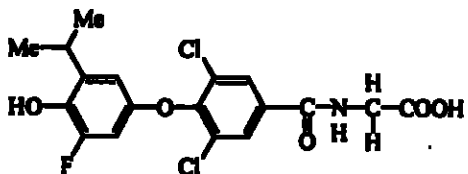
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E4);



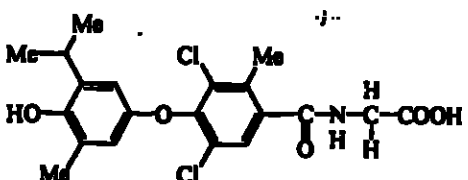
N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E5);



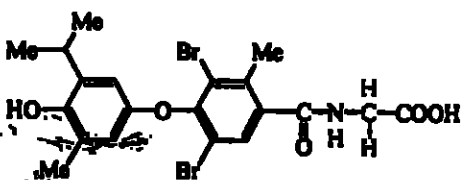
10 N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E6);



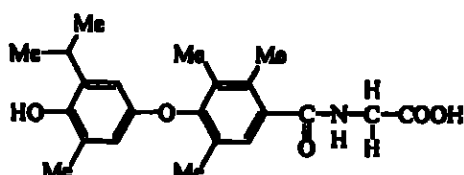
N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E7);



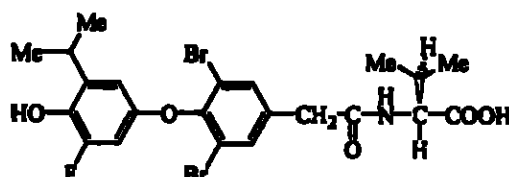
15 N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E8).



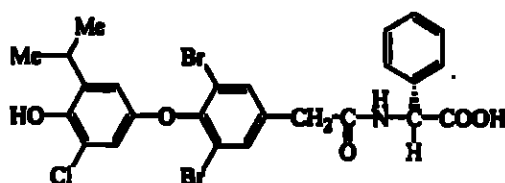
- 5 N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E9).



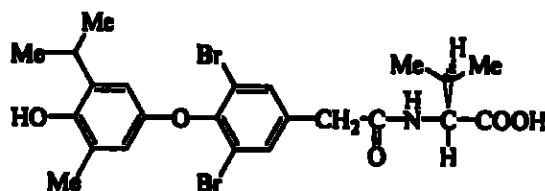
- 10 L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine (E10).



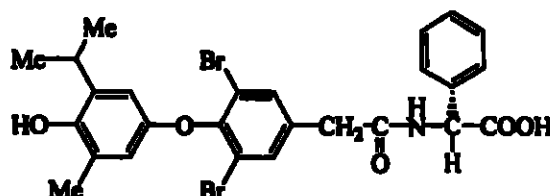
- D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine (E11)



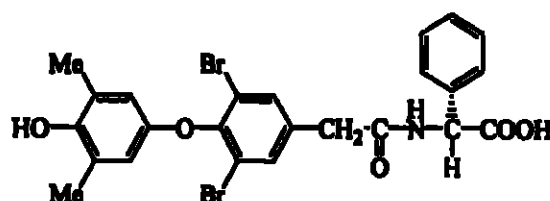
- L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine (E12)



- 5 L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl]phenylglycine (E13)



- L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]phenylglycine (E14)



DETAILED DESCRIPTION OF THE INVENTION

- 15 The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "thyroid receptor ligand" as used herein is intended to cover any moiety, which binds to a thyroid receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist. Another term for "thyroid receptor ligand" is "thyromimetic".

25 Unless otherwise indicated, the term "alkyl" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 12 carbons (in the case of alkyl or alk), in the normal chain, preferably 1 to 4 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, or isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl. As defined and claimed herein, the term "alkyl" includes alkyl groups as defined above optionally substituted with 1 to 4 substituents which may halo, for example F, Br, Cl or I

15 or CF₃, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkyloxy, optionally substituted amino, hydroxy, hydroxyalkyl, acyl, oxo, alkanoyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, 10 alkoxycarbonyl, alkylaminocarbonyl, nitro, cyano, thiol, haloalkyl, trihaloalkyl, alkylthio or carboxyl(or alkyl ester thereof).

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated cyclic hydrocarbon groups or partially unsaturated 15 (containing 1 or 2 double bonds) cyclic hydrocarbon groups, containing one ring and a total of 3 to 8 carbons, preferably 3 to 6 carbons, forming the ring. As defined and claimed herein, the term "cycloalkyl" includes cycloalkyl groups as defined above optionally substituted with 1 or more substituents, such as those defined for alkyl.

20 The term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl). As defined and claimed herein, the term "aryl" includes aryl groups as defined above optionally substituted through any available carbon atom(s) with 1 or more substituents, such as 25 halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, hydroxy, amino, nitro, cyano, carboxyl(or alkyl ester thereof) or any of the other substituents described for alkyl.

Unless otherwise indicated, the term "heteroaryl" or "heteroaromatic" as used herein 30 alone or as part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen, or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indole), and includes possible N-oxides. A "substituted heteroaryl" group includes a heteroaryl optionally substituted with one or more substituents such as any of the alkyl or 35 aryl substituents set out above. As defined and claimed herein, the term "heteroaryl" includes heteroaryl groups as defined above optionally substituted through any available

- 5 carbon atom(s) with 1 or more substituents, such as any of the substituents described for alkyl or aryl.

Unless otherwise indicated, the term "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 2 to 8 carbons in the normal chain, which include one or more double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like. As defined and claimed herein, the term "alkenyl" includes alkenyl groups as defined above optionally substituted through any available carbon atom(s) with 1 or more substituents, such as any of the substituents described for alkyl or aryl.

Unless otherwise indicated, the term "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one or more triple bonds in the normal chain, such as 2-propynyl, 3-butenyl, 2-butenyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like. As defined and claimed herein, the term "alkynyl" includes alkynyl groups as defined above optionally substituted through any available carbon atom(s) with 1 or more substituents, such as any of the substituents described for alkyl or aryl.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl. As defined and claimed herein, the term "cycloalkenyl" includes cycloalkenyl groups as defined above optionally substituted through any available carbon atom(s) with 1 or more substituents, such as any of the substituents described for alkyl or aryl.

5 The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3 , with chlorine or bromine being preferred.

The term "alkanoyl" as employed herein alone or as part of another group is alkyl or
10 cycloalkyl linked to a carbonyl group.

The term "aroyl" as employed herein alone or as part of another group is aryl or heteroaryl linked to a carbonyl group.

15 Unless otherwise indicated, the terms "alkoxy", "aryloxy" or "heteroaryloxy" as employed herein alone or as part of another group includes any of the above alkyl, aryl or heteroaryl groups linked thorough an oxygen atom.

The term "cyano," as used herein, refers to a $-\text{CN}$ group.
20

The term "arylalkyl" and "heteroarylalkyl" as employed herein alone or as part of another group refer to alkyl groups as described above having an aryl or heteroaryl substituent. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl.

25 Unless otherwise indicated, the terms "arylalkoxy" and "cycloalkoxy" as employed herein alone or as part of another group include and aryl cycloalkyl groups linked thorough an oxygen atom.

30 The term "carboxylic acid" or "carboxyl", as used herein, refers to a $-\text{COOH}$ group.

The term "benzyl" as used herein refers to $-\text{CH}_2\text{C}_6\text{H}_5$, which may optionally be substituted as defined above for alkyl.

35 The compounds of formula I can be present as salts, which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable)

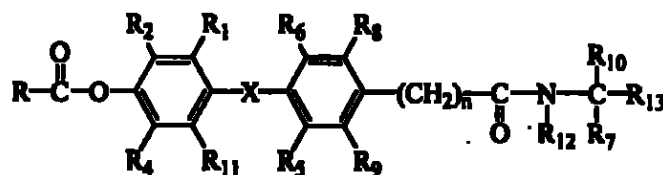
5 salts are preferred. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for
10 example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C₁-C₄) alkyl or arylsulfonic acids
15 which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for
20 example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts that
25 are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of formula I or their pharmaceutically acceptable salts, are also included. Preferred salts of the compounds of formula I which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate. Preferred salts of the compounds of formula I which contain an acid
30 group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

The compounds of formula I may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound of formula I) is a
35 prodrug within the scope and spirit of the invention.

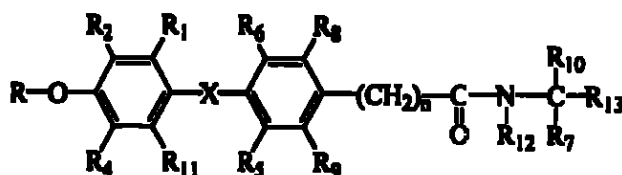
- 5 Various forms of prodrugs are well known in the art. A comprehensive description of prodrugs and prodrug derivatives may be found in: (i) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996); (ii) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985); and (iii) *A Textbook of Drug Design and Development*, P. Krogsgaard-Larson and H. Bundgaard, eds. Ch 5, pgs 113 – 191
 10 (Harwood Academic Publishers, 1991). Said references are incorporated herein by reference.

Embodiments of prodrugs suitable for use in the present invention include lower alkyl esters, such as ethyl ester, or acyloxyalkyl esters such as pivaloyloxymethyl (POM) of a
 15 carboxylic acid group for R₁₃.

Embodiments of prodrugs suitable for use in the present invention include prodrugs which mask the free phenolic hydroxyl group present in formula I, as depicted in the structure below where the prodrug aroyl or alkanoyl group is the moiety, R-CO-, in
 20 which R is alkyl, heteroaryl or aryl.



Furthermore, embodiments of prodrugs suitable for masking the phenolic hydroxyl group discussed above include phenolic alkyl ethers, such as depicted in the structure below where R = alkyl. Metabolic hydroxylation of the carbon of the alkyl group R that is
 25 attached to the phenolic oxygen leads to an intermediate capable of further decomposition to release the free phenol form of compounds of formula I.



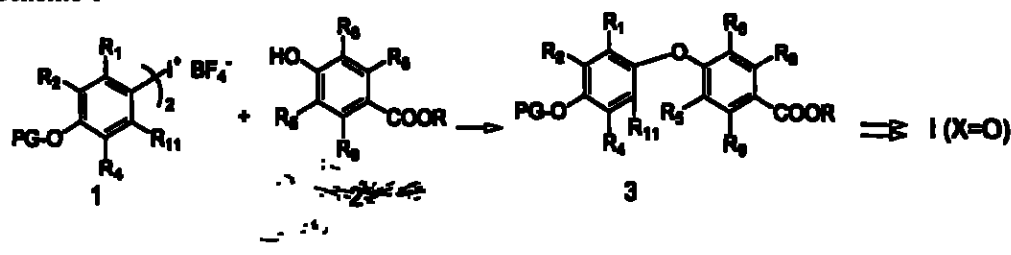
All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention

5 can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for
10 for example, chromatographic or fractional crystallization.

An administration of a therapeutic agent of the invention includes administration of a therapeutically effective amount of the agent of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat or
15 prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated,
20 recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

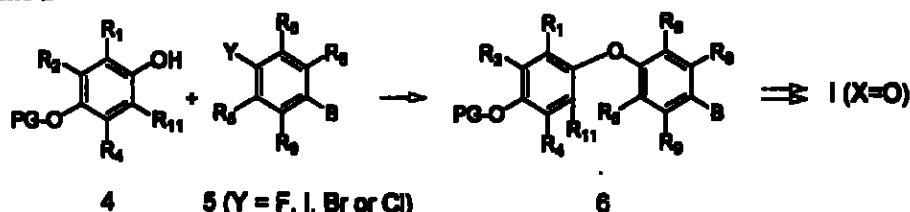
The compounds of formula I may be prepared by the exemplary processes described in
25 the following reaction schemes, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art (see, for example, T. W. Greene & P. G. M. Wuts, "Protecting Groups in Organic Synthesis", 3rd
30 Edition, Wiley, 1999).

Scheme 1



- 5 The iodonium salt methodology depicted in Scheme 1 is amply described in the literature for the synthesis of thyroid hormone analogs ("Novel Thyroid Receptor Ligands and Methods, Y.-L. Li, Y. Liu, A. Hedfors, J. Malm, C. Mellin, M. Zhang, PCT Int. App. WO 9900353 A1 990107; D. M. B. Hickey et al., J. Chem. Soc. Perkin Trans. I, 3103-3111, 1988; N. Yokoyama et al., J. Med. Chem., 38, 695-707, 1995), and to diaryl ethers in
 10 general (E. A. Couladouros, V. I. Moutsos, Tetrahedron Lett., 40, 7023-7026, 1999). The reaction of an iodonium salt 1 with an appropriate hydroxy benzoic acid intermediate 2 provides the diaryl ether product 3 which may be readily converted by those of normal skill in the art to compounds of formula I in which X = O.

15 Scheme 2



- Scheme 2 depicts another general synthetic approach to compounds of formula I for which X = O. An appropriately substituted phenol 4 is alkylated with an appropriately substituted intermediate 5, in which Y is a displaceable group such as fluoro, chloro, iodo or bromo and the activating group B is one that both activates the group Y towards
 20 nucleophilic displacement and is capable of being subsequently transformed to a carboxylic acid (such as formyl (CHO) or nitro (NO₂), to provide the intermediate 6. The activating group B in intermediate 6 is then subsequently transformed to a carboxylic acid or derivative which can then be further converted to compounds of formula I for which X = O. Such activating functional groups and their means of conversion are well-
 25 known to those skilled in the art. For example, when B is a nitro function in intermediate 6, the nitro group can be reduced to an amino group by methods well known in the art, such as the use of catalytic hydrogenation in the presence of, for example, Raney nickel or palladium on charcoal catalyst, in a polar solvent such as glacial acetic acid or ethanol.
 30 Alternatively, the reduction can be accomplished using iron powder in aqueous glacial acetic acid at ambient temperatures. The resulting aryl amine can be converted to the corresponding diazonium salt by the use, for example, of a mixture of sodium nitrite and sulfuric acid in appropriate solvents. The resulting diazonium group can then be converted to a formyl group (CHO) by the reaction with carbon monoxide catalyzed by

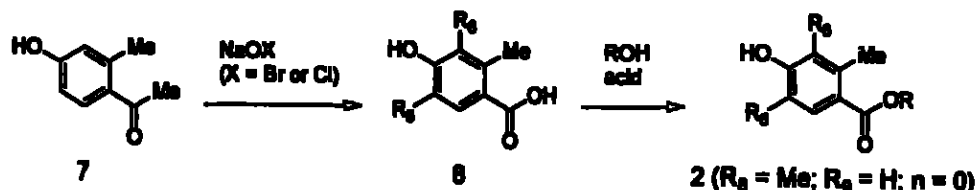
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5 an appropriate palladium catalyst such as palladium acetate. After coupling to the intermediate 5, subsequent protecting group and functional group manipulation provides the desired compounds of formula I in which X = O. Another activating group is formyl (B = -CHO). After coupling to the second aromatic ring, the aldehyde group can be oxidized to a carboxylic acid, then converted to the compounds of formula I in which n =
10 0. Furthermore, the same resulting carboxylic acid can be homologated to an acetic acid group by well known means such as the Arndt-Eistert homologation to ultimately provide examples of I for which n = 1. The approach depicted in Scheme 2 for the general synthesis of diaryl ethers for thyromimetics is well precedented in the literature (P. D. Leeson, J. C. Emmett, J. Chem. Perkin Trans. I, 3085-3096, 1988; N. Yokoyama et al., J.
15 Med. Chem., 38, 695-707, 1995).

Further means for synthesizing compounds of formula I in which X = O, NH, S, CO or CH₂ are generally described in the literature (for X = O: D. M. B. Hickey et al., J. Chem. Soc. Perkin Trans. I, 3097-3102, 1988; Z.-W. Guo et al., J. Org. Chem., 62, 6700-6701, 1997; D. M. T. Chan et al., Tetrahedron Lett., 39, 2933-2936, 1998; D. A. Evans et al.,
20 Tetrahedron Lett., 39, 2937-2940, 1998; G. M. Salamonczyk et al., Tetrahedron Lett., 38, 6965-6968, 1997; J.-F. Marcoux, J. Am. Chem. Soc., 119, 10539-10540, 1997; A. V. Kalinin et al., J. Org. Chem., 64, 2986-2987, 1999; for X = N: D. M. T. Chan et al., Tetrahedron Lett., 39, 2933-2936, 1998; J. P. Wolfe et al., J. Am. Chem. Soc., 118, 7215,
25 1996; M. S. Driver, J. F. Hartwig, J. Am. Chem. Soc., 118, 7217, 1996; see references in the review by C. G. Frost, P. Mendonca, J. Chem. Soc. Perkin I, 2615-2623, 1998; for X = S: C. R. Harrington, Biochem. J., 43, 434-437, 1948; A. Dibbo et al., J. Chem. Soc., 2890-2902, 1961; N. Yokoyama et al., United States Patent 5,401,772, 1995; for X = CO or CH₂: L. Horner, H. H. G. Medem, Chem. Ber., 85, 520-530, 1952; G. Chiellini et al.,
30 Chemistry & Biology, 5, 299-306, 1998; and for X = CF₂, see G. S. Lal et al., J. Org. Chem., 65, 4830-4832, 2000).

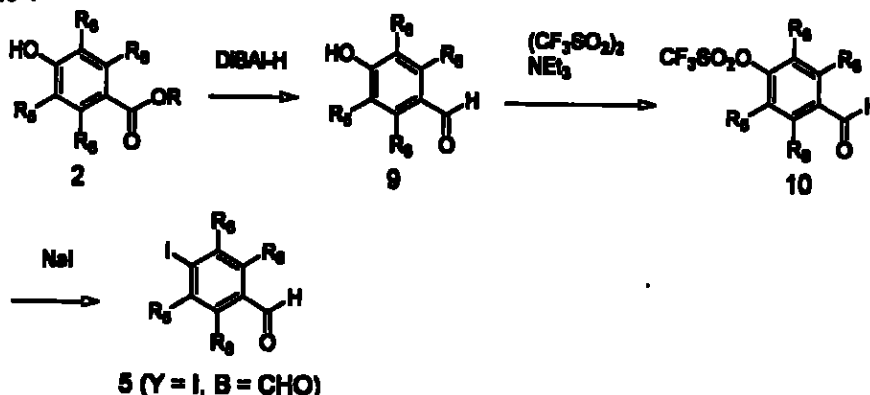
Methods applicable to the synthesis of compounds of formula I in which X = O and R₂ and R₃ are independently varied as hydrogen, halogen and alkyl are described in "Novel
35 Thyroid Receptor Ligands and Methods, Y.-L. Li, Y. Liu, A. Hedfors, J. Malm, C. Mellin, M. Zhang, PCT Int. App. WO 9900353 A1 990107.

5 Scheme 3



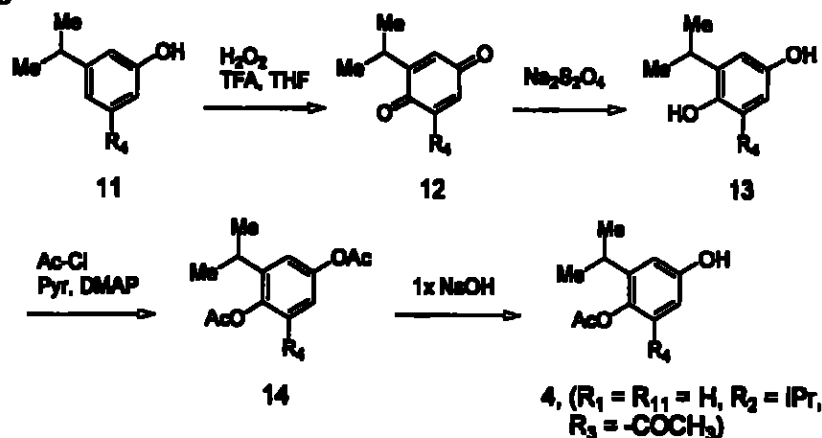
Scheme 3 describes the synthesis of intermediate 2 in which $R_5 = R_6 = \text{Br or Cl}$, $R_4 = \text{Me}$, $R_3 = \text{H}$, $R = \text{H}$ and $n = 0$. Acetophenone 7 (commercially available) is subjected to haloform reaction conditions with sodium hypochlorite or hypobromite to simultaneously
 10 convert the acetyl function to carboxyl and to halogenate the two positions ortho to the phenolic hydroxyl group. Esterification gives the target intermediate 2 which is employed in the chemistry described in Scheme 4.

Scheme 4



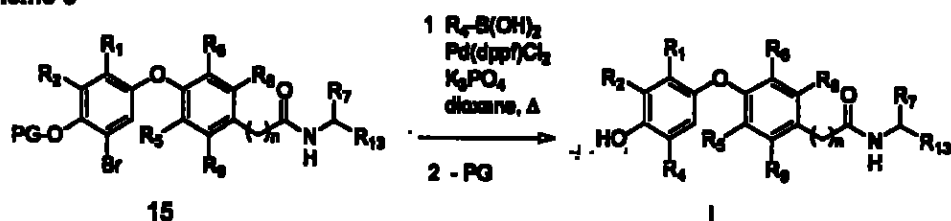
15 Scheme 4 describes the use of intermediate 2 for the synthesis of intermediate 5 in which $Y = \text{I}$ and $B = \text{CHO}$. Intermediate ester 2 is reduced to aldehyde 9 by reducing agents such as diisobutylaluminum hydride (DIBAL-H). Compound 9 is converted to triflate 10 by the use of triflic anhydride and an organic amine base such as triethylamine. Reaction
 20 of triflate 10 with sodium iodide provides the target aryl iodide aldehyde 5 which can be utilized in the chemistry described in Scheme 2 above.

5 Scheme 5



Scheme 5 describes the synthesis of intermediate 4 in which R_1 and $R_{11} = \text{H}$, $R_2 =$ isopropyl and R_3 is an acetyl protecting group ($-\text{COCH}_3$). Phenol 11 is oxidized to quinone 12, which upon reduction with sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_4$) is converted to hydroquinone 13. Acetylation of 13 under standard conditions gives bis-acetate 14 which provides the desired target compound 4 after treatment with 1 equivalent of sodium hydroxide to remove the least hindered acetate group to provide the compound 4 which can be utilized in the chemistry described in Scheme 2 above.

15 Scheme 6

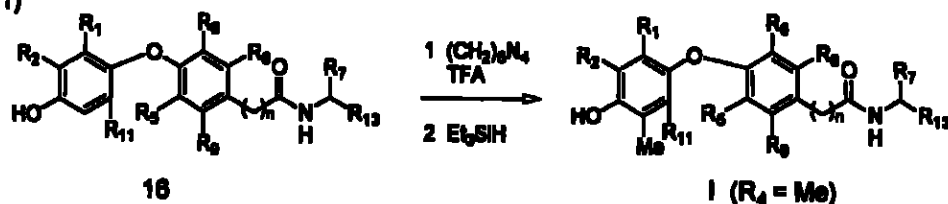


Scheme 6 describes an approach to the synthesis of compounds of formula I in which the group R_4 is a lower alkyl group, such as methyl or ethyl. Aryl bromide intermediate 15 is obtained by bromination of the corresponding free phenol ($R_3 = \text{OH}$; obtained by procedures such as those described in Scheme 1 and Scheme 2), followed by installation of a protecting group (PG) on the phenolic hydroxyl. The group R_4 is introduced by coupling the aryl bromide intermediate 15 with an alkyl boronic acid in the presence of an appropriate palladium catalyst, such as [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (Miyada et al, Synlett, 1995, 283). The aryl bromide

- 5 intermediate 15 may be substituted by the corresponding aryl iodide or aryl triflate and undergo the same transformation.

Scheme 7

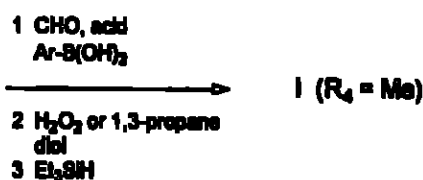
(7.1)



(7.2)

Alternatively

16



- 10 Scheme 7 depicts two procedures for the specific introduction of a methyl group in the R_4 position. Both methods proceed by (1) hydroxymethylation ortho to the phenolic hydroxyl group (R_3) in intermediate 16 (obtained by following procedures such as those described in Scheme 1 and Scheme 2, followed by (2) reduction of the hydroxymethyl group to a methyl group using a reagent such as triethylsilane. In reaction 7.1,
- 15 hydroxymethylation is achieved by the use of hexamethylenetetramine in the presence of trifluoroacetic acid. In reaction 7.2, the hydroxymethylation step is promoted by the use of benzene boronic acid which complexes the initial adduct in the form of a dioxaborin intermediate. The desired hydroxymethyl compound is liberated either by exchange with ethylene glycol or reaction with hydrogen peroxide (Nagata et al, Synthesis, 1979, 365).

20

Other means are known to those of normal skill in the art for installing a methyl group on an aromatic ring. For example: (1) aryl bromides and iodides may be methylated by treatment with Me_4Sn (tetramethyltin) in the presence of palladium catalyst (Tet Lett, 1999, 40, 2719-2722); (2) aryl triflates are methylated by treatment with Me_3In (trimethylindium) in the presence of palladium catalyst (Org Lett, 1999, 1, 1267-1269;

25 (3) aryl triflates are converted to aryl methyl compounds by treatment with Me_3Al (trimethylaluminum) in the presence of palladium catalyst; (4) aryl triflates are also methylated by treatment with methylboronic acid in the presence of palladium catalyst (Synlett, 1995, 283-284).

5

UTILITIES & COMBINATIONS

UTILITIES: The compounds of the present invention are thyroid receptor ligands, and include compounds that are, for example, selective agonists, partial agonists, antagonists or partial antagonists 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, and may be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, compounds of the present invention may be used in the treatment of diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T₃ regulated gene.

Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but 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;

- 23
- 5 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 glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical
- 10 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
- 15 local treatment with glucocorticoids, UV-induced dermal atrophy, dermal atrophy induced by aging (wrinkles, etc.), wound healing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
- The term treatment is also intended to include prophylactic treatment. In addition, the
- 20 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.

- COMBINATIONS:** The present invention includes within its scope pharmaceutical
- 25 compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), e.g., an antidiabetic agent or other pharmaceutically active
- 30 material.

- The compounds of the present invention may be employed in combination with other modulators and/or ligands of the thyroid receptor or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents;
- 35 anti-osteoporosis agents; anti-obesity agents; growth promoting agents (including growth hormone secretagogues); anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; cardiac glycosides; cholesterol/lipid lowering agents; appetite

5 suppressants; bone resorption inhibitors; thyroid mimetics (including other thyroid receptor agonists); anabolic agents; and anti-tumor agents.

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
10 inhibitors (e.g., acarbose or miglitol), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone),
PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2
15 inhibitors, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), glucagon-like peptide-1 (GLP-1), 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,
20 calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-1 inhibitors.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors, PPAR gamma antagonists, PPAR delta
25 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
30 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,
35 phenylpropanolamine or mazindol.

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

10

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-
15 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
20 parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate).

A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators, such as those disclosed in Edwards, J. P. et al., *Bio.*
25 *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 steroidal or non-steroidal progesterone receptor agonists ("PRA"), such as levonorgestrel,
30 medroxyprogesterone acetate (MPA).

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,
35 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 integrin antagonists,

5 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 the treatment of irritable bowel syndrome (e.g., Zelmac® and
10 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.

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

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

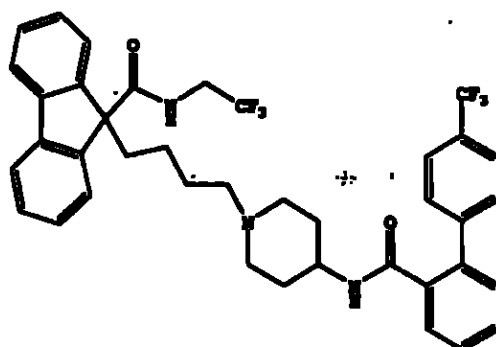
Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel
25 blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid, triacrynaf, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE
30 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)
35 inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

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

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors, squalene
10 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).

MTP inhibitors which may be employed herein in combination with one or more
15 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.

- 20 A preferred MTP inhibitor is
9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide:



- 25 The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of formula I include mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S.
30 Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent

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

The squalene synthetase inhibitors which may be used in combination with the compounds of the 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.
25 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. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard,
30 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, 1-40 (1996).

35 Bile acid sequestrants which may be used in combination with the compounds of the present invention include cholestyramine, colestipol and DEAE-Sephadex (Secholex®).

- 5 Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives),
10 nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.
- 15 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", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT
20 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 alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-
25 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
30 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.
- 35 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).

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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).

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

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

20 The aforementioned patents and patent applications are incorporated herein by reference.

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

25 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:

30

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.

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جمله نهایی

- 5 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.

- 10 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.

- 15 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
20 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.

- 25 Metformin, or salt thereof, may be employed with the compounds of formula I in amounts within the range from about 500 to about 2000 mg per day, which may be administered in single or divided doses one to four times daily.

- The compounds of 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
30 an aP2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1..

- An MTP inhibitor may be administered orally with the compounds of formula I in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably
35 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

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5 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.

10 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 more preferably from about 10 to about 40 mg.

15 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 in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The compounds of formula I of the invention can be administered orally or parenterally, such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g.,
25 humans, in an effective amount within the dosage range of about 0.01 µg/kg to about 1000 µg/kg, preferably about 0.1 µg/kg to 100 µg/kg, more preferably about 0.2 µg/kg to about 50 µg/kg (or from about 0.5 to 2500 mg, preferably from about 1 to 2000 mg) in a regimen of single, two or four divided daily doses.

30 The compounds of the formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including
35 administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or

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5 diluents. The present compounds can, for example, be administered in a form suitable for
immediate release or extended release. Immediate release or extended release can be
achieved by the use of suitable pharmaceutical compositions comprising the present
compounds, or, particularly in the case of extended release, by the use of devices such as
subcutaneous implants or osmotic pumps. The present compounds can also be
10 administered liposomally.

Exemplary compositions for oral administration include suspensions which can contain,
for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium
alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners
15 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 and/or buccal
20 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
25 can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose
(HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose
(SCMC), 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.

30 Exemplary compositions for nasal aerosol or inhalation administration include solutions
in saline, which can contain, for example, benzyl alcohol or other suitable preservatives,
absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing
agents such as those known in the art.

35 Exemplary compositions for ~~parenteral~~ administration include injectable solutions or
suspensions which can contain, for example, suitable non-toxic, parenterally acceptable

- 5 diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.
- 10 Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.
- 15 Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

20 It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

25

EXAMPLES

- The following Examples represent preferred embodiments of the present invention.
- 30 However, they should not be construed as limiting the invention in any way. The ¹H NMR spectra were consistent with the assigned structures. Mass spectra were recorded on a Perkin-Elmer, API 150Ex spectrometer, with turbo "ion spray" on negative ion mode (ES-1) or positive (ES+1), using a Zorbax SB-C8 column (LC-MS). Appropriate procedures for the preparation of methyl[3,5-chloro-4-(4-methoxy-3-isopropylphenoxy)]
- 35 benzoate and methyl- N-[3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoyl]glycine can be found in: "Novel Thyroid Receptor Ligands

- 5 and Methods." Li, Y.-L.; Liu, Y.; Hedfors, A.; Malm, J.; Mellin, C.; Zhang, M. WO99/00353, PCT/EP98/04039 and "Novel diphenyl ether derivatives which are thyroid hormone beta-receptor ligands useful for treating metabolic disorders." Hangeland, J.; Zhang, M.; Caringal, Y.; Ryono, D.; Li, Y.-L.; Malm, J.; Liu, Y.; Garg, N.; Litten, C.; Garcia Collazo, A. M.; Koehler, K. WO00/039077, PCT/IB99/02084, respectively.
- 10 Procedures for the preparation of 3,5-dichloro-2-methyl-4-(4-hydroxy-3-isopropylphenoxy)-benzoic acid can be found in "Benzamide ligands for the thyroid receptor". Ryono, Denis E.. WO01/94293, US6395784.

- Example 1: N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl]
15 glycine (E1)
- (a) Nitric acid (2.84 mL, 65 %) was added to a stirred solution of methyl[3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate (2.84 g, 7.64 mmol) in benzene (200 mL). The resulting yellow reaction mixture was stirred at room temperature for three hours and then poured out in sodium hydrogencarbonate (saturated solution). The resulting organic
20 and aqueous phases was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases was dried over sodium sulfate and concentrated to give 2.40 g of a light yellow solid. The solid was solved in ethanol (150 mL, 95.5 %), sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$, 85% purity, 7.12 g, 35.0 mmol) was added and the reaction mixture heated to reflux. After 16 hours, a second batch of sodium dithionite (3.00 g,
25 14.7 mmol) was added to the reaction mixture. After three hours, the reaction mixture was cooled down to room temperature, neutralized with sodium hydrogencarbonate (saturated solution) and concentrated. The residue was diluted with ethyl acetate (75 mL) and washed with water (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated to give a light yellow solid. The yellow solid was filtered
30 through a short plug of silica, to give 2.2 g (75 %) of methyl[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxyphenoxy)] benzoate.

5 (b) A solution of sodium nitrite (0.30 g, 13 mmol) in water (5 mL) was added to a vigorously stirred mixture of methyl[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxyphenoxy)] benzoate (1.1 g, 2.86 mmol), methanol (100 mL) and hydrochloric acid (75 mL, 37 %). The reaction mixture was stirred for one hour and then a solution of potassium iodide (1.43 g, 8.6 mmol) in water (5 mL) was added and the reaction mixture
10 was stirred for 30 minutes. The temperature was kept at 0°C inside the flask during the whole course of reaction. After attaining room temperature the brownish reaction mixture was extracted with chloroform (3x 50 mL), the combined organic phases washed with sodium hydrogensulphate (saturated solution) followed by sodium thiosulphate (saturated solution). The organic phase was concentrated to give a dark red oily residue which was
15 purified on column (silica gel, *n*-heptane/ethyl acetate 95:5), to give 0.78 g (71 %) of methyl[3,5-dichloro-4-(3-iodo-5-isopropyl-4-methoxyphenoxy)] benzoate as a pale yellow mass.

(c) Methyl[3,5-dichloro-4-(3-iodo-5-isopropyl-4-methoxyphenoxy)] benzoate (0.500 mg, 1.01 mmol), tripotassium phosphate (1.07 g, 5.05 mmol), methyl boronic acid (0.303 mg, 5.05 mmol) and dioxane was mixed in a Schlenk tube under nitrogen gas. PdCl₂(dppf) was added to the tube under nitrogen gas and the reaction mixture was heated at 100°C for 16 hours. The reaction mixture was filtered through a short pad of silica and concentrated. The dark residue was purified on column (silica gel, *n*-heptane/ethyl
25 acetate 95:5) to give a 85:15 mixture of methyl[3,5-dichloro-4-(3-isopropyl-4-methoxy-5-methylphenoxy)] benzoate and methyl[3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate. The mixture was obtained as a white solid mass (0.250 mg, 55 %) and was used without further purification in the next step.

30 (d) The mixture of methyl[3,5-dichloro-4-(3-isopropyl-4-methoxy-5-methylphenoxy)] benzoate and methyl[3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate above (250 mg) was solved in tetrahydrofuran (15 mL) and lithium hydroxide (1 N, 15 mL) was added. After 90 minutes stirring at room temperature, the reaction mixture was acidified

- 5 with hydrochloride (1 N) and the aqueous and organic phase separated. The organic phase was dried over sodium sulfate and concentrated to give 0.250 g of a white solid mass, which was mixed with glycine methyl ester (164 mg, 1.30 mmol), 3-ethyl-1-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (EDCI) (118 mg, 0.978 mmol) and N,N-dimethyl-formamide (20 mL). The reaction mixture was stirred for 10 minutes at
- 10 room temperature, whereafter 1-hydroxybenzotriazole hydrate (HOBt) (150 mg, 0.978 mmol) and triethyl-amine (0.272 mL, 1.96 mmol) was added. After 48 hours at room temperature, the reaction mixture was poured out in water (150 mL) and neutralized with sodium hydrogencarbonate. The aqueous phase was extracted with ethyl acetate (4x 100 mL), the collected organic phases dried over magnesium sulfate and concentrated.
- 15 The residue was purified on column (silica gel, gradient elution: *n*-heptane/ethyl acetate from 7:3 to 5:5). This gave 165 mg (60 %) of methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-methylphenoxy)benzoyl]glycine as a white solid mass.

- (e) Boron trifluoride dimethyl sulfide (1.48 mL, 13.7 mmol) was added at 4°C to a
- 20 stirred solution of methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-methylphenoxy)-benzoyl] glycine (155 mg, 0.352 mmol) and dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 24 hours and then treated with ice-water (30 mL), extracted with ethyl acetate and concentrated. The residue was purified on column (MPLC, silica gel, chloroform/methanol/acetic acid, gradient elution from 1/0/0 to
- 25 95/5/0.5) to give 110 mg (76 %) of N-[3,5-dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine. LC-MS (ES-1): *m/z* 410.

Example 2: N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]

30 glycine (E2)

- (a) Borontribromide (1 N, in dichloromethane) was added to a solution of methyl-N-[3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoyl]glycine (114 mg, 0.267 mmol) in dichloromethane (5 mL) at -78°C. The resulting brown reaction mixture was left at -

5 25°C for 16 hours and at 4°C for two hours. A mixture of methanol (5 mL) and water (5 mL) was added at -70°C, the reaction mixture concentrated and diluted with ethyl acetate. The organic phase was washed with water, dried over sodium sulfate and concentrated. This gave 107 mg of methyl-N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine as a beige solid mass.

10

(b) Bromine (33 µL) was added dropwise to a well stirred mixture of methyl-N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine (240 mg, 0.582 mmol), acetic acid (4 mL), sodium acetate (88 mg, 0.64 mmol) and a few drops of water. The reaction mixture was stirred at room temperature for 16 hours, sodium thiosulfate
15 (saturated) was added and the yellow mixture concentrated. The residue was diluted with ethyl acetate and washed with water. The aqueous phase was extracted with dichloromethane, the combined organic phases washed with brine and dried over sodium sulfate. After concentration, 330 mg of a yellow solid was obtained that was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 100 % *n*-heptane to a
20 mixture of 20 % *n*-heptane and 80 % ethyl acetate). This gave 200 mg (70 %) of methyl-N-[3,5-dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine as a white solid mass.

(c) Lithium hydroxide (1 N, 9 mL) was added at room temperature to a mixture of
25 methyl-N-[3,5-dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine (150 mg, 0.305 mmol) and tetrahydrofuran (9 mL). After 16 hours, the reaction mixture was acidified with hydrochloric acid (1 N) and extracted with ethyl acetate. Filtration through a pad of silica gave N-[3,5-dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]-glycine in quantitative yield as a light yellow solid. LC-MS
30 (ES-1): *m/z* 476.

Example 3: N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]
glycine (E3)

5 (a) Bromine (13 μ L, 0.26 mmol) was added dropwise to a well stirred mixture of methyl-N-[3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoyl]glycine (50 mg, 0.12 mmol), acetic acid (1.0 mL), sodium acetate (35 mg, 0.26 mmol) and a few drops of water. The reaction mixture was stirred at room temperature for three hours, heated at 40°C for 90 minutes and finally left at room temperature for 16 hours. Sodium acetate (17 mg) and
10 bromine (6 μ L) was added and the reaction mixture heated to 40°C for two hours. The reaction mixture was left at 4°C for three days. Sodium thiosulfate (saturated) was added and the yellow mixture concentrated. The residue was diluted with ethyl acetate and washed with water. The aqueous phase was extracted with dichloromethane, the combined organic phases washed with brine and dried over sodium sulfate. After
15 concentration, the residue was purified on column (hplc, C_{18} , acetonitrile/water/formic acid, gradient elution from 20/80/0.5 to 100/0/0) to give 1.0 mg (2 %) of methyl-N-[3,5-dichloro-4-(2-bromo-4-methoxy-5-isopropylphenoxy)benzoyl]glycine.

(b) Boron trifluoride dimethyl sulfide (10 μ L, 80 μ mol) was added at room temperature
20 to a stirred solution of methyl-N-[3,5-dichloro-4-(2-bromo-4-methoxy-5-isopropylphenoxy)benzoyl] glycine (1.0 mg, 2.0 μ mol) and dichloromethane (0.50 mL). The reaction mixture was stirred at room temperature for 8 hours and then treated with ice-water, extracted with ethyl acetate and washed with water. The organic phase was dried over sodium sulphate and concentrated to give a light yellow solid. The solid was
25 purified on column (MPLC, silica gel, chloroform/methanol/acetic acid, gradient elution from 1/0/0 to 95/5/0.5) to give 0.90 mg (94 %) of N-[3,5-dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine. LC-MS (ES-1): m/z 476.

Example 4: N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl]
30 glycine (IE4)

(a) Methyl[3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate (664 mg, 1.8 mmol) dissolved in acetone (40 mL), was added during 5 minutes at 0°C to a stirred mixture of calcium hypochlorite (515 mg, 3.6 mmol), water (10 mL) and acetic acid (4

5 mL). The reaction mixture was stirred at 0°C for 30 minutes and then 30 minutes at room temperature. The reaction mixture was poured out in water, extracted with ethyl acetate (3x 50 mL), the combined organic phases washed with water (4x 30 mL) and concentrated. The residue was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 90:10) to give 240 mg (60 %) of methyl[3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)] benzoate. The calcium hypochlorite used in this step could be exchanged to *t*-butyl hypochlorite.

(b) Methyl[3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)] benzoate, methanol (25 mL) and sodium hydroxide (6 N, 4 mL) was stirred at room temperature for 8 hours. The reaction mixture was neutralized with aqueous hydrochloric acid and extracted with ethyl acetate (3x 30 mL). The combined organic phases were washed with water, concentrated and the residue titrated with *n*-heptane. This gave 133 mg (58 %) of 3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)benzoic acid obtained as a white solid.

(c) Glycine methyl ester hydrochloride (83 mg, 0.66 mmol) and triethylamine (100 mg, 0.99 mmol) was added to a stirred mixture of 3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)benzoic acid (130 mg, 0.33 mmol), EDCI (88 mg, 0.46 mmol), HOBt (86 mg, 0.56 mmol) and *N,N*-dimethylformamide (15 mL). The reaction mixture was stirred for 48 hours at room temperature, poured out in a mixture of hydrochloric acid (1 N, 5.0 mL) and water (50 mL), and extracted with ethyl acetate (4x 20 mL). The collected organic phases dried was washed with water (4x 15 mL), the organic phase concentrated and the residue purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 90:10 to 75:25). This gave 90 mg (59 %) of methyl-*N*-[3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)benzoyl] glycine.

(d) Boron trifluoride dimethyl sulfide (1.0 mL) was added at room temperature to a stirred solution of methyl-*N*-[3,5-dichloro-4-(3-chloro-5-isopropyl-4-

5 methoxyphenoxy)benzoyl] glycine (90 mg) and dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 24 hours, poured out in water and extracted with ethyl acetate (3x 30 mL). The combined organic phases were washed with water (4x 20 mL), concentrated and the resulting residue purified on column (silica gel, chloroform/methanol/acetic acid 94:6:0.65). This gave 53 mg (63 %) of N-[3,5-dichloro-
10 4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine. LC-MS (ES+1): m/z 434.

Example 5: N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (ES)

(a) Methyl [3,5-dichloro-4-(3-iodo-5-isopropyl-4-methoxyphenoxy)] benzoate (for
15 preparation see ex. 1 a-b) (200 mg, 0.40 mmol), copper cyanide (50 mg, 0.56 mmol) and DMF (4ml) was heated to 120°C for 16h. After attaining room temperature, the dark reaction mixture was quenched by saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was purified on column (MPLC, silica gel, gradient elution: n-
20 heptane/ethyl acetate from 1:0 to 9:1) to give 65 mg (41 %) of methyl [3,5-dichloro-4-(3-cyano-5-isopropyl-4-methoxyphenoxy)] benzoate.

(b) Boron tribromide (1 N in dichloromethane, 0.93mL) was added to a solution of methyl [3,5-dichloro-4-(3-cyano-5-isopropyl-4-methoxyphenoxy)] benzoate (32 mg,
25 81 µmol) in dichloromethane (0.75mL) at -78°C. After 20h at -25°C and 16h at room temperature, the reaction mixture was quenched by ice water at 0°C and the organic solvent was removed by evaporation. The residue was acidified by hydrochloric acid (1 N) and extracted by ethyl acetate. The organic phase was dried over sodium sulfate and filtrated through a pad of silica. The resulting yellow solid was mixed with glycine
30 methyl ester (23 mg, 0.18 mmol), EDCI (35 mg, 0.18 mmol) and N,N-dimethylformamide (1 mL). The reaction mixture was stirred for 10 minutes at room temperature, where after HOBt (28 mg, 0.18 mmol) and triethylamine (38 µL, 0.27 mmol) was added. After 16 hours at room temperature, the reaction mixture was poured out in

5 water (5 mL) and neutralized with sodium hydrogencarbonate. The aqueous phase was extracted with ethyl acetate (2x 10 mL) and the collected organic phases was dried over sodium sulfate and concentrated. The residue was purified on column (MPLC, silica gel, gradient elution: *n*-heptane/ethyl acetate from 9:1 to 7:3). This gave 15 mg (42 %) of methyl-N-[3,5-dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine as a
10 white solid mass.

(c) Boron tribromide (1 N in dichloromethane, 0.11 mL) was added to a solution of methyl-N-[3,5-dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine (7 mg, 16 µmol) in dichloromethane (0.5 mL) at -78°C. The resulting reaction mixture was
15 stirred at room temperature for 16h and thereafter quenched by ice water. The organic solvent was removed with evaporation and the remaining residue was acidified by hydrochloric acid (1 N) and extracted by ethyl acetate. Drying over sodium sulfate, concentration and purification on a silica SPE column (0.5g, 3mL, gradient elution: chloroform/methanol/acetic acid from 1:0:0 to 98:2:0.5) gave 3 mg (44%) of N-[3,5-dichloro-4-(3-cyano-4-hydroxy-5-isopropyl-phenoxy)benzoyl]glycine. LC-MS (ES-1):
20 m/z 421.

Example 6: N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine (E6)

25 (a) To a solution of methyl [3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate (2.0 g, 5.4 mmol) in benzene (200 ml), nitric acid (2.07 ml, 65%) was added drop wise. The mixture was further stirred for 1h at room temperature. The reaction was monitored by TLC (65:35 *n*-heptane/ethyl acetate) and the mixture was quenched with saturated aqueous solution of sodium hydrogencarbonate. The resulting organic and aqueous
30 phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water, brine, and the organic phase was dried over magnesium sulfate, and concentrated. The crude product was crystallize from

5 methanol to give 1.8g, (80%) of methyl[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)] benzoate.

(b) To the solution of methyl[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)] benzoate (500mg, 1.21mmol) in tetrahydrofuran (10mL), lithium hydroxide (5mL, 1M) 10 was added. The mixture was stirred over night at room temperature. The reaction mixture was acidified with hydrochloric acid (1 N) and the aqueous and organic phase separated. The aqueous phase extracted with ethyl acetate. The combined organic phase was washed with water and dried over magnesium sulfate and concentrated. The crude product was purified on column (silica gel, chloroform/methanol/acetic acid 98: 2: 0.3) to 15 give 418mg (86%) of 3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy) benzoic acid.

(c) Glycine methyl ester hydrochloride (262mg, 2.08 mmol) and triethylamine (317 mg, 3.13 mmol) was added to a stirred mixture of 3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)] benzoic acid (418mg, 1.04mmol), EDCI (401mg, 2.08mmol), HOBt 20 (320mg, 2.08 mmol) in *N,N*-dimethylformamide (50 mL). The reaction mixture was stirred for 24 hours at room temperature, poured out in a mixture of hydrochloric acid (1 N, 10 mL) and water (50 mL), and extracted with ethyl acetate. The collected organic phases dried was washed with water, the organic phase concentrated and the residue was 25 purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 60:40) to give 380 mg (78 %) of methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitro-phenoxy)benzoyl] glycine.

(d) A mixture of methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitro- 30 phenoxy)benzoyl] glycine (380 mg, 0.81 mmol) and PtO₂ (40 mg) in ethyl acetate (10 mL) was stirred at room temperature under hydrogen (atmospheric pressure) for 24h. Pt catalyst was removed by filtration through celite and the filtrate was concentrated, which was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to

- 5 60:40) to give 320mg (89%) of methyl-N-[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxyphenoxy)benzoyl] glycine.

(e) A solution of nitrosonium tetrafluoroborate (55mg, 0.47mmol) in dichloromethane (5mL) was cooled to 0 °C and methyl-N-[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxyphenoxy) benzoyl] glycine (189mg, 0.43mmol) was added. The reaction mixture
10 was further stirred at 0 °C for 1h. Dichloromethane was removed from nitrogen and o-xylene (10mL) was added to the reaction mixture. The reaction mixture was refluxed for 1h and the solvent was removed. The crude reaction mixture was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 60:40) to give 50mg
15 (26%) of methyl-N-[3,5-dichloro-4-(3-fluoro-5-isopropyl-4-methoxyphenoxy)benzoyl] glycine.

(f) Boron trifluoride dimethyl sulfide (2.0 mL) was added at room temperature to a stirred solution of methyl-N-[3,5-dichloro-4-(3-fluoro-5-isopropyl-4-methoxyphenoxy)benzoyl]
20 glycine (50 mg, 0.11 mmol) and dichloromethane (8 mL). The reaction mixture was stirred at room temperature for 24 hours, poured out in water and extracted with ethyl acetate. The combined organic phases were washed with water, concentrated and the resulting residue purified on column (HPLC, ACE-C₈, acetonitrile/0.05%formic acid in water, gradient elution from 5/95 to 60/40) to give 5 mg (20 %) of N-[3,5-dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine. LC-MS (ES-1): m/z 414.
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Example 7: N-[3,5-Dichloro-2-methyl-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)-2-methyl-benzoyl] glycine (IE7)

(a) A suspension of benzytrimethylammonium tribromide (2.2 g, 5.63 mmol) and CaCO₃
30 (0.28 g, 2.82 mmol) was stirred for 2 hr at 20°C in a 1:1 MeOH/CH₂Cl₂ solution (10 mL) containing 3,5-dichloro-2-methyl-4-(4-hydroxy-3-isopropylphenoxy)-benzoic acid (1.0 g, 2.82 mmol). Once HPLC analysis indicated that conversion to the desired monobrominated phenol was optimal, the reaction was quenched by addition of 15 mL of

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5 IN HCl. After removal of the organic solvents under vacuum using a rotary evaporator, the aqueous suspension was extracted twice with EtOAc. After drying the combined EtOAc layers over MgSO_4 , the salts were filtered prior to removal of the EtOAc under vacuum. The resulting residue after purification by gradient elution from a reverse phase C18 column employing MeOH/ H_2O containing 0.1% TFA yielded 3,5-dichloro-2-

10 methyl-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoic acid (400 mg).

(b) HCl gas was bubbled through a solution of 3,5-dichloro-2-methyl-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoic acid (375 mg, 0.86 mmol) in MeOH (20 mL) for 5 min. Upon stirring at 20°C for 22 hr, HPLC analysis revealed esterification was

15 complete. After removal of the solvent under vacuum and dissolution of the residue in EtOAc, the EtOAc layer was washed 2x with H_2O then with brine prior to drying over MgSO_4 . Removal of the volatiles yielded 391 mg of crude methyl 3,5-dichloro-2-methyl-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoate as a brown solid which was not further purified.

20 (c) A stirred suspension of powdered anhydrous K_3PO_4 (473 mg, 2.23 mmol) and methylboronic acid (133 mg, 2.23 mmol) in a dioxane solution (5 mL) containing methyl 3,5-dichloro-2-methyl-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoate (263 mg, 0.59 mmol) was flushed with Ar for 15 min prior to addition of $\text{Pd}(\text{dppf})\text{Cl}_2$ (168 mg, 0.21 mmol). After refluxing for 3 hr, the reaction was cooled, diluted with EtOAc, and

25 filtered. The residue remaining after removal of the volatiles was chromatographed on silica gel. Progressive elution with 1:1 and then 3:1 CH_2Cl_2 /hexane eluted 125 mg of methyl 3,5-dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoate as an orange foam.

30 (d) A solution of methyl 3,5-dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoate (125 mg, 0.33 mmol) and LiOH $\cdot$ H_2O (68 mg, 1.63 mmol) in a 5:1 THF/ H_2O (6 mL) was stirred overnight at 20°C under N_2 . The solution was

5 concentrated under vacuum and acidified to pH 1 with 1N HCl. The resulting tan solid was collected by filtration, washed with H₂O and air dried to yield 114 mg of 3,5-dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoic acid.

(e) To a stirred DMF solution (5 mL) of crude 3,5-dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoic acid (114 mg, 0.31 mmol) under N₂ was added sequentially EDCI (83 mg, 0.43 mmol), HOBT (80 mg, 0.53 mmol), methyl glycinate hydrochloride (78 mg, 0.62 mmol) and Et₃N (0.13 mL, 0.93 mmol). After stirring for 21 hr at 20°C, detection of starting benzoic acid by LCMS analysis prompted addition of 8 mg of methyl glycinate hydrochloride and 13 mL of Et₃N. The reaction was terminated 3
15 hr later by dilution with 3 mL of 1N HCl and 25 mL of H₂O. After extracting the aqueous phase 3x with EtOAc, the combined EtOAc layers were washed 2x with H₂O and 1x with brine prior to drying over MgSO₄. Concentration yielded 163 mg of crude glycineamide which was chromatographed on silica gel; 1:4 EtOAc/hexane eluted 96 mg of desired methyl N-(3,5-dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl)glycinate as a beige solid.
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(f) A solution of methyl N-(3,5-dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl)glycinate (96 mg, 0.22 mmol) and LiOH H₂O (46 mg, 1.09 mmol) in a 5:1 THF/H₂O (6 mL) was stirred overnight at 20°C under N₂. The solution
25 was concentrated under vacuum and acidified to pH 1 with 1N HCl. After extracting the aqueous phase 3x with EtOAc, the combined EtOAc layers were dried over MgSO₄. Concentration yielded 92 mg of crude glycineamide which was purified by reverse phase chromatography (C18 column). Gradient elution with MeCN/H₂O containing 0.1% TFA eluted 72 mg of desired N-(3,5-dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl)glycinic acid.
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Example 8: N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine (8a)

5 Example E8 is prepared by a procedure similar to that described for Example E7.

Example 9: N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine (E9)

Example E9 is prepared by a procedure similar to that described for Example E7.

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Example 10: L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenyl-acetyl] valine (E10)

(a) To a solution of methyl[3,5-dibromo-4-(3-isopropyl-4-methoxyphenoxy)phenyl] acetate (1.0 g, 2.12 mmol) in benzene (150 mL), nitric acid (0.81 mL, 65%) was added drop-wise. The mixture was further stirred for 1 hour at room temperature. The reaction
15 was monitored by TLC (65:35 *n*-heptane/ethyl acetate) and the reaction mixture was quenched with a saturated aqueous solution of sodium hydrogen carbonate. The resulting organic and aqueous phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water, brine, and the
20 organic phase was dried over magnesium sulfate, and concentrated. The crude product was crystallized from methanol to give 1.1 g, (99%) of methyl[3,5-dibromo-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)phenyl] acetate.

(b) Methyl[3,5-dibromo-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)phenyl] acetate (1.1
25 g, 2.12 mmol) was dissolved in ethanol (50 mL) and sodium hydrosulfite (1.85 g, 10.6 mmol) was added. The reaction mixture was heated at reflux for 48 hours. The reaction monitored by TLC (65:35 *n*-heptane: EtOAc) and when complete, diluted with ethyl acetate and washed with water and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified on column (silica gel, *n*-heptane/ EtOAc 1:1) to
30 yield methyl[3,5-dibromo-4-(3-amino-5-isopropyl-4-methoxyphenoxy)phenyl] acetate (457 mg, 44%).

- 5 (c) A solution of nitrosonium tetrafluoroborate (121 mg, 1.03 mmol) in dichloromethane (10 mL) was cooled to 0 °C and methyl[3,5-dibromo-4-(3-amino-5-isopropyl-4-methoxyphenoxy)phenyl] acetate (457 mg, 0.94 mmol) was added. The reaction mixture was stirred at 0 °C for one hour. Dichloromethane was removed by flushing of nitrogen gas and o-xylene (10 mL) was added to the residue. The reaction mixture was heated at reflux
10 for one hour and the organic phase concentrated *in vacuo*. The residue was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 60:40) to give 205 mg (44 %) of methyl[3,5-dibromo-4-(3-fluoro-5-isopropyl-4-methoxyphenoxy)-phenyl] acetate.
- 15 (d) To a solution of methyl[3,5-dibromo-4-(3-fluoro-5-isopropyl-4-methoxyphenoxy)-phenyl] acetate (205 mg, 0.42 mmol) in tetrahydrofuran (30 mL), lithium hydroxide (30 mL, 1N) was added. The reaction mixture was stirred over night at room temperature, acidified with hydrochloric acid (1 N) and the aqueous and organic phase separated. The aqueous phase extracted with ethyl acetate. The combined organic phase was washed
20 with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified on column (silica gel, chloroform/methanol/acetic acid 98:2:0.3) to give 210 mg (99%) of 3,5-dibromo-4-(3-fluoro-5-isopropyl-4-methoxyphenoxy)phenylacetic acid.
- (e) L-valine methyl ester hydrochloride (148 mg, 0.88 mmol) and triethylamine (134 mg, 1.32 mmol) was added to a stirred mixture of 3,5-dibromo-4-(3-fluoro-5-isopropyl-4-methoxyphenoxy)phenylacetic acid (210 mg, 0.44 mmol), EDCI (169 mg, 0.88 mmol), HOBt (135 mg, 0.88 mmol) in *N,N*-dimethylformamide (25 mL). The reaction mixture was stirred for 24 hours at room temperature, poured out in a mixture of hydrochloric acid (1 N, 5 mL) and water (30 mL), and extracted with ethyl acetate. The collected
30 organic phases were dried, the organic phase concentrated and the residue purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 60:40) to give 224 mg (86 %) of L-methyl-N-[3,5-dibromo-4-(3-fluoro-5-isopropyl-4-methoxyphenoxy)phenylacetyl] valinate.

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(f) Boron trifluoride dimethyl sulfide (4.0 mL) was added at room temperature to a stirred solution of L-methyl-N-[3,5-dibromo-4-(3-fluoro-5-isopropyl-4-methoxy-phenoxy)-phenylacetyl] valine (224 mg, 0.38mmol) in dichloromethane (25 mL). The reaction mixture was stirred at room temperature for 24 hours, poured out in water and extracted with ethyl acetate. The combined organic phases were washed with water, concentrated and the resulting residue purified on column (silica gel, chloroform/methanol/acetic acid 98:2: 0.3) to give 93 mg (44 %) of L-N-[3,5-dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine.

15 **Example 11: D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenyl-acetyl] phenylglycine (E11)**

(a) To a stirred solution of 3,5-dibromo-4-(3-isopropyl-4-methoxyphenoxy)phenylacetic acid (1.5 g, 3.4 mmol) in acetic acid (40 mL) at room temperature was added benzyl-trimethylammonium tetrachloroiodate (1.42 g, 3.4 mmol). The reaction mixture was stirred for one hour and was filtered. The filtrate was concentrated, and the product was extracted with ethyl acetate, washed with saturated NaHCO₃ (aq), NaCl (aq), and dried over MgSO₄ and concentrated *in vacuo*. The residue was purified on column (silica gel, chloroform/methanol/acetic acid 98:2:0.3) to give 802 mg (50 %) of 3,5-dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetic acid.

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(b) D-phenylglycine methyl ester hydrochloride (674 mg, 3.34 mmol) and triethylamine (507 mg, 5.02 mmol) was added to a stirred mixture of 3,5-dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetic acid (800 mg, 1.7 mmol), EDCI (641 mg, 3.34 mmol), HOBt (512 mg, 3.34 mmol) in *N,N*-dimethylformamide (100 mL). The reaction mixture was stirred for 24 hours at room temperature, poured out into a mixture of hydrochloric acid (1 N, 5 mL) and water (30 mL), and extracted with ethyl acetate. The collected organic phases were dried, the organic phase concentrated and the residue purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to

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- 5 60:40) to give 800 mg (75 %) of D-methyl-N-[3,5-dibromo-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)phenylacetyl] phenylglycinate.

(c) Boron trifluoride dimethyl sulfide (10 mL) was added at room temperature to a stirred solution of D-methyl-N-[3,5-dibromo-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)-
 10 phenylacetyl] phenylglycinate (800 mg, 1.3 mmol) and dichloromethane (80 mL). The reaction mixture was stirred at room temperature for 24 hours, poured out in water and extracted with ethyl acetate. The combined organic phases were washed with water, concentrated and the resulting residue purified on column (silica gel, chloroform/methanol/acetic acid 98:2:0.3) to give 350 mg (44 %) of D-N-[3,5-dibromo-
 15 4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine.

Example 12: L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenyl-acetyl] valine (E12)

(a) Methyl[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenyl] acetate (2.0 g, 4.4
 20 mmol), SnCl_4 (25 μl , 0.2 mmol), trioctyl amine (0.77 mL, 1.76 mmol) and toluene (15 mL) were mixed in a reaction vial. After 20 minutes stirring at room temperature, paraformaldehyde (0.264 g, 8.8 mmol) was added to the reaction solution. The reaction vial was sealed and the temperature increased to 105°C. After 20 hours stirring, the reaction was quenched with ice-water and acidified with hydrochloric acid (1 N).
 25 Extraction with ethyl acetate, washing with brine, drying over Na_2SO_4 and concentration gave the crude product. The residue was purified on column (silica, gradient elution: *n*-heptane/ethyl acetate from 1:0 to 4:1) to give 1.08g (51 %) of methyl[3,5-dibromo-4-(3-formyl-4-hydroxy-5-isopropylphenoxy)phenyl] acetate.

30 (b) Triethylsilane was added to a mixture of methyl[3,5-dibromo-4-(3-formyl-4-hydroxy-5-isopropylphenoxy)phenyl] acetate (243 mg, 0.5 mmol) and trifluoroacetic acid (10 mL) at room temperature. After 12 hours stirring, the reaction mixture was concentrated via co-evaporated with toluene. The residue was purified on column (silica, gradient elution:

5 *n*-heptane/ethyl acetate from 9:1 to 7:3) to give 197 mg (84%) of methyl[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenyl] acetate.

(c) A mixture of methyl[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)-phenyl] acetate (194 mg, 0.41 mmol) and lithium hydroxide (20 mL, 1 N) in
10 tetrahydrofuran (10 mL) was stirred for 10 hours at room temperature. The reaction mixture was neutralized with cold aqueous hydrochloric acid followed by extraction with ethyl acetate (3x30 mL). The combined organic layers were washed with water (4x25 mL) and co-evaporated with acetonitrile. The residue was purified on column (silica, gradient elution: chloroform/methanol/acetic acid from 1:0:0 to 90:10:1) to yield 169 mg
15 (90 %) of 3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenyl] acetic acid.

(d) A mixture of compound 3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)-phenylacetyl] acetic acid (0.44g, 0.96mmol), L-valine methylester (322 mg, 1.92 mmol), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (174 mg, 1.44
20 mmol) and N,N-dimethyl- formamide (9 mL) was stirred for 5 minutes at room temperature, where after 1-hydroxybenzotriazole hydrate (HOBt) (220 mg, 1.44 mmol) and triethylamine (0.401 mL, 12.88 mmol) were added. After 16 hours bromotripyrrolidinophosphonium hexafluorophosphate (0.2 g, 0.43 mmol) was added. After 1.75 hours of stirring at room temperature the obtained reaction mixture was diluted
25 with water (10 mL) and hydrochloric acid (10 ml, 1 N), the aqueous layer extracted with ethyl acetate (3 x20mL) and the combined organic layers washed with brine (40 mL). After drying over Na₂SO₄, filtration and concentration the crude product was filtrated through a short silica pad. Purification on a chromatotron (silica, 4 mm, *n*-heptane/ethyl acetate 6:4) gave 240 mg (44%) of L-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-
30 5-methylphenoxy)phenylacetyl] valinate.

(e) To a stirred solution of compound L-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methyl-phenoxy)phenylacetyl] valinate (240 mg, 0.42 mmol) and

5 tetrahydrofuran (4 mL) was added lithium hydroxide (4 mL, 1N). After one hour stirring the pH of reaction was adjusted to 1 with hydrochloric acid (1 N). The organic phase was concentrated in vacuo. The residue was extracted with ethyl acetate and the combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified on column (MPLC, silica, gradient elution: chloroform/methanol/acetic acid from 1:0:0 to
10 98:2:0.3) to yield compound L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine as a white solid (0.14 g, 60 %). LC-MS (ES-1): m/z 554.

Example 13: L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl]phenylglycine (E13)

15 (a) A solution of 3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetic acid (18 mg, 0.04 mmol), diisopropylethylamine (33 µl, 0.2 mmol), bromotripyrrolidinophosphonium hexafluorophosphate (22 mg, 0.05 mmol), 1-hydroxybenzotriazole hydrate (7 mg, 0.05 mmol), D-phenylglycine methylester (16 mg, 0.08 mmol) and dichloromethane (1 mL) was stirred for 30 minutes at room temperature. There after
20 was the reaction washed with hydrochloric acid (2ml, 1 N) and the aqueous layer was extracted with chloroform (3 x2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Purification on a column (silica, gradient elution: *n*-heptane/ethyl acetate from 4:1 to 7:3) yielded 16 mg (74%) of L-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] phenylglycinate.

25 (b) L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] phenylglycinate (15 mg, 0.025 mmol) was dissolved in tetrahydrofuran (0.5 mL) and the resulting solution was treated with aqueous lithium hydroxide (0.5 mL, 1 N) for 1 hour at room temperature. The reaction was acidified with hydrochloric acid (1 N) and the
30 organic phase was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x5 mL) and the combined organic phases were dried over Na₂SO₄ before concentration *in vacuo*. The residue was purified on column (HPLC, C8, gradient elution: acetonitrile/water (0.5% formic acid) from 1:4 to 1:0) to give L-N-[3,5-dibromo-4-(4-hydroxy-3-

- 5 isopropyl-5-methylphenoxy)phenylacetyl] phenylglycine as a white solid (6 mg, 41 %).
LC-MS (ES-1): m/z 588.

Example 14: L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]-phenylglycine (E14)

- 10 (a) Bis-(4-methoxyphenyl) iodonium tetrafluoroborate (5.48 g, 12.8 mmol) and copper powder (1.25 g, 19.6 mmol) was suspended in dichloromethane (25 mL) and the resulting suspension was cooled to 0°C. While stirring, a solution of methyl(3,5-dibromo-4-hydroxyphenyl) acetate (3.19 g, 9.8 mmol), triethylamine (1.64 mL, 11.8 mmol) and dichloromethane (35 mL) was added to the suspension covered by aluminum foil. After
15 20 hours stirring in the dark at room temperature the crude reaction mixture was washed with hydrochloric acid (1 N) and a phase separator (IST) was used to separate the two phases. The remaining acidic aqueous phase was extracted by chloroform and the collected organic phases were concentrated *in vacuo*. The residue was purified on column (MPLC, silica gel, gradient elution: *n*-heptane/ethyl acetate from 1:0 to 4:1) to give 2.5 g
20 (45 %) of methyl[3,5-dibromo-4-(4-hydroxyphenoxy)phenyl] acetate.

- (b) BF₃·SMe₂ (24 mL, 228 mmol) was added to a stirred solution of methyl[3,5-dibromo-4-(4-methoxyphenoxy)phenyl] acetate (2.5 g, 5.8 mmol) and dichloromethane (50 mL) at 0°C. The reaction mixture was stirred for 20 hours at room temperature and
25 subsequently quenched with ice water (50 mL). The two layers were separated with a phase separator and the remaining water phase was extracted with ethyl acetate. Filtration through a silica pad gave the crude 3,5-dibromo-4-(4-hydroxyphenoxy)phenylacetic acid. The residue was dissolved in methanol (40 mL) and thionyl chloride (4 mL) was added carefully to the reaction. After 1.5 hours of heating at reflux, the organic phase was
30 removed *in vacuo* and the residue was dissolved in chloroform. The organic phase was washed with water and concentrated to give methyl[3,5-dibromo-4-(4-hydroxyphenoxy)-phenyl] acetate as beige solid (1.8 g, 75 %).

- 5 (c) Hexamethylenetetramine (262 mg, 1.87 mmol) was added to a solution of methyl[3,5-dibromo-4-(4-hydroxyphenoxy)phenyl] acetate (370 mg, 0.89 mmol) and trifluoroacetic acid (1.5 mL). The reaction mixture was stirred for 16 hours at 95°C before cooling to room temperature. Hydrochloric acid (3 mL, 2 N) was added and the reaction mixture was stirred for one hour and extracted with chloroform. The organic phase was
- 10 concentrated *in vacuo* and dissolved in ethyl acetate. The organic phase was washed with hydrochloric acid (2 N), water and brine, dried over Na₂SO₄ and concentrated. The residue was purified on a column (MPLC, silica, gradient eluent: *n*-heptane/ethyl acetate from 1:0 to 4:1) to give yielded methyl[3,5-dibromo-4-(3-formyl-4-hydroxyphenoxy)-phenyl] acetate as a white solid (150 mg, 38 %).
- 15 (d) A mixture of compound methyl[3,5-dibromo-4-(3-formyl-4-hydroxyphenoxy)-phenyl] acetate (250 mg, 0.56 mmol) and trifluoroacetic acid (5.5 mL) was treated with triethylsilane (0.34 mL, 2.13 mmol) and the reaction mixture was stirred for 16 hours at room temperature. The reaction was concentrated and co-evaporated (toluene,
- 20 dichloromethane), which gave a residue that was filtrated through a pad of silica. Purification on a column (MPLC, silica, gradient elution: *n*-heptane/ethyl acetate from 1:0 to 4:1) gave 110 mg (46 %) of methyl[3,5-dibromo-4-(4-hydroxy-3-methyl-phenoxy)phenyl] acetate.
- 25 (e) A solution of methyl[3,5-dibromo-4-(4-hydroxy-3-methyl-phenoxy)phenyl] acetate (110 mg, 0.26 mmol), hexamethylenetetramine (77 mg, 0.55 mmol) and trifluoroacetic acid (2.5 mL) was stirred at 100°C for 20 hours. The reaction solution was diluted with hydrochloric acid (5 mL, 2 N) and the resulting mixture was stirred at room temperature for 30 minutes before it was extracted with chloroform. The organic phase was
- 30 concentrated and diluted with ethyl acetate, and washed with hydrochloric acid (2 x 10 mL, 2 N), water (10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, concentrated and filtrated through a silica pad to give 60 mg (50 %) of methyl[3,5-dibromo-4-(3-formyl-4-hydroxy-5-methylphenoxy)phenyl] acetate.

5

(f) To a stirred mixture of methyl[3,5-dibromo-4-(3-formyl-4-hydroxy-5-methylphenoxy)phenyl] acetate (60 mg, 0.13 mmol) and trifluoroacetic acid (1.5 mL), triethylsilane (62 μ l, 0.39 mmol) was added. The reaction mixture was stirred at room temperature for 20 hours, the organic phase concentrated and the residue was co-
10 evaporated (toluene) to give 60 mg of crude methyl[3,5-dibromo-4-(3,5-dibromo-4-hydroxyphenoxy)phenyl] acetate. The crude product was used in next step. Lithium hydroxide (1.5 ml, 1N) was added to a stirred solution of crude methyl[3,5-dibromo-4-(3,5-dibromo-4-hydroxyphenoxy)phenyl] acetate and tetrahydrofuran (1.5 mL). The resulting mixture was stirred for 2 hours at room temperature, acidified with hydrochloric
15 acid (1 N) and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on column (HPLC, C8, gradient eluent: acetonitrile/water (0.5% formic acid) from 1:4 to 1:0) to give 16 mg (14 % for both steps) of 3,5-dibromo-4-(3,5-dibromo-4-hydroxyphenoxy)phenylacetic acid.

(g) 3,5-Dibromo-4-(3,5-dibromo-4-hydroxyphenoxy)phenylacetic acid (16 mg, 0.037 mmol), diisopropylethyl amine (33 μ l, 0.2 mmol), bromotripyrrolidinophosphonium hexafluorophosphate (21 mg, 0.044 mmol), 1-hydroxybenzotriazole hydrate (7 mg, 0.05 mmol), D-phenylglycine methylester (15 mg, 0.074 mmol) and dichloromethane (0.5 mL) were mixed and stirred for 1 hour at room temperature, and thereafter stored at 4°C
25 for 20 hours. The reaction mixture was washed with hydrochloric acid (1 N) and the remaining aqueous layer extracted with chloroform. The combined organic layers were concentrated *in vacuo* and the residue was purified on a column (silica, eluent: chloroform) to give 10 mg (47 %) of L-methyl-N-[3,5-dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]phenylglycinate .

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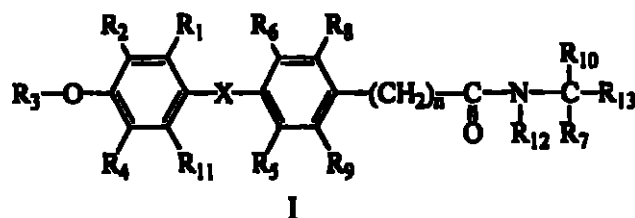
(h) L-Methyl-N-[3,5-dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]-phenylglycinate (10 mg, 0.017 mmol) was dissolved in tetrahydrofuran (0.25 mL) and lithium hydroxide (0.25 mL, 1 N) was added. The reaction mixture was stirred for 1 hour

5 at room temperature and 1 M hydrochloric acid (1 N) was added subsequently until pH reached 1. The obtained mixture was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 . After concentration and purification on preparative TLC (silica, eluent: chloroform/methanol/acetic acid 9:1:0.1), 5 mg (52%) of L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]phenylglycine was
10 obtained. LC-MS (ES-1): m/z 560.

The compounds of Examples 1-6 exhibit binding affinities to the thyroid receptor beta in the range of IC_{50} of 1.0 to 100 nM.

CLAIMS

1. A Compound of the general formula:



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from a group consisting of hydrogen, halogen, and C_1 to C_6 alkyl;

R_2 is selected from the group consisting of halogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_4 to C_7 cycloalkenyl, C_3 to C_7 cycloalkoxy, $SO_2(NR_{14}R_{15})$, $N(R_{16})SO_2R_{17}$, SR_{17} , SOR_{17} , SO_2R_{17} , COR_{16} , and $CR_{18}(OR_{16})R_{19}$; or R_2 is hydrogen when R_4 is alkyl and R_1 is halogen;

R_3 is selected from the group consisting of hydrogen, alkyl, benzyl, aroyl, and alkanoyl;

R_4 is halogen, cyano or alkyl;

R_5 and R_6 are independently selected from hydrogen, halogen; cyano, C_{1-4} alkyl, C_3 to C_6 cycloalkyl; where at least one of R_5 and R_6 is not hydrogen;

R_7 and R_{10} are independently selected from hydrogen, halogen, aryl and alkyl, and R_7 and R_{10} may be joined so as to comprise a chain of 2 to 6 methylene groups to form a ring of 3 to 7-membered in size;

R_8 and R_9 are each independently selected from the group consisting of hydrogen, halogen, alkoxy, hydroxy (OH), cyano, and alkyl;

provided that not more than one of R_2 , R_4 , R_8 and R_9 are hydrogen;

5

R₁₁ is hydrogen, halogen or alkyl;

R₁₂ is hydrogen or alkyl;

10

R₁₃ is carboxylic acid (COOH) or esters thereof, phosphonic and phosphinic acid or esters thereof, sulfonic acid, tetrazole, hydroxamic acid, thiazolidinedione, acylsulfonamide, or other carboxylic acid surrogates known in the art;

15

R₁₄ and R₁₅ for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, and R₁₄ and R₁₅ may be joined so as to comprise a chain of 3 to 6 methylene groups to form a ring of 4 to 7-membered in size;

20

R₁₆ is selected from a group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;

R₁₇ is selected from a group consisting of alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;

25

R₁₈ and R₁₉ for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;

30

n is an integer of 0, 1 or 2;

X is selected from: -O-, -CH₂-, -CF₂-, -Se-, -NH-, -S-, -SO-, -SO₂- and -CO-;

and pharmaceutically acceptable salts, prodrug forms and stereoisomers thereof.

35

- 2. A compound according to claim 1, which has one or more asymmetric centers and can exist in the form of racemates, single and multiple enantiomers, as individual diastereomers, with all possible isomers, and mixtures thereof.**

- 5
3. A compound according to claim 1 or 2 said compound being:
- N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine (E1);
- 10 (E2); N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E3);
- N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E4);
- 15 N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E5);
- N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E6).
- 20 N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E7).
- L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine (E10)
- D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine (E11)
- 25 L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine (E12)
- L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl]phenylglycine (E13)
- 30 L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]-phenylglycine (E14)
4. N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E8).
- 35 N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E9).
5. A compound according to any one of claims 1 to 3 for use in medical therapy.

- 5
3. A compound according to claim 1 or 2 said compound being:
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine
(E1);
N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
10 (E2);
N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E3);
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E4);
15 N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E5);
N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E6).
N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]
20 glycine (E7).
L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl]
valine (E10)
D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl]
phenylglycine (E11)
25 L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl]
valine (E12)
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenyl-
acetyl]phenylglycine (E13)
L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]-
30 phenylglycine (E14)
4. N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]
glycine (E8).
N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]
35 glycine (E9).
5. A compound according to any one of claims 1 to 3 for use in medical therapy.

- 5
6. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 to 3 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.
- 10 7. A process for making a pharmaceutical composition comprising combining a compound according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier.
- 15 8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 and at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, 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, cholesterol/lipid lowering agents, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.
- 20 9. The pharmaceutical composition of claim 8 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of a biguanide, a glucosidase inhibitor, a meglitinide, a sulfonylurea, a thiazolidinedione, a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR alpha/gamma dual agonist, an SGLT2 inhibitor, a glycogen phosphorylase inhibitor, an α P2 inhibitor, a glucagon-like peptide-1 (GLP-1), a dipeptidyl peptidase IV inhibitor and insulin.
- 25 10. The pharmaceutical composition of claim 8 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of metformin, glyburide, glimepiride, glipyrider, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, pioglitazone, englitazone, darglitazone, rosiglitazone and insulin.
- 30 11. The pharmaceutical composition of claim 8 wherein said additional therapeutic agent is an anti-obesity agent selected from the group consisting of an α P2
- 35

- 5 inhibitor, a PPAR gamma antagonist, a PPAR delta agonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake inhibitor, a cannabinoid-1 receptor antagonist and an anorectic agent.
- 10 12. The pharmaceutical composition of claim 8 wherein said additional therapeutic agent is a hypolipidemic agent selected from the group consisting of a thiazolidinedione, an MTP inhibitor, a squalene synthetase inhibitor, an HMG CoA reductase inhibitor, a fibric acid derivative, an ACAT inhibitor, a cholesterol absorption inhibitor, an ileal Na⁺/bile cotransporter inhibitor, a bile acid sequestrant and a nicotinic acid or a derivative thereof.
- 15 13. A method for preventing, inhibiting or treating a disease which is dependent on the expression of a T₃ regulated gene or associated with metabolic dysfunction, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in claims 1 to 3.
- 20 14. A method for treating or delaying the progression or onset of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass, density or growth, eating disorders, reduced cognitive function, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or
- 25 disease, which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.
- 30 15. The method as defined in claim 13, wherein the said disease is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.
- 35 16. The method according to claim 14, wherein the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis,

- 5 Dermier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
17. The method according to claim 13 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional
10 therapeutic agent selected from the group consisting of other compounds of formula I, 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, cholesterol/lipid lowering agents, appetite suppressants, bone resorption inhibitors, thyroid
15 mimetics, anabolic agents, anti-tumor agents and retinoids.
18. A method of treating or delaying the progression or onset of a skin disorder or disease which comprises administering to a mammalian patient a therapeutically effective amount of a compound as defined in claim 1 in combination with a
20 retinoid or a vitamin D analog.
19. A method for treating or delaying the progression or onset of obesity which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.
25
20. A method according to claim 19 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.
30
21. A method according to claim 20 wherein said anti-obesity agent is selected from the group consisting of α P2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-1 receptor antagonists, other thyroid receptor
35 agents and anorectic agents.

- 5 22. The use of a compound according to any of claims 1 to 4 in the preparation of a medicament to inhibit or treat a disease which is dependent on the expression of a T₂ regulated gene or associated with metabolic dysfunction.
- 10 23. The use according to claim 22, wherein said disease is selected from obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass density or growth, eating disorders, reduced cognitive function, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or disease.
- 15 24. The use according to claim 23, wherein the skin disorder or disease is selected from dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis, Demier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
- 20 25. Use according to claim 22 in combination with at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, 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, cholesterol/lipid lowering agents, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.
- 25 26. Use according to claim 22 in combination with a retinoid or a vitamin D analog wherein said disease is a skin disorder or disease.
- 30 27. Use according to claim 22 wherein said disease is obesity.
- 35 28. Use according to claim 27 in combination with at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.

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29. Use according to claim 28, wherein said anti-obesity agent is selected from the group consisting of α P2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-1 receptor antagonists, other thyroid receptor agents and anorectic agents.

10

30. A pharmaceutical composition which functions as a selective agonist of the thyroid hormone receptor comprising a compound as defined in claim 1.

15

Título: COMPUESTOS NOVEDOSOS

Resumen: Esta invención se refiere a compuestos novedosos, los cuales son ligandos de receptores tiroideos, y a los métodos para la preparación de dichos compuestos. Adicionalmente, es proporcionado un método para la prevención, inhibición o tratamiento de enfermedades o trastornos asociados con una disfunción del metabolismo o que dependen de la expresión de un gen regulado por T_3 , en donde un compuesto de acuerdo con lo aquí descrito es administrado en una cantidad terapéuticamente efectiva.

CAMPO DE LA INVENCION

Esta invención se refiere a compuestos novedosos los cuales son ligandos de receptores tiroideos, y a los métodos para la preparación de dichos compuestos y a los métodos para el uso de dichos compuestos tales como la regulación del metabolismo.

ANTECEDENTES DE LA INVENCION

Mientras que el papel extenso de las hormonas tiroideas en la regulación del metabolismo en humanos es ampliamente reconocido, el descubrimiento y desarrollo de nuevos medicamentos específicos para mejorar el tratamiento de hipertiroidismo e

hipotiroidismo han sido lentos. Esto también ha limitado el desarrollo de agonistas y antagonistas para el tratamiento de otros síntomas clínicos importantes, tales como hipercolesterolemia, obesidad y arritmias cardíacas.

Las hormonas tiroideas afectan el metabolismo de virtualmente cada célula del cuerpo. En niveles normales, estas hormonas mantienen el peso corporal, el índice metabólico, la temperatura corporal y el humor, e influye en los niveles de lipoproteínas de baja densidad (LDL) del suero sanguíneo. Así, en el hipotiroidismo hay una ganancia de peso, altos niveles de colesterol LDL y depresión. En el hipertiroidismo, estas hormonas conducen a la pérdida de peso, hipermetabolismo, disminución de los niveles de LDL del suero, arritmias cardíacas, insuficiencia cardíaca, debilidad muscular, pérdida de masa ósea en mujeres post-menopáusicas y ansiedad.

En la actualidad las hormonas tiroideas son utilizadas principalmente como una terapia de reemplazo para pacientes con hipotiroidismo. La terapia con L-tiroxina retoma las funciones metabólicas al estado normal y puede ser fácilmente monitoreada con mediciones rutinarias en el suero de los niveles de hormona estimulante de la tiroides (THS, por sus siglas en inglés), tiroxina (3,5,3',5'-tetrayodo-L-tironina, o T_4) y triyodotironina (3,5,3'-triyodo-L-tironina, o T_3). Sin embargo, la terapia de reemplazo, particularmente en individuos más viejos, puede ser restringida por ciertos efectos perjudiciales de las hormonas tiroideas.

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Adicionalmente, algunos efectos de las hormonas tiroideas pueden ser terapéuticamente útiles en trastornos no-tiroideos si los efectos nocivos pueden ser reducidos al mínimo o eliminados. Estas consecuencias potencialmente útiles incluyen reducción de peso, disminución de los niveles de LDL en el suero, mejoramiento de la depresión y estimulación de la formación de huesos. Los intentos anteriores de utilizar hormonas tiroideas para tratar farmacológicamente estos trastornos han sido limitados por manifestaciones de hipertiroidismo y en particular por toxicidad cardiovascular.

Además, los medicamentos útiles agonistas de la tiroides deben minimizar el potencial de consecuencias indeseadas debido a un hipotiroidismo localmente inducido, i.e. niveles sub-normales de la actividad de la hormona tiroidea en ciertos tejidos u órganos. Esto puede presentarse debido a que el incremento en las concentraciones del agonista de la hormona tiroidea circulante puede causar que la pituitaria suprima la secreción de hormona estimulante de la tiroides (TSH), en consecuencia reduciendo la síntesis de la hormona tiroidea por la glándula tiroides (control de retroalimentación negativo). Dado que se reducen los niveles endógenos de la hormona tiroidea, el hipotiroidismo localizado puede resultar donde quiera que el medicamento agonista de la tiroides administrado no pueda compensar la reducción en los niveles endógenos de la hormona en tejidos específicos. Por ejemplo, si la droga agonista de la tiroides no penetra la barrera de sangre del cerebro, el efecto de la supresión de TSH puede conducir a hipotiroidismo del SNC y a riesgos asociados tales como depresión.

El desarrollo de ligandos específicos y selectivos del receptor de la hormona tiroidea, particularmente agonistas del receptor de la hormona tiroidea podría conducir a terapias

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específicas para estos trastornos comunes, al tiempo que evita la toxicidad cardiovascular u otra de las hormonas tiroideas nativas. Los agonistas tejido-selectivos de la hormona tiroidea pueden ser obtenidos mediante la compresión o extrusión de tejido selectivo, administración tópica o local, alcanzando a la célula a través de otros ligandos unidos al agonista y alcanzando subtipos de receptor. La selectividad del tejido también puede ser obtenida mediante regulación selectiva de los genes de respuesta de la hormona tiroidea en una forma específica del tejido.

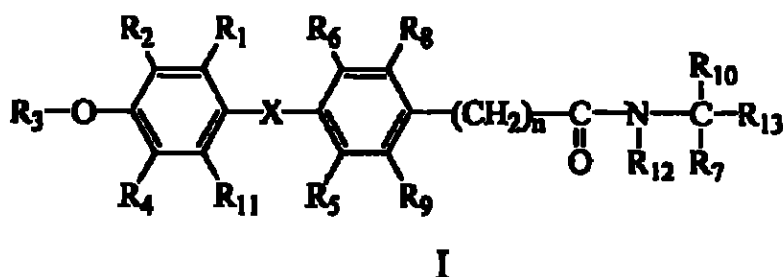
Por consiguiente, el descubrimiento de compuestos que son ligandos del receptor de la hormona tiroidea, particularmente agonistas selectivos del receptor de la hormona tiroidea, podría mostrar una utilidad para el tratamiento o prevención de enfermedades o trastornos asociados con la actividad de la hormona tiroidea, por ejemplo: (1) terapia de reemplazo en sujetos de edad avanzada con hipotiroidismo, los cuales están en riesgo de complicaciones cardiovasculares; (2) terapia de reemplazo en sujetos de edad avanzada con hipotiroidismo subclínico los cuales están en riesgo de complicaciones cardiovasculares; (3) obesidad; (4) hipercolesterolemia debida a elevaciones de los niveles de LDL del plasma; (5) depresión y (6) osteoporosis conjuntamente con un inhibidor de la resorción ósea.

RESUMEN DE LA INVENCION

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De acuerdo con el modo de realización ilustrativo y demostrando características destacadas de la presente invención, son proporcionados compuestos los cuales son ligandos de receptores tiroideos, y tienen la formula I:



o una sal farmacéuticamente aceptable de este, en donde:

R_1 es seleccionado de un grupo que contiene hidrógeno, halógeno y alquilo de C_1 a C_6 ;

R_2 es seleccionado del grupo que contiene halógeno, alquilo de C_1 a C_6 , alquenilo de C_2 a C_6 , alquinilo de C_2 a C_6 , cicloalquenilo de C_4 a C_7 , cicloalcoxi de C_3 a C_7 , $SO_2(NR_{14}R_{15})$, $NR_{16}SO_2R_{17}$, SR_{17} , SOR_{17} , SO_2R_{17} , COR_{18} y $CR_{18}(OR_{18})R_{19}$; o R_2 es hidrógeno cuando R_4 es alquilo y R_1 es halógeno;

R_3 es seleccionado del grupo que contiene hidrógeno, alquilo, bencilo, aroilo y alcanilo;

R_4 es halógeno, ciano o alquilo;

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R_5 y R_6 son independientemente seleccionados de hidrógeno, halógeno; ciano, alquilo de C_{1-4} , cicloalquilo de C_3 a C_6 ; en donde al menos uno de R_5 y R_6 no es hidrógeno;

R_7 y R_{10} son independientemente seleccionados de hidrógeno, halógeno, arilo y alquilo, y R_7 y R_{10} pueden ser unidos para integrar una cadena de 2 a 6 grupos metilenos para formar un anillo de 3 a 7 miembros de tamaño;

R_8 y R_9 son cada uno independientemente seleccionados de hidrógeno, halógeno, alcoxi, hidroxilo (OH), ciano y alquilo;

con la condición de que no mas de uno de R_2 , R_4 , R_8 y R_9 son hidrógenos;

R_{11} es hidrógeno halógeno o alquilo;

R_{12} es hidrógeno o alquilo;

R_{13} es ácido carboxílico (COOH) o ésteres de este, ácido fosfónico o fosfínico o ésteres de estos, ácido sulfónico, tetrazol, ácido hidroxámico, tiazolidindiona, acilsulfonamida, u otros substitutos de ácido carboxílico conocido en el estado del arte;

R_{14} y R_{15} para cada caso son cada uno seleccionados independientemente del grupo que contiene hidrógeno, alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo y R_{14} y R_{15} pueden ser unidos para integrar una cadena de 3 a 6 grupos metilenos para formar un anillo de 4 a 7 miembros de tamaño;

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R₁₆ es seleccionado de un grupo que contiene hidrógeno, alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo;

R₁₇ es seleccionado del grupo que contiene alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo;

R₁₈ y R₁₉ para cada caso son cada uno seleccionados independientemente del grupo que contiene hidrógeno, alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo;

n es un estero de 0, 1 o 2;

X es seleccionado de: -O-, -CH₂-, -CF₂-, -Se-, -NH-, -S-, -SO-, -SO₂- y -CO -;

La definición de la fórmula I presentada anteriormente incluye todos los profármacos, estereoisómeros y sales farmacéuticamente aceptables de la fórmula I.

Los compuestos con la fórmula I son ligandos del receptor de la hormona tiroidea e incluyen compuestos los cuales son, por ejemplo, agonistas selectivos, agonistas parciales, antagonistas o antagonistas parciales del receptor tiroideo. Preferiblemente, los compuestos con la fórmula I poseen actividad como agonistas del receptor tiroideo, y pueden ser usados en el tratamiento de enfermedades o trastornos asociados con la actividad del receptor tiroideo. En particular, los compuestos con la fórmula I pueden ser

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usados en el tratamiento de enfermedades o trastornos asociados con una disfunción del metabolismo o aquellas que dependen de la expresión de un gen regulado por T_3 , tales como obesidad, hipercolesterolemia, aterosclerosis, arritmias cardíacas, depresión, osteoporosis, hipotiroidismo, bocio, cáncer de tiroides, glaucoma, trastornos o enfermedades en la piel e insuficiencia cardíaca congestiva.

La presente invención prevé para los compuestos con la fórmula I, formulaciones farmacéuticas que empleen tales compuestos y los métodos de uso para tales compuestos. En particular la presente invención prevé una formulación farmacéutica que contiene una cantidad terapéuticamente efectiva de un compuesto con la fórmula I, solo o combinado con un vehículo farmacéuticamente aceptable.

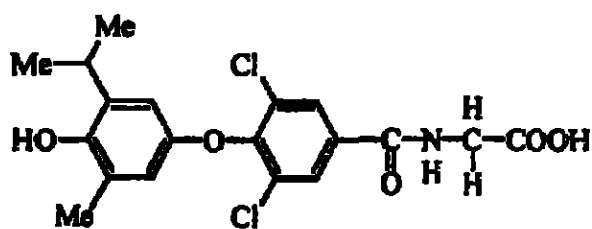
Además, de acuerdo con la actual invención, es proporcionado un método para la prevención, inhibición o tratamiento del avance o inicio de enfermedades o trastornos asociados con el receptor tiroideo, tales como las enfermedades o trastornos definidos anteriormente o a continuación, en donde una cantidad terapéuticamente efectiva de un compuesto con la fórmula I es administrado a un mamífero, e.g., un paciente humano en necesidad del tratamiento.

Los compuestos de la invención pueden ser usados solos, conjuntamente con otros compuestos de la presente invención o conjuntamente con otro(s) agente(s) activo(s) en las áreas terapéuticas aquí descritas.

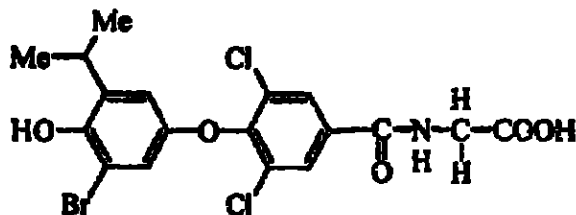
Adicionalmente, es proporcionado un método para la prevención, inhibición o tratamiento de enfermedades como las definidas anteriormente y a continuación, en donde una cantidad terapéuticamente efectiva de una combinación de un compuesto con la fórmula I y otro compuesto de la invención y/u otro tipo de agente terapéutico, es administrado a un paciente mamífero en necesidad del tratamiento.

Los compuestos de la invención incluyen, pero no están limitados a, los siguientes:

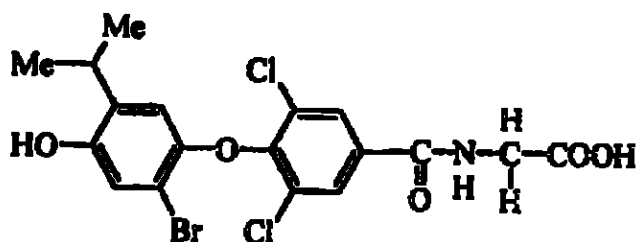
N-[3,5-Dicloro-4-(4-hidroxi-3-isopropil-5-metilfenoxi)benzoil] glicina (E1);



N-[3,5-Dicloro-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E2);



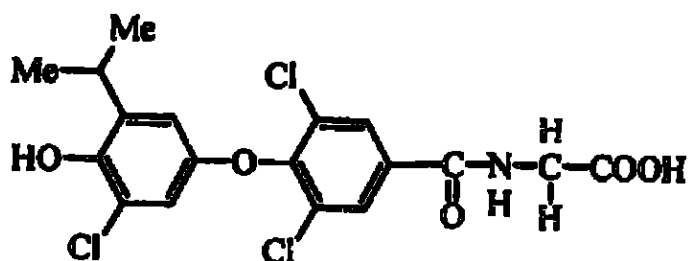
N-[3,5-Dicloro-4-(2-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E3);



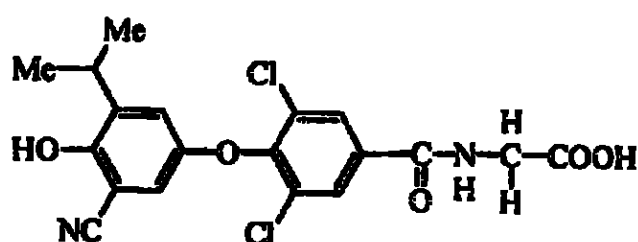
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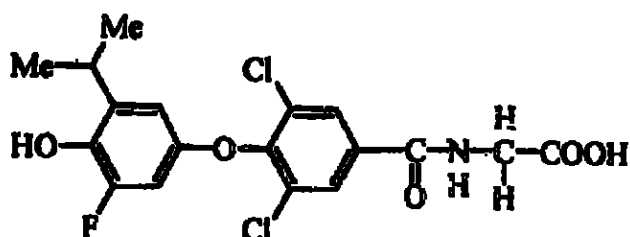
N-[3,5-Dicloro-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E4);



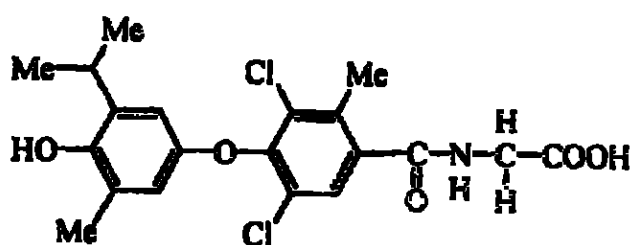
N-[3,5-Dicloro-4-(3-ciano-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E5);



N-[3,5-Dicloro-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E6);



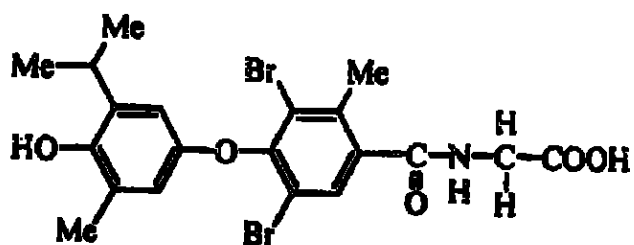
N-[3,5-Dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E7);



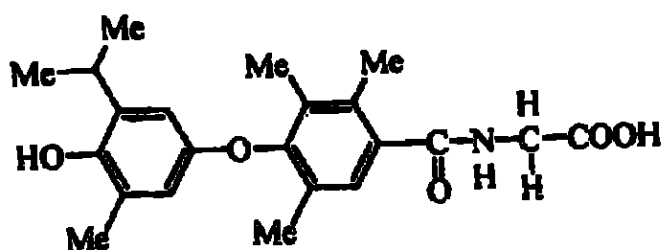
N-[3,5-Dibromo-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E8);

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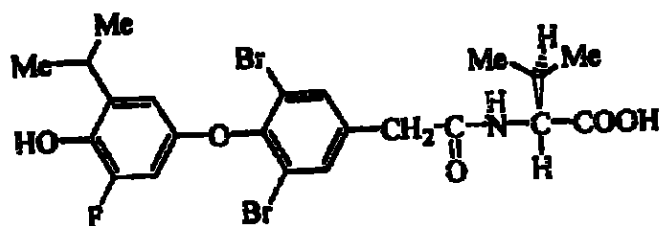
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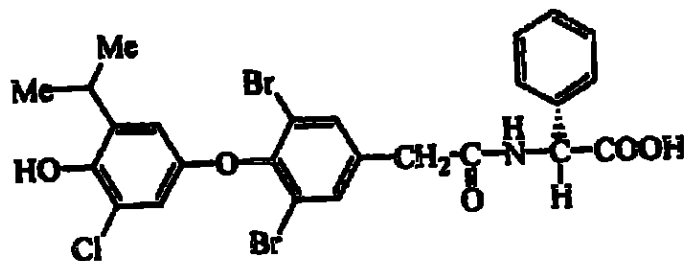
N-[3,5-Dimetil-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoksi)benzoil] glicina (E9);



L-N-[3,5-Dibromo-4-(3-fluoro-4-hidroxi-5-isopropilfenoksi)fenilacetil] valina (E10);



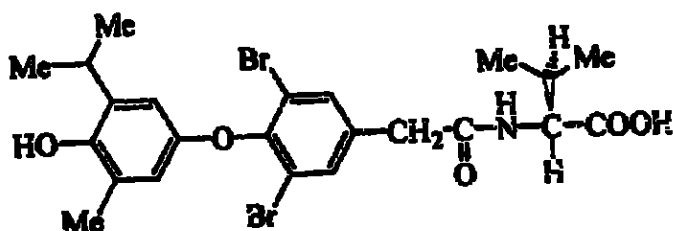
D-N-[3,5-Dibromo-4-(3-cloro-4-hidroxi-5-isopropilfenoksi)fenilacetil] fenilglicina (E11);



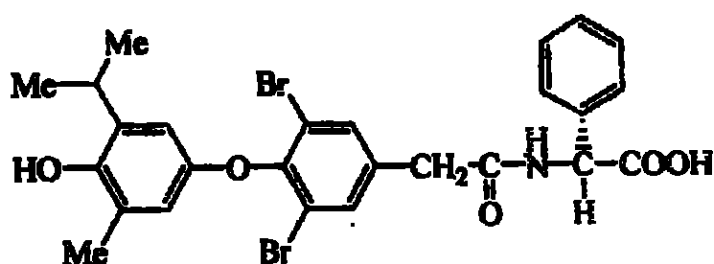
L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoksi)fenilacetil] valina (E12);

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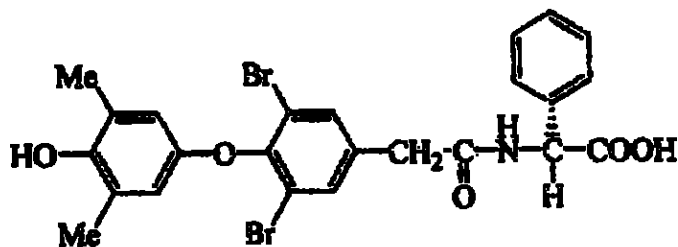
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L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] fenilglicina (E13);



L-N-[3,5-Dibromo-4-(3,5-dimetil-4-hidroxifenoxi)fenilacetil] fenilglicina (E14);



DESCRIPCIÓN DETALLADA DE LA INVENCION

Las siguientes definiciones aplican para los términos de acuerdo con su uso a través de esta especificación, a menos que sean limitados en otro sentido en instancias específicas.

El término "ligandos de receptores tiroideos" tal como es usado aquí es pensado para cubrir cualquier parte de una molécula, la cual se enlaza a un receptor tiroideo. El

ligando puede actuar como un agonista, un antagonista, un agonista parcial o un antagonista parcial. Otro término para "ligandos de receptores tiroideos" es "tiromimético".

A menos que otra cosa lo indique, el término "alquilo" tal como es empleado aquí solo o como parte de otro grupo incluye cadenas de hidrocarburos lineales y ramificadas, que contienen de 1 a 12 carbonos (en el caso de alquil o alqu), en la cadena normal preferiblemente de 1 a 4 carbonos, tales como metilo, etilo, propilo, isopropilo, butilo, t-butilo o isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetilpentilo, nonilo, decilo, undecilo, dodecilo. Como esta definido y reivindicado aquí, el término "alquilo" incluye grupos alquilo como los definidos anteriormente substituidos de manera opcional con 1 a 4 substituyentes los cuales pueden ser halógenos, como por ejemplo F, Br, Cl o I, o CF₃, alquilo, alcoxi, arilo, ariloxi, aril(aril) o diarilo, arilalquilo, arilalcoxi, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, cicloalquilalquilo, cicloalquilalcoxi, opcionalmente amino, hidroxilo, hidroxialquilo, acilo, oxo, alcanilo, heteroarilo, heteroariloxi, cicloheteroalquilo, arilheteroarilo, arilalcoxycarbonilo, heteroarilalquilo, heteroarilalcoxi, ariloxialquilo, ariloxiarilo, alquilamido, alcanilamino, arilcarbonilamino, alcoxycarbonilo, alquilaminocarbonilo, nitro, ciano, tiol, halogenuro de alquilo, trihalogenuro de alquilo, alquiltio o carboxilo (el alquiléster de este) substituidos.

A menos que otra cosa sea indicada, el término "cicloalquilo" como es empleado aquí solo o como parte de otro grupo incluye grupos de hidrocarburos cíclicos saturados o grupos de hidrocarburos cíclicos parcialmente insaturados (que contienen 1 o 2 dobles

enlaces), que contienen un anillo y un total de 3 a 8 carbonos, preferiblemente 3 a 6 carbonos, que forman un anillo. Como es definido y reivindicado aquí, el término "cicloalquilo" incluye grupos cicloalquilo como los definidos anteriormente substituidos de manera opcional con 1 o más substituyentes, tales como aquellos definidos para alquilo.

El término "arilo" o "Ar" como es empleado aquí solo o como parte de otro grupo se refiere a grupos aromáticos monocíclicos o bicíclicos que contienen de 6 a 10 carbonos en la fracción que forma parte del anillo (tales como fenilo o naftilo que incluye 1- naftilo y 2- naftilo). Como es definido reivindicado aquí, el término "arilo" incluye grupos arilo como los definidos anteriormente substituidos de manera opcional en cualquier átomo o átomos de carbono disponible(s) con uno a más substituyentes, tales como halógeno, alquilo, halogenuro de alquilo alcoxi, halogenuro de alcoxi, alquenilo, trifluorometilo, trifluorometoxi, alquinilo, hidroxilo, amino, nitro, ciano, carboxilo (o alquil éster de este) o cualquiera de los otros substituyentes descritos para alquilo.

A menos que otra cosa sea indicada, el término "heteroarilo" o "heteroaromático" como es empleado aquí solo o como parte de otro grupo se refiere a un anillo aromático de 5- o 6- miembros el cual incluye 1, 2, 3 o 4 hetero átomos tales como nitrógeno, oxígeno o azufre, y a tales anillos fusionados a un anillo arilo, cicloalquilo, heteroarilo, cicloheteroalquilo, (e.g. benzotiofenilo, indolilo), e incluye los N-óxidos posibles. Un grupo "heteroarilo substituido" incluye un grupo heteroarilo substituido de manera opcional con uno o mas substituyentes tales como cualquiera de los substituyentes del alquilo o arilo especificados anteriormente. Como es definido y reivindicado aquí, el

término "heteroarilo" incluye grupos heteroarilo como los definidos anteriormente substituidos de manera opcional en cualquier átomo o átomos de carbono disponible(s) con uno a más substituyentes, tales como cualquiera de los substituyentes descritos para alquilo o arilo.

A menos que otra cosa sea indicada, el término "alquenilo" como es empleado aquí por si mismo o como parte de otro grupo se refiere a una cadena de radicales lineales o ramificados de 2 a 20 carbonos, preferiblemente de 2 a 12 carbonos, y con mayor preferencia e 2 a 8 carbonos en la cadena normal, la cual incluye uno o mas dobles enlaces en la cadena normal, tales como vinilo, 2-propenilo, 3-butenilo, 2-butenilo, 4-pentenilo, 3-pentenilo, 2-hexenilo, 3-hexenilo, 2-heptenilo, 3-heptenilo, 4-heptenilo, 3-octenilo, 3-nonenilo, 4-decenilo, 3-undecenilo, 4-dodecenilo, 4,8,12-tetradecatrienilo y los similares. Como es definido y reivindicado aquí, el término "alquenilo" incluye grupos alquenilo como los definidos anteriormente substituidos de manera opcional en cualquier átomo o átomos de carbono disponible(s) con uno a más substituyentes, tales como cualquiera de los substituyentes descritos para alquilo o arilo.

A menos que otra cosa sea indicada, el término "alquinilo" como es empleado aquí por si mismo o como parte de otro grupo se refiere a una cadena de radicales lineales o ramificados de 2 a 20 carbonos, preferiblemente de 2 a 12 carbonos, y con mayor preferencia e 2 a 8 carbonos en la cadena normal, la cual incluye uno o mas triples enlaces en la cadena normal, tales como 2-propinilo, 3-butinilo, 2-butinilo, 4-pentinilo, 3-pentinilo, 2-hexinilo, 3-hexinilo, 2-heptinilo, 3-heptinilo, 4-heptinilo, 3-octinilo, 3-noninilo, 4-decinilo, 3-undecinilo, 4-dodecinilo y los similares. Como es definido y

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reivindicado aquí, el término "alquinilo" incluye grupos alquinilo como los definidos anteriormente substituidos de manera opcional en cualquier átomo o átomos de carbono disponible(s) con uno a más substituyentes, tales como cualquiera de los substituyentes descritos para alquilo o arilo.

El término "cicloalquenilo" como es empleado aquí solo o como parte de otro grupo se refiere a hidrocarburos cíclicos que contienen de 3 a 12 carbonos, preferiblemente de 5 a 10 carbonos y con 1 o dos dobles enlaces. Ejemplos de grupos cicloalquenilos incluyen ciclopentenilo, ciclohexenilo, ciclohexadienilo y cicloheptadienilo, los cuales pueden ser substituidos de manera opcional como se definió para cicloalquilo. Como es definido reivindicado aquí, el término "cicloalquenilo" incluye grupos cicloalquenilo como los definidos anteriormente substituidos de manera opcional en cualquier átomo o átomos de carbono disponible(s) con uno a más substituyentes, tales como cualquiera de los otros substituyentes descritos para alquilo o arilo.

El término "halógeno" o "halogenuro" como es empleado aquí solo o como parte de otro grupo se refiere a cloruro, bromuro, fluoruro y yoduro así como a CF_3 , siendo preferidos cloruro y bromuro.

El término "alcanoilo" como es empleado aquí solo o como parte de otro grupo es alquilo o cicloalquilo unido a un grupo carbonilo.

El término "aroilo" como es empleado aquí solo o como parte de otro grupo es arilo o heteroarilo unido a un grupo carbonilo.

A menos que otra cosa sea indicada, los términos "alcoxi", "ariloxi", "heteroariloxi" como son empleados aquí solos o como parte de otro grupo incluyen cualquiera de los grupos alquilo, arilo o heteroarilo señalados anteriormente que se encuentra unido a través de un átomo de oxígeno.

El término "ciano" como es empleado aquí, se refiere a un grupo -CN .

El término "arilalquilo" o "heteroarilalquilo" como es empleado aquí solo o como parte de otro grupo se refiere a grupos alquilo como los descritos anteriormente que tienen un arilo o heteroarilo como substituyentes. Ejemplos representativos de arilalquilo incluyen, pero no están limitados a bencilo, 2-feniletilo, 3-fenilpropilo.

A menos que otra cosa sea indicada, los términos "arilalcoxi" y "cicloalcoxi" como son empleados aquí solos o como parte de otro grupo incluyen grupos arilo y cicloalquilo que están unidos a través de un átomo de oxígeno.

EL término "ácido carboxílico" o "carboxilo", como es empleado aquí, se refiere al grupo -COOH .

El término "bencilo" como es empleado aquí se refiere a $\text{-CH}_2\text{C}_6\text{H}_5$, el cual puede estar opcionalmente substituido como se definió anteriormente para alquilo.

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Los compuestos con la fórmula I pueden ser presentados como sales, las cuales también están dentro del alcance de la presente invención. Son preferidas las sales farmacéuticamente aceptables (i.e., no-tóxicas, fisiológicamente aceptables). Si los compuestos de la fórmula I tienen, por ejemplo, al menos un centro básico, estos pueden formar sales con algún ácido adicionado. Estas son formadas, por ejemplo, con ácidos inorgánicos fuertes, tales como ácidos minerales, por ejemplo ácido sulfúrico, ácido fosfórico o un ácido halohídrico, con ácidos orgánicos carboxílicos fuertes, tales como ácidos alcano carboxílicos de 1 a 4 átomos los cuales pueden estar o no substituidos, por ejemplo, por un halógeno, por ejemplo ácido acético, tales como ácidos dicarboxílicos saturados o insaturados, por ejemplo ácido oxálico, malónico, succínico, maleico, fumárico, ftálico o tereftálico, tales como ácidos hidroxicarboxílicos, por ejemplo ácido ascórbico, glicólico, láctico, málico, tartárico o cítrico, tales como aminoácidos, (por ejemplo ácido aspártico o glutámico o lisina o arginina), o ácido benzoico, o con ácidos sulfónicos orgánicos, tales como ácido (C₁-C₄) alquil o arilsulfónicos los cuales no están o están substituidos con, por ejemplo halógeno, por ejemplo ácido metil- o p-toluen- sulfónico. La sal correspondiente del ácido adicionado también puede ser formada teniendo, si se desea, un centro básico adicional presente. Los compuestos con la fórmula I que tienen al menos un grupo ácido carboxílico (por ejemplo COOH) pueden también formar sales con bases. Sales convenientes con bases son, por ejemplo, sales de metales, tales como metales alcalinos o sales de metales alcalinotérreos, por ejemplo sales de sodio, potasio o magnesio, o sales con amoníaco o una amina orgánica tales como morfolina, tiomorfolina, piperidina, pirrolidina, una mono, di o tri-alquilamina de cadena corta, por ejemplo etil, terbutil, dietil, diisopropil, trietil, tributil o dimetil-propilamina, una mono, di o tri- hidroxil

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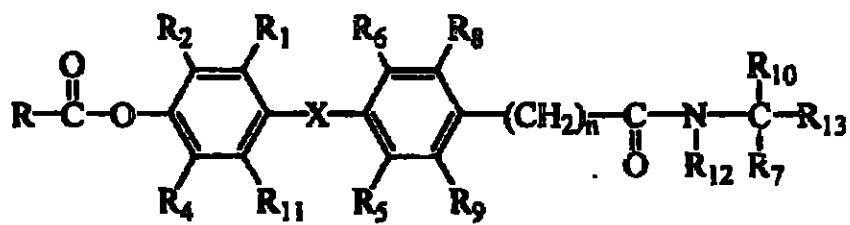
alquilamina de cadena corta, por ejemplo mono, di o trietanolamina. Además pueden ser formadas las sales internas correspondientes. También están incluidas, sales que son inadecuadas para usos farmacéuticos pero las cuales pueden ser empleadas, por ejemplo, para el aislamiento o purificación de compuestos puros con la fórmula I o sus sales farmacéuticamente aceptables. Sales preferidas de los compuestos con la fórmula I los cuales contienen un grupo básico incluyen monoclóhidrato, bisulfato, metanosulfonato, fosfato o nitrato. Sales preferidas de los compuestos con la fórmula I los cuales contienen un grupo ácido incluyen sales sodio, potasio y magnesio y aminas orgánicas farmacéuticamente aceptables.

Los compuestos con la fórmula I pueden estar también en forma de profármaco. Cualquier compuesto sea transformado in vivo para proporcionar el agente bioactivo (i.e. el compuesto con la fórmula I) es un profármaco incluido dentro del alcance y espíritu de la invención.

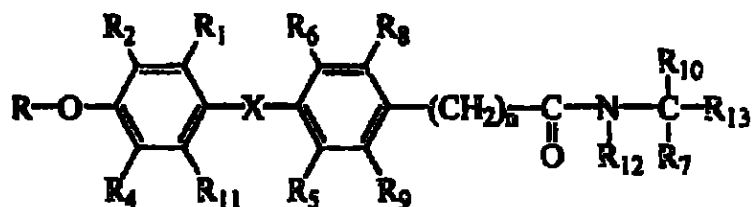
Varias formas de profármacos son bien conocidas en el estado del arte. Una amplia descripción de profármacos y derivados de profármacos puede ser encontrada en: (i) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Capítulo 31, (Academic Press, 1996); (ii) *Design of Prodrugs*, editado by H. Bundgaard, (Elsevier, 1985); y (iii) *A Textbook of Drug Design and Development*, P. Krogsgaard-Larson y H. Bundgaard, eds. Capítulo 5, pgs 113-191 (Harwood Academic Publishers, 1991). Dichas citas son incorporadas aquí por referencia.

Formas de ejecución de profármacos adecuadas para el uso dentro de la presente invención incluyen alquil ésteres de cadenas cortas, tales como etil ésteres, o aciloxialquil ésteres tales como pivaloiloximetil (POM) de un grupo ácido carboxílico para R₁₃.

Formas de ejecución de profármacos adecuadas para el uso dentro de la presente invención incluyen aquellos profármacos que enmascaran el grupo hidroxilo fenólico libre presente en la fórmula I, como se muestra en la estructura a continuación en donde en el profármaco está la fracción, R-CO, grupo aroilo o alcanilo, en la cual R es alquilo, heteroarilo o arilo.



Además, formas de ejecución de profármacos adecuadas para enmascarar el grupo hidroxilo fenólico discutida anteriormente incluyen éteres alquil fenólicos, tal como es representado en la estructura a continuación donde R = alquilo. La hidroxilación metabólica de el carbón de el grupo alquilo R que está unido al oxígeno fenólico da paso a un intermediario capaz de descomponerse aún más para dejar expuesta la forma de fenol libre que tienen los compuestos con la fórmula I.



Todos los estereoisómeros de los compuestos de la presente invención son contemplados, ya sea en forma de mezcla o puros o substancialmente puros. Los compuestos de la presente invención pueden tener centros asimétricos en cualquiera de los átomos de carbono incluyendo cualquiera de los sustituyentes R. En consecuencia, los compuestos de la fórmula I pueden existir en formar enantioméricas o diastereoméricas o en mezclas de estos. El proceso de preparación puede utilizar como materiales de partida racematos, enantiomeros o diastereomeros. Cuando son preparados productos diastereoméricos o enantioméricos, estos pueden ser separados mediante métodos convencionales por ejemplo, cromatográficos o cristalización fraccionada.

La administración de un agente terapéutico de la presente invención incluye la administración de cantidades terapéuticamente efectivas del agente de la invención. El término "cantidad terapéuticamente efectiva" como es empleado aquí se refiere a una cantidad de un agente terapéutico para tratar o prevenir una condición tratable mediante la administración de una formulación de la invención. Esta cantidad es la cantidad suficiente para exhibir un efecto terapéutico o preventivo o de mejoría perceptible. El efecto puede incluir, por ejemplo, el tratamiento o la prevención de las condiciones aquí enumeradas. La cantidad efectiva precisa para un sujeto dependerá del tamaño y salud del sujeto, la naturaleza y el grado de la condición que sea tratada,

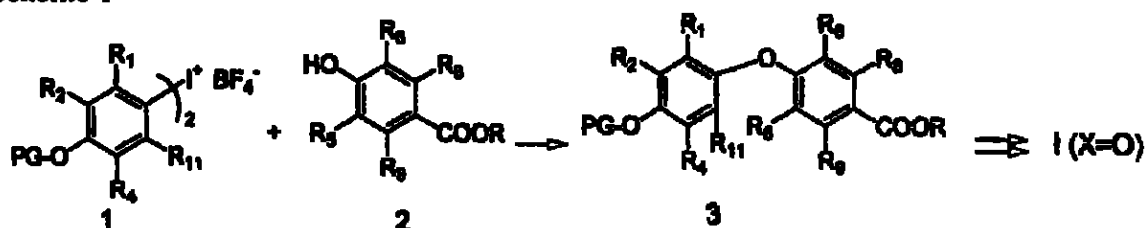
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las recomendaciones del médico que atiende el caso y del tratamiento terapéutico o combinación de tratamientos terapéuticos seleccionados para la administración. De tal forma, no resulta útil especificar una cantidad efectiva exacta por adelantado.

Los compuestos con la fórmula I pueden ser preparados mediante los procesos propuestos como ejemplos descritos en los siguientes esquemas de reacción, así como los procedimientos pertinentes publicados en la literatura que son utilizados por la persona calificada. Los reactivos y procedimientos demostrativos para estas reacciones aparecen a continuación y en los ejemplos de trabajo. La protección y desprotección en los siguientes esquemas abajo se pueden realizar mediante procedimientos conocidos de manera general en el estado del arte (ver, por ejemplo, T. W. Greene & P. G. M. Wuts, "Protecting Groups in Organic Synthesis", 3ra Edición, Wiley, 1999).

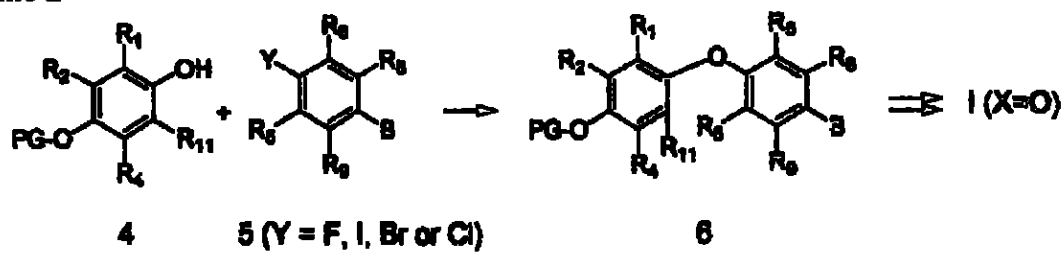
Scheme 1



La metodología de la sal de yodonio representada en el esquema 1 está ampliamente descrita en la literatura para la síntesis de análogos de la hormona de tiroidea ("Novel Thyroid Receptor Ligands and Methods", Y. -L. Li, Y. Liu, A. Hedfors, J. Malm, C. Mellin, M. Zhang, PCT Int. App. WO 9900353 A1 990107; D. M. B. Hickey et al., *J. Chem. Soc.*

Perkin Trans.1,3103-3111,1988; N. Yokoyama et al., *J. Med. Chem.*, 38, 695-707,1995), y para diaril éteres en general (E. A. Couladouros, V.1. Moutsos, *Tetrahedron Lett.*, 40, 7023-7026,1999). La reacción de la sal de yodonio 1 con un ácido hidroxí benzoico apropiado (intermediario 2) genera el diaril éter (producto 3) el cual puede ser convertido fácilmente por aquellos con el entrenamiento adecuado en el estado del arte en los compuestos con la fórmula I en los cuales X = O.

Scheme 2



El esquema 2 presenta otra aproximación sintética general a los compuestos con la fórmula I para los cuales X = O. Un fenol sustituido de manera apropiada 4 es alquilado con un intermediario apropiadamente sustituido 5, en el cual Y es un grupo saliente tal como fluoruro, cloruro, ioduro o bromuro y el grupo activante B es tal que activa el grupo Y favoreciendo el desplazamiento nucleofílico y es capaz de ser posteriormente transformado en un ácido carboxílico (tal como formilo (CHO) o nitro (NO₂)), para proporcionar el intermediario 6. Entonces el grupo activante B en el intermediario 6 es subsecuentemente transformado en un ácido carboxílico o un derivado que puede ser transformado entonces aún mas y convertido en los compuestos con la fórmula I para los cuales X = O. Tales grupos funcionales activantes y los métodos para su conversión son bien conocidos por los expertos en la materia.

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Por ejemplo, cuando B es la función nitro en el intermediario 6, el grupo nitro puede ser reducido a un grupo amino por los métodos bien conocidos en el estado del arte, tales como el uso de hidrogenación catalítica en la presencia de, por ejemplo, níquel Raney o catalizador de paladio soportado en carbón activado, en un solvente polar tal como ácido acético glacial o etanol. Alternativamente, la reducción se puede llevar a cabo usando hierro en polvo en ácido acético glacial acuoso a temperatura ambiente. La anilamina resultante puede ser convertida a la sal de diazonio correspondiente mediante el uso de, por ejemplo, una mezcla del nitrito de sodio y ácido sulfúrico en solventes apropiados. El grupo diazonio resultante puede ser convertido entonces en un grupo formilo (CHO) por la reacción con monóxido de carbono catalizada por un catalizador de paladio apropiado tal como acetato de paladio. Después de unirse al intermediario 5, la protección del grupo y la manipulación funcional del grupo subsecuentes proporciona los compuestos objetivo con la fórmula I en los cuales $X = O$. Otro grupo activante es el formilo ($B = -CHO$). Después de acoplarse al segundo anillo aromático, el grupo aldehído puede ser oxidado a ácido carboxílico, y entonces ser convertido en los compuestos de la fórmula I en los cuales $n = 0$. Además, el mismo ácido carboxílico resultante puede ser homologado para obtener un grupo ácido acético mediante métodos bien conocidos tales como la homologación de Arndt-Eistert para proporcionar en última instancia ejemplos de I para los cuales $n = 1$. La aproximación presentada en el esquema 2 para la síntesis general de diaril éteres para tiromiméticos cuenta con suficientes precedentes en la literatura (P. D. Leeson, J. C. Emmett, *J. Chem. Perkin Trans. I*, 3085-3096, 1988; N. Yokoyama et al., *J. Med. Chem.*, 38, 695-707, 1995).

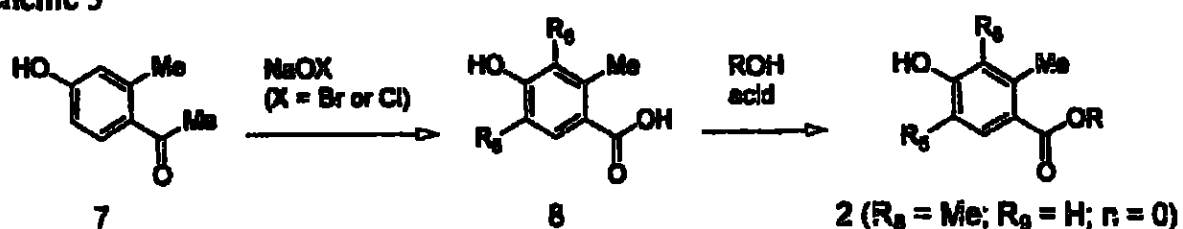
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Otros métodos para la síntesis de compuestos con la fórmula I en los cuales X = O, NH, S, CO o CH₂ están descritos de forma general en la literatura (para X = O : D. M. B. Hickey et al., *J. Chem. Soc. Perkin Trans. I*, 3097-3102, 1988 ; Z. -W. Guo et al., *J. Org. Chem.*, 62, 6700-6701, 1997; D. M. T. Chan et al. , *Tetrahedron Lett.*, 39, 2933-2936, 1998 ; D. A. Evans et al., *Tetrahedron Lett.*, 39, 2937-2940, 1998; G. M. Salamonczyk et al., *Tetrahedron Lett.*, 38, 6965-6968, 1997; J.-F. Marcoux, *J. Am. Chem. Soc.*, 119, 10539-10540, 1997; A. V. Kalinin et al., *J. Org. Chem.*, 64, 2986-2987, 1999; para X = N: D. M. T. Chan et al., *Tetrahedron Lett.*, 39, 2933-2936, 1998; J.P. Wolfe et al., *J. Am. Chem. Soc.*, 118, 7215, 1996; M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.*, 118, 7217, 1996; ver referencias en la revisión de C. G. Frost, P. Mendonca, *J. Chem. Soc. Perkin I*, 2615-2623, 1998; para X = S: C. R. Harrington, *Biochem. J.*, 43, 434-437, 1948; A. Dibbo et al., *J. Chem. Soc.*, 2890-2902, 1961; N. Yokoyama et al., United States Patent 5,401,772, 1995; for X = CO o CH₂: L. Homer, H. H. G. Medem, *Chem. Ber.*, 85, 520-530, 1952; G. Chiellini et al., *Chemistry & Biology*, 5, 299-306, 1998; y para X = CF₂, ver G. S. Lal et al., *J. Org. Chem.*, 65, 4830-4832, 2000.

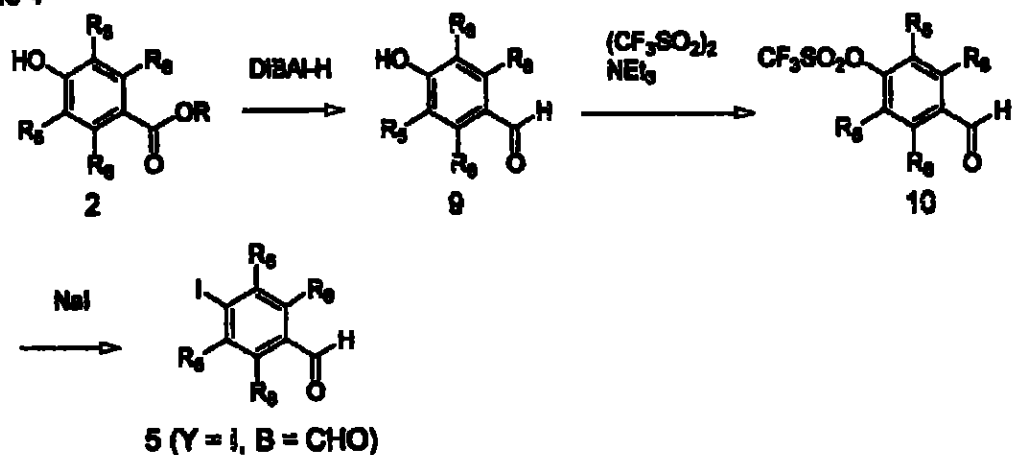
Métodos aplicables para la síntesis de compuestos con la fórmula I en los cuales X = O y R₂ y R₃ son modificados independientemente con hidrógeno, halógeno y alquilo son descritos en "Novel Thyroid Receptor Ligands and Methods, Y.-L. Li, Y. Ull, A. Hedfors, J. Malm, C. Mellin, M. Zharng, PCT Int. App. WO 9900353 A1 990107.

Scheme 3



El esquema 3 describe la síntesis del intermediario 2 en la cual $R_5 = R_6 = \text{Br o Cl}$, $R_8 = \text{Me}$, $R_9 = \text{H}$, $R = \text{H}$ y $n = 0$. La acetofenona 7 (comercialmente disponible) es sujeta a las condiciones de la reacción del haloformo con el hipoclorito o el hipobromito de sodio para convertir simultáneamente la función del acetilo a carboxilo y para halogenar las dos posiciones orto al grupo hidroxilo fenólico. La esterificación da el intermedio objetivo 2 que es empleado en la química descrita en el esquema 4.

Scheme 4



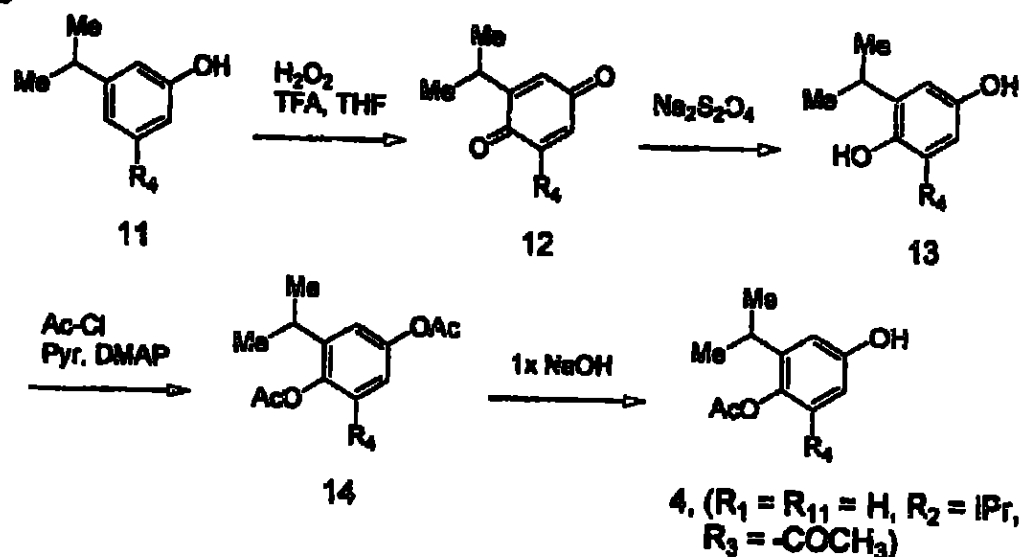
El esquema 4 describe el uso del intermediario 2 para la síntesis del intermediario 5 en la cual $Y = \text{I}$ y $B = \text{CHO}$. El éster, intermediario 2, es reducido al aldehído 9 mediante agentes reductores tales como hidruro de diisobutil aluminio (DIBAL-H). El compuesto 9

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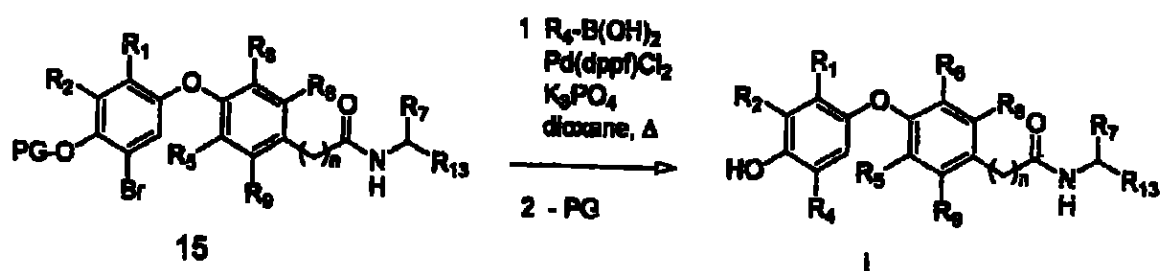
es convertido al triflato 10 por el uso del anhídrido triflico y una amina orgánica básica tal como trietilamina. La reacción del triflato 10 con yoduro de sodio genera el aril yoduro aldehído 5 objetivo que puede ser utilizado en la química descrita anteriormente en el esquema 2.

Scheme 5



El esquema 5 describe la síntesis del intermediario 4 en la cual R_1 y $R_{11} = H$, $R_2 =$ isopropilo y R_3 es un grupo acetilo protector ($-COCH_3$). El fenol 11 es oxidado a la quinona 12, que durante la reducción con hidrosulfito de sodio ($Na_2S_2O_4$) es convertido en la hidroquinona 13. La acetilación de 13 bajo condiciones estándares da el bis-acetato 14 que genera el compuesto objetivo deseado 4 después del tratamiento con 1 equivalente de hidróxido de sodio para remover el grupo acetato menos impedido para generar le compuesto 4 el cual puede ser utilizado en la química descrita anteriormente en el esquema 2.

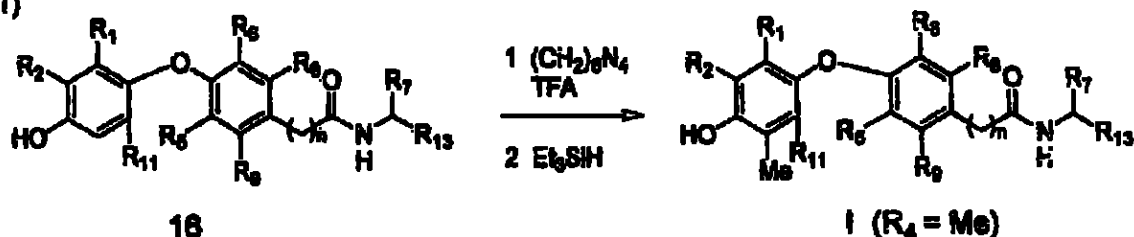
Scheme 6



El esquema 6 describe una aproximación para la síntesis de los compuestos con fórmula I en los cuales el grupo R₄ es un grupo alquilo de cadena corta, tal como metilo o etilo. El bromuro de arilo, intermediario 15, es obtenido mediante la bromación del fenol libre correspondiente (R₃ = OH; obtenido por procedimientos tales como los descritos en el esquema 1 y el esquema 2), seguida por la instalación de un grupo protector (PG) en el hidroxilo fenólico. El grupo R₄ es introducido acoplando el bromuro de arilo, intermediario 15, con un ácido alquil borónico en presencia de un catalizador de paladio apropiado, tal como [1, 1'-bis(difenilfosfino)-ferroceno] dicloro paladio (II) (Harada et al, *Synlett*, 1995, 283). El bromuro de arilo, intermediario 15, puede ser substituido por el yoduro de arilo o el aril triflato correspondiente y llevar a cabo la misma transformación.

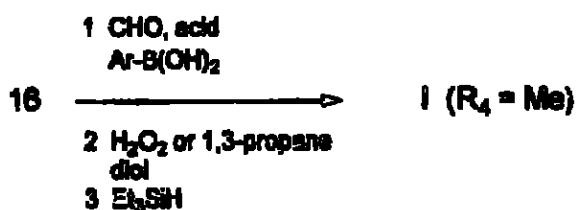
Scheme 7

(7.1)



(7.2)

Alternatively



El esquema 7 presenta dos procedimientos para la introducción específica de un grupo metilo en la posición R_4 . Ambos métodos proceden mediante (1) la hidroximetilación en la posición orto al grupo hidroxilo (R_3) en el intermediario 16 (obtenido siguiendo procedimientos tales como aquellos descritos en los esquemas 1 y 2), seguido por (2) la reducción del grupo hidroximetilo a metilo usando un reactivo tal como trietilsilano. En la reacción 7.1. la hidroximetilación es llevada a cabo mediante el uso de hexametilentetramina en presencia de ácido trifluoroacético. En la reacción 7.2. el paso de hidroximetilación es promovido mediante el uso de ácido bécen borónico el cual acompleja el aducto inicial en la forma de un intermediario dioxaborino. El compuesto hidroximetilado objetivo es liberado por el intercambio con etilenglicol o la reacción con peróxido de hidrógeno (Nagata et al, *Synthesis*, 1979, 385).

A continuación son enunciados otros métodos que son conocidos por personas con la experiencia estándar en el estado del arte, para la inserción de un grupo metilo en un anillo aromático. (1) los bromuros de arilo y yoduros de arilo pueden ser metilados por

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el tratamiento con Me_4Sn (tetrametilestano) en presencia de catalizador de paladio (*Tet Lett*, 1999, 40.2719-2722); (2) los aril triflatos son metilados por el tratamiento con Me_3In (trimetilindio) en presencia de catalizador de paladio (*Org Lett*, 1999, 1, 1267-1269); (3) los aril triflatos son convertidos a compuestos aril metílicos por el tratamiento con Me_3Al (trimetilaluminio) en la presencia de catalizador de paladio; (4) los aril triflatos también son metilados por el tratamiento con el ácido metil borónico en la presencia de catalizador de paladio (Synlett, 1995, 283-284).

USOS Y COMBINACIONES

USOS: Los compuestos de la presente invención son ligandos de receptores tiroideos, e incluyen los compuestos que son, por ejemplo, agonistas selectivos, agonistas parciales, antagonistas o antagonistas parciales del receptor tiroideo. Preferiblemente los compuestos de la presente invención poseen actividad como agonistas del receptor tiroideo, preferiblemente agonistas selectivos del receptor tiroideo-beta, y pueden ser utilizados en el tratamiento de enfermedades o trastornos asociados con la actividad del receptor tiroideo. En particular, los compuestos de la presente invención pueden ser

utilizados en el tratamiento de enfermedades o trastornos asociados con una disfunción del metabolismo o que dependen de la expresión de un gen regulado por T₃.

De acuerdo con lo anterior, los compuestos de la presente invención pueden ser administrados a mamíferos, preferiblemente seres humanos, para el tratamiento de una variedad de condiciones y trastornos, que incluyen, pero no están limitados al hipotiroidismo; hipertiroidismo subclínico; bocio no tóxico; aterosclerosis; la terapia de reemplazo de la hormona tiroidea (e. g., en ancianos); la presencia de células de tumor maligno contenidas en el receptor tiroideo; cáncer papilar o folicular; el mantenimiento de la fuerza y función muscular (e. g., en ancianos); la revocación o prevención de debilidad o disminución funcional relacionada con la edad ("ARFD" por sus siglas en ingles) en los ancianos (e. g., sarcopenia); el tratamiento de efectos catabólicos secundarios de glucocorticoides; la prevención y/o tratamiento de la reducción de la masa, densidad o crecimiento óseo (e. g., osteoporosis y osteopenia); el tratamiento del síndrome de fatiga crónica (SFC); la aceleración de la curación de fracturas complicadas, e. g., distracción osteogénica; el reemplazo de articulaciones; trastornos alimenticios (e. g., anorexia); el tratamiento de la obesidad y retrasos en el crecimiento asociados con obesidad; el tratamiento de la depresión, nerviosismo, irritabilidad y estrés; el tratamiento de la disminución de la energía mental y de la baja autoestima (e. g., motivación/asertividad); el mejoramiento de la función cognoscitiva (e. g., el tratamiento de la demencia, incluyendo la enfermedad de Alzheimer y pérdidas temporales de la memoria); el tratamiento de catabolismo relacionado con disfunción pulmonar y dependencia ventilatoria; el tratamiento de disfunción cardíaca (e. g.,

asociado con una enfermedad valvular, infarto miocárdico, hipertrofia cardíaca o insuficiencia cardíaca congestiva); la disminución de la presión arterial; la protección contra la disfunción ventricular o prevención de eventos de repercusión; el tratamiento de hiperinsulinemia; la simulación de osteoblastos, la remodelación ósea y el crecimiento cartilaginoso; la regulación de la ingesta de alimentos; el tratamiento de la resistencia de insulina, incluyendo NIDDM, en mamíferos (e. g., humanos); el tratamiento de la resistencia de insulina en el corazón; tratamiento de la insuficiencia cardíaca congestiva; el tratamiento de la deficiencia musculoesquelética (e. g., en ancianos); el mejoramiento de la función pulmonar global; enfermedades o trastornos en la piel, tales como atrofia dérmica inducida por glucocorticoide, incluyendo la restauración de la atrofia dérmica inducida por glucocorticoides tópicos y la prevención de atrofia dérmica inducida por los glucocorticoides tópicos (tales como el tratamiento simultáneo con glucocorticoide tópico o un producto farmacológico incluyendo glucocorticoide y un compuesto de la presente invención), la restauración/prevención de atrofia dérmica inducida por el tratamiento sistémico con glucocorticoides, la restauración/prevención de atrofia en el sistema respiratorio inducida por tratamientos locales con glucocorticoides, atrofia dérmica inducida por radiación UV, atrofia dérmica inducido por envejecimiento (arrugas, etc.), cicatrización de heridas, queloides, estrías, celulitis, piel áspera, daños actínicos de la piel, liquen plano, ictiosis, acné, soriasis, la enfermedad de Demier, eccema, dermatitis atópica, cloracne, pitiriasis y cicatrices en la piel.

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El término tratamiento es también previsto para incluir tratamientos profilácticos. Adicionalmente, las condiciones, enfermedades y trastornos referidos colectivamente como el "Síndrome X" o Síndrome Metabólico según lo detallado en Johannsson J. *Clin. Endocrinol. Metab.*, 82, 727-34 (1997), pueden ser tratadas empleando los compuestos de la invención.

COMBINACIONES: La presente invención incluye dentro de su alcance formulaciones farmacéuticas que contienen, como ingrediente activo, una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la fórmula I, solo o combinado con un vehículo o un diluyente farmacéutico. Opcionalmente, los compuestos de la presente invención pueden ser utilizados solos, combinados con otros compuestos de la invención, o combinados con otro u otros agentes(s) terapéutico(s), e.g., un agente anti-diabético u otro material farmacéuticamente activo.

Los compuestos de la presente invención pueden ser empleados en combinación con otros moduladores y/o los ligandos de los receptores tiroideos u otros agentes terapéuticos convenientes útiles en el tratamiento de los desórdenes ya mencionados incluyendo: agentes anti-diabéticos; agentes anti-osteoporosis; agentes anti-obesidad; agentes promotores de crecimiento (incluyendo secretagogos de la hormona de crecimiento); agentes anti-inflamatorios; agentes anti-ansiedad; anti-depresivos; agentes anti-hipertensivos; glicósidos cardíacos; agentes reductores de colesterol/lípido;

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supresores de apetito; inhibidores de la resorción ósea; miméticos tiroideos (incluyendo otros agonistas de receptores tiroideos); agentes anabólicos y agentes antitumorales.

Ejemplos de agentes anti-diabéticos convenientes para el uso combinado con los compuestos de la presente invención incluyen biguanidas (e. g., metformina o fenformina), inhibidores de la glucosidasa (e. g. acarbosa o miglitol), insulinas (incluyendo secretagogos de insulina o sensitizadores de insulina), meglitinidas (e. g., repaglinida), sulfonilureas (e. g., glimepirida, gliburida, gliclazida, clorpropamida y glipizida), combinaciones de biguanida/gliburida (e. g., Glucovance®), tiazolidindionas (e. g., troglitazona, rosiglitazona y pioglitazona), agonistas de la PPAR-alfa, agonistas de la PPAR-gama, agonistas duales PPAR alfa/gama, inhibidores del SGLT2, inhibidores de la glicógeno forforilasa, inhibidores de la proteína enlazante de ácido graso (aP2), péptido-1 similar al glucagón (GLP-1, por sus siglas en inglés), y los inhibidores de la dipeptidil peptidasa IV (DP4).

Ejemplos de agentes anti-osteoporosis convenientes para el uso combinado con los compuestos de la presente invención incluyen alendronato, risedronato, PTH, fragmentos de PTH, raloxifeno, calcitonina, antagonistas ligando RANK (receptor activador del factor nuclear Kappa B), antagonistas del receptor detector de calcio, inhibidores de la TRAP (fosfatasa ácida tartrato resistente), moduladores selectivos del receptor estrogénico (SERM, por sus siglas en inglés) e inhibidores AP-1.

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Ejemplos de agentes anti-obesidad convenientes de la para el uso combinado con los compuestos de la presente invención incluyen inhibidores $\alpha P2$, antagonistas de la PPAR gama, agonistas de la PPAR delta, agonistas de los adrenérgicos beta 3, tales como AJ9677 (Takeda/Dainippon), L750355 (Merck), o CP331648 (Pfizer) u otros agonistas beta 3 conocidos como los divulgados en las Patentes de Estados Unidos Nos. 5,541, 204, 5,770,615, 5,491,134, 5,776,983 y 5,488,064, un inhibidor de la lipasa, tal como orlistat o ATL-962 (Alyzime), un inhibidor de la recaptación de la serotonina (y dopamina), tal como sibutramina, topiramato (Johnson y Johnson) o axokina (Regeneron), otros medicamentos del receptor beta de la tiroides, tales como ligandos de receptores tiroideos como los divulgados en WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) y GB98/284425 (KaroBio), antagonistas CB-1 (receptor cannabinoide) (ver G. Colombo et al, *"Appetite Suppression and Weight Loss After the Cannabionid Antagonist SR 141716"*, Life Sciences, Vol 63, PL 113-117(1998)) y/o un agente anoréxico, tal como dexamfetamina, fentermina, fenilpropanolamina o mazindol.

Los compuestos de la presente invención pueden ser combinados con agente promotores de crecimiento, tales como, pero no limitado a, TRH, dietilestilbesterol, teofilina, encefalinas, prostaglandinas de la serie de E, los compuestos divulgados en la Patente de Estados Unidos No. 3,239, 345, e. g., zeranol, y los compuestos divulgados en la Patente de Estados Unidos No. 4,036, 979, e. g., sulbenox o los peptides divulgados en la Patente de Estados Unidos No. 4,411, 890.

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Los compuestos de la invención pueden ser también utilizados combinados con secretagogos de la hormona del crecimiento tales como GHRP-6, GHRP-1 (según lo descrito en la Patente de Estados Unidos 4,411,890 y las publicaciones WO89/07110 y WO 89/07111), GHRP-2 (según lo descrito en WO 93/04081), NN703 (Novo Nordisk), LY444711(Lilly), MK-677 (Merck), CP424391 (Pfizer) y B-HT920, o con el factor que libera la hormona de crecimiento y sus análogos o somatomedinas que incluyen IGF-I y IGF-2, o con los agonistas de los alfa-adrenérgicos, tales como agonistas de clonidina o serotonina 5-HT_D, tales como sumatriptano, o agentes que inhiban la somatostatina o su liberación, tales como fisostigmina y piridostigmina. Inclusive otro uso adicional de los compuestos divulgados en esta invención es su combinación con la hormona paratiroidea, PTH(1-34) o bisfosfonatos, tales como MK-217 (alendronato).

Inclusive otro uso adicional de los compuestos divulgados en esta invención es su combinación con estrógeno, testosterona, un modulador selectivo del receptor estrogénico, por ejemplo tamoxifen o raloxifeno, u otros moduladores de receptores androgénicos, tales como aquellos divulgados en Edwards, J. P. et al., *Bio Med. Chem. Let.*, 9.1003-1008 (1999) y Hamann, L. G. et al., *J. Med. Chem.*, 42, 210- 212 (1999).

Otro uso de los compuestos de esta invención es su combinación con los agonistas esteroideal o no esteroideal del receptor de la progesterona ("PRA", por sus siglas en ingles), por ejemplo el levonorgestrel, acetato de medroxiprogesterona (MPA).

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Los ejemplos de los agentes anti-inflamatorios convenientes para el uso combinado con los compuestos de la presente invención incluyen prednisona, dexametasona, Enbrel® (D), inhibidores de la cyclooxygenasa (i.e., inhibidores COX-I y/o COX-2, tales como NSAIDs, aspirina, indometacina, ibuprofeno, piroxicam, Naproxen®, Celebrex®, Vioxx®), agonistas/antagonistas de la CTLA4-Ig, antagonistas ligandos de CD40, inhibidores de la IMPDH, tales como micofenolato (CellCept®), antagonistas de la integrina, antagonistas de la integrina alfa-4 beta-7, inhibidores de la adhesión celular, antagonistas del gama interferón, ICAM-1, antagonistas del factor de necrosis tumoral (TNF, por sus siglas en ingles) (e. g., infliximab, OR1384), inhibidores de síntesis de prostaglandina, budesonida, clofazimina, CNI-1493, antagonistas CD4 (e. g., priliximab), inhibidores de los mitógenos p38 que activan la proteína quinasa, inhibidores de la proteína tirosina quinasa (PTK por sus siglas en ingles), inhibidores de la IKK, y las terapias para el tratamiento del síndrome intestino irritable (e. g., Zelmac® y Maxi-K® agentes de apertura tales como los divulgados en la Patente de Estados Unidos No. 6,184,231 B1).

Ejemplos de agentes anti-ansiedad convenientes para el uso combinado con los compuestos de la presente invención incluyen diazepam, lorazepam, buspirona, oxazepam y pamoato de hidroxicina.

Ejemplos de anti-depresivos convenientes para el uso combinado con los compuestos de la presente invención incluyen el citalopran, fluoxetina, nefazodona, sertralina y paroxetina.

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Para el tratamiento de trastornos o enfermedades de la piel como los descritos anteriormente, los compuestos de la presente invención pueden ser utilizados solos u opcionalmente en combinación con un retinoide, tal como tretinoína, o un análogo de la vitamina D.

Ejemplos de agentes anti-hipertensivos convenientes para el uso combinado con los compuestos de la presente invención incluyen a bloqueadores beta adrenérgicos, bloqueadores del canal del calcio (tipo-L y tipo-T; e.g. diltiazem, verapamil, nifedipina, amlodipina y mibefradil), diuréticos (e.g., clorotiacida, hidroclorotiacida, flumetiácida, hidroflumetiácida, bendroflumetiácida, metilclorotiacida, triclormetiácida, politiacida, benztiácida, ácido etacrínico, tricinafeno, clortalidona, furosemida, musolimina, bumetanida, triamtrenona, amilorida, espironolactona), inhibidores de la renina, inhibidores de la ACE (e. g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), antagonistas del receptor AT-1 (e. g., losartan, irbesartan, valsartan), antagonistas del receptor ET (e. g., sitaxsentan, atrsentan y los compuestos divulgados en las Patentes de Estados Unidos. 5,612,359 y 6,043,265), antagonista dual de ET/AlI (e. g., compuestos divulgados en WO 00/01389), inhibidores de la endopeptidasa neutral (NEP, por sus siglas en inglés), inhibidores del vasopepsidasa (inhibidores duales NEP-ACE) (e.g., omapatrilat y gemopatrilat), y nitratos.

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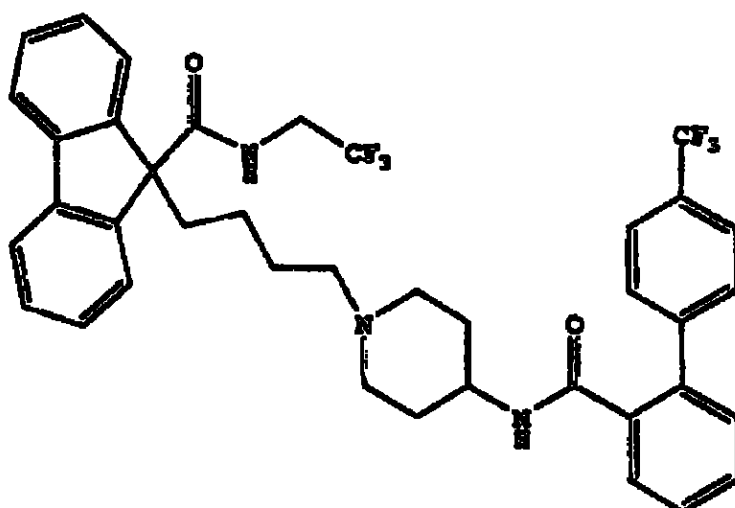
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Ejemplos de glicósidos cardíacos convenientes para el uso combinado con los compuestos de la presente invención incluyen la digitalis y ouabaina.

Ejemplos de agentes reductores de colesterol/lípido convenientes para el uso combinado con los compuestos de la presente invención incluyen inhibidores de la HMG-CoA reductasa, inhibidores de la esqualeno sintetasa, fibratos, secuestrantes de ácido biliar, inhibidores de la ACAT, inhibidores de la MTP, los inhibidores del lipooxigenasa, inhibidores del co-transportador ileal de Na⁺/ácido biliar, inhibidores absorción del colesterol, y los inhibidores de proteínas de transferencia de ésteres de colesterol (e. g., CP-529414).

Inhibidores de la MTP que pueden ser empleados en combinación con uno o más compuestos con la fórmula I incluyen inhibidores de la MTP como los divulgados en las Patentes de Estados Unidos No. 5,595, 872; 5,739, 135; 5,712, 279; 5,760, 246; 5,827, 875; 5,885, 983 y 5,962, 440 todos incorporados aquí por referencia.

Un inhibidor de la MTP preferido es 9-[4-[4-[2-(2,2-Trifluoroetoxi) benzoil]amino]-1-piperidinil] butil]-N-(2,2,2-trifluoroetil)-9H-fluoreno-9-carboxamida:



Inhibidores de la HMG CoA reductasa que pueden ser empleados en combinación con unos o más compuestos con la fórmula I incluyen mevastatina y compuestos relacionados como los divulgados en la Patente de Estados Unidos No. 3,983,140, lovastatina (mevinolina) y compuestos relacionados como los divulgados en la Patente de Estados Unidos No. 4,231,938, pravastatina y compuestos relacionados tales como los divulgados en la Patente de Estados Unidos No. 4,346,227, simvastatina y compuestos relacionados como los divulgados en las Patentes de Estados Unidos Nos. 4,448,784 y 4,450,171. Otros inhibidores de la HMG CoA reductasa que pueden ser empleados aquí incluyen fluvastatina, divulgada en la Patente de Estados Unidos No. 5,354,772, cerivastatina divulgada en las Patentes de Estados Unidos Nos. 5,006,530 y 5.177,080, atorvastatina divulgada en las Patentes de Estados Unidos Nos. 4,681,893, 5, 273,995, 5,385,929 y 5,686,104, análogos del pirazol de derivados de mevalonolactona como los divulgados en la Patente de Estados Unidos No. 4,613, 610, análogos del indeno de derivados de mevalonolactona, como los divulgados en la solicitud PCT WO 86/03488, 6-[2-(pirrol-1-il-substituidos)-alquil]piran-2-onas y derivados

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de estos, como los divulgados en la Patente de Estados Unidos No. 4,647,576, SC-45355 (un derivado del ácido pentanodioico 3-substituido) dicloroacetato de Searle, análogos del imidazole de derivados de mevalonolactona, como los divulgados en la solicitud PCT WO86/07054, derivados del ácido 3-carboxi-2-hidroxi-propano-fosfónico, como los divulgados en la Patente Francesa No. 2.596,393, derivados de pirrol 2,3-disubstituido, furano y tiopheno, como los divulgados en la solicitud de Patente Europea No. 0221025, análogos del naftaleno de derivados de mevalonolactona, como los divulgados en las Patentes de Estados Unidos No. 4,686,237, octahidronaftalenos, tales como los divulgados en las Patentes de Estados Unidos No. 4,499, 289, análogos ceto derivados de la mevinolina (lovastatina), como los divulgados en la solicitud de Patentes de Europea No. 0,142.146 A2, así como otros inhibidores conocidos de la HMG CoA reductasa.

Inhibidores de la escualeno sintetasa que pueden ser utilizados en combinación con los compuestos de la presente invención que incluyen, pero no se limitan a, los α -fosfono-sulfonatos- como los divulgados en la Patente de Estados Unidos No. 5,712,396, aquellos divulgados por Biller et al., *J. Med. Chem*, 1988, vol. 31, No. 10, p. 1869-1871, incluyendo fosfonatos isoprenoides (fosfinilmetil), pirofosfatos terpenoides como los divulgados por P. Ortiz de Montellano et al., *J. Med. Chem.*, 1977, 20, 243-249, análogo A del farnesil difosfato y análogos del preescualeno pirofosfato (PSQ-PP) como los divulgados por Corey y Volante, *J. Am. Chem. Soc.*, 1976.98, 1291-1293, fosfinilfosfonatos reportados por McClard, R. W. et al., *J. A. C. S.*, 1987.109, 5544 y ciclopropanes reportados por Capson, T. L., tesis de Doctorado, junio de 1987, Dept.

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Med. Chem. U of Utah, resumen, tabla de contenido, pg. 16, 17, 40-43, 48-51, así como otros inhibidores de la escualeno sintetasa como los divulgados en las Patentes de Estados Unidos No. 4,871,721 y 4,924,024 y en Biller, S. A., Neuenschwander, K., Ponpipom, M. M., y Poulter, C. D., Current Pharmaceutical Design, 2.1-40 (1996).

Secuestrantes de ácidos biliares que pueden ser utilizados en combinación con los compuestos de la presente invención incluyen colestiramina, colestipol y DEAE-Sefadex (Secholex®, Policexide®), así como lipostabil (Rhone-Poulenc), Eisai E-5050 (un derivado n-sustituido de la etanolamina), imanixil (HOE-402), tetrahidrolipstatina (THL), istigmastanilfos-forilcolina (SPC, Roche), aminociclodextrina (Tanabe Seiyoku), Ajinomoto AJ-814 (derivado del azuleno), melinamida (Sumitomo), Sandoz 58-035, CL-277,082 y CL-283,546 American Cyanamid (derivados disustituidos de la urea), ácido nicotínico, acipimox, acifran, neomicina, ácido p-aminosalicílico, aspirina, derivados del poli(dialilmetilamina) tales como los divulgados en las Patentes de Estados Unidos No. 4.759,923, la sal de amonio cuaternaria poli(dialildimetil cloruro de amonio) y ionenos tales como los divulgados en la Patente de Estados Unidos No. 4,027,009 y otros agentes conocidos que reducen el colesterol en el suero.

Inhibidores de la ACAT que pueden ser empleados en combinación con unos o más compuestos con la fórmula I incluyen los inhibidores de la ACAT como los descritos en, *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",

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Nicolosi et al., *Atherosclerosis* (Shannon, Ireland). (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 ApoB 100-containing lipoprotein", Ghiselli, Giancarlo, *Cardiovasc. Drug Rev.* (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al., *Bioorg. Med. Chem. Lett.* (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al., Editor(es): 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.

Ejemplos de inhibidores de la absorción del colesterol convenientes para el uso combinado con los compuestos de invención incluyen SCH48461 (Schering-Plough), así como aquellos divulgados en el *Atherosclerosis* 115, 45-63 (1995) y *J. Med. Chem.* 41, 973 (1998).

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Ejemplos de inhibidores del co-transportador ileal de Na⁺/ácido biliar convenientes para el uso combinado con los compuestos de la presente invención incluyen compuestos como los divulgados en *Drug of the Future*, 24, 425-430 (1999).

Ejemplos miméticos tiroideos convenientes para el uso combinado con los compuestos de la presente invención incluyen tirotropina, politiroide, KB-130015 y dronedarona.

Ejemplos de agentes anabólicos convenientes para el uso combinado con los compuestos de la presente invención incluyen testosterona, TRH, dietilestilbestrol, estrógenos, β -agonistas, teofilina, esteroides anabólicos, dehidroepiandrosterona, encefalinas, prostaglandinas de la serie de E, ácido retinoico y compuestos como los divulgados en la Patente de Estados Unidos No. 3,239, 345, e. g., Zeranol ®; en la Patente de Estados Unidos No. 4,036, 979, e. g., Sulbenox® o peptidos como los divulgados en la Patente de Estados Unidos No. 4,411,890.

Las patentes y las solicitudes de patentes antes mencionados son incorporadas aquí por referencia.

Los otros agentes terapéuticos antes mencionados, cuando son empleados en combinación con los compuestos de la presente invención, pueden ser utilizados, por

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ejemplo, en las cantidad indicadas en el Physician's Desk Reference (PDR) o determinadas por otra manera por alguien con la experiencia ordinaria en el estado del arte.

En los casos donde los compuestos de la invención son utilizados en combinación con uno o más de los otros agentes terapéuticos, de forma concurrente o secuencial, las siguientes relaciones de combinación e intervalos de dosificación son preferidos:

Cuando están combinados con un agente hipolipidémico, un antidepresivo, un inhibidor de la resorción ósea y/o un supresor de apetito, los compuestos con la fórmula I pueden ser empleados usando una relación en peso con respecto al agente adicional dentro del intervalo comprendido desde alrededor de 500: 1 hasta aproximadamente 0.005: 1, preferiblemente desde alrededor de 300: 1 hasta aproximadamente 0.01:1.

En los casos donde el agente anti-diabético es una biguanida, los compuestos con la fórmula I pueden ser empleados usando una relación en peso con respecto a la biguanida dentro del intervalo comprendido desde alrededor de 0.01:1 hasta aproximadamente 100:1, preferiblemente desde alrededor de 0.5:1 hasta aproximadamente 2:1.

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Los compuestos con la fórmula I pueden ser empleados usando una relación en peso con respecto a un inhibidor de la glucosidasa dentro del intervalo comprendido desde alrededor de 0.01:1 hasta aproximadamente 100:1, preferiblemente desde alrededor de 0.5: 1 hasta aproximadamente 50:1.

Los compuestos con la fórmula I pueden ser empleados usando una relación en peso con respecto a una sulfonilurea dentro del intervalo comprendido desde alrededor de 0.01:1 hasta aproximadamente 100:1, preferiblemente desde alrededor de 0.2: 1 hasta aproximadamente 10:1.

Los compuestos con la fórmula I pueden ser empleados usando una relación en peso con respecto a una tiazolidindiona dentro del intervalo comprendido desde alrededor de 0.01:1 hasta aproximadamente 100:1, preferiblemente desde alrededor de 0.5: 1 hasta aproximadamente 5:1. La tiazolidindiona puede ser empleada en cantidades dentro del intervalo comprendido desde alrededor de 0.01 hasta aproximadamente 2000 mg/día, las cuales pueden ser administradas opcionalmente en una dosis individual o dividida en una a cuatro veces por día. Además, en los casos donde la sulfonilurea y la tiazolidindiona son administrados oralmente en una cantidad menor que aproximadamente 150 mg, estos agentes adicionales pueden ser incorporados en una tableta individual combinados con una cantidad terapéuticamente efectiva de los compuestos con la fórmula I.

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Metformina, o una sal de esta, puede ser empleada con los compuestos con la fórmula I en cantidades dentro del intervalo comprendido desde alrededor de 500 hasta aproximadamente 2000 mg/día, las cuales pueden ser administradas una dosis individual o dividida en una a cuatro veces por día.

Los compuestos con la fórmula I pueden ser empleados usando una relación en peso con respecto un agonista de la PPAR-alfa, un agonista de la PPAR-gama, un agonista dual de la PPAR alfa/gama, un inhibidor del SGLT2 y/o un inhibidor de la aP2 dentro del intervalo comprendido desde alrededor de 0.01:1 hasta aproximadamente 100:1, preferiblemente desde alrededor de 0.5: 1 hasta aproximadamente 5:1.

Un inhibidor de la MTP puede ser administrado oralmente con los compuestos de la fórmula I en una cantidad dentro del intervalo comprendido desde alrededor de 0.01 mg/kg hasta aproximadamente 100 mg/kg y preferiblemente desde alrededor de 0.1 mg/kg hasta aproximadamente 75 mg/kg, de una a cuatro veces por día. Una forma de dosificación oral adecuada, tal como tabletas o cápsulas, puede contener el inhibidor de la MTP en una cantidad que va desde alrededor de 1 hasta aproximadamente 500 mg, preferiblemente desde alrededor de 2 hasta aproximadamente 400 mg, y aún con mayor preferencia desde alrededor de 5 hasta aproximadamente 250 mg, administrados en un régimen de una a cuatro veces por día. Para la administración parenteral, el inhibidor de la MTP puede ser empleado en una cantidades dentro del intervalo comprendido desde alrededor de 0.005 mg/kg hasta aproximadamente 10 mg/kg preferiblemente desde alrededor de 0.005 mg/kg hasta aproximadamente 8 mg/kg, administradas en un régimen de una a cuatro veces por día.

Un inhibidor de la HMG CoA reductasa se puede administrar oralmente con los compuestos de la fórmula I dentro del intervalo comprendido desde alrededor de 1 hasta 2000 mg, y preferiblemente desde alrededor de 4 hasta aproximadamente 200 mg. Una forma de dosificación oral adecuada, tal como tabletas o cápsulas, contendrá el inhibidor de la HMG CoA reductasa en una cantidad dentro del intervalo comprendido desde alrededor de 0.1 hasta aproximadamente 100 mg, preferiblemente desde alrededor de 5 hasta aproximadamente 80 mg, y aún con mayor preferencia desde alrededor de 10 hasta aproximadamente 40 mg.

Un inhibidor de la escualeno sintetasa puede ser administrado con los compuestos de la fórmula I dentro del intervalo comprendido desde alrededor de 10 mg hasta aproximadamente 2000 mg y preferiblemente desde alrededor de 25 mg hasta aproximadamente 200 mg. Una forma de dosificación oral adecuada, tal como tabletas o cápsulas, contendrá el inhibidor de la escualeno sintetasa en una cantidad desde alrededor de 10 hasta aproximadamente 500 mg, preferiblemente desde alrededor de 25 hasta aproximadamente 200 mg.

Los compuestos con la fórmula I de la invención pueden ser administrados oral o parenteralmente, tales como por vía subcutánea o intravenosa, así como por aplicación nasal, rectal o sublingual a varias especies de mamíferos que se sabe están sujetos a trastornos como los ya mencionados, e. g., humanos, en una cantidad efectiva dentro

del intervalo comprendido desde alrededor de 0.01 $\mu\text{mg/kg}$ hasta aproximadamente 1000 $\mu\text{mg/kg}$ y preferiblemente desde alrededor de 0.1 $\mu\text{mg/kg}$ hasta aproximadamente 100 $\mu\text{mg/Kg}$, aún con mayor preferencia desde alrededor de 0.2 $\mu\text{mg/kg}$ hasta aproximadamente 50 $\mu\text{mg/kg}$ (o desde alrededor de 0.5 hasta 2500 mg, preferiblemente desde alrededor de 1 hasta 2000 mg) en un régimen de una, dos o cuatro dosis por día.

Los compuestos de la fórmula pueden ser administrados para cualquiera de los usos descritos aquí mediante cualquier método conveniente, por ejemplo, oralmente, por ejemplo en forma de tabletas, cápsulas, gránulos o polvos; sublingualmente; bocalmente; parenteralmente, por ejemplo mediante técnicas subcutáneas, intravenosas, intramusculares, o de inyección intraesternal o de infusión (e. g., como soluciones o suspensiones estériles inyectables acuosas o no acuosas); nasalmente, incluyendo la administración a las membranas nasales, por ejemplo mediante la inhalación de un spray; tópicamente, por ejemplo en la forma de una crema o ungüento; o rectalmente, por ejemplo en la forma de supositorios; formulaciones de dosis unitaria que contienen vehículos o diluyentes no-tóxicos, farmacéuticamente aceptables. Los compuestos en cuestión pueden ser, por ejemplo, administrados en una forma conveniente para la liberación inmediata o extendida. La liberación inmediata o extendida se puede alcanzar mediante el uso de formulaciones farmacéuticas convenientes que contienen los compuestos en cuestión, o, particularmente en el caso de la liberación extendida, por el uso de dispositivos tales como implantes subcutáneos o bombas osmóticas. Los compuestos en cuestión también pueden ser administrados en forma de liposoma.

Formulaciones ejemplares para la administración oral incluyen suspensiones que pueden contener, por ejemplo, celulosa microcristalina para impartir volumen, ácido algínico o alginato de sodio como agente que promueve la suspensión, metilcelulosa para aumentar la viscosidad, y agentes endulzantes o saborizantes tales como aquellos conocidos en estado del arte; y tabletas de liberación inmediata las cuales pueden contener, por ejemplo, celulosa microcristalina, fosfato dicálcico, almidón, estearato del magnesio y/o lactosa y/u otros excipientes, aglutinantes, cargas, disgregantes, diluyentes y lubricantes tales como aquellos conocidos en el arte. Los compuestos con la fórmula I pueden también ser administrados a través de la cavidad oral por la administración sublingual y/o bucal. Tabletas moldeadas, tabletas comprimidas o tabletas liofilizadas son las formas ejemplares que pueden ser utilizadas. Formulaciones ejemplares incluyen éstos que formulan el(los) compuesto(s) en cuestión con diluyentes de disolución rápida tales como manitol, lactosa, sucrosa y/o ciclodextrinas. También pueden estar incluidos en tales formulaciones excipientes con alto peso molecular tales como celulosas (Avicel) o polietilen glicoles (PEG). Tales formulaciones también pueden incluir un excipiente para ayudar a la adherencia a las mucosas tal como hidroxipropil celulosa (HPC), hidroxipropil metil celulosa (HPMC), carboximetil celulosa sódica (SCMC, por sus siglas en inglés), un copolímero de anhídrido maleico (e. g., Gantrez), y agentes para controlar la liberación tal como copolímero poliacrílico (e. g. Carbopol 934). Lubricantes, deslizantes, sabores, agentes colorantes y estabilizadores también pueden ser adicionados para facilitar la fabricación y uso.

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Formulaciones ejemplares para la administración por aerosol nasal o inhalación incluyen soluciones salinas, que puede contener, por ejemplo, alcohol bencílico u otros preservativos convenientes, promotores de absorción para aumentar la biodisponibilidad, y/o otros agentes solubilizantes o dispersantes tales como aquellos conocidos en el estado arte.

Formulación ejemplares para la administración parenteral incluyen soluciones o suspensiones inyectables las cuales pueden contener, por ejemplo, diluyentes o solventes convenientes, no tóxicos, parenteralmente aceptables, tales como manitol, 1,3-butanodiol, agua, solución de Ringer, una solución isotónica de cloruro de sodio, u otro agente conveniente dispersante o humectante y de suspensión, incluyendo mono- o di-gliceridos sintéticos, y ácidos grasos, incluyendo el ácido oleico, o Cremaphor.

Formulaciones ejemplares para la administración rectal incluyen supositorios que pueden contener, por ejemplo, un excipiente conveniente no-irritante, tal como manteca de cacao, los ésteres glicéridos sintéticos o polietilen glicoles, que son sólidos a temperaturas ordinarias, pero que se vuelven líquidos y/o se disuelven en la cavidad rectal para liberar el medicamento.

Formulaciones ejemplares para la administración tópica incluyen un vehículo tópico tal como Plastibasa (aceite mineral gelificado con polietileno).

Será entendido que el nivel y la frecuencia de las dosis específicas para la dosificación de cualquier sujeto particular pueden ser variados y dependerán de una variedad de factores que incluyen actividad del compuesto específico empleado, estabilidad metabólica y amplitud de acción de dicho compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo y periodo de administración, velocidad de excreción, combinación del medicamento, y severidad de la condición particular.

EJEMPLOS

Los siguientes ejemplos representan formas de ejecución preferidas de la presente invención. Sin embargo, no deben ser interpretados en ningún caso como limitantes de la invención. Los espectros de ^1H RMN fueron consistentes con las estructuras asignadas. Los espectros de Masas fueron registrados en un espectrómetro Perkin-Elmer, API 150Ex, usando electrospray asistido por turbo nebulización con modo de ion negativo (ES-1) o positivo (ES+1), usando una columna de Zorbax SB-C8 (LC-MS). Procedimientos apropiados para la preparación de [3,5-dicloro-4-(4-metoxi-3-isopropilfenoxi)] benzoato de metilo y metil-N-[3,5-dicloro-4-(4-metoxi-3-isopropilfenoxi)benzoil] glicina pueden ser encontrados en: *"Novel Thyroid Receptor Ligands and Methods."* Li, Y. -L.; Liu, Y.; Hedfors, A.; Malm, J.; Mellin, C.; Zhang, M.

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W099/00353, PCT/EP98/04039 y *"Novel diphenyl ether derivatives which are thyroid hormone beta-receptor ligands useful for treating metabolic disorders."* Hangeland, J.; Zhang, M.; Caringal, Y.; Ryono, D.; Li, Y. -L. ; Malm, J.; Liu, Y.; Garg, N.; Litten, C.; GarciaCollazo, A. M.; Kohler, K. WO00/039077, PCT/IB99/02084, respectivamente.

Procedimientos para la preparación del ácido 3,5-dicloro-2-metil-4-(4-hidroxi-3-isopropilfenoxi)-benzoico puede ser encontrados en *"Benzamide ligands for the thyroid receptor"*. Ryono, Denis E.. WO01/94293, US6395784.

Ejemplo 1: N-[3,5-Dicloro-4-(4-hidroxi-3-isopropil-5-metilfenoxi)benzoi] glicina (E1)

(a) Ácido nítrico (2.84 ml, 65 %) fueron adicionados a una solución agitada [3,5-dicloro-4-(3-isopropil-4-metoxifenoxi)] benzoato de metilo (2.84 g, 7.64 mmol) en el benceno (200 ml). La mezcla de reacción amarilla que resultaba fue agitada a la temperatura ambiente por tres horas y después vertida sobre bicarbonato de sodio (solución saturada). Las fases orgánica y acuosa resultantes fueron separadas y la fase acuosa fue extraída con acetato de etilo. La combinación de las fases orgánicas fue secada sobre el sulfato de sodio y concentrada para dar 2.40g de un sólido amarillo claro. El sólido fue disuelto en etanol (150 ml, 95.5 %), fue adicionado hidrosulfito de sodio ($\text{Na}_2\text{S}_2\text{O}_4$, 85% de pureza, 7.12 g, 35.0 mmol) y la mezcla de reacción fue calentada al reflujo. Después de 16 horas, una segunda porción de hidrosulfito de sodio (3.00 g, 14.7 mmol) fue adicionado a la mezcla de reacción. Después de tres horas, la mezcla de

reacción fue enfriada a la temperatura ambiente, neutralizada con bicarbonato de sodio (solución saturada) y concentrada. El residuo fue diluido con acetato de etilo (75 ml) y lavado con agua (50 ml). La fase orgánica fue secada sobre el sulfato de sodio anhidro y concentrada para dar un sólido amarillo claro. El sólido amarillo fue filtrado a través de una pequeña capa de sílica, para dar 2.2 g (75 %) de [3,5-dicloro-4-(3-amino-5-isopropil-4-metoxifenoxi)] benzoato de metilo.

(b) Una solución de nitrito de sodio (0.30 g, 13 mmol) en agua (5 ml) fue adicionada a un mezcla vigorosamente agitada de [3,5-dicloro-4-(3-amino-5-isopropil-4-metoxifenoxi)] benzoato de metilo (1.1 g, 2.86 mmol), metanol (100 ml) y ácido clorhídrico (75 ml, 37 %). La mezcla de reacción fue agitada por una hora y entonces una solución de yoduro de potasio (1.43 g, 8.6 mmol) en agua (5 ml) fue adicionada y la mezcla de reacción fue agitada por 30 minutos. La temperatura fue mantenida a 0°C dentro del frasco durante el curso entero de la reacción. Después de alcanzar la temperatura ambiente la mezcla de reacción con tonalidad pardusca fue extraída con cloroformo (3x 50 ml). La combinación de las fases orgánicas fue lavada con bisulfato de sodio (solución saturada) seguido por tiosulfato de sodio (solución saturada). La fase orgánica fue concentrada para dar un residuo aceitoso rojo oscuro que fue purificado usando una columna (sílica gel, n-heptano/acetato de etilo 95:5), para dar 0.78 g (71 %) de [3,5-dicloro-4-(5-isopropil-4-metoxi-3-yodofenoxi)] benzoato de metilo como una masa amarilla pálida.

(c) [3,5-dicloro-4-(5- isopropil-4-metoxi-3-yodofenoxi)] benzoato de metilo (0.500 mg, 1.01 mmol), fosfato tripotásico (1.07 g, 5.05 mmol), ácido metil borónico (0.303 mg, 5.05 mmol) y dioxano fueron mezclados en un balón de Schlenk bajo atmósfera de nitrógeno. PdCl_2 (dppf, siglas en ingles del 1,1-Bis(difenilfosfino)ferroceno) fue adicionado al balón con atmósfera de nitrógeno y la mezcla de reacción fue calentada 100°C por 16 horas. La mezcla de reacción fue filtrada a través de una pequeña capa de la silicona y luego concentrada. El residuo oscuro fue purificado en columna (sílica gel, n-heptano/acetato de etilo 95:5) para dar una mezcla 85:15 de [3,5-dicloro-4-(3-isopropil-5-metil-4-metoxifenoxi)] benzoato de metilo y [3,5-dicloro-4-(3-isopropil-4-metoxifenoxi)] benzoato de metilo. La mezcla fue obtenida como una masa sólida blanca (0.250 mg, 55 %) y fue utilizada sin purificación adicional en el paso siguiente.

(d) La mezcla [3,5-dicloro-4-(3-isopropil-5-metil-4-metoxifenoxi)] benzoato de metilo y [3,5-dicloro-4-(3-isopropil-4-metoxifenoxi)] benzoato de metilo del paso anterior (250 mg) fue disuelta en tetrahidrofurano (15 ml) e hidróxido del litio (1 N, 15 ml) fue adicionado. Después de 90 minutos de agitación a temperatura ambiente, la mezcla de reacción fue acidificada con ácido clorhídrico (1 N) y las fases acuosa y orgánica fueron separadas. La fase orgánica fue secada sobre el sulfato de sodio y concentrada para generar 0.250 g de una masa sólida blanca, que fue mezclada con el éster metílico de la glicina (164 mg, 1.30 mmol), clorhidrato de 3-etil-1-[3-(dimetilamino)-dimetilamino]-propil] carbodiimide (EDCI) (118 mg, 0.978 mmol) y N,N-dimetil-formamida (20 ml). La mezcla de reacción fue agitada por 10 minutos a temperatura ambiente, tras lo cual 1-hidroxibenzotriazol hidrato (HOBt) (150 mg, 0.978 mmol) y trietil-amina (0.272 ml, 1.96

mmol) fueron adicionados. Después de 48 horas a temperatura ambiente, la mezcla de reacción fue vertida en agua (150 ml) y neutralizada con bicarbonato de sodio. La fase acuosa fue extraída con acetato de etilo (4x 100 ml), las fases orgánicas recolectadas fueron secadas sobre sulfato de magnesio y concentradas. El residuo fue purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elución desde 7:3 hasta 5:5). Esta operación dio 165 mg (80 %) de metil-N-[3,5-dicloro-4-(5-isopropil-3-metil-4-metoxifenoxi)benzoil] glicina como una masa sólida blanca.

(e) El complejo trifluoruro de boro y sulfuro de dimetilo (1.48 ml, 13.7 mmol) fue adicionado a 4°C a una solución agitada de metil-N-[3,5-dicloro-4-(5-isopropil-3-metil-4-metoxifenoxi)benzoil] glicina (155 mg, 0.352 mmol) y diclorometano (15 ml). La mezcla de reacción fue agitada a temperatura ambiente por 24 horas y después tratada con el hielo-agua (30 ml), extraída con acetato de etilo y concentrada. El residuo fue purificado en columna (MPLC, sílica gel, cloroformo/metanol/ácido acético, gradiente de elución desde 1/0/0 hasta 95/5/0.5) para dar a 110 mg (78 %) de N-[3,5-dicloro-4-(4-hidroxi-3-isopropil-5-metilfenoxi)benzoil] glicina. LC-MS (ES-1): m/z 410.

Ejemplo 2: N-[3,5-Dicloro-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E2)

(a) Tribromuro de Boro (1N, en diclorometano) fue adicionado a una solución metil-N-[3,5-dicloro-4-(4-metoxi-3-isopropilfenoxi)benzoil] glicina (114 mg, 0.267 mmol) en diclorometano (5 ml) a -78°C. La mezcla de reacción marrón que resultaba fue dejada

en 25 °C por 16 horas y a 4 °C por dos horas. Una mezcla del metanol (5 ml) y agua (5 ml) fue adicionada a -70°C, la mezcla de reacción concentrada y diluida con el acetato de etilo. La fase orgánica fue lavada con agua, secada sobre sulfato de sodio y concentrada. Esto dio 107 mg de metil-N-[3,5-dicloro-4-(4-hidroxi-3-isopropilfenoxi)benzoil] glicina como una masa sólida amarillenta.

(b) Bromo (33 µl) fue adicionado gota a gota a una mezcla bien agitada de metil-N-[3,5-dicloro-4-(4-hidroxi-3-isopropilfenoxi)benzoil] glicina (240 mg, 0.582 mmol), ácido acético (4 ml), acetato de sodio (88 mg, 0.64 mmol) y algunas gotas de agua. La mezcla de reacción fue agitada a la temperatura ambiente por 16 horas, tiosulfato de sodio (saturado) fue adicionado y la mezcla amarilla fue concentrada. El residuo fue diluido con el acetato de etilo y lavado con agua. La fase acuosa fue extraída con diclorometano, las fases orgánicas reunidas lavadas con una solución acuosa de cloruro de sodio y secadas sobre sulfato de sodio. Tras su concentración, 330 mg de un sólido amarillo obtenido fue purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elución desde 100 % n-heptano hasta una mezcla de 20 % n-heptano y 80 % acetato de etilo). Éste procedimiento da 200 mg (70 %) metil-N-[3,5-dicloro-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina como una masa sólida blanca.

(c) Hidróxido de litio (1 N, 9 ml) fue adicionado a temperatura ambiente a una mezcla de metil-N-[3,5-dicloro-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (150 mg, a

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0.305 mmol) y tetrahidrofurano (9 ml). Después de 16 horas, la mezcla de reacción fue acidificada con ácido clorhídrico (1 N) y extraída con el acetato de etil. Filtrado a través de una capa de sílica para dar N-[3,5-dicloro-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina con un rendimiento cuantitativo un sólido amarillo claro. LC-MS (ES-1):m/z 476.

Ejemplo 3: N-[3,5-Dicloro-4-(2-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E3):

(a) Bromo (13 μ l, 0.26 mmol) fue adicionado gota a gota a un mezcla bien agitada de metil-N-[3,5-dicloro-4-(4-metoxi-3-isopropilfenoxi)benzoil] glicina (50 mg, 0.12mmol), ácido acético (1.0 ml), acetato de sodio (35 mg, 0.26 mmol) y de algunas gotas de agua. La mezcla de reacción fue agitada a temperatura ambiente por tres horas, calentada a 40°C por 90 minutos y finalmente dejada a temperatura ambiente por 16 horas. Acetato del sodio (17 mg) y bromo (6 μ l) fueron adicionados y la mezcla de reacción calentada a 40°C por dos horas. La mezcla de reacción fue dejada a 4°C por tres días. Tiosulfato de sodio (saturado) fue adicionado y la mezcla amarilla concentrada. El residuo fue diluido con el acetato de etilo y lavado con agua. La fase acuosa fue extraída con diclorometano, la fase orgánica combinada lavada con una solución acuosa de cloruro de sodio y secada sobre sulfato de sodio. Tras su concentración, el residuo fue purificado en columna (HPLC, C₈, acetonitrilo/agua/ácido fórmico, gradiente de elusión desde 20/80/0.5 hasta 100/0/0) para dar 1.0 mg (2%) de metil-N-[3,5-dicloro-4-(2-bromo-4-metoxi-5-isopropilfenoxi)benzoil] glicina.

(b) El complejo trifluoruro de boro y sulfuro de dimetilo (10 μ l, 80 μ mol) fue adicionado a temperatura ambiente a una solución agitada de metil-N-[3,5-dicloro-4-(2-bromo-4-metoxi-5-isopropilfenoxi)benzoil] glicina (1.0 mg, 2.0 μ mol) y diclorometano (0.50 ml). La mezcla de reacción fue agitada a temperatura ambiente durante 8 horas y entonces tratada con hielo-agua, extraída con acetato de etilo y lavada con agua. La fase orgánica fue secada sobre sulfato de sodio y concentrada para dar un sólido amarillo claro. El sólido fue purificado en columna (MPLC, sílica gel, cloroformo/metanol/ácido acético, gradiente de elusión desde 1/0/0 hasta 95/5/0.5) para dar 0.90 mg (94 %) de N-[3,5-dicloro-4-(2-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina. LC-MS (ES-1): m/z 476.

Ejemplo 4: N-[3,5-Dicloro-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E4)

(a) [3,5-dicloro-4-(3-isopropil-4-metoxifenoxi)] benzoato de metilo (664 mg, 1.8 mmol) disuelto en la acetona (40 ml), fue adicionado durante 5 minutos a 0°C a una mezcla agitada de hipoclorito de calcio (515 mg, 3.6 mmol), agua (10 ml) y ácido acético (4 ml). La mezcla de reacción fue agitada a 0°C por 30 minutos y entonces 30 minutos más a temperatura ambiente. La mezcla de reacción fue vertida en agua, extraída con acetato de etilo (3x 50mL), La combinación de las fases orgánicas fue lavada con agua (4x 30 ml) y concentrada. El residuo fue purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elusión desde 98:2 hasta 90:10) para dar a 240 mg (60 %) [3,5-dicloro-4-(3-cloro-5-isopropil-4-metoxifenoxi)] benzoato de metilo. El hipoclorito de calcio usado en este paso puede ser intercambiado con hipoclorito de t-butilo.

(b) [3,5-dicloro-4-(3-cloro-5-isopropil-4-metoxifenoxi)] benzoato de metilo, metanol (25 ml) e hidróxido del sodio (6 N, 4 ml) fueron agitados a temperatura ambiente por 8 horas. La mezcla de reacción fue neutralizada con ácido clorhídrico acuoso y extraída con acetato de etilo (3x 30 ml). La combinación de las fases orgánicas fue lavada con agua, concentrada y el residuo triturado con n-heptano. Esto dio a 133 mg (58 %) ácido [3,5-cloro-4-(3-cloro-5-isopropil-4-metoxifenoxi)] benzoico obtenido como un sólido blanco.

(c) El clorhidrato del éster metílico del glicina (83 mg, 0.66 mmol) y trietilamina (100 mg, 0.99 mmol) fueron adicionados a una mezcla agitada de ácido [3,5-cloro-4-(3-cloro-5-isopropil-4-metoxifenoxi)] benzoico (130 mg, 0.33mmol), EDCI (88 mg, 0.46 mmol), HOBt (86 mg, 0.56 mmol) y N,N-dimetilformamida (15 ml). La mezcla de reacción fue agitada por 48 horas a temperatura ambiente, vertida en una mezcla de ácido clorhídrico (1 N, 5.0 ml) y agua (50 ml), y extraída con acetato etilo (4x 20 ml). Las fases orgánicas fueron recolectadas, lavadas con agua (4x 15 ml) y secadas, la fase orgánica fue concentrada y el residuo purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elusión desde 90:10 hasta 75:25). Esto dio 90 mg (59 %) de metil-N-[3,5-dicloro-4-(3-cloro-5-isopropil-4-metoxifenoxi)benzoil] glicina.

(d) El complejo trifluoruro de boro y sulfuro de dimetilo (1.0 ml) fue adicionado a temperatura ambiente a un solución agitada de metil-N-[3,5-dicloro-4-(3-cloro-5-

isopropil-4-metoxifenoxi)benzoil] glicina (90 mg) y diclorometano (10 ml). La mezcla de reacción fue agitada a temperatura ambiente por 24 horas, vertida en agua y extraída con acetato etilo (3x 30 ml). Las fases orgánicas combinadas fueron lavadas con agua (4x 20 ml), concentradas y residuo resultante purificado en columna (sílica gel, cloroformo/metanol/ácido acético 94: 6:0.65). Este procedimiento da 53 mg (63 %) de N-[3,5-dicloro-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina. LC-MS (ES+1):m/z 434.

Ejemplo 5: N-[3,5-Dicloro-4-(3-ciano-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E5)

(a) [3,5-dicloro-4-(5-isopropil-4-metoxi-3-yodofenoxi)] benzoato de metilo (para su preparación ver ex.1 a-b) (200 mg, 0.40 mmol), cianuro de cobre (50 mg, 0.56 mmol) y DMF (4 ml) fueron calentados a 120°C por 16h. Después de alcanzar la temperatura ambiente, la mezcla de reacción oscura fue detenida usando una solución de saturada de bicarbonato de sodio y extraída con acetato de etilo. La fase orgánica fue secada sobre sulfato de sodio y concentrada. El residuo fue purificado en columna (MPLC, sílica gel, n-heptano/acetato de etilo, gradiente de elusión desde 1:0 hasta 9:1) para dar 85 mg (41 %) de [3,5-dicloro-4-(3-ciano-5-isopropil-4-metoxifenoxi)] benzoato de metilo.

(b) Tribromuro de boro (1 N en el diclorometano, 0.93mL) fue adicionado a una solución [3,5-dicloro-4-(3-ciano-5-isopropil-4-metoxifenoxi)] benzoato de metilo (32 mg, μmol 81)

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en diclorometano (0.75mL) a -78°C. Después de 20h a -25 °C y 16h en la temperatura ambiente, la mezcla de reacción fue detenida usando hielo agua a 0°C del hielo y el solvente orgánico es removido por evaporación. El residuo fue acidificado con ácido clorhídrico (1 N) y extraído usando acetato de etilo. La fase orgánica fue secada sobre sulfato de sodio y filtrada a través de una capa de sílica. El sólido amarillo resultante fue mezclado con el éster metílico de la glicina (23 mg, 0.18 mmol), EDCI (35 mg, 0.18 mmol) y N,N-dimetilformamida (1 ml). La mezcla de reacción fue agitada por 10 minutos a temperatura ambiente, tras lo cual HOBt (28 mg, 0.18 mmol) y trietilamina (38 µl, 0.27 mmol) fueron adicionados. Después de 16 horas en la temperatura ambiente, la mezcla de reacción fue vertida en agua (5 ml) y neutralizada con bicarbonato de sodio. La fase acuosa fue extraída con acetato etilo (2x 10 ml) y las fases orgánicas recolectadas fueron secadas sobre el sulfato de sodio y concentradas. El residuo fue purificado en columna (MPLC, sílica gel, n-heptano/acetato de etilo, gradiente de elusión desde 9:1 hasta 7:3) Esto dio a 15 mg (42 %) de metil-N-[3,5-dicloro-4-(3-ciano-4-hidroxi-5-isopropilfenoxi)benzoil] glicina como masa sólida blanca.

(c) Tribromuro de boro (1 N en diclorometano, 0.1 ml) fue adicionado a una solución de metil-N-[3,5-dicloro-4-(3-ciano-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (7 mg, 16, µmol) en diclorometano (0.5 ml) a -78°C. La mezcla de reacción resultante fue agitada a temperatura ambiente por 16h y después detenida usando hielo agua. El solvente orgánico fue retirado mediante evaporación y el residuo resultante fue acidificado con ácido clorhídrico (1 N) y extraído mediante acetato de etilo. Secando sobre sulfato de sodio, concentrando y purificando con una columna de sílica SPE (siglas en ingles de

extracción en fase sólida) (0.5g, 3 ml, gradiente de elución: cloroformo/metanol/ácido acético desde 1:0:0 hasta 98:2:0.5) dio 3 mg (44%) de N-[3,5-dicloro-4-(3-ciano-4-hidroxi-5-isopropilfenoxi)benzoil] glicina. LC-MS (ES-1):m/z 421.

Ejemplo 6: N-[3,5-Dicloro-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E6)

(a) A una solución de [3,5-dicloro-4-(3-isopropil-4-metoxifenoxi)] benzoato de metilo (2.0 g, 5.4 mmol) en benceno (200 ml), fue adicionado ácido nítrico (2.07 ml, el 65%) gota a gota. La mezcla fue agitada por 1 h mas a temperatura ambiente. El desarrollo de la reacción fue seguida usando TLC (65:35 n-heptano/acetato de etilo) y la mezcla de reacción fue detenida con la solución saturada acuosa de bicarbonato de sodio. Las fases orgánica y acuosa resultantes fueron separadas y la fase acuosa fue extraída con acetato etilo. La combinación de las fases orgánicas fue lavada con agua, una solución acuosa de cloruro de sodio, y la fase orgánica fue secada sobre el sulfato del magnesio, y concentrada. El producto crudo fue cristalizado en metanol para dar 1.8g, (80%) de [3,5-dicloro-4-(5-isopropil-4-metoxi-3-nitrofenoxi)] benzoato de metilo.

(b) A la solución de [3,5-dicloro-4-(5-isopropil-4-metoxi-3-nitrofenoxi)] benzoato de metilo (500 mg, 1.21 mmol) en tetrahidrofurano (10 ml), hidróxido de litio (5 ml, 1N) fue adicionado. La mezcla fue agitada durante toda la noche a temperatura ambiente. La mezcla de reacción fue acidificada con ácido clorhídrico (1 N) y las fase acuosa y orgánica fueron separadas. La fase acuosa fue extraída con el acetato etilo. La

combinación de las fases orgánicas fue lavada con agua y secada sobre sulfato magnesio y concentrada. El producto crudo fue purificado en columna (sílica gel, cloroformo/metanol/ácido acético 98:2:0.3) para dar 418 mg (86%) de ácido 3,5-dicloro-4-(5-isopropil-4-metoxi-3-nitrofenoxi)-benzoico.

(c) El clorhidrato del éster metílico de la glicina (262 mg, 2.08 mmol) y trietilamina (317 mg, 3.13 mmol) fueron adicionados a una mezcla agitada de ácido [3,5-cloro-4-(5-isopropil-4-metoxi-3-nitrofenoxi)] benzoico (418 mg, 1.04 mmol), EDCI (401 mg, 2.08 mmol), HOBt (320 mg, 2.08 mmol) y N,N-dimetilformamida (50 ml). La mezcla de reacción fue agitada por 24 horas a temperatura ambiente, vertida en una mezcla de ácido clorhídrico (1 N, 10 ml) y agua (50 ml), y extraída con acetato etilo. Las fases orgánicas fueron recolectadas, lavadas con agua y secadas, la fase orgánica fue concentrada y el residuo purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elución desde 98:2 hasta 60:40). Esto dio 380 mg (78 %) de metil-N-[3,5-dicloro-4-(5-isopropil-4-metoxi-3-nitrofenoxi)benzoil] glicina.

(d) Una mezcla de metil-N-[3,5-dicloro-4-(5-isopropil-4-metoxi-3-nitrofenoxi)benzoil] glicina (380 mg, 0.81 mmol) y PtO_2 (40 mg) en acetato de etilo (10 ml) fueron agitados a temperatura ambiente en atmósfera de hidrógeno (a presión atmosférica) por 24h. El catalizador de Pt fue removido por la filtración a través de celite y el filtrado fue concentrado, y luego purificado en columna (sílica gel, n-heptano/acetato de etilo,

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gradiente de elusión desde 98:2 hasta 60:40) para dar 320 mg (89%) de metil-N-[3,5-dicloro-4-(3-amino-5-isopropil-4-metoxifenoxi)benzoil] glicina.

(e) Una solución de tetrafluoroborato de nitrosonio (55mg, 0.47mmol) en diclorometano (5 ml) fue enfriada a 0°C y metil-N-[3,5-dicloro-4-(3-amino-5-isopropil-4-metoxifenoxi)benzoil] glicina (189mg, 0.43mmol) fue adicionada. La mezcla de reacción fue agitada por 1h mas a 0°C. El diclorometano fue removido en nitrógeno y o-xileno (10 ml) fue adicionado a la mezcla de reacción. La mezcla de reacción fue sujeta a reflujo por 1 h y el solvente fue removido. La mezcla de reacción cruda fue purificada en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elusión desde 98:2 hasta 60:40) para dar 50 mg (26%) de metil-N-[3,5-dicloro-4-(3-fluoro-5-isopropil-4-metoxifenoxi)benzoil] glicina.

(f) El complejo trifluoruro de boro y sulfuro de dimetilo (2.0 ml) fue adicionado a temperatura ambiente a una solución agitada de metil-N-[3,5-dicloro-4-(3-fluoro-5-isopropil-4-metoxifenoxi)benzoil] glicina (50 mg, 0.11 mmol) y diclorometano (8 ml). La mezcla de reacción fue agitada a temperatura ambiente por 24 horas, vertido en agua y extraída con el acetato de etilo. La combinación de fases orgánicas fue lavada con agua, concentrada y el residuo resultante purificado en columna (HPLC, C₈, acetonitrilo/0.05% ácido fórmico en agua, gradiente de elusión desde 5/95 hasta 60/40) para dar 5 mg (20%) de N-[3,5-dicloro-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina. LC-MS (ES-1): m/z 414.

**Ejemplo 7: N-[3,5-Dicloro-2-metil-4-(4-hidroxi-3-isopropil-5-metilfenoxi)benzoi]
glicina**

(a) Una suspensión de tribromuro de benciltrimetilamonio (2.2 g, 5.63 mmol) y CaCO_3 (0.28 g, 2.82 mmol) fue agitada por 2 h a 20°C en una solución 1:1 de MeOH/ CH_2Cl_2 (10 ml) que contiene ácido 3,5-dicloro-2-metil-4-(4-hidroxi-3-isopropilfenoxi)-benzoico (1.0 g, 2.82mmol). Una vez que el análisis HPLC indicó que conversión al fenol monobromado objetivo fue óptima, la reacción fue detenida mediante la adición 15 ml HCl 1 N. Después de la remoción de solventes orgánicos bajo vacío usando un rotaevaporador, la suspensión acuosa fue extraída dos veces con EtOAc. Después de secar las fases combinadas EtOAc sobre MgSO_4 , las sales fueron filtradas previa remoción de EtOAc usando vacío. El residuo resultante después de la purificación por gradiente elusión obtenido de una columna C18 en fase reversa empleando MeOH/ H_2O que contiene 0.1 % TFA produjo ácido 3,5-dicloro-2-metil-4-(3-bromo-4-hidroxi-5-isopropilfenoxi) benzoico (400 mg).

(b) HCl fue burbujeado a través de un solución de ácido 3,5-dicloro-2-metil-4-(3-bromo-4-hidroxi-5-isopropilfenoxi) benzoico (375 mg, 0.86 mmol) en MeOH (20 ml) por 5 minutos. Una vez fue agitado por 22 h a 20°C, el análisis del HPLC reveló que la esterificación fue completa. Después de la remoción de solvente al vacío y disolución del residuo en EtOAc, de la fase de EtOAc fue lavada dos veces con H_2O y entonces con una solución acuosa de NaCl para luego ser secado sobre MgSO_4 . El retiro de los volátiles produjo 391 mg de 3,5-dicloro-2-metil-4-(3-bromo-4-hidroxi-5-

isopropilfenoxi)benzoato de metilo crudo como un sólido marrón que no fue sometido a procesos de purificación adicionales.

(c) Una suspensión K_3PO_4 anhidro en polvo (473 mg, 2.23 mmol) y ácido metilborónico (133 mg, 2.23 mmol) en una solución de dioxano (5 ml) que contenía 3,5-dicloro-2-metil-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoato de metilo (263 mg, 0.59 mmol) fue purgada Ar por 15 minutos antes de la adición de $Pd(dppf)Cl_2$ (168 mg, 0.21 mmol). Después de ser someterse a reflujo por 3 horas, la reacción fue enfriada, diluida con EtOAc, y filtrada. El residuo resultante después de ser retirados los volátiles fue purificado por cromatografía en sílica gel. La elución progresiva con CH_2Cl_2 /hexano 1:1 y entonces 3:1 generó 125 mg de 3,5-dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoato de metilo como una espuma anaranjada.

(d) Una solución 3,5-dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoato de metilo (125 mg, 0.33 mmol) y LiOH (68 mg, 1.63 mmol) en THF/H₂O 5:1 (6 ml) fue agitada durante toda la noche a 20°C bajo N₂. La solución fue concentrada al vacío y acidificada hasta pH 1 con HCl 1N. El sólido anaranjado resultante fue recolectado por filtración, lavado con H₂O y secado con aire para producir 114 mg de ácido 3,5-dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi) benzoico.

(e) A una solución agitada de ácido 3,5-dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi) benzoico (114 mg, 0.31 mmol) crudo en DMF (5 ml) bajo N₂ fueron secuencialmente adicionados EDCI (83 mg, 0.43mmol), HOBt (80 mg, 0.53mmol), clorhidrato de glicinato de metilo (78 mg, 0.62 mmol) y Et₃N (0.13 ml, 0.93 mmol). Después de agitar por 21 h a 20°C, la detección del ácido benzoico inicial mediante análisis LCMS incitó la adición de 8 mg de clorhidrato de glicinato de metilo y de 13 ml de Et₃N. La reacción fue terminada 3 h después por la dilución con 3 ml de HCl 1 N y 25 ml de H₂O. Después de la extracción de la fase acuosa tres veces con EtOAc, las fases combinadas de EtOAc fueron lavadas dos veces con H₂O y una vez con solución acuosa de NaCl antes de ser secado sobre MgSO₄. La concentración produjo 163 mg de glicinamida cruda que fue purificada por cromatografía en sílica gel; 1:4 EtOAc/hexano lo que generó 96 mg de N-(3,5-dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi) glicinato de metilo objetivo como un sólido beige.

(f) Una solución de N-(3,5-dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi) glicinato de metilo (96 mg, 0.22 mmol) y LiOH (46 mg, 1.09 mmol) en THF/H₂O 5:1 (6 ml) fue agitada durante toda la noche a 20°C bajo N₂. La solución fue concentrada al vacío y acidificada hasta pH 1 con HCl 1N. Después de la extracción de la fase acuosa tres veces con EtOAc, las fases combinadas de EtOAc fueron secadas sobre MgSO₄. La concentración produjo 92 mg de glicinamida cruda la cual fue purificada por cromatografía en fase reversa (columna C18). Gradiente de elución con MeCN/H₂O que contiene 0.1% TFA produjo 72 mg del ácido N-(3,5-dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi) glicínico objetivo.

**Ejemplo 8: N-[3,5-Dibromo-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoi]
glicina (E8)**

El ejemplo E8 es preparado por un procedimiento similar al descrito para el ejemplo E7.

**Ejemplo 9: N-[3,5-Dimetil-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoi]
glicina (E9)**

El ejemplo E9 es preparado por un procedimiento similar al descrito para el ejemplo E7.

**Ejemplo 10: L-N-[3,5-Dibromo-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)fenil]acetil]
valina (E10)**

(a) A una solución de [3,5-dibromo-4-(3-isopropil-4-metoxifenoxi)fenil] acetato de metilo (1.0 g, 2.12 mmol) en benceno (150 ml), ácido nítrico (0.81 ml, el 65%) fue adicionado gota a gota. La mezcla fue agitada por 1 h mas a temperatura ambiente. El desarrollo de la reacción fue seguida usando TLC (85:35 n-heptano/acetato de etilo) y la mezcla de reacción fue detenida con la solución saturada acuosa de bicarbonato de sodio. Las fases orgánica y acuosa resultantes fueron separadas y la fase acuosa fue extraída con acetato etilo. La combinación de las fases orgánicas fue lavada con agua, una solución acuosa de cloruro de sodio, y la fase orgánica fue secada sobre el sulfato del magnesio, y concentrada. El producto crudo fue cristalizado en metanol para dar 1.1g, (99%) de [3,5-dibromo-4-(5-isopropil-4-metoxi-3-nitrofenoxi)fenil] acetato de metilo.

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(b) [3,5-dibromo-4-(5-isopropil-4-metoxi-3-nitrofenoxi)fenil] acetato de metilo (1.1 mg, mmol 2.12) fue disuelto en el etanol (50 ml) e hidrosulfito de sodio (1.85 g, 10.6 mmol) fue adicionado. La mezcla de reacción fue calentada usando reflujo por 48 horas. El desarrollo de la reacción fue seguida usando TLC (65:35 n-heptano/acetato de etilo) y cuando fue completado, fue diluido con acetato de etilo y lavado con agua y una solución acuosa de cloruro de sodio. La fase orgánica fue secada sobre MgSO_4 y concentrada. El residuo fue purificado en columna (sílica gel, n-heptano/EtOAc 1:1) para producir [3,5-dibromo-4-(3-amino-5-isopropil-4-metoxifenoxi)fenil] acetato de metilo (457 mg, 44%).

c) Una solución de tetrafluoroborato de nitrosonio (121 mg, 1.03 mmol) en diclorometano (10 ml) fue enfriada a 0°C y [3,5-dibromo-4-(3-amino-5-isopropil-4-metoxifenoxi)fenil] acetato de metilo (457mg, 0.94 mmol) fue adicionada. La mezcla de reacción fue agitada por 1 hora más a 0°C . El diclorometano fue removido purgando en atmósfera de nitrógeno y o-xileno (10 ml) fue adicionado al residuo. La mezcla de reacción fue sujeta a reflujo por 1 h y la fase orgánica fue concentrada al vacío. El fue purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elusión desde 98:2 hasta 60:40) para dar 205 mg (44%) de [3,5-dibromo-4-(3-fluoro-5-isopropil-4-metoxifenoxi)-fenil] acetato de metilo.

(d) A una solución de [3,5-dibromo-4-(3-fluoro-5-isopropil-4-metoxifenoxi)-fenil] acetato de metilo (205 mg, 0.42 mmol) en tetrahidrofurano (30 ml), hidróxido de litio (30 ml, 1N) fue adicionado. La mezcla de reacción fue agitada durante la noche a temperatura ambiente, acidificada con ácido clorhídrico (1 N) y la fase acuosa y orgánica separadas. La fase acuosa extraída con acetato de etilo. La combinación de las fases orgánicas fue lavada con agua y secada sobre sulfato magnesio y concentrada al vacío. El residuo fue purificado en columna (sílica gel, cloroformo/metanol/ácido acético 98:2:0.3) para dar 210 mg (99%) de ácido 3,5-dibromo-4-(3-fluoro-5-isopropil-4-metoxifenoxi) fenilacético.

(e) El clorhidrato del éster metílico de la L-valina (148 mg, 0.88 mmol) y trietilamina (134 mg, 1.32 mmol) fueron adicionados a una mezcla agitada de ácido 3,5-dibromo-4-(3-fluoro-5-isopropil-4-metoxifenoxi) fenilacético (210 mg, 0.44 mmol), EDCI (169 mg, 0.88 mmol), HOBt (135 mg, 0.88 mmol) y N,N-dimetilformamida (25 ml). La mezcla de reacción fue agitada por 24 horas a temperatura ambiente, vertida en una mezcla de ácido clorhídrico (1 N, 5 ml) y agua (30 ml), y extraída con acetato etilo. Las fases orgánicas fueron secadas, la fase orgánica fue concentrada y el residuo purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elución desde 98:2 hasta 60:40) para dar 224 mg (86 %) de L-N-[3,5-dibromo-4-(3-fluoro-5-isopropil-4-metoxifenoxi)fenilacetil] valinato de metilo.

(f) El complejo trifluoruro de boro y sulfuro de dimetilo (4.0 ml) fue adicionado a temperatura ambiente a una solución agitada de L-N-[3,5-dibromo-4-(3-fluoro-5-isopropil-4-metoxifenoxi)fenilacetil] valinato de metilo (224 mg, 0.38 mmol) en

diclorometano (25 ml). La mezcla de reacción fue agitada a temperatura ambiente por 24 horas, vertida en agua y extraída con acetato de etilo. La combinación de las fases orgánicas fue lavada con agua, concentrada y el residuo fue purificado en columna (sílica gel, cloroformo/metanol/ácido acético, 98:2:0.3) para dar 93 mg (44 %) de L-N-[3,5-dibromo-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)fenilacetil] valina.

Ejemplo 11: D-N-[3,5-Dibromo-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)fenilacetil] fenilglicina (E11)

(a) A una solución agitada de ácido 3,5-dibromo-4-(3-isopropil-4-metoxifenoxi)fenilacético (1.5 g, 3.4 mmol) en ácido acético (40 ml) a temperatura ambiente fue adicionado tetracloroyodato de benciltrimetilamonio (1.42 g, 3.4 mmol). La mezcla fue agitada por 1 h y fue filtrada. El filtrado fue concentrado, y el producto fue extraído con acetato de etilo, lavado con una solución saturada de NaHCO_3 (aq), NaCl (aq), secado sobre MgSO_4 y luego concentrado al vacío. El residuo fue purificado en columna (sílica gel, cloroformo/metanol/ácido acético, 98:2:0.3) para dar 802 mg (50 %) de ácido 3,5-dibromo-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)fenilacético.

(b) El clorhidrato del éster metílico de la D-fenilglicina (674 mg, 3.34 mmol) y trietilamina (507 mg, 5.02 mmol) fueron adicionados a una mezcla agitada de ácido 3,5-dibromo-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)fenilacético (800 mg, 1.7 mmol), EDCI (641 mg, 3.34 mmol), HOBt (512 mg, 3.34 mmol) y N,N-dimetilformamida (100 ml). La mezcla de reacción fue agitada por 24 horas a temperatura ambiente, vertida en una mezcla de

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ácido clorhídrico (1 N, 5 ml) y agua (30 ml), y extraída con acetato etilo. Las fases orgánicas fueron secadas, la fase orgánica fue concentrada y el residuo purificado en columna (sílica gel, n-heptano/acetato de etilo, gradiente de elución desde 98:2 hasta 60:40) para dar 800 mg (75 %) de D-N-[3,5-dibromo-4-(3-cloro-5-isopropil-4-metoxifenoxi)fenilacetil] fenilglicinato de de metilo.

(c) El complejo trifluoruro de boro y sulfuro de dimetilo (10 ml) fue adicionado a temperatura ambiente a una solución agitada de D-N-[3,5-dibromo-4-(3-cloro-5-isopropil-4-metoxifenoxi)fenilacetil] fenilglicinato de de metilo (800 mg, 1.3 mmol) y diclorometano (80 ml). La mezcla de reacción fue agitada a temperatura ambiente por 24 horas, vertida en agua y extraída con acetato de etilo. La combinación de las fases orgánicas fue lavada con agua, concentrada y el residuo fue purificado en columna (sílica gel, cloroformo/metanol/ácido acético, 98:2:0.3) para dar 350 mg (44 %) de D-N-[3,5-Dibromo-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)fenilacetil] fenilglicina.

Ejemplo 12: L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] valina (E12)

(a) [3,5-dibromo-4-(4-hidroxi-3-isopropilfenoxi)fenil] acetato de metilo (2.0 g, 4.4 mmol), SnCl_4 (25 μl , 0.2mmol), trioctil amina (0.77 ml, 1.76 mmol) y tolueno (15 ml) fueron mezclados en un vial de reacción. Después de un periodo de agitación de 20 minutos a temperatura ambiente, paraformaldehído (0.264 g, 8.8 mmol) fue adicionado a la solución de reacción. El vial de reacción fue sellado y la temperatura incrementada a

105 °C. Después de 20 horas de agitación, la reacción fue detenida con hielo-agua y acidificada con ácido clorhídrico (1 N). La extracción con acetato de etilo, el lavado con una solución acuosa de NaCl, el secado sobre Na₂SO₄ y la concentración dan el producto crudo. El residuo fue purificado en la columna (sílica gel, gradiente de elusión: n-heptano/acetato de etilo, desde 1:0 hasta 4:1) para dar 1.08g (51 %) de [3,5-dibromo-4-(3-formil-4-hidroxi-5-isopropilfenoxi)fenil] acetato de metilo.

(b) Trietilsilano fue adicionado a una mezcla de [3,5-dibromo-4-(3-formil-4-hidroxi-5-isopropilfenoxi)fenil] acetato de metilo (243 mg, 0.5 mmol) y ácido trifluoro acético (10 ml) a temperatura ambiente. Después de 12 horas de agitación, la mezcla de reacción fue concentrada vía co-evaporación con tolueno. El residuo fue purificado en columna (sílica, gradiente de elusión: n-heptano/acetato de etilo, desde 9:1 hasta 7:3) para dar a 197 mg (84%) de [3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenil] acetato de metilo.

(c) Una mezcla de [3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenil] acetato de metilo (194 mg, 0.41 mmol) e hidróxido del litio (20 ml, 1 N) en tetrahidrofurano (10 ml) fueron agitados por 10 horas a temperatura ambiente. La mezcla de reacción fue neutralizada con ácido clorhídrico acuoso frío seguida por la extracción con acetato de etilo (3x30 ml). Las fases orgánicas combinadas fueron lavadas con agua (4x25mL) y co-evaporadas con acetonitrilo. El residuo fue purificado en la columna (sílica, gradiente

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elución: cloroformo/metanol/ácido acético desde 1:0:0 hasta 90:10:1) para producir 169 mg (90 %) ácido [3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenil] acético.

(d) Una mezcla del compuesto ácido [3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenil] acético (0.44 g, 0.96 mmol), éster metílico de la L-valina (322 mg, 1.92 mmol), clorhidrato de 3-etil-1-[3-(dimetilamino)-dimetilamino)-propil] carbodiimide (EDCI) (174 mg, 1.44 mmol) y N,N-dimetil-formamida (9 ml) fue agitada por 5 minutos a temperatura ambiente, tras lo cual 1-hidroxibenzotriazol hidrato (HOBt) (220 mg, 1.44 mmol) y trietil-amina (0.401 ml, 12.88 mmol) fueron adicionados. Después de 16 horas fue adicionado hexafluorofosfato de bromotripirrolidinofosfonio (0.2 g, 0.43 mmol). Tras 1.75 horas de agitación a temperatura ambiente la mezcla de reacción obtenida fue diluida con agua (10 ml) y ácido clorhídrico (10 ml, 1 N), la fase acuosa fue extraída con acetato de etilo (3x 20 ml), la combinación de las fases orgánicas fue lavada con una solución acuosa de NaCl (40 ml). Después de fue secado sobre Na₂SO₄, filtrado y concentrado el producto crudo fue filtrado a través de una capa corta de sílica. Purificación en un cromatotrón (cromatografía circular) (sílica, 4 milímetros, n-heptano/acetato de etilo 6:4) dio 240 mg (44%) de L-N-[3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] valinato de metilo.

(e) A una solución agitada del compuesto L-N-[3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] valinato de metilo (240 mg, 0.42 mmol) y de tetrahidrofurano (4 ml), hidróxido de litio (4 ml, 1N) fue adicionado. Después de una hora de agitación el

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pH de reacción fue ajustado llevado a 1 con ácido clorhídrico (1 N). La fase orgánica fue concentrada al vacuo. El residuo fue extraído con el acetato de etilo y la combinación de las fases orgánicas fue secada sobre Na_2SO_4 y concentrada. El residuo fue purificado en columna (MPLC, sílica, gradiente de elusión: cloroformo/metanol/ácido acético, desde 1:0:0 hasta 98:2:0.3) para producir (0.14 g, 60 %) de L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] valina como sólido blanco. LC-MS (ES-1): m/z 554.

Ejemplo 13: L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] fenilglicina (E13)

(a) Una solución de ácido 3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi) fenilacético (18 mg, 0.04mmol), diisopropiletilamina (33 μl , 0.2 mmol), hexafluorofosfato de bromotripirrolidinofosfonio (22 mg, 0.05 mmol), 1-hidroxibenzotriazol hidrato (7 mg, 0.05 mmol), éster metílico de la D-fenilglicina (16 mg, 0.08 mmol) y diclorometano (1 ml) fue agitada por 30 minutos a temperatura ambiente. Después de esto la reacción fue lavada con ácido clorhídrico (2 ml, 1 N) y la fase acuosa fue extraída con cloroformo (3 x2 ml). La combinación de las fases orgánicas fue secada sobre Na_2SO_4 y concentrada al vacío. La purificación en columna (sílica, gradiente de elusión: n-heptano/acetato de etilo desde 4:1 hasta 7:3) produjo 16 mg (74%) de L-N-[3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi) fenilacetil] fenil glicinato de metilo.

(b) L-N-[3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi) fenilacetil] fenil glicinato de metilo (15 mg, 0.025 mmol) fue disueltos en tetrahidrofurano (0.5 ml) y la solución resultante fue tratada con hidróxido de litio acuoso (0.5 ml, 1 N) por 1 hora a temperatura ambiente. La reacción fue acidificada con ácido clorhídrico (1 N) y la fase orgánica fue removida al vacío. El residuo fue extraído con el acetato de etilo (3 x5 ml) y la combinación de las fases orgánicas fue secada sobre Na₂SO₄ antes de ser concentrada al vacío. El residuo fue purificado en columna (HPLC, C8, gradiente de elusión: acetonitrilo/agua (0.5% ácido fórmico) desde 1:4 hasta 1:0) para dar L-N-[3,5-dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi) fenilacetil] fenil glicina como un sólido blanco (6 mg, 41 %). LC-MS(ES-1)-MS(ES-1): m/z 588.

Ejemplo 14: L-N-[3,5-Dibromo-4-(3,5-dimetil-4-hidroxifenoxi)fenilacetil] fenilglicina (E14)

(a) Bis-(4-metoxifenil) tetrafluoroborato de yodonio (5.48 g, 12.8 mmol) y cobre en polvo (1.25 g, 19.6 mmol) fueron suspendidos en diclorometano (25 ml) y la suspensión que resultante fue enfriada a 0°C. Durante la agitación, una solución de (3,5-dibromo-4-hidroxifenil) acetato de metilo (3,19 g, 9.8mmol), trietilamina (1.64 ml, 11.8 mmol) y diclorometano (35 ml) fue adicionada a la suspensión cubierta por papel de aluminio. Después de 20 horas de agitación en la oscuridad a temperatura ambiente la mezcla de reacción cruda fue lavada con ácido clorhídrico (1 N) y un separador de fases (IST) fue utilizado para separar las dos fases. La fase acuosa ácida remanente fue extraída con cloroformo y las fases orgánicas recolectadas fueron concentradas al

vacío. El residuo fue purificado en columna (MPLC, sílica gel, gradiente de elusión: n-heptano/acetato de etilo, desde 1:4 hasta 4:1) para dar 2.5 g (45 %) de [3,5-dibromo-4-(4-hidroxifenoxi)fenil] acetato de metilo.

(b) $\text{BF}_3\text{-SMe}_2$ (24.0 ml, 228 mmol) fue adicionado a una solución agitada de [3,5-dibromo-4-(4-hidroxifenoxi)fenil] acetato de metilo (2.5 g, 5.8 mmol) y diclorometano (50 ml) a 0°C. La mezcla de reacción fue agitada a temperatura ambiente por 20 horas y subsecuentemente detenida con hielo-agua (50 ml). Las dos fases fueron separadas con un separador de fases y la fase acuosa remanente fue extraída con acetato de etilo. La filtración a través de una capa de sílica dio el ácido 3,5-dibromo-4-(4-hidroxifenoxi)fenil acético. El residuo fue disuelto en metanol (40 ml) y cloruro de tionilo (4 ml) fue adicionado cuidadosamente a la reacción. Después de calentar 1.5 horas bajo reflujo, la fase orgánica fue removida al vacío y el residuo fue disuelto en cloroformo. La fase orgánica fue lavada con agua y concentrada para dar [3,5-dibromo-4-(4-hidroxifenoxi)-fenil] acetato de metilo como un sólido beige (1.8 g, 75%).

(c) Hexametilentetramina (262 mg, 1.87 mmol) fue adicionada a una solución de [3,5-dibromo-4-(4-hidroxifenoxi)-fenil] acetato de metilo (370 mg, 0.89 mmol) y ácido trifluoroacético (1.5 ml). La mezcla de reacción fue agitada por 16 horas a 95°C antes de ser enfriada a temperatura ambiente. Ácido clorhídrico (3 ml, 2 N) fue adicionado y la mezcla de reacción fue agitada por una hora y extraída con cloroformo. La fase orgánica fue concentrada al vacío y disuelta en acetato de etilo. La fase orgánica fue

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lavada con ácido clorhídrico (2 N), agua y una solución acuosa de NaCl, secada sobre Na_2SO_4 y concentrada. El residuo fue purificado en una columna (MPLC, sílica, gradiente de elusión: n-heptano/acetato de etilo desde 1:4 hasta 4:1) para producir [3,5-dibromo-4-(3-formil-4-hidroxifenoxi)-fenil] acetato de metilo como un sólido blanco (150 mg, 38 %).

(d) Una mezcla del compuesto [3,5-dibromo-4-(3-formil-4-hidroxifenoxi)-fenil] acetato de metilo (250 mg, 0.56 mmol) y ácido trifluoroacético (5.5 ml) fue tratada con trietilsilano (0.34 ml, 2.13 mmol) y la mezcla de reacción fue agitada por 16 horas a temperatura ambiente. La reacción fue concentrada y co-evaporada (tolueno, diclorometano), lo cual dio un residuo que fue filtrado a través de una capa de sílica. La purificación en columna (MPLC, sílica, gradiente de elusión: n-heptano/acetato de etilo desde 1:0 hasta 4:1) dio 110 mg (46 %) de [3,5-dibromo-4-(4-hidroxi-3-metilfenoxi)fenil] acetato de metilo.

(e) Una solución de [3,5-dibromo-4-(4-hidroxi-3-metilfenoxi)fenil] acetato de metilo (110 mg, 0.26 mmol), hexametilentetramina (77 mg, 0.55 mmol) y ácido trifluoroacético (2.5 ml) fue agitada a 100°C durante 20 horas. La solución fue diluída con ácido clorhídrico (5 ml, 2 N) y la mezcla resultante fue agitada a temperatura ambiente por 30 minutos antes de ser extraída con cloroformo. La fase orgánica fue concentrada y diluída con acetato de etilo y lavada con ácido clorhídrico (2x10 ml, 2 N), agua (10 ml) y una solución acuosa de NaCl (10 ml). La fase orgánica fue secada sobre Na_2SO_4 y filtrada

a través de una capa de sílica para dar 60 mg (50 %) de [3,5-dibromo-4-(3-formil-4-hidroxi-5-metilfenoxi)fenil] acetato de metilo.

(f) A una mezcla agitada de [3,5-dibromo-4-(3-formil-4-hidroxi-5-metilfenoxi)fenil] acetato de metilo (60.0 mg, 0.13 mmol) y ácido trifluoroacético (1.5 ml), trietilsilano (62 μ l, 0.39 mmol) fue adicionado. La mezcla de reacción fue agitada a temperatura ambiente por 20 horas, la fase orgánica concentrada y el residuo co-evaporado (tolueno), para dar 60 mg de [3,5-dibromo-4-(3,5-dibromo-4-hidroxifenoxi)fenil] acetato de metilo crudo. El producto crudo fue utilizado en el siguiente paso. Hidróxido de litio (1.5 ml, 1 N) fue adicionado a una solución de [3,5-dibromo-4-(3,5-dibromo-4-hidroxifenoxi)fenil] acetato de metilo crudo y tetrahidrofurano (1.5 ml). La mezcla resultante fue agitada por 2 horas a temperatura ambiente, acidificada con ácido clorhídrico (1 N) y extraída con acetato de etilo. La fase orgánica fue secada sobre Na_2SO_4 y concentrada al vacío. El residuo fue purificado en columna (HPLC, C8, gradiente de elusión: acetonitrilo/agua (0.5% ácido fórmico) desde 1:4 hasta 1:0) para dar 16 mg (14 % para ambos pasos) de ácido 3,5-dibromo-4-(3,5-dibromo-4-hidroxifenoxi)fenilacético.

(g) Ácido 3,5-dibromo-4-(3,5-dibromo-4-hidroxifenoxi)fenilacético (16 mg, 0.037 mmol), diisopropiletilamina (33 μ l, 0.2 mmol), hexafluorofosfato de bromotripirrolidinofosfonio (21 mg, 0.044 mmol), 1-hidroxibenzotriazol hidrato (7 mg, 0.05 mmol), éster metílico de la D-fenilglicina (15 mg, 0.074 mmol) y diclorometano (0.5 ml) fueron mezclados y

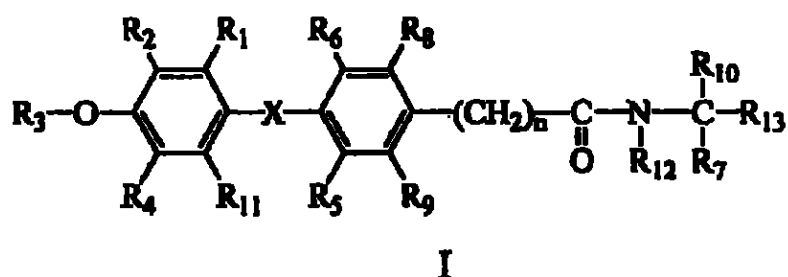
agitados por 1 hora a temperatura ambiente, y después de esto almacenados a 4°C por 20 horas. La mezcla de reacción fue lavada con ácido clorhídrico (1 N) y la fase acuosa remanente extraída con cloroformo. La combinación de las fases orgánicas fue concentrada al vacío y el residuo fue purificado en columna (sílica, eluyente: cloroformo) para dar 10 mg (47 %) de L-N-[3,5-dibromo-4-(3,5-dimetil-4-hidroxifenoxi)fenilacetil] fenilglicinato de metilo.

(h) L-N-[3,5-dibromo-4-(3,5-dimetil-4-hidroxifenoxi)fenilacetil] fenilglicinato de metilo (10 mg, 0.017 mmol) fue disuelto en tetrahidrofurano (0.25 ml) e hidróxido de litio (0.25 ml, 1 N) fue adicionado. La mezcla de reacción fue agitada por 1 hora a temperatura ambiente y 1 M de ácido clorhídrico (1 N) fue adicionado posteriormente hasta alcanzar pH 1. La mezcla obtenida fue extraída con el acetato de etilo y la combinación de las fases orgánicas fue secada sobre Na₂SO₄. Tras la concentración y purificación mediante TLC preparativa (sílica, eluyente: cloroformo/metanol/ácido acético 9:1:0.1), 5 mg (52%) de L-N-[3,5-dibromo-4-(3,5-dimetil-4-hidroxifenoxi)fenilacetil]fenilglicina fue obtenido. LC-MS (ES-1): m/z 560.

Los compuestos de los ejemplos 1-6 exhiben afinidades de unión al receptor beta de la tiroides en el intervalo de IC₅₀ de 1.0 a 100 nM.

REVINDICACIONES

1. Un compuesto con la fórmula general:



o una sal farmacéuticamente aceptable de este, en donde:

R_1 es seleccionado de un grupo que contiene hidrógeno, halógeno y alquilo de C_1 a C_6 ;

R_2 es seleccionado del grupo que contiene halógeno, alquilo de C_1 a C_6 , alquenilo de C_2 a C_6 , alquinilo de C_2 a C_6 , cicloalquenilo de C_4 a C_7 , cicloalcoxi de C_3 a C_7 , $SO_2(NR_{14}R_{15})$, $NR_{16}SO_2R_{17}$, SR_{17} , SOR_{17} , SO_2R_{17} , COR_{18} y $CR_{18}(OR_{18})R_{19}$; o R_2 es hidrógeno cuando R_4 es alquilo y R_1 es halógeno;

R_3 es seleccionado del grupo que contiene hidrógeno, alquilo, bencilo, aroilo y alcanilo;

R₄ es halógeno, ciano o alquilo;

R₅ y R₆ son independientemente seleccionados de hidrógeno, halógeno; ciano, alquilo de C₁₋₄, cicloalquilo de C₃ a C₆; en donde al menos uno de R₅ y R₆ no es hidrógeno;

R₇ y R₁₀ son independientemente seleccionados de hidrógeno, halógeno, arilo y alquilo, y R₇ y R₁₀ pueden ser unidos para integrar una cadena de 2 a 6 grupos metilenos para formar un anillo de 3 a 7 miembros de tamaño;

R₈ y R₉ son cada uno independientemente seleccionados de hidrógeno, halógeno, alcoxi, hidroxilo (OH), ciano y alquilo;

con la condición de que no mas de uno de R₂, R₄, R₈ y R₉ son hidrógenos;

R₁₁ es hidrógeno halógeno o alquilo;

R₁₂ es hidrógeno o alquilo;

R₁₃ es ácido carboxílico (COOH) o ésteres de este, ácido fosfónico o fosfínico o ésteres de estos, ácido sulfónico, tetrazol, ácido hidroxámico, tiazolidindiona, acilsulfonamida, u otros substitutos de ácido carboxílico conocido en el estado del arte;

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R_{14} y R_{15} para cada caso son cada uno seleccionados independientemente del grupo que contiene hidrógeno, alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo y R_{14} y R_{15} pueden ser unidos para integrar una cadena de 3 a 6 grupos metilenos para formar un anillo de 4 a 7 miembros de tamaño;

R_{16} es seleccionado de un grupo que contiene hidrógeno, alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo;

R_{17} es seleccionado del grupo que contiene alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo;

R_{18} y R_{19} para cada caso son cada uno seleccionados independientemente del grupo que contiene hidrógeno, alquilo, cicloalquilo, arilo, heteroarilo, arilalquilo y heteroarilalquilo;

n es un estero de 0, 1 o 2;

X es seleccionado de: $-O-$, $-CH_2-$, $-CF_2-$, $-Se-$, $-NH-$, $-S-$, $-SO-$, $-SO_2-$ y $-CO-$;

y sales farmacéuticamente aceptables, formas profármaco y estereoisómeros de estos.

2. Un compuesto acorde con la reivindicación 1, el cual tenga uno o más centros asimétricos y pueda existir en la forma de racematos, uno o múltiples estereoisómeros, como diastereómeros individuales, con todos los isómeros posibles y mezclas de estos.

3. Un compuesto acorde con la reivindicación 1 o 2 donde dicho compuesto sea:

N-[3,5-Dicloro-4-(4-hidroxi-3-isopropil-5-metilfenoxi)benzoil] glicina (E1);

N-[3,5-Dicloro-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E2);

N-[3,5-Dicloro-4-(2-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E3);

N-[3,5-Dicloro-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E4);

N-[3,5-Dicloro-4-(3-ciano-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E5);

N-[3,5-Dicloro-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E6);

N-[3,5-Dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E7);

L-N-[3,5-Dibromo-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)fenilacetil] valina (E10);

D-N-[3,5-Dibromo-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)fenilacetil] fenilglicina (E11);

L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] valina (E12);

L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] fenilglicina (E13);

L-N-[3,5-Dibromo-4-(3,5-dimetil-4-hidroxifenoxi)fenilacetil] fenilglicina (E14);

4. N-[3,5-Dibromo-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E8);

N-[3,5-Dimetil-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E9);

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5. Un compuesto acorde con cualquiera de las reivindicaciones 1 a 3 para uso en terapia médica.
6. Una formulación farmacéutica que contiene una cantidad efectiva de un compuesto acorde con las reivindicaciones 1 a 3 o una sal farmacéuticamente efectiva de este, junto con un vehículo farmacéuticamente aceptable.
7. Un proceso para elaborar una formulación farmacéutica que contiene la combinación de un compuesto acorde con cualquiera de las reivindicaciones 1 a 3 y un vehículo farmacéuticamente aceptable.
8. Una formulación farmacéutica que contiene un compuesto acorde con cualquiera de las reivindicaciones 1 a 3 y al menos un agente terapéutico adicional seleccionado del grupo que consta de otros compuestos con la formula 1, agentes anti-diabéticos, agentes anti-osteoporosis, agentes anti-obesidad, agentes promotores de crecimiento, agentes anti-inflamatorios, agentes anti-ansiedad, anti-depresivos, agentes anti-hipertensivos, glicósidos cardíacos, agentes reductores de colesterol/lípido, supresores de apetito, inhibidores de la resorción ósea, miméticos tiroideos, agentes anabólicos, agentes antitumorales y retinoides.
9. La formulación farmacéutica de la reivindicación 8 en donde dicho agente terapéutico adicional es un agente anti-diabético seleccionado del grupo que

consta de una biguanida, un inhibidor de la glucosidasa, una meglitinida, una sulfonilurea, una tiazolidindiona, un agonista de la PPAR-alfa, un agonista de la PPAR-gama, un agonista dual PPAR alfa/gama, un inhibidor del SGLT2, un inhibidor de la glicógeno fosforilasa, un inhibidor de la α P2, un péptido-1 similar al glucagón (GLP-1), un inhibidor de la dipeptidil peptidasa IV e insulina.

10. La formulación farmacéutica de la reivindicación 8 en donde dicho agente terapéutico adicional es un agente anti-diabético seleccionado del grupo que consta de metformina, gliburida, glimepirida, glipirida, glipizida, clorpropamida, gliclazida, acarbosa, miglitol, troglitazona, pioglitazona, englitazona, darglitazona, rosiglitazona e insulina.
11. La formulación farmacéutica de la reivindicación 8 en donde dicho agente terapéutico adicional es un agente anti-obesidad seleccionado del grupo que consta de un inhibidor de la α P2, un antagonista de la PPAR gama, un antagonista de la PPAR delta, un agonista de los adrenérgicos beta 3, un inhibidor de la lipasa, un inhibidor de la recaptación de la serotonina, un antagonista del receptor canabinoide-1 y un agente anoréxico.
12. La formulación farmacéutica de la reivindicación 8 en donde dicho agente terapéutico adicional es un agente hipolipidémico seleccionado del grupo que

consta de una tiazolidindiona, un inhibidor de la MTP, un inhibidor de la escualeno sintetasa, un inhibidor de la HMG-CoA reductasa, un derivado del ácido fibrico, un inhibidor de la ACAT, un inhibidor de la absorción del colesterol, un inhibidor del co-transportador ileal de Na⁺/ácido biliar, un secuestrante de ácido biliar y un ácido nicotínico o un derivado de este.

13. Un método para prevenir, inhibir o tratar una enfermedad que depende de la expresión de un gen regulado por T₃ o asociada con una disfunción del metabolismo, que consiste en administrar a un paciente que requiera de tratamiento una cantidad terapéuticamente efectiva de un compuesto como los definidos en las reivindicaciones 1 a 3.
14. Un método para tratar o retrasar la progresión o el inicio de obesidad, hipercolesterolemia, aterosclerosis, depresión, osteoporosis, hipotiroidismo, hipertiroidismo subclínico, bocio no tóxico, cáncer de tiroides, masa, densidad o crecimiento óseo reducido, trastornos alimenticios, función cognoscitiva reducida, cáncer de tiroides, glaucoma, arritmia cardíaca, insuficiencia cardíaca congestiva, o trastornos o enfermedades de piel, el cual consiste en administrar a un paciente mamífero que requiera de tratamiento una cantidad terapéuticamente efectiva de un compuesto como los definidos en la reivindicación 1.

15. El método que fue definido en la reivindicación 13, en donde dicha enfermedad es obesidad, hipercolesterolemia, aterosclerosis, depresión, osteoporosis, hipotiroidismo, bocio, cáncer de tiroides, glaucoma, arritmia cardíaca, insuficiencia cardíaca congestiva o trastornos de piel.
16. El método acorde con la reivindicación 14, en donde el trastorno o la enfermedad de la piel es atrofia dérmica, lesión post quirúrgica causada por resurfacing láser, queloides, estría, celulitis, piel áspera, daño actínico de la piel, liquen plano, ictiosis, acné, soriasis, la enfermedad de Demier, eccema, dermatitis atópica, cloracne, pitiriasis y cicatrices en la piel.
17. El método acorde con la reivindicación 13 que además incluye la administración, concurrente o secuencialmente, de una cantidad terapéuticamente efectiva de al menos un agente terapéutico adicional seleccionado del grupo que consta de otros compuestos con la formula I, agentes anti-diabéticos, agentes anti-osteoporosis, agentes anti-obesidad, agentes promotores de crecimiento, agentes anti-inflamatorios, agentes anti-ansiedad, anti-depresivos, agentes anti-hipertensivos, glicósidos cardíacos, agentes reductores de colesterol/lípido, supresores de apetito, inhibidores de la resorción ósea, miméticos tiroideos, agentes anabólicos, agentes antitumorales y retinoides.

18. Un método para tratar o retrasar la progresión o el inicio de un trastorno o enfermedad de la piel el cual consiste en administrar a un paciente mamífero una cantidad terapéuticamente efectiva de un compuesto como los definidos en la reivindicación 1 en combinación con un retinoide o un análogo de la vitamina D.
19. Un método para tratar o retrasar la progresión o el inicio de obesidad el cual consiste en administrar a un paciente mamífero una cantidad terapéuticamente efectiva de un compuesto como los definidos en la reivindicación 1.
20. Un método acorde con la reivindicación 19 que además incluye la administración, concurrente o secuencialmente, de una cantidad terapéuticamente efectiva de al menos un agente terapéutico adicional seleccionado del grupo que consta de un agente anti-obesidad y un supresor de apetito.
21. Un método acorde con la reivindicación 20 en donde dicho agente anti-obesidad es seleccionado del grupo que consta de inhibidor de la $\alpha P2$, antagonista de la PPAR gama, agonista de la PPAR delta, un agonista de los adrenérgicos beta 3, inhibidor de la lipasa, inhibidor de la recaptación de la serotonina (y dopamina), antagonista del receptor canabinoide-1, otro agente receptor tiroideo y agente anoréxico.

22. El uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 4 en la preparación de un medicamento para inhibir o tratar una enfermedad que depende de la expresión de un gen regulado por T_3 o asociada con una disfunción del metabolismo.
23. El uso acorde con la reivindicación 22, en donde dicha enfermedad es seleccionada entre obesidad, hipercolesterolemia, aterosclerosis, depresión, osteoporosis, hipotiroidismo, hipertiroidismo subclínico, bocio no tóxico, cáncer de tiroides, masa, densidad o crecimiento óseo reducido, trastornos alimenticios, función cognoscitiva reducida, cáncer de tiroides, glaucoma, arritmia cardíaca, insuficiencia cardíaca congestiva, o trastornos o enfermedades de piel.
24. El uso acorde con la reivindicación 23, en donde el trastorno o enfermedad de la piel es seleccionado entre atrofia dérmica, lesión post quirúrgica causada por resurfacing láser, queloides, estría, celulitis, piel áspera, daño actínico de la piel, liquen plano, ictiosis, acné, soriasis, la enfermedad de Demier, eccema, dermatitis atópica, cloracne, pitiriasis y cicatrices en la piel.
25. Uso acorde con la reivindicación 22 en combinación con al menos un agente terapéutico adicional seleccionado del grupo que consta de otros compuestos con la fórmula I, agentes anti-diabéticos, agentes anti-osteoporosis, agentes anti-

obesidad, agentes promotores de crecimiento, agentes anti-inflamatorios, agentes anti-ansiedad, anti-depresivos, agentes anti-hipertensivos, glicósidos cardiacos, agentes reductores de colesterol/lípido, supresores de apetito, inhibidores de la resorción ósea, miméticos tiroideos, agentes anabólicos, agentes antitumorales y retinoides.

26. Uso acorde con la reivindicación 22 en combinación con un retinoide o un análogo de la vitamina D en donde dicha enfermedad es un trastorno o enfermedad de la piel.
27. Uso acorde con la reivindicación 22 en donde dicha enfermedad es obesidad.
28. Uso acorde con la reivindicación 27 en combinación con al menos un agente terapéutico adicional seleccionado del grupo que consta de un agente anti-obesidad y un supresor de apetito.
29. Uso acorde con la reivindicación 28, en donde dicho agente anti-obesidad es seleccionado del grupo que consta de inhibidor de la $\alpha P2$, antagonista de la PPAR gama, agonista de la PPAR delta, agonista de los adrenérgicos beta 3, inhibidor de la lipasa, inhibidor de la recaptación de la serotonina (y dopamina), un antagonista del receptor canabinoide-1, otro agente receptor tiroideo y un agente anoréxico.

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30. Una formulación farmacéutica la cual funciona como un agonista selectivo del receptor de la hormona tiroidea que contiene un compuesto como los definidos en la reivindicación 1.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference KB523 PCT/DGB	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/07333	International filing date (day/month/year) 08/07/2003	(Earliest) Priority Date (day/month/year) 10/07/2002
Applicant KARO BIO AB		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

BENZAMIDE OR PHENYLACETAMIDE DERIVATIVES USEFUL AS THYROID RECEPTOR LIGANDS

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07333

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition which have been searched.
2. ☒ Claims Nos.: 1,2,5-12,22-30 all partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/07333

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C235/52 C07C235/34 A61K31/195 A61P5/16

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 C07C A61K

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

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

EPO-Internal, 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 94293 A (SQUIBB BRISTOL MYERS CO ;RYONO DENIS E (US)) 13 December 2001 (2001-12-13) the whole document	1,2, 5-12, 22-30
X	WO 00 39077 A (GARG NEERAJ ;LI YI LIN (SE); KAROBIO AB (SE); KOEHLER KONRAD (SE);) 6 July 2000 (2000-07-06) the whole document	1,2, 5-12, 22-30
P,X	WO 02 094319 A (HAYASHI MORIMICHI ;KISSEI PHARMACEUTICAL (JP); NISHIMURA TOSHIHIRO) 28 November 2002 (2002-11-28) abstract; pages 18-25; claims	1,2, 5-12, 22-30
	-/-	



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
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"A" document member of the same patent family

Date of the actual completion of the international search

1 December 2003

Date of mailing of the international search report

16/12/2003

Name and mailing address of the ISA

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Authorized officer

Rufet, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/07333

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 57, no. 7, 1 October 1962 (1962-10-01) Columbus, Ohio, US; abstract no. 8493g, JEAN ROCHE ET AL.: "Synthesis of new derivatives of iodothyroacetic acid, the iodothyroacetyl glycines." page 8493; column 1; XP002263402 abstract & BULL. SOC. CHIM. FRANCE, 1959, pages 1547-1550, -----	1,2, 5-12, 22-30

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,5-12,22-30 all partially

Present claims 1, 2, 5-12, 22-30 relate to an extremely large number of possible compounds/compositions/uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/apparatus/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to formula (I) of claim 1 wherein:

R3 is hydrogen,

X is O,

R13 is COOH,

R7 is H and R10 is H, halogen phenyl or an alkyl group,

the other substituents are defined according to the corresponding definitions given in claim 1 whereby expressions like "alkyl, aroyl, alkanaoyl, aryl, ester thereof, carboxylic acid surrogates known in the art, heteroaryl, arylalkyl, heteroarylalkyl, etc..." have not been considered, as far as they have been supported by examples, since those expressions are speculative and it is not reasonable to predict that all variants covered by such expressions have the alleged effect.

It is stressed that the compounds of claims 3 and 4 are not comprised by the scope of claim 1 due to the proviso concerning R2, R4, R8 and R9.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07333

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0194293	A	13-12-2001	AU 6813201 A	17-12-2001
			CA 2411062 A1	13-12-2001
			EP 1292568 A2	19-03-2003
			WO 0194293 A2	13-12-2001
			US 6395784 B1	28-05-2002
WO 0039077	A	06-07-2000	AU 758202 B2	20-03-2003
			AU 1885500 A	31-07-2000
			BR 9916851 A	16-10-2001
			CA 2356319 A1	06-07-2000
			CN 1337953 T	27-02-2002
			CZ 20012204 A3	14-11-2001
			EP 1144370 A2	17-10-2001
			HU 0104666 A2	28-03-2002
			WO 0039077 A2	06-07-2000
			JP 2002533432 T	08-10-2002
			NO 20012931 A	21-08-2001
			TR 200101834 T2	21-12-2001
WO 02094319	A	28-11-2002	WO 02094319 A1	28-11-2002

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 December 2001 (13.12.2001)

PCT

(10) International Publication Number
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64/210,102 7 June 2000 (07.06.2000) US

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(74) Agents: KILCOYNE, John, M. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States (national): AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

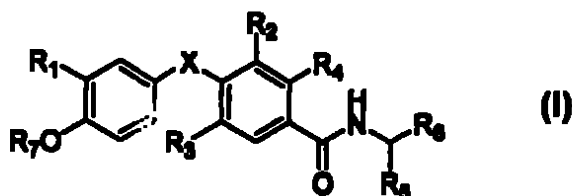
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BENZAMIDE LIGANDS FOR THE THYROID RECEPTOR



(57) Abstract: New thyroid receptor ligands are provided which have the general formula (I) in which: X is -O-, -S-, -CH2-, -CO-, or -NH-; R₁ is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons; R₂ and R₃ are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 6 carbons, at least one of R₂ and R₃ being other than hydrogen; R₄ is methyl, ethyl, n-propyl or trifluoromethyl; R₅ is hydrogen or lower alkyl; R₆ is carboxylic acid, or esters or amides; R₇ is hydrogen

or an alkanoyl or an aroyl. In addition, a method is provided for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T₃ regulated gene, wherein a compound as described above is administered in a therapeutically effective amount. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T₃ regulated gene include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma, congestive heart failure and skin disorders.

WO 01/94293 A2

BENZAMIDE LIGANDS FOR THE THYROID RECEPTOR

5 This invention relates to novel compounds which are thyroid receptor ligands, and are preferably selective for the thyroid hormone receptor β , and to methods of preparing such compounds and to methods for using such compounds such as in the regulation of metabolism.

10

 While the extensive role of thyroid hormones in regulating metabolism in humans is well recognized, the discovery and development of new specific drugs for improving the treatment of hyperthyroidism and

15 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, obesity and cardiac arrhythmias.

 Thyroid hormones affect the metabolism of virtually

20 every cell of the body. At normal levels, these hormones maintain body weight, the metabolic rate, body temperature, and mood, and influence serum low density lipoprotein (LDL) levels. Thus, in hypothyroidism there is weight gain, high levels of LDL cholesterol, and

25 depression. In excess with hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

30 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

170
(TSH), thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T_4) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or T_3). However, replacement therapy, particularly in older individuals is limited by certain of the deleterious effects of 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 weight reduction, lowering of serum LDL levels, 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.

Development of specific and selective thyroid hormone receptor agonists could lead to specific therapies for these common disorders while avoiding the cardiovascular and other toxicities of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Thyroid hormone receptor agonists that interact selectively with the β -form of the thyroid hormone receptor offers an especially attractive method for avoiding cardio-toxicity.

Thyroid hormone receptors (TRs) are, like other nuclear receptors, single polypeptide chains. The various receptor forms appear to be products of two different genes α and β . Further isoform differences are due to the fact that differential RNA processing results in at least two isoforms from each gene. The $TR\alpha_1$, $TR\beta_1$ and $TR\beta_2$ isoforms bind thyroid hormone and act as ligand-regulated transcription factors. In adults, the $TR\beta_1$ isoform is the most prevalent form in most tissues, especially in the liver and muscle. The $TR\alpha_2$ isoform is

prevalent in the pituitary and other parts of the central nervous system, does not bind thyroid hormones, and acts in many contexts as a transcriptional repressor. The TR α_1 isoform is also widely distributed, although its levels are generally lower than those of the TR β_1 isoform. This isoform may be especially important for development. Whereas many mutations in the TR β gene have been found and lead to the syndrome of generalized resistance to thyroid hormone, mutations leading to impaired TR α function have not been found.

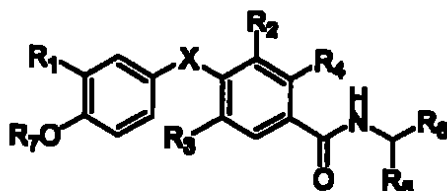
A growing body of data suggest that many or most effects of thyroid hormones on the heart, and in particular on the heart rate and rhythm, are mediated through the α -form of the TR α_1 isoform, whereas most actions of the hormone such as on the liver, muscle and other tissues are mediated more through the β -forms of the receptor. Thus, a TR β -selective agonist might not elicit the cardiac rhythm and rate influences of the hormones but would elicit many other actions of the hormones. It is believed that the α -form of the receptor is the major driver to heart rate for the following reasons:

- 1) tachycardia is very common in the syndrome of generalized resistance to thyroid hormone in which there are defective TR β -forms, and high circulating levels of T₄ and T₃;
- 2) there was a tachycardia in the only described patient with a double deletion of the TR β gene (Takeda et al, J. Clin. Endocrinol. & Metab. 1992, Vol. 74, p. 49);
- 3) a double knockout TR α gene (but not β -gene) in the mouse has a slower pulse than control mice; and,
- 4) western blot analysis of human myocardial TRs show presence of the TR α_1 , TR α_2 and TR β_2 proteins, but not TR β_1 .

If these indications are correct, then it may be possible that a TR β -selective agonist could be used to mimic a number of thyroid hormone actions, while having a lesser effect on the heart. Such a compound may be used for: (1) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (2) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (3) obesity; (4) hypercholesterolemia due to elevations of plasma LDL levels; (5) depression; and, (6) osteoporosis in combination with a bone resorption inhibitor.

In accordance with the present invention, compounds are provided which are thyroid receptor ligands, and have the general formula I:

I



in which:

X is oxygen (-O-), sulfur (-S-), methylene (-CH₂-), carbonyl (-CO-), or di-substituted nitrogen (-NH-);

R₁ is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

R₂ and R₃ are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 6 carbons, at least one of R₂ and R₃ being other than hydrogen;

R₄ is methyl, ethyl, n-propyl or trifluoromethyl;

R₅ is hydrogen or lower alkyl;

R₆ is carboxylic acid, or an ester thereof (preferably an alkyl ester), or a prodrug thereof;

R₇ is hydrogen or an alkanoyl or aroyl (such as acetyl or benzoyl) or other group capable of

bioconversion to generate the free phenol structure
(wherein R₁ = H);

including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof.

5 In addition, in accordance with the present invention, a method for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T₁ regulated gene is provided, wherein a compound of formula
10 I is administered in a therapeutically effective amount. The compound of formula I is preferably an agonist that is preferably selective for the thyroid hormone receptor-beta. Examples of such diseases associated with metabolism dysfunction or are dependent upon the
15 expression of a T₁ regulated gene are set out hereinafter and include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma and congestive heart failure.

20

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

25 The term "thyroid receptor ligand" as used herein is intended to cover any moiety which binds to a thyroid receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist. Another term for "thyroid receptor ligand" is "thyromimetic".

30 Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 12 carbons (in the case of alkyl or alk), in the normal chain, preferably 1 to 4
35 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, or isobutyl, pentyl, hexyl, isohexyl, heptyl,

4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, which may be optionally substituted with 1 to 4 substituents which may include alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino, halo, carboxyl or alkyl ester thereof and/or carboxamide, substituted or unsubstituted.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, hydroxy, amino, nitro, cyano and/or carboxyl or alkyl ester thereof.

The term "heteroaryl" or "heteroaromatic moiety" as used herein alone or as a part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3, or 4 heteroatoms, one of which must be a nitrogen atom; the other atoms when present may be nitrogen, oxygen or sulfur, and such rings may be fused to another aryl or heteroaryl ring, and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, cyano, nitro, amino and/or carboxyl, or alkyl ester thereof.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 5 carbons, in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl,

3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, and the like, which may be substituted as in the case of "alkyl".

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 8 carbons, in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, which may be substituted as in the case of "alkyl".

The term "alkanoyl" as employed herein alone or as part of another group is alkyl linked to a carbonyl group.

The term "aroyl" as employed herein alone or as part of another group is aryl linked to a carbonyl group.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated cyclic hydrocarbon groups or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups, containing one ring and a total of 3 to 7 carbons, preferably 3 to 6 carbons, forming the ring, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl and cyclohexenyl, , which may be substituted as in the case of "alkyl".

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF₃, with chlorine or bromine being preferred.

The compounds of formula I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid,

phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C1-C4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methanesulfonic acid or p-toluenesulfonic acid.

Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethylpropylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I which include a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

Preferred salts of the compounds of formula I which include an acid group include sodium, potassium and

magnesium salts and pharmaceutically acceptable organic amines.

Carboxylic acid prodrugs and prodrugs in general are described in standard references such as Chapter 31, written by Camille G. Wermuth et al., in "The Practice of Medicinal Chemistry", ed. C. G. Wermuth, Academic Press, 1996 (and the references contained therein).

Preferred prodrugs include lower alkyl esters such as ethyl ester, or acyloxyalkyl esters such as pivaloyloxymethyl (POM).

Preferred are compounds of the invention of formula I wherein X = O.

Further preferred compounds are those of formula I wherein X = O;

R₁ is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons;

R₂ and R₃ are independently bromo, chloro or methyl;

R₄ is methyl or trifluoromethyl;

R₅ is hydrogen;

R₆ is carboxyl; and

R₇ is hydrogen.

Most preferred compounds of the invention are those of formula I wherein X = O;

R₁ is alkyl of 1 to 6 carbons;

R₂ and R₃ are independently bromo, chloro or methyl;

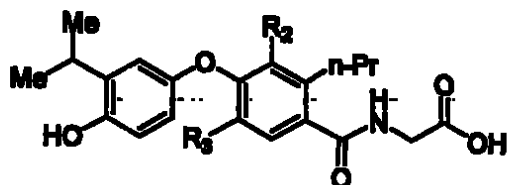
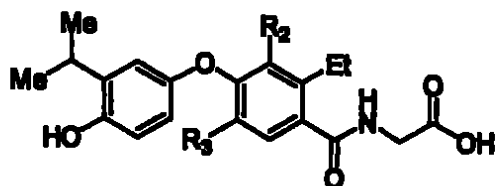
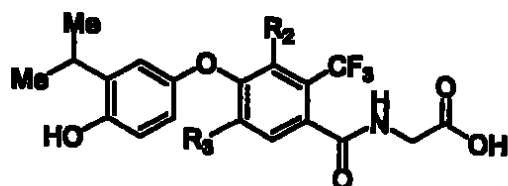
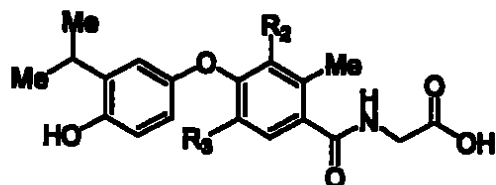
R₄ is methyl;

R₅ is hydrogen;

R₆ is carboxyl; and

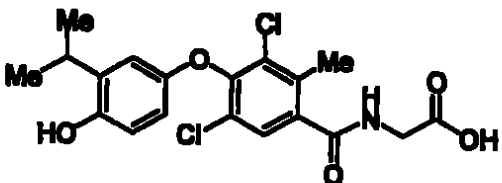
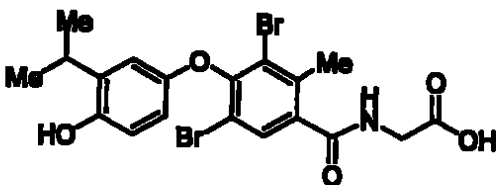
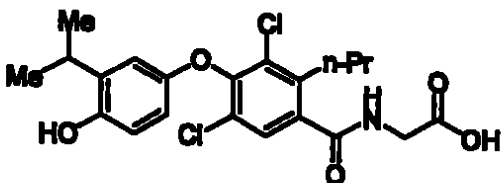
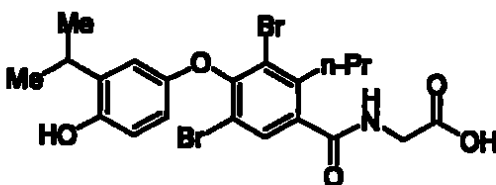
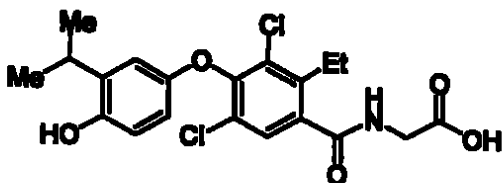
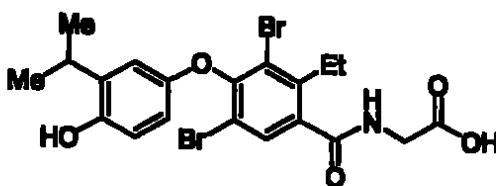
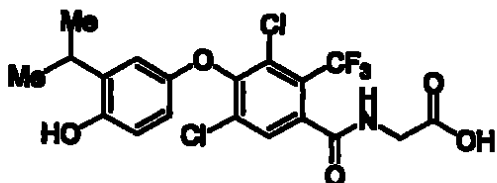
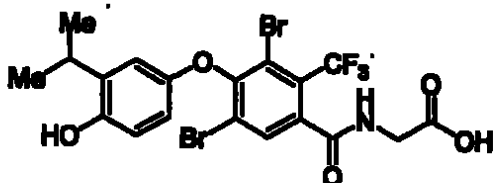
R₇ is hydrogen.

Thus, preferred compounds of the invention will have the structures:



or an alkyl ester thereof.

Preferred compounds have the structures:

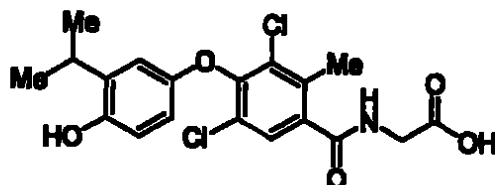
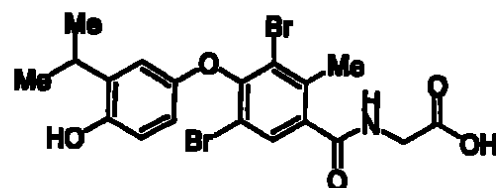


5

or alkyl esters thereof such as the methyl or ethyl ester thereof.

The most preferred compounds of the invention have the structures:

10



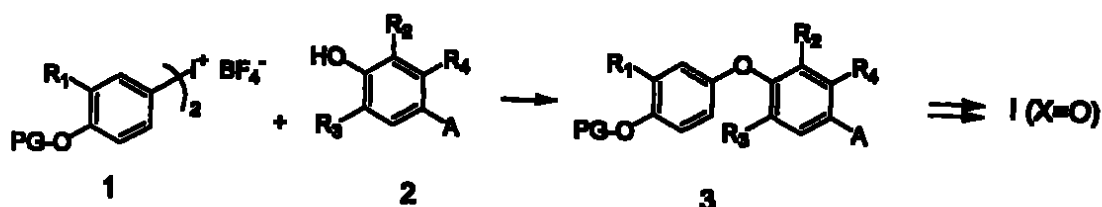
or alkyl esters thereof such as the methyl or ethyl ester.

The compounds of formula I may be prepared by the exemplary processes described in the following reaction schemes, as well as relevant published literature procedures that are used by one skilled in the art.

- 5 Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art (see, for example, T. W. Greene & P. G. M. Wuts,
10 "Protecting Groups in Organic Synthesis", 3rd Edition, Wiley, 1999).

- Scheme 1 depicts a general synthetic approach to compounds of formula I for which $X = O$ that utilizes the coupling of an appropriately substituted iodonium salt 1
15 to the appropriate phenol 2 to provide intermediate 3. In structure 1 and all other applicable structures contained in further schemes described below, PG refers to a protecting group appropriate for the functional group indicated (in this instance, for a phenolic
20 oxygen). The specific protecting groups for each particular intermediate are well understood by those versed in the art (see also the reference, "Protecting Groups in Organic Synthesis", cited above). Subsequent protecting group and functional group manipulation
25 provides the desired compounds of formula I. In structures 2 and 3, the group A represents a functional group that is a carboxylic acid or derivative (such as an ester, COOR), or another functional group which can be subsequently converted to a carboxylic acid, and further
30 manipulations provide compounds of formula I. Such functional groups and their means of conversion are well-known to those skilled in the art. For example, A may be a formyl group (CHO) which can be oxidized to a carboxylic acid (COOH) by the use any one of many known
35 oxidizing agents capable of effecting such a transformation.

Scheme 1

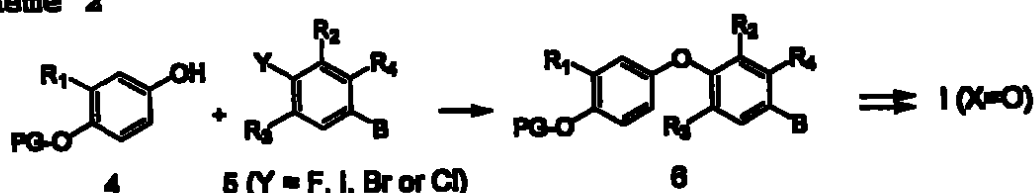


The iodonium salt methodology depicted in Scheme 1 is amply described in the literature for the synthesis of thyroid hormone analogs ("Novel Thyroid Receptor Ligands and Methods, Y.-L. Li, Y. Liu, A. Hedfors, J. Malm, C. Mellin, M. Zhang, PCT Int. App. WO 9900353 A1 990107; D. M. B. Hickey et al., J. Chem. Soc. Perkin Trans. I, 3103-3111, 1988; N. Yokoyama et al., J. Med. Chem., 38, 695-707, 1995), and to diaryl ethers in general (E. A. Couladouros, V. I. Moutsos, Tetrahedron Lett., 40, 7023-7026, 1999).

Scheme 2 depicts another general synthetic approach to compounds of formula I for which X = O in which an appropriately substituted phenol 4 is alkylated with an appropriately substituted intermediate 5 (for which Y is fluoro, chloro, iodo or bromo) to provide the intermediate 6. In structures 5 and 6, the group B represents a functional group such as nitro or formyl that is capable of activating the aryl halide (Y = F, I, Br or Cl) to displacement. The activating group B is then subsequently transformed to a carboxylic acid or derivative which can then be further converted to compounds of formula I for which X = O. Such functional groups and their means of conversion are well-known to those skilled in the art. For example, when B is a nitro function in intermediate 6, the nitro group can be reduced to an amino group by methods well known in the art, such as the use of catalytic hydrogenation in the presence of, for example, Raney nickel or palladium on charcoal catalyst, in a polar solvent such as glacial acetic acid or ethanol. Alternatively, the reduction can be accomplished using iron powder in aqueous glacial

acetic acid at ambient temperatures. The resulting aryl amine can be converted to the corresponding diazonium salt by the use, for example, of a mixture of sodium nitrite and sulfuric acid in appropriate solvents. The resulting diazonium group can then be converted to a formyl group (CHO) by the reaction with carbon monoxide catalyzed by an appropriate palladium catalyst such as palladium acetate. Subsequent protecting group and functional group manipulation provides the desired compounds of formula I in which X = O.

Scheme 2



The approach depicted in Scheme 2 for the general synthesis of diaryl ethers for thyromimetics is well preceded in the literature (P. D. Leeson, J. C. Emmett, J. Chem. Perkin Trans. I, 3085-3096, 1988; N. Yokoyama et al., J. Med. Chem., 38, 695-707, 1995).

Further means for synthesizing compounds of formula I in which X = O, NH, S, CO or CH₂ are generally described in the literature (for X = O: D. M. B. Hickey et al., J. Chem. Soc. Perkin Trans. I, 3097-3102, 1988; Z.-W. Guo et al., J. Org. Chem., 62, 6700-6701, 1997; D. M. T. Chan et al., Tetrahedron Lett., 39, 2933-2936, 1998; D. A. Evans et al., Tetrahedron Lett., 39, 2937-2940, 1998; G. M. Salamonczyk et al., Tetrahedron Lett., 38, 6965-6968, 1997; J.-F. Marcoux, J. Am. Chem. Soc., 119, 10539-10540, 1997; A. V. Kalinin et al., J. Org. Chem., 64, 2986-2987, 1999; for X = N: D. M. T. Chan et al., Tetrahedron Lett., 39, 2933-2936, 1998; J. P. Wolfe et al., J. Am. Chem. Soc., 118, 7215, 1996; M. S. Driver, J. F. Hartwig, J. Am. Chem. Soc., 118, 7217, 1996; see references in the review by C. G. Frost, P. Mendonca, J. Chem. Soc. Perkin I, 2615-2623, 1998; for X = S: C. R.

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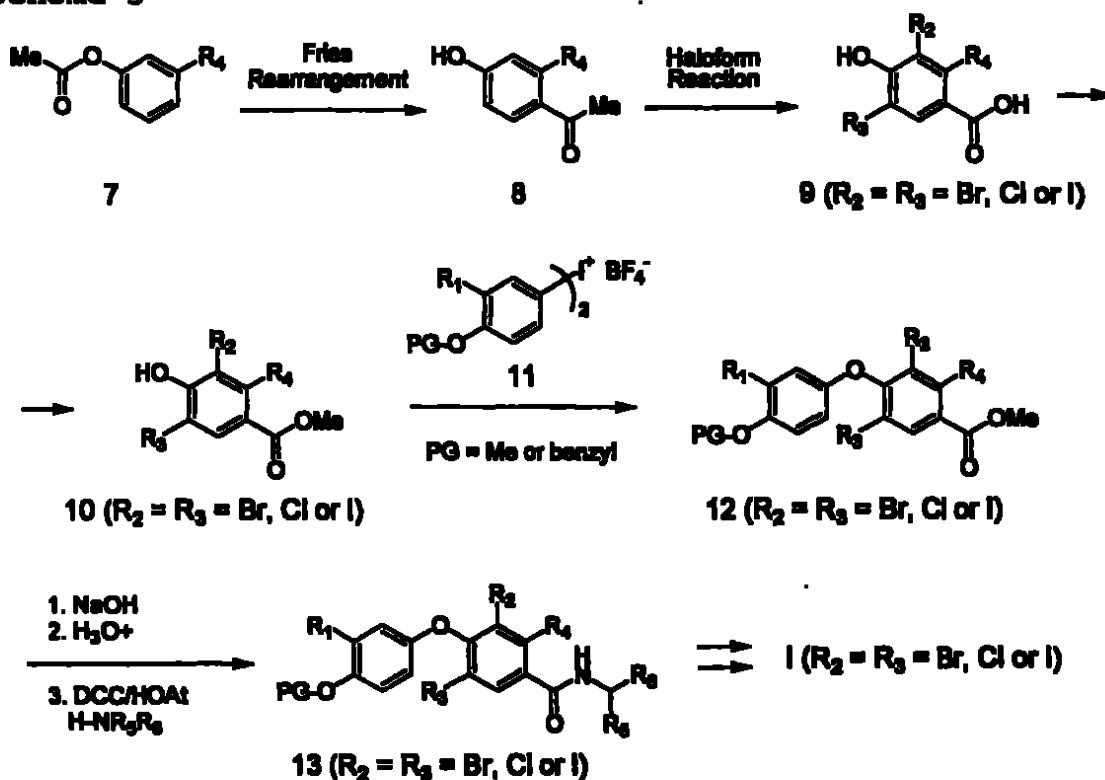
Harrington, Bi chem. J., 43, 434-437, 1948; A. Dibbo et al., J. Chem. S c., 2890-2902, 1961; N. Yokoyama et al., United States Patent 5,401,772, 1995; for X = CO or CH₂: L. Horner, H. H. G. Medem, Chem. Ber., 85, 520-530, 1952; 5 G. Chiellini et al., Chemistry & Biology, 5, 299-306, 1998).

Methods applicable to the synthesis of compounds of formula I in which X = O and R₂ and R₃ are independently varied as hydrogen, halogen and alkyl are described in 10 "Novel Thyroid Receptor Ligands and Methods, Y.-L. Li, Y. Liu, A. Hedfors, J. Malm, C. Mellin, M. Zhang, PCT Int. App. WO 9900353 A1 990107.

Scheme 3 shows an example of the approach described in Scheme 1 wherein the group A is a carboxylic ester 15 function and R₂ = R₃ = Br, Cl or I. Readily available meta-OH substituted alkyl benzene compounds can be acetylated to give the intermediate O-acetyl phenol 7 which undergoes a Fries rearrangement (Shine, "Aromatic Rearrangements", American Elsevier, 72-82, 365-368, 1967) 20 to provide the acetophenone intermediate 8. Intermediate 8 is converted to carboxylic acid 9 using the haloform reaction (Chakrabarty, "Oxidation in Organic Chemistry", part C, ed. Trahanovsky, Academic Press, New York, 343-370, 1978). Esterification of acid 9 to methyl ester 10 25 is accomplished by standard means (such as the use of methanol saturated with HCl). Alternatively, other ester protecting groups can be used. The resulting ester 10 is coupled to iodonium salt 11 to give the diphenyl ether intermediate 12. Conversion of the ester group back to 30 the carboxylic acid is followed by coupling to an amine HNR₃R₆ using standard reagents such as dicyclohexylcarbodiimide with HOAt catalyst to give, after removal of protecting groups, the compound of formula I in which R₂ = R₃ = Br, Cl or I.

35

Scheme 3



All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

The compounds of the invention are agonists, that are preferably selective for the thyroid hormone receptor-beta, and as such are useful in the treatment of obesity, hypercholesterolemia and atherosclerosis by lowering of serum LDL levels, alone or optionally in combination with a lipid modulating drug such as an HMG-CoA reductase inhibitor, fibrate, MTP inhibitor, squalene

synthetase inhibitor and/or ther hypolipidemic agent and/or optionally in combination with an antidiabetic agent; useful in the amelioration of depression, alone or optionally in combination with an antidepressant such as fluoxetine and desipramine; and useful in the stimulation of bone formation to treat osteoporosis, alone or optionally in combination with any known bone resorption inhibitor such as alendronate sodium. In addition, the compounds of the invention may be useful as replacement therapy in elderly patients with hypothyroidism or subclinical hypothyroidism who are at risk for cardiovascular complications, in the treatment of the elderly to provide a sense of well-being, and in the treatment of non-toxic goiter; in the management of papillary or follicular thyroid cancer (alone or with T4); in the treatment of skin disorders such as psoriasis, glaucoma, cardiovascular disease such as in the prevention or treatment of atherosclerosis, and congestive heart failure.

The compounds of the invention may be employed alone or in combination with an appetite suppressant such as sibutramine, and/or in combination with anti-obesity agents such as orlistat, and/or in combination with a $\beta 3$ agonist, for treating obesity.

The compounds of the invention may also be used to treat skin disorders or diseases involving dermal atrophy such as glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical glucocorticoids, 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, or dermal

atrophy induced by aging (wrinkles, etc.), wound healing, 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 treating skin disorders or diseases as described above, the compounds of the invention may be used alone or optionally in combination with a retinoid such as tretinoin or a vitamin D analog, employing amounts as disclosed in the PDR.

The hypolipidemic agent which may be optionally employed in combination with the compounds of formula I of the invention may include thiazolidinediones, MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, cholesterol absorption inhibitors, ileal Na⁺/bile acid cotransporter inhibitors, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

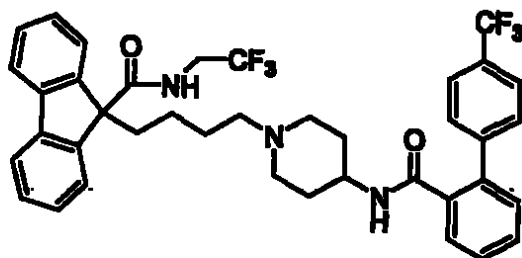
20 MTP inhibitors employed herein include MTP
inhibitors disclosed in U.S. Patent No. 5,595,872, U.S.
Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S.
Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S.
Patent No. 5,885,983 and U.S. Application Serial No.
25 09/175,180 filed October 20, 1998, now U.S. Patent No.
5,962,440. Preferred are each of the preferred MTP
inhibitors disclosed in each of the above patents and
applications.

30 All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

35 The most preferred MTP inhibitor is

9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



5 The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, 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. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-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, octahydro-naphthalenes such as disclosed in

U.S. Patent No. 4,499,289, ket analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

5 In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α -phosphono-
10 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 as well as other squalene synthetase inhibitors as disclosed in U.S. Patent No.
15 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, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid
20 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. Soc., 1976, 98, 1291-1293, phosphinylphosphonates
25 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, Summary.

30 Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S.
35 Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as

well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

The other hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCK 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 alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "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
5 hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62.

The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 as well as those disclosed in Atherosclerosis
10 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

The hypolipidemic agent may be an ileal Na⁺/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin and cerivastatin.
15

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference
20 and/or in the patents set out above.

The compounds of formula I of the invention will be employed in a weight ratio to the hypolypidemic agent, the antidepressant, and/or bone resorption inhibitor and/or appetite suppressant (where present), within the
25 range from about 500:1 to about 0.005:1, preferably from about 300:1 to about 0.01:1.

The antidiabetic agent which may be optionally employed in combination with compounds of formula I of the invention may include biguanides, sulfonyl ureas, glucosidase inhibitors, thiazolidinediones and/or αP2
30 inhibitors and/or PPAR α agonists, PPAR γ agonists or PPAR α/γ dual agonists, and/or SGLT2 inhibitors, or meglitinide.

The antidiabetic agent may be an oral
35 antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof.

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Where the antidiabetic agent is a biguanide, the compounds of structure I will 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 antidiabetic agent may also preferably be a sulfonylurea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent N . 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic
10 agents which act on the ATP-dependent channel of the β -cells, with glyburide and glipizide being preferred.

 The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to
15 about 10:1.

 The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in a
20 separate oral dosage form.

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

25 The compounds of structure I may be employed in combination with a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin[®], disclosed in
30 U.S. Patent No. 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Welcome's GI-262570, englitazone (CP-68722, Pfizer), or darglitazone (CP-86325, Pfizer).

35 The compounds of structure I will be employed in a weight ratio to the 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 sulfonylurea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

The compounds of structure I may also be employed in combination with a non-oral antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), which may be administered via injection, intranasal, or by transdermal or buccal devices.

Where present, metformin, the sulfonylureas, such as glyburide, glimepiride, glipyrizide, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference.

Where present, metformin or salt thereof may be employed 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.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

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The antidiabetic agent may also be a PPAR α/γ dual agonist such as disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998).

The antidiabetic agent may be an $\alpha P2$ inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and U.S. provisional application No. 60/127,745, filed April 5, 1999 (attorney file LA27*), employing dosages as set out herein.

The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. provisional application 60/158,773 filed October 12, 1999 (Attorney file LA0049*).

The compounds of formula I will be employed in a weight ratio to the PPAR α agonist, PPAR γ agonist, PPAR γ/α dual agonists, SGLT2 inhibitor and/or $\alpha P2$ inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the hypolipidemic agent and antidiabetic agent will be as disclosed in the various patents and applications discussed above and in the PDR.

The dosages and formulations for the other hypolipidemic agent, antidepressant, bone resorption inhibitor, appetite suppressant and anti-obesity agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor 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
t about 75 mg/kg, ne to four times daily.

A preferred oral dosage form, such as tablets or
capsules, will contain the MTP inhibitor in an amount of
5 from about 1 to about 500 mg, preferably from about 2 t
about 400 mg, and more preferably from about 5 to about
250 mg, one to four times daily.

For parenteral administration, the MTP inhibitor
will be employed in an amount within the range of from
10 about 0.005 mg/kg to about 10 mg/kg and preferably from
about 0.005 mg/kg to about 8 mg/kg, one to four times
daily.

For oral administration, a satisfactory result may
be obtained employing an HMG CoA reductase inhibitor, for
15 example, pravastatin, lovastatin, simvastatin,
atorvastatin, fluvastatin or cerivastatin in dosages
employed as indicated in the Physician's Desk Reference,
such as in an amount within the range of from about 1 to
2000 mg, and preferably from about 4 to about 200 mg.

20 The squalene synthetase inhibitor may be employed
in dosages in an amount 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
25 capsules, will contain the HMG CoA reductase inhibitor in
an amount from about 0.1 to about 100 mg, preferably from
about 5 to about 80 mg, and more preferably from about 10
to about 40 mg.

A preferred oral dosage form, such as tablets or
30 capsules will contain the squalene synthetase inhibitor
in an amount of from about 10 to about 500 mg, preferably
from about 25 to about 200 mg.

The compounds of formula I and the hypolipidemic
agent, antidepressant or bone resorption inhibitor may be
35 employed together in the same oral dosage form or in
separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

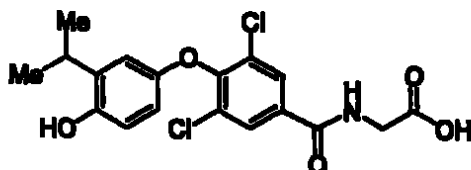
10 The compounds of formula I of the invention can be administered orally or parenterally such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, 15 e.g., humans, cats, dogs and the like in an effective amount within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 20 mg) on a regimen in single or 2 to 4 divided daily doses.

The active substance can be utilized in a composition such as tablet, capsule, ointment, hydrophilic ointment, cream, lotion, solution or suspension or in other type carrier materials such as 25 transdermal devices, iontophoretic devices, rectal suppositories, inhalant devices and the like. The composition or carrier will contain about 5 to about 500 mg per unit of dosage of a compound of formula I. They may be compounded in conventional matter with a 30 physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, and flavor, as called for by accepted pharmaceutical practice.

The following working Examples represent preferred embodiments of the present invention.

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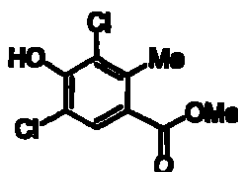
Example 1



N-[3,5-dichloro-4-[4-hydroxy-3-(1-methylethyl)phenoxy]benzoyl]glycine

10

Compound 1A:



[From P. F. Juby et al., J. Med. Chem., 11, 111-117, 1968; and P. F. Juby, US Patent 3,294,813]

15 To a solution of sodium hypochlorite (120 mL) in H₂O (150 mL) cooled with an ice-water bath was added 4'-hydroxy-2'-methylacetophenone. After 30 min of cooling, the mixture was allowed to stir at RT for 30 min, and then it was heated to 40°C and maintained at this
20 temperature for an hour. A solution of NaHSO₃ (10 g in 100 mL H₂O) was added to the mixture. The mixture was acidified to pH 2 with concentrated HCl. The precipitates formed were filtered off. The wet filter cake was taken up in EtOAc (400 mL) and then washed with brine (2 x 100
25 mL). The EtOAc extract was dried (Na₂SO₄), filtered, concentrated and dried in vacuo to give 8.826 g of crude 3,5-dichloro-4-hydroxy-2-methylbenzoic acid as a yellow solid (78% desired product by analytical HPLC analysis).

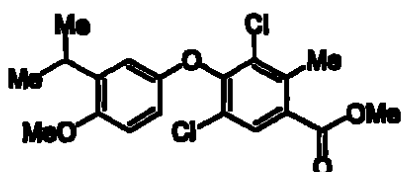
30 A solution of the crude 3,5-dichloro-4-hydroxy-2-methylbenzoic acid (1.5 g) in methanolic HCl (50 mL) was heated to 80°C and maintained at this temperature

overnight (ca. 15 h). The mixture was cooled down to RT and concentrated in vacuo. The crude product was purified by chromatography (100 g silica gel, 20% EtOAc in hexane as eluent) to give 1.1033 g of purified methyl ester as product (69% yield for the two steps).

¹H NMR (500 MHz, CDCl₃, δ) 7.89 (s, 1H), 6.23 (s, 1H), 3.87 (s, 3H), 2.65 (s, 3H).

MS ESI⁺ [MH]⁺ = 233, 235, 237 (100:64:10).

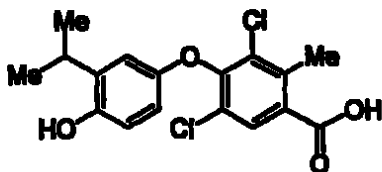
10 Compound 1B:



To a stirring mixture of bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate (4.36 g, 8.51 mmol) and copper (0.54 g, 8.50 mmol) in CH₂Cl₂ (10 mL) was added a solution of compound 1A (1.00 g, 4.25 mmol) and triethylamine (1.2 mL, 0.87 g, 8.61 mmol) in CH₂Cl₂ (10 mL). The mixture was stirred at ambient RT in the dark for 3 days under N₂. The mixture was filtered through a short pad of celite. The filtrate was concentrated in vacuo. The crude product was purified by chromatography (250 g of silica gel, 3% EtOAc in hexane as eluent) to give 1.56 g (95%) of desired product as a white solid.

¹H NMR (500 MHz, CDCl₃, δ) 7.89 (s, 1H), 6.845 (d, 1H, J = 3.3 Hz), 6.68 (d, 1H, J = 8.8 Hz), 6.395 (dd, 1H, J = 8.8, 3.3 Hz), 3.92 (s, 3H), 3.77 (s, 3H), 3.27 (septet, 1H, J = 7 Hz), 2.64 (s, 3H), 1.165 (d, 6H, J = 7.1 Hz).

Compound 1C:



30 To a solution of compound 1B (0.88 g, 2.30 mmol) in anhydrous CH₂Cl₂ (23 mL) cooled with an ice-H₂O bath was added boron trichloride (5.83 g, 2.2 mmol, 23.27 mmol). The

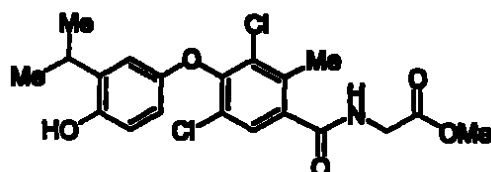
mixture was allowed to warm up to RT. After 2 h, the mixture was slowly poured into a flask containing ice-H₂O (100 mL). After 15 min of stirring, EtOAc (100 mL) was added. The organic layer was separated and the H₂O layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄), filtered, concentrated and dried in vacuo to give 0.83 g of slightly brownish solid product (94% pure by HPLC analysis).

¹H NMR (500 MHz, CD₃OD, δ) 7.91 (s, 1H), 6.665 (d, 1H, J = 3.3 Hz), 6.62 (d, 1H, J = 8.8 Hz), 6.295 (dd, 1H, J = 8.8, 3.3 Hz), 3.23 (septet, 1H, J = 7 Hz), 2.63 (s, 3H), 1.155 (d, 6H, J = 7.1 Hz).

LC MS ESI⁻ [M-H]⁻ = 353, 355, 357 (100:64:10).

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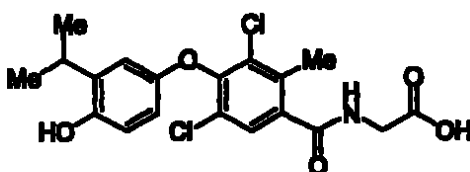
Compound 1D:



To a stirring mixture of compound 1C (0.83 g, 2.34 mmol), methyl glycine ester hydrochloride (0.58 g, 4.62 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.66 g, 3.44 mmol) and 1-hydroxybenzotriazole (0.46 g, 3.44 mmol) in CH₂Cl₂ (20 mL) and DMF (3 mL) cooled with an ice-H₂O bath was added N-methylmorpholine (0.55 g, 0.6 mL, 5.46 mmol). The mixture was allowed to warm up to RT and left to stir overnight (ca. 18 h) under N₂. CH₂Cl₂ was removed in vacuo and the residue was taken up in EtOAc (75 mL) and H₂O (25 mL). The EtOAc extract was washed successively with 1N HCl (2 x 50 mL), saturated aqueous NaHCO₃ (2 x 50 mL), and brine (2 x 50 mL). The EtOAc extract was dried (Na₂SO₄), filtered and concentrated in vacuo to give 1.17 g of crude product as an orange solid. The crude product was purified by chromatography (50 g silica gel, 40% EtOAc in hexane) to give 0.87 g (88.7% yield) of slightly pinkish solid as purified product.

¹H NMR (500 MHz, CDCl₃, δ) 7.44 (s, 1H), 6.825 (d, 1H, J = 3.3 Hz), 6.60 (d, 1H, J = 8.8 Hz), 6.325 (dd, 1H, J = 8.8, 3.3 Hz) 6.30 (t, 1H, J = 5 Hz), 4.76 (s, 1H), 4.235 (d, 2H, J = 5.5 Hz), 3.82 (s, 3H), 3.16 (septet, 1H, J = 7 Hz), 2.47 (s, 3H), 1.225 (d, 6H, J = 7.1 Hz).
¹³C NMR (δ) 170.00, 167.95, 150.74, 149.03, 148.19, 136.22, 135.47, 134.27, 131.94, 126.99, 126.82, 115.64, 114.00, 111.98, 52.66, 41.61, 27.39, 22.39, 17.34
MS ESI⁻ [M-H]⁻ = 424, 426, 428 (100:64:10).

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Example 1:

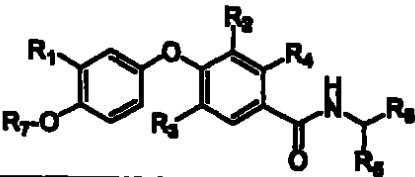
To a solution of compound 1D (0.8 g, 1.88 mmol) in THF (12 mL) was added 1N aqueous lithium hydroxide solution (6 mL, 6 mmol). After 2 h, the mixture was acidified with 1N HCl and then extracted with EtOAc (75 mL). The EtOAc extract was washed with brine (2 x 25 mL), dried (Na₂SO₄), filtered, concentrated and dried in vacuo to give 0.71 g of example 1 (92% yield).
¹H NMR (500 MHz, CD₃OD, δ) 7.53 (s, 1H), 6.645 (d, 1H, J = 3.3 Hz), 6.62 (d, 1H, J = 8.8 Hz), 6.335 (dd, 1H, J = 8.8, 3.3 Hz), 4.07 (s, 2H), 3.25 (septet, 1H, J = 7 Hz), 2.46 (s, 3H), 1.145 (d, 6H, J = 7.1 Hz)
¹³C NMR (δ) 172.59, 170.91, 151.39, 150.91, 150.10, 137.57, 136.44, 132.52, 128.34, 127.98, 116.36, 114.06, 113.15, 42.09, 28.21, 22.88, 17.45.
MS ESI⁻. [M-H]⁻ = 410, 412, 414 (100:64:10)

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Examples 2 - 28

By appropriate application of the procedures described above combined with those described for analogous examples found in "Novel Thyroid Receptor Ligands and Methods, Y.-L. Li, C. Liu, A. Hedfors, J.

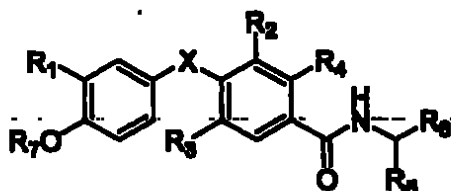
Malm, C. Mellin, M. Zhang, PCT Int. App. WO 9900353 A1 990107, the Examples 2 - 28 described in the table below are prepared.



Ex.	R1	R2	R3	R4	R5	R6	R7
2	i-Pr	Me	Me	Me	H	COOH	H
3	i-Pr	Me	Br	Me	H	COOH	H
4	i-Pr	Me	Cl	Me	H	COOH	H
5	i-Pr	Me	I	Me	H	COOH	H
6	i-Pr	Br	Cl	Me	H	COOH	H
7	i-Pr	Br	I	Me	H	COOH	H
8	i-Pr	Br	Br	Me	H	COOH	H
9	i-Pr	Cl	I	Me	H	COOH	H
10	i-Pr	I	I	Me	H	COOH	H
11	i-Pr	H	Me	Me	H	COOH	H
12	i-Pr	H	Br	Me	H	COOH	H
13	i-Pr	H	Cl	Me	H	COOH	H
14	i-Pr	H	I	Me	H	COOH	H
15	i-Pr	Cl	Cl	CF3	H	COOH	H
16	i-Pr	Br	Br	CF3	H	COOH	H
17	i-Pr	Cl	Cl	Et	H	COOH	H
18	i-Pr	Br	Br	Et	H	COOH	H
19	i-Pr	Cl	Cl	n-Pr	H	COOH	H
20	i-Pr	Br	Br	n-Pr	H	COOH	H
21	Br	Cl	Cl	Me	H	COOH	H
22	Me	Br	Br	Me	H	COOH	H
23	n-Bu	Cl	Cl	Me	H	COOH	H
24		Cl	Cl	Me	H	COOH	H
25	i-Pr	Cl	Cl	Me	Me	COOH	H
26	i-Pr	Br	Br	Me	Me	COOH	H
27	i-Pr	Cl	Cl	Me	H	COOEt	H
28	i-Pr	Br	Br	Me	H	COOEt	H
29	i-Pr	Cl	Cl	Me	H	COOH	Acetyl

What is claimed is:

1. A compound of the formula



5

wherein

X is oxygen (-O-), sulfur (-S-), carbonyl (-CO-), methylene (-CH₂-), or disubstituted nitrogen (-NH-);

10 R₁ is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

R₂ and R₃ are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 6 carbons, at least one of R₂ and R₃ being other than hydrogen;

15 R₄ is methyl, ethyl, n-propyl or trifluoromethyl;

R₅ is hydrogen or lower alkyl;

R₆ is carboxylic acid, or ester thereof, or a prodrug thereof;

20 R₇ is hydrogen, or an alkanoyl or aroyl group, or other group capable of bioconversion to generate the free phenol structure (wherein R₇ = H);

including all stereoisomers thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof.

25 2. The compound as defined in Claim 1 wherein X is oxygen.

3. The compound as defined in Claim 2 wherein R₂ is hydrogen.

30

4. The compound as defined in Claim 3 wherein R₁ is isopropyl.

5. The compound as defined in Claim 3 wherein R_2 and R_3 are each independently halogen.

6. The compound as defined in Claim 3 wherein R_2 and R_3 are each independently an alkyl group.

7. The compound as defined in Claim 3 wherein one of R_2 and R_3 is halogen and the other is an alkyl group.

8. The compound as defined in Claim 3 wherein one of R_2 and R_3 is halogen and the other is hydrogen.

9. The compound as defined in Claim 3 wherein one of R_2 and R_3 is alkyl and the other is hydrogen.

10. The compound as defined in Claim 3 wherein R_2 and R_3 are independently Cl, Br, methyl or ethyl.

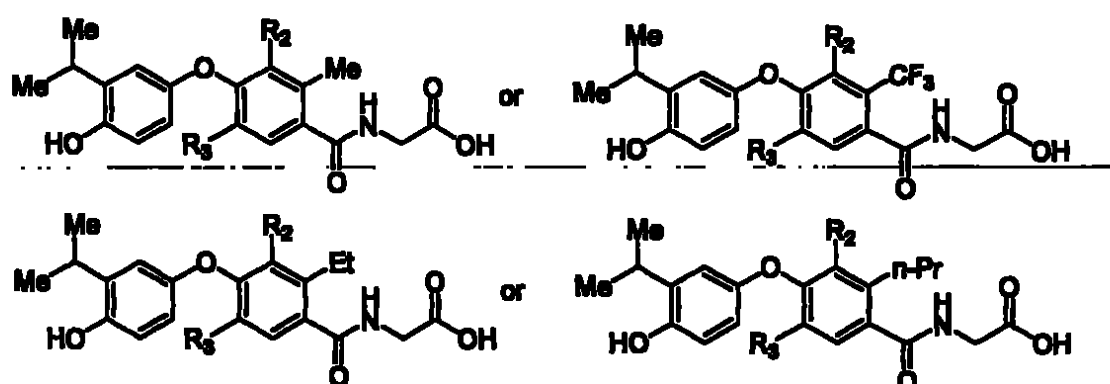
11. The compound as defined in Claim 3 wherein R_4 is trifluoromethyl or methyl.

12. The compound as defined in Claim 3 wherein R_4 is methyl.

13. The compound as defined in Claim 1 wherein
 $X = O$;
 R_1 is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons;
 R_2 and R_3 are independently bromo, chloro or methyl;
 R_4 is methyl or trifluoromethyl;
 R_5 is hydrogen;
 R_6 is carboxyl; and
 R_7 is hydrogen..

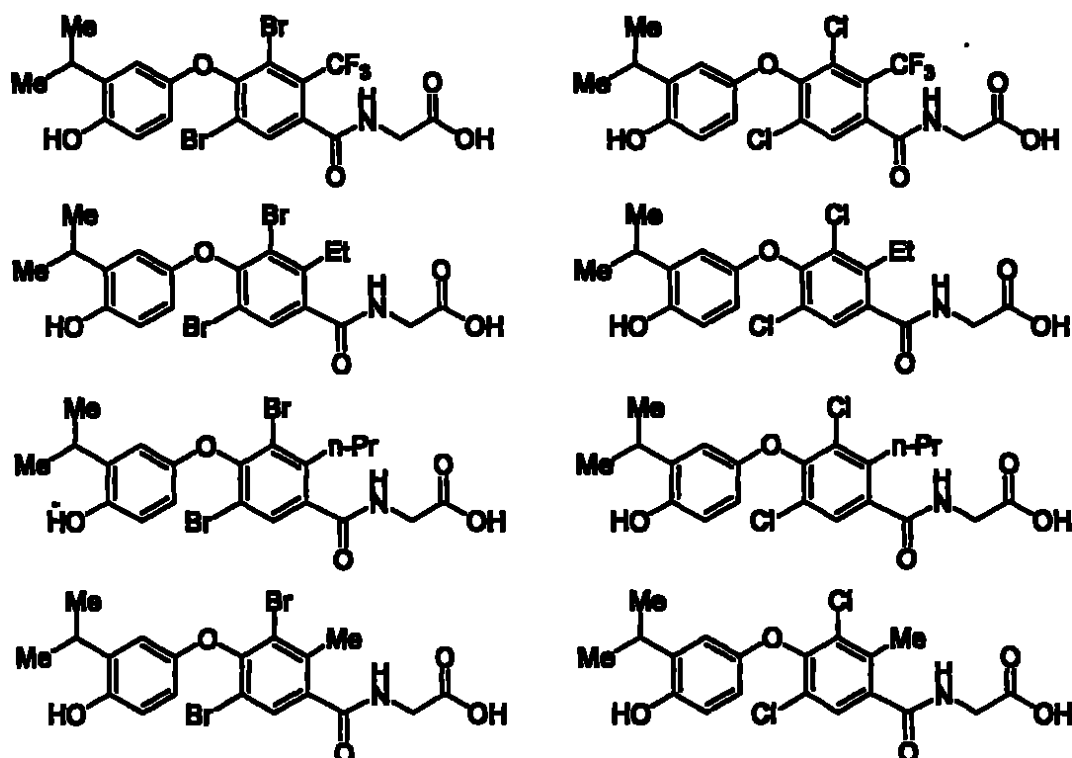
14. The compound as defined in Claim 13 wherein R_1 is alkyl of 1 to 6 carbons.

15. The compound as defined in Claim 3 having the structure



5 or an alkyl ester thereof.

16. The compound as defined in Claim 1 having the structure

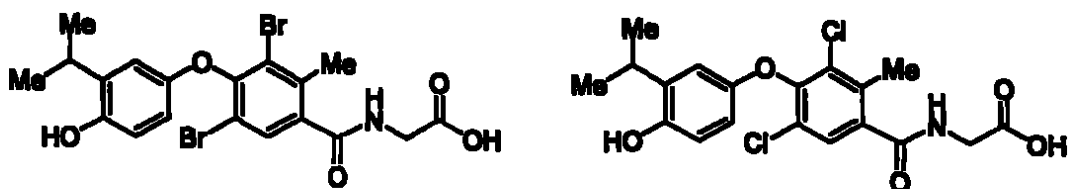


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or or an alkyl ester thereof.

17. The compound as defined in Claim 1 having the structure

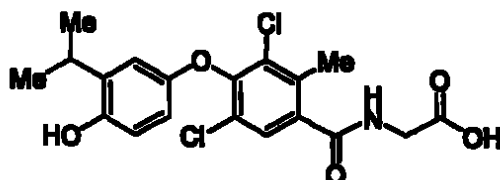
15



or an alkyl ester thereof.

18. The compound as defined in Claim 1 which is

5



19. A method for preventing, inhibiting or
treating a disease associated with metabolism
dysfunction, or which is dependent on the expression of a
T₁ regulated gene, which comprises administering to a
patient in need of treatment a therapeutically effective
amount of a compound as defined in Claim 1.

15 20. The method as defined in Claim 19 wherein the
disease associated with metabolism dysfunction or which
is dependent on the expression of a T₁ regulated gene is
obesity, hypercholesterolemia, atherosclerosis,
depression, osteoporosis, hypothyroidism, goiter, thyroid
20 cancer, glaucoma, cardiac arrhythmia, congestive heart
failure, or a skin disorder or disease.

21. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

22. The method according to Claim 20 in which the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen

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planus, ichthyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

5 23. A method to treat skin disorder or disease by the use of a compound of Claim 1 in combination with a retinoid or a vitamin D analog.

10 24. A pharmaceutical combination comprising a compound as defined in Claim 1 and a hypolipidemic agent, an antidiabetic agent, an antidepressant, a bone resorption inhibitor, an appetite suppressant and/or an anti-obesity agent.

15 25. The combination as defined in Claim 25 wherein the hypolipidemic agent is a thiazolidinedione, an MTP inhibitor, a squalene synthetase inhibitor, an HMG CoA reductase inhibitor, a fibric acid derivative, an ACAT inhibitor, a cholesterol absorption inhibitor, an ileal
20 Na⁺/bile cotransporter inhibitor, a bile acid sequestrant and/or nicotinic acid or a derivative thereof.

 26. The combination as defined in Claim 24 wherein the hypolipidemic agent is pravastatin, simvastatin,
25 lovastatin, atorvastatin, fluvastatin or cerivastatin.

 27. The combination as defined in Claim 24 wherein the compound is present in a weight ratio to the hypolipidemic agent or antidiabetic agent within the
30 range from about 0.01:1 to about 300:1.

 28. The combination as defined in Claim 24, wherein the antidiabetic agent is a biguanide, a sulfonylurea, a glucosidase inhibitor, a
35 thiazolidinedione, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1) or insulin.

29. The combination as defined in Claim 28 wherein
the antidiabetic agent is metformin, glyburide,
glimepiride, glipyrider, glipizide, chlorpropamide,
gliclazide, acarbose, miglitol, troglitazone,
5 pioglitazone, rosiglitazone, and/or insulin.

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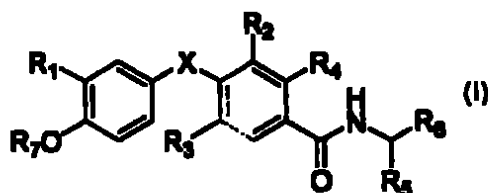
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: BENZAMIDE LIGANDS FOR THE THYROID RECEPTOR



(57) Abstract: New thyroid receptor ligands are provided which have the general formula (I) in which: X is -O-, -S-, -CH2-, -CO-, or -NH-; R₁ is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons; R₂ and R₃ are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 6 carbons, at least one of R₂ and R₃ being other than hydrogen; R₄ is methyl, ethyl, n-propyl or trifluoromethyl; R₅ is hydrogen or lower alkyl; R₆ is carboxylic acid, or esters or prodrugs; R₇ is hydrogen or an alkanoyl or an aryl. In addition,

a method is provided for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T₃ regulated gene, wherein a compound as described above is administered in a therapeutically effective amount. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T₃ regulated gene include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma, congestive heart failure and skin disorders.

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INTERNATI NAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C235/52 A61K31/166

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 C07C A61K

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

No.	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 39077 A (GARG NEERAJ ;LI YI LIN (SE); KAROBIO AB (SE); KOEHLER KONRAD (SE);) 6 July 2000 (2000-07-06) page 3, line 3 -page 4, line 11	1-7,10, 19-23
A	WO 99 00353 A (HEDFORS ASA ;LI YI LIN (SE); KAROBIO AB (SE); LIU YE (SE); MALM JO) 7 January 1999 (1999-01-07) cited in the application page 4, line 5 - line 24 schemes 1-5 -/-	1-29

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

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page 1 of 2

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INTERNATIONAL SEARCH REPORT

Inter 'onal Application No
PCT/US 01/17742

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	YOKOYAMA N: "Synthesis and structure-activity relationships of oxamic acid and acetic acid derivatives related to L-thyronine" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US; - - - vol. 38, 1995, pages 695-707, XP002080908 ISSN: 0022-2623 table 1	1-29
A	DE 10 78 582 B (FARBWERKE HOECHST AKTIENGESELLSCHAFT) 31 March 1960 (1960-03-31) column 1, line 28 -column 2, line 20	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

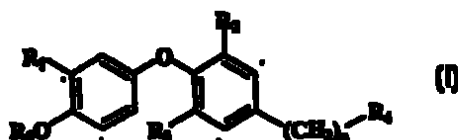
International Application No

PCT/US 01/17742

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			CZ	20012204 A3		14-11-2001
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			AU	8440598 A		19-01-1999
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			EP	1000008 A1		17-05-2000
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(21) International Application Number: PCT/IB99/02084 (22) International Filing Date: 23 December 1999 (23.12.99) (30) Priority Data: 9828442.5 24 December 1998 (24.12.98) GB (71) Applicant (for all designated States except US): KARO BIO AB [SE/SE]; Novum, S-141 57 Huddinge (SE). (72) Inventors; and (73) Inventors/Applicants (for US only): HANGELAND, Jan [US/US]; 234 Louise Drive, Morrisville, PA 19067 (US). ZHANG, Minsheng [CN/US]; 31 Scheurman Terrace, Warren, NJ 07059 (US). CARINGAL, Yolanda [US/US]; 24 Coral Tree Court, Lawrenceville, NJ 08648 (US). RYONO, Denis [US/US]; 28 Marion Road West, Princeton, NJ 08540 (US). LI, Yi-Lin [CN/SE]; Kallbriktavägen 38C, S-141 31 Huddinge (SE). MALM, Johan [SE/SE]; Kornnagavägen 53, S-142 40 Skogås (SE). LIU, Ye [CN/SE]; Smedvägen 23, S-146 36 Tullinge (SE). GARG, Neeraj [IN/SE]; Barkvägen 15, S-147 52 Tumba (SE). LITTEN, Chris [IN/SE]; Stubbestigen 6, S-147 52 Tumba (SE). GARCIA COLLAZO, Ana Maria [ES/SE]; Moregatan 10, S-118 27 Stockholm (SE). KOEHLER, Konrad [US/SE]; Visnåvågen 27, S-141 50 Huddinge (SE).	(74) Agents: BANNERMAN, David, Gardner et al.; Withers & Rogers, Goldings House, 2 Hays Lane, London SE1 2HW (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	

(54) Title: **NOVEL THYROID RECEPTOR LIGANDS AND METHOD II**

(57) Abstract

New thyroid receptor ligands are provided which have general formula (I) in which: n is an integer from 0 to 4; R_1 is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons; R_2 and R_3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 5 carbons, at least one of R_2 and R_3 being other than hydrogen; R_4 is a carboxylic acid amide (CONR'R'') or an acylsulphonamide (CONHSO₂R') derivative, or a pharmaceutically acceptable salt thereof, and all stereoisomers thereof; or when n is equal to or greater than one, R_4 may be a heteroaromatic moiety which may be substituted or unsubstituted, or an amine (NR'R''). R_5 is hydrogen or an acyl (such as acetyl or benzoyl) or other group capable of bioconversion to generate the free phenol structure (wherein R_5 =H). In addition, a method is provided for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T_3 regulated gene, wherein a compound as described above is administered in a therapeutically effective amount. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T_3 regulated gene include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma, congestive heart failure and skin disorders.

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NOVEL THYROID RECEPTOR LIGANDS AND METHOD II

Field of the Invention

This invention relates to novel compounds which are thyroid receptor ligands, and are preferably selective for the thyroid hormone receptor β , to methods of preparing such compounds and to methods for using such compounds such as in the regulation of metabolism.

Background of the Invention

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

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

Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with 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 T_4) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or T_3). However, replacement therapy, particularly in older individuals is limited by certain of the deleterious effects of 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 weight reduction, lowering of serum LDL levels, 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.

Development of specific and selective thyroid hormone receptor agonists could lead to specific therapies for these common disorders while avoiding the cardiovascular and other toxicities of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Thyroid

hormone receptor agonists that interact selectively with the β -form of the thyroid hormone receptor offers an especially attractive method for avoiding cardio-toxicity.

Thyroid hormone receptors (TRs) are, like other nuclear receptors, single polypeptide chains. The various receptor forms appear to be products of two different genes α and β . Further isoform differences are due to the fact that differential RNA processing results in at least two isoforms from each gene. The TR α_1 , TR β_1 and TR β_2 isoforms bind thyroid hormone and act as ligand-regulated transcription factors. In adults, the TR β_1 isoform is the most prevalent form in most tissues, especially in the liver and muscle. The TR α_2 isoform is prevalent in the pituitary and other parts of the central nervous system, does not bind thyroid hormones, and acts in many contexts as a transcriptional repressor. The TR α_1 isoform is also widely distributed, although its levels are generally lower than those of the TR β_1 isoform. This isoform may be especially important for development. Whereas many mutations in the TR β gene have been found and lead to the syndrome of generalized resistance to thyroid hormone, mutations leading to impaired TR α function have not been found.

A growing body of data suggest that many or most effects of thyroid hormones on the heart, and in particular on the heart rate and rhythm, are mediated through the α -form of the TR α_1 isoform, whereas most actions of the hormone such as on the liver, muscle and other tissues are mediated more through the β -forms of the receptor. Thus, a TR β -selective agonist might not elicit the cardiac rhythm and rate influences of the hormones but would elicit many other actions of the hormones. It is believed that the α -form of the receptor is the major drive to heart rate for the following reasons:

- 1) tachycardia is very common in the syndrome of generalized resistance to thyroid hormone in which there are defective TR β -forms, and high circulating levels of T₄ and T₃;
- 2) there was a tachycardia in the only described patient with a double deletion of the TR β gene (Takeda et al, J. Clin. Endocrinol. & Metab. 1992, Vol. 74, p. 49);
- 3) a double knockout TR α gene (but not β -gene) in the mouse has a slower pulse than control mice; and,
- 4) western blot analysis of human myocardial TRs show presence of the TR α_1 , TR α_2 and TR β_2 proteins, but not TR β_1 .

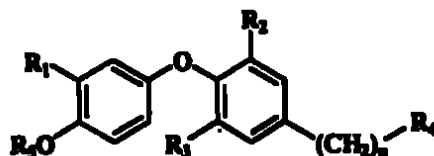
If these indications are correct, then a TR β -selective agonist could be used to mimic a number of thyroid hormone actions, while having a lesser effect on the heart. Such a compound may be used for: (1) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (2) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (3) obesity; (4) hypercholesterolemia due to

elevations of plasma LDL levels; (5) depression; and, (6) osteoporosis in combination with a bone resorption inhibitor.

Description of the Invention

In accordance with the present invention, compounds are provided which are
5 thyroid receptor ligands, and have the general formula I:

I



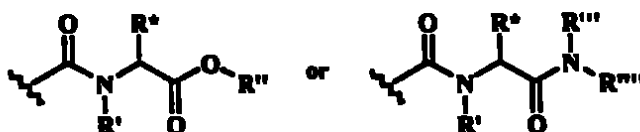
in which:

n is an integer from 0 to 4;

R₁ is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7
carbons;

R₂ and R₃ are the same or different and are hydrogen, halogen, alkyl of 1 to 4
carbons or cycloalkyl of 3 to 5 carbons, at least one of R₂ and R₃ being other than hydrogen;

R₄ is a heteroaromatic moiety which may be substituted or unsubstituted and is
15 linked to (CH₂)_n via a nitrogen atom or a carbon atom; an amine (NR'R''), including those in
which the amine is derived from an alpha amino acid of either natural (L) or unnatural (D)
stereochemistry; an acylsulphonamide (CONHSO₂R') or a carboxylic acid amide
(CONR'R'') in which the amine portion of the carboxylic amide can be derived from an
achiral or a L or D alpha amino acid such as when the general structure -CONR'R'' can be
20 represented by



and R', R'', R''' and R'''' are the same or different and are independently selected from
hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and R* may be hydrogen,
alkyl, aryl and heteroaryl, substituted or unsubstituted, and may also be any of the side chains
25 found in the naturally occurring alpha-amino acids and their analogs, including those examples
wherein R' and R* are connected to form 4 to 8-membered rings (such as when R' and R*
comprise consecutive -(CH₂)- groups to form proline or homoproline); and with the proviso
that when n equals zero (n = 0), then R₄ can only be a carboxylic acid amide or an
acylsulphonamide.

30 R₄ is hydrogen or an acyl (such as acetyl or benzoyl) or other group capable of
bioconversion to generate the free phenol structure (wherein R₃ = H);

including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T_3 regulated gene is provided, wherein a compound of formula I is administered in a therapeutically effective amount. The compound of formula I is preferably an agonist that is preferably selective for the thyroid hormone receptor-beta. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T_3 regulated gene are set out hereinafter and include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma and congestive heart failure.

Detailed Description of the Invention

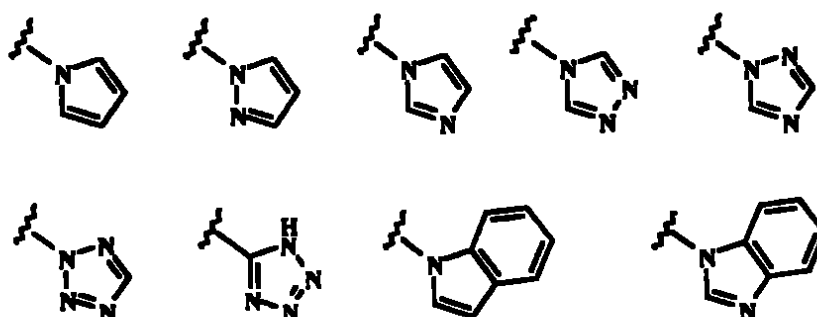
The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

15 The term "thyroid receptor ligand" as used herein is intended to cover any moiety which binds to a thyroid receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist.

The term "aliphatic hydrocarbon(s)" as used herein refers to acyclic straight or branched chain groups which include alkyl, alkenyl or alkynyl groups.

20 The term "aromatic hydrocarbon(s)" as used herein refers to groups including aryl groups as defined herein.

The term "heteroaryl" or "heteroaromatic moiety" as used herein alone or as a part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3, or 4 heteroatoms, one of which must be a nitrogen atom; the other heteroatoms when present may be nitrogen, oxygen or sulfur, and such rings may be fused to another aryl or heteroaryl ring, and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, cyano, nitro, amino and/or carboxyl, and including the following



30 and the like.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 12 carbons (in the case of alkyl or alk), in the normal chain, preferably 1 to 4 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, or isobutyl, 5 pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, which may be optionally substituted with 1 to 4 substituents which may include alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino and/or carboxyl.

The term "aryl" as employed herein alone or as part of another group refers to 10 monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, hydroxy, amino, nitro, cyano and carboxylic acids.

15 Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 5 carbons, in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 20 4-decenyl, 3-undecenyl, 4-dodecenyl, and the like, which may be substituted as in the case of "alkyl".

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 8 carbons, in the normal chain, which include one triple bond in the 25 normal chain, such as 2-propynyl, 3-butylnyl, 2-butylnyl, 4-pentylnyl, 3-pentylnyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonylnyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, which may be substituted as in the case of "alkyl".

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated cyclic hydrocarbon groups or partially unsaturated 30 (containing 1 or 2 double bonds) cyclic hydrocarbon groups, containing one ring and a total of 3 to 7 carbons, preferably 3 to 5 carbons, forming the ring, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl and cyclohexenyl, which may be substituted as in the case of "alkyl".

The term "halogen" or "halo" as used herein alone or as part of another group 35 refers to chlorine, bromine, fluorine, and iodine as well as CF₃, with chlorine or bromine being preferred.

The compounds of formula I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C₁-C₄) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or *p*-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases.

Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or trilower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I which include a basic groups include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

Preferred salts of the compounds of formula I which include an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

Preferred are compounds of the invention of formula I wherein R₁ is isopropyl;

R₂ and R₃ are independently halogen such as bromo or chloro; or

R₂ and R₃ are each methyl or one is methyl and the other is ethyl;

or one of R₂ and R₃ is halogen such as bromo or chloro, and the other is alkyl such as methyl, or hydrogen; and

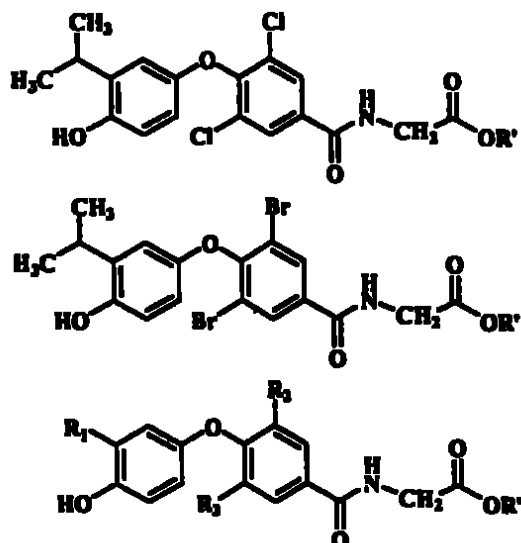
n is 0, 1 or 2;

R₄ is carboxylic acid derivative of the type: amides, acylsulphonamides or an

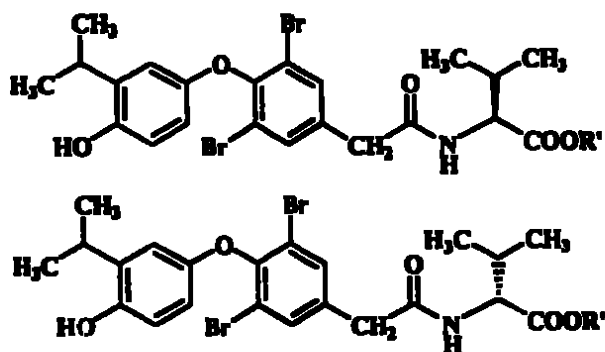
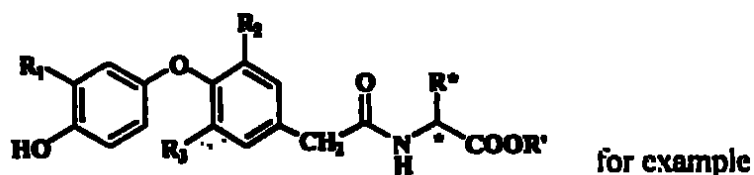
amide formed from an amino acid residue; and

R₅ is hydrogen.

The most preferred compounds have the structures:



and other preferred compounds of the invention have the structures:



5

wherein R_1 = isopropyl, methyl, ethyl, tertiary-butyl, cyclopentyl, cyclohexyl; R_2 and R_3 may be independently selected from Br, Cl and Me; R^* may be hydrogen, alkyl, cycloalkyl, aryl and heteroaryl; * denotes either D or L stereochemistry; and R' is selected from hydrogen, lower alkyl, especially ethyl and methyl or where the group $COOR'$ represents prodrug ester forms known in the art such as pivaloyloxymethyl or

dioxolenylmethyl. Such prodrug esters are described in standard references such as Chapter 31, written by Camille G. Wermuth et al., in "The Practice of Medicinal Chemistry", ed. C. G. Wermuth. Academic Press, 1996 (and the references contained therein).

The compounds of formula I may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

Compounds of formula I of the invention can be prepared using the sequence of steps outlined in Schemes 1 to 5 set out below.

Scheme 1 depicts a synthesis of compounds of formula I in which R_4 = an amino acid, aniline derivative or aza containing heterocyclic ring, which through their nitrogen atom is connected to the aromatic ring by an intervening $(CH_2)_n$ group.

In Scheme 1, the amino acid, aniline derivative or aza containing heterocyclic ring, dissolved in a suitable solvent, is treated with 1-3 molar equivalents of an appropriate base, such as potassium carbonate, cesium carbonate, potassium hydroxide or sodium hydride. The resulting anion is then alkylated with the substituted iodide 5. Other combinations of alkylating agents or bases may be employed and are known to those skilled in the art. The reaction mixture is stirred at room temperature or heated until the starting materials are consumed. After standard work-up and purification, the methyl ether function is removed by treatment with 3-6 molar equivalents of a strong acid such as boron tribromide at 0°C to 25°C in an inert solvent such as dichloromethane. The reaction mixture gives after standard work-up and purification, the end products 6. Numerous alternative methodologies for the conversion of intermediates such as 3 and 4 to products 6 are well known to those skilled in the art.

Scheme 1 also outlines the preparation of the intermediate iodide 5, the sequence similar to what is employed in: "Novel Thyroid Receptor Ligands and Methods. Li, Yi-Lin; Liu, Ye; Hedfors, Asa; Malm, Johan; Mellin, Charlotta; Zhang, Minsheng. PCT Int. Appl., 40 pp. CODEN: PIXXD2. WO 9900353 A1 990107". An anisole-derived iodonium salt 2 and copper bronze in an inert solvent such as dichloromethane are mixed at room temperature. A mixture of the appropriate phenol ester 1 and a base such as triethylamine in an inert solvent such as dichloromethane was added to the mixture, generally using 2 molar equivalents each of the phenol and base, and 3 molar equivalents of iodonium salt 2. After stirring overnight at room temperature, the reaction mixture is purified via chromatography on silica gel, to give biaryl ether products 3. Other methods exist in the literature for the synthesis of diaryl ethers, for example, two references directly apply to the synthesis of thyroid hormone analogs: D. A. Evans et al., Tet. Letters, volume 39, 2937-2940 (1998) and G. M. Salamonczyk et al., Tet. Letters, volume 38, 6965-6968 (1997). The carboxylic acid ester can be hydrolyzed with a mixture of aqueous sodium hydroxide and methanol. The methyl ether function can be removed by treatment of the free acid product of the previous procedure with 4-6 molar

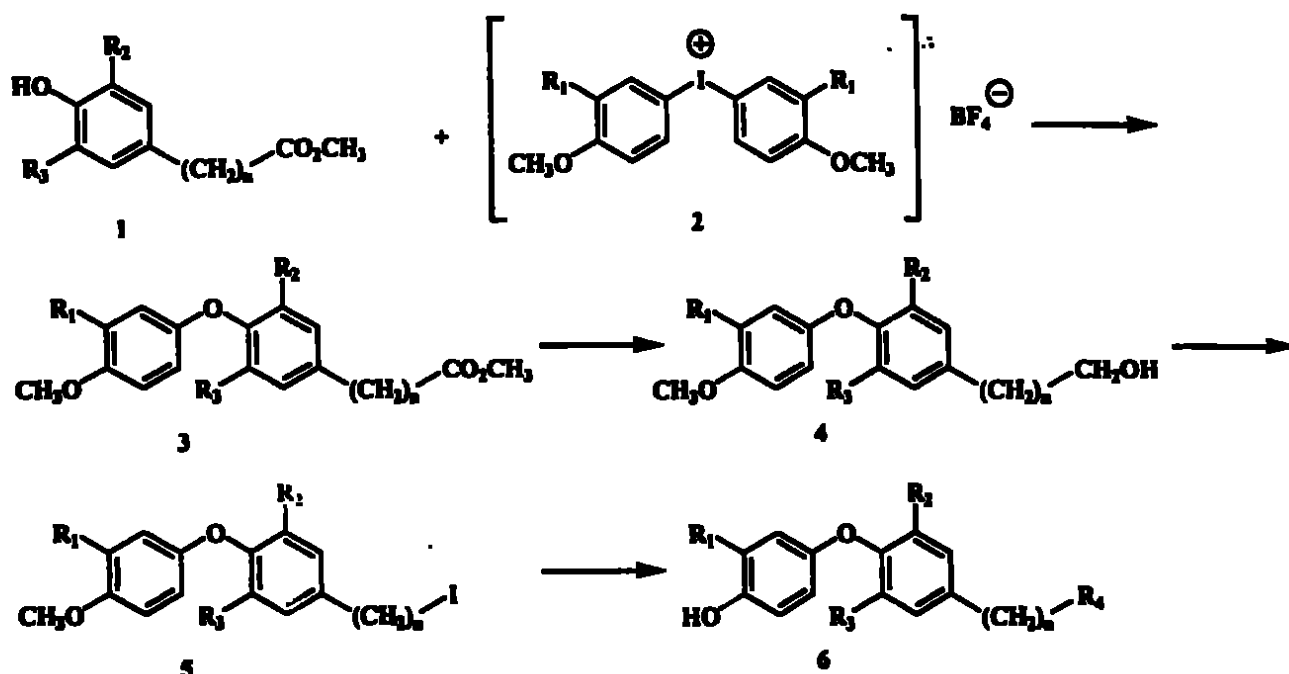
equivalents of a strong acid such as boron tribromide at 0°C in an inert solvent such as dichloromethane. Other combinations of protecting groups for the carboxylic acid present in 1 and phenolic hydroxyl in iodonium salt 2 can be employed, and their usage is known to those skilled in the art (references describing protecting group strategy include, for example,

- 5 "Protecting Groups in Organic Chemistry", J. F. W. McOmie, Plenum Press, London, New York, 1973, and "Protective Groups in Organic Synthesis", T. W. Greene, Wiley, New York, 1984).

The intermediate ester product 3 is reduced by treatment with an appropriate reducing agent such as diisobutyl aluminium hydride in an inert solvent such as
10 tetrahydrofuran at 0°C. If R₁ and R₃ are alkyl, then lithium aluminum hydride may be employed without the risk of reducing away halogen substituents at those positions. Standard work-up and purification yields the desired alcohol product 4. Other reducing agents may be employed and are known to those skilled in the art.

Intermediate 4 in Scheme 1 is finally converted to the intermediate iodide 5 by
15 treatment of alcohol 4 with 2 molar equivalents of sodium iodide, phosphorous pentaoxide and phosphorous acid, and heated at 120°C for 15 minutes. Numerous other methodologies for conversion of simple hydroxyl groups to the corresponding alkyl iodides are well known to those skilled in the art.

20 Scheme 1

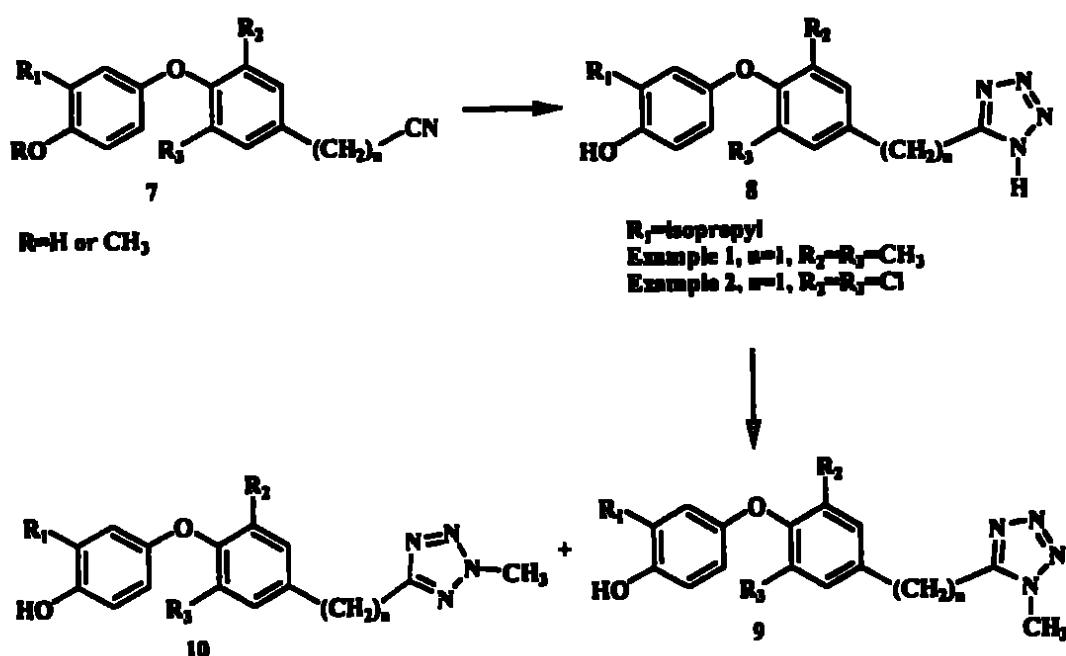


R₄ = amino acid, aniline, heterocyclic ring

Scheme 2 depicts a synthesis of compounds of formula I in which R_4 is a tetrazole ring. Phenylacetone nitrile 7 is readily prepared from benzylic iodide 5 by standard means such as reaction with sodium cyanide in a solvent mixture such as water/ethanol. Reaction of phenylacetone nitrile 7, with sodium azide and ammonium chloride in dimethylformamide at elevated temperatures gives tetrazole derivatives 8 (Example 1 and 2), after standard work-up and purification procedures. In Example 2 this step was followed by a standard demethylation procedure, as above, in order to remove the protecting group.

Examples of substituted tetrazoles that can be prepared by further chemistry are also depicted in Scheme 2. Tetrazole derivative 8 can for instance be treated with an appropriate base such as sodium hydrogen carbonate in acetone, followed by N-alkylation with methyl iodide to afford derivatives 9 and 10, after standard work-up and purification procedures. Other alkylating agents and bases may be employed and are known to those skilled in the art.

15 Scheme 2



Examples of compounds of formula I in which R_4 is an amide produced by coupling to an amino acid are shown in Scheme 3. The following procedures all involve the coupling of benzoic or acetic acid derivative 11 ($n=0$ or 1), with its phenolic hydroxyl group either protected by a methyl, left unprotected or bound to a resin, with various protected amino acids, to afford the corresponding amides 10 of 3,5-dihalo-4-(4-hydroxy-3-isopropylphenoxy) carboxylic acids. The carboxylic acids 11 are readily obtained, for example, by hydrolysis of the corresponding esters 3.

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In one procedure, a mixture of 11 with R=Me, a coupling reagent such as 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), and a base such as 1-hydroxybenzotriazole hydrate (HBT) in dichloromethane is stirred at room temperature. The appropriate protected amino acid and N-methylmorpholine is added. The reaction mixture yields after work-up and purification by either chromatography or recrystallization the corresponding coupled material, which after standard demethylation and hydrolysis procedures, gives the desired final amide products (Example 87).

Several examples of coupled products, employing different protecting groups for the carboxylic acid group was also prepared and isolated (Examples 29, 57, 71-72, 75, 77, 80-82, 84). Alternatively, amide end-products which contain free carboxylic acid groups can be re-esterified by standard procedures by, for instance, heating them in a mixture of refluxing methanol and thionyl chloride, to give the corresponding alkyl acid ester derivatives (Example 82).

In another more fruitful modification of the same procedure as above, 11 is kept unprotected (R=H) from the beginning of the sequence to give, after basic hydrolysis or treatment with a Lewis acid as BBr₃, and standard work-up and purification procedures, other examples of carboxylic acid amides (Example 3-24, 25-28, 56, 73-74, 76, 78-79, 83, 85-86, 203, 207-208).

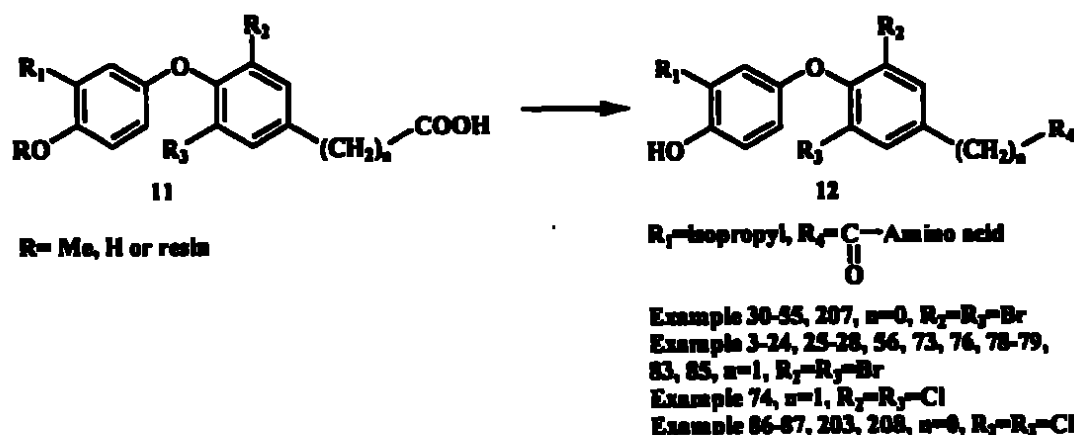
An amide library can also be prepared by solid phase synthesis (Examples 30-55). In this procedure a methyl ester of intermediate 11 is loaded on a resin such as a Merrifield resin by standard procedures, well known to those skilled in the art. The resulting resin is then treated with sodium hydroxide in methanol to provide the resin-bound free carboxylic acid form of 11. Each resin pin is then filled with a solution of the corresponding amino acid ester, PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino phosphonium hexafluorophosphate), HBT, and N,N-diisopropylethylamine (Hunig's base, DIEA) and an inert solvent such as dichloromethane and is stirred at room temperature for days. Other combinations of base and coupling reagents can be employed here with successful results. After treatment of each of the individual pins with an appropriate base such as aqueous potassium hydroxide and washing of the resin, the amides are disassembled from the resin by treatment of a mixture of trifluoroacetic acid, dimethylsulfite and water.

Several other related methodologies exist for the coupling of amino acids with aromatic, as well as non-aromatic, carboxylic acids in solution or solid phase and are known to those skilled in the art.

The amino acid product 12 can be reduced by treatment with an appropriate reagent such as sodium borohydride in a polar solvent such as ethanol at room temperature. If R₂ and R₃ are alkyl, then lithium aluminum hydride may be employed without the risk of reducing the halogen substituents at those positions. Standard work-up and purification yields the

desired alcohol product. Other reducing agents may be employed and are known to those skilled in the art.

Scheme 3



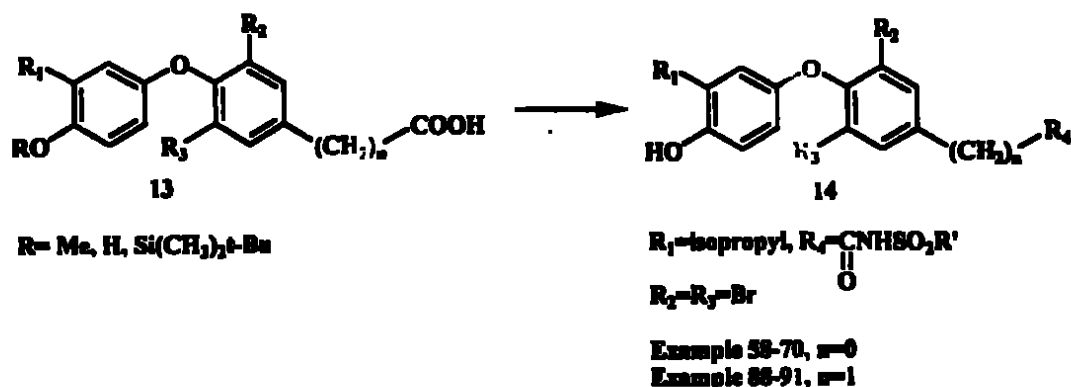
5 Scheme 4 depicts a synthesis of compounds of formula I in which R_4 is an acylsulphonamide. Similar procedures as for the coupling of amino acids above are employed.

In one procedure, 13 is kept unprotected ($R=\text{H}$), mixed with a base such as DIEA and the appropriate sulphonamide in dichloromethane. Dimethylformamide is added to the
 10 mixture if the sulphonamide does not dissolve completely. Treatment of the mixture with a base and coupling reagent combinations such as HOBt and PyBOP, gives after heating and subsequent mild acid treatment during work-up and purification by HPLC, the desired acylsulphonamides (Example 58-70).

In an exemplified procedure, a mixture of 13 with $R=\text{Me}$, a coupling reagent such
 15 as 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), and a base such as dimethylaminopyridine (DMAP) and the appropriate sulphonamide in dichloromethane is stirred at room temperature. The reaction mixture yields after work-up and purification by either chromatography or recrystallization the corresponding coupled material, which after standard demethylation procedures, yields yet other acylsulphonamides.

20 Other combinations of protecting groups and procedures can be employed. For example, applying similar chemistry as above, but with $R = \text{Si}(\text{CH}_3)_2\text{-Bu}$, gives further examples of acylsulphonamides after removal of the protecting silyl group with ammonium fluoride (Examples 88-91).

Scheme 4



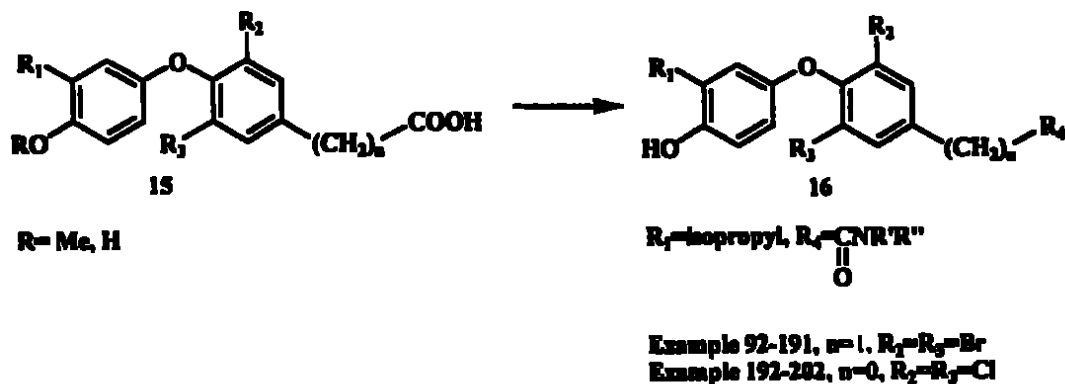
The procedures described in Scheme 5 further exemplify methods for the synthesis of compounds of formula I. Several structurally diverse amides, primary as well as secondary, were prepared as outlined in Scheme 5. Many alternative procedures for the coupling of amino acids above can be employed and are well known to those skilled in the art.

For example, in one procedure secondary diacetic acids amides are obtained through the treatment of 15 by dimethyliminodiacetate and EDCI in dimethylformamide or dichloromethane, followed by standard work-up procedures and final basic hydrolysis of the ester function (Example 206).

10 In another procedure, aromatic amides were obtained by a similar procedure as in Example 3-24 above (Example 192-202).

A library comprising 100 diverse primary and secondary amides was also prepared in an automated fashion, using standard literature methods (Example 92-191).

Scheme 5



15

With respect to the above reaction schemes, although the various R_1 , R_2 , R_3 , R_4 and n moieties are specifically defined, unless otherwise indicated, it is to be understood that R_1 , R_2 , R_3 , and R_4 may be any of the groups encompassed thereby and n may be 0, 1, 2, 3 or 4.

The compounds of the invention are agonist that are preferably selective for the thyroid hormone receptor-beta, and as such are useful in the treatment of obesity, hypercholesterolemia and atherosclerosis by lowering of serum LDL levels, alone or in combination with a lipid modulating drug such as an HMG-CoA reductase inhibitor, fibrate, thiazolidinedione, or MTP inhibitor, amelioration of depression alone or in combination with an antidepressant, and stimulation of bone formation to treat osteoporosis in combination with any known bone resorption inhibitor such as alendronate sodium. In addition, the compounds of the invention may be useful as replacement therapy in elderly patients with hypothyroidism or subclinical hypothyroidism who are at risk of cardiovascular complications, in the treatment of the elderly to provide a sense of well-being, and in the treatment of non-toxic goiter; in the management of papillary or follicular thyroid cancer (alone or with T₄); in the treatment of skin disorders such as psoriasis, glaucoma, cardiovascular disease such as in the prevention or treatment of atherosclerosis, and congestive heart failure.

The compounds of the invention may also be used to treat skin disorders or diseases involving dermal atrophy such as glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical glucocorticoids, 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, or dermal atrophy induced by aging (wrinkles, etc.), wound healing, 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 treating skin disorders or diseases as described above, the compounds of the invention may be used in combination with a retinoid or a vitamin D analog.

The compounds of the invention can be administered orally or parenterally such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, cats, dogs and the like in an effective amount within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses.

The active substance can be utilized in a composition such as tablet, capsule, ointment, hydrophilic ointment, cream, lotion, solution or suspension or in other types of carrier of materials such as transdermal devices, iontophoretic devices, rectal suppositories, inhalant devices and the like. The composition or carrier will contain about 5 to about 500

mg per unit of dosage of a compound of formula I. They may be compounded in conventional matter with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice.

- 5 The following working Examples represent preferred embodiments of the present invention. Appropriate procedures for the preparation of starting materials can be found in: "Novel Thyroid Receptor Ligands and Methods. Li, Yi-Lin; Liu, Ye; Hedfors, Asa; Malm, Johan; Mellin, Charlotta; Zhang, Minsheng. PCT Int. Appl., 40 pp. CODEN: PDXD2. WO 9900353 A1 990107". The ¹H NMR spectra was all consistent with the assigned structures.

Example 1

10 3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole.

- To a stirred solution of 3,5-dimethyl-4-(4-hydroxy-3-isopropylphenoxy)-phenylacetonitrile (154 mg) in 6.3 ml of dimethyl formamide, ammonium chloride (297 mg, 5.21 mmol) and sodium azide (339 mg, 5.21 mmol) was added at reflux. After 4.5 hours the
15 reaction mixture was concentrated, treated with 6 M hydrochloric acid and extracted several times with ethyl acetate. The combined organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 96:4:1 chloroform/methanol/acetic acid) to give 68 mg (37%) of the title compound.

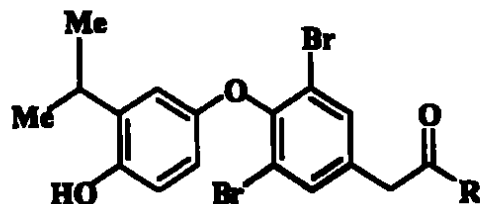
Example 2

20 3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole.

- (a) To a stirred solution of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)-phenylacetonitrile (160 mg) in 3.0 ml of dimethyl formamide, ammonium chloride (500 mg) and sodium azide (600 mg) was added at reflux. After 2 hours the reaction mixture was concentrated, treated with 6 M hydrochloric acid and extracted several times with ethyl
25 acetate. The combined organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 96:4:1 chloroform/methanol/acetic acid) to give 60 mg (34%) of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzyltetrazole.

- (b) A reaction mixture of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)-benzyltetrazole (60 mg), BF₃·Me₂S (0.5 ml) and CH₂Cl₂ (6 ml) was stirred at room
30 temperature over night. The yield after purification was quantitative.

Examples 3-24

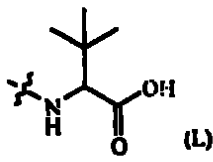
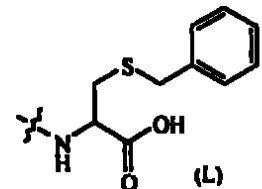
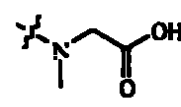
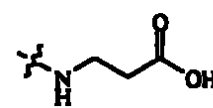
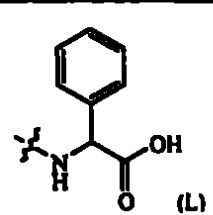
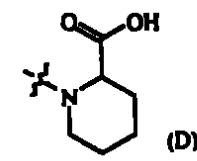
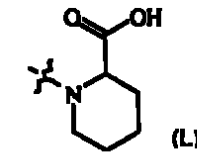


General Procedure

A mixture of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (95 mg), 1-hydroxybenzotriazole hydrate (HBT), (91 mg), in dichloromethane (5 ml) was stirred under argon at room temperature for 2 h. In a separate flask, the appropriate amino acid, triethylamine (100 mg) and 5 ml of dichloromethane was stirred for 1 h under N₂. The two mixtures were combined and the reaction mixture stirred at 40C over night. When the starting carboxylic acid was consumed, the organic phase was removed *in vacuo* and the residue dissolved in methanol (20 ml) and 1N NaOH (10 ml). The reaction mixture was stirred at 40C for 24 h and evaporated. The residue was subjected to semi-preparative HPLC, using gradient elution as outlined below. The amine part "R", and the stereochemistry of the aminoacids is indicated in the table below.

¹HPLC retention time in minutes and gradient method. Reverse phase HPLC analyses performed on Zorbax-C8-5u-4.6x50 mm analytical columns, flow rate 3 ml/min, detection at 220 nm, and a 10 minute gradient elution by solvent A (10 % CH₃CN+10 mmol HOOH) and B (CH₃CN + 10 mmol HOOH). Gradient elution was done in the following way: 0-1 min 90% A, 1-7 min to 100% B, 7-9 min 100% B and 9-10 min return to 10% A. Purification of the Examples were done using a Zorbax-C8-5u-21.5x50 mm semi-preperative column, flow rate 25 ml/min, detection at 220 nm, using the same gradient as for the analytical column. ²MS result obtained on a PESciEx API150EX using electrospray, both positive and negative ion modes.

Example	R	Mol Formel	MS m/z (M+H) ⁺	HPLC ³
3	L-Val	C22H25Br2NO5	544.0	8.10
4	L-Val	C22H25Br2NO5	544.0	6.07
5	L-Tyr	C28H25Br2NO6	608.5	5.67

6		C ₂₃ H ₂₇ Br ₂ NO ₅	558.1	6.03
7		C ₂₇ H ₂₇ Br ₂ NO ₅ S	638.2	5.49
8	D-Leu	C ₂₃ H ₂₇ Br ₂ NO ₅	558.1	5.38
9	D-Tyr	C ₂₈ H ₂₅ Br ₂ NO ₆	608.2	5.00
10	D-Trp	C ₂₈ H ₂₆ Br ₂ N ₂ O ₅	631.3	5.38
11	L-Arg	C ₂₃ H ₂₈ Br ₂ N ₄ O ₅	601.3	4.54
12	L-Abu	C ₂₁ H ₂₃ Br ₂ NO ₅	530.2	6.22
13		C ₂₀ H ₂₁ Br ₂ NO ₅	516.1	4.77
14		C ₂₀ H ₂₁ Br ₂ NO ₅	516.1	4.61
15	L-Leu	C ₂₃ H ₂₇ Br ₂ NO ₅	558.1	5.38
16		C ₂₅ H ₂₃ Br ₂ NO ₅	578.2	5.23
17	D-Pro	C ₂₂ H ₂₃ Br ₂ NO ₅	542.2	4.92
18	L-Ile	C ₂₃ H ₂₇ Br ₂ NO ₅	558.1	5.38
19		C ₂₃ H ₂₅ Br ₂ NO ₅	556.3	5.23
20	L-Phe	C ₂₈ H ₂₅ Br ₂ NO ₅	582.0	5.46
21	L-Lys	C ₂₃ H ₂₈ Br ₂ N ₂ O ₅	573.1	3.77
22		C ₂₃ H ₂₅ Br ₂ NO ₅	556.0	5.30
23	L-Pro	C ₂₂ H ₂₃ Br ₂ NO ₅	542.2	4.84

24	The structure shows a central benzene ring with two bromine atoms at the 3 and 5 positions. At the 4 position, there is an ether linkage to another benzene ring. This second benzene ring has a hydroxyl group (-OH) at the 4 position and an isopropyl group (-CH(CH₃)₂) at the 3 position. The central benzene ring also has a carboxylic acid group (-COOH) at the 1 position. The label (D) is present below the structure.	C ₂₅ H ₂₃ Br ₂ NO ₅	578.2	5.30
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Example 25***D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine**

- (a) A solution of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (106 mg), 1-hydroxybenzotriazole hydrate (HBT), (101 mg) in dimethyl formamide (5.5 ml) was stirred at room temperature for 0.5 h followed by addition of a solution of *D*-methionine methyl ester hydrochloride (298 mg) and triethylamine (111 mg) in dimethyl formamide (2.2 ml). After stirring for one hour, the mixture was partitioned between water and chloroform.
- 10 The organic phase was dried, filtered and concentrated. The residue was subjected to column chromatography (Silica gel, gradient elution with 20% to 40% ethyl acetate in petroleum ether), to give 256 mg (87%) of *D*-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] methionate. LC-MS (electrospray): *m/z* 590 (M+H).

- (b) *D*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-methionate (88 mg) was hydrolyzed by treatment with 1 M aqueous sodium hydroxide (1 ml) in methanol (2.25 ml), to give 81 mg (94%) of the title compound after column chromatography (Silica gel, gradient elution with chloroform, methanol and acetic acid). LC-MS (electrospray): *m/z* 574 (M-H).

Example 26***L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine**

- (a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg) was coupled with *D*-methionine hydrochloride (298 mg) using the method described in Example 25(a), to give 236 mg (80%) of *L*-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionate after column chromatography. (Silica gel, gradient elution with 20% to 40% ethyl acetate in petroleum ether). LC-MS (electrospray): *m/z* 590 (M+H).

(b) *D*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-methionate (24 mg) was hydrolyzed using the method described in Example 25(b) to give 20 mg (87%) of the title compound after column chromatography (Silica gel, gradient elution with chloroform, methanol and acetic acid). LC-MS (electrospray): m/z 574 (M-H).

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Example 27

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] α -methylalanine

(a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg) was coupled with *D*- α -methylalanine hydrochloride (238 mg) using the method described in Example 25(a), to give 269 mg (92%) of *D*-*t*-butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] α -methylalanine after column chromatography (Silica gel, gradient elution with 20% to 40% ethyl acetate in petroleum ether). LC-MS (electrospray): m/z 586 (M+H).

(b) *D*-*t*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] α -methylalanine (88 mg) was treated with boron tribromide (1 M in dichloromethane, 2.3 ml) at 0°C. The mixture was stirred overnight at room temperature before ice/water was added. The layers were separated and the water layer was extracted with dichloromethane. The combined organic layer was dried, filtered and concentrated, to give 46 mg (58%) of the title compound after column chromatography (Silica gel, gradient elution with chloroform, methanol and acetic acid). LC-MS (electrospray): m/z 528 (M-H).

Example 28

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine.

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (444 mg) was mixed with 10 ml thionyl chloride and heated at reflux for 3 h. The reaction mixture was co-evaporated with toluene to give the crude 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl chloride. N,O-bis(trimethylsilyl)acetamide (670 mg) was added at 0°C, under nitrogen atmosphere, to a mixture of *D*-Asparagine (225 mg) and 10 ml acetonitrile. The reaction mixture was further stirred at room temperature and a solution of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl chloride in 10 ml acetonitrile was added.

After stirring for 16 h, the reaction mixture was poured into water and the solid filtered off. The solid was dissolved in methanol and the organic phase removed *in vacuo*. The residue was purified by HPLC to give 76 mg (14%) of *D*- N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine. LC-MS (electrospray): *m/z* 557 (M-H).

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Example 29

L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-methyl alanine hydrochloride (126 mg) using the method described in Example 25(a), to give 140 mg (60%) of the title compound. LC-MS (electrospray): *m/z* 530
10 (M+1).

General procedure for the preparation of the amino acid library by solid phase synthesis
(Examples 30-55)

Loading of the resin with 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy benzoic acid:

A mixture of methyl 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoate (7.6g,
15 17.1mmol), Merrifield resin (5g, 1.2mmol/g) and sodium hydride (432 mg, 18 mmol) in 100 ml of dimethyl formamide was stirred in a 250 ml round flask at 50 °C for 40 hours. After cooling, the mixture was filtered and the resin was washed with water (3x 10 ml), dimethyl formamide (3x10 ml), ethyl acetate(3x10 ml) and dichloromethane(3x10 ml). The resulting resin was dried in vacuum overnight to give 8.54g of resin, loaded with the methyl ester.

20 To the resin was added methanol (100 ml) and an aqueous solution of sodium hydroxide (100 ml, 1M). The suspension was stirred under at 80°C for one day, cooled to room temperature and filtered. The resin was washed with water (3x10 ml), tetrahydrofuran (3x10 ml), ethyl acetate (3x10 ml) and dichloromethane(3x10 ml). After drying under vacuum, 5.94 g of resin loaded with the title compound was obtained.

25 ***Determination of the loading capacity of the resin:***

The resin (100 mg) was treated with a mixture of trifluoroacetic acid, dimethyl sulphite and water (85:15:5). The mixture was stirred at room temperature for two days. The resin was removed by filtration and the organic phase was collected and concentrated under vacuum. The resulting residue was chromatographed on silica gel (methanol/chloroform/

acetic acid 10:90:1). The pure fractions were pooled and concentrated affording 17.5 mg (51%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid as white solid. The loading rate was estimated as 0.04 mmol (17.5 mg) per 100 mg of loaded resin.

Coupling of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy) benzoic acid to different amino acids

DIVERSOMER® 8-100 synthesizer was used for syntheses and Savant SpeedVac® system for concentration.

To each of eight PINs was added 100 (± 5) mg of the loaded resin (17.5 mg /100 mg; 0.04 mmol/100 mg). The resin-filled PINs were placed in the holder block. Eight vials (12 ml) were placed into the reservoir rack, equipped with a magnetic stir bar and filled with a mixture consisting of the corresponding aminoacid ester (0.4 mmol), PyBOP (104 mg, 0.2 mmol), HBT (27 mg, 0.2 mmol), DIEA (52 mg, 0.4 mmol) and dichloromethane (5 ml). The holder block was assembled with the reservoir rack. The reaction was carried out at room temperature with stirring for two days. The reservoir rack was disassembled from the holder block. Each resin in the PINs was dispensed with 2 ml each of dimethyl formamide, water, ethyl acetate and dichloromethane. The washing procedure was repeated twice. The resin in PINs was finally dried by pressed air-flow.

Eight new vials (12 ml) were placed into the reservoir rack and each vial was equipped with a magnetic stir bar. The holder block was assembled with the reservoir rack. A methanolic solution of potassium hydroxide (5 ml, 2 M) was in 1 ml increments down through the inside of each PIN. The apparatus was allowed to stand in a fume hood with stirring for two days. The synthesizer was disassembled and the resins were washed with water (4x2 ml), methanol (4x2 ml) and dichloromethane (4x2 ml). The resin in PINs was dried by pressed air-flow.

The holder block was reassembled from the reservoir rack. A 50 ml stock solution of trifluoroacetic acid/dimethyl sulphite/water(85:15:5; v/v) was prepared. The solution (5 ml) was added to each of the eight PINs in 1 ml increments. The apparatus was allowed to stand in a fume hood with stirring for 2 days. The reservoir rack and the holder block was disassembled. Each PIN was washed with 1 ml of the above solution. The contents of the 8 reservoir vials were concentrated to dryness. Each vial was partitioned between aqueous hydrochloric acid (1 ml, 1 M) and ethyl acetate (2 ml). The content of the eight reservoir vials were carefully transferred into the eight drying cartridges (Chem elute CE1003, VARIAN), equipped with test tubes underneath. The cartridges were allowed to drain by gravity, rinsed with ethyl acetate (3x1.5 ml) after 5 min and finally forced to drain under reduced pressure. The organic layer was collected and concentrated to give the following products in the yields mentioned below.

Example 30

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine

12.2mg (57.7%)

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Example 31

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine

20.1mg (92.5%)

Example 32

L-S-Benzyl, N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine

10 14.9mg(60%)

Example 33

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine

5.9mg(24.8%)

Example 34

15 *L*-N-δ-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl),
N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]arginine

10.7mg(31%)

Example 35

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobutyric acid

20 15.6 mg (75,5%)

Example 36

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine

19.7 mg (93%)

Example 37

202

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine
14.8 mg (68%)

Example 38

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]proline
5 8.6 mg (41%)

Example 39

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine

2.88 mg (13.5%)

Example 40

10 N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine

15.8 mg (81%)

Example 41

L-N- α -[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine

23.5 mg (105%)

15

Example 42

D-N- α -[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine

24.9 mg (112%)

Example 43

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminoisobutyric acid

20 6.72 mg (32.6%)

Example 44

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine

7.1 mg (31%)

Example 45

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine

15.1 mg (67%)

Example 46

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine

5 6.7 mg (33.4%)

Example 47

DL-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]- α -methylphenylalanine

7.4 mg (31.4%)

Example 48

10 *L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]isoleucine

16.1 mg (70%)

Example 49

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine

11.7 mg (52%)

15 Example 50

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine

13.2 mg (58.6%)

Example 51

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine

20 9.7 mg (41.9%)

Example 52

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine

12.2 mg (52.9%)

Example 53

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cyclohexylalanine

10.1mg(43.7%)

Example 54

5

L-N-ε-(Benzyloxycarbonyl), N-α-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl]lysine

10 mg (36%)

Example 55

10 *D*-N-ε-(Benzyloxycarbonyl), N-α-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl]lysine

24.4 mg (88%)

Example 56

L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine

15 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-methyl alanine hydrochloride (126 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 40 mg (21%) of *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine. LC-MS
20 (electrospray): m/z 516 (M+H).

Example 57

L-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-dimethyl glutamate hydrochloride (190 mg) using the method described in
25 Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 150 mg (55%) of the title compound. LC-MS (electrospray): m/z 601 (M+1).

Example 58

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-hydroxy-1-naphthalenesulphonamide

To a stirred mixture of 5-hydroxy-1-naphthalenesulphonamide (0.175 mmol) in
5 dichloromethane (0.2 ml) was added a solution of
3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (0.035 mmol), DIEA (0.175
mmol) and dichloromethane (0.2 ml). dimethyl formamide was added to the solution if the
sulphonamide not dissolved completely in dichloromethane. After 15 minutes PyBOP (0.042
mmol) and HOBt (0.001 mmol) in dichloromethane (0.3 ml) was added. The reaction
10 mixture was heated at 50°C for 20 hours. After cooling to room temperature,
dichloromethane (1 ml) and citric acid solution (5%, 1ml) was added and stirred vigorously
for 30 min. The organic phase was dried, concentrated and the residue was finally subjected
to semi-preparative HPLC (Silica column: 250x20mm, ethyl acetate/n-heptane (both with
0.5% acetic acid). Gradient: first 2min 15% ethyl acetate, then over 13min to 100% ethyl
15 acetate, then additional 5 min 100% ethyl acetate) to give 12 mg (54 %) of the title
compound.

Example 59

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-toluenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled
20 with toluenesulphonamide (0.175 mmol) using the method described in Example 58.
Purification on HPLC of the residue gave 14 mg (69 %) of the title compound.

Example 60

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-nitrobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (, 0.035 mmol) was coupled
25 with 4-nitrophenylsulfonamid (0.175 mmol) using the method described in Example 58.
Purification on HPLC of the residue gave 8 mg (37 %) of the title compound.

Example 61

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl sulfamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with sulfamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 13 mg (73 %) of the title compound.

Example 62

5 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-dimethylamino-1-naphthalene-sulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 5-dimethylamino-1-naphthalenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 8 mg (34 %) of the title compound.

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Example 63

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-aminobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-aminobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 7 mg (34 %) of the title compound.

15

Example 64

Methyl-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-sulphonamide] benzoate

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with methyl 2-sulphonamide benzoate (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 12 mg (55 %) of the title compound.

20

Example 65

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-aminobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 2-aminobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 11 mg (54 %) of the title compound.

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Example 66

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-toluenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 2-toluenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 15 mg (74 %) of the title compound.

Example 67

5 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminoethyl)benzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-(2-aminoethyl)benzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 10 mg (47 %) of the title compound.

Example 68

10 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminomethyl)benzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (, 0.035 mmol) was coupled with 4-(2-aminomethyl)benzenesulphonamide (0.175 mmol) using the method described in

15 Example 58. Purification on HPLC of the residue gave 16 mg (76 %) of the title compound.

Example 69

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-3-nitrobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 3-nitrobenzenesulphonamide (0.175 mmol) using the method described in Example 58.

20 Purification on HPLC of the residue gave 7 mg (33 %) of the title compound.

Example 70

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-chlorobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-chlorobenzenesulphonamide (0.175 mmol) using the method described in Example 58.

25 Purification on HPLC of the residue gave 13 mg (62 %) of the title compound.

Example 71

L-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-dimethyl glutamate hydrochloride (190 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 150 mg (55%) of the title compound. LC-MS (electrospray): *m/z* 601 (M+H).

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Example 72

L-(*O*-*tert*-butyl)methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-(*O*-*tert*butyl)methyl glutamate hydrochloride (228 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 70 mg (24%) of the title compound. LC-MS (electrospray): *m/z* 643 (M+H).

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Example 73

L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-dimethyl glutamate hydrochloride (190 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 62 mg (31%) of the title compound. LC-MS (electrospray): *m/z* 574 (M+H).

15

Example 74

20 *L*-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid.

(a) A solution of 3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (50 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (30 mg), 1-hydroxybenzotriazole hydrate (HBT), (28 mg) in dimethyl formamide (1 ml) was stirred at room temperature for 0.5 h followed by addition of a solution of *L*-di-*t*-butyl aspartate hydrochloride (52 mg) and triethylamine (32 mg) in dimethyl formamide (1 ml). After stirring for three days, the mixture was partitioned between water and ethyl acetate. The organic phase was washed with brine and then dried, filtered and concentrated. The residue was

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chromatographed on silica gel eluted with ethyl acetate/light petroleum ether (1:4). Pure fractions were pooled and concentrated to give *L*-di-*t*-butyl *N*-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate (68 mg, 83%).

(b) The above ester (48 mg) was hydrolyzed using the method described in Example 25(b) to give *L*-*N*-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid (27 mg, 70%).

Example 75

D-di-*tert*-butyl-*N*-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *D* - di-*tert*-butyl glutamate hydrochloride (266 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 170 mg (70%) of the title compound. LC-MS (electrospray): *m/z* 685 (M+H).

Example 76

D-*N*-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *D*-di-*tert*-butyl glutamate hydrochloride (190 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 60 mg (23%) of the title compound. LC-MS (electrospray): *m/z* 574 (M+H).

Example 77

L-*O*-*tert*-Butyl-*N*-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-*O*-*tert*-butyl glutamine hydrochloride (230 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 100 mg (44%) of the title compound. LC-MS (electrospray): *m/z* 629 (M+H).

Example 78

L-*N*-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L-tert*-butyl glutamine hydrochloride (230 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 40 mg (15%) of the title compound. LC-MS (electrospray): m/z 574 (M+H).

Example 79

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *D*-glutamine hydrochloride (163 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The reaction mixture was concentrated *in vacuo*. The residue was subjected to semi-preparative HPLC, to give 30 mg (12%) of the title compound. LC-MS (electrospray): m/z 574 (M+H).

Example 80

L-O-Benzyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-O-Benzyl aspartic acid (266 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 140 mg (38%) of the title compound. LC-MS (electrospray): m/z 650 (M+1).

Example 81

L-O-*tert*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-O-*tert*-butyl asparagine hydrochloride (170 mg) using the method described in Example 25(a). The crude mixture was purified by HPLC, to give 40 mg (16%) of the title compound. LC-MS (electrospray): m/z 558 (M+H).

Example 82

L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine.

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylacetic acid (134 mg) was coupled with *L*-homoserine (36 mg) using the method described in Example 25(a). The crude
5 residue was dissolved in MeOH and heated at reflux with SOCl₂ for 2 h. After evaporation of the solvent, the residue was chromatographed on column (silica gel, CHCl₃/MeOH 97:3). Pure fractions were pooled and concentrated to give 100 mg (64%) of the title compound.

Example 83

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine

10 *L*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-homoserine (100 mg) was hydrolyzed using the method described in Example 25(b). The crude product was purified by HPLC to give 30 mg (30%) of *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl]homoserine

Example 84

15 *D*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine.

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylacetic acid (140 mg) was coupled with *L*-homoserine (36 mg) and re-esterified using the method described in Example 82. This gave 100 mg (64 %) of *D*-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl]homoserine.

20 **Example 85**

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine

D-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-homoserine (100 mg) was hydrolyzed using the method described in Example 25(b). The crude product was purified by HPLC to give 30 mg (30%) of *D*-N-[3,5-dibromo-4-(4-
25 hydroxy-3- isopropyl-phenoxy)phenylacetyl]homoserine.

Example 86**N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine**

- (a) A stirred mixture of 3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (9.56 g, 28.02 mmol), methyl glycine ester hydrochloride (5.28 g, 42.05 mmol),
 5 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.45 g, 33.64 mmol), 1-hydroxybenzotriazole (4.54 g, 33.60 mmol), CH₂Cl₂ (260 mL) and DMF (20 mL) was cooled with an ice-H₂O bath. N-methylmorpholine (5.7 g, 6.2 mL, 56.35 mmol) was added under N₂ and the reaction mixture was allowed to attain room temperature. After 18 h, CH₂Cl₂ was removed *in vacuo* and the residue partitioned between EtOAc (300 mL) and
 10 H₂O (150 mL). The organic phase was successively washed with 1N HCl (2 x 150 mL), saturated aqueous NaHCO₃ (2 x 150 mL), and brine (2 x 150 mL). The organic phase was dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 11.5 g of crude product as an orange solid. The crude product was purified by chromatography (Silica gel, 40 % EtOAc in hexane) to give 9.76 g (84 % yield) of slightly yellowish solid. ¹H NMR (500 MHz, CDCl₃): δ
 15 7.82 (s, 2H), 6.78 (d, 1H, J = 2.7 Hz), 6.63 (d, 1H, J = 8.8 Hz), 6.61 (t, 1H, J = 4.9 Hz), 6.38 (dd, 1H, J = 8.8, 3.3 Hz), 4.65 (s, 1H), 4.24 (d, 2H, J = 5 Hz), 3.82 (s, 3H), 3.16 (heptet, 1H, 6.6 Hz), 1.22 (d, 6H, J = 6.6 Hz); ¹³C NMR: δ 170.18, 164.65, 150.66, 148.36, 136.26, 131.63, 130.57, 128.10, 115.76, 113.94, 112.28, 52.69, 41.87, 27.34, 22.38; MS-ESI⁻ [M-H]⁻ = 410, 412, 414 (100:64:10).
- (b) To a solution of methyl N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl] glycinate (7.30 g, 17.71 mmol) in THF (106 mL) was added 1 N aqueous lithium hydroxide solution (53 mL, 53 mmol). After 2h, the mixture was acidified with 1 N HCl and extracted with EtOAc (200 mL). The organic phase was washed with brine (2 x 75 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The concentrate was triturated with CH₂Cl₂ (100
 25 mL) and the white solid material obtained was dried *in vacuo* to give 6.85 g of the title product (97% yield). ¹H NMR (500 MHz, CD₃OD): δ 7.82 (s, 2H), 6.78 (d, 1H, J = 2.7 Hz), 6.63 (d, 1H, J = 8.8 Hz), 6.61 (t, 1H, J = 4.9 Hz), 6.38 (dd, 1H, J = 8.8, 3.3 Hz), 4.65 (s, 1H), 4.24 (d, 2H, J = 5 Hz), 3.16 (heptet, 1H, 6.6 Hz), 1.22 (d, 6H, J = 6.6 Hz); ¹³C NMR: δ
 172.88, 167.20, 151.31, 151.34, 151.13, 137.67, 133.40, 131.39, 129.63, 116.41, 114.13,
 30 113.28, 42.27, 28.19, 22.85; MS-ESI⁻ [M-H]⁻ = 396, 398, 400 (100:64:10).

Example 87**N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine**

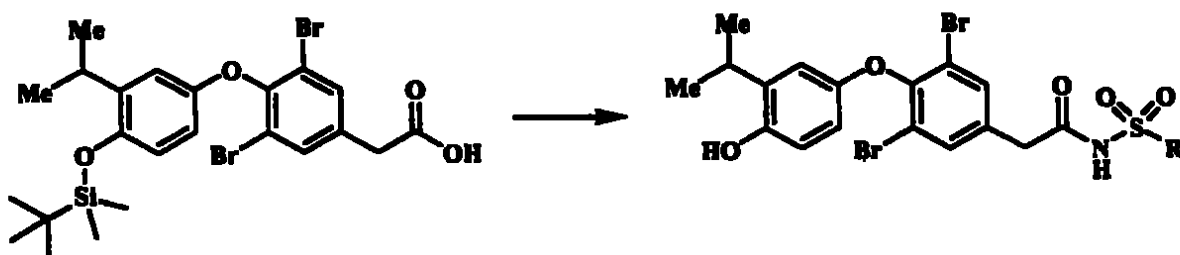
- (a) To a solution of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (60 mg, 0.169 mmol) in CH_2Cl_2 (10 mL) cooled with an ice- H_2O bath was added sarcosine methyl ester hydrochloride (35.4 mg, 0.253 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38.9 mg, 0.203 mmol) and 1-hydroxy-7-azabenzotriazole (27.6 mg, 0.203 mmol) and N-methylmorpholine (34.2 mg, 37 μL , 0.338 mmol). The mixture was allowed to warm up to RT and left to stir overnight (ca. 18h). The mixture was taken up in EtOAc (50 mL) and H_2O (20 mL). The organic layer was separated and then it was washed successively with 1N HCl (2 x 25 mL), saturated NaHCO_3 aqueous solution (2 x 25 mL) and brine (2 x 25 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by chromatography (25 g silica gel, 30% EtOAc in hexane) to give 41 mg of purified material (55% yield). Satisfactory proton and LC-MS were obtained.
- (b) To a solution of the product above (30 mg, 0.068 mmol) in anhydrous CH_2Cl_2 (3 mL) cooled with an ice- H_2O bath was added boron tribromide (0.7 mL, 1.0 M in CH_2Cl_2 , 0.7 mmol). After 2h, the mixture was poured into ice- H_2O (25 mL). After 15 min of stirring, the product was extracted with EtOAc (50 mL). The organic extract was washed with brine (2 x 25 mL), dried (MgSO_4), filtered and concentrated in vacuo. The crude product, a mixture of free acid and methyl ester, was dissolved in THF (2 mL) and 1N lithium hydroxide aqueous solution (1 mL) was added. After an hour, the mixture was acidified with 1N HCl and then extracted with EtOAc (25 mL). The EtOAc extract was washed with brine (2 x 15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give 35 mg of crude product. The crude product was purified by prep HPLC to give 12.3 mg of slightly yellowish solid as purified material (44% yield). Satisfactory proton and mass spectra were obtained.

Example 88**3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl-5-dimethylamino-1-naphthalenesulphonamide**

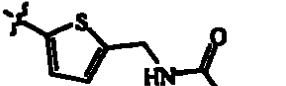
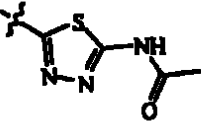
To a solution of the 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (50 mg, 0.09 mmol), dimethylaminopyridine (4 mg, 0.018 mmol) and 5-dimethylamino-1-naphthalenesulphonamide (45 mg, 0.18 mmol) in 50% dichloromethane in dimethyl formamide (0.2 ml) was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28 mg, 0.13 mmol) and diisopropylethyl amine (17 mg, 0.13 mmol) in 50% methylene chloride in dimethyl formamide (0.2 ml). The reaction mixture was vortexed and allowed to stand at room temperature for 6 hours. A solution of ammonium fluoride (0.5 M in methanol; 0.4 ml) was added. After 16 hours, the reaction mixture was evaporated to dryness, re-dissolved in a solvent mixture containing 90% methanol, 10% water and 0.1% trifluoroacetic acid (2 ml) and purified by preparative HPLC (YMC S5 ODS 30 x 250 mm: 50-100% solvent B in 30 min: solvent A - 90% water, 10% methanol, 0.1% trifluoroacetic acid; solvent B - 10% water, 90% methanol, 0.1% trifluoroacetic acid: flow rate 25 ml per min: detection 220 nm). The yield was 10.1 mg (16%).

Example 89-91

These compounds were prepared and purified in a similar manner as above. For a table of Examples 88-91 comprising the coupled sulphonamide, retention times and mass spectra, see Scheme below.

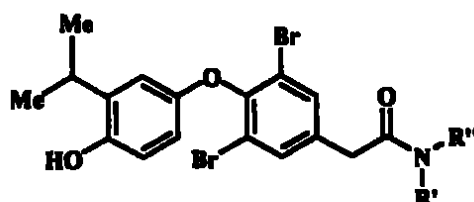


Example	R	MS (ESI+)	R _t (min) ¹
88		677	6.9
89		598	4.3

90		722	5.1
91		648	4.9

1YMC ODS 4.6 x 50 mm: 50-100% solvent B in 8 min: solvent A - 90% water, 10% methanol, 0.2% phosphoric acid; solvent B – 10% water, 90% methanol, 0.2% phosphoric acid; flow rate 2.5 ml per min: detection 220 nm

Examples 92-191



Procedures for the synthesis of the library compounds indicated in the Table below are described in Lawrence, R.M.; Biller, S.A.; Fryszman, O.M.; Poss, M.A. *Synthesis* 1997, 553.

¹HPLC retention time in minutes and gradient method. Reverse phase HPLC analyses performed on YMC S5 ODS 4.6 x 50 mm analytical columns, detection at 220 nm, and 4 minute gradient elutions by either: method a, 0% B, 100% A to 100% B, 0% A; or method b, 20% B, 80% A to 100% B, 0% A, where solvent A is 90% water, 10% methanol, 0.2% phosphoric acid and solvent B is 10% water, 90% methanol, 0.2% phosphoric acid.

²MS result obtained on a Micromass Platform II using electrospray, both positive and negative ion modes.

³Method A examples were prepared by synthesis procedure A in the reference cited above. In these examples, a second basic nitrogen is present in the amine coupling partner. However, only one nitrogen is capable of giving the normal acylation product. Method B examples were prepared by procedure C in the reference cited above.

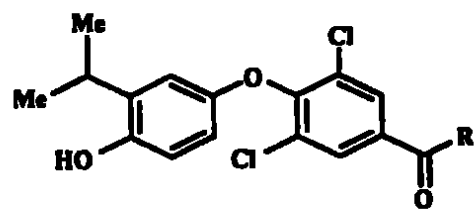
Example	NR'R"	HPLC ¹	MS ²	Formula	Method ³
92	3-(AMINOMETHYL)PYRIDINE	2.76, _a	m/z 534.84 (M+H)	C ₂₃ H ₂₂ Br ₂ N ₂ O ₃	A
93	2-(2-AMINOETHYL)PYRIDINE	2.73, _a	m/z 548.83 (M+H)	C ₂₄ H ₂₄ Br ₂ N ₂ O ₃	A
94	3-(2-AMINOETHYL)PYRIDINE	2.73, _a	m/z 548.82 (M+H)	C ₂₄ H ₂₄ Br ₂ N ₂ O ₃	A
95	2-(AMINOMETHYL)PYRIDINE	2.64, _a	m/z 534.85 (M+H)	C ₂₄ H ₃₀ Br ₂ N ₂ O ₃	A
96	4-(AMINOMETHYL)PYRIDINE	2.74, _a	m/z 534.82 (M+H)	C ₂₄ H ₃₀ Br ₂ N ₂ O ₃	A
97	1-(4-METHOXYPHENYL)PIPE RAZINE DIHYDROCHLORIDE	3.33, _a	m/z 618.81 (M+H)	C ₂₉ H ₃₂ Br ₂ N ₂ O ₃	A

Example	-NR'R"	HPLC ¹	MS ²	Formula	Method ³
98	1-(2-FLUOROPHENYL)PIPERAZINE	3.53,a	m/z 607.16 (M+H)	C ₃₄ H ₃₂ Br ₂ N ₂ O ₃	A
99	2-(2 (AMINOMETHYL)PHENYLTHIO)BENZYL ALCOHOL	4.42,a	m/z 671.97 (M+H)	C ₃₁ H ₂₉ Br ₂ N ₂ O ₄ S	B
100	2-(1-CYCLOHEXENYL)ETHYLAMINE	4.56,a	m/z 551.98 (M+H)	C ₂₅ H ₂₉ Br ₂ N ₂ O ₃	B
101	2-AMINOINDAN	4.44,a	m/z 559.88 (M+H)	C ₂₆ H ₂₅ Br ₂ N ₂ O ₃	B
102	2-AMINOMETHYLBENZODIOXAN	4.39,a	m/z 591.93 (M+H)	C ₂₆ H ₂₅ Br ₂ N ₂ O ₅	B
103	3-PHENYL-1-PROPYLAMINE	4.44,a	m/z 560.00 (M+H)	C ₂₆ H ₂₇ Br ₂ N ₂ O ₃	B
104	2-(P-TOLYL)ETHYLAMINE	4.48,a	m/z 559.95 (M+H)	C ₂₆ H ₂₇ Br ₂ N ₂ O ₃	B
105	1-(3-AMINOPROPYL)-2-PYRROLIDINONE	3.97,a	m/z 588.97 (M+H)	C ₂₄ H ₂₈ Br ₂ N ₂ O ₄	B
106	BETA-ALANINE	4.52,a	m/z 670.88 (M+H)	C ₃₁ H ₃₀ Br ₂ N ₂ O ₅	B
	4-METHOXY-BETA-NAPHTHYLAMIDE				
107	2-CHLOROBENZYLAMINE	4.38,a	m/z 612.98 (M+?)	C ₂₄ H ₂₂ Br ₂ ClNO ₃	B
108	2-AMINOMETHYL-3-CHLORODIPHENYLETHER	4.65,a	m/z 660.08 (M+H)	C ₃₀ H ₂₆ Br ₂ ClNO ₄	B
109	DL-ALPHA-AMINO-EPSILON-CAPROLACTAM	4.03,a	m/z 554.86 (M+H)	C ₂₃ H ₂₆ Br ₂ N ₂ O ₄	B
110	L-PHENYLALANINOL	4.22,a	m/z 577.92 (M+H)	C ₂₆ H ₂₇ Br ₂ N ₂ O ₄	B
111	4-(1,2,3-THIAZOL-4-YL)BENZYLAMINE	4.21,a	m/z 617.89 (M+H)	C ₂₆ H ₂₃ Br ₂ N ₃ O ₃ S	B
112	2-AMINOMETHYLTHIOPHENE	4.21,a	m/z 539.84 (M+H)	C ₂₂ H ₂₁ Br ₂ N ₂ O ₃ S	B
113	1-(1-NAPHTHYL)ETHYLAMINE	4.54,a	m/z 597.83 (M+H)	C ₂₉ H ₂₇ Br ₂ N ₂ O ₃	B
114	3-CHLORO-4-METHYLBENZYLAMINE	4.53,a	m/z 581.80 (M+H)	C ₂₅ H ₂₄ Br ₂ ClNO ₃	B
115	TETRAHYDROFURFURYLAMINE	4.07,a	m/z 527.90 (M+H)	C ₂₂ H ₂₅ Br ₂ N ₂ O ₄	B
116	2,4-DICHLOROPHENETHYLAMINE	4.86,a	m/z 615.73 (M+H)	C ₂₅ H ₂₃ Br ₂ Cl ₂ NO ₃	B
117	ETHYL 4-AMINO-1-PIPERIDINECARBOXYLATE	4.21,a	m/z 599.05 (M+H)	C ₂₅ H ₃₀ Br ₂ N ₂ O ₅	B
118	2,6-DIFLUOROBENZYLAMINE	4.25,a	m/z 589.82 (M+H)	C ₂₄ H ₂₁ Br ₂ F ₂ NO ₃	B
119	2-IODOBENZYLAMINE	4.46,a	m/z 659.45 (M+H)	C ₂₄ H ₂₂ Br ₂ INO ₃	B
120	2-METHYLBENZYLAMINE	4.38,a	m/z 547.89 (M+H)	C ₂₅ H ₂₅ Br ₂ N ₂ O ₃	B
121	BENZYLAMINE	4.27,a	m/z 533.85 (M+H)	C ₂₄ H ₂₃ Br ₂ N ₂ O ₃	B
122	3-METHYLBENZYLAMINE	4.38,a	m/z 547.89 (M+H)	C ₂₅ H ₂₅ Br ₂ N ₂ O ₃	B
123	2-METHOXYPHENETHYLAMINE	4.41,a	m/z 577.81 (M+H)	C ₂₆ H ₂₇ Br ₂ N ₂ O ₄	B
124	3-METHOXYPHENETHYLAMINE	4.35,a	m/z 577.87 (M+H)	C ₂₆ H ₂₇ Br ₂ N ₂ O ₄	B
125	2-ETHOXYBENZYLAMINE	4.42,a	m/z 577.86 (M+H)	C ₂₆ H ₂₇ Br ₂ N ₂ O ₄	B
125	(R)-(-)-1-CYCLO-HEXYLETHYLAMINE	4.56,a	m/z 553.90 (M+H)	C ₂₅ H ₃₁ Br ₂ N ₂ O ₃	B
127	4-METHOXYPHENETHYLAMINE	4.32,a	m/z 577.83 (M+H)	C ₂₆ H ₂₇ Br ₂ N ₂ O ₄	B
128	2-FLUOROBENZYLAMINE	4.27,a	m/z 551.85 (M+H)	C ₂₄ H ₂₃ Br ₂ FNO ₃	B
129	2-CHLORO-6-METHYLBENZYLAMINE	4.48,a	m/z 581.85 (M+H)	C ₂₅ H ₂₄ Br ₂ ClNO ₃	B

Example	-NR'R"	HPLC ¹	MS ²	Formula	Method ³
130	4-CHLOROBENZYLAMINE	4.42,a	m/z 567.83 (M+H)	C ₂₄ H ₂₂ Br ₂ ClNO ₃	B
131	BETA-METHYLPHENETHYLAMINE	4.43,a	m/z 581.88 (M+H)	C ₂₆ H ₂₇ Br ₂ NO ₃	B
132	1,1-DI(P-ANISYL)METHYLAMINE	4.47,a	m/z 689.88 (M+H)	C ₃₂ H ₃₁ Br ₂ NO ₅	B
133	MAYBRIDGE BTB 12133	4.18,a	m/z 623.84 (M+H)	C ₂₇ H ₂₉ Br ₂ NO ₆	B
134	DL-2-AMINO-1-PENTANOL	4.12,a	m/z 529.91 (M+H)	C ₂₂ H ₂₇ Br ₂ NO ₄	B
135	L-PHENYLALANINE P-NITROANILIDE	4.56,a	m/z 711.88 (M+H)	C ₃₂ H ₂₉ Br ₂ N ₃ O ₆	B
136	ETHYL 3-AMINO BUTYRATE	4.16,a	m/z 557.85 (M+H)	C ₂₃ H ₂₇ Br ₂ NO ₅	B
137	(1S,2R)-(+)-2-AMINO-1,2-DIPHENYLETHANOL	4.28,a	m/z 639.92 (M+H)	C ₃₁ H ₂₉ Br ₂ NO ₄	B
138	2-FLUOROPHENETHYLAMINE	4.37,a	m/z 585.90 (M+H)	C ₂₅ H ₂₄ Br ₂ FNO ₃	B
139	2-ETHYLHEXYLAMINE	4.70,a	m/z 555.93 (M+H)	C ₂₅ H ₃₃ Br ₂ NO ₃	B
140	3-FLUOROPHENETHYLAMINE	4.36,a	m/z 585.85 (M+H)	C ₂₅ H ₂₄ Br ₂ FNO ₃	B
141	(1S,2S)-(+)-2-AMINO-3-METHOXY-1-PHENYL-1-PROPANOL	4.19,a	m/z 607.89 (M+H)	C ₂₇ H ₂₉ Br ₂ NO ₅	B
142	NONYLAMINE	4.88,a	m/z 569.95 (M+H)	C ₂₈ H ₃₅ Br ₂ NO ₃	B
143	2,5-DICHLOROBENZYLAMINE	4.49,a	m/z 601.72 (M+H)	C ₂₄ H ₂₁ Br ₂ Cl ₂ NO ₃	B
144	2-METHYLCYCLOHEXYLAMINE	4.44,a	m/z 539.91 (M+H)	C ₂₄ H ₂₉ Br ₂ NO ₃	B
145	3-METHYLCYCLOHEXYLAMINE	4.51,a	m/z 539.90 (M+H)	C ₂₄ H ₂₉ Br ₂ NO ₃	B
146	3-N-PROPOXYPROPYLAMINE	4.30,a	m/z 543.90 (M+H)	C ₂₃ H ₂₉ Br ₂ NO ₄	B
147	2,3-DIMETHYLBENZYLAMINE	4.48,a	m/z 581.91 (M+H)	C ₂₆ H ₂₇ Br ₂ NO ₃	B
148	3-CHLOROBENZYLAMINE	4.40,a	m/z 567.79 (M+H)	C ₂₄ H ₂₂ Br ₂ ClNO ₃	B
149	4-TERT-BUTYLCYCLOHEXYLAMINE	4.80,a	m/z 581.97 (M+H)	C ₂₇ H ₃₅ Br ₂ NO ₃	B
150	(1S,2S)-(+)-THIOMICAMINE	3.94,a	m/z 639.80 (M+H)	C ₂₇ H ₂₉ Br ₂ NO ₅ S	B
151	2,4-DIMETHYLBENZYLAMINE	4.49,a	m/z 581.89 (M+H)	C ₂₆ H ₂₇ Br ₂ NO ₃	B
152	2-AMINOETHYL PHENYL SULFIDE	4.44,a	m/z 579.83 (M+H)	C ₂₅ H ₂₅ Br ₂ NO ₃ S	B
153	PHENETHYLAMINE	4.36,a	m/z 547.87 (M+H)	C ₂₅ H ₂₅ Br ₂ NO ₃	B
154	TYRAMINE	4.04,a	m/z 583.86 (M+H)	C ₂₅ H ₂₅ Br ₂ NO ₄	B
155	L-TYROSINE METHYL ESTER	4.01,a	m/z 621.97 (M+H)	C ₂₇ H ₂₇ Br ₂ NO ₆	B
156	BENZHYDRYLAMINE	4.52,a	m/z 609.82 (M+H)	C ₃₀ H ₂₇ Br ₂ NO ₃	B
157	4-METHOXYBENZYLAMINE	4.25,a	m/z 563.85 (M+H)	C ₂₅ H ₂₅ Br ₂ NO ₄	B
158	2,3-DICHLOROBENZYLAMINE	4.52,a	m/z 601.71 (M+H)	C ₂₄ H ₂₁ Br ₂ Cl ₂ NO ₃	B
159	GLYCINE N-BUTYL ESTER HYDROCHLORIDE	4.03,b	m/z 557.85 (M+H)	C ₂₃ H ₂₇ Br ₂ NO ₅	B
160	D-(-)-ALPHA-PHENYLGLYCINE ETHYL ESTER HYDROCHLORIDE	4.11,b	m/z 605.84 (M+H)	C ₂₇ H ₂₇ Br ₂ NO ₅	B
161	4-CHLORO-2-FLUOROBENZYLAMINE HYDROCHLORIDE	4.27,b	m/z 585.80 (M+H)	C ₂₄ H ₂₁ Br ₂ ClFNO ₃	B
162	TRANS-2-PHENYLCYCLOPROPYLAMINE HYDROCHLORIDE	4.22,b	m/z 559.86 (M+H)	C ₂₆ H ₂₅ Br ₂ NO ₃	B

Example	-NR'R"	HPLC ¹	MS ²	Formula	Method ³
163	ETHYL 4-AMINO BUTYRATE HYDROCHLORIDE	3.87, b	m/z 557.85 (M+H)	C ₂₃ H ₂₇ Br ₂ NO ₅	B
164	DL-HOMOCYSTEINE THIOLACTONE HYDROCHLORIDE	3.65, b	m/z 543.80 (M+H)	C ₂₁ H ₂₁ Br ₂ NO ₄ S	B
165	4-NITROBENZYLAMINE HYDROCHLORIDE	3.99, b	m/z 578.85 (M+H)	C ₂₄ H ₂₂ Br ₂ N ₂ O ₅	B
166	NORPHENYLEPHRINE HYDROCHLORIDE	3.60, b	m/z 579.84 (M+H)	C ₂₅ H ₂₅ Br ₂ NO ₅	B
167	GLYCINE ETHYL ESTER HYDROCHLORIDE	3.71, b	m/z 529.87 (M+H)	C ₂₁ H ₂₃ Br ₂ NO ₅	B
168	DL-ALANINE ETHYL ESTER HYDROCHLORIDE	3.83, b	m/z 543.86 (M+H)	C ₂₂ H ₂₅ Br ₂ NO ₅	B
169	SARCOSINE ETHYL ESTER HYDROCHLORIDE	3.79, b	m/z 543.92 (M+H)	C ₂₂ H ₂₅ Br ₂ NO ₅	B
170	4-NITRO-N-PROPYLBENZYL AMINE HYDROCHLORIDE	4.29, b	m/z 620.89 (M+H)	C ₂₇ H ₂₈ Br ₂ N ₂ O ₅	B
171	PIPERIDINE	3.98, b	m/z 511.93 (M+H)	C ₂₂ H ₂₅ Br ₂ NO ₃	B
172	3-METHYLPYPERIDINE	4.14, b	m/z 525.91 (M+H)	C ₂₃ H ₂₇ Br ₂ NO ₃	B
173	3-(HYDROXYMETHYL)-PIPE RIDINE	3.66, b	m/z 541.89 (M+H)	C ₂₃ H ₂₇ Br ₂ NO ₄	B
174	1,2,3,4-TETRAHYDROISOQU INOLINE	4.23, b	m/z 559.85 (M+H)	C ₂₆ H ₂₆ Br ₂ NO ₃	B
175	2-ETHYLPYPERIDINE	4.25, b	m/z 539.90 (M+H)	C ₂₄ H ₂₉ Br ₂ NO ₃	B
176	3,4-DICHLORO-N-ETHYLBEN ZYLAMINE	4.54, b	m/z 629.75 (M+H)	C ₂₆ H ₂₅ Br ₂ Cl ₂ NO ₃	B
177	2-METHYLPYRROLIDINE	3.99, b	m/z 511.90 (M+H)	C ₂₂ H ₂₅ Br ₂ NO ₃	B
178	N-ETHYL-N-PROPYLAMINE	4.11, b	m/z 513.89 (M+H)	C ₂₂ H ₂₇ Br ₂ NO ₃	B
179	4-METHYLPYPERIDINE	4.15, b	m/z 525.91 (M+H)	C ₂₃ H ₂₇ Br ₂ NO ₃	B
180	(S)-(+)-2-(METHOXYMETHYL) PYRROLIDINE	3.99, b	m/z 541.90 (M+H)	C ₂₃ H ₂₇ Br ₂ NO ₄	B
181	N-BENZYLETHANOLAMINE	4.01, b	m/z 577.86 (M+H)	C ₂₆ H ₂₇ Br ₂ NO ₄	B
182	DIBENZYLAMINE	4.56, b	m/z 623.79 (M+H)	C ₃₁ H ₂₉ Br ₂ NO ₃	B
183	4-BENZYL-4-HYDROXYPIPE RIDINE	4.12, b	m/z 617.88 (M+H)	C ₂₉ H ₃₁ Br ₂ NO ₄	B
184	(R)-(-)-2-BENZYLAMINO-1-BU TANOL	4.16, b	m/z 605.83 (M+H)	C ₂₈ H ₃₁ Br ₂ NO ₄	B
185	N-(N-ETHYLAMINOACETYL)- 2,6-DIMETHYLANILINE	4.00, b	m/z 632.69 (M+H)	C ₂₉ H ₃₂ Br ₂ N ₂ O ₄	B
186	N-ETHYL-O-METHOXYBENZ YLAMINE	4.35, b	m/z 591.83 (M+H)	C ₂₇ H ₂₉ Br ₂ NO ₄	B
187	MAYBRIDGE NRB 01981	4.40, b	m/z 647.88 (M+H)	C ₃₀ H ₃₃ Br ₂ NO ₅	B
188	2-((N-ETHYLAMINO)METHYL) -4-NITROPHENOL	4.05, b	m/z 622.80 (M+H)	C ₂₈ H ₂₆ Br ₂ N ₂ O ₆	B
189	MAYBRIDGE SEW 01484	4.48, b	m/z 671.89 (M+H)	C ₃₁ H ₂₉ Br ₂ NO ₄ S	B
190	3-AZABICYCLO-[3.2.2]NONA NE	4.28, b	m/z 551.89 (M+H)	C ₂₅ H ₂₉ Br ₂ NO ₃	B
191	N-(2-METHOXY-ETHYL)ETH YLAMINE	3.89, b	m/z 529.88 (M+H)	C ₂₂ H ₂₇ Br ₂ NO ₄	B

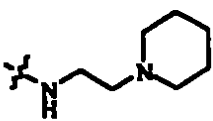
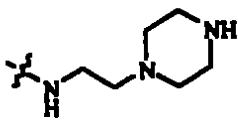
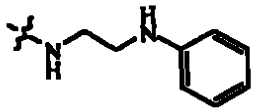
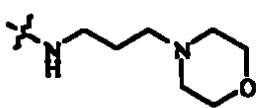
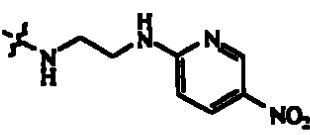
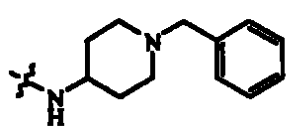
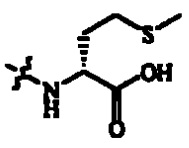
Examples 192-203



General Procedure

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid was coupled with the appropriate amino acid, using the general procedure outlined for Examples 3-24. The residue was subjected to semi-preparative HPLC, using the same gradient elution as outlined for Examples 3-24. The amine part "R" and the stereochemistry of the aminoacids is indicated in the table below. Retention times, yields and the mass of the individual products are also given below.

Example	R	Yield (%)	MS m/z (M+H) ⁺	HPLC
192		64	407.3	7.3
193		61	426.1	7.1
194		59	435.2	6.6
195		40	440.1	6.7
196		88	452.3	6.6

197		78	452.2	6.7
198		71	453.2	6.5
199		39	480.1	7.6
200		55	487.9	6.7
201		31	506.3	7.5
202		72	514.4	7.0
203		52	473.2	8.0

Example 204**2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-thiazole acetic acid**

(a) A reaction mixture of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl acetamide (150 mg) and Lawesson's reagent (100 mg) in dioxane (3 mL) was stirred at room temperature for 15 hours. The resulting suspension was filtered and poured onto ice-water and stirred. The water phase was extracted with EtOAc (3x7 mL) and the combined organic phases were washed with water. The organic phase was dried over Na₂SO₄, concentrated and gave 153 mg of crude 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl thioamide. The crude product was used directly in the next step.

(b) To a suspension of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl thioamide (80 mg) in EtOH (2 mL), ethylchloroacetoacetate (0.03 mL) was added. The

mixture was stirred in a closed tube at 75 C for 2 h. The reaction mixture was concentrated and EtOAc and water was added. The water phase was extracted with EtOAc (3x5 mL) and the combined organic phases were washed with NaHCO₃ (sat. solution). The organic phase was dried over Na₂SO₄, concentrated and purified by chromatography (silica gel, 15 %

5 EtOAc/p-ether). This gave 80 mg (86%) of ethyl-2-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-thiazole acetate.

(c) BF₃.Et₂ (0.06 mL) was added slowly to a solution of the ethyl ester (60 mg) in CH₂Cl₂ (4 mL). The reaction mixture was stirred at room temperature for 2 days. Water was added. The water phase was extracted with EtOAc (3x5 mL) and the combined organic
10 phases were washed with an aqueous solution of HCl (1N). The organic phase was dried over Na₂SO₄, concentrated and purified by semi-preparative HPLC. This gave 20 mg (37 %) of the title compound.

Example 205

2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methylthiazole

15 (a) 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl thioamide (70 mg) in EtOH (2 mL) was reacted with ethylchloroacetoacetate (0.014 mL) using the method described in Example 204(b). The crude product was purified by chromatography (silica gel, 15 % EtOAc/p-ether). This gave 60 mg (78 %) of 2-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl]-4-methylthiazole.

20 (b) The above methoxy compound (50 mg) was demethylated with BF₃.Et₂ (0.06 mL), using the method described above. The crude mixture was purified by semi-preparative HPLC. This gave 20 mg (41 %) of the title compound.

Example 206

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylformylimino diacetic acid

25 (a) To a solution of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (60 mg, 0.169 mmol) in CH₂Cl₂ (10 mL) cooled with an ice-H₂O bath was added diethyliminodiacetate (35.4 mg, 0.253 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38.9 mg, 0.203 mmol) and 1-hydroxy-7-azabenzotriazole (27.6 mg, 0.203mmol) . The mixture was allowed to warm up to room temperature and left to

stir overnight (ca. 18h). The mixture was taken up in EtOAc (50 mL) and H₂O (20 mL). The organic layer was separated and then it was washed successively with 1N HCl (2 x 25 mL), saturated NaHCO₃ aqueous solution (2 x 25 mL) and brine (2 x 25 mL). The organic extract was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography (25 g silica gel, 15% EtOAc in hexane) to give 31 mg of purified material (35% yield). Satisfactory proton and LC-MS were obtained.

(b) To a solution of above ethyl ester (25 mg, 0.047 mmol) in anhydrous CH₂Cl₂ (3 mL) cooled with an ice-H₂O bath was added boron tribromide (0.7 mL, 1.0 M in CH₂Cl₂, 0.7 mmol). After 2h, the mixture was poured into ice-H₂O (25 mL). After 15 min of stirring, the product was extracted with EtOAc (50 mL). The organic extract was washed with brine (2 x 25 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product, a mixture of free acid and methyl ester, was dissolved in THF (2 mL) and 1N lithium hydroxide aqueous solution (1 mL) was added. After an hour, the mixture was acidified with 1N HCl and then extracted with EtOAc (25 mL). The EtOAc extract was washed with brine (2 x 15 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 27.7 mg of crude product. The crude product was purified by prep HPLC to give 9.2 mg (38 %) of the title compound as a slightly yellow solid. Satisfactory proton and mass spectra were obtained.

Example 207

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine

(a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (50 mg, 0.116 mmol), beta-alanine methyl ester hydrochloride (70 mg, 0.42 mmol), and hydroxy-benzotriazole (78 mg, 0.57 mmol) were dissolved in dichloromethane (0.6 mL), N,N-dimethylformamide (0.2 mL) and triethyl amine (0.12 mL, 0.58 mmol). The solution was cooled to 0 °C and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride (110 mg, 0.58 mmol) was added. The reaction was warmed to room temperature and stirred for 12 hours. The reaction was diluted with dichloromethane (100 mL) and washed with water (2 x 150 mL). The organic layer was washed once with brine (100 mL), dried over sodium sulfate and concentrated *in vacuo*. The methyl ester (50 mg, 90 % yield) was purified by chromatography (silica gel, 7:3 hexane/ethyl acetate).

(b) The crude ester was dissolved in 1.0 mL of methanol and 0.4 mL of 1 N sodium hydroxide. The hydrolysis was complete in 2 hours. The methanol was removed and the

aqueous layer was acidified with aqueous hydrochloric acid (1 N). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (2 x 75 mL) and dried over sodium sulfate. The organic layer was concentrated *in vacuo*. The title compound (51 mg, 98%) was obtained without further purification.

5 Satisfactory ¹H-NMR, ¹³C-NMR and mass spectra was obtained for the title compound.

Example 208

N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine

(a) The ester was prepared by adding the reagents to the reaction in the manner described in Example 207. The starting acid (122 mg, 0.356 mmol), B-alanine methyl ester
10 hydrochloride, and hydroxybenzotriazole (240 mg, 1.76 mmol) were dissolved in triethyl amine (0.6 mL, 2.5 mmol), dichloromethane 1.2 mL, and 0.8 mL of dimethylamide. The 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride (110 mg, 0.58 mmol) was added in the manner as described above. The ester (75 mg, 50 %) was isolated without further purification.

15 (b) The ester was dissolved in 3.0 mL of methanol and 1.6 mL of 1 N sodium hydroxide using the procedure described for title acid. The title acid (72 mg, 98 % yield) was obtained from the reaction. The acid was further purified by preparative HPLC using a YMC ODS 20 x 100 mm column which yielded 53.6 mg (74 % yield) of the purified acid.

Example 209

20 L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (122 mg) was coupled with L-serin methyl ester hydrochloride using the method described in Example 207(a) and subsequently hydrolyzed using the method described in Example 207(b). The crude mixture was purified as above. Satisfactory ¹H-NMR, ¹³C-NMR and mass spectra was obtained for the
25 title compound.

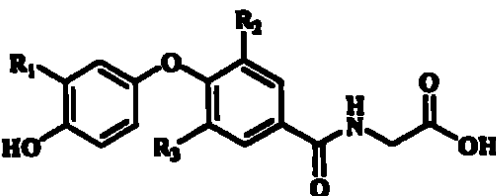
Example 210

D-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (122 mg) was coupled with D-serin methyl ester hydrochloride using the method described in Example 207(a) and subsequently hydrolyzed using the method described in Example 207(b). The crude mixture was purified as above. Satisfactory ¹H-NMR, ¹³C-NMR and mass spectra was obtained for the title compound.

Examples 211-228

The compounds indicated in the table below are all examples of further compounds, that can readily be prepared via the synthetic procedure described in Example 86.



Example	R ₁	R ₂	R ₃
211	Isopropyl	Me	Me
212	Isopropyl	Me	Br
213	Isopropyl	Me	Cl
214	Isopropyl	Me	I
215	Isopropyl	I	I
216	Isopropyl	I	Cl
217	Isopropyl	I	Br
218	Isopropyl	Br	Cl
219	I	Me	Me
220	I	Me	Br
221	I	Me	Cl
222	I	Me	I
223	I	I	I
224	I	Br	Cl
225	I	Br	Br
226	I	Cl	Cl
227	I	I	Br
228	I	I	Cl

10

Examples 229-231

N-[3,5-Dichloro-4-(4-hydroxy-3-bromophenoxy)benzoyl]glycine

N-[3,5-Dichloro-4-(4-hydroxy-3-methylphenoxy)benzoyl]glycine

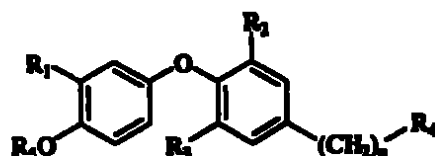
N-[3,5-Dichloro-4-(4-hydroxy-3-ethylphenoxy)benzoyl]glycine

These compounds were all prepared by a method analogous to that used in Example 86.

Satisfactory ¹H-NMR, ¹³C-NMR and mass spectra were obtained for all three compounds.

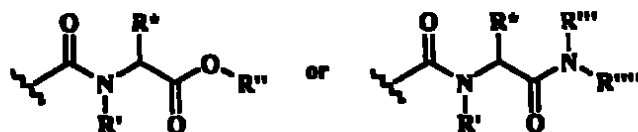
What is claimed is:

1. A compound having the formula



wherein

- 5 n is an integer from 0 to 4;
 R_1 is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;
 R_2 and R_3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons, at least one of R_2 and R_3 being other than hydrogen;
 10 R_4 is a heteroaromatic moiety which may be substituted or unsubstituted and is linked to $(CH_2)_n$ via a nitrogen atom or a carbon atom; an amine ($NR'R''$), including those in which the amine is derived from an alpha amino acid of either natural (L) or unnatural (D) stereochemistry; an acylsulphonamide ($CONHSO_2R'$); or a carboxylic acid amide ($CONR'R''$) with the proviso that when n equals zero ($n = 0$), then R_4 can only be a
 15 carboxylic acid amide or an acylsulphonamide;
 R_3 is hydrogen or an acyl (such as acetyl or benzoyl) or other group capable of bioconversion to generate the free phenol structure (wherein $R_3 = H$);
 including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof.
- 20 2. A compound as defined in Claim 1 where R_4 is a carboxylic acid amide ($CONR'R''$) in which the amine portion of the carboxylic amide can be derived from an achiral or a L or D alpha amino acid such as when the general structure $-CONR'R''$ can be represented by



- 25 and R' , R'' , R''' and R'''' are the same or different and are independently selected from hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and R^* may be hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and may also be any of the side chains found in the naturally occurring alpha-amino acids

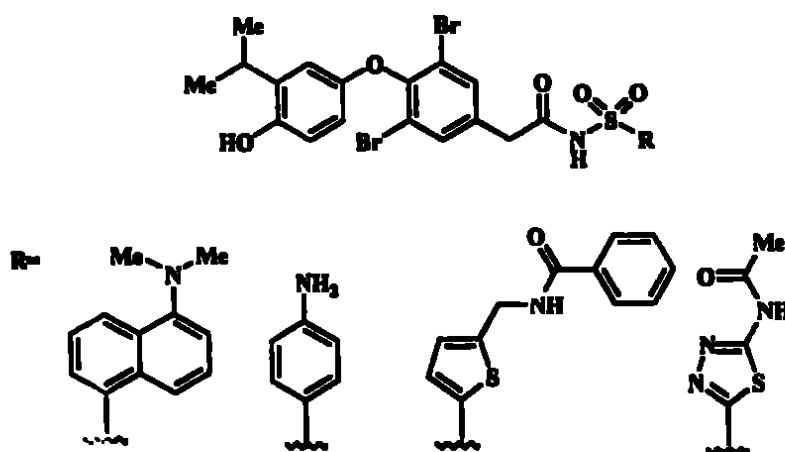
3. The compound as defined in Claim 2 where R' and R* are connected to form a 4 to 8-membered ring.
4. The compound as defined in Claim 2 where R' and R* comprise consecutive -(CH₂)- groups to form proline or homoproline.
- 5 5. The compound as defined in Claim 1 where n is 0 or 1 or 2.
6. The compound as defined in Claim 1 wherein R₂ and R₃ are each independently halogen.
7. The compound as defined in Claim 1 wherein R₂ and R₃ are each independently an alkyl group.
- 10 8. The compound as defined in Claim 1 wherein one of R₂ and R₃ is halogen and the other is an alkyl group.
9. The compound as defined in Claim 1 wherein one of R₂ and R₃ is halogen and the other is hydrogen.
10. The compound as defined in Claim 1 wherein one of R₂ and R₃ is alkyl and
15 the other is hydrogen.
11. The compound as defined in Claim 1 wherein R₂ and R₃ are independently Cl, Br, methyl or ethyl.
12. The compound as defined in Claim 1 wherein R₁ is isopropyl.
13. The compound as defined in Claim 1 wherein R₄ is heteroaromatic
20 hydrocarbon, carboxylic acid amide, or an acylsulphonamide.
14. The compound as defined in Claim 1 wherein R₅ is hydrogen.
15. The compound as defined in Claim 1 which is
3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
25 2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-thiazole acetic acid,

2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methylthiazole,

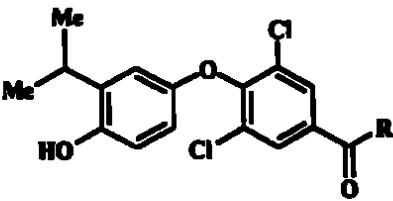
16. The compound as defined in Claim 1 which is

- 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-hydroxy-1-naphthalenesulphonamide,
 5 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-toluenesulphonamide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-nitrobenzenesulphonamide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl sulfamide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-dimethylamino-1-naphthalenesulphonamide,
 10 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-aminobenzenesulphonamide,
 Methyl-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-sulphonamide] benzoate,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-aminobenzenesulphonamide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-toluenesulphonamide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminoethyl)benzenesulphonamide,
 15 ide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminomethyl)benzenesulphonamide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-3-nitrobenzenesulphonamide,
 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-chlorobenzenesulphonamide,

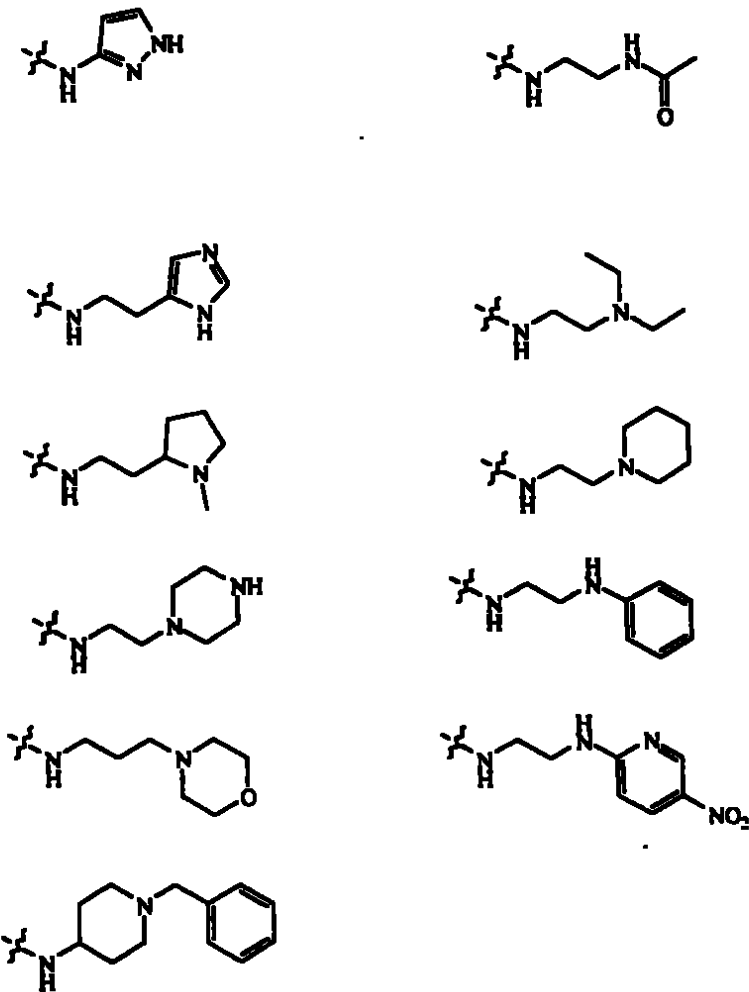
20 and the compounds shown below,



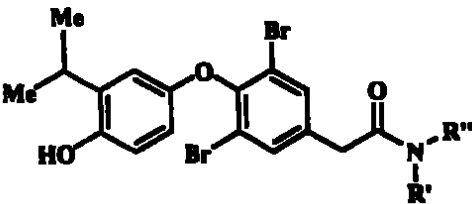
17. The compound as defined in Claim 1 which is in the table below,



R=



and the compounds indicated in the table below,



-NR'R''	Formula
3-(AMINOMETHYL)PYRIDINE	C23H22Br2N2O3
2-(2-AMINOETHYL)PYRIDINE	C24H24Br2N2O3

-NR'R"	Formula
3-(2-AMINOETHYL)PYRIDINE	C ₂₄ H ₂₄ Br ₂ N ₂ O ₃
2-(AMINOMETHYL)PYRIDINE	C ₂₄ H ₃₀ Br ₂ N ₂ O ₃
4-(AMINOMETHYL)PYRIDINE	C ₂₄ H ₃₀ Br ₂ N ₂ O ₃
1-(4-METHOXYPHENYL)PIPERAZINE DIHYDROCHLORIDE	C ₂₉ H ₃₂ Br ₂ N ₂ O ₃
1-(2-FLUOROPHENYL)PIPERAZINE	C ₃₄ H ₃₂ Br ₂ N ₂ O ₃
2-(2-(AMINOMETHYL)PHENYLTHIO)BENZYL ALCOHOL	C ₃₁ H ₂₉ Br ₂ N ₂ O ₄ S
2-(1-CYCLOHEXYNYL)ETHYLAMINE	C ₂₅ H ₂₉ Br ₂ N ₂ O ₃
2-AMINOINDAN	C ₂₈ H ₂₅ Br ₂ N ₂ O ₃
2-AMINOMETHYLBENZODIOXAN	C ₂₈ H ₂₅ Br ₂ N ₂ O ₅
3-PHENYL-1-PROPYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₃
2-(P-TOLYL)ETHYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₃
1-(3-AMINOPROPYL)-2-PYRROLIDINONE	C ₂₄ H ₂₈ Br ₂ N ₂ O ₄
BETA-ALANINE 4-METHOXY-BETA-NAPHTHYLAMIDE	C ₃₁ H ₃₀ Br ₂ N ₂ O ₅
2-CHLOROBENZYLAMINE	C ₂₄ H ₂₂ Br ₂ CINO ₃
2-AMINOMETHYL-3-CHLORODIPHENYLETHER	C ₃₀ H ₂₆ Br ₂ CINO ₄
DL-ALPHA-AMINO-EPSILON-CAPROLACTAM	C ₂₃ H ₂₈ Br ₂ N ₂ O ₄
L-PHENYLALANINOL	C ₂₈ H ₂₇ Br ₂ N ₂ O ₄
4-(1,2,3-THIADIAZOL-4-YL)BENZYLAMINE	C ₂₈ H ₂₃ Br ₂ N ₃ O ₃ S
2-AMINOMETHYLTHIOPHENE	C ₂₂ H ₂₁ Br ₂ N ₂ O ₃ S
1-(1-NAPHTHYL)ETHYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₃
3-CHLORO-4-METHYL BENZYLAMINE	C ₂₅ H ₂₄ Br ₂ CINO ₃
TETRAHYDROFURFURYLAMINE	C ₂₂ H ₂₅ Br ₂ N ₂ O ₄
2,4-DICHLOROPHENETHYLAMINE	C ₂₅ H ₂₃ Br ₂ C ₂ N ₂ O ₃
ETHYL 4-AMINO-1-PIPERIDINECARBOXYLATE	C ₂₅ H ₃₀ Br ₂ N ₂ O ₅
2,6-DIFLUOROBENZYLAMINE	C ₂₄ H ₂₁ Br ₂ F ₂ N ₂ O ₃
2-IODOBENZYLAMINE	C ₂₄ H ₂₂ Br ₂ I ₂ N ₂ O ₃
2-METHYLBENZYLAMINE	C ₂₅ H ₂₅ Br ₂ N ₂ O ₃
BENZYLAMINE	C ₂₄ H ₂₃ Br ₂ N ₂ O ₃
3-METHYLBENZYLAMINE	C ₂₅ H ₂₅ Br ₂ N ₂ O ₃
2-METHOXYPHENETHYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₄
3-METHOXYPHENETHYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₄
2-ETHOXYBENZYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₄
(R)-(-)-1-CYCLO-HEXYLETHYLAMINE	C ₂₅ H ₃₁ Br ₂ N ₂ O ₃
4-METHOXYPHENETHYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₄
2-FLUOROBENZYLAMINE	C ₂₄ H ₂₂ Br ₂ F ₂ N ₂ O ₃
2-CHLORO-6-METHYLBENZYLAMINE	C ₂₅ H ₂₄ Br ₂ CINO ₃
4-CHLOROBENZYLAMINE	C ₂₄ H ₂₂ Br ₂ CINO ₃
BETA-METHYLPHENETHYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₃
1,1-DI(P-ANISYL)METHYLAMINE	C ₃₂ H ₃₁ Br ₂ N ₂ O ₅
MAYBRIDGE BTB 12133	C ₂₇ H ₂₈ Br ₂ N ₂ O ₆
DL-2-AMINO-1-PENTANOL	C ₂₂ H ₂₇ Br ₂ N ₂ O ₄
L-PHENYLALANINE P-NITROANILIDE	C ₃₂ H ₂₉ Br ₂ N ₃ O ₆
ETHYL 3-AMINO BUTYRATE	C ₂₃ H ₂₇ Br ₂ N ₂ O ₅
(1S,2R)-(+)-2-AMINO-1,2-DIPHENYLETHANOL	C ₃₁ H ₂₉ Br ₂ N ₂ O ₄
2-FLUOROPHENETHYLAMINE	C ₂₅ H ₂₄ Br ₂ F ₂ N ₂ O ₃
2-ETHYLHEXYLAMINE	C ₂₅ H ₃₃ Br ₂ N ₂ O ₃
3-FLUOROPHENETHYLAMINE	C ₂₅ H ₂₄ Br ₂ F ₂ N ₂ O ₃
(1S,2S)-(+)-2-AMINO-3-METHOXY-1-PHENYL-1-PROPANOL	C ₂₇ H ₂₈ Br ₂ N ₂ O ₅
NONYLAMINE	C ₂₈ H ₃₅ Br ₂ N ₂ O ₃
2,5-DICHLORO BENZYLAMINE	C ₂₄ H ₂₁ Br ₂ C ₂ N ₂ O ₃
2-METHYL-3-CYCLOHEXYLAMINE	C ₂₄ H ₂₉ Br ₂ N ₂ O ₃
3-METHYL-3-CYCLOHEXYLAMINE	C ₂₄ H ₂₉ Br ₂ N ₂ O ₃
3-N-PROPOXY-3-PROPYLAMINE	C ₂₃ H ₂₉ Br ₂ N ₂ O ₄
2,3-DIMETHYLBENZYLAMINE	C ₂₈ H ₂₇ Br ₂ N ₂ O ₃
3-CHLOROBENZYLAMINE	C ₂₄ H ₂₂ Br ₂ CINO ₃
4-TERT-BUTYL CYCLOHEXYLAMINE	C ₂₇ H ₃₅ Br ₂ N ₂ O ₃

-NR'R"	Formula
(1S,2S)-(+)-THIOMICAMINE	C27H29Br2NO5S
2,4-DIMETHYLBENZYLAMINE	C28H27Br2NO3
2-AMINOETHYL PHENYL SULFIDE	C25H25Br2NO3S
PHENETHYLAMINE	C25H25Br2NO3
TYRAMINE	C25H25Br2NO4
L-TYROSINE METHYL ESTER	C27H27Br2NO8
BENZHYDRYLAMINE	C30H27Br2NO3
4-METHOXYBENZYLAMINE	C25H25Br2NO4
2,3-DICHLOROBENZYLAMINE	C24H21Br2Cl2NO3
GLYCINE N-BUTYL ESTER HYDROCHLORIDE	C23H27Br2NO5
D-(-)-ALPHA-PHENYLGLYCINE ETHYL ESTER HYDROCHLORIDE	C27H27Br2NO5
4-CHLORO-2-FLUOROBENZYLAMINE HYDROCHLORIDE	C24H21Br2ClFNO3
TRANS-2-PHENYLCYCLOPROPYLAMINE HYDROCHLORIDE	C28H25Br2NO3
ETHYL 4-AMINO BUTYRATE HYDROCHLORIDE	C23H27Br2NO5
DL-HOMOCYSTEINE THIOLACTONE HYDROCHLORIDE	C21H21Br2NO4S
4-NITROBENZYLAMINE HYDROCHLORIDE	C24H22Br2N2O5
NORPHENYLEPHRINE HYDROCHLORIDE	C25H25Br2NO5
GLYCINE ETHYL ESTER HYDROCHLORIDE	C21H23Br2NO5
DL-ALANINE ETHYL ESTER HYDROCHLORIDE	C22H25Br2NO5
SARCOSINE ETHYL ESTER HYDROCHLORIDE	C22H25Br2NO5
4-NITRO-N-PROPYLBENZYLAMINE HYDROCHLORIDE	C27H28Br2N2O5
PIPERIDINE	C22H25Br2NO3
3-METHYLPYRROLIDINE	C23H27Br2NO3
3-(HYDROXYMETHYL)-PIPERIDINE	C23H27Br2NO4
1,2,3,4-TETRAHYDROISOQUINOLINE	C28H25Br2NO3
2-ETHYLPYRROLIDINE	C24H29Br2NO3
3,4-DICHLORO-N-ETHYLBENZYLAMINE	C28H25Br2Cl2NO3
2-METHYLPYRROLIDINE	C22H25Br2NO3
N-ETHYL-N-PROPYLAMINE	C22H27Br2NO3
4-METHYLPYRROLIDINE	C23H27Br2NO3
(S)-(+)-2-(METHOXYMETHYL)PYRROLIDINE	C23H27Br2NO4
N-BENZYLETHANOLAMINE	C28H27Br2NO4
DIBENZYLAMINE	C31H29Br2NO3
4-BENZYL-4-HYDROXYPIPERIDINE	C29H31Br2NO4
(R)-(-)-2-BENZYLAMINO-1-BUTANOL	C28H31Br2NO4
N-(N-ETHYLAMINOACETYL)-2,6-DIMETHYLANILINE	C29H32Br2N2O4
N-ETHYL-O-METHOXYBENZYLAMINE	C27H29Br2NO4
MAYBRIDGE NRB 01981	C30H33Br2NO5
2-((N-ETHYLAMINO)METHYL)-4-NITROPHENOL	C28H28Br2N2O6
MAYBRIDGE SEW 01484	C31H29Br2NO4S
3-AZABICYCLO-[3.2.2]NONANE	C25H29Br2NO3
N-(2-METHOXY-ETHYL)ETHYLAMINE	C22H27Br2NO4

18. The compound as defined in Claim 1 which is

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine,

5 *L*-S-Benzyl, N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine,

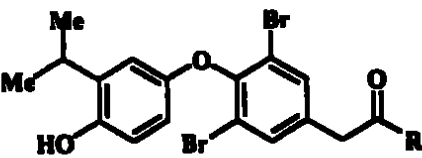
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- L*-N-d-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl),
 N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]arginine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobutyric acid,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine,
 5 *L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]proline,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine,
 N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
L-N- α -[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
 10 *D*-N- α -[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
 N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminoisobutyric acid,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine,
 N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine,
 15 *DL*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]- α -methylphenylalanine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]isoleucine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine,
 20 *D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cyclohexylalanine,
L-N- ϵ -(Benzyloxycarbonyl), N- α -[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-
 benzoyl]lysine,
D-N- ϵ -(Benzyloxycarbonyl), N- α -[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-
 25 benzoyl]lysine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]homoserine,
 N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
 N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine,
 3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylformylimino diacetic acid,
 30 N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine,
 N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine,
D-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine.
L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine
D-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine
 35 N-[3,5-Dichloro-4-(4-hydroxy-3-bromophenoxy)benzoyl]glycine
 N-[3,5-Dichloro-4-(4-hydroxy-3-methylphenoxy)benzoyl]glycine
 N-[3,5-Dichloro-4-(4-hydroxy-3-ethylphenoxy)benzoyl]glycine

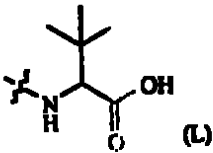
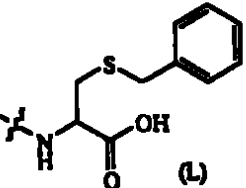
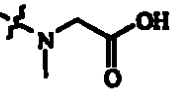
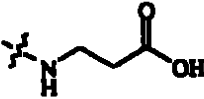
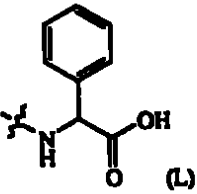
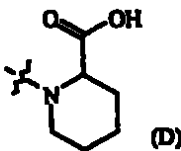
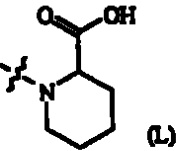
19. The compound as defined in Claim 1 which is

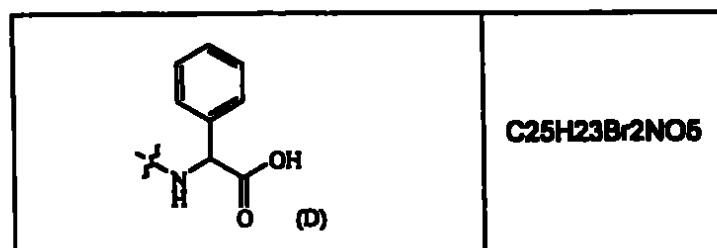
- D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine,
- L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine,
- D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] α -methylalanine,
- D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine,
- L*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine,
- L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine,
- L*-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,
- L*-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,
- L*-(*O*-*tert*-butyl)methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] glutamate,
- L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid,
- L*-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid,
- D*-di-*tert*-butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,
- D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid,
- L*-*O*-*tert*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,
- L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,
- D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,
- L*-*O*-Benzyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid,
- L*-*O*-*tert*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine,
- L*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine,
- L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine,
- D*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine,

and the compounds showed in the table below,

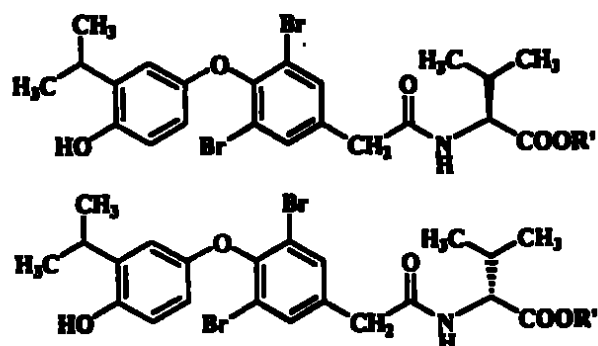


R	Mol Formel
L-Val	C22H25Br2NO5
L-Val	C22H25Br2NO5
L-Tyr	C26H25Br2NO6
	C23H27Br2NO5

 (L)	
 (L)	C27H27Br2NO5S
D-Leu	C23H27Br2NO5
D-Tyr	C28H25Br2NO6
D-Trp	C28H28Br2N2O5
L-Arg	C23H28Br2N4O5
L-Abu	C21H23Br2NO5
	C20H21Br2NO5
	C20H21Br2NO5
L-Leu	C23H27Br2NO5
 (L)	C25H23Br2NO5
D-Pro	C22H23Br2NO5
L-Ile	C23H27Br2NO5
 (D)	C23H25Br2NO5
L-Phe	C28H25Br2NO5
L-Lys	C23H28Br2N2O5
 (L)	C23H25Br2NO5
L-Pro	C22H23Br2NO5



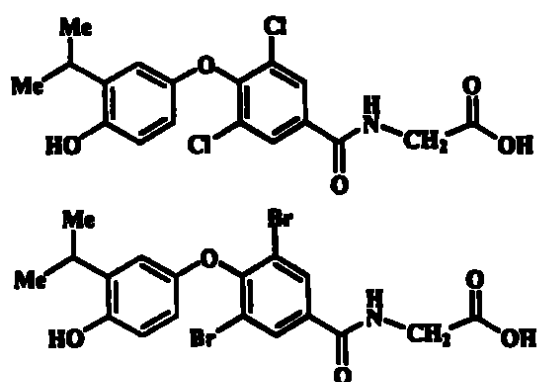
20. The compounds as defined in Claim 1 having the structures



or a pharmaceutically acceptable salt or ester(s) thereof.

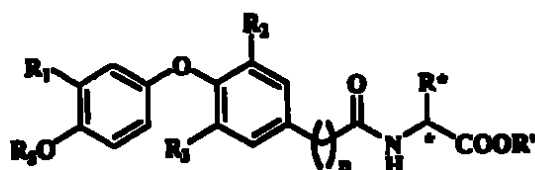
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21. The compounds as defined in Claim 1 having the structures



or a pharmaceutically acceptable salt or ester(s) thereof.

22. The compounds as defined in Claim 1 having the structures



wherein R_1 = isopropyl, methyl, ethyl; R_2 and R_3 may be independently selected from Br, Cl and Me; $n = 0$ or 1 ; R^* may be hydrogen, alkyl, cycloalkyl, aryl and heteroaryl; * denotes either D or L stereochemistry when R^* is not hydrogen; R_4 is hydrogen; and R' is selected from hydrogen, lower alkyl, especially ethyl and methyl.

23. A method for preventing, inhibiting or treating a disease associated with metabolism dysfunction, or which is dependent on the expression of a T_3 regulated gene, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

24. The method as defined in Claim 23 wherein the disease associated with metabolism dysfunction or which is dependent on the expression of a T_3 regulated gene is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.

25. The use of a compound according to Claim 1 in the preparation of a medicament for the treatment of a disease or disorders which is dependent on the expression of a T_3 regulated gene.

26. The use of a compound according to Claim 1 in which the disease or disorder is selected from hypothyroidism, hypercholesterolemia, obesity, skin disorders, glaucoma, cardiovascular disease, congestive heart failure and other endocrine disorders related to thyroid hormone.

27. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.

28. The method according to Claim 24 in which the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis, Dermier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

- 5 29. A method to treat skin disorder or disease by the use of a compound of Claim 1 in combination with a retinoid or a vitamin D analog.

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/IB99/02084 (22) International Filing Date: 23 December 1999 (23.12.99) (30) Priority Data: 9828442.5 24 December 1998 (24.12.98) GB (71) Applicant (for all designated States except US): KARO BIO AB (SE/SE); Novum, S-141 57 Huddinge (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): HANGELAND, Jon [US/US]; 234 Louisa Drive, Morrisville, PA 19067 (US). ZHANG, Minsheng [CN/US]; 31 Scheurman Terrace, Warren, NJ 07059 (US). CARINGAL, Yolanda [US/US]; 24 Coral Tree Court, Lawrenceville, NJ 08648 (US). RYONO, Denis [US/US]; 28 Marion Road West, Princeton, NJ 08540 (US). LI, Yi-Lin [CN/SE]; Kalibrinkavagen 38C, S-141 31 Huddinge (SE). MALM, Johan [SE/SE]; Korsnagavagen 53, S-142 40 Skogas (SE). LIU, Ye [CN/SE]; Smedvagen 23, S-146 36 Tullinge (SE). GARG, Neera [IN/SE]; Barkvilgen 15, S-147 52 Tunbsa (SE). LITTEN, Chris [IN/SE]; Stubbestigen 6, S-147 52 Tunbsa (SE). GARCIA COLLAZO, Ana Maria [ES/SE]; Morogatan 10, S-118 27 Stockholm (SE). KOEHLER, Konrad [US/SE]; Vastravagen 27, S-141 50 Huddinge (SE).	(74) Agents: BANNERMAN, David, Gardner et al.; Withers & Rogers, Goldings House, 2 Hays Lane, London SE1 2HW (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. (88) Date of publication of the international search report: 21 September 2000 (21.09.00)	
(54) Title: THYROID RECEPTOR LIGANDS (57) Abstract New thyroid receptor ligands are provided which have general formula (I) in which: n is an integer from 0 to 4; R₁ is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons; R₂ and R₃ are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 5 carbons, at least one of R₂ and R₃ being other than hydrogen; R₄ is a carboxylic acid amide (CONR'R'') or an acylsulphonamide (CONHSO₂R') derivative, or a pharmaceutically acceptable salt thereof, and all stereoisomers thereof; or when n is equal to or greater than one, R₄ may be a heteroaromatic moiety which may be substituted or unsubstituted, or an amine (NR'R''). R₅ is hydrogen or an acyl (such as acetyl or benzoyl) or other group capable of bioconversion to generate the free phenol structure (wherein R₅=H). In addition, a method is provided for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T₃ regulated gene, wherein a compound as described above is administered in a therapeutically effective amount. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T₃ regulated gene include: obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma, congestive heart failure and skin disorders.		

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.
PCT/IB 99/02084

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D257/04 C07C235/34 C07C323/59 C07D209/20 C07C279/14 C07D207/16 C07D211/60 C07C237/06 C07C235/52 A61K31/195 A61K31/41					
According to International Patent Classification (IPC) as to both national classification and IPC					
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D C07C A61K C07B					
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)					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	DATABASE CHEMABS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US STN, CAPLUS accession no. 1971:540431, XP002139408 abstract; RN 33927-24-1, 34043-79-3 -& CHEMICAL ABSTRACTS, vol. 75, no. 23, 6 December 1971 (1971-12-06) Columbus, Ohio, US; abstract no. 140431, XP002139407 abstract & K. MASUDA ET AL: TAKEDA KENKYUSHO HO, vol. 29, no. 4, 1970, pages 545-552, -/-				1,2,5,6, 13,14, 23-27
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.					
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Date of the actual completion of the international search 7 June 2000			Date of mailing of the international search report 28/06/2000		
Name and mailing address of the ISA European Patent Office, P.O. Box 5818 Patentkan 2 D-8250 HV Rmünch Tel. (+41-70) 340-3040, Tx. 31 651 650 01, Fax (+41-70) 340-3018			Authorized officer Van Amsterdam, L		

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40048 A (KARO BIO AB) 19 December 1996 (1996-12-19) claims 1-14, 18-19, 21, 23-30, in particular claims 5, 25, 28: Trifodothyronamine	1,5,6, 14,23-29
X	DE 32 31 541 A (HENNING BERLIN GMBH) 1 March 1984 (1984-03-01) claims 1-3	1,5,6, 14,27
X	M. ANDRE ET AL: J. CHROMATOGR. A, vol. 725, no. 2, 1996, pages 287-294, XP004039616 page 293, figure 7, compound VI	1,2,5,6, 13,14
X	M. ADAMCZYK ET AL: BIOCONJUGATE CHEM., vol. 8, no. 2, 1997, pages 133-145, XP000906993 page 140, scheme 2, compounds 40, 41	1,2,5,6, 13,14
X	US 4 741 897 A (J. ANDREWS ET AL) 3 May 1988 (1988-05-03) examples 2-3	1,2,5,6, 13,14
A	EP 0 580 550 A (CIBA-GEIGY AG) 26 January 1994 (1994-01-26) page 6, lines 4-14; examples 1-15, 29-30	1,6,7, 10-12, 14,23-27
P,X	M. EBISAWA ET AL: CHEM. PHARM. BULL., vol. 47, no. 9, 1999, pages 1348-1350, XP000906992 figures 1 and 2, compounds 3b, 6b, 7b	1,5,6, 12-14, 23-27

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Int **Internal Application No****Int** **Internal Application No****Int** **Internal Application No**

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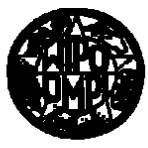
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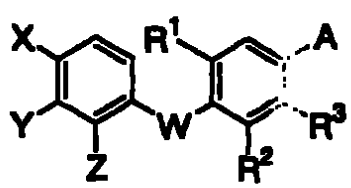
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2 文字コード及び他の略語については、定期発行される各 PCT ガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: PREVENTIVE OR RECURRENCE-SUPPRESSIVE AGENTS FOR LIVER CANCER

(54) 発明の名称: 肝癌の予防または再発抑制剤



(I)

(57) Abstract: Preventive or recurrence-suppressive agents for liver cancer containing as the active ingredient thyroid hormone receptor agonists, having an effect of inhibiting the expression of liver estrogen sulfotransferase; and usage of the agents. The thyroid hormone receptor agonists are preferably compounds represented by the general formula (I) or pharmaceutically acceptable salts thereof (I) wherein R¹ and R² are each alkyl, halogeno, or the like; R³ is hydrogen, alkyl, halogeno, or the like; X is hydroxyl or the like; W is O, S, CH₂, or the like; Y is alkyl, -Q-T (wherein Q is O, CH₂, CH(OH), or the like; and T is optionally substituted aryl or the like), or the like; Z is hydrogen, alkoxy, or the like; and A is -NHCO-Y¹-CO₂R³, -CH₂CH(NR¹⁰R¹¹), or the like.

【続き】

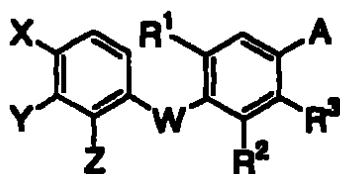
WO 02/094319 A1



(57) 要約:

本発明は、肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する
甲状腺ホルモン受容体アゴニスト、好ましくは一般式 (I) :

[R¹及びR²はアルキル基、ハロゲン原子等を表し、R³は水素、アルキル、



(I)

ハロゲン等を表し、Xは水酸基等を表し、WはO、S、CH₂等を表し、Yは
アルキル、-Q-T (QはO、CH₂、CH(OH)等を表し、Tは置換され
てもよいアリール基などを表す) 等を表し、Zは水素、アルコキシ等を表し、
Aは-NHCO-Y¹-CO₂R⁹、-CH₂CH(R⁹)NR¹⁰R¹¹等を表す]
で表される化合物またはその薬学的に許容される塩を有効成分として含有する
肝癌の予防または再発抑制剤、およびそれらの使用方法に関する。

明細書

肝癌の予防または再発抑制剤

5 〔技術分野〕

本発明は、肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有し、好ましくはさらに肝グルタチオン低下作用を有する甲状腺ホルモン受容体アゴニストを有効成分として含有する肝癌の予防または再発抑制剤、およびその使用方法に関する。

10

〔背景技術〕

近年、多くの国において肝癌の発生率が増加している。わが国においては肝癌の90%以上がB型またはC型肝炎に起因する慢性肝炎疾患（特に肝硬変）を母地として発症すると考えられている（Tsukuma H.ら, N. Engl. J. Med., 1

15 993, 328巻, 1797）。

現在、肝癌の治療には外科手術、経皮的エタノール注入療法（Percutaneous ethanol injection therapy; PEIT）、肝動脈塞栓療法（Transcatheter arterial embolization; TAE）、経皮的マイクロ波凝固療法（percutaneous microwave coagulation therapy）、および制癌剤による薬物療法などが用いられてい

20 る（吉川ら、医薬ジャーナル 35巻、1519～1524頁（1999））。

薬物療法としては、ドキソルビシン、エピルビシンなどのアントラサイクリン系、ニムスチンなどのニトロソウレア系、5-フルオロウラシルなどの代謝拮抗剤、マイトマイシンCなどの抗生物質、シスプラチンなどの白金錯体などの制癌剤が使用されているが、一般に肝癌は制癌剤に対して感受性が低いため

25 、制癌剤単独での治療効果はPEITやTAEに比べて低いのが現状であり、現在、確実な治療効果を有する薬剤はない（岡田ら、総合臨床 50巻、262～267頁（2001））。

肝癌はいったん発症すると難治性の経過をたどることが多く、また他の臓器の癌と異なり根治的治療後も再発率が極めて高く、例えば、根治的肝切除後、

5 年以内に70～90%の症例で残肝再発がみられ (Ikeda K. ら, Cancer 1993, 71巻, 19頁)、治療上の大きな問題点となっている。これは、肝癌が、他の臓器の癌とは異なり、多中心性発癌、すなわち前癌病変である癌発生母地が広範囲に形成され、従来の外科手術やPEITなどの治療では肝癌の再発を有効に抑制できないためと考えられている。このため肝癌の予防または再発抑制のための新規な薬剤の開発が切望されている。

10 甲状腺ホルモンは、哺乳動物の正常な発育および分化に不可欠であり、代謝恒常性の維持に重要な役割を果たしている。例えば、甲状腺ホルモンは、脂質、糖質およびタンパク質の代謝、エネルギー代謝などの代謝制御に関与し、さらには心拍数、心収縮力、末梢血管の抵抗などの心血管系機能にも深く影響を及ぼしている。

天然に存在する甲状腺ホルモンの活性体である3, 5, 3'-トリヨード-L-サイロニン (T3) は、核内の甲状腺ホルモン受容体 (TR) に結合する。T3とTRとから形成される複合体は、標的遺伝子の上流域にある甲状腺ホルモン応答配列 (TRE) と称される、T3調節遺伝子のプロモーター領域に結合し、この遺伝子の発現を活性化または抑制する。甲状腺ホルモンが示すほとんど作用は、この核内での遺伝子の発現を調節することによってもたらされると考えられている。

20 Ledda-Columbano GMらは、ラット肝化学発癌モデルにおいて、3, 5, 3'-トリヨード-L-サイロニン (T3) の投与により肝癌の発生が減少し、肺への転移が抑制されることを報告している (Cancer Res., 2000, 60(3): 603-9頁)。しかしながら、甲状腺ホルモンのどのような作用が、肝発癌を抑制しているのかについては明らかになっていないため、全ての甲状腺ホルモンアナログに同様の作用が有るかどうかについては不明である。また、甲状腺ホルモンそのものを肝発癌の抑制剤として使用することは、その全身作用として、頻脈・不整脈を伴う心機能亢進や、四肢の振戦、筋肉の萎縮などのリスクがあることが知られているため、困難であると考えられている。

甲状腺ホルモンと類似の作用を有する様々な甲状腺ホルモン受容体アゴニストが報告されている。

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WO 01/60784、WO 01/94293には、肥満症、高脂血症、アテローム性動脈硬化症、うつ病、骨粗しょう症、甲状腺機能低下症、甲状腺腫、甲状腺癌、緑内障、心不整脈、うっ血性心不全、皮膚疾患の予防または治療に有用である甲状腺ホルモン受容体リガンド、当該リガンドを有効成分として含有する医薬組成物、および当該リガンドの製造方法が開示されている。これらの開示は、本明細書中で、その全体が参考として援用される。

JP 06/172275には、高脂血症、アテローム性動脈硬化症の予防または治療に有用なヘテロ酢酸誘導体、当該誘導体を有効成分として含有する医薬組成物、および当該誘導体の製造方法が開示されている。これらの開示は、本明細書中で、その全体が参考として援用される。

JP 61/167643には、肥満症、高脂血症、アテローム性動脈硬化症の予防または治療に有用である、甲状腺ホルモン様作用を有する化合物、当該化合物を有効成分として含有する医薬組成物、および当該化合物の製造方法が開示されている。これらの開示は、本明細書中で、その全体が参考として援用される。

EP 1033364、EP 1088819、EP 1127882、EP 1148054、WO 00/51971、WO 01/72692には、肥満症、尿病、高脂血症、アテローム性動脈硬化症、緑内障、心不整脈、皮膚疾患、甲状腺疾患、甲状腺機能低下症、甲状腺癌、高血圧、うっ血性心不全、うつ病、骨粗しょう症、脱毛の治療に有用である甲状腺ホルモン受容体リガンド、当該リガンドを有効成分として含有する医薬組成物、および当該リガンドの製造方法が開示されている。これらの開示は、本明細書中で、その全体が参考として援用される。

WO 01/70687、WO 01/90053には、高コレステロール血症、アテローム動脈硬化症の予防または治療に有用な甲状腺ホルモン受容体リガンドが開示されている。これらの開示は、本明細書中で、その全体が参考として援用される。

WO 00/39077、WO 01/98256には、肥満症、高コレステロール血症、アテローム性動脈硬化症、うつ病、骨粗しょう症、甲状腺機能低下

症、甲状腺腫、甲状腺癌、緑内障、心不整脈、うっ血性心不全、皮膚疾患の予防または治療に有用である甲状腺ホルモン受容体リガンド、当該リガンドを有効成分として含有する医薬組成物、および当該リガンドの製造方法が開示されている。これらの開示は、本明細書中で、その全体が参考として援用される。

- 5 これまで天然に存在する甲状腺ホルモン以外に肝癌の予防または再発抑制に有用な甲状腺ホルモン受容体リガンドについては知られていない。

〔発明の開示〕

- 10 本発明者らは、種々の甲状腺ホルモン受容体アゴニストについて研究を行った結果、ある種の甲状腺ホルモン受容体アゴニストが、肝エストロゲンスルホトランスフェラーゼの発現レベルを低下させ、さらにこの中のある種のものが肝臓内グルタチオンの含量を減少させることを見出した。

- 15 エストロゲンスルホトランスフェラーゼ (EST) は、発現組織におけるエストロゲンの感受性を調節する酵素であり、その抑制は、該当臓器におけるエストロゲン作用の過剰発現を誘発することが、KOマウスの解析から明らかにされている (Endocrinology, 2001, 142(12):5342-5350頁)。エストロゲンが肝癌に対して抑制的に作用することや、女性は男性に比べて肝癌になりにくいことが疫学的に証明されていることから (Medical Hypotheses, 2000, 55(4): 348-350頁)、肝エストロゲンスルホトランスフェラーゼの発現を抑制する薬
20 剤は、肝発癌の抑制に有用であると考えられる。また、肝内グルタチオン (GSH) の低下については、Huang ZZらが、正常肝に比べて肝細胞癌 (hepatocellular carcinoma) ではグルタチオン量が増加し、肝細胞癌では、その増殖に、細胞内グルタチオンの含量が重要な役割を果たしていることを報告しており (FASEB J., 2001, 15(1): 19-21頁)、肝グルタチオン含量を低下させる薬
25 剤は、すでに癌化した肝癌クローン細胞の増殖を抑制することで、肝癌の再発を抑制すると考えられる。

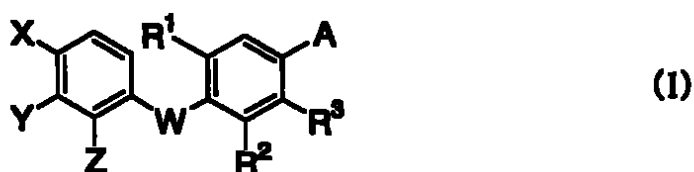
上述の如く、慢性肝炎疾患に罹患する患者の多くが肝癌に移行することから、このような肝発癌のリスクの高い患者において、肝発癌抑制作用を有する薬剤は極めて有用であると考えられる。さらに肝癌は多中心性に発生し高頻度に

再発することから、当該肝発癌抑制作用に加えて、外科手術などによって除去しきれなかった微小癌病変の増殖を抑制する薬剤は、肝癌の再発抑制に極めて有用であると考えられる。

本発明者らは、このような肝エストロゲンスルホトランスフェラーゼの発現を低下させ、好ましくはさらに肝臓内グルタチオンの含量を低下させる甲状腺ホルモン受容体アゴニストについてさらに研究を行った結果、一般式 (I) で表される化合物が、優れた発癌抑制作用を有すること、肝癌細胞の増殖を抑制すること、さらには甲状腺ホルモンに認められる副作用が軽減され極めて安全性の高いことを見出し、これらの知見に基づき本発明を完成した。

すなわち、本発明は、肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有し、好ましくはさらに肝グルタチオン低下作用を有する甲状腺ホルモン受容体アゴニストを有効成分として含有する肝癌の予防または再発抑制剤に関する。

本発明の有効成分である甲状腺ホルモン受容体アゴニストの好ましい態様として、下記的一般式 (I) :



[式中、

R^1 および R^2 は、それぞれ独立して、 C_{1-3} アルキル基、トリフルオロメチル基、ハロゲン原子またはシアノ基を表し；

R^3 は、水素原子、 C_{1-3} アルキル基、トリフルオロメチル基またはハロゲン原子を表し；

Wは、 $-O-$ 、 $-S-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、 $-CO-$ 、 $-SO-$ 、または $-SO_2-$ を表し；

Xは、水酸基、または一般式 $-NH-G-V$ で表される基を表し；

Gは、 $-CO-$ 、 $-SO-$ 、 $-SO_2-$ 、 $-CS-NH-$ または $-CO-NH-$ を表し；

Vは、 C_{1-10} アルキル基、 C_{3-8} シクロアルキル基、あるいは非置換または

置換アリール基を表し；

Yは、 C_{1-10} アルキル基、トリフルオロメチル基、 C_{3-8} シクロアルキル基、非置換または置換アリール基、 $-S(O)_2NR^4R^5$ 、 $-C(O)NR^4R^5$ 、 $-S(O)_2R^5$ 、6-オキソ-1, 6-ジヒドロピリジン-3-イルメチル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基または一般式-Q-Tで表される基を表すか、あるいはXとYが一緒になって、 $-NH-C=C(R^7)-$ を形成し；

R⁴およびR⁵は、それぞれ独立して、水素原子、 C_{1-10} アルキル基、 C_{3-8} シクロアルキル基、 C_{3-8} シクロアルキル C_{1-8} アルキル基、あるいは非置換または置換アリール基を表すか、あるいはR⁴およびR⁵が、それらが結合している窒素原子と一緒にあって5～7員の環状アミンを形成し；

R⁶は、 C_{1-10} アルキル基、 C_{3-8} シクロアルキル基、 C_{3-8} シクロアルキル C_{1-8} アルキル基、あるいは非置換または置換アリール基を表し；

R⁷は、水素原子、または C_{1-8} アルキル基を表し；

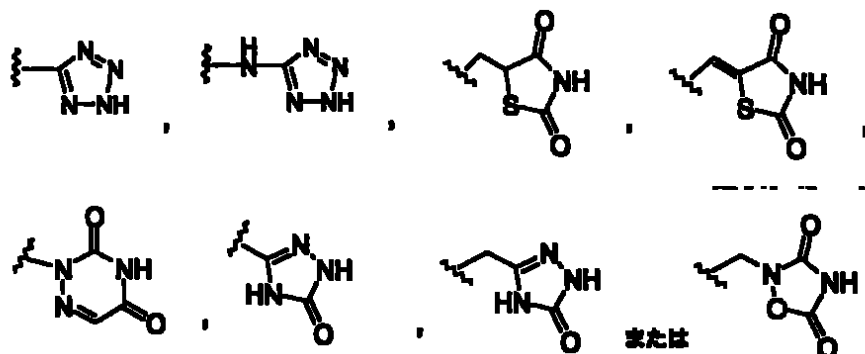
Qは、 $-O-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、または $-CO-$ を表し；

Tは、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよい C_{3-8} シクロアルキル基、あるいは環内に酸素原子を有してもよい C_{3-8} シクロアルキルメチル基を表し；

Zは、水素原子または C_{1-3} アルコキシ基を表すか、YとZが、一緒になって $-(CH_2)_m-$ を形成し；

mは、3～4の整数を表し；

Aは、 $-NHCO-Y^1-CO_2R^8$ 、 $-CONHCH_2CO_2R^8$ 、 $-CH_2CH(R^9)NR^{10}R^{11}$ 、または $-Y^2-COR^{12}$ を表すか、あるいは以下の式：



で表される基を表し；

Y^1 は、結合、 C_{1-6} アルキレン基、または $-CH=CH-$ を表し；

R^8 は、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基を表し；

5 R^9 は、カルボキシ基または C_{1-6} アルコキシカルボニル基を表し；

R^{10} は、水素原子または C_{1-6} アルキル基を表し；

R^{11} は、水素原子、 C_{1-6} アルキル基または C_{1-4} アルカノイル基を表し；

Y^2 は、結合または C_{1-6} アルキレン基を表し；

R^{12} は、ヒドロキシ基または C_{1-6} アルコキシ基を表す]

10 で表される化合物またはそれらの薬理学的に許容される塩が挙げられる。

また別の局面において本発明は、外科手術、経皮的エタノール注入療法、肝動脈塞栓療法および経皮的マイクロ波凝固療法から選択される肝癌の根治治療後に使用される、肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストを有効成分として含有する肝癌の予防または再発抑制剤に関する。

さらに別の局面において本発明は、肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストと、インターフェロン α 、NIK-333、およびウルソデオキシコール酸から選択される少なくとも1種とを組み合わせる肝癌の予防または再発抑制用の医薬に関する。

20 なおさらに別の局面において本発明は、肝癌の予防または再発抑制剤を製造するための肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストの使用に関する。

なおさらに別の局面において本発明は、肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストの有効量を投与

することからなる、肝癌の予防または再発抑制方法に関する。

本発明において、下記の用語は、特に断らない限り、以下の意味を有する。

「ハロゲン原子」とはフッ素原子、塩素原子、臭素原子またはヨウ素原子を
5 意味する。

「C₁₋₃アルキル基」とは、炭素数1～3の直鎖状または枝分かれ状のアルキル基を意味し、例えば、メチル基、エチル基、プロピル基、イソプロピル基が挙げられる。

「C₁₋₆アルキル基」とは、炭素数1～6の直鎖状または枝分かれ状のアル
10 キル基を意味し、例えば、メチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、ペンチル基、イソペンチル基、ネオペンチル基、tert-ペンチル基、ヘキシル基などが挙げられる。

「C₁₋₁₀アルキル基」とは、炭素数1～10の直鎖状または枝分かれ状のアル
15 キル基を意味し、例えば、メチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、ペンチル基、イソペンチル基、ネオペンチル基、tert-ペンチル基、ヘキシル基、ヘプチル基、1-イソプロピル-2-メチルプロピル基、オクチル基、ノニル基などが挙げられる。

「C₃₋₆シクロアルキル基」とは、3～6員の飽和環状炭化水素基を意味し、
20 シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基、が挙げられる。

「C₃₋₈シクロアルキル基」とは、3～8員の飽和環状炭化水素を意味し、
例えば、シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキ
25 シル基、シクロヘプチル基、シクロオクチル基が挙げられる。

「環内に酸素原子を有するC₃₋₈シクロアルキル基」とは、環内に酸素原子
を有する3～8員環の飽和環状炭化水素基を意味し、例えば、オキセタニル基、
テトラヒドロフラニル基、テトラヒドロピラニル基、オキセパニル基などが挙
げられる。

「C₅₋₆シクロアルキル基」とは、5～6員環の飽和環状炭化水素基を意味し、シクロペンチル基、シクロヘキシル基が挙げられる。

「環内に酸素原子を有するC₅₋₆シクロアルキル基」とは、環内に酸素原子を有する5～6員環の飽和環状炭化水素基を意味し、例えば、テトラヒドロフ
6 ラニル基、テトラヒドロピラニル基が挙げられる。

「環内に酸素原子を有してもよいC₅₋₆シクロアルキル基」とは、上記C₅₋₆シクロアルキル基または環内に酸素原子を有するC₅₋₆シクロアルキル基で置換されたメチル基を意味する。

「環内に酸素原子を有してもよいC₅₋₆シクロアルキル基」とは、上記C₅₋₆
10 シクロアルキル基または環内に酸素原子を有するC₅₋₆シクロアルキル基で置換されたメチル基を意味する。

「C₃₋₆シクロアルキルC₁₋₆アルキル基」とは、C₃₋₆シクロアルキル基で置換されたC₁₋₆アルキル基を意味し、例えば、シクロプロピルメチル基、1-シクロプロピルエチル基、2-シクロプロピルエチル基、シクロブチルメチル基、1-シクロブチルエチル基、2-シクロブチルエチル基、シクロペンチルメチル基、1-シクロペンチルエチル基、2-シクロペンチルエチル基、シクロヘキシルメチル基、1-シクロヘキシルエチル基、2-シクロヘキシルエチル基、シクロヘプチルメチル基などが挙げられる。

「C₁₋₆アルコキシ基」とは、炭素数1～3の直鎖状または枝分かれ状のアルコキシ基を意味し、例えば、メトキシ基、エトキシ基、プロポキシ基、イソ
20 プロポキシ基が挙げられる。

「C₁₋₆アルコキシ基」とは、炭素数1～6の直鎖状または枝分かれ状のアルコキシ基を意味し、例えば、メトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、ブトキシ基、イソブトキシ基、sec-ブトキシ基、tert-
25 ブトキシ基、ペンチルオキシ基、イソペンチルオキシ基、ネオペンチルオキシ基、tert-ペンチルオキシ基、ヘキシルオキシ基などが挙げられる。

「C₁₋₆アルコキシカルボニル基」とは、C₁₋₆アルコキシ基で置換されたカルボニル基を意味し、例えば、メトキシカルボニル基、エトキシカルボニル基、プロポキシカルボニル基、イソプロポキシカルボニル基、ブトキシカルボ

ニル基、イソブトキシカルボニル基、sec-ブトキシカルボニル基、tert-ブトキシカルボニル基、ペンチルオキシカルボニル基、ヘキシルオキシカルボニル基などが挙げられる。

「C₁₋₄アルカノイル基」とは、水素原子またはC₁₋₉アルキル基で置換されたカルボニル基を意味し、ホルミル基、アセチル基、プロピオニル基、イソプロピオニル基、ブチリル基、イソブチリル基が挙げられる。

「カルボキシ (C_{1-6} アルキル) 基」とは、カルボキシ基で置換された C_{1-6} アルキル基を意味し、例えば、カルボキシメチル基、2-カルボキシエチル基などが挙げられる。

10 「C₁₋₆アルキルオキシカルボニル (C₁₋₆アルキル) 基」とは、C₁₋₆アルコキシカルボニル基で置換されたC₁₋₆アルキル基を意味し、例えば、メトキシカルボニルメチル基、エトキシカルボニルメチル基などが挙げられる。

「アリール基」とは、1～3個の環により構成される芳香族炭化水素基を意味し、例えば、フェニル基、ナフチル基などが挙げられる。

15 「置換アリール基」とは、水酸基、 C_{1-6} アルキル基、 C_{1-6} アルコキシ基、カルボキシ（ C_{1-6} アルキル）基、 C_{1-6} アルコキシカルボニル（ C_{1-6} アルキル）基およびハロゲン原子からなる群から選択される基で置換されたアリール基を意味し、例えば、2-フルオロフェニル、3-フルオロフェニル、4-フルオロフェニル、4-クロロフェニル、2-ヒドロキシフェニル、2-メトキシフェニル、3-（2-カルボキシエチル）フェニルなどの基が挙げられる。

「非置換または置換アリールメチル基」とは、上記アリール基または置換アリール基で置換されたメチル基を意味する。

「アリール (C_{1-6} アルキル) 基」とは、アリール基により置換された C_{1-6} アルキル基を意味し、例えば、ベンジル基、フェネチル基、1-フェニルエ
25 ール基、3-フェニルプロピル基、2-フェニルプロピル基、1-フェニルプロ
ピル基、ナフチルメチル基などが挙げられる。

「C₁₋₆-アルキレン基」とは、直鎖または分岐鎖状の炭素数1～6の2価の飽和炭化水素鎖を意味し、例えば、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}(\text{C}\text{H}_3)-$ 、 $-\text{CH}_2\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}(\text{CH}_3)\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}(\text{C}$

H₃) -、-C(CH₃)₂-、-CH(CH₂CH₃)-、-CH₂CH₂CH₂CH₂-、-CH₂CH₂CH₂CH₂CH₂-などの基が挙げられる。

「5～7員の環状アミン」または「5～7員の環状アミノ基」とは、5～7員の飽和環状アミノ基を意味し、ピロリジル基、ピペリジル基などが挙げられる。また当該環状アミノ基は、必要に応じて1～2個のC₁₋₆アルキル基で置換されてもよく、このようなC₁₋₆アルキル置換環状アミノ基として、例えば、3, 3-ジメチルピロリジニル基、3, 3-ジメチルピペリジニル基などが挙げられる。

10 本発明の有効成分である前記一般式(I)で表される化合物において、

R¹およびR²は、それぞれ独立して、好ましくはC₁₋₃アルキル基、トリフルオロメチル基、またはハロゲン原子であり、さらに好ましくはC₁₋₃アルキル基またはハロゲン原子であり、最も好ましくはメチル基であり；

15 R³は、好ましくは水素原子、C₁₋₃アルキル基、またはトリフルオロメチル基であり、最も好ましくは水素原子であり；

Wは、好ましくは-O-または-CH₂-であり、最も好ましくは-O-であり；

Xは、好ましくは水酸基であり；

20 Yは、好ましくはC₁₋₆アルキル基、トリフルオロメチル基、-S(O)₂R⁶、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基または一般式-Q-Tで表される基であるか、あるいはXとYが一緒になって、-NH-C=C(R⁷)-を形成し、さらに好ましくは、C₁₋₆アルキル基、トリフルオロメチル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基または一般式-Q-Tで表される基であり、最も好ましくは、一般式-Q-Tで表される基であり、

25 ここで、R⁶は、好ましくは、非置換または置換アリール基であり、さらに好ましくは置換アリール基であり、最も好ましくは4-フルオロフェニル基であり、R⁷は、好ましくは、水素原子またはC₁₋₃アルキル基であり、さらに好ましくはC₁₋₃アルキル基であり、なおさらに好ましくはメチル基またはイソ

プロピル基であり、最も好ましくはメチル基であり、Qは、好ましくは、 $-CH_2-$ 、または $-CH(OH)-$ であり、最も好ましくは $-CH(OH)-$ であり、Tは、好ましくは、非置換または置換アリール基であり、さらに好ましくは置換アリール基であり、最も好ましくは4-フルオロフェニル基であり；

5 Zは、好ましくは水素原子であり；

Aは、好ましくは $-NHCO-Y^1-CO_2R^8$ 、 $-CONHCH_2CO_2R^8$ 、または $-CH_2CH(R^9)NH_2$ であり、さらに好ましくは、 $-NHCO-Y^1-CO_2R^8$ であり、

10 ここで、 Y^1 は、好ましくは、結合、または $-CH_2-$ であり、最も好ましくは $-CH_2-$ である。

前記一般式(I)で表される化合物の好ましい態様では、 R^1 および R^2 は、それぞれ独立して、 C_{1-8} アルキル基、トリフルオロメチル基、またはハロゲン原子であり；Aは、 $-NHCO-Y^1-CO_2R^8$ 、 $-CONHCH_2CO_2R^8$ 、または $-CH_2CH(R^9)NH_2$ であり； Y^1 は、結合、または $-CH_2-$ であり； R^8 は、水素原子、 C_{1-8} アルキル基、またはアリール C_{1-8} アルキル基であり； R^9 は、カルボキシ基または C_{1-8} アルコキシカルボニル基である。

前記一般式(I)で表される化合物のさらに好ましい態様では、 R^1 および R^2 は、それぞれ独立して、 C_{1-8} アルキル基、トリフルオロメチル基、またはハロゲン原子であり；Xは、水酸基であり；Yは、 C_{1-8} アルキル基、トリフルオロメチル基、 $-S(O)_2R^8$ 、6-オキソ-1,6-ジヒドロピリダジン-3-イルメチル基、または一般式 $-Q^1-T^1$ で表される基を表すか、あるいはXとYが一緒になって、 $-NH-C=C(R^7)-$ を形成し； R^6 は、非置換または置換アリール基を表し； R^7 は、 C_{1-8} アルキル基を表し； Q^1 は、 $-O-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、または $-CO-$ であり； T^1 は、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよい C_{6-8} シクロアルキル基、あるいは環内に酸素原子を有してもよい C_{6-8} シクロアルキルメチル基であり；Aは、 $-NHCO-Y^1-CO_2R^8$ 、 $-CONHCH_2CO_2R^8$ 、または $-CH_2CH(R^9)NH_2$ であり； Y^1 は、結合、または $-CH_2-$ であり； R^8 は、水素原子、 C_{1-8} アルキル基、また

はアリール C_{1-6} アルキル基であり； R^8 は、カルボキシ基または C_{1-6} アルコキシカルボニル基である。

前記一般式（I）で表される化合物のなおさらに好ましい態様では、 R^1 および R^2 は、それぞれ独立して、 C_{1-6} アルキル基またはハロゲン原子であり；

5 R^3 は、水素原子であり； W は、 $-O-$ であり； X は、水酸基であり； Y は、一般式 $-Q^1-T^1$ で表される基であり； Q^1 は、 $-CH(OH)-$ であり； T^1 は、非置換または置換アリール基であり； Z は、水素原子であり； A は、 $-NHCOCO_2R^8$ であり； R^8 は、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基である。

10 前記一般式（I）で表される化合物の別のなおさらに好ましい態様では、 R^1 および R^2 は、それぞれ独立して、 C_{1-6} アルキル基、トリフルオロメチル基、またはハロゲン原子であり； X は、水酸基であり； Y は、 C_{1-6} アルキル基、トリフルオロメチル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基、または一般式 $-Q^1-T^1$ で表される基であり； Q^1 は、 $-O-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、または $-CO-$ であり； T^1 は、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよい C_{5-6} シクロアルキル基、あるいは環内に酸素原子を有してもよい C_{5-6} シクロアルキルメチル基であり； Z は、水素原子または C_{1-6} アルコキシ基を表すか、あるいは Y と Z が、一緒になって $-(CH_2)_4-$ を形成し；

15 20 A は、 $-NHCOCH_2CO_2R^8$ であり； R^8 は、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基である。

前記一般式（I）で表される化合物のなおさらに好ましい態様では、 R^1 および R^2 は、それぞれ独立して、 C_{1-6} アルキル基、トリフルオロメチル基、またはハロゲン原子であり； W は、 $-O-$ であり； X は、水酸基であり； Y は、

25 C_{1-6} アルキル基、トリフルオロメチル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基、または一般式 $-Q^1-T^1$ で表される基であり； Q^1 は、 $-O-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、または $-CO-$ であり； T^1 は、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよい C_{5-6} シクロアルキル基、あるいは環内に酸素原子

を有してもよい C_{5-8} シクロアルキルメチル基であり；Aは、 $-NHCOCH_2CO_2R^8$ であり； R^8 は、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基である。

前記一般式（I）で表される化合物のなおさらに好ましい態様では、 R^1 および R^2 は、それぞれ独立して、 C_{1-6} アルキル基、またはハロゲン原子であり； R^3 が、水素原子であり；Wは、 $-O-$ であり；Xは、水酸基であり；Yは、 C_{1-6} アルキル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基、または一般式 $-Q^2-T^2$ で表される基であり； Q^2 は、 $-CH_2-$ 、または $-CH(OH)-$ であり； T^2 は、非置換または置換アリール基であり；Zが水素原子であり；Aは、 $-NHCOCH_2CO_2R^8$ であり； R^8 は、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基である。

前記一般式（I）で表される化合物の特に好ましい態様では、 R^1 および R^2 は、それぞれ独立して、 C_{1-6} アルキル基であり； R^3 が、水素原子であり；Wは、 $-O-$ であり；Xは、水酸基であり；Yは一般式 $-Q^3-T^3$ で表される基であり； Q^3 は、 $-CH(OH)-$ であり； T^3 は、非置換または置換アリール基であり；Zが水素原子であり；Aは、 $-NHCOCH_2CO_2R^8$ であり； R^8 は、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基である。

本発明の肝癌の予防または再発抑制剤に使用される好ましい化合物として、以下の群；

4-〔3-〔（4-フルオロフェニル）ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔3-〔（4-フルオロフェニル）メチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔3-〔（4-クロロフェニル）ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔3-〔（4-クロロフェニル）メチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔4-ヒドロキシ-3-（6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル）フェノキシ〕-3, 5-ジメチルマロンアニリド酸；

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4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルメチル)フェノキシ〕-3, 5-ジメチルマロンアニリド酸;

4-〔4-ヒドロキシ-3-{2-(3-テトラヒドロフラニル)エチル}フェノキシ〕-3, 5-ジメチルマロンアニリド酸;

5 4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸;

4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジプロモマロンアニリド酸;

10 4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジクロロマロンアニリド酸;

N-{4-[3-(4-フルオロベンゼンスルホニル)-4-ヒドロキシフェノキシ]-3, 5-ジメチルフェニル}マロンアミド酸;

N-{3-クロロ-4-[3-(4-フルオロベンゼンスルホニル)-4-ヒドロキシフェノキシ]-5-メチルフェニル}マロンアミド酸;

15 N-{3, 5-ジクロロ-4-[3-(4-フルオロベンゼンスルホニル)-4-ヒドロキシフェノキシ]フェニル}オキサミド酸;

N-{4-[3-(4-フルオロベンゼンスルホニル)-4-ヒドロキシフェノキシ]-3, 5-ジメチルフェニル}オキサミド酸;

20 N-{3-クロロ-4-[3-(4-フルオロベンゼンスルホニル)-4-ヒドロキシフェノキシ]-5-メチルフェニル}オキサミド酸;

N-[4-[3-{(4-フルオロフェニル)ヒドロキシメチル}-4-ヒドロキシフェノキシ]-3, 5-ジメチルフェニル]オキサミド酸;

N-[4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルフェニル]オキサミド酸;

25 3, 5-ジプロモ-3'-(6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル)-L-サイロニン;

3, 5-ジクロロ-3'-(6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル)-L-サイロニン;

3, 5-ジヨード-3'-(6-オキソ-1, 6-ジヒドロピリダジン-3

－イルメチル)－L－サイロニン；

3, 5－ジブロモ－3'－(6－オキソ－1, 6－ジヒドロピリジン－3－イルメチル)－L－サイロニン；

3, 5－ジクロロ－3'－(6－オキソ－1, 6－ジヒドロピリジン－3－イルメチル)－L－サイロニン；

3, 5－ジヨード－3'－(6－オキソ－1, 6－ジヒドロピリジン－3－イルメチル)－L－サイロニン；

N－[3, 5－ジメチル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

10 N－[3, 5－ジクロロ－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

N－[3, 5－ジブロモ－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

15 N－[3, 5－ジブロモ－2－トリフルオロメチル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

N－[3, 5－ジクロロ－2－トリフルオロメチル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

N－[3, 5－ジブロモ－2－エチル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

20 N－[3, 5－ジクロロ－2－エチル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

N－[3, 5－ジブロモ－2－プロピル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

25 N－[3, 5－ジクロロ－2－プロピル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

N－[3, 5－ジブロモ－2－メチル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

N－[3, 5－ジクロロ－2－メチル－4－(4－ヒドロキシ－3－イソプロピルフェノキシ)ベンゾイル]グリシン；

N-〔4-（1H-インドール-5-イルオキシ）-3, 5-ジメチルフェニル〕オキサミド酸；

N-〔4-（3-メチル-1H-インドール-5-イルオキシ）-3, 5-ジメチルフェニル〕オキサミド酸；

5 N-〔4-（3-イソプロピル-1H-インドール-5-イルオキシ）-3, 5-ビス（トリフルオロメチル）フェニル〕オキサミド酸；

N-〔4-（3-エチル-1H-インドール-5-イルオキシ）-3, 5-ビス（トリフルオロメチル）フェニル〕オキサミド酸；

10 N-〔4-（1H-インドール-5-イルオキシ）-3, 5-ビス（トリフルオロメチル）フェニル〕オキサミド酸から選択される化合物、あるいはそれらのC₁₋₆アルキルエステルまたは薬理学的に許容される塩が挙げられる。

本発明の肝癌の予防または再発抑制剤に使用されるさらに好ましい化合物として、以下の群；

15 4-〔3-〔（4-フルオロフェニル）ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔4-ヒドロキシ-3-（6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル）フェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-（4-ヒドロキシ-3-イソプロピルフェノキシ）-3, 5-ジメチルマロンアニリド酸；

20 3, 5-ジブromo-3'-（6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル）-L-サイロニン；

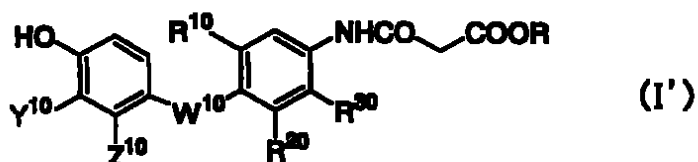
N-〔4-〔3-〔（4-フルオロフェニル）ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルフェニル〕オキサミド酸；

25 N-〔4-（3-メチル-1H-インドール-5-イルオキシ）-3, 5-ジメチルフェニル〕オキサミド酸から選択される化合物、あるいはそれらのC₁₋₆アルキルエステルまたは薬理学的に許容される塩が挙げられる。

本発明の肝癌の予防または再発抑制剤に使用する特に好ましい化合物は、4-〔3-〔（4-フルオロフェニル）ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸、あるいはそのC₁₋₆アルキ

ルエステルまたは薬理学的に許容される塩である。

本発明の有効成分である前記一般式 (I) で表される化合物のうち下記一般式 (I') :



5 [式中、

R¹⁰およびR²⁰は、それぞれ独立して、C₁₋₃アルキル基、トリフルオロメチル基、またはハロゲン原子であり；

R³⁰は、水素原子、C₁₋₃アルキル基、トリフルオロメチル基またはハロゲン原子であり；

10 Rは、水素原子、C₁₋₆アルキル基またはアリール (C₁₋₆アルキル) 基であり；

W¹⁰は、-O-、-S-、-CH₂-、-CH(OH)-、-CO-、-SO-、または-SO₂-であり；

15 Y¹⁰が、C₁₋₆アルキル基、トリフルオロメチル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基または一般式-Q¹⁰-T¹⁰で表される基であり；

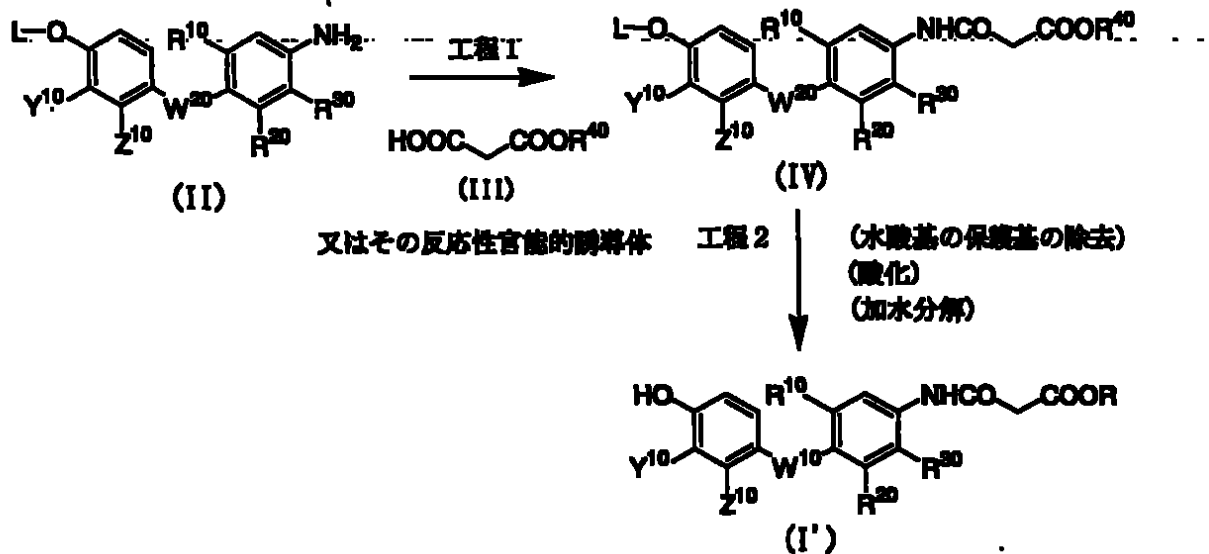
Q¹⁰は、-O-、-CH₂-、-CH(OH)-、または-CO-を表し；

20 T¹⁰は、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよいC₆₋₈シクロアルキル基、あるいは環内に酸素原子を有してもよいC₆₋₈シクロアルキルメチル基であり；

Z¹⁰は、水素原子またはC₁₋₃アルコキシ基を表すか、Y¹⁰とZ¹⁰が結合してテトラメチレン基を形成する]

で表される化合物は、下記のスキーム1～8に示す方法により製造することができる。

スキーム1



(式中、Lは水素原子または水酸基の保護基を表し、R、R¹⁰、R²⁰、R³⁰、W¹⁰、Y¹⁰およびZ¹⁰は前記と同じ意味であり、R⁴⁰はC₁₋₈アルキル基を表し、W²⁰は-O-、-S-、-CH₂-、-CH(OH)-または-CO-を表す)

工程1

化合物(II)と1～2当量の化合物(III)とを、ジシクロヘキシルカルボジイミド、1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド塩酸塩、シアノリン酸エチル、アジ化ジフェニルホスホリル等の縮合剤の存在下、アセトニトリル、N,N-ジメチルホルムアミド、テトラヒドロフラン、塩化メチレン等の不活性溶媒中、通常0℃～室温で1～24時間反応させることにより、化合物(IV)が得られる。

また、化合物(II)と1～20当量の化合物(III)の酸ハライド、混合酸無水物、活性エステル等の反応性官能的誘導体とを、無溶媒またはテトラヒドロフラン、塩化メチレン等の不活性溶媒中、炭酸カリウム、トリエチルアミン、ピリジン等の塩基の存在下または非存在下、通常0℃～還流温度で20分～24時間反応させることにより、化合物(IV)が得られる。

工程2

得られた化合物(IV)において水酸基の保護基の除去が必要な場合は、保

保護基の種類に応じ、常法により適宜処理することにより保護基の除去を行うことができる。

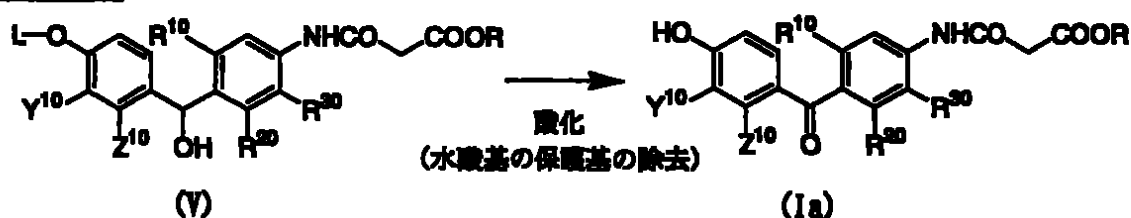
- 5 得られた化合物 (I V) を酸化する場合は、1 当量以上の *m*-クロロ過安息香酸、過酢酸等の過オキシ酸を酸化剤として用いて、塩化メチレン、テトラヒドロフラン等の溶媒中、通常 0℃～室温で 5～24 時間処理することにより、相当するスルホキシド誘導体またはスルホン誘導体を得られる。

得られた化合物 (I V)、そのスルホキシド誘導体またはスルホン誘導体においてエステル基を加水分解する場合は、常法に従いアルカリ加水分解することにより、相当するカルボン酸誘導体を得られる。

10

前記一般式 (I') で表される化合物の中、下記一般式 (I a) で表される化合物は、下記のスキーム 2 により表される反応に従い製造することもできる。

スキーム 2

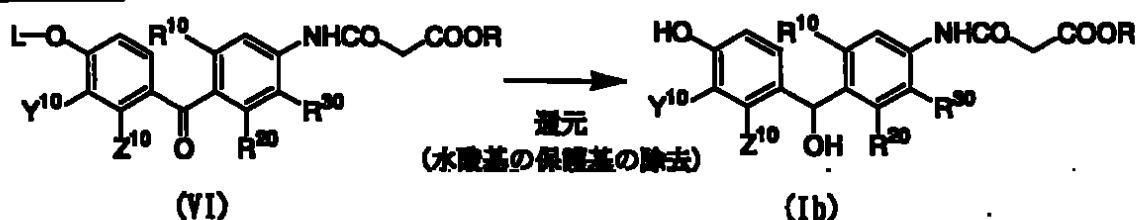


(式中の L、R、R¹⁰、R²⁰、R³⁰、Y¹⁰ および Z¹⁰ は前記と同じ意味をもつ)

- 15 化合物 (V) を、塩化メチレン等の不活性溶媒中、二酸化マンガン、過マンガン酸カリウム等の酸化剤を用いて、通常 0℃～還流温度で 1～72 時間酸化した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物 (I a) が得られる。

- 20 前記一般式 (I') で表される化合物の中、下記一般式 (I b) で表される化合物は、下記のスキーム 3 により表される反応に従い製造することもできる。

スキーム3



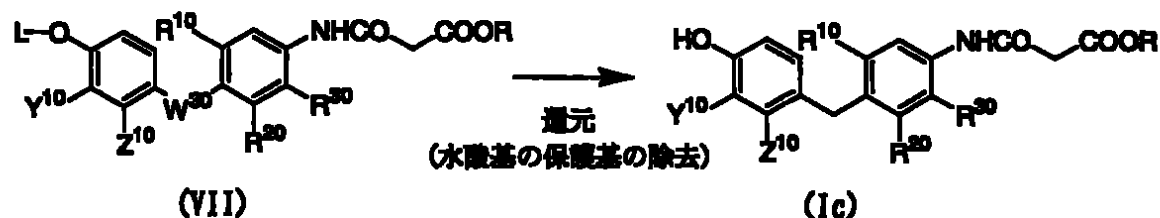
(式中のL、R、R¹⁰、R²⁰、R³⁰、Y¹⁰およびZ¹⁰は前記と同じ意味をもつ)

化合物(VI)を、メタノール、酢酸等の極性溶媒中、水素化ホウ素ナトリウム、ナトリウムトリアセトキシボロヒドリド等の還元剤を用いて、通常0℃
5 ～室温で1～48時間還元した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(Ib)が得られる。

また、化合物(VI)をテトラヒドロフラン、メタノール、エタノール、酢酸エチル等の溶媒中、パラジウム炭素、酸化白金等の触媒の存在下、通常室温
10 ～還流温度で1～48時間1～5気圧にて接触水素添加して還元した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(Ib)が得られる。

前記一般式(I')で表される化合物の中、下記一般式(Ic)で表される
15 化合物は、下記のスキーム4により表される反応に従い製造することもできる。

スキーム4



(式中のW³⁰はヒドロキシメチレン基またはカルボニル基を表し、L、R、R¹⁰、R²⁰、R³⁰、Y¹⁰およびZ¹⁰は前記と同じ意味をもつ)

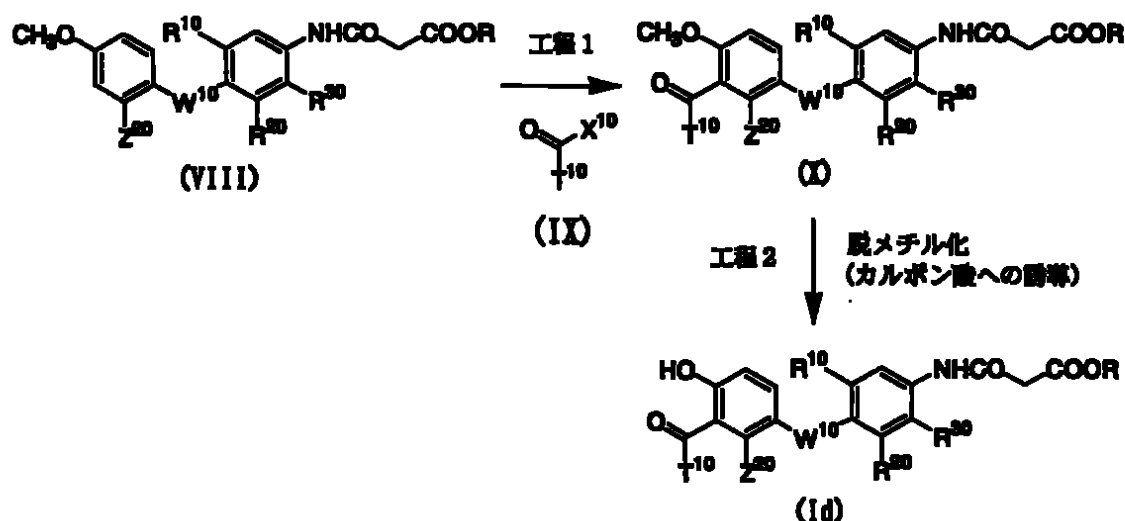
化合物(VII)を、塩化メチレン等の溶媒中、トリエチルシランとトリフルオロ酢酸または三フッ化ホウ素ジエチルエーテル錯体を用いて、通常0℃
20 ～還流温度で1～48時間還元した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(Ic)が

得られる。

また、化合物(VII)をテトラヒドロフラン、メタノール、エタノール、酢酸エチル、酢酸等の溶媒中、パラジウム炭素等の触媒の存在下、通常室温～還流温度で1～48時間1～5気圧にて接触水素添加して還元した後、必要に
5 応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(Ic)が得られる。

前記一般式(I')で表される化合物の中、下記一般式(Id)で表される化合物は、下記のスキーム5により表される反応に従い製造することもできる。

スキーム5



20 (式中のX¹⁰はハロゲン原子または水酸基を表し、Z²⁰は水素原子またはC₁-₉アルコキシ基であり、R、R¹⁰、R²⁰、R³⁰、T¹⁰およびW¹⁰は前記と同じ意味をもつ)

工程1

化合物(VIII)を1～2当量の化合物(IX)で、四塩化チタン等のルイス酸またはトリフルオロメタンスルホン酸無水物の存在下、塩化メチレン等の溶媒中、通常0℃～室温で3～72時間フリーデル・クラフツ反応によりアシル化反応を行うことにより、化合物(X)が得られる。

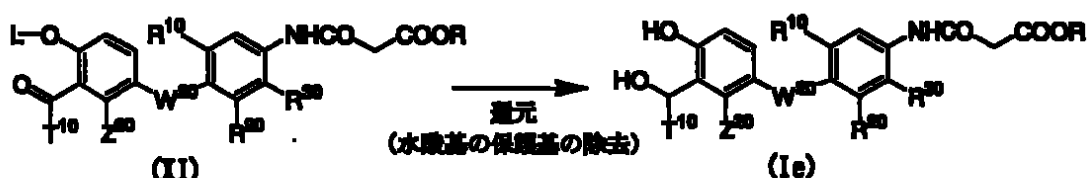
工程2

られた化合物(X)を塩化メチレン等の溶媒中、四塩化チタン等のルイス

酸の存在下、通常室温～還流温度で3～72時間処理するか、或いは塩化メチレン等の溶媒中、四塩化錫および三塩化ホウ素、三臭化ホウ素等の三ハロゲン化ホウ素の存在下、通常－78℃～還流温度で1～24時間処理してメチル基を除去することにより、化合物(I d)が得られる。尚、Rが低級アルキル基である化合物においては、エステル基を同時にカルボキシ基へ変換することもできる。

前記一般式(I')で表される化合物の中、下記一般式(I e)で表される化合物は、下記のスキーム6により表される反応に従い製造することもできる。

スキーム6



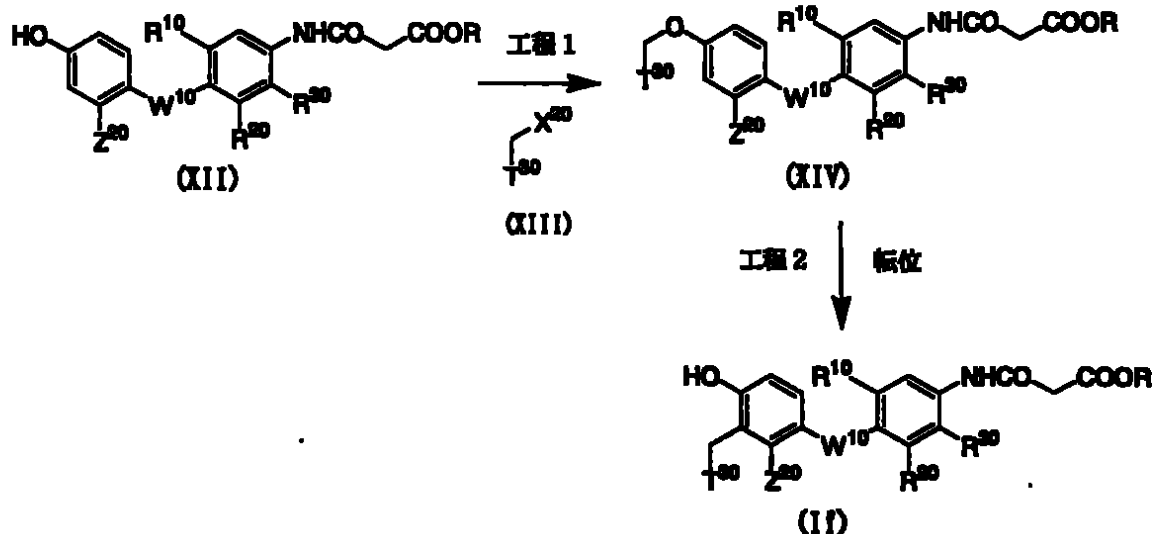
10 (式中のL、R、R¹⁰、R²⁰、R³⁰、T¹⁰、W²⁰およびZ²⁰は前記と同じ意味をもつ)

化合物(X I)を、メタノール、酢酸等の極性溶媒中、水素化ホウ素ナトリウム、ナトリウムトリアセトキシボロヒドリド等の還元剤を用いて、通常0℃～室温で1～48時間還元した後、必要に応じ、水酸基の保護基の種類に応じ、
15 常法により適宜処理して保護基を除去することにより、化合物(I e)が得られる。

また、化合物(X I)をテトラヒドロフラン、メタノール、エタノール、酢酸エチル等の溶媒中、パラジウム炭素、酸化白金等の触媒の存在下、通常室温～還流温度で1～48時間1～5気圧にて接触水素添加して還元した後、必要
20 に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(I e)が得られる。

前記一般式(I')で表される化合物の中、下記一般式(I f)で表される化合物は、下記のスキーム7により表される反応に従って製造することもできる。

スキーム7



(式中のT³⁰は非置換または置換アリール基を表し、X³⁰はハロゲン原子を表し、R、R¹⁰、R²⁰、R³⁰、W¹⁰およびZ²⁰は前記と同じ意味をもつ)

工程1

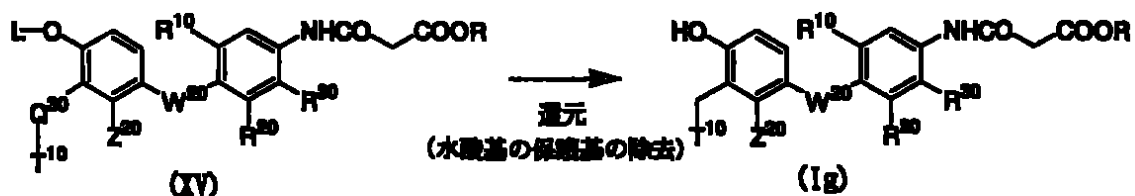
化合物(XII)と1～1.5当量の化合物(XIII)とを、アセトン、
5 N,N-ジメチルホルムアミド、ジメチルスルホキシド等の溶媒中、炭酸カリウム、炭酸セシウム等の塩基の存在下、通常室温～還流温度で1～48時間反応させることにより、化合物(XIV)が得られる。

工程2

得られた化合物(XIV)を無溶媒または塩化メチレン等の不活性溶媒中、
10 トリフルオロ酢酸等の強酸の存在下、通常室温～還流温度で1～48時間処理して転位させることにより、化合物(I)が得られる。

本発明の前記一般式(I')で表される化合物の中、下記一般式(Ig)で表される化合物は、下記のスキーム8により表される反応に従い製造することもできる。
15

スキーム8



(式中のQ³⁰はヒドロキシメチレン基またはカルボニル基を表し、L、R、R

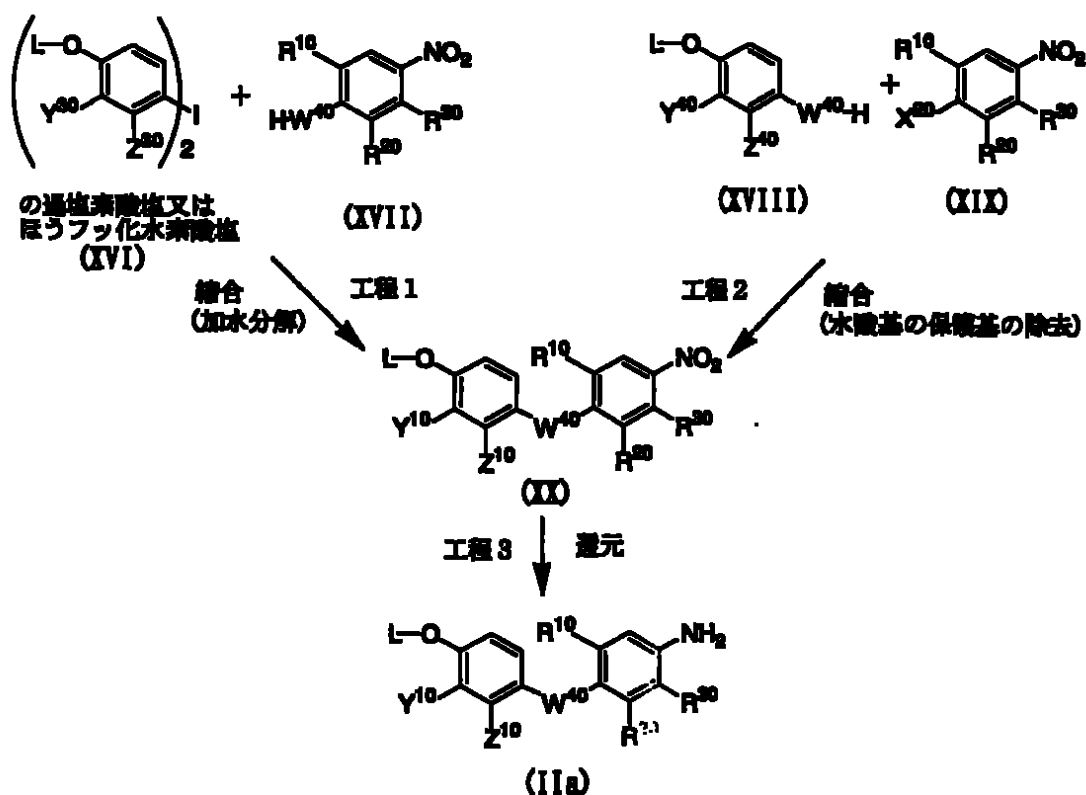
¹⁰、 R^{20} 、 R^{30} 、 T^{10} 、 W^{20} および Z^{20} は前記と同じ意味をもつ

化合物(XV)を、塩化メチレン等の溶媒中、トリエチルシランとトリフル
 オロ酢酸を用いて、通常0℃～還流温度で1～48時間還元した後、必要に応
 じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去する
 5 ことにより、化合物(Ig)が得られる。

また、化合物(XV)をテトラヒドロフラン、メタノール、エタノール、酢
 酸エチル、酢酸等の溶媒中、パラジウム炭素等の触媒の存在下、通常室温～還
 流温度で1～48時間1～5気圧にて接触水素添加して還元した後、必要に応
 じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去する
 10 ことにより、化合物(Ig)が得られる。

前記製造方法において出発原料として用いられる前記一般式(II)の化合
 物の中、下記一般式(IIa)の化合物は、例えば、下記のスキーム9により
 表される反応に従い製造することができる。

スキーム9



15 〔式中の W^{40} は酸素原子または硫黄原子を表し、 Y^{30} は C_{1-6} アルキル基、6
 -クロロ-3-ピリダジニルメチル基または一般式 $-Q^{10}-T^{10}$ （式中の Q^{10}

⁰および T^{10} は前記と同じ意味をもつ)で表される基を表し、 Y^{40} は C_{1-6} アルキル基、保護基を有する6-ヒドロキシ-3-ピリダジニルメチル基または一般式 $-Q^{10}-T^{10}$ (式中の Q^{10} および T^{10} は前記と同じ意味をもつ)で表される基を表し、 Z^{30} および Z^{40} は水素原子または C_{1-3} アルコキシ基を表す
 5 か、 Y^{30} または Y^{40} と結合してテトラメチレン基を形成し、 L 、 R^{10} 、 R^{20} 、 R^{30} 、 X^{20} 、 Y^{10} および Z^{10} は前記と同じ意味をもつ]

工程1

化合物(XVI)と0.7~1.5当量の化合物(XVII)とを、銅とトリエチルアミン等の塩基の存在下、塩化メチレン等の不活性溶媒中、通常0℃
 10 ~室温で12~72時間反応させた後、必要に応じ、酢酸中、酢酸ナトリウムの存在下、通常0℃~室温で1~5時間処理した後、水を加えて加水分解させることにより、化合物(XX)が得られる。

工程2

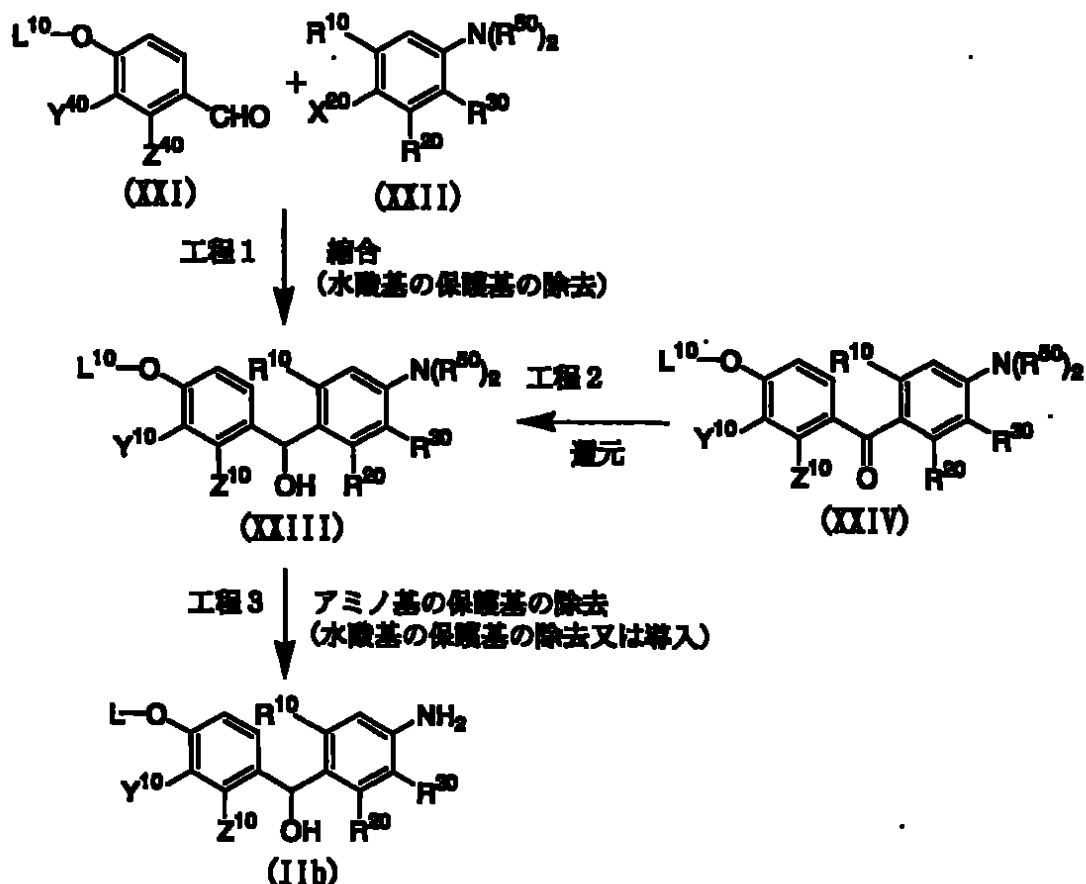
化合物(XVIII)と0.7~1.5当量の化合物(XX)とを、炭酸カリウム等の塩基の存在下、ジメチルスルホキシド、ジメチルアセトアミド等の不活性溶媒中、通常0℃~還流温度で3~24時間反応させた後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(XX)が得られる。

工程3

20 得られた化合物(XX)を、テトラヒドロフラン、メタノール、エタノール、酢酸エチル等の溶媒中、パラジウム炭素、酸化白金等の触媒の存在下、通常室温~還流温度で1~48時間1~5気圧にて接触水素添加して還元することにより、化合物(IIa)が得られる。

前記製造方法において出発原料として用いられる前記一般式 (I I) の化合物の中、下記一般式 (I I b) の化合物は、例えば、下記のスキーム 10 により表される反応に従い製造することができる。

スキーム 10



(式中の L^{10} は水酸基の保護基を表し、 R^{50} はアミノ基の保護基を表し、 L 、
5 R^{10} 、 R^{20} 、 R^{30} 、 X^{20} 、 Y^{10} 、 Y^{40} 、 Z^{10} および Z^{40} は前記と同じ意味をもつ)

工程 1

化合物 (XXII) をテトラヒドロフラン等の不活性溶媒に溶解し、1~1.5
5 当量の *tert*-ブチルリチウム等の有機リチウムと $-100 \sim -78^\circ\text{C}$ で
10 20分~1時間反応させた後、0.7~1.5当量の化合物 (XXI) と -100°C ~
室温で30分~2時間反応させ、必要に応じ、水酸基の保護基の種類
に応じ、適法により適宜処理して保護基を除去することにより、化合物 (XX
III) が得られる。

工程 2

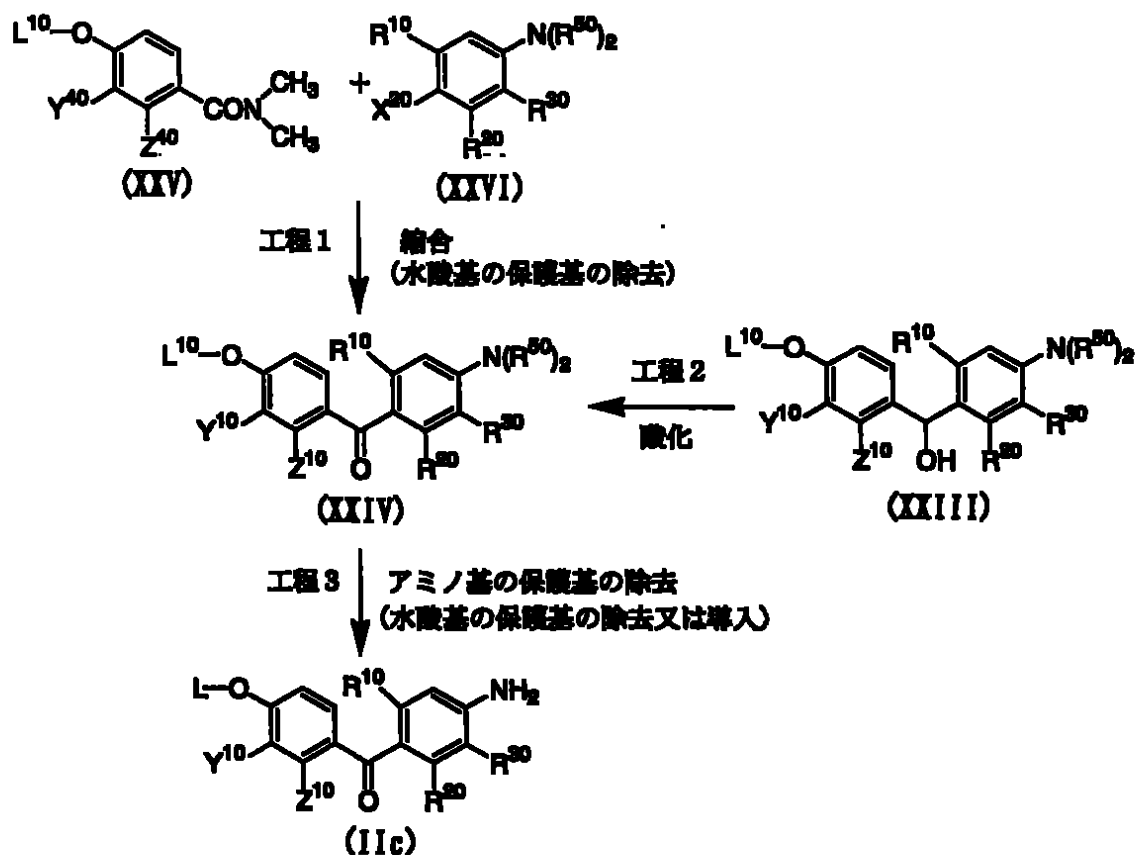
化合物 (XXIV) を、メタノール、酢酸、テトラヒドロフラン等の極性溶媒中、水素化ホウ素ナトリウム、ナトリウムトリアセトキシボロヒドリド、水素化リチウムアルミニウム等の還元剤を用いて、0℃～還流温度で1～48時間還元することにより、化合物 (XXIII) が得られる。

- 5 また、化合物 (XXIV) をテトラヒドロフラン、メタノール、エタノール、酢酸エチル等の溶媒中、パラジウム炭素、酸化白金等の触媒の存在下、通常室温～還流温度で1～48時間1～5気圧にて接触水素添加して還元することにより、化合物 (XXIII) が得られる。

工程3

- 10 得られた化合物 (XXIII) において、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物 (IIb) が得られる。
- 15 前記製造方法において出発原料として用いられる前記一般式 (II) の化合物の中、下記一般式 (IIc) の化合物は、例えば、下記のスキーム11により表される反応に従い製造することができる。

スキーム11



(式中の L 、 L^{10} 、 R^{10} 、 R^{20} 、 R^{30} 、 R^{50} 、 X^{20} 、 Y^{10} 、 Y^{40} 、 Z^{10} および Z^{40} は前記と同じ意味をもつ)

工程1

化合物 (XXVI) をテトラヒドロフラン等の不活性溶媒に溶解し、1~1.5当量の *tert*-ブチリチウム等の有機リチウムと-100~-78℃で20分~1時間反応させた後、0.7~1.5当量の化合物 (XXV) と-100℃~室温で30分~2時間反応させ、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物 (XXIV) が得られる。

工程2

化合物 (XXIII) を、塩化メチレン等の不活性溶媒中、二酸化マンガ、過マンガン酸カリウム等の酸化剤を用いて、通常0℃~還流温度で1~72時間酸化することにより、化合物 (XXIV) が得られる。

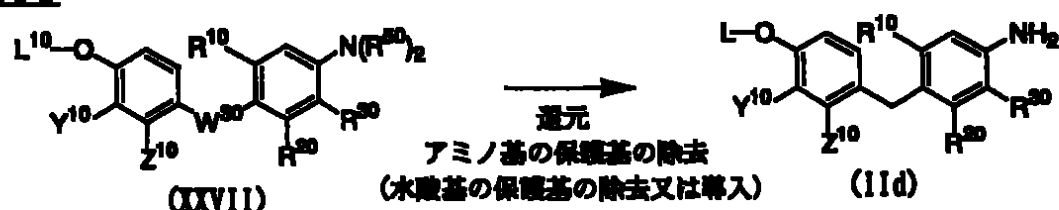
工程3

得られた化合物 (XXIV) において、アミノ基の保護基の種類に応じ、常

法により適宜処理して保護基を除去した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物 (I c) が得られる。

- 5 前記製造方法において出発原料として用いられる前記一般式 (I I) の化合物の中、下記一般式 (I I d) の化合物は、例えば、下記のスキーム 12 により表される反応に従い製造することができる。

スキーム 12

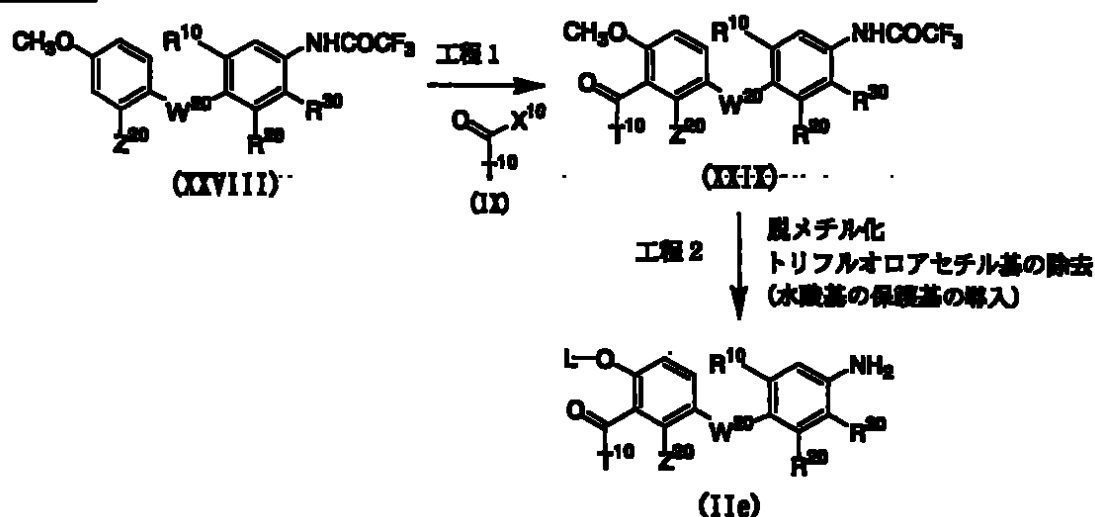


(式中の L、L¹⁰、R¹⁰、R²⁰、R³⁰、R⁵⁰、W³⁰、Y¹⁰および Z¹⁰は前記と同じ意味をもつ)

- 10 化合物 (XXVII) を、塩化メチレン等の溶媒中、トリエチルシランとトリフルオロ酢酸を用いて、通常 0℃～還流温度で 1～48 時間還元し、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物 (II d) が得られる。
- 16 また、化合物 (XXVII) をテトラヒドロフラン、メタノール、エタノール、酢酸エチル、酢酸等の溶媒中、パラジウム炭素等の触媒の存在下、通常室温～還流温度で 1～48 時間 1～5 気圧にて接触水素添加して還元し、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去
- 20 することにより、化合物 (II d) が得られる。

前記製造方法において出発原料として用いられる前記一般式 (I I) の化合物の中、下記一般式 (I I e) の化合物は、例えば、下記のスキーム 13 により表される反応に従い製造することができる。

スキーム13



(式中のL、 R^{10} 、 R^{20} 、 R^{30} 、 T^{10} 、 W^{20} 、 X^{10} および Z^{20} は前記と同じ意味をもつ)

工程 1

化合物 (XXVII) を1～1.5当量の化合物 (IX) で、四塩化チタン等のルイス酸またはトリフルオロメタンスルホン酸無水物の存在下、塩化メチレン等の溶媒中、通常0℃～室温で3～72時間フリーデルクラフツ反応によりアシル化反応を行うことにより、化合物 (XXIX) が得られる。

工程 2

得られた化合物 (XXIX) を塩化メチレン等の溶媒中、四塩化チタン等のルイス酸または濃臭化ホウ素酸-酢酸の存在下、通常室温～還流温度で3～72時間処理するか、或いは塩化メチレン等の溶媒中、四塩化錫および三塩化ホウ素、三臭化ホウ素等の三ハロゲン化ホウ素の存在下、通常-78℃～還流温度で1～24時間処理してメチル基を除去した後、常法に従いアルカリ存在下にトリフルオロアセチル基を除去し、必要に応じ、水酸基に適切な保護基を常法により導入することにより、化合物 (IIe) が得られる。

前記製造方法において出発原料として用いられる前記一般式 (II) の化合物の中、下記一般式 (II f) の化合物は、例えば、下記のスキーム14により表される反応に従い製造することができる。

スキーム14



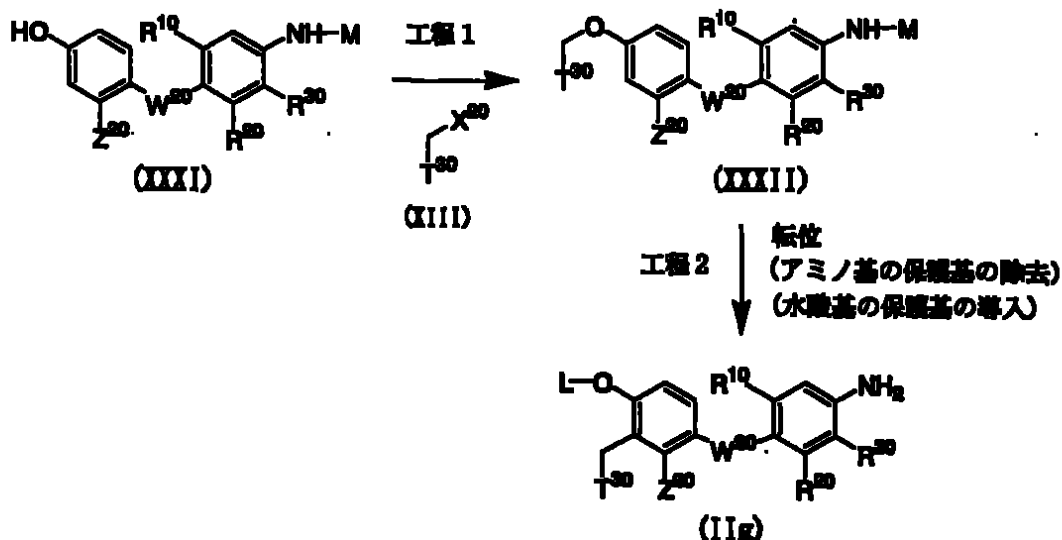
(式中のMは水素原子またはアミノ基の保護基を表し、L、 R^{10} 、 R^{20} 、 R^{30} 、 T^{10} 、 W^{20} および Z^{20} は前記と同じ意味をもつ)

化合物(XXX)を、メタノール、酢酸等の極性溶媒中、水素化ホウ素ナトリウム、ナトリウムトリアセトキシボロヒドリド等の還元剤を用いて、0℃～
 5 還流温度で1～48時間還元した後、必要に応じ、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(IIIf)が得られる。

また、化合物(XXX)をテトラヒドロフラン、メタノール、エタノール、酢酸エチル等の溶媒中、パラジウム炭素、酸化白金等の触媒の存在下、通常室
 10 温～還流温度で1～48時間1～5気圧にて接触水素添加して還元した後、必要に応じ、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(IIIf)が得られる。

前記製造方法において出発原料として用いられる前記一般式(II)の化合物
 15 物の中、下記一般式(IIg)の化合物は、例えば、下記のスキーム15により表される反応に従い製造することができる。

スキーム 15



(式中のL、M、 R^{10} 、 R^{20} 、 R^{30} 、 T^{30} 、 W^{20} 、 X^{20} および Z^{20} は前記と同じ意味をもつ)

工程 1

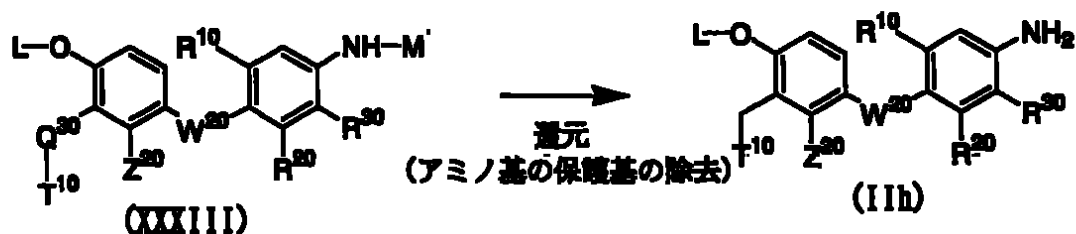
化合物 (XXXI) と 1～1.5 当量の化合物 (XII) とを、アセトン、
 5 N、N-ジメチルホルムアミド、ジメチルスルホキシド等の溶媒中、炭酸カリウム、炭酸セシウム等の塩基の存在下、通常室温～還流温度で 1～48 時間反応させることにより、化合物 (XXXII) が得られる。

工程 2

得られた化合物 (XXXII) を無溶媒または塩化メチレン等の不活性溶媒
 10 中、トリフルオロ酢酸等の強酸の存在下、通常室温～還流温度で 1～48 時間処理して転位させた後、必要に応じ、アミノ基の種類に応じ、常法により適宜処理して保護基を除去し、必要に応じ、水酸基に適当な保護基を常法により導入することにより、化合物 (IIg) が得られる。

15 前記製造方法において出発原料として用いられる前記一般式 (II) の化合物の中、下記一般式 (IIh) の化合物は、例えば、下記のスキーム 16 により表される反応に従い製造することができる。

スキーム16



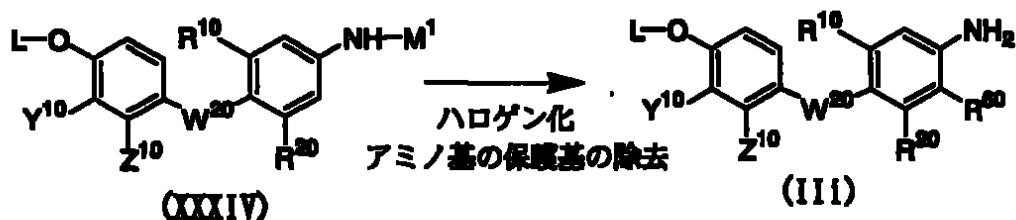
(式中のL、M、 Q^{30} 、 R^{10} 、 R^{20} 、 R^{30} 、 T^{10} 、 W^{20} および Z^{20} は前記と同じ意味をもつ)

化合物(XXXIII)を、塩化メチレン等の溶媒中、トリエチルシランとトリフルオロ酢酸を用いて、0℃～還流温度で1～48時間還元した後、必要に応じて、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(IIh)が得られる。

また、化合物(XXXIII)をテトラヒドロフラン、メタノール、エタノール、酢酸エチル、酢酸等の溶媒中、パラジウム炭素等の触媒の存在下、通常室温～還流温度で1～48時間1～5気圧にて接触水素添加して還元した後、必要に応じて、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(IIh)が得られる。

前記製造方法において出発原料として用いられる前記一般式(II)の化合物の中、下記一般式(III)の化合物は、例えば、下記のスキーム17により表される反応に従い製造することができる。

スキーム17



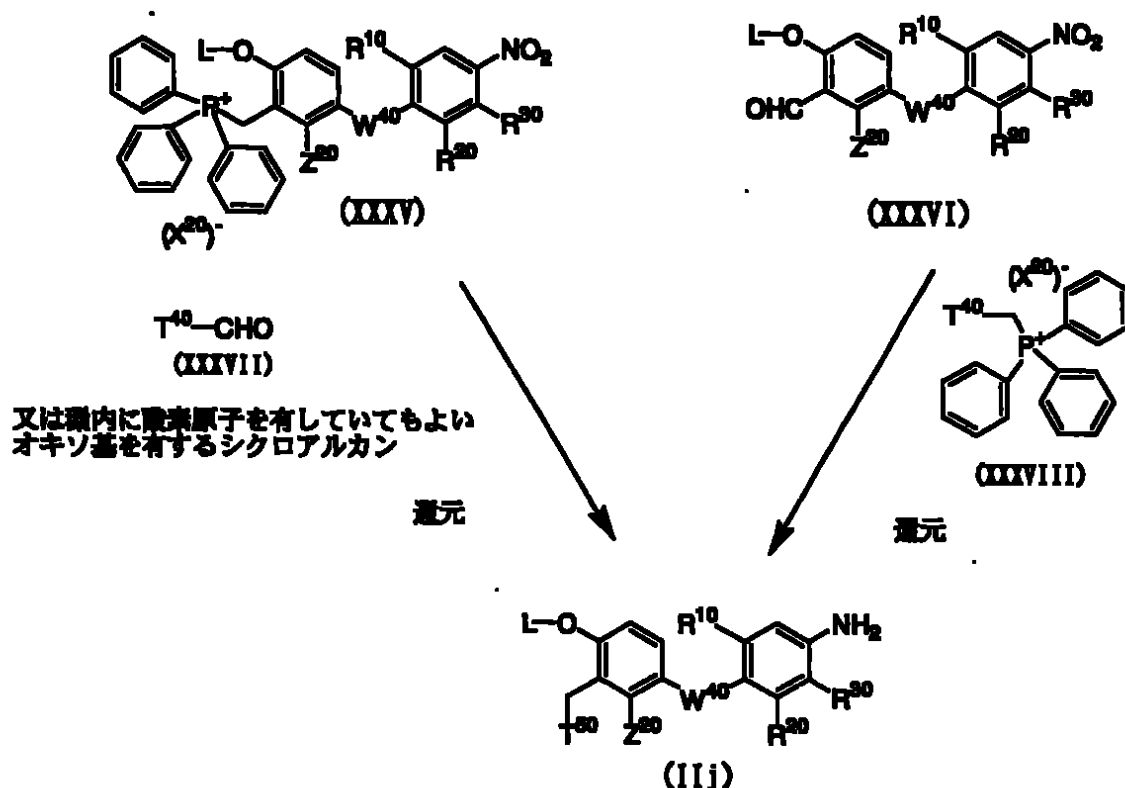
(式中の M^1 はアミノ基の保護基を表し、 R^{40} はハロゲン原子を表し、L、 R^{10} 、 R^{20} 、 W^{20} 、 Y^{10} および Z^{10} は前記と同じ意味をもつ)

化合物(XXXIV)を、塩化メチレン、1,2-ジクロロエタン、テトラヒドロフラン等の溶媒中、N-フルオロ-6-(トリフルオロメチル)ピリジニウム-2-スルホネート等のハロゲン化剤を用いて、室温～還流温度で12

～24時間ハロゲン化した後、アミノ基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(III)が得られる。

前記製造方法において出発原料として用いられる前記一般式(II)の化合物の中、下記一般式(III)の化合物は、例えば、下記のスキーム18により表される反応に従い製造することができる。

スキーム18



(式中の T^{40} は非置換または置換アリール基、または環内に酸素原子を有していてもよいシクロアルキル基を表し、 T^{50} は非置換またはアリールメチル基、環内に酸素原子を有していてもよいシクロアルキル基、または環内に酸素原子を有していてもよいシクロアルキルメチル基を表し、 L 、 R^{10} 、 R^{20} 、 R^{30} 、 W^{40} 、 X^{20} および Z^{20} は前記と同じ意味をもつ)

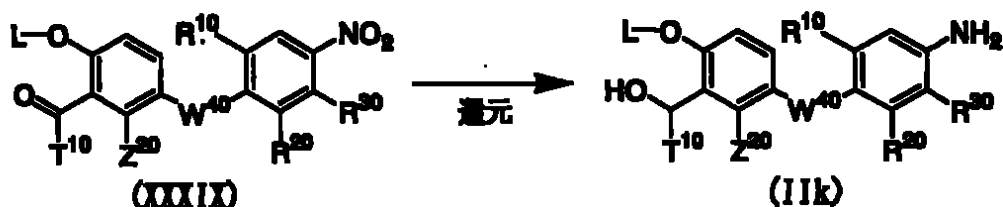
化合物(XXXV)または(XXXVI)と0.7～1.5当量の化合物(XXXVII)または(XXXVII)とを、アルゴン等の不活性ガスの雰囲気下、テトラヒドロフラン、塩化ベンゼン等の不活性溶媒中、カリウムtert-ブトキシド、水素化ナトリウム等の塩基の存在下、通常0℃～還流温

度で1～24時間反応させた後、テトラヒドロフラン、メタノール、エタノール、酢酸エチル等の溶媒中、パラジウム炭素、酸化白金等の触媒の存在下、通常室温～還流温度で1～48時間1～5気圧にて接触水素添加して還元することにより、化合物(IIj)が得られる。

5

前記製造方法において出発原料として用いられる前記一般式(II)の化合物の中、下記一般式(IIk)の化合物は、例えば、下記のスキーム19により表される反応に従い製造することができる。

スキーム19



(式中のL、R¹⁰、R²⁰、R³⁰、T¹⁰、W⁴⁰およびZ²⁰は前記と同じ意味をもつ)

10

化合物(XXXIX)をテトラヒドロフラン、メタノール、エタノール、酢酸エチル等の溶媒中、パラジウム炭素、酸化白金等の触媒の存在下、通常室温～還流温度で1～48時間1～5気圧にて接触水素添加して還元した後、必要に応じ、水酸基の保護基の種類に応じ、常法により適宜処理して保護基を除去することにより、化合物(IIk)が得られる。

15

前記製造方法において出発原料として用いられる前記一般式(II)の化合物の中、下記一般式(III)の化合物は、例えば、下記のスキーム20により表される反応に従い製造することができる。

スキーム20



(式中のL、Q³⁰、R¹⁰、R²⁰、R³⁰、T¹⁰、W⁴⁰およびZ²⁰は前記と同じ意味をもつ)

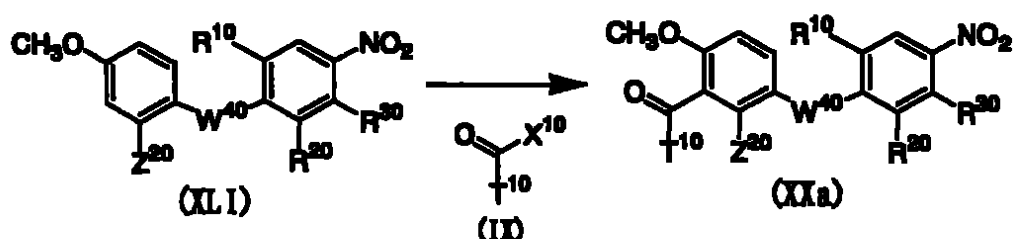
20

また、化合物 (XL) をテトラヒドロフラン、メタノール、エタノール、酢酸エチル、酢酸等の溶媒中、パラジウム炭素等の触媒の存在下、通常室温～還流温度で1～48時間1～5気圧にて接触水素添加して還元することにより、化合物 (III) が得られる。

5

前記製造方法において用いられる前記一般式 (XX) の化合物の中、下記一般式 (XXa) の化合物は、例えば、下記のスキーム21により表される反応に従い製造することができる。

スキーム21



(式中の R^{10} 、 R^{20} 、 R^{30} 、 T^{10} 、 W^{40} 、 X^{10} および Z^{20} は前記と同じ意味をもつ)

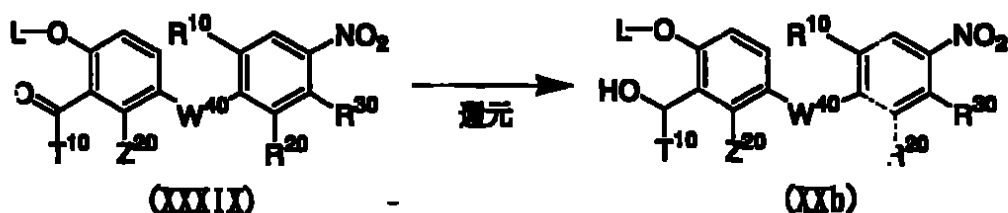
10

化合物 (XLI) を1～1.5当量の化合物 (IX) で、四塩化チタン等のルイス酸またはトリフルオロメタンスルホン酸無水物の存在下、塩化メチレン等の溶媒中、通常0℃～室温で3～72時間フリーデルクラフツ反応によりアシル化反応を行うことにより、化合物 (XXa) が得られる。

15

前記製造方法において用いられる前記一般式 (XX) の化合物の中、下記一般式 (XXb) の化合物は、例えば、下記のスキーム22により表される反応に従い製造することができる。

スキーム22



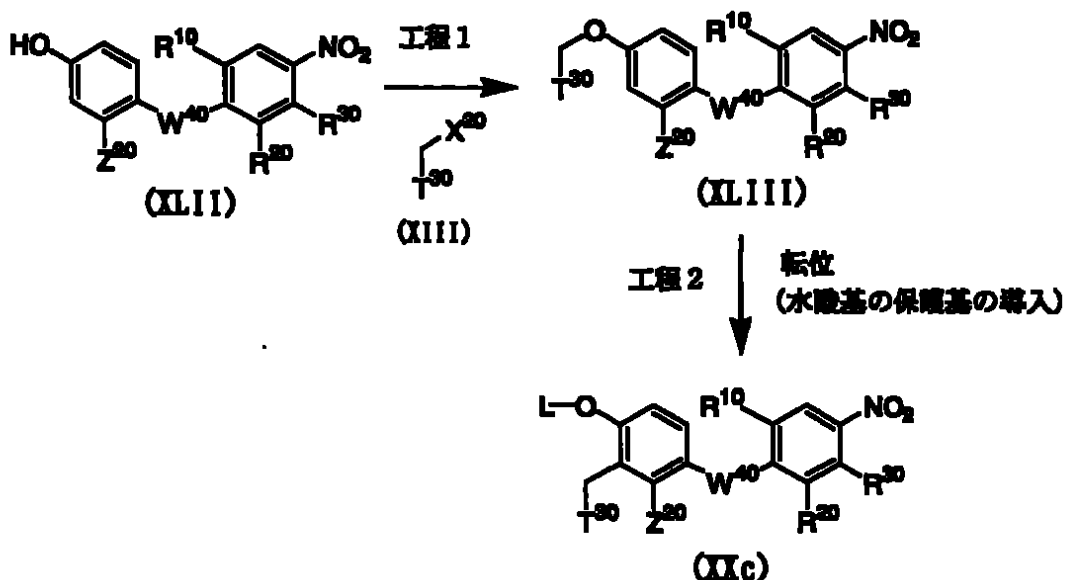
(式中の L 、 R^{10} 、 R^{20} 、 R^{30} 、 T^{10} 、 W^{40} および Z^{20} は前記と同じ意味を

もつ)

化合物 (XXXIX) を、メタノール、酢酸等の極性溶媒中、水素化ホウ素ナトリウム、ナトリウムトリアセトキシボロヒドリド等の還元剤を用いて、通常 0℃～室温で 1～48 時間還元することにより、化合物 (XXb) が得られる。

前記製造方法において用いられる前記一般式 (XX) の化合物の中、下記一般式 (XXc) の化合物は、例えば、下記のスキーム 23 により表される反応に従い製造することができる。

スキーム 23



- 10 (式中の L、R¹⁰、R²⁰、R³⁰、T³⁰、W⁴⁰、X²⁰ および Z²⁰ は前記と同じ意味をもつ)

工程 1

- 15 化合物 (XLI I) と 1～1.5 当量の化合物 (XIII) とを、アセトン、N、N-ジメチルホルムアミド、ジメチルスルホキシド等の溶媒中、炭酸カリウム、炭酸セシウム等の塩基の存在下、通常室温～還流温度で 1～48 時間反応させることにより、化合物 (XLI II) が得られる。

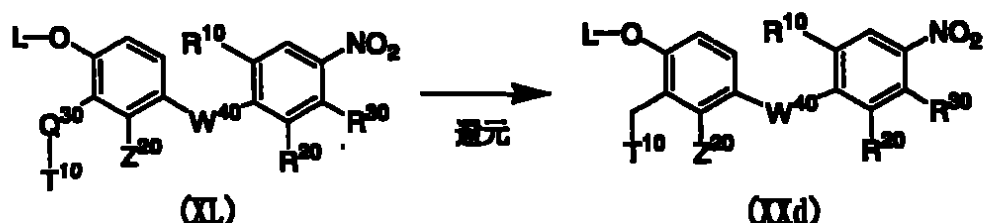
工程 2

得られた化合物 (XLI II) を無溶媒または塩化メチレン等の不活性溶媒中、トリフルオロ酢酸等の強酸の存在下、通常室温～還流温度で 1～48 時間

処理して転位させた後、必要に応じ、水酸基に適切な保護基を常法により導入することにより、化合物 (XXc) が得られる。

- 前記製造方法において用いられる前記一般式 (XX) の化合物の中、下記一般式 (XXd) の化合物は、例えば、下記のスキーム 24 により表される反応に従い製造することができる。

スキーム 24



(式中の L、Q³⁰、R¹⁰、R²⁰、R³⁰、T¹⁰、W⁴⁰ および Z²⁰ は前記と同じ意味をもつ)

- 化合物 (XL) を、塩化メチレン等の溶媒中、トリエチルシランとトリフルオロ酢酸を用いて、通常 0℃～還流温度で 1～48 時間還元することにより、化合物 (XXd) が得られる。

前記一般式 (XVI) で表される化合物は、公知の方法に準じて製造することができる。例えば、一般式 (XLIV)



- (式中の L、Y⁴⁰ および Z³⁰ は前記と同じ意味をもつ) で表されるフェノール誘導体をトリス (トリフルオロアセチル) ヨウ素と縮合した後、過塩素酸やほうフッ化水素酸を用いて処理することにより製造することができる。

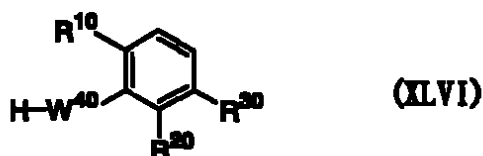
- 前記一般式 (XVII) で表される化合物は、公知の方法に準じて製造することができる。例えば、前記一般式 (XXI) で表される化合物を、m-クロロ過安息香酸等の過オキシ酸を用いて、Baeyer-Villiger 条件下に酸化し、得られた酸エステルを加水分解した後、必要に応じて M. S. Newman らの方法 (J. Org. Chem., Vol. 31, pp. 3980-3984 (1966)) に準じてチオフェノール誘導体へ変換すること

により製造することができる。尚、前記一般式 (XXI) で表される化合物は、例えば、一般式 (XLV)



(式中の L^{10} 、 Y^{40} および Z^{40} は前記と同じ意味をもつ) で表されるフェノール誘導体を、ジクロロメチルメチルエーテルと四塩化チタンを用いてホルミル化することにより製造することができる。

前記一般式 (XIX) で表される化合物は、公知の方法に準じて製造することができる。例えば、 W^3 が酸素原子である前記一般式 (XVII) で表される化合物をトリフルオロメタンスルホン酸と反応してエステル化した後、N-メチルピロリドン、ジメチルホルムアミド等の不活性溶媒中、ハロゲン化リチウムの存在下に加熱攪拌することにより製造することができる。尚、前記一般式 (XVII) で表される化合物は、例えば、一般式 (XLVI)



(式中の R^{10} 、 R^{20} 、 R^{30} および W^{40} は前記と同じ意味をもつ) で表されるフェノール誘導体又はチオフェノール誘導体を酢酸-硝酸、トリフルオロ酢酸-亜硝酸ナトリウム或いはテトラフルオロホウ酸ニトロニウム等のニトロ化剤を用いてニトロ化し、必要に応じて M. S. Newman らの方法 (J. Org. Chem., Vol. 31, pp. 3980-3984 (1966)) に準じてフェノール誘導体をチオフェノール誘導体へ変換することにより製造することができる。

前記一般式 (XXII) で表される化合物は、公知の方法に準じて製造することができる。例えば、前記一般式 (XIX) で表される化合物を、酢酸、エタノール、酢酸エチル、テトラヒドロフラン等の溶媒中、酸化白金やパラジウム炭素等を触媒として用いて接触水素添加により還元した後、アミノ基に適切な保護基を常法により導入することにより製造することができる。

前記一般式 (XXXV) で表される化合物は、前記一般式 (XXXVI) で

表される化合物を、メタノール、酢酸等の極性溶媒中、水素化ホウ素ナトリウム等の還元剤を用いて還元し、得られたアルコール体をテトラヒドロフラン、塩化メチレン等の溶媒中、四臭化炭素とトリフェニルホスフィン等を用いてハロゲン化させることによりハロゲン体を得た後、トルエン等の溶媒中、トリフェニルホスフィンと反応させることにより製造することができる。

上記製造方法において用いられる水酸基やアミノ基の保護基については、例えば、「Protective Groups in Organic Synthesis」T. W. Greene et al., Wiley (1999)に記載されており、反応条件に応じて適宜選択して使用することができる。

前記製造方法において得られる化合物は、慣用の分離手段である分別再結晶法、クロマトグラフィーを用いた精製法、溶媒抽出法等により単離精製することができる。

本発明の有効成分である前記一般式(I)で表される化合物は、常法により、その薬理学的に許容される塩とすることができる。このような塩としては、塩酸、臭化水素酸、ヨウ化水素酸、硫酸、硝酸、リン酸などの鉱酸との付加塩、ギ酸、酢酸、メタンスルホン酸、ベンゼンスルホン酸、p-トルエンスルホン酸、プロピオン酸、クエン酸、コハク酸、酒石酸、フマル酸、酪酸、シュウ酸、マロン酸、マレイン酸、乳酸、リンゴ酸、炭酸、グルタミン酸、アスパラギン酸等の有機酸との付加塩、ナトリウム塩、カリウム塩、カルシウム塩等の無機塩基との塩、アルギニン、リジン、チロシンアミド等の有機塩基との付加塩を挙げることができる。

本発明の有効成分である前記一般式(I)で表される化合物には、水和物やエタノール等の医薬品として許容される溶媒との溶媒和物も含まれる。

本発明の有効成分である前記一般式(I)で表される化合物において、不斉炭素原子が存在する場合、R配置の化合物、S配置の化合物およびその混合物のいずれも含む。また本発明の有効成分である前記一般式(I)で表される化合物において、幾何学異性体が存在する場合、シスおよびトランス配置の化合物のいずれも含む。

本発明の肝臓の予防または再発抑制剤を実際の治療に用いる場合、用法に必ず種々の剤型のものが経口または非経口的に使用される。このような剤型とし

ては例えば、散剤、顆粒剤、細粒剤、ドライシロップ剤、錠剤、カプセル剤などの経口剤、または注射剤、軟膏剤、坐剤、貼付剤などの非経口剤を挙げることができる。

これらの医薬組成物は、その剤型に応じて適当な賦形剤、滑沢剤、結合剤、
5 崩壊剤、溶剤、希釈剤、溶解補助剤、懸濁化剤、等張化剤、緩衝剤、無痛化剤、防腐剤、矯味矯臭剤などの医薬品添加物を選択し、当該分野で周知の方法に従って調剤することにより、製造することができる。

賦形剤としては、例えば、乳糖、白糖、D-マンニトール、デンプン、コーンスターチ、結晶セルロースなどの有機賦形剤、および軽質無水珪酸、リン酸
10 カルシウム、炭酸カルシウムなどの無機賦形剤を挙げることができる。滑沢剤としては、例えば、ステアリン酸、ステアリン酸マグネシウム、ステアリン酸ナトリウム、タルク、ラウリル硫酸ナトリウム、ラウリル硫酸マグネシウム、無水珪酸などを挙げることができる。結合剤としては、例えば、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリ
15 ドン、マクロゴール、アラビアゴム末、ゼラチンなどが挙げられる。

崩壊剤としては、例えば、クロスカルメロースナトリウム、カルボキシメチルスターチナトリウム、コーンスターチ、架橋ポリビニルピロリドンなどを挙げることができる。

溶剤としては、例えば、注射用水、アルコール（例えば、エタノール、プロ
20 パノール、イソプロパノール、1, 2-プロピレングリコールなど）、マクロゴール、ゴマ油、トウモロコシ油、オリーブ油、ヒマシ油などが挙げられる。溶解補助剤としては、例えば、ポリエチレングリコール、プロピレングリコール、D-マンニトール、エタノール、トリエタノールアミン、炭酸ナトリウム、クエン酸ナトリウムなどが挙げられる。懸濁化剤としては、例えば、ラウリル
25 硫酸ナトリウム、ラウリルアミノプロピオン酸、ステアリルトリエタノールアミン、塩化ベンザルコニウム、塩化ベンゼトニウムなどの界面活性剤、およびポリビニルアルコール、ポリビニルピロリドン、カルボキシメチルセルロースナトリウム、メチルセルロース、ヒドロキシメチルセルロース、ヒドロキシエチルセルロース、ヒドロキシプロピルセルロースなどの親水性高分子などが挙

げられる。

等張化剤として、例えば、ブドウ糖、D-ソルビトール、塩化ナトリウム、グリセリン、D-マンニトールなどが挙げられる。緩衝剤としては、例えば、リン酸塩、酢酸塩、炭酸塩、クエン酸塩などの緩衝液などが挙げられる。無痛化剤としては、例えば、ベンジルアルコールなどが挙げられる。防腐剤としては、例えば、パラオキシ安息香酸エステル類、ベンジルアルコール、フェネチルアルコール、デヒドロ酢酸、ソルビン酸などが挙げられる。

矯味矯臭剤としては、例えば、サッカリンナトリウム、アスパルテーム、ステビアなどの甘味剤、クエン酸、酒石酸、リンゴ酸などの酸味剤、およびレモン、ライム、オレンジ、メントールなどの香料を挙げることができる。

例えば、散剤は、有効成分に、必要に応じて適当な賦形剤、滑沢剤などを加え、よく混和することにより調製することができる。

錠剤は、有効成分に、必要に応じて適当な賦形剤、崩壊剤、結合剤、滑沢剤などを添加し圧縮成形することにより調製することができる。さらに錠剤は必要に応じて、適宜コーティングを施し、フィルムコート錠、糖衣錠、腸溶性皮錠などにすることができる。

カプセル剤は、有効成分に、必要に応じて適切な賦形剤、滑沢剤などを加え、よく混和した後、あるいは又、常法により、顆粒あるいは細粒とした後、適切なカプセルに充填することにより調製することができる。

本発明の医薬組成物を実際の治療に用いる場合、その有効成分である前記一般式(I)で表される化合物またはその薬理学的に許容される塩の投与量は患者の年齢、性別、体重、疾患および治療の程度等により適宜決定されるが、経口投与の場合成人1日当たり概ね $1\mu\text{g}\sim 100\text{mg}$ の範囲で、非経口投与の場合は、成人1日当たり概ね $0.1\mu\text{g}\sim 30\text{mg}$ の範囲で、一回または数回に分けて適宜投与することができる。

本発明の有効成分である前記一般式(I)で表される化合物またはその薬理学的に許容される塩と、インターフェロン α 、NIK-333、およびウルソデオキシコール酸から選択される少なくとも1種とを組み合わせる医薬は、これらの有効成分を別々にまたは同時に、薬理学的に許容される賦形剤、崩壊

剤、結合剤、滑沢剤、希釈剤、緩衝剤、等張化剤、防腐剤、湿潤剤、乳化剤、分散剤、安定化剤、溶解補助剤などと混合し、医薬組成物として経口または非経口的に投与することができる。このとき有効成分を別々に製剤化した場合、別々に製剤化したものを使用時に希釈剤などを用いて混合して投与することができるが、別々に製剤化したものを、別々に、同時に、または時間差をおいて同一対象に投与してもよい。

本発明の有効成分である前記一般式 (I) で表される化合物またはその薬理的に許容される塩と、インターフェロン α 、NIK-333、およびウルソデオキシコール酸から選択される少なくとも1種とを組み合わせる医薬において、薬剤の配合比は、患者の年齢、性別、および体重、症状、投与時間、剤形、投与方法、薬剤の組み合わせなどにより、適宜選択することができる。

本発明の医薬組成物は、肝発癌のリスクのある疾患（例えば、B型もしくはC型肝炎ウイルス性慢性肝炎、または肝硬変など）に罹患する患者、あるいは肝癌根治治療（肝切除、経皮的エタノール注入療法、肝動脈塞栓療法、経皮的マイクロ波凝固療法など）後に肝癌の再発のリスクのある患者への使用に特に好適である。

〔発明を実施するための最良の形態〕

本発明の内容を以下の参考例、実施例および試験例でさらに詳細に説明するが、本発明はその内容に限定されるものではない。

（試験例1）

受容体結合試験

昆虫細胞で発現した、遺伝子組み替えヒト甲状腺ホルモン受容体 α または β (Miyamoto Tら, J Biol Chem, 272 (12) 7752-8, (1997))を、0.4M KCl, 1mM $MgCl_2$, 10mM Tris-HCl, 1mM dithiothreitol (pH8.0) の緩衝液中で、L-3, 5, 3' - [^{125}I] - Triiodothyronine ([^{125}I] - T3, 0.95nM, 160Ci/mmol, NENの放射性同位体をSigmaのT3で希釈して作成) および所定濃度の薬物とともに、ガラス試験管を用いて0.5mL/tubeで、氷浴中、16-48時間インキュベートした。インキュベート終了

後、上記緩衝液に懸濁したイオン交換樹脂（室町化学，Dowex 1-X8，80mg/mL）を、0.5mL/tubeで加え、試験管を撈拌した。樹脂が沈殿するのを待って、撈拌をさらに2回同様に繰り返し、1℃に冷却した遠心分離機（KUBOTA，8800）で1000rpm、5分間遠心した。上清0.5mlを別のチューブに移し、 γ カウンターで上清中の放射活性を測定し、受容体に結合したT3の量を測定した。なお、本結合実験に用いる遺伝子組替え甲状腺ホルモン受容体の量は、上述の実験系において、受容体添加量の用量反応性曲線をあらかじめ作成し、T3の結合量が添加受容体量と比例する範囲で妥当なカウントが得られる量を使用した。

●10 T3のKd値は、 $[^{125}\text{I}]$ -T3の濃度を変化させて結合量を測定し、常法にしたがってスキャッチャードプロットを行いそれに基づいて算出した。本法によるT3のKi値は、 α および β 受容体に対してそれぞれ、0.268nMおよび0.304nMであった。

15 Ki値の算出は、各薬物のIC₅₀の値から、以下の計算式によって算出し、その結果を下記の表1に示した。

$$K_i (\text{nM}) = [\text{IC}_{50}] / (1 + K_d / 0.95)$$

(表1)

化合物番号	β 受容体に対する Ki値 (nM)	α 受容体に対する Ki値 (nM)
39	0.69	20.41

(試験例2)

20 肝グルタチオン含量、肝エストロゲンスルホトランスフェラーゼ発現量、および血中T4濃度の変動評価試験

F344/N（日本エルエスシー株式会社）ラット雄9週齢を用い、薬物を1日1回2日間連続投与した。薬物は、0.15M NaCl、0.01M NaOH、40%エタノールに溶解して、30nmol/kg、1ml/kgで皮下投与し、対照群には溶媒を投与した。2日目の投薬の翌日午後に、エーテル麻酔で下腹部大動脈より全血採血し、凝固後血清を遠心分離して、血中の3、

5, 3', 5' -テトラヨード-L-サイロニン (T4) を全身性作用の指標として市販のラジオイムノアッセイキット (榮研化学、I-AC16) を用いて測定した。

5 肝臓中のグルタチオン (GSH) の測定は、0.2~0.5 gのラット肝臓に対し、重量の20倍の5%メタリン酸(w/v)を加え、テフロンホモジナイザーでホモジナイズ後、市販のグルタチオン評価キット(カルピオケム、Cat No. 354102)を用いて付属のマニュアルに従って定量した。

また、肝臓中エストロゲンスルホトランスフェラーゼ (EST) の発現量は、ESTをコードするmRNA発現量を指標として以下のように測定した。ラットの肝臓50~100mgを採取し、1mLのアイソゲン (登録商標) (ニッポンジーン) 中でオムニミキサー (登録商標) (ヤマト科学、μH) を用いてホモジナイズした。0.2mLのクロロホルムを加えた後、15秒間激しく振盪し、室温に5分間放置後、12000×gで15分間、4℃にて遠心した。上清を単離し、0.5mLのイソプロパノールを加え、5~10分間室温に放置した後、12000×g、10分間、4℃にて遠心した。上清を除去し、沈殿に1mLの70%エタノールを加え、攪拌した後、7500×g、5分間、4℃で遠心した。沈殿を風乾し、0.5mLのトリス-エチレンジアミン四酢酸緩衝液(pH8.0)に溶解し、総RNA溶液とした。RNA溶液の吸光度(260及び280 nm)を測定し、各サンプル当たり100 ngのRNAを用いて逆転写反応-ポリメラーゼチェーン反応 (RT-PCR) 反応を行った。RT-PCR反応は、市販のGene Amp (登録商標) RT-PCRキット (パーキンエルマー) を用い、特に記述する部分以外は、付属マニュアルに従って行った。RT反応は、キットに付属のランダムヘキサマーをプライマーとして用いた。また、PCR反応は、5'-GGATATCCGAAGAGAAGTTGTGAAGC-3' および5'-TCAGAGCTCTGCTCTAAATTTACACAGG-3' のプライマーを用いて、ラットエストロゲンスルホトランスフェラーゼ3' 末端の295塩基対DNAを増幅した。PCR反応産物は、1.2%アガロースゲルにて泳動し、増幅された特異的なバンドを画像解析装置 (フルオロー S マルチイメージャー (登録商標), バイオラッド) にて解析することで、総RNA中に含まれるエ

ストロゲンスルホトランスフェラーゼをコードするmRNAの相対量の指標とした。

これらの結果を表2に示した。

(表2)

5 肝臓内GSH含量、肝ESTをコードするmRNA発現量、血中T4の変動

群	GSH (nmol/g)	EST (arbitrary unit)	血中T4 (μ g/dL)
対照群	6966 $\pm$ 22	1213 $\pm$ 108	3.84 $\pm$ 0.25
化合物69	5650 $\pm$ 146*	788 $\pm$ 135*	2.41 $\pm$ 0.14**
化合物70	5324 $\pm$ 178*	520 $\pm$ 28**	2.29 $\pm$ 0.20**
化合物77	5869 $\pm$ 166*	506 $\pm$ 80**	2.56 $\pm$ 0.11**
化合物78	4957 $\pm$ 143***	460 $\pm$ 39**	2.03 $\pm$ 0.08**
化合物79	6291 $\pm$ 275	510 $\pm$ 7	3.26 $\pm$ 0.17*
T3	5853 $\pm$ 207*	684 $\pm$ 133*	0.67 $\pm$ 0.03**

数値：平均値 $\pm$ 標準偏差

*, ** および ***: $P < 0.05$, 0.01 および 0.001 vs 対照群 (Student's t検定)

10 このように本発明の化合物は、肝臓内GSH含量および肝EST発現量を顕著に低下させるが、全身性作用の指標である血中T4への影響は極めて軽微であり、肝臓選択的な作用を示した。

(試験例3)

インビトロ細胞増殖抑制作用

15 ヒト肝癌細胞HepG2細胞(大日本製薬)を、24穴プレートに 10^4 細胞/ウェルで播種し、薬物と共に10%FCSを含むDMEMで培養した。被験化合物およびインターフェロン α (スミフェロン300(登録商標),住友製薬)を培地で希釈して使用した。2~3日間隔で薬物を含む培地を新しいものに交換しながら、12日間培養を継続した。培養終了時に、上清の培地を除去

し、0.5 mLの氷冷したダブルベッコリン酸緩衝液（PBS）で一回洗浄後、トリプシンを加えて細胞をプレートから剥がした後、トリパンブルー染色を行って、生細胞数を計測した。結果を表3に示した。

(表3)

5 Hep G2細胞増殖抑制作用

群	生細胞数 (10 ⁴ 細胞/ウェル)
対照群	33.6±0.76
化合物70 10μM	24.8±1.54***
IFN 100 IU/mL	28.2±0.64***
IFN 1000 IU/mL	21.5±2.13**
IFN 10000 IU/mL	11.1±1.28***
化合物70 10μM + IFN 100 IU/mL	18.4±2.31***. #
化合物70 10μM + IFN 1000 IU/mL	13.4±1.02***. #
化合物70 10μM + IFN 10000 IU/mL	5.6±0.44***. #

数値：平均値±標準偏差

** および ***: P<0.01 および 0.001 vs 対照群

: P<0.001 vs 化合物70無し

10 (試験例4)

ラット肝腫瘍抑制試験

雄のフィッシャーF344ラット用い、7週齢時にジエチルニトロサミン（DEN、150mg/kg）を単回腹腔内投与した。9週齢時より2-アセチルアミノフルオレン（2-AAF、7.5mg/kg）を2週間反復経口投与し、2-AAF投与期間中の10週齢時に2/3部分肝切除を施して肝腫瘍を誘発した。これらのラットを被験薬物投与群および対照群（各8匹/群）に群分けし、被験薬物投与群には被験薬物を0.5%カルボキシメチルセルロース水溶液に懸濁したものを40、100および250μg/kgの用量となるように16週齢時より3週間経口投与した。同様に0.5%カルボキシメチル

セルロース水溶液を投与し、対照群とした。

被験薬物投与群および対照群の投与開始日および終了日に体重を測定し、投与2日目および終了日に前日からの1日摂餌量を測定した。

その結果は下記の表4および表5に示す通りであり、本発明の化合物は体重に影響を与えず、また摂餌量を有意に増加させた。

(表4)

体重

群	投与開始日 体重 (g)	投与終了日 体重 (g)
対照群	260.4±12.2	273.4±13.1
化合物70 40 µg/kg	259.4±12.2	282.8±15.0
化合物70 100 µg/kg	260.1±10.0	284.5±11.7
化合物70 250 µg/kg	259.8±10.4	284.3±11.7

数値：平均値±標準偏差

(表5)

10 摂餌量

群	投与2日目 摂餌量 (g)	投与最終日 摂餌量 (g)
対照群	15.6±1.4	15.6±1.7
化合物70 40 µg/kg	14.8±1.2	17.4±1.5*
化合物70 100 µg/kg	15.7±1.0	17.5±1.0*
化合物70 250 µg/kg	16.0±1.4	17.5±1.1*

数値：平均値±標準偏差

* : $p < 0.05$

最終投与翌日に全てのラットを剖検し、肝臓を10%リン酸緩衝ホルマリン液にて固定した。この肝臓を常法に従いパラフィン包埋ブロックとし、抗胎嚢型グルタチオンS-トランスフェラーゼ (GSTP) 抗体 (式会社医学生物

学研究所) による免疫組織化学的染色切片を作製した。これらの切片について、GSTP陽性変異巣数およびGSTP陽性変異巣の面積比を下式に従い計測した(全自動画像解析装置LUZEX3;株式会社ニコン)。結果を表6に示した。

$$\text{GSTP陽性変異巣数 (個/cm}^2\text{)} = \frac{\text{GSTP陽性変異巣数}}{\text{肝臓の総面積}}$$
$$\text{GSTP陽性変異巣の面積比 (\%)} = \frac{\text{GSTP陽性変異巣の総面積}}{\text{肝臓の総面積}}$$

6

(表6)
GSTP陽性変異巣数およびGSTP陽性変異巣の面積比

群および用量	GSTP陽性変異巣数 (個/cm ²)	GSTP陽性変異巣 の面積比 (%)
対照群	59.4±10.4	62.1±11.1
化合物70 40μg/Kg	47.2±3.1	40.7±8.9**
化合物70 100μg/Kg	34.3±3.5**	37.2±11.3**
化合物70 250μg/Kg	32.9±3.9**	31.6±7.7**

数値：平均値±標準偏差

**：p<0.01

10 このように本発明の化合物は癌または前癌病変のマーカー酵素であるGSTPが発現した変異巣数および面積比を有意に低下させた。

また剖検時に腹部大動脈より採血し、血漿中のアラニンアミノトランスフェラーゼ(ALT)、アルカリンホスファターゼ(ALP)、乳酸脱水素酵素
15 (LDH) およびγ-グルタミルトランスフェラーゼ(GGT)量を7150形自動分析装置(日立製作所)を用いて測定した。結果を表7に示した。

(表 7)

群	ALT (U/l)	ALP (U/l)	LDH (U/l)	GGT (IU/l)
対照群	107.75 ±28.50	1126.88 ±99.49	943.13 ±342.22	48.50 ±12.27
化合物70 250 µg/kg	102.50 ±16.45	1163.38 ±83.20	596.50 ±284.93 [*]	15.75 ±5.09 ^{***}

数値：平均値±標準偏差

^{*} : $p < 0.05$, ^{***} : $p < 0.001$

5 このように本発明の化合物はLDH、および癌または前癌状態で増加する血中のマーカー酵素であるGGTを有意に低下させ、ALTおよびALPに影響しなかった。

 このように本発明の化合物は、体重、摂餌量および肝機能に悪影響を与えることなく有意な肝腫瘍抑制作用を示した。

10 (試験例 5)

心毒性試験

15 正常Wistarラット雄6週齢に対して、薬物として被験化合物およびT3を1日1回14日間経口投与し、最終投薬日の翌日に、エーテル麻酔下にて全血採血後、心臓を摘出し重量を測定した。薬物は、5%エタノール、0.5%カルボキシメチルセルロース(CMC)に懸濁または溶解して5mL/kgで投与し、対照群には溶媒を投与した。結果を表8に示した。

(表 8)

心重量

群および投与量 (nmol/kg)		心重量 (体重%)
化合物70	0	0.307 ± 0.008
化合物70	5	0.310 ± 0.008
化合物70	15	0.321 ± 0.014
化合物70	50	0.333 ± 0.012
化合物70	150	0.334 ± 0.010
化合物70	500	0.316 ± 0.017
T 3	0	0.322 ± 0.011
T 3	10	0.314 ± 0.012
T 3	30	0.338 ± 0.008
T 3	100	0.369 ± 0.009**
T 3	300	0.425 ± 0.007***

数値：平均値±標準偏差

** および ***: P< 0.01 および 0.001 vs 対照群 (Student's t検定)

5 このようにT 3が100 nmol/kgより用量依存的な心重量の増加を示したのに対し、本発明の化合物は心臓への影響が極めて軽微であった。

(試験例 6)

急性毒性試験

10 6週齢のICRマウス雄5匹に対して、被験薬物を0.5%カルボキシメチルセルロース、5%エタノールに溶解して経口投与し、投与後、31時間後に死亡例の有無を観察した。

その結果は下記の表9に示す通りであり、本発明の化合物は100mg/kgの用量で死亡例がみられず、極めて高い安全性を示した。

(表 9)

化合物番号	用量 (mg/kg)	死亡例
70	100	0/5

(参考例 1)

1-ベンジルオキシ-2-イソプロピルベンゼン

- 5 2-イソプロピルフェノール 21.8 g をアセトニトリル 100 mL に溶かし、ベンジルブロミド 18.8 mL と炭酸カリウム 27 g を加え、29 時間加熱還流した。反応混合物を減圧濃縮し、得られた残渣に水を加え、酢酸エチルで抽出した。有機層を 1 mol/L 水酸化ナトリウム水溶液、水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、1-ベンジルオキシ-2-イソプロピルベンゼン 35.7 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.24 (6H, d, $J=6.9\text{Hz}$), 3.42 (1H, h eptet, $J=6.9\text{Hz}$), 5.08 (2H, s), 6.88-6.97 (2H, m), 7.12-7.17 (1H, m), 7.22-7.25 (1H, m), 7.30-7.47 (5H, m)

15 (参考例 2)

参考例 1 と同様の方法により、以下の化合物を合成した。

2, 6-ジベンジルオキシアセトフェノン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.50 (3H, s), 5.09 (4H, s), 6.60 (2H, d, $J=8.4\text{Hz}$), 7.19 (1H, t, $J=8.4\text{Hz}$), 7.23-7.45 (10H, m)

20

1-ベンジルオキシ-5, 6, 7, 8-テトラヒドロナフタレン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.68-1.90 (4H, m), 2.60-2.90 (4H, m), 5.06 (2H, s), 6.65-6.78 (2H, m), 6.98-7.12 (1H, m), 7.22-7.53 (5H, m)

25

(参考例 3)

2, 3, 6-トリクロロ-4-ニトロフェノール

2, 3, 6-トリクロロフェノール 3.58 g をトリフルオロ酢酸 15 mL に懸濁させ、亜硝酸ナトリウム 4.02 g を加え、室温にて一晩攪拌した。反応混合物を氷水 100 mL と塩化メチレン 100 mL の混合液に加え、室温にて 2 時間攪拌した。有機層を分離し、水層を塩化メチレンにて抽出した。有機層を合わせ、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮した。得られた残渣を酢酸エチルとヘキサンより結晶化し、2, 3, 6-トリクロロ-4-ニトロフェノール 3.28 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 6.47 (1H, s), 8.01 (1H, s)

10 (参考例 4)

参考例 3 と同様の方法により、以下の化合物を合成した。

2, 3, 6-トリメチル-4-ニトロフェノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.24 (3H, s), 2.27 (3H, s), 2.42 (3H, s), 5.13 (1H, s), 7.61 (1H, s)

15

(参考例 5)

4-ヨード-3, 5-ジメチルニトロベンゼン

トリフルオロメタンスルホン酸 2, 6-ジメチル-4-ニトロフェニル 9.15 g を N, N-ジメチルアセトアミド 30 mL に溶かし、ヨウ化リチウム 12.3 g を加え、アルゴン雰囲気下 150℃にて 3.5 時間攪拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄した後、活性炭で処理し、無水硫酸マグネシウムで乾燥後、減圧濃縮した。

得られた残渣にヘキサンを加えて結晶化し、4-ヨード-3, 5-ジメチルニトロベンゼン 5.21 g を得た。

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.58 (6H, s), 7.89 (2H, s)

(参考例 6)

4-ヨード-3, 5-ジメチルアニリン

4-ヨード-3, 5-ジメチルニトロベンゼン 4.58 g を酢酸エチル 15

mLに溶かし、酸化白金（IV）458mgを加え、室温にて水素雰囲気下常圧で3時間攪拌した。不溶物をろ去し、ろ液を減圧濃縮し、4-ヨード-3,5-ジメチルアニリン4.06gを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.37 (6H, s), 3.55 (2H, brs), 6.46 (2H, s)

(参考例7)

3-メトリルプロピオン酸メチル

3-メチルベンズアルデヒド8.77gとホスホノ酢酸トリメチル12mLをテトラヒドロフラン20mLに溶かし、氷冷下カリウムtert-ブトキシド9.99gを数回に分けて加えた。アルゴン雰囲気下室温にて一晩攪拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を2mol/L水酸化ナトリウム水溶液、水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、3-メトリルアクリル酸メチル10.8gを得た。

得られた3-メトリルアクリル酸メチル6.28gを酢酸エチル20mLに溶かし、10%パラジウム炭素触媒635mgを加え、室温にて水素雰囲気下常圧で一晩攪拌した。不溶物をろ去し、ろ液を減圧濃縮し、3-メトリルプロピオン酸メチル6.30gを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.32 (3H, s), 2.62 (2H, t, $J=7.9\text{Hz}$), 2.91 (2H, t, $J=7.9\text{Hz}$), 3.67 (3H, s), 6.97-7.03 (3H, m), 7.13-7.21 (1H, m)

(参考例8)

3-ブロモ-3-(3-ブロモメチルフェニル)プロピオン酸メチル

3-メトリルプロピオン酸メチル1.15gとN-ブロモスクシンイミド1.32gを四塩化炭素15mLに溶かし、4時間加熱還流した。反応混合物を室温まで冷却後、不溶物をろ去し、ろ液を減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：酢酸エチル-ヘキサン）にて精製し、3-ブロモ-3-(3-ブロモメチルフェニル)プロピオン酸メチル5

19mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.21 (1H, dd, $J=6.1, 16.3\text{Hz}$), 3.34 (1H, dd, $J=9.0, 16.3\text{Hz}$), 3.71 (3H, s), 4.48 (2H, s), 5.38 (1H, dd, $J=6.1, 9.0\text{Hz}$), 7.31-7.40 (3H, m), 7.44 (1H, brs)

6

(参考例9)

(テトラヒドロピラン-4-イリデン) 酢酸エチル

ホスホノ酢酸トリエチル10.7mLをテトラヒドロフラン15mLに溶かし、カリウムtert-ブトキシド7.26gを加え、アルゴン雰囲気下室温にて5分間攪拌した。反応混合物にテトラヒドロピラン-4-オン5.0mLを加え、アルゴン雰囲気下60℃にて一晩攪拌した。反応混合物を減圧濃縮し、
10 られた残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：酢酸エチル-ヘキサン）にて精製し、(テトラヒドロピラン-4-イリデン) 酢酸エチル2.72gを得た。

15 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.23-1.32 (3H, m), 2.31-2.35 (2H, m), 3.00-3.05 (2H, m), 3.73-3.81 (4H, m), 4.11-4.20 (2H, m), 5.67-5.99 (1H, m)

(参考例10)

20 4-テトラヒドロピラニル酢酸エチル

(テトラヒドロピラン-4-イリデン) 酢酸エチル2.72gをテトラヒドロフラン15mLに溶かし、10%パラジウム炭素触媒（50%含水晶）424mgを加え、室温にて水素雰囲気下常圧で一晩攪拌した。不溶物をろ去し、ろ液を減圧濃縮し、4-テトラヒドロピラニル酢酸エチル3.97gを得た。

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.26 (3H, t, $J=7.1\text{Hz}$), 1.28-1.40 (2H, m), 1.61-1.69 (2H, m), 1.96-2.07 (1H, m), 2.21-2.28 (2H, m), 3.36-3.46 (2H, m), 3.92-3.97 (2H, m), 4.14 (2H, q, $J=7.1\text{Hz}$)

(参考例11)

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4-テトラヒドロピラニル酢酸

4-テトラヒドロピラニル酢酸エチル 3.90 g にエタノール 20 mL と 1 mol/L 水酸化ナトリウム水溶液 20 mL を加え、アルゴン雰囲気下 60℃ にて 20 分間撹拌した。反応混合物を減圧濃縮し、得られた残渣に水を加え、ジエチルエーテルで洗浄した。水層を濃塩酸で中和し、飽和食塩水を加え、ジエチルエーテルで抽出した。有機層を無水硫酸マグネシウムで乾燥後、減圧濃縮し、4-テトラヒドロピラニル酢酸 2.23 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.31-1.43 (2H, m), 1.63-1.73 (2H, m), 1.97-2.10 (1H, m), 2.27-2.32 (2H, m), 3.37-3.45 (2H, m), 3.91-3.99 (2H, m), 9.5-11.2 (1H, brs)

(参考例 12)

4-テトラヒドロピラニルアセチルクロリド

4-テトラヒドロピラニル酢酸 2.23 g に塩化チオニル 3.4 mL を加え、50℃ にて 20 分間撹拌した。反応混合物を減圧濃縮し、得られた残渣にトルエンを加え、減圧濃縮後、得られた残渣に再度トルエンを加え、減圧濃縮し、4-テトラヒドロピラニルアセチルクロリド 2.44 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.32-1.42 (2H, m), 1.64-1.73 (2H, m), 2.05-2.20 (1H, m), 2.80-2.86 (2H, m), 3.37-3.46 (2H, m), 3.92-4.01 (2H, m)

(参考例 13)

参考例 12 と同様の方法により、以下の化合物を合成した。

シクロヘキシルアセチルクロリド

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.90-1.40 (5H, m), 1.59-2.00 (6H, m), 2.75 (2H, d, $J=6.9\text{Hz}$)

(参考例 14)

4-ベンジルオキシ-3-ヒドロキシベンズアルデヒド

3, 4-ジヒドロキシベンズアルデヒド 175.0 g と炭酸カリウム 175.0 g を N, N-ジメチルホルムアミド 600 mL に懸濁し、氷冷下撹拌した。反応混合物にベンジルブロミド 150 mL を滴下し、室温で 6 時間撹拌した。反応混合物に希塩酸を加え酸性とし、析出物をろ取した後、ジエチルエーテル
5 で洗浄し、4-ベンジルオキシ-3-ヒドロキシベンズアルデヒド 179.0 g を得た。

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 5.21 (2H, s), 5.82 (1H, s), 7.04 (1H, d, J=8.3Hz), 7.33-7.52 (7H, m), 9.84 (1H, s)

10 (参考例 15)

2-ベンジルオキシ-5-(1, 3-ジオキサラン-2-イル)フェノール

4-ベンジルオキシ-3-ヒドロキシベンズアルデヒド 2.38 g をベンゼン 15 mL に溶かし、エチレングリコール 5.57 g と p-トルエンスルホン酸 198 mg を加え、水を除去しながら、アルゴン雰囲気下一晩加熱還流した。
15 室温まで冷却後、反応混合物を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄した。有機層を無水硫酸マグネシウムで乾燥後、減圧濃縮し、2-ベンジルオキシ-5-(1, 3-ジオキサラン-2-イル)フェノール 2.70 g を得た。

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 3.96-4.04 (2H, m), 4.06-4.14 (2H, m), 5.12 (2H, s), 5.68 (1H, s), 5.73 (1H, s), 6.91 (1H, d, J=8.3Hz), 6.96 (1H, dd, J=2.0, 8.3Hz), 7.08 (1H, d, J=2.0Hz), 7.33-7.45 (5H, m)

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(参考例 16)

2-[4-ベンジルオキシ-3-(4-フルオロフェノキシ)フェニル]-1, 3-ジオキサラン
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2-ベンジルオキシ-5-(1, 3-ジオキサラン-2-イル)フェノール 506 mg、ジヒドロキシ(4-フルオロフェニル)ボラン 260 mg、酢酸銅 (II) 338 mg 及びモレキュラーシーブス 4A (1/16) 500 mg に塩化メチレン 19 mL とトリエチルアミン 1.30 mL を加え、室温にて一

晩攪拌した。反応混合物を減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：酢酸エチル－ヘキサン）にて精製し、2-〔4-ベンジルオキシ-3-（4-フルオロフェノキシ）フェニル〕-1,3-ジオキソラン356mgを得た。

- 5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.95-4.05 (2H, m), 4.05-4.15 (2H, m), 5.10 (2H, s), 5.70 (1H, s), 6.85-7.05 (5H, m), 7.10-7.40 (7H, m)

（参考例17）

4-ベンジルオキシ-3-（4-フルオロフェノキシ）ベンズアルデヒド

- 10 2-〔4-ベンジルオキシ-3-（4-フルオロフェノキシ）フェニル〕-1,3-ジオキソラン356mgをテトラヒドロフラン20mLに溶かし、1mol/L塩酸20mLを加え、アルゴン雰囲気下60℃にて30分間攪拌した。反応混合物を酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、
- 15 4-ベンジルオキシ-3-（4-フルオロフェノキシ）ベンズアルデヒド340mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 5.20 (2H, s), 6.90-7.05 (4H, m), 7.13 (1H, d, $J=8.4\text{Hz}$), 7.22-7.38 (5H, m), 7.49 (1H, d, $J=2.0\text{Hz}$), 7.61 (1H, dd, $J=2.0, 8.4\text{Hz}$), 9.88 (1H, s)

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（参考例18）

4-ベンジルオキシ-3-（4-テトラヒドロピラニルオキシ）ベンズアルデヒド

- 25 テトラヒドロピラン-4-オール717 μL とトリフェニルホスフィン3.15gをテトラヒドロフラン20mLに溶かし、アルゴン雰囲気下にて、氷冷下40%ジエチルアゾジカルボキシラートのトルエン溶液5.44mLおよび4-ベンジルオキシ-3-ヒドロキシベンズアルデヒド2.29gを加えた。アルゴン雰囲気下室温にて一晚攪拌後、反応混合物を減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：酢酸エチル－ヘキサ

ン) にて精製し、4-ベンジルオキシ-3-(4-テトラヒドロピラニルオキシ) ベンズアルデヒド 1.16 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.80-1.90 (2H, m), 1.98-2.06 (2H, m), 3.53-3.58 (2H, m), 3.95-4.04 (2H, m), 4.52-4.61 (1H, m), 5.22 (2H, s), 7.05 (1H, d, $J=8.2\text{Hz}$), 7.30-7.48 (7H, m), 9.84 (1H, s)

(参考例 19)

4-ベンジルオキシ-3-(4-フルオロフェノキシ) フェノール

4-ベンジルオキシ-3-(4-フルオロフェノキシ) ベンズアルデヒド 2

- 40 mg を塩化メチレン 10 mL に溶かし、炭酸水素ナトリウム 375 mg、
m-クロロ過安息香酸 257 mg を加え、室温にて一晚攪拌した。反応混合物
を水で希釈し、塩化メチレンで抽出した。有機層を水、飽和炭酸水素ナトリウ
ム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃
縮した。得られた残渣をエタノール 3 mL に溶かし、2 mol/L 水酸化ナト
リウム水溶液 2 mL を加え、アルゴン雰囲気下 60℃ にて 30 分間攪拌した。
反応混合物を減圧濃縮し、得られた残渣に 2 mol/L 塩酸を加えて中和した。
反応混合物を飽和重曹水で希釈し、塩化メチレンで抽出した。有機層を飽和炭
酸水素ナトリウム水溶液で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮
し、得られた残渣をシリカゲル薄層クロマトグラフィー (展開溶媒: ヘキサン
-酢酸エチル) にて精製し、4-ベンジルオキシ-3-(4-フルオロフェノ
キシ) フェノール 141 mg を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 4.62 (1H, s), 5.02 (2H, s), 6.49 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.52 (1H, d, $J=3.0\text{Hz}$), 6.89 (1H, d, $J=8.8\text{Hz}$), 6.88-7.03 (4H, m), 7.20-7.44 (5H, m)

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(参考例 20)

参考例 19 と同様の方法により、以下の化合物を合成した。

4-ベンジルオキシ-3-(4-テトラヒドロピラニルオキシ) フェノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.78-1.88 (2H, m), 1.95-2.04 (2H,

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254

m), 3.50-3.58 (2H, m), 3.95-4.02 (2H, m), 4.41-4.47 (1H, m), 4.69 (1H, s), 5.03 (2H, s), 6.35 (1H, dd, J=2.9, 8.6Hz), 6.50 (1H, d, J=2.9Hz), 6.81 (1H, d, J=8.6Hz), 7.27-7.47 (5H, m)

5 (参考例 2 1)

ジメチルチオカルバミド酸O- (2, 6-ジメチル-4-ニトロフェニル)

2, 6-ジメチル-4-ニトロフェノール 20.0 g を N, N-ジメチルホルムアミド 5 mL に溶解し、室温攪拌下トリエチレンジアミン 26.8 g、ジメチルチオカルバモイルクロリド 22.2 g を加え、75℃で30分間攪拌した。放冷後、反応混合物に水 100 mL を加え、不溶物をろ取した。不溶物をジエチルエーテルで洗浄後、乾燥し、ジメチルチオカルバミド酸O- (2, 6-ジメチル-4-ニトロフェニル) 25.0 g を得た。

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 2.26 (6H, s), 3.41 (3H, s), 3.49 (3H, s), 7.98 (2H, s)

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(参考例 2 2)

ジメチルチオカルバミド酸S- (2, 6-ジメチル-4-ニトロフェニル)

ジメチルチオカルバミド酸O- (2, 6-ジメチル-4-ニトロフェニル) 25.0 g を 180℃にて融解し、10時間攪拌した。放冷後、ジメチルチオカルバミド酸S- (2, 6-ジメチル-4-ニトロフェニル) 25.0 g を得た。

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 2.52 (6H, s), 3.02 (3H, brs), 3.19 (3H, brs), 7.99 (2H, s)

25 (参考例 2 3)

2, 6-ジメチル-4-ニトロベンゼンチオール

ジメチルチオカルバミド酸S- (2, 6-ジメチル-4-ニトロフェニル) 25.0 g を 2 mol/L 水酸化ナトリウム水溶液 200 mL およびメタノール 200 mL に懸濁し、90℃で6時間攪拌した。放冷後、反応混合物に 1 m

○ 1/L塩酸を加え酸性とし、酢酸エチルで抽出した。有機層を飽和食塩水で洗淨し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：ヘキサン-酢酸エチル）で精製し、2, 6-ジメチル-4-ニトロベンゼンチオール 12.0 gを得た。

- 5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.43 (6H, s), 3.66 (1H, s), 7.91 (2H, s)

(参考例 2 4)

- 10 5- (2, 6-ジメチル-4-ニトロフェノキシ) -2-メトキシベンズアルデヒド

3, 5-ジメチル-4- (4-メチルオキシフェノキシ) ニトロベンゼン 5.85 g とジクロロメチルメチルエーテル 9.87 mL を塩化メチレン 50 mL に溶解し、氷冷攪拌下四塩化チタン 4.70 mL 滴下した。アルゴン雰囲気下室温にて 20 時間攪拌した後、反応混合物に氷水 300 mL をゆっくり加え、

15 酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗淨し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をヘキサン 50 mL およびジエチルエーテル 5 mL にて懸濁させた。不溶物をろ取後、ヘキサンで洗淨し、5- (2, 6-ジメチル-4-ニトロフェノキシ) -2-メトキシベンズアルデヒド 5.56 g を得た。

- 20 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.20 (6H, s), 3.92 (3H, s), 6.93-7.16 (3H, m), 8.01 (2H, s), 10.40 (1H, s)

(参考例 2 5)

参考例 2 4 と同様の方法により、以下の化合物を合成した。

- 25 4-ベンジルオキシ-3-イソプロピルベンズアルデヒド

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.27 (6H, d, $J=6.9\text{Hz}$), 3.42 (1H, heptet, $J=6.9\text{Hz}$), 5.18 (2H, s), 7.01 (1H, d, $J=8.4\text{Hz}$), 7.33-7.47 (5H, m), 7.69 (1H, dd, $J=2.1, 8.4\text{Hz}$), 7.80 (1H, d, $J=2.1\text{Hz}$), 9.88 (1H, s)

253
255

(参考例 26)

テトラフルオロホウ酸ビス(4-ベンジルオキシ-3-イソプロピルフェニル) ヨードニウム

氷冷撹拌下無水酢酸 55.9 mL に発煙硝酸 20.2 mL を滴下した。反応
5 混合物にヨウ素 18.78 g を加え、次にトリフルオロ酢酸 34.2 mL を滴
下後、室温にて 1 時間撹拌し、減圧濃縮した。得られた残渣に氷冷下無水酢酸
450 mL および 1-ベンジルオキシ-2-イソプロピルベンゼン 100.5
g を加えた後、トリフルオロ酢酸 37.5 mL を滴下し、4℃にて 24 時間撹
10 拌した。反応混合物を減圧濃縮し、残渣にメタノール 250 mL、10% 亜硫
酸水素ナトリウム水溶液 200 mL、2 M テトラフルオロホウ酸ナトリウム水
溶液 1250 mL を順次加え、2 時間撹拌した。沈殿物が凝集した後、上澄み
を除去した。残渣をヘキサンで懸濁させ、不溶物をろ取し、ヘキサンで洗浄後、
減圧下 40℃ で乾燥し、テトラフルオロホウ酸ビス(4-ベンジルオキシ-3-
イソプロピルフェニル) ヨードニウム 55.96 g を得た。

15 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.20 (12H, d, $J=6.9\text{Hz}$), 3.35 (2H, heptet, $J=6.9\text{Hz}$), 5.11 (4H, s), 6.95 (2H, d, $J=8.9\text{Hz}$), 7.26-7.53 (10H, m), 7.69 (2H, d, $J=2.4\text{Hz}$), 7.78 (2H, d, $J=2.4, 8.9\text{Hz}$)

(参考例 27)

20 参考例 26 と同様の方法により、以下の化合物を合成した。

テトラフルオロホウ酸ビス(3-アセチル-2,4-ジベンジルオキシフェニル) ヨードニウム

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.49 (6H, s), 4.98 (4H, s), 5.11 (4H, s), 6.73 (2H, d, $J=9.1\text{Hz}$), 7.31-7.45 (20H, m), 7.48 (2H, d, $J=9.1$
25 Hz)

テトラフルオロホウ酸ビス(4-ベンジルオキシ-5,6,7,8-テトラヒドロ-1-ナフチル) ヨードニウム

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.56-1.90 (8H, m), 2.56-2.90 (8H,

m), 5.08 (4H, s), 6.78 (2H, d, J=8.9Hz), 7.17-7.58 (10H, m), 7.73 (2H, d, J=8.9Hz)

(参考例 28)

- 5 1-ベンジルオキシ-4-(2,6-ジメチル-4-ニトロフェノキシ)-5,6,7,8-テトラヒドロナフタレン

2,6-ジメチル-4-ニトロフェノール 45mg、テトラフルオロホウ酸
ビス(4-ベンジルオキシ-5,6,7,8-テトラヒドロ-1-ナフチル)
ヨードニウム 200mg、銅粉末 54mg を室温にて塩化メチレン 10mL
10 に懸濁させ、攪拌下トリエチルアミン 0.1mL を加え、室温にて 4 日間攪拌
した。不溶物をろ去し、ろ液を減圧濃縮した。得られた残渣をシリカゲルカラ
ムクロマトグラフィー(溶出溶媒:ヘキサン-酢酸エチル)で精製し、1-ベ
ンジルオキシ-4-(2,6-ジメチル-4-ニトロフェノキシ)-5,6,
7,8-テトラヒドロナフタレン 64.4mg を得た。

- 15 $^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.70-1.94 (4H, m), 2.18 (6H, s), 2.68-2.95 (4H, m), 4.97 (2H, s), 5.94 (1H, d, J=8.8Hz), 6.48 (1H, d, J=8.8Hz), 7.20-7.50 (5H, m), 8.00 (2H, s)

(参考例 29)

- 20 参考例 28 と同様の方法により、以下の化合物を合成した。

4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-2,3,5-トリクロロニトロベンゼン

- $^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.22 (6H, d, J=6.9Hz), 3.39 (1H, h
eptet, J=6.9Hz), 5.03 (2H, s), 6.42 (1H, dd, J=3.1, 8.8Hz), 6.78 (1H,
25 d, J=8.8Hz), 6.89 (1H, d, J=3.1Hz), 7.29-7.57 (5H, m), 7.95 (1H, s)

4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-3,5-ジプロ
モニトロベンゼン

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.22 (6H, d, J=6.9Hz), 3.40 (1H, h

eptet, $J=6.9\text{Hz}$), 5.04 (2H, s), 6.43 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.80 (1H, d, $J=8.9\text{Hz}$), 6.86 (1H, d, $J=3.1\text{Hz}$), 7.32-7.46 (5H, m), 8.51 (2H, s)

4 - (4-ベンジルオキシ-3-イソプロピルフェノキシ) - 2, 3, 5-トリメチルニトロベンゼン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.20 (6H, d, $J=6.9\text{Hz}$), 2.14 (3H, s), 2.15 (3H, s), 2.41 (3H, s), 3.38 (1H, heptet, $J=6.9\text{Hz}$), 5.01 (2H, s), 6.28 (1H, dd, $J=3.1, 8.8\text{Hz}$), 6.74 (1H, d, $J=8.8\text{Hz}$), 6.79 (1H, d, $J=3.1\text{Hz}$), 7.28-7.47 (5H, m), 7.58 (1H, s)

10

1 - [2, 6-ジベンジルオキシ-3-(2, 6-ジメチル-4-ニトロフェノキシ) フェニル] エタノン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.25 (6H, s), 2.45 (3H, s), 5.00 (2H, s), 5.21 (2H, s), 6.23 (1H, d, $J=9.0\text{Hz}$), 6.50 (1H, d, $J=9.0\text{Hz}$), 7.

15 27-7.43 (8H, m), 7.43-7.47 (2H, m), 8.02 (2H, s)

1-ベンジルオキシ-4-(2, 3, 6-トリクロロ-4-ニトロフェノキシ) - 5, 6, 7, 8-テトラヒドロナフタレン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.77-1.88 (4H, m), 2.73-2.82 (2H, m), 2.87-2.93 (2H, m), 4.99 (2H, s), 6.04 (1H, d, $J=8.8\text{Hz}$), 6.53 (1H, d, $J=8.8\text{Hz}$), 7.28-7.44 (5H, m), 7.94 (1H, s)

20

3-クロロ-6-[5-(2, 6-ジメチル-4-ニトロフェノキシ) - 2-メトキシベンジル] ピリダジン

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.18 (6H, s), 3.77 (3H, s), 4.27 (2H, s), 6.51 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.75 (1H, d, $J=8.9\text{Hz}$), 6.78 (1H, d, $J=3.1\text{Hz}$), 7.30 (1H, d, $J=8.8\text{Hz}$), 7.33 (1H, d, $J=8.8\text{Hz}$), 7.99 (1H, s)

(参考例30)

1-〔6-ベンジルオキシ-3-(2,6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕エタノン

1-〔2,6-ジベンジルオキシ-3-(2,6-ジメチル-4-ニトロフェノキシ)フェニル〕エタノン 3.79 g にトリフルオロ酢酸/水/ジメチルスルフィド (7:3:1) 混合液 10 mL を加え、室温にて一晩攪拌した。反応混合物を減圧濃縮し、得られた残渣に水を加え、塩化メチレンで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムにて乾燥後、減圧濃縮し、得られた残渣にヘキサンを加え結晶化し、1-〔6-ベンジルオキシ-3-(2,6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕エタノン 1.81 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.24 (6H, s), 2.67 (3H, s), 5.07 (2H, s), 6.25 (1H, d, $J=9.0\text{Hz}$), 6.43 (1H, d, $J=9.0\text{Hz}$), 7.33-7.45 (5H, m), 8.00 (2H, s), 13.67 (1H, s)

(参考例31)

1-〔6-ベンジルオキシ-3-(2,6-ジメチル-4-ニトロフェノキシ)-2-メトキシフェニル〕エタノン

1-〔6-ベンジルオキシ-3-(2,6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕エタノン 1.81 g をテトラヒドロフラン 15 mL に溶かし、氷冷下炭酸セシウム 1.59 g を加え、ヨウ化メチル 0.56 mL を少しずつ滴下した。アルゴン雰囲気下室温にて一晩攪拌後、反応混合物を減圧濃縮し、得られた残渣に酢酸エチル 30 mL を加え 30 分間攪拌した。セライトろ過にて不溶物をろ去後、ろ液を減圧濃縮し、1-〔6-ベンジルオキシ-3-(2,6-ジメチル-4-ニトロフェノキシ)-2-メトキシフェニル〕エタノン 1.87 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.23 (6H, s), 2.57 (3H, s), 4.02 (3H, s), 5.00 (2H, s), 6.20 (1H, d, $J=9.0\text{Hz}$), 6.48 (1H, d, $J=9.0\text{Hz}$), 7.28-7.40 (5H, m), 8.02 (2H, s)

(参考例 3 2)

1-〔3-(4-アミノ-2, 6-ジメチルフェノキシ)-6-ベンジルオキシ-2-メトキシフェニル〕エタノン

- 5 1-〔6-ベンジルオキシ-3-(2, 6-ジメチル-4-ニトロフェノキシ)-2-メトキシフェニル〕エタノン 1.87 g を酢酸エチル 50 mL に懸濁し、5%白金-炭素触媒 200 mg を加え、室温にて水素雰囲気下常圧で 6 時間攪拌した。不溶物をろ去後、ろ液を減圧濃縮し、1-〔3-(4-アミノ-2, 6-ジメチルフェノキシ)-6-ベンジルオキシ-2-メトキシフェニル〕エタノンを 1.74 g 得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.12 (6H, s), 2.55 (3H, s), 4.00 (3H, s), 4.98 (2H, s), 6.18 (1H, d, $J=9.0\text{Hz}$), 6.45 (2H, brs), 6.47 (1H, d, $J=9.0\text{Hz}$), 7.26-7.39 (5H, m)

15 (参考例 3 3)

1-〔6-ベンジルオキシ-3-(4-ジベンジルアミノ-2, 6-ジメチルフェノキシ)-2-メトキシフェニル〕エタノン

- 1-〔3-(4-アミノ-2, 6-ジメチルフェノキシ)-6-ベンジルオキシ-2-メトキシフェニル〕エタノンを 1.74 g を N,N -ジメチルホルムアミド 30 mL に溶かし、ベンジルブロミド 1.62 mL、炭酸カリウム 6.14 g 及びよう化カリウム 226 mg を加え、アルゴン雰囲気下 80℃にて 7 時間攪拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: 酢酸エチル-ヘキサン) にて精製し、1-〔6-ベンジルオキシ-3-(4-ジベンジルアミノ-2, 6-ジメチルフェノキシ)-2-メトキシフェニル〕エタノン 1.35 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.01 (6H, s), 2.54 (3H, s), 4.00 (3H, s), 4.60 (4H, s), 4.97 (2H, s), 6.32 (1H, d, $J=9.0\text{Hz}$), 6.45 (1H,

d, $J=9.0\text{Hz}$), 6.47 (2H, s), 7.22-7.38 (16H, m)

(参考例 3 4)

参考例 3 3 と同様の方法により、以下の化合物を合成した。

5 N, N-ジベンジル-4-ヨード-3, 5-ジメチルアニリン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.34 (6H, s), 4.59 (4H, s), 6.52 (2H, s), 7.20-7.27 (6H, m), 7.27-7.35 (4H, m)

(参考例 3 5)

10 (4-ベンジルオキシ-3-イソプロピルフェニル) (4-ジベンジルアミノ-2, 6-ジメチルフェニル) メタノール

N, N-ジベンジル-4-ヨード-3, 5-ジメチルアニリン 659mg を乾燥テトラヒドロフラン 5mL に溶かし、 -100°C にて 1.6M *tert*-ブチルリチウムの *n*-ペンタン溶液 1.44mL を加えた。そのまま 10分

15 間攪拌後、4-ベンジルオキシ-3-イソプロピルベンズアルデヒド 392mg のテトラヒドロフラン 5mL 溶液を滴下した。そのまま 15 分間攪拌後、室温まで昇温した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を無水硫酸マグネシウムで乾燥後、減圧濃縮し、(4-ベンジルオキシ-3-イソプロピルフェニル) (4-ジベンジルアミノ-2, 6-ジメチルフェニル) メタノール 964mg を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.17-1.28 (6H, m), 2.00 (1H, d, $J=4.0\text{Hz}$), 2.16 (6H, s), 3.34-3.44 (1H, m), 4.61 (4H, s), 5.05 (2H, s), 6.22 (1H, d, $J=4.0\text{Hz}$), 6.44 (2H, s), 6.80 (1H, d, $J=8.4\text{Hz}$), 6.87-6.92 (1H, m), 7.22-7.46 (16H, m)

25

(参考例 3 6)

参考例 3 5 と同様の方法により、以下の化合物を合成した。

(4-ジベンジルアミノ-2, 6-ジメチルフェニル) (4-メトキシフェニル) メタノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.99 (1H, d, $J=3.9\text{Hz}$), 2.16 (6H, s), 3.79 (3H, s), 4.61 (4H, brs), 6.21 (1H, d, $J=3.9\text{Hz}$), 6.43 (2H, s), 6.82-6.86 (2H, m), 7.18-7.36 (12H, m)

- 5 [4-ベンジルオキシ-3-(4-フルオロフェノキシ)フェニル] (4-ジベンジルアミノ-2, 6-ジメチルフェニル) メタノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.96 (1H, d, $J=3.8\text{Hz}$), 2.14 (6H, s), 4.60 (4H, s), 5.04 (2H, s), 6.17 (1H, d, $J=3.8\text{Hz}$), 6.40 (2H, s), 6.82-6.88 (2H, m), 6.90-7.00 (4H, m), 7.06 (1H, d, $J=1.1\text{Hz}$), 7.14-7.38 (15H, m)

10

[4-ベンジルオキシ-3-(4-テトラヒドロピラニルオキシ)フェニル] (4-ジベンジルアミノ-2, 6-ジメチルフェニル) メタノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.73-1.83 (2H, m), 1.89-1.96 (2H, m), 2.12 (1H, brs), 2.13 (6H, s), 3.43-3.50 (2H, m), 3.93-3.99 (2H, m), 4.39-4.44 (1H, m), 4.60 (4H, s), 5.07 (2H, s), 6.16 (1H, d, $J=3.2\text{Hz}$), 6.42 (2H, s), 6.72-6.76 (1H, m), 6.84-6.86 (1H, m), 7.01-7.03 (1H, m), 7.22-7.37 (13H, m), 7.39-7.44 (2H, m)

15

- 20 (参考例 37)

4-[4-ベンジルオキシ-3-(4-フルオロフェノキシ)フェノキシ]-3, 5-ジメチルニトロベンゼン

4-ベンジルオキシ-3-(4-フルオロフェノキシ)フェノール 141mg と 4-クロロ-3, 5-ジメチルニトロベンゼン 101mg を N, N-ジメチルアセトアミド 3mL に溶かし、炭酸カリウム 188mg を加え、アルゴン雰囲気下 150℃ にて一晚攪拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー (展開溶媒: ヘキサン-酢酸エチル) にて精製し、4-[4-ベンジルオキシ-3-

25

(4-フルオロフェノキシ)フェノキシ]-3, 5-ジメチルニトロベンゼン
127mgを得た。

¹H-NMR (CDCl₃) δ ppm: 2.20 (6H, s), 5.01 (2H, s), 6.36
(1H, dd, J=3.0, 9.0Hz), 6.52 (1H, d, J=3.0Hz), 6.85-6.95 (3H, m), 6.95
5 -7.02 (2H, m), 7.17-7.20 (2H, m), 7.23-7.31 (3H, m), 7.98 (2H, s)

(参考例38)

参考例37と同様の方法により、以下の化合物を合成した。

4-[4-ベンジルオキシ-3-(4-テトラヒドロピラニルオキシ)フェノ
10 キシ]-3, 5-ジメチルニトロベンゼン

¹H-NMR (CDCl₃) δ ppm: 1.75-1.85 (2H, m), 1.95-2.00 (2H, m),
2.21 (6H, s), 3.50-3.56 (2H, m), 3.95-4.02 (2H, m), 4.42-4.48 (1H, m),
5.04 (2H, s), 6.12 (1H, dd, J=3.0, 8.8Hz), 6.55 (1H, d, J=3.0Hz), 6.8
1 (1H, d, J=8.8Hz), 7.28-7.44 (5H, m), 7.99 (2H, s)

15

(参考例39)

(4-ベンジルオキシ-3-イソプロピルフェニル) (4-ジベンジルアミノ
-2, 6-ジメチルフェニル) メタノン

(4-ベンジルオキシ-3-イソプロピルフェニル) (4-ジベンジルアミ
20 ノー2, 6-ジメチルフェニル) メタノール858mgを塩化メチレン10m
Lに溶かし、二酸化マンガン5.36gを加え、室温にて3日間激しく攪拌し
た。不溶物をろ去後、ろ液を減圧濃縮し、(4-ベンジルオキシ-3-イソプ
ロピルフェニル) (4-ジベンジルアミノ-2, 6-ジメチルフェニル) メタ
ノン736mgを得た。

25 ¹H-NMR (CDCl₃) δ ppm: 1.25 (6H, d, J=6.9Hz), 2.02 (6H,
s), 3.39 (1H, heptet, J=6.9Hz), 4.64 (4H, s), 5.13 (2H, s), 6.44 (2H,
s), 6.85 (1H, d, J=8.6Hz), 7.23-7.45 (15H, m), 7.50 (1H, dd, J=2.0, 8.
6Hz), 7.91 (1H, d, J=2.0Hz)

(考例 4 0)

6-〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-メトキシベン
ジル〕-2H-ピリダジン-3-オン

3-クロロ-6-〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-
5-メトキシベンジル〕ピリダジン 1. 37 g に酢酸ナトリウム 50 mg と酢酸
10 mL を加え、アルゴン雰囲気下 2 時間加熱還流した。反応混合物に水 10
mL を加え、30 分間攪拌した後、塩化メチレンで抽出した。有機層を 1 mol/L 水酸化ナトリウム水溶液、水、飽和食塩水で順次洗浄し、無水硫酸マグ
ネシウムで乾燥後、減圧濃縮し、6-〔5-(2, 6-ジメチル-4-ニトロ
10-フェノキシ)-2-メトキシベンジル〕-2H-ピリダジン-3-オン 29
0 mg を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.19 (6H, s), 3.78 (3H, s), 3.86
(2H, s), 6.50 (1H, dd, $J=2.8, 8.8\text{Hz}$), 6.68 (1H, d, $J=2.8\text{Hz}$), 6.75 (1H,
d, $J=8.8\text{Hz}$), 6.83-6.87 (1H, m), 7.14-7.18 (1H, m), 8.00 (2H, s)

15

(参考例 4 1)

6-〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシベン
ンジル〕-2H-ピリダジン-3-オン

6-〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-メトキシベン
20-ンジル〕-2H-ピリダジン-3-オン 290 mg を酢酸 10 mL に溶かし、
48% 臭化水素酸 10 mL を加え、アルゴン雰囲気下 2 日間加熱還流した。反
応混合物を水で希釈し、塩化メチレンで抽出した。有機層を水、水と飽和食塩
水の混合溶液で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、6
-〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシベン
25-ンジル〕-2H-ピリダジン-3-オンを 139 mg 得た。

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.19 (6H, s), 3.86 (2H,
s), 6.44 (1H, dd, $J=2.0, 8.8\text{Hz}$), 6.61 (1H, d, $J=3.0\text{Hz}$), 6.73 (1H, d,
 $J=8.8\text{Hz}$), 6.86-6.92 (1H, m), 7.25-7.32 (1H, m), 7.99 (2H, s)

(参考例 4 2)

5- (2, 6-ジメチル-4-ニトロフェノキシ) -2-ヒドロキシベンズアルデヒド

5- (2, 6-ジメチル-4-ニトロフェノキシ) -2-メトキシベンズアルデヒド 5.56 g を塩化メチレン 400 mL に溶解後、氷冷撹拌下 1 M 三塩化ホウ素の塩化メチレン溶液 95 mL を滴下し、室温にて 24 時間撹拌した。氷冷撹拌下、反応混合物にメタノールを 10 mL 滴下し、希塩酸を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、5- (2, 6-ジメチル-4-ニトロフェノキシ) -2-ヒドロキシベンズアルデヒド 4.51 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.23 (6H, s), 6.77 (1H, d, $J=3.0\text{Hz}$), 6.98 (1H, d, $J=9.1\text{Hz}$), 7.10 (1H, dd, $J=9.1, 3.0\text{Hz}$), 8.04 (2H, s), 9.76 (1H, s), 10.72 (1H, s)

15 (参考例 4 3)

2-ベンジルオキシ-5- (2, 6-ジメチル-4-ニトロフェノキシ) ベンズアルデヒド

5- (2, 6-ジメチル-4-ニトロフェノキシ) -2-ヒドロキシベンズアルデヒド 4.85 g と炭酸カリウム 2.33 g を N, N-ジメチルホルムアミド 25 mL に懸濁し、氷冷下撹拌した。反応混合物にベンジルブロミド 2.40 mL を滴下し、室温で 24 時間撹拌した。反応混合物に希塩酸を加え酸性とし、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチル) で精製し、2-ベンジルオキシ-5- (2, 6-ジメチル-4-ニトロフェノキシ) ベンズアルデヒド 6.20 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.19 (6H, s), 5.17 (2H, s), 6.97-7.15 (3H, m), 7.30-7.50 (5H, m), 8.01 (2H, s), 10.47 (1H, s)

(参考例 4 4)

〔2-ベンジルオキシ-5-(2, 6-ジメチル-4-ニトロフェノキシ)フェニル〕メタノール

氷冷下水素化ホウ素ナトリウム 662mg をテトラヒドロフラン 20mL
5 に懸濁し、2-ベンジルオキシ-5-(2, 6-ジメチル-4-ニトロフェノキシ)ベンズアルデヒド 6.6g を加えた後、メタノールを 5mL 滴下し、室温で 6 時間攪拌した。反応混合物に希塩酸を加え酸性とし、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、〔2-ベンジルオキシ-5-(2, 6-ジメチル-4-ニトロフェノキシ)フェニル〕メタノール 6.50g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (6H, s), 4.67 (2H, s), 5.06 (2H, s), 6.55 (1H, dd, $J=3.1, 8.8\text{Hz}$), 6.77-6.88 (2H, m), 7.31-7.47 (5H, m), 8.00 (2H, s)

15 (参考例 4 5)

参考例 4 4 と同様の方法により、以下の化合物を合成した。

〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-メトキシフェニル〕メタノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (6H, s), 2.28 (1H, t, $J=5.3\text{Hz}$), 3.83 (3H, s), 4.63 (2H, d, $J=5.3\text{Hz}$), 6.56 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.76 (1H, d, $J=8.9\text{Hz}$), 6.78 (1H, d, $J=3.1\text{Hz}$), 8.01 (2H, s)

(参考例 4 6)

2-ベンジルオキシ-5-(2, 6-ジメチル-4-ニトロフェノキシ)ベン
25 ジルクロリド

〔2-ベンジルオキシ-5-(2, 6-ジメチル-4-ニトロフェノキシ)フェニル〕メタノール 950mg をジエチルエーテル 30mL に溶解後、氷冷攪拌下塩化チオニル 1mL を滴下し、室温にて 6 時間攪拌した。反応混合物を減圧濃縮し、残渣に水を加え、ジエチルエーテルで抽出した。有機層を飽和食

塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、2-ベンジルオキシ-5-(2,6-ジメチル-4-ニトロフェノキシ)ベンジルクロリド845mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (6H, s), 4.62 (2H, s), 5.08 (2H, s), 6.60 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.79-6.89 (2H, m), 7.30-7.47 (5H, m), 8.01 (2H, s)

(参考例47)

参考例46と同様の方法により、以下の化合物を合成した。

10 5-(2,6-ジメチル-4-ニトロフェノキシ)-2-メトキシベンジルクロリド

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (6H, s), 3.84 (3H, s), 4.58 (2H, s), 6.62 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.78 (1H, d, $J=8.9\text{Hz}$), 6.83 (1H, d, $J=3.1\text{Hz}$), 8.01 (2H, s)

15

(参考例48)

〔2-ベンジルオキシ-5-(2,6-ジメチル-4-ニトロフェノキシ)ベンジル〕トリフェニルホスホニウムクロリド

2-ベンジルオキシ-5-(2,6-ジメチル-4-ニトロフェノキシ)ベンジルクロリド5.22gとトリフェニルホスフィン6.0gをトルエン100mLに懸濁させ、12時間加熱還流した。放冷後、析出物をろ取し、ジエチルエーテルで洗浄して、〔2-ベンジルオキシ-5-(2,6-ジメチル-4-ニトロフェノキシ)ベンジル〕トリフェニルホスホニウムクロリド6.47gを得た。

25 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 1.95 (6H, s), 4.60 (2H, s), 4.93 (2H, d, $J=14.9\text{Hz}$), 6.23-6.33 (1H, m), 6.89-7.02 (2H, m), 7.10-7.18 (2H, m), 7.27-7.38 (3H, m), 7.46-7.70 (12H, m), 7.79-7.92 (3H, m), 8.04 (2H, s)

(参考例 49)

参考例 48 と同様の方法により、以下の化合物を合成した。

[5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-メトキシベンジル] トリフェニルホスホニウムクロリド

- 5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.03 (6H, s), 3.19 (3H, s), 5.47 (2H, d, $J=14.4\text{Hz}$), 6.50-6.54 (1H, m), 6.64-6.67 (1H, m), 6.70-6.73 (1H, m), 7.56-7.62 (6H, m), 7.67-7.78 (9H, m), 7.90 (2H, s)

(参考例 50)

- 10 4-[2-ベンジルオキシ-5-(2, 6-ジメチル-4-ニトロフェノキシ)ベンジリデン]テトラヒドロピラン

[2-ベンジルオキシ-5-(2, 6-ジメチル-4-ニトロフェノキシ)ベンジル] トリフェニルホスホニウムクロリド 500mg をジメチルスルホキシド 50mL に懸濁させ、室温にて水素化ナトリウム 30mg を加え、15分
 15 間攪拌した。反応混合物にテトラヒドロピラン-4-オン 0.1mL 加え、室温で6時間攪拌した。反応混合物に希塩酸を滴下し充分酸性とし、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：ヘキサン-酢酸エチル）で精製し、4-[2-ベンジルオキシ-5-(2,
 20 6-ジメチル-4-ニトロフェノキシ)ベンジリデン]テトラヒドロピラン 202mg を得た。

- $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (6H, s), 2.31-2.44 (4H, m), 3.61 (2H, t, $J=5.5\text{Hz}$), 3.75 (2H, t, $J=5.5\text{Hz}$), 5.03 (2H, s), 6.33 (1H, s), 6.47 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.60 (1H, d, $J=3.1\text{Hz}$), 6.80 (1H, d, $J=8.9\text{Hz}$), 7.26-7.48 (5H, m), 8.00 (2H, s)
 25

(参考例 51)

参考例 50 と同様の方法により、以下の化合物を合成した。

4-[4-メトキシ-3-(2-メトキシステリル)フェノキシ]-3, 5-

ジメチルニトロベンゼン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.00 (6H, s), 3.69 (3H, s), 3.83 (3H, s), 6.17 (1H, d, $J=3.0\text{Hz}$), 6.63-6.75 (5H, m), 6.80-6.84 (1H, m), 6.93-6.98 (1H, m), 7.11-7.16 (1H, m), 7.81 (2H, s)

5

(参考例 5 2)

4- (4-アミノ-2, 6-ジメチルフェノキシ) -2- [2- (3-テトラヒドロフラニル) エチル] フェノール

- フルフリルトリフェニルホスホニウムブロミド 376mg をテトラヒドロフ
 10 ラン 20mL に懸濁させ、室温にて *tert*-ブトキシカリウム 112mg を
 加え、15 分間攪拌した。反応混合物に 2-ベンジルオキシ-5- (2, 6-
 ジメチル-4-ニトロフェノキシ) ベンズアルデヒド 250mg を加え、室温
 で 6 時間攪拌した。反応混合物に希塩酸を滴下し充分酸性とし、酢酸エチルで
 抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減
 15 圧濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー (溶出溶
 媒: ヘキサン-酢酸エチル) で精製し、オレフィン体 205mg を得た。得ら
 れたオレフィン体をエタノール 10mL、酢酸エチル 2mL の混合溶媒に溶解
 し、氷冷下 10% パラジウム炭素触媒 100mg を加え、室温にて水素雰囲気
 下常圧で 24 時間攪拌した。不溶物をろ去後、ろ液を減圧濃縮し、得られた残
 20 渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチ
 ル) で精製して、4- (4-アミノ-2, 6-ジメチルフェノキシ) -2-
 [2- (3-テトラヒドロフラニル) エチル] フェノール 120mg を得た。
 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.48-1.74 (3H, m), 1.98-2.12 (7H, m), 2.14-2.27 (1H, m), 2.48-2.66 (2H, m), 3.33-3.42 (1H, m), 3.53 (2H, brs), 3.69-3.79 (1H, m), 3.81-3.96 (2H, m), 5.05-5.30 (1H, m), 6.32 (1H, dd, $J=2.8, 8.7\text{Hz}$), 6.39-6.52 (3H, m), 6.60 (1H, d, $J=2.8\text{Hz}$)

25

(参考例 5 3)

4- (4-ベンジルオキシ-3-イソプロピルフェニルスルファニル) -3,

88
262

5-ジメチルアニリン

- 2, 6-ジメチル-4-ニトロベンゼンチオール 6.0 g、テトラフルオ
ロホウ酸ビス(4-ベンジルオキシ-3-イソプロピルフェニル) ヨードニウ
ム28.3 g、銅粉末2.71 gを室温にて塩化メチレン100 mLに懸濁さ
5 せ、攪拌下トリエチルアミン6 mLを加え、室温にて5日間攪拌した。不溶物
をろ去し、ろ液を減圧濃縮した。得られた残渣を酢酸エチル300 mLに溶解
後、1 mol/L塩酸、1 mol/L水酸化ナトリウム水溶液、飽和炭酸水素
ナトリウム水溶液、飽和食塩水で順次洗浄し、有機層を無水硫酸マグネシウム
で乾燥後、減圧濃縮し、スルファニル体を得た。得られたスルファニル体をエ
10 タノール100 mLと酢酸エチル20 mLの混合溶媒に溶解し、氷冷下10%
パラジウム炭素触媒2.0 gを数回に分けて加え、室温にて水素雰囲気下常圧
で24時間攪拌した。不溶物をろ去後、ろ液を減圧濃縮し、得られた残渣を酢
酸エチルに溶解後、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し
た。有機層を無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシ
15 リカゲルカラムクロマトグラフィー(溶出溶媒:ヘキサン-酢酸エチル)で精
製し、4-(4-ベンジルオキシ-3-イソプロピルフェニルスルファニル)
-3, 5-ジメチルアニリン3.71 gを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.16 (6H, d, $J=6.9\text{Hz}$), 2.34 (6H,
s), 3.32 (1H, heptet, $J=6.9\text{Hz}$), 3.67 (2H, brs), 4.98 (2H, s), 6.49 (2H,
20 s), 6.57 (1H, dd, $J=2.0, 8.5\text{Hz}$), 6.70 (1H, d, $J=8.5\text{Hz}$), 6.96 (1H, d,
 $J=2.0\text{Hz}$), 7.26-7.50 (5H, m)

(参考例54)

- 2-シクロヘキシル-1-[5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル] エタノン、および2-シクロヘキシル-1-
25 [5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-メトキシフェニル] エタノン

3, 5-ジメチル-4-(4-メトキシフェノキシ)ニトロベンゼン5.0
gとシクロヘキシルアセチルクロリド7.35 gを塩化メチレン25 mLに溶

解し、氷冷撹拌下四塩化チタン10 mL滴下した。アルゴン雰囲気下室温にて20時間撹拌した後、反応混合物に氷水をゆっくり加え、酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：ヘキサン-酢酸エチル）で精製し、先に溶出したフラクションより0.69 gの2-シクロヘキシル-1-〔5-（2,6-ジメチル-4-ニトロフェノキシ）-2-ヒドロキシフェニル〕エタノンを得、後に溶出したフラクションより2.74 gの2-シクロヘキシル-1-〔5-（2,6-ジメチル-4-ニトロフェノキシ）-2-メトキシフェニル〕エタノンを得た。

2-シクロヘキシル-1-〔5-（2,6-ジメチル-4-ニトロフェノキシ）-2-ヒドロキシフェニル〕エタノン

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 0.77-1.35 (5H, m), 1.60-1.95 (6H, m), 2.23 (6H, s), 2.67 (2H, d, $J=6.7\text{Hz}$), 6.84-7.00 (2H, m), 7.07 (1H, d, $J=2.6\text{Hz}$), 8.04 (2H, s), 12.07 (1H, s)

2-シクロヘキシル-1-〔5-（2,6-ジメチル-4-ニトロフェノキシ）-2-メトキシフェニル〕エタノン

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 0.88-1.35 (5H, m), 1.45-2.00 (6H, m), 2.20 (6H, s), 2.81 (2H, d, $J=6.7\text{Hz}$), 3.86 (3H, s), 6.82 (1H, dd, $J=3.1, 9.0\text{Hz}$), 6.87 (1H, d, $J=9.0\text{Hz}$), 7.01 (1H, d, $J=3.1\text{Hz}$), 8.00 (2H, s)

(参考例55)

参考例54と同様の方法により、以下の化合物を合成した。

〔5-（2,6-ジメチル-4-ニトロフェノキシ）-2-メトキシフェニル〕（2-メトキシフェニル）メタノン

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 2.22 (6H, s), 3.60 (3H, s), 3.66 (3H, s), 6.77-6.84 (2H, m), 6.88-6.93 (2H, m), 6.96-7.03 (1H, m), 7.40

-7.47 (1H, m), 7.51-7.55 (1H, m), 7.99 (2H, s)

(参考例56)

〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕 (2-メトキシフェニル) メタノン、および〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕 (2-ヒドロキシフェニル) メタノン

〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-メトキシフェニル〕 (2-メトキシフェニル) メタノン1.01gを塩化メチレン30mLに溶かし、氷冷下1M三塩化ホウ素の塩化メチレン溶液12mLを滴下した後、室温にて一晩攪拌した。反応混合物を氷水200mLと塩化メチレン50mLの混合液に加え、室温にて一晩攪拌した。有機層を分離し、水層を塩化メチレンで抽出した。有機層を合わせ、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮した。得られた残渣

をシリカゲルカラムクロマトグラフィー (溶出溶媒：酢酸エチル-ヘキサン) にて精製し、〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕 (2-メトキシフェニル) メタノンと〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕 (2-ヒドロキシフェニル) メタノンの混合物 (38:62) 148mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.23 (6H, s), 3.73 (3H, s), 6.72 (1H, d, $J=3.0\text{Hz}$), 6.78-6.86 (2H, m), 6.87-7.05 (2H, m), 7.27-7.32 (1H, m), 7.43-7.53 (1H, m), 8.00 (2H, s), 11.99 (1H, s)

25

〔5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル〕 (2-ヒドロキシフェニル) メタノン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.23 (6H, s), 6.77-6.92 (2H, m), 6.95-7.06 (3H, m), 7.39-7.54 (2H, m), 8.00 (2H, s), 10.08 (1H, s), 10.60

(1H, s)

(参考例 57)

2-シクロヘキシル-1-[5-(2,6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル] エタノン

2-シクロヘキシル-1-[5-(2,6-ジメチル-4-ニトロフェノキシ)-2-メトキシフェニル] エタノン 2.62 g を塩化メチレン 100 mL に溶解後、氷冷撹拌下 1 M 三塩化ホウ素の塩化メチレン溶液 13.2 mL を滴下し、室温にて 24 時間撹拌した。氷冷撹拌下反応混合物にメタノールを 10 mL 滴下後、希塩酸を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、2-シクロヘキシル-1-[5-(2,6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル] エタノン 2.45 g を得た。

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 0.77-1.35 (6H, m), 1.60-1.95 (6H, m), 2.23 (6H, s), 2.67 (2H, d, J=6.7Hz), 6.84-7.00 (2H, m), 7.07 (1H, d, J=2.6Hz), 8.04 (2H, s), 12.07 (1H, s)

(参考例 58)

2-(2-シクロヘキシルエチル)-4-(2,6-ジメチル-4-ニトロフェノキシ) フェノール

2-シクロヘキシル-1-[5-(2,6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル] エタノン 2.60 g を塩化メチレン 50 mL に溶解後、室温撹拌下トリフルオロ酢酸 10 mL およびトリエチルシラン 5.5 mL を滴下し、室温にて 24 時間撹拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチル) で精製し、2-(2-シクロヘキシルエチル)-4-(2,6-ジメチル-4-ニトロフェノキシ) フェノール 2.0 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.80-1.01 (2H, m), 1.07-1.35 (4H, m), 1.37-1.50 (2H, m), 1.57-1.80 (5H, m), 2.21 (6H, s), 2.45-2.60 (2H, m), 4.56 (1H, s), 6.39 (1H, dd, $J=3.0, 8.6\text{Hz}$), 6.53 (1H, d, $J=3.0\text{Hz}$), 6.65 (1H, d, $J=8.6\text{Hz}$), 8.00 (2H, s)

5

(参考例 59)

参考例 58 と同様の方法により、以下の化合物を合成した。

4- (2, 6-ジメチル-4-ニトロフェノキシ) -2- [2- (4-テトラヒドロピラニル) エチル] フェノール

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.27-1.38 (2H, m), 1.47-1.56 (3H, m), 1.61-1.68 (2H, m), 2.21 (6H, s), 2.53-2.60 (2H, m), 3.32-3.40 (2H, m), 3.93-3.99 (2H, m), 4.62 (1H, s), 6.38 (1H, dd, $J=3.0, 8.6\text{Hz}$), 6.56 (1H, d, $J=3.0\text{Hz}$), 6.63 (1H, d, $J=8.6\text{Hz}$), 8.00 (2H, s)

15 (参考例 60)

2- [6-ベンジルオキシ-3- (4-ジベンジルアミノ-2, 6-ジメチルフェノキシ) -2-メトキシフェニル] プロパン-2-オール

1- [6-ベンジルオキシ-3- (4-ジベンジルアミノ-2, 6-ジメチルフェノキシ) -2-メトキシフェニル] エタノン 1.32 g をテトラヒドロ
 20 フラン 100 mL に溶かし、アルゴン雰囲気下 -78°C にて 1.14 M メチルリチウムのジエチルエーテル溶液 4.05 mL を数回に分けて加えた。そのまま 30 分間攪拌後、反応混合物をゆっくり室温まで昇温した。反応混合物に飽和塩化アンモニウム水溶液 40 mL を加え、10 分間攪拌した後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、
 25 減圧濃縮し、2- [6-ベンジルオキシ-3- (4-ジベンジルアミノ-2, 6-ジメチルフェノキシ) -2-メトキシフェニル] プロパン-2-オール 1.37 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.72 (6H, s), 2.02 (6H, s), 4.03 (3H, s), 4.61 (4H, s), 5.00 (2H, s), 6.25 (1H, d, $J=9.1\text{Hz}$), 6.47 (2H,

s), 6.53 (1H, d, J=9.1Hz), 7.22-7.42 (15H, m)

(参考例 6 1)

N, N-ジベンジル-〔4-(4-ベンジルオキシ-3-イソプロペニル-2-
6-メトキシフェノキシ)-3, 5-ジメチル〕アニリン

2-〔6-ベンジルオキシ-3-(4-ジベンジルアミノ-2, 6-ジメチル
ルフェノキシ)-2-メトキシフェニル〕プロパン-2-オール 1.37 g を
塩化メチレン 20 mL に溶かし、濃塩酸 10 mL を加え、激しく 20 分間撹拌
した。反応混合物を分液し、水層を塩化メチレンで抽出した。有機層を合わせ、
10 2 mol/L 水酸化ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マ
グネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲルカラムクロマト
グラフィー（溶出溶媒：酢酸エチル-ヘキサン）にて精製し、N, N-ジベン
ジル-〔4-(4-ベンジルオキシ-3-イソプロペニル-2-メトキシフェ
ノキシ)-3, 5-ジメチル〕アニリン 898 mg を得た。

¹H-NMR (CDCl₃) δ ppm: 2.03 (6H, s), 2.12 (3H, s), 3.95
15 (3H, s), 4.60 (4H, s), 4.97 (2H, s), 4.99 (1H, s), 5.35 (1H, s), 6.22
(1H, d, J=9.0Hz), 6.44 (1H, d, J=9.0Hz), 6.47 (2H, s), 7.23-7.44 (15H,
m)

(参考例 6 2)

4-(2, 6-ジメチル-4-ニトロフェノキシ)フェノール

4-(4-メトキシフェノキシ)-3, 5-ジメチルニトロベンゼン 20
3 mg を塩化メチレン 25 mL に溶かし、-78℃にて 1 M 三臭化ホウ素の塩
化メチレン溶液 150 μL を滴下した後、室温にて一晩撹拌した。反応混合物
25 を氷水 50 mL に加え、1 時間撹拌した後、反応混合物を塩化メチレンで抽出
した。有機層を飽和炭酸水素ナトリウム水溶液と飽和食塩水の 1:1 混合溶液
で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣を塩化
メチレンとヘキサンにて結晶化し、4-(2, 6-ジメチル-4-ニトロフェ
ノキシ)フェノール 84 mg を得た。

n65

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (6H, s), 4.49 (1H, s), 6.58-6.65 (2H, m), 6.72-6.78 (2H, m), 8.00 (2H, s)

(参考例 6 3)

- 5 3-[3-[4-(2, 6-ジメチル-4-ニトロフェノキシ) フェノキシメチル] フェニル] アクリル酸メチル

4-(2, 6-ジメチル-4-ニトロフェノキシ) フェノール 400mg と
3-ブロモ-3-(3-ブロモメチルフェニル) プロピオン酸メチル 514mg
をアセトン 40mL に溶かし、炭酸カリウム 700mg を加え、3日間加熱
10 還流した。反応混合物を減圧濃縮し、得られた残渣に水を加え、酢酸エチルで
抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減
圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒:
酢酸エチル-ヘキサン) にて精製し、3-[3-[4-(2, 6-ジメチル-
4-ニトロフェノキシ) フェノキシメチル] フェニル] アクリル酸メチル 60
15 4mg を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (6H, s), 3.81 (3H, s), 5.02
(2H, s), 6.48 (1H, d, $J=16.0\text{Hz}$), 6.65-6.80 (2H, m), 6.85-6.90 (2H, m),
7.37-7.50 (3H, m), 7.57 (1H, brs), 7.70 (1H, d, $J=16.0\text{Hz}$), 8.00 (2H,
s)

20

(参考例 6 4)

- 3-[3-[5-(2, 6-ジメチル-4-ニトロフェノキシ) -2-ヒドロ
キシベンジル] フェニル] アクリル酸メチル

3-[3-[4-(2, 6-ジメチル-4-ニトロフェノキシ) フェノキシ
25 メチル] フェニル] アクリル酸メチル 600mg にトリフルオロ酢酸 4mL を
加え、一晩加熱還流した。反応混合物に飽和炭酸水素ナトリウム水溶液と酢酸
エチルを加え、室温にて1時間攪拌した。反応混合物を分液し、水層を酢酸エ
チルで抽出した。有機層を合わせ、飽和食塩水で洗浄し、無水硫酸マグネシウ
ムで乾燥後、減圧濃縮した。得られた残渣をシリカゲルカラムクロマトグラフ

ィー（溶出溶媒：酢酸エチル－ヘキサン）にて精製し、3－〔3－〔5－（2，6－ジメチル－4－ニトロフェノキシ）－2－ヒドロキシベンジル〕フェニル〕アクリル酸メチル204mgを得た。

¹H-NMR (CDCl₃) δ ppm: 2.19 (6H, s), 3.81 (3H, s), 3.94
5 (2H, s), 6.38 (1H, d, J=16.0Hz), 6.45 (1H, dd, J=3.0, 8.7Hz), 6.56 (1H, d, J=3.0Hz), 6.68 (1H, d, J=8.7Hz), 7.18-7.40 (4H, m), 7.64 (1H, d, J=16.0Hz), 7.98 (2H, s)

（考例65）

10 3－〔3－〔5－（4－アミノ－2，6－ジメチルフェノキシ）－2－ヒドロキシベンジル〕フェニル〕プロピオン酸

3－〔3－〔5－（2，6－ジメチル－4－ニトロフェノキシ）－2－ヒドロキシベンジル〕フェニル〕アクリル酸メチル204mgをテトラヒドロフラン30mLに溶かし、2mol/L水酸化ナトリウム水溶液2mLを加え、アルゴン雰囲気下50℃にて一晩撹拌した。反応混合物を減圧濃縮し、得られた
15 残渣に2mol/L塩酸を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、3－〔3－〔5－（2，6－ジメチル－4－ニトロフェノキシ）－2－ヒドロキシベンジル〕フェニル〕アクリル酸198mgを得た。得られた3－〔3－〔5－（2，6－ジメチル－4－ニトロフェノキシ）－2－ヒドロキシベンジル〕フェニル〕ア
20 クリル酸を用い、下記の参考例66と同様の方法により、3－〔3－〔5－（4－アミノ－2，6－ジメチルフェノキシ）－2－ヒドロキシベンジル〕フェニル〕プロピオン酸を合成した。

¹H-NMR (CDCl₃) δ ppm: 2.00 (6H, s), 2.57 (2H, t, J=7.8H
25 z), 2.88 (2H, t, J=7.8Hz), 3.87 (2H, s), 6.42 (2H, s), 6.43-6.48 (2H, m), 6.66 (1H, d, J=8.7Hz), 7.00-7.05 (3H, m), 7.15-7.19 (1H, m)

（参考例66）

4－（4－アミノ－2，6－ジメチルフェノキシ）－2－（4－テトラヒドロ

ピラニルメチル) フェノール

4-〔2-ベンジルオキシ-5-(2,6-ジメチル-4-ニトロフェノキシ)ベンジリデン〕テトラヒドロピラン202mgをエタノール10mL、酢酸エチル2mLの混合溶媒に溶解し、氷冷下10%パラジウム炭素触媒50mgを数回に分けて加え、室温にて水素雰囲気下常圧で24時間攪拌した。不溶物をろ去後、ろ液を減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒:ヘキサン-酢酸エチル)で精製し、4-(4-アミノ-2,6-ジメチルフェノキシ)-2-(4-テトラヒドロピラニルメチル)フェノール119mgを得た。

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.26-1.41 (2H, m), 1.49-1.61 (2H, m), 1.74-1.88 (1H, m), 2.03 (6H, s), 2.42-2.52 (2H, m), 3.26-3.40 (2H, m), 3.55 (2H, brs), 3.89-4.00 (2H, m), 5.30 (1H, brs), 6.31 (1H, dd, $J=3.0, 8.6\text{Hz}$), 6.39-6.48 (3H, m), 6.56 (1H, d, $J=3.0\text{Hz}$)

15 (参考例67)

参考例66と同様の方法により、以下の化合物を合成した。

1-〔5-(4-アミノ-2,6-ジメチルフェノキシ)-2-ヒドロキシフェニル]-2-シクロヘキシルエタノン

20 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.76-1.38 (5H, m), 1.45-1.95 (6H, m), 2.04 (6H, s), 2.67 (2H, d, $J=6.7\text{Hz}$), 3.54 (2H, brs), 6.44 (2H, s), 6.87 (1H, d, $J=9.0\text{Hz}$), 6.94 (1H, dd, $J=2.9, 9.0\text{Hz}$), 7.07 (1H, d, $J=2.9\text{Hz}$), 12.00 (1H, s)

25 4-(4-アミノ-2,6-ジメチルフェノキシ)-2-(2-シクロヘキシルエチル)フェノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.85-0.98 (2H, m), 1.08-1.33 (4H, m), 1.40-1.50 (2H, m), 1.59-1.81 (5H, m), 2.03 (6H, s), 2.48-2.58 (2H, m), 3.50 (2H, brs), 4.52 (1H, brs), 6.38 (1H, dd, $J=3.1, 8.6\text{Hz}$), 6.42 (2H, s), 6.56 (1H, d, $J=8.6\text{Hz}$), 6.58 (1H, d, $J=3.1\text{Hz}$)

4- (4-アミノ-2, 6-ジメチルフェノキシ) -2-イソプロピル-3-
メトキシフェノール

¹H-NMR (CDCl₃+CD₃OD) δ ppm: 1.39 (6H, d, J=7.1Hz),
5 2.05 (6H, s), 3.55 (1H, heptet, J=7.1Hz), 3.96 (3H, s), 6.02 (1H, d, J
=8.8Hz), 6.24 (1H, d, J=8.8Hz), 6.47 (2H, s)

4- [4-メトキシ-3- [2- (2-メトキシフェニル) エチル] フェノキ
シ] -3, 5-ジメチルアニリン

10 ¹H-NMR (CDCl₃) δ ppm: 2.01 (6H, s), 2.80-2.90 (4H, m), 3.
48 (2H, brs), 3.75 (3H, s), 3.80 (3H, s), 6.41 (2H, s), 6.44 (1H, dd,
J=3.1, 8.8Hz), 6.59 (1H, d, J=3.1Hz), 6.67 (1H, d, J=8.8Hz), 6.82-6.85
(2H, m), 7.03-7.06 (1H, m), 7.12-7.18 (1H, m)

15 (4-アミノ-2, 6-ジメチルフェニル) (4-ヒドロキシ-3-イソプロ
ピルフェニル) メタノン

¹H-NMR (CDCl₃) δ ppm: 1.22 (6H, d, J=6.9Hz), 2.03 (6H,
s), 3.25 (1H, heptet, J=6.9Hz), 6.40 (2H, s), 6.64-6.68 (1H, m), 7.34-
7.41 (1H, m), 7.81 (1H, brs)

20

4- (4-アミノ-2, 6-ジメチルベンジル) -2-イソプロピルフェノー
ル

¹H-NMR (CDCl₃) δ ppm: 1.19 (6H, d, J=6.9Hz), 2.15 (6H,
s), 3.08 (2H, brs), 3.21 (1H, heptet, J=6.9Hz), 3.86 (2H, s), 6.45 (2H,
25 s), 6.51-6.59 (2H, m), 6.89-6.92 (1H, m)

4- (4-メトキシベンジル) -3, 5-ジメチルアニリン

¹H-NMR (CDCl₃) δ ppm: 2.14 (6H, s), 3.48 (2H, brs), 3.76
(3H, s), 3.88 (2H, s), 6.43 (2H, s), 6.74-6.78 (2H, m), 6.90-6.93 (2H,
30 m)

4- (4-アミノ-2, 6-ジメチルフェノキシ) -2- (4-フルオロフェノキシ) フェノール

¹H-NMR (CDCl₃+CD₃OD) δ ppm: 2.00 (6H, s), 6.34-6.41
5 (2H, m), 6.37 (2H, s), 6.86 (1H, d, J=8.7Hz), 6.93-7.05 (4H, m)

4- (4-アミノ-2, 6-ジメチルフェノキシ) -2- (4-テトラヒドロ
ピラニルオキシ) フェノール

¹H-NMR (CDCl₃) δ ppm: 1.73-1.83 (2H, m), 2.01-2.07 (2H,
10 m), 2.04 (6H, s), 3.53 (2H, brs), 3.53-3.60 (2H, m), 3.95-4.00 (2H, m),
4.38-4.46 (1H, m), 5.24 (1H, brs), 6.14 (1H, dd, J=2.8, 8.7Hz), 6.14
(2H, s), 6.49 (1H, d, J=2.8Hz), 6.75 (1H, d, J=8.7Hz)

4- (4-アミノ-2, 6-ジメチルベンジル) -2- (4-テトラヒドロピ
15 ラニルオキシ) フェノール

¹H-NMR (CDCl₃+CD₃OD) δ ppm: 1.72-1.80 (2H, m), 1.97
-2.04 (2H, m), 2.14 (6H, s), 3.48-3.57 (2H, m), 3.85 (2H, s), 3.93-4.0
0 (2H, m), 4.33-4.60 (1H, m), 6.45 (2H, s), 6.45-6.50 (1H, m), 6.54-6.
56 (1H, m), 6.76-6.80 (1H, m)

20

(参考例68)

1- (4-アミノ-2, 6-ジメチルフェノキシ) -4-ベンジルオキシ-5,
6, 7, 8-テトラヒドロナフタレン

1-ベンジルオキシ-4- (2, 6-ジメチル-4-ニトロフェノキシ) -
25 5, 6, 7, 8-テトラヒドロナフタレン 15.5mg をエタノール 5mL、
テトラヒドロフラン 1mL の混合溶媒に溶解し、氷冷下 10% 白金炭素触媒 5
mg を数回に分けて加え、室温にて水素雰囲気下常圧で 24 時間攪拌した。不
溶物をろ去後、ろ液を減圧濃縮し、得られた残渣をシリカゲルカラムクロマト
グラフィー (溶出溶媒: ヘキサン-酢酸エチル) で精製し、1- (4-アミノ

－2，6－ジメチルフェノキシ）－4－ベンジルオキシ－5，6，7，8－テトラヒドロナフタレン14.0mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.70-1.94 (4H, m), 2.04 (6H, s), 2.68-2.95 (4H, m), 3.47 (2H, s), 4.96 (2H, s), 6.02-6.12 (1H, m), 6.38-6.

5 54 (3H, m), 7.20-7.50 (5H, m)

(参考例69)

参考例68と同様の方法により、以下の化合物を合成した。

4－（4－ベンジルオキシ－3－イソプロピルフェノキシ）－2，3，5－トリクロロアニリン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.21 (6H, d, $J=6.9\text{Hz}$), 3.37 (1H, heptet, $J=6.9\text{Hz}$), 4.19 (2H, brs), 5.01 (2H, s), 6.42 (1H, dd, $J=3.1, 8.8\text{Hz}$), 6.76 (1H, d, $J=8.8\text{Hz}$), 6.82 (1H, s), 6.88 (1H, d, $J=3.1\text{Hz}$), 7.29-7.47 (5H, m)

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4－（4－ベンジルオキシ－3－イソプロピルフェノキシ）－3，5－ジブロモアニリン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.21 (6H, d, $J=6.9\text{Hz}$), 3.37 (1H, heptet, $J=6.9\text{Hz}$), 3.71 (2H, brs), 5.01 (2H, s), 6.45 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.77 (1H, d, $J=8.9\text{Hz}$), 6.85 (1H, d, $J=3.1\text{Hz}$), 6.90 (2H, s), 7.28-7.46 (5H, m)

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4－（4－ベンジルオキシ－3－イソプロピルフェノキシ）－2，3，5－トリメチルアニリン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.19 (6H, d, $J=6.9\text{Hz}$), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.36 (1H, heptet, $J=6.9\text{Hz}$), 3.46 (2H, brs), 4.99 (2H, s), 6.33 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.46 (1H, s), 6.72 (1H, d, $J=8.8\text{Hz}$), 6.80 (1H, d, $J=3.0\text{Hz}$), 7.27-7.46 (5H, m)

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4 - (4-ベンジルオキシ-5, 6, 7, 8-テトラヒドロ-1-ナフチルオキシ) - 2, 3, 5-トリクロロアニリン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.75-1.88 (4H, m), 2.74-2.80 (2H, m), 2.87-2.95 (2H, m), 4.18 (2H, s), 4.98 (2H, s), 6.10 (1H, d, $J=8.8\text{Hz}$), 6.52 (1H, d, $J=8.8\text{Hz}$), 6.82 (1H, s), 7.28-7.45 (5H, m)

6 - [5 - (4-アミノ-2, 6-ジメチルフェノキシ) - 2-ヒドロキシベンジル] - 2H-ピリダジン-3-オン

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.01 (6H, s), 3.84 (2H, s), 6.43 (2H, s), 6.50 (1H, dd, $J=3.0, 8.7\text{Hz}$), 6.55 (1H, d, $J=3.0\text{Hz}$), 6.70 (1H, d, $J=8.7\text{Hz}$), 6.86 (1H, d, $J=9.7\text{Hz}$), 7.26 (1H, d, $J=9.7\text{Hz}$)

4 - (4-アミノ-2, 6-ジメチルフェノキシ) - 2 - [2 - (4-テトラヒドロピラニル) エチル] フェノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.23-1.35 (2H, m), 1.45-1.55 (3H, m), 1.60-1.68 (2H, m), 2.04 (6H, s), 2.52-2.58 (2H, m), 2.73 (2H, s), 3.31-3.40 (2H, m), 3.91-3.98 (2H, m), 6.39 (1H, dd, $J=3.0, 8.7\text{Hz}$), 6.44 (2H, s), 6.54 (1H, d, $J=3.0\text{Hz}$), 6.59 (1H, d, $J=8.7\text{Hz}$)

4 - (4-ベンジルオキシ-3-イソプロピルフェノキシ) - 3, 5-ジメチルアニリン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.19 (6H, d, $J=6.9\text{Hz}$), 2.04 (6H, m), 3.36 (1H, heptet, $J=6.9\text{Hz}$), 4.99 (2H, s), 6.38 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.42 (2H, s), 6.73 (1H, d, $J=8.8\text{Hz}$), 6.79 (1H, d, $J=3.0\text{Hz}$), 7.23-7.48 (5H, m)

(参考例70)

N - [4 - (4-ベンジルオキシ-3-イソプロピルフェノキシ) - 3, 5-ジメチルフェニル] カルバミド酸エチル

4- (4-ベンジルオキシ-3-イソプロピルフェノキシ) -3, 5-ジメチルアニリン 1.37 g を塩化メチレン 30 mL に溶解し、ピリジン 0.076 mL を加えた。氷冷攪拌下クロロ炭酸エチル 0.047 mL を滴下し、3時間室温で攪拌した。反応混合物に希塩酸 5 mL を加え、酢酸エチルで抽出した。

5 有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：ヘキサン-酢酸エチル）にて精製し、N- [4- (4-ベンジルオキシ-3-イソプロピルフェノキシ) -3, 5-ジメチルフェニル] カルバミド酸エチル 1.47 g を得た。

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.19 (6H, d, $J=6.9\text{Hz}$), 1.32 (3H, t, $J=7.1\text{Hz}$), 2.11 (6H, s), 3.37 (1H, heptet, $J=6.9\text{Hz}$), 4.23 (2H, q, $J=7.1\text{Hz}$), 5.00 (2H, s), 6.35 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.50 (1H, brs), 6.73 (1H, d, $J=8.8\text{Hz}$), 6.78 (1H, d, $J=3.0\text{Hz}$), 7.11 (2H, s), 7.23-7.48 (5H, m)

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（参考例 7 1）

N- [4- (4-ベンジルオキシ-3-イソプロピルフェノキシ) -2-フルオロ-3, 5-ジメチルフェニル] カルバミド酸エチル

20 N- [4- (4-ベンジルオキシ-3-イソプロピルフェノキシ) -3, 5-ジメチルフェニル] カルバミド酸エチル 743.6 mg を 1, 2-ジクロロエタン 50 mL に溶解し、N-フルオロ-6- (トリフルオロメチル) ピリジニウム-2-スルホネートを加えた後、室温で 15 分間攪拌し、更に 12 時間加熱還流した。放冷後、反応混合物に希塩酸 20 mL を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：ヘキサン-酢酸エチル）にて精製し、N- [4- (4-ベンジルオキシ-3-イソプロピルフェノキシ) -2-フルオロ-3, 5-ジメチルフェニル] カルバミド酸エチル 348.0 mg を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.19 (6H, d, $J=6.9\text{Hz}$), 1.34 (3H, t,

J=7.1Hz), 1.96-2.20 (6H, m), 3.36 (1H, heptet, J=6.9Hz), 4.26 (2H, q, J=7.1Hz), 5.00 (2H, s), 6.34 (1H, dd, J=3.1, 8.8Hz), 6.66-6.84 (2H, m), 7.16-7.53 (5H, m), 7.73-7.92 (1H, m)

5 (参考例72)

4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-2-フルオロ-3, 5-ジメチルアニリン

N-[4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-2-フルオロ-3, 5-ジメチルフェニル]カルバミド酸エチル 340mgをエタノール10mLに溶解し、1mol/L水酸化ナトリウム水溶液8mLを加え、90℃で3時間撹拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒:ヘキサン-酢酸エチル)にて精製し、4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-2-フルオロ-3, 5-ジメチルアニリン 200mgを得た。

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.19 (6H, d, J=6.9Hz), 1.93-2.10 (6H, m), 3.36 (1H, heptet, J=6.9Hz), 3.57 (2H, brs), 5.00 (2H, s), 6.36 (1H, dd, J=3.1, 8.8Hz), 6.51 (1H, d, J=9.9Hz), 6.73 (1H, d, J=8.8Hz), 6.77 (1H, d, J=3.1Hz), 7.20-7.54 (5H, m)

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(参考例73)

(4-アミノ-2, 6-ジメチルフェニル)(4-ベンジルオキシ-3-イソプロピルフェニル)メタノン

(4-アミノ-2, 6-ジメチルフェニル)(4-ヒドロキシ-3-イソプロピルフェニル)メタノン 86mgをテトラヒドロフラン15mLに溶かし、氷冷下炭酸セシウム99mgとベンジルブロミド36 μ Lを加え、アルゴン雰囲気下室温にて一晩撹拌した。不溶物をろ去後、ろ液を減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー(展開溶媒:ヘキサン-酢酸エチル)にて精製して、(4-アミノ-2, 6-ジメチルフェニル)(4-ベンジ

ルオキシ-3-イソプロピルフェニル) メタノン 28 mg を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.24 (6H, d, $J=6.9\text{Hz}$), 2.04 (6H, s), 3.39 (1H, heptet, $J=6.9\text{Hz}$), 3.66 (2H, brs), 5.13 (2H, s), 6.39 (2H, s), 6.83-6.88 (1H, m), 7.32-7.44 (5H, m), 7.48-7.53 (1H, m), 7.88 (1H, brs)

(参考例 7 4)

2, 2, 2-トリフルオロ-N-[4-(4-メトキシベンジル)-3, 5-ジメチルフェニル] アセトアミド

10 4-(4-メトキシベンジル)-3, 5-ジメチルアニリン 662 mg を塩化メチレン 30 mL に溶かし、ピリジン 266 μL を加えた後、氷冷下にてトリフルオロ酢酸無水物 420 μL を加え、室温にて一晩攪拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、2, 2, 2-トリフルオロ-N-[4-(4-メトキシベンジル)-3, 5-ジメチルフェニル] アセトアミド 836 mg を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.25 (6H, s), 3.76 (3H, s), 3.97 (2H, s), 6.75-6.83 (2H, m), 6.86-6.92 (2H, m), 7.27 (2H, s), 7.73 (1H, brs)

(参考例 7 5)

2, 2, 2-トリフルオロ-N-[4-[3-(4-フルオロベンゾイル)-4-ヒドロキシベンジル]-3, 5-ジメチルフェニル] アセトアミド

25 2, 2, 2-トリフルオロ-N-[4-(4-メトキシベンジル)-3, 5-ジメチルフェニル] アセトアミド 836 mg を塩化メチレン 5 mL に溶かし、4-フルオロベンゾイルクロリド 70 μL と塩化アルミニウム 111 mg を加え、室温にて一晩攪拌した。反応混合物に水 20 mL を加え、30 分間室温にて攪拌した後、反応混合物を塩化メチレンで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃

縮し、得られた残渣をシリカゲル薄層クロマトグラフィー（展開溶媒：ヘキサン-酢酸エチル）にて精製して、2, 2, 2-トリフルオロ-N-〔4-〔3-（4-フルオロベンゾイル）-4-ヒドロキシベンジル〕-3, 5-ジメチルフェニル〕アセトアミド48mgを得た。

- 5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.22 (6H, s), 3.94 (2H, s), 6.98 (1H, d, $J=8.6\text{Hz}$), 7.07-7.20 (4H, m), 7.26 (2H, s), 7.55-7.61 (2H, m), 7.76 (1H, brs), 11.68 (1H, s)

（参考例76）

- 0 〔5-（4-アミノ-2, 6-ジメチルベンジル）-2-ヒドロキシフェニル〕（4-フルオロフェニル）メタノン

2, 2, 2-トリフルオロ-N-〔4-〔3-（4-フルオロベンゾイル）-4-ヒドロキシベンジル〕-3, 5-ジメチルフェニル〕アセトアミド45mgをエタノール3mLに溶かし、1mol/L水酸化ナトリウム水溶液3mLを加え、アルゴン雰囲気下60℃にて30分間攪拌した。反応混合物を減圧濃縮し、得られた残渣を水に溶かし、塩化メチレンで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、〔5-（4-アミノ-2, 6-ジメチルベンジル）-2-ヒドロキシフェニル〕（4-フルオロフェニル）メタノン26mgを得た。

- 20 $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.11 (6H, s), 3.85 (2H, s), 6.42 (2H, s), 6.95 (1H, d, $J=8.5\text{Hz}$), 7.10-7.17 (2H, m), 7.16 (1H, d, $J=2.0\text{Hz}$), 7.22 (1H, dd, $J=2.0, 8.5\text{Hz}$), 7.57-7.64 (2H, m)

（参考例77）

- 25 4-（4-アミノ-2, 6-ジメチルフェノキシ）-2-（2-シクロヘキシル-1-ヒドロキシエチル）フェノール

氷冷下水素化ホウ素ナトリウム5.6mgをテトラヒドロフラン10mLに懸濁し、1-〔5-（4-アミノ-2, 6-ジメチルフェノキシ）-2-ヒドロキシフェニル〕-2-シクロヘキシルエタノン52.3mgを加え、室温で

6時間撹拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒：ヘキサン-酢酸エチル）にて精製し、4-（4-アミノ-2, 6-ジメチルフェノキシ）-2-（2-シクロヘキシル-1-ヒドロキシエチル）フェノール50.0mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.73-1.94 (13H, m), 2.03 (6H, s), 3.53 (2H, brs), 4.75-4.93 (1H, m), 6.30-6.50 (3H, m), 6.50 (1H, d, $J=8.6\text{Hz}$), 6.60 (1H, d, $J=2.8\text{Hz}$), 7.29 (1H, d, $J=3.1\text{Hz}$)

10 (参考例78)

〔5-（4-アミノ-2, 6-ジメチルフェノキシ）-2-ヒドロキシフェニル〕（2-メトキシフェニル）メタノン、および〔5-（4-アミノ-2, 6-ジメチルフェノキシ）-2-ヒドロキシフェニル〕（2-ヒドロキシフェニル）メタノール

15 〔5-（2, 6-ジメチル-4-ニトロフェノキシ）-2-ヒドロキシフェニル〕（2-メトキシフェニル）メタノンと〔5-（2, 6-ジメチル-4-ニトロフェノキシ）-2-ヒドロキシフェニル〕（2-ヒドロキシフェニル）メタノンの混合物（38:62）148mgを酢酸エチル20mLに溶かし、酸化白金（IV）17mgを加え、室温にて水素雰囲気下常圧で2時間撹拌した。不溶物をろ去し、ろ液を減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー（展開溶媒：ヘキサン-酢酸エチル（3:1））にて精製して、

20 〔5-（4-アミノ-2, 6-ジメチルフェノキシ）-2-ヒドロキシフェニル〕（2-メトキシフェニル）メタノン42mgと〔5-（4-アミノ-2, 6-ジメチルフェノキシ）-2-ヒドロキシフェニル〕（2-ヒドロキシフェニル）メタノール72mgを得た。

〔5-（4-アミノ-2, 6-ジメチルフェノキシ）-2-ヒドロキシフェニル〕（2-メトキシフェニル）メタノン

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.05 (6H, s), 3.48 (2H, brs), 3.71 (3H, s), 6.40 (2H, s), 6.68-6.72 (1H, m), 6.77-6.84 (1H, m), 6.87-6.91 (2H, m), 6.98-7.03 (1H, m), 7.32-7.36 (1H, m), 7.43-7.49 (1H, m), 12.

08 (1H, s)

[5-(4-アミノ-2, 6-ジメチルフェノキシ)-2-ヒドロキシフェニル] (2-ヒドロキシフェニル) メタノール

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.04 (6H, s), 3.48 (2H, brs), 3.86 (1H, brs), 6.11 (1H, brs), 6.38 (2H, s), 6.43-6.46 (1H, m), 6.54-6.57 (1H, m), 6.68-6.73 (1H, m), 6.81-6.85 (2H, m), 6.88-6.92 (1H, m), 7.18-7.26 (1H, m)

10 (参考例79)

1-[5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル]-2-(4-テトラヒドロピラニル) エタノン

4-(4-メトキシフェノキシ)-3, 5-ジメチルニトロベンゼン 1.99 mg を塩化メチレン 15 mL に溶かし、4-テトラヒドロピラニルアセチルクロリド 4.73 mg を加え、四塩化チタン 2.6 mL を滴下した後、室温にて2日間攪拌した。反応混合物を氷水 100 mL にあけ、塩化メチレン 30 mL を加えて20分間攪拌した。反応混合物を分液し、水層を塩化メチレンで抽出した。有機層を合わせ、1 mol/L 塩酸、水、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー (展開溶媒: ヘキサン-酢酸エチル) にて精製して、1-[5-(2, 6-ジメチル-4-ニトロフェノキシ)-2-ヒドロキシフェニル]-2-(4-テトラヒドロピラニル) エタノンを 96 mg 得た。

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33-1.43 (2H, m), 1.60-1.70 (2H, m), 2.14-2.28 (1H, m), 2.23 (6H, s), 2.77-2.82 (2H, m), 3.38-3.47 (2H, m), 3.92-3.97 (2H, m), 6.86 (1H, dd, $J=3.0, 9.1\text{Hz}$), 6.97 (1H, d, $J=9.1\text{Hz}$), 7.15 (1H, d, $J=3.0\text{Hz}$), 8.04 (2H, s), 11.98 (1H, s)

(参考例80)

4- (4-アミノ-2, 6-ジメチルベンジル) -2- (4-フルオロフェノキシ) フェノール、および4- [(4-アミノ-2, 6-ジメチルフェニル) ヒドロキシメチル] -2- (4-フルオロフェノキシ) フェノール

- 5 [4-ベンジルオキシ-3- (4-フルオロフェノキシ) フェニル] (4-ジベンジルアミノ-2, 6-ジメチルフェニル) メタノール66mgをテトラヒドロフラン10mLに溶かし、10%パラジウム炭素触媒(50%含水晶) 66mgを加え、室温にて水素雰囲気下常圧で一晩攪拌した。不溶物をろ去し、ろ液を減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー(展開溶媒: ヘキサン-酢酸エチル(1:1))にて精製して、4- (4-アミノ-
- 10 2, 6-ジメチルベンジル) -2- (4-フルオロフェノキシ) フェノール12mgと4- [(4-アミノ-2, 6-ジメチルフェニル) ヒドロキシメチル] -2- (4-フルオロフェノキシ) フェノール3mgを得た。

4- (4-アミノ-2, 6-ジメチルベンジル) -2- (4-フルオロフェノキシ) フェノール

- 15 $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.11 (6H, s), 3.81 (2H, s), 6.41 (2H, s), 6.56-6.57 (1H, m), 6.62-6.65 (1H, m), 6.83-6.95 (3H, m), 6.95-7.05 (2H, m)

- 20 4- [(4-アミノ-2, 6-ジメチルフェニル) ヒドロキシメチル] -2- (4-フルオロフェノキシ) フェノール

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.94 (1H, brs), 2.15 (6H, s), 3.55 (2H, brs), 5.46 (1H, brs), 6.13 (1H, s), 6.34 (2H, s), 6.77-6.82 (1H, m), 6.92-7.03 (6H, m)

25 (参考例81)

4- (4-ベンジルオキシ-3-イソプロピルベンゾイル) -3, 5-ジメチルマロンアニリド酸エチル

(4-アミノ-2, 6-ジメチルフェニル) (4-ベンジルオキシ-3-イソプロピルフェニル) メタノン27mgをテトラヒドロフラン3mLに溶解し、

ピリジン7 μ Lを加えた。氷冷撹拌下エチルマロニルクロリド10 μ Lを滴下し、室温にて一晩撹拌した。反応混合物に1mol/L塩酸5mLを加え、酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、4-(4-ベンジルオキシ-3-イソプロピルベンゾイル)-3,5-ジメチルマロンアニリド酸エチル38mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.24 (6H, d, $J=6.9\text{Hz}$), 1.34 (3H, t, $J=7.1\text{Hz}$), 2.12 (6H, s), 3.39 (1H, heptet, $J=6.9\text{Hz}$), 3.49 (2H, s), 4.28 (2H, q, $J=7.1\text{Hz}$), 5.14 (2H, s), 6.83-6.88 (1H, m), 7.30 (2H, s), 7.31-7.50 (6H, m), 7.88 (1H, brs), 9.25 (1H, brs)

(参考例82)

参考例81と同様の方法により、以下の化合物を合成した。

4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-3,5-ジメチルマロンアニリド酸エチル

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.19 (6H, d, $J=6.9\text{Hz}$), 1.34 (3H, t, $J=7.1\text{Hz}$), 2.12 (6H, s), 3.36 (1H, heptet, $J=6.9\text{Hz}$), 3.47 (2H, s), 4.27 (2H, q, $J=7.1\text{Hz}$), 5.00 (2H, s), 6.35 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.73 (1H, d, $J=8.8\text{Hz}$), 6.78 (1H, d, $J=3.0\text{Hz}$), 7.20-7.50 (7H, m), 9.14 (1H, s)

4-(4-ベンジルオキシ-5,6,7,8-テトラヒドロ-1-ナフチルオキシ)-3,5-ジメチルマロンアニリド酸エチル

$^1\text{H-NMR}$ (CD_3OD) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 1.70-1.94 (4H, m), 2.09 (6H, s), 2.66-2.98 (4H, m), 3.47 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 4.96 (2H, s), 6.01 (1H, d, $J=8.8\text{Hz}$), 6.47 (1H, d, $J=8.8\text{Hz}$), 7.18-7.52 (7H, m), 9.11 (1H, s)

4-(4-ベンジルオキシ-3-イソプロピルフェニルスルファニル)-3,5-ジメチルマロンアニリド酸エチル

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.16 (6H, d, $J=6.9\text{Hz}$), 1.34 (3H, t, $J=7.1\text{Hz}$), 2.42 (6H, s), 3.31 (1H, heptet, $J=6.9\text{Hz}$), 3.47 (2H, s), 4.27 (2H, q, $J=7.1\text{Hz}$), 5.00 (2H, s), 6.50 (1H, dd, $J=2.4, 8.4\text{Hz}$), 6.71 (1H, d, $J=8.4\text{Hz}$), 6.97 (1H, d, $J=2.4\text{Hz}$), 7.20-7.40 (7H, m), 9.23 (1H, s)

5 2-フルオロ-4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-3,5-ジメチルマロンアニリド酸エチル

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.19 (6H, d, $J=6.9\text{Hz}$), 1.34 (3H, t, $J=7.1\text{Hz}$), 1.95-2.18 (6H, m), 3.36 (1H, heptet, $J=6.9\text{Hz}$), 3.52 (2H, s), 4.28 (2H, q, $J=7.1\text{Hz}$), 5.00 (2H, s), 6.36 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.74 (1H, d, $J=8.8\text{Hz}$), 6.77 (1H, d, $J=3.0\text{Hz}$), 7.10-7.56 (5H, m), 8.01 (1H, d, $J=8.6\text{Hz}$), 9.40 (1H, s)

4-(4-ベンジルオキシ-5,6,7,8-テトラヒドロ-1-ナフチルオキシ)-2,3,5-トリクロロマロンアニリド酸エチル

15 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.35 (3H, t, $J=7.1\text{Hz}$), 1.72-1.88 (4H, m), 2.73-2.80 (2H, m), 2.87-2.93 (2H, m), 3.55 (2H, s), 4.31 (2H, q, $J=7.1\text{Hz}$), 4.98 (2H, s), 6.06 (1H, d, $J=8.8\text{Hz}$), 6.51 (1H, d, $J=8.8\text{Hz}$), 7.27-7.45 (5H, m), 8.59 (1H, s), 10.03 (1H, s)

20 4-[4-メトキシ-3-{2-(2-メトキシフェニル)エチル}フェノキシ]-3,5-ジメチルマロンアニリド酸エチル

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.34 (3H, t, $J=7.1\text{Hz}$), 2.07 (6H, s), 2.79-2.89 (4H, m), 3.47 (2H, s), 3.76 (3H, s), 3.79 (3H, s), 4.27 (2H, q, $J=7.1\text{Hz}$), 6.43 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.56 (1H, d, $J=3.1\text{Hz}$), 6.67 (1H, d, $J=8.9\text{Hz}$), 6.80-6.85 (2H, m), 7.00-7.05 (1H, m), 7.12-7.18 (1H, m), 7.28 (2H, s), 9.13 (1H, s)

4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-2,3,5-トリクロロマロンアニリド酸エチル

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.21 (6H, d, $J=6.9\text{Hz}$), 1.35 (3H, t, $J=7.1\text{Hz}$), 3.36 (1H, heptet, $J=6.9\text{Hz}$), 3.56 (2H, s), 4.31 (2H, q, $J=7.1\text{Hz}$), 5.02 (2H, s), 6.41 (1H, dd, $J=3.1, 8.9\text{Hz}$), 6.76 (1H, d, $J=8.9\text{Hz}$), 6.87 (1H, d, $J=3.1\text{Hz}$), 7.29–7.47 (5H, m), 8.60 (1H, s), 10.06 (1H, s)

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4- (4-ベンジルオキシ-3-イソプロピルフェノキシ) -2, 3, 5-トリメチルマロンアニリド酸エチル

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.20 (6H, d, $J=6.9\text{Hz}$), 1.34 (3H, t, $J=7.1\text{Hz}$), 2.09 (6H, s), 2.20 (3H, s), 3.36 (1H, heptet, $J=6.9\text{Hz}$), 3.51 (2H, s), 4.28 (2H, q, $J=7.1\text{Hz}$), 4.99 (2H, s), 6.31 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.71 (1H, d, $J=8.8\text{Hz}$), 6.82 (1H, d, $J=3.0\text{Hz}$), 7.27–7.44 (5H, m), 7.51 (1H, s), 9.03 (1H, brs)

(製造例1)

15 4- [3- (4-フルオロベンゾイル) -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸エチル (化合物1)

[5- (4-アミノ-2, 6-ジメチルフェノキシ) -2-ヒドロキシフェニル] (4-フルオロフェニル) メタノン 28.88 g を塩化メチレン 1000 mL とテトラヒドロフラン 700 mL の混合溶媒に溶解し、ピリジン 7.31 mL を加えた。氷冷撹拌下エチルマロニルクロリド 11.05 mL を滴下し、2時間室温で撹拌した。反応混合物に希塩酸 300 mL を加え、酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチル) にて精製し、4- [3- (4-フルオロベンゾイル) -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸エチル 38.20 g を得た。

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$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 2.10 (6H, s), 3.47 (2H, s), 4.27 (2H, q, $J=7.1\text{Hz}$), 6.94–6.98 (3H, m), 7.11–7.17 (2H, m), 7.28 (2H, s), 7.64–7.69 (2H, m), 9.17 (1H, s), 11.42 (1H, s)

(製造例 2)

製造例 1 と同様の方法により、以下の化合物を合成した。

4-〔3-(2-シクロヘキシルエチル)-4-ヒドロキシフェノキシ〕-3,

5 5-ジメチルマロンアニリド酸エチル（化合物2）

¹H-NMR (CDCl₃) δ ppm: 0.77-1.00 (2H, m), 1.08-1.50 (9H, m), 1.56-1.80 (5H, m), 2.10 (6H, s), 2.46-2.62 (2H, m), 3.47 (2H, s), 4.26 (2H, q, J=7.1Hz), 4.67 (1H, s), 6.39 (1H, dd, J=3.0, 8.7Hz), 6.55 (1H, d, J=3.0Hz), 6.62 (1H, d, J=8.7Hz), 7.28 (2H, s), 9.15 (1H, s)

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4-〔3-(2-シクロヘキシル-1-ヒドロキシエチル)-4-ヒドロキシフェノキシ〕-3,5-ジメチルマロンアニリド酸エチル (化合物3)

¹H-NMR (CDCl₃) δ ppm: 0.77-1.90 (16H, m), 2.10 (6H, s), 3.47 (2H, s), 4.27 (2H, q, J=7.2Hz), 4.76-4.88 (1H, m), 6.36 (1H, d, J=2.8Hz), 6.55 (1H, dd, J=2.8, 8.8Hz), 6.74 (1H, d, J=8.8Hz), 7.29 (2H, s), 7.47 (1H, s), 9.14 (1H, s)

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4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルメチル)フェノキシ〕-3,5-ジメチルマロンアニリド酸エチル (化合物4)

20 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.26–1.40 (5H, m), 1.50–1.60 (2H, m), 1.73–1.89 (1H, m), 2.08 (6H, s), 2.48 (2H, d, $J=7.1\text{Hz}$), 3.28–3.40 (2H, m), 3.48 (2H, s), 3.88–4.00 (2H, m), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.76 (1H, brs), 6.38 (1H, dd, $J=2.9, 8.6\text{Hz}$), 6.50 (1H, d, $J=2.9\text{Hz}$), 6.61 (1H, d, $J=8.6\text{Hz}$), 7.28 (2H, s), 9.20 (1H, s)

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4-〔4-ヒドロキシ-3-〔2-(3-テトラヒドロフランニル)エチル〕フェノキシ〕-3,5-ジメチルマロンアニリド酸エチル(化合物5)

 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.34 (3H, t, $J=7.1\text{Hz}$), 1.48-1.74 (3H, m), 1.98-2.27 (8H, m), 2.45-2.65 (2H, m), 3.32-3.42 (1H, m), 3.47

(2H, s), 3.68-3.80 (1H, m), 3.82-3.95 (2H, m), 4.27 (2H, q, J=7.1Hz), 4.78 (1H, brs), 6.40 (1H, dd, J=3.0, 8.6Hz), 6.55 (1H, d, J=3.0Hz), 6.60 (1H, d, J=8.6Hz), 7.29 (2H, s), 9.15 (1H, s)

- 5 4-[4-ヒドロキシ-3-(6-オキソ-1,6-ジヒドロピリダジン-3-イルメチル)フェノキシ]-3,5-ジメチルマロンアニリド酸エチル(化合物6)

¹H-NMR (CDCl₃) δ ppm: 1.33 (3H, t, J=7.1Hz), 2.08 (6H, s), 3.47 (2H, s), 3.85 (2H, s), 4.26 (2H, q, J=7.1Hz), 6.48 (1H, dd, J=3.0, 8.7Hz), 6.53 (1H, d, J=3.0Hz), 6.70 (1H, d, J=8.7Hz), 6.87 (1H, d, J=9.7Hz), 7.27 (2H, s), 7.28 (1H, d, J=9.7Hz), 9.32 (1H, s)

4-[4-ヒドロキシ-3-(2-メトキシベンゾイル)フェノキシ]-3,5-ジメチルマロンアニリド酸エチル(化合物7)

15 ¹H-NMR (CDCl₃) δ ppm: 1.33 (3H, t, J=7.1Hz), 2.13 (6H, s), 3.45 (2H, s), 3.72 (3H, s), 4.26 (2H, q, J=7.1Hz), 6.71 (1H, d, J=3.0Hz), 6.77-6.92 (3H, m), 6.99-7.03 (2H, m), 7.29 (2H, s), 7.44-7.48 (1H, m), 9.13 (1H, s), 12.05 (1H, s)

- 20 4-[4-ヒドロキシ-3-[(2-ヒドロキシフェニル)ヒドロキシメチル]フェノキシ]-3,5-ジメチルマロンアニリド酸エチル(化合物8)

¹H-NMR (CDCl₃) δ ppm: 1.32 (3H, t, J=7.1Hz), 2.02 (6H, s), 3.44 (2H, s), 4.26 (2H, q, J=7.1Hz), 6.08 (1H, s), 6.38 (1H, d, J=3.0Hz), 6.54 (1H, dd, J=3.0, 8.7Hz), 6.76 (1H, d, J=8.7Hz), 6.77-6.90 (3H, m), 7.10-7.20 (1H, m), 7.19 (2H, s), 9.16 (1H, s)

4-[4-ヒドロキシ-3-[2-(4-テトラヒドロピラニル)エチル]フェノキシ]-3,5-ジメチルマロンアニリド酸エチル(化合物9)

¹H-NMR (CDCl₃) δ ppm: 1.25-1.35 (2H, m), 1.33 (3H, t, J=

7.1Hz), 1.45-1.56 (3H, m), 1.61-1.66 (2H, m), 2.09 (6H, s), 2.52-2.58 (2H, m), 3.32-3.40 (2H, m), 3.47 (2H, s), 3.92-3.98 (2H, m), 4.26 (2H, q, J=7.1Hz), 5.31 (1H, s), 6.38 (1H, dd, J=3.0, 8.7Hz), 6.54 (1H, d, J=3.0Hz), 6.61 (1H, d, J=8.7Hz), 7.28 (2H, s), 9.17 (1H, s)

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4- (4-ヒドロキシ-3-イソプロピルベンジル) -3, 5-ジメチルマロンアニリド酸エチル (化合物10)

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.21 (6H, d, J=6.9Hz), 1.33 (3H, t, J=7.1Hz), 2.22 (6H, s), 3.15 (1H, heptet, J=6.9Hz), 3.46 (2H, s), 3.92 (2H, s), 4.26 (2H, q, J=7.1Hz), 4.77 (1H, s), 6.54 (1H, dd, J=2.0, 8.1Hz), 6.58 (1H, d, J=8.1Hz), 6.91 (1H, d, J=2.0Hz), 7.26 (2H, s), 9.06 (1H, s)

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4- [3- (4-フルオロベンゾイル) -4-ヒドロキシベンジル] -3, 5-ジメチルマロンアニリド酸エチル (化合物11)

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.34 (3H, t, J=7.1Hz), 2.19 (6H, s), 3.47 (2H, s), 3.91 (2H, s), 4.27 (2H, q, J=7.1Hz), 6.96 (1H, d, J=8.5Hz), 7.08-7.13 (3H, m), 7.20 (1H, dd, J=2.0, 8.5Hz), 7.25 (2H, s), 7.54-7.60 (2H, m), 9.11 (1H, s)

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4- [3- (4-フルオロフェノキシ) -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸エチル (化合物12)

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.32 (3H, t, J=7.1Hz), 2.08 (6H, s), 3.44 (2H, s), 4.25 (2H, q, J=7.1Hz), 5.30 (1H, s), 6.32-6.37 (2H, m), 6.88 (1H, d, J=9.3Hz), 6.93-6.98 (2H, m), 6.98-7.03 (2H, m), 7.25 (2H, s), 9.09 (1H, s)

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4- [[3- (4-フルオロフェノキシ) -4-ヒドロキシフェニル] ヒドロキシメチル] -3, 5-ジメチルマロンアニリド酸エチル (化合物13)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 2.05 (1H, d, $J=3.9\text{Hz}$), 2.23 (6H, s), 3.45 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.50 (1H, s), 6.19 (1H, d, $J=3.9\text{Hz}$), 6.73-6.78 (1H, m), 6.91-7.04 (6H, m), 7.22 (2H, s), 9.14 (1H, s)

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4-〔3-(4-フルオロフェノキシ)-4-ヒドロキシベンジル〕-3, 5-ジメチルマロンアニリド酸エチル (化合物 14)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 2.18 (6H, s), 3.45 (2H, s), 3.87 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.41 (1H, s), 6.53 (1H, d, $J=2.0\text{Hz}$), 6.61 (1H, dd, $J=2.0, 8.2\text{Hz}$), 6.88 (1H, d, $J=8.2\text{Hz}$), 6.88-6.96 (2H, m), 6.97-7.05 (2H, m), 7.23 (2H, s), 9.07 (1H, s)

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4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルオキシ)フェノキシ〕-3, 5-ジメチルマロンアニリド酸エチル (化合物 15)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.34 (3H, t, $J=7.1\text{Hz}$), 1.73-1.83 (2H, m), 2.02-2.08 (2H, m), 2.11 (6H, s), 3.47 (2H, s), 3.53-3.60 (2H, m), 3.94-4.01 (2H, m), 4.27 (2H, q, $J=7.1\text{Hz}$), 4.38-4.45 (1H, m), 5.27 (1H, s), 6.12 (1H, dd, $J=2.7, 8.8\text{Hz}$), 6.48 (1H, d, $J=2.7\text{Hz}$), 6.76 (1H, d, $J=8.8\text{Hz}$), 7.29 (2H, s), 9.15 (1H, s)

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4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルオキシ)ベンジル〕-3, 5-ジメチルマロンアニリド酸エチル (化合物 16)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 1.70-1.80 (2H, m), 1.95-2.03 (2H, m), 2.22 (6H, s), 3.47 (2H, s), 3.50-3.58 (2H, m), 3.92 (2H, s), 3.90-3.97 (2H, m), 4.26 (2H, q, $J=7.1\text{Hz}$), 4.33-4.40 (1H, m), 5.51 (1H, s), 6.47 (1H, brd, $J=8.1\text{Hz}$), 6.52 (1H, brs), 6.79 (1H, d, $J=3.1\text{Hz}$), 7.25 (2H, s), 9.09 (1H, s)

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4-(4-ヒドロキシ-3-イソプロピル-2-メチルオキシフェノキシ)-

3, 5-ジメチルマロンアニリド酸エチル (化合物 17)

¹H-NMR (CDCl₃) δ ppm: 1.26 (3H, t, J=7.1Hz), 1.39 (6H, d, J=7.1Hz), 2.08 (6H, s), 3.47 (2H, s), 3.56 (1H, heptet, J=7.1Hz), 3.96 (3H, s), 4.26 (2H, q, J=7.1Hz), 5.29 (1H, brs), 5.95 (1H, d, J=8.8Hz), 6.25 (1H, d, J=8.8Hz), 7.27 (2H, s), 9.16 (1H, s)

(製造例 3)

4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸エチル (化合物 18)

10 4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸エチル 37.3 g をトリフルオロ酢酸-ジメチルスルフィド-水 (95:5:10) の混合溶媒 100 mL に溶解し、室温で 12 時間放置した。溶媒を減圧下に留去後、残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチル) にて精製し、4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸エチル 22.1 g を得た。

¹H-NMR (CDCl₃) δ ppm: 1.20 (6H, d, J=6.9Hz), 1.33 (3H, t, J=7.1Hz), 2.09 (6H, s), 3.18 (1H, heptet, J=6.9Hz), 3.47 (2H, s), 4.26 (2H, q, J=7.1Hz), 5.14 (1H, s), 6.27 (1H, dd, J=3.0, 8.6Hz), 6.59 (1H, d, J=8.6Hz), 6.72 (1H, d, J=3.0Hz), 7.28 (2H, s), 9.16 (1H, s)

(製造例 4)

製造例 3 と同様の方法により、以下の化合物を合成した。

2-フルオロ-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸エチル (化合物 19)

25 ¹H-NMR (CDCl₃) δ ppm: 1.21 (6H, d, J=6.9Hz), 1.34 (3H, t, J=7.1Hz), 2.00-2.13 (6H, m), 3.16 (1H, heptet, J=6.9Hz), 3.52 (2H, s), 4.28 (2H, q, J=7.1Hz), 6.29 (1H, dd, J=3.0, 8.6Hz), 6.59 (1H, d, J=8.6Hz), 6.71 (1H, d, J=3.0Hz), 7.99 (1H, d, J=8.8Hz), 9.41 (1H, s)

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26

4- (4-ヒドロキシ-3-イソプロピルフェニルスルファニル) -3, 5-ジメチルマロンアニリド酸エチル (化合物20)

¹H-NMR (CDCl₃) δ ppm: 1.18 (6H, d, J=6.9Hz), 1.33 (3H, t, J=7.1Hz), 2.40 (6H, s), 3.13 (1H, heptet, J=6.9Hz), 3.47 (2H, s), 4.26 (2H, q, J=7.1Hz), 6.50 (1H, dd, J=2.0, 8.3Hz), 6.57 (1H, d, J=8.3Hz), 6.94 (1H, d, J=2.0Hz), 7.38 (2H, s), 9.25 (1H, s)

4- (4-ヒドロキシ-5, 6, 7, 8-テトラヒドロ-1-ナフチルオキシ) -3, 5-ジメチルマロンアニリド酸エチル (化合物21)

¹H-NMR (CD₃OD) δ ppm: 1.33 (3H, t, J=7.1Hz), 1.74-1.92 (4H, m), 2.07 (6H, s), 2.60-2.73 (2H, m), 2.89-2.95 (2H, m), 3.47 (2H, s), 4.26 (2H, q, J=7.1Hz), 4.85 (1H, s), 5.95 (1H, d, J=8.6Hz), 6.39 (1H, d, J=8.6Hz), 7.28 (2H, s), 9.15 (1H, s)

2, 3, 5-トリクロロ-4- (4-ヒドロキシ-3-イソプロピルフェノキシ) マロンアニリド酸エチル (化合物22)

¹H-NMR (CDCl₃) δ ppm: 1.23 (6H, d, J=6.9Hz), 1.35 (3H, t, J=7.1Hz), 3.18 (1H, heptet, J=6.9Hz), 3.56 (2H, s), 4.30 (2H, q, J=7.1Hz), 4.88 (1H, s), 6.37 (1H, dd, J=3.0, 8.7Hz), 6.63 (1H, d, J=8.7Hz), 6.81 (1H, d, J=3.0Hz), 8.58 (1H, s), 10.07 (1H, s)

4- (4-ヒドロキシ-3-イソプロピルフェノキシ) -2, 3, 5-トリメチルマロンアニリド酸エチル (化合物23)

¹H-NMR (CDCl₃) δ ppm: 1.22 (6H, d, J=6.9Hz), 1.34 (3H, t, J=7.1Hz), 2.08 (6H, s), 2.20 (3H, s), 3.17 (1H, heptet, J=6.9Hz), 3.51 (2H, s), 4.23 (2H, q, J=7.1Hz), 4.45 (1H, s), 6.26 (1H, dd, J=3.0, 8.6Hz), 6.57 (1H, d, J=8.6Hz), 6.75 (1H, d, J=3.0Hz), 7.50 (1H, s), 9.04 (1H, s)

2, 3, 5-トリクロロ-4-(4-ヒドロキシ-5, 6, 7, 8-テトラヒドロ-1-ナフチルオキシ) マロンアニリド酸エチル (化合物 24)

¹H-NMR (CDCl₃) δ ppm: 1.35 (3H, t, J=7.1Hz), 1.79-1.91
5 (4H, m), 2.63-2.72 (2H, m), 2.87-2.94 (2H, m), 3.55 (2H, s), 4.30 (2H, q, J=7.1Hz), 4.53 (1H, s), 6.02 (1H, d, J=8.7Hz), 6.44 (1H, d, J=8.7Hz), 8.57 (1H, s), 10.01 (1H, s)

(製造例 5)

10 4-(4-ヒドロキシ-3-イソプロピルベンゼンスルホニル)-3, 5-ジメチルマロンアニリド酸エチル (化合物 25)

4-(4-ヒドロキシ-3-イソプロピルフェニルスルファニル)-3, 5-ジメチルマロンアニリド酸エチル 60 mg を塩化メチレン 20 mL に溶解し、m-クロロ過安息香酸 65 mg 加え、室温にて 20 時間攪拌した。不溶物をろ去し、ろ液に亜硫酸水素ナトリウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和重曹水、水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチル) にて精製し、4-(4-ヒドロキシ-3-イソプロピルベンゼンスルホニル)-3, 5-ジメチルマロンアニリド酸エチル 51 mg
20 を得た。

¹H-NMR (CDCl₃) δ ppm: 1.20 (6H, d, J=6.9Hz), 1.32 (3H, t, J=7.1Hz), 2.61 (6H, s), 3.21 (1H, heptet, J=6.9Hz), 3.47 (2H, s), 4.26 (2H, q, J=7.1Hz), 6.30 (1H, brs), 6.74 (1H, d, J=8.5Hz), 7.30-7.44 (3H, m), 7.64 (1H, d, J=2.3Hz), 9.44 (1H, s)

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(製造例 6)

4-[3-[(4-フルオロフェニル) ヒドロキシメチル]-4-ヒドロキシフェノキシ]-3, 5-ジメチルマロンアニリド酸エチル (化合物 26)

水素化ホウ素ナトリウム 6 mg をテトラヒドロフラン 0.5 mL に懸濁させ、

- 酢酸 22 μ L を加え、室温にて 1 時間撹拌した。反応混合物に 4-〔3-(4-フルオロベンゾイル)-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸エチル 23 mg のテトラヒドロフラン 2 mL 溶液を加え、室温にて 13 時間撹拌した。反応混合物を飽和炭酸水素ナトリウム溶液で希釈し、
- 5 酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム溶液と飽和食塩水の 1:1 混合溶液で洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー（展開溶媒：ヘキサン-酢酸エチル）にて精製して、4-〔3-〔(4-フルオロフェニル)ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸エチル 18 mg を得た。
- 10 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.32 (3H, t, $J=7.1\text{Hz}$), 2.04 (6H, s), 3.42 (2H, s), 3.52 (1H, d, $J=3.5\text{Hz}$), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.84 (1H, d, $J=3.5\text{Hz}$), 6.36 (1H, d, $J=3.0\text{Hz}$), 6.51 (1H, dd, $J=3.0, 8.8\text{Hz}$), 6.73 (1H, d, $J=8.8\text{Hz}$), 6.98-7.03 (2H, m), 7.23 (2H, s), 7.28-7.33 (2H, m), 7.50 (1H, s), 9.17 (1H, s)
- 15

(製造例 7)

製造例 6 と同様の方法により、以下の化合物を合成した。

- 4-〔3-〔(4-フルオロフェニル)ヒドロキシメチル〕-4-ヒドロキシベンジル〕-3, 5-ジメチルマロンアニリド酸エチル (化合物 27)
- 20 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 2.16 (6H, s), 3.14 (1H, brs), 3.45 (2H, s), 3.85 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.87 (1H, s), 6.46 (1H, d, $J=1.8\text{Hz}$), 6.76 (1H, d, $J=8.3\text{Hz}$), 6.81 (1H, dd, $J=1.8, 8.3\text{Hz}$), 6.98-7.04 (2H, m), 7.21 (2H, s), 7.25-7.31 (2H, m), 7.56 (1H, brs), 9.08 (1H, s)
- 25

(製造例 3)

4-〔3-(4-フルオロベンジル)-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸エチル (化合物 28)

4-〔3-〔(4-フルオロフェニル)ヒドロキシメチル]-4-ヒドロキシ
 シフェノキシ]-3, 5-ジメチルマロンアニリド酸エチル713.5mgを
 エタノール10mLに溶解し、氷冷撹拌下10%パラジウム炭素触媒 700
 mgを加え、室温にて水素雰囲気下常圧で24時間撹拌した。不溶物をろ去後、
 5 ろ液を減圧濃縮し、4-〔3-(4-フルオロベンジル)-4-ヒドロキシフ
 ェノキシ]-3, 5-ジメチルマロンアニリド酸エチル620mgを得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 2.08 (6H, s), 3.46 (2H, s), 3.87 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 6.41 (1H, dd, $J=3.0, 8.7\text{Hz}$), 6.56 (1H, d, $J=3.0\text{Hz}$), 6.64 (1H, d, $J=8.7\text{Hz}$), 6.88-7.01
 10 (2H, m), 7.08-7.23 (2H, m), 7.27 (2H, s), 9.15 (1H, s)

(製造例9)

4-〔4-ヒドロキシ-3-(2-ヒドロキシベンゾイル)フェノキシ]-3,
 5-ジメチルマロンアニリド酸 (化合物29)

15 4-〔4-ヒドロキシ-3-(2-メトキシベンゾイル)フェノキシ]-3,
 5-ジメチルマロンアニリド酸エチル39mgを塩化メチレン10mLに溶解
 し、 -78°C にて1M三臭化ホウ素の塩化メチレン溶液800 μL を滴下した
 後、室温にて一晩撹拌した。反応混合物に氷を加え、1時間撹拌した後、塩化
 メチレンで抽出した。有機層を2mol/L塩酸にて洗浄した後、2mol/
 20 L水酸化ナトリウム水溶液で抽出した。水層を塩化メチレンで洗浄し、氷と濃
 塩酸にて酸性にした後、塩化メチレン-メタノール(20:1)混合溶媒で抽
 出した。有機層を無水硫酸マグネシウムで乾燥後、減圧濃縮し、4-〔4-ヒ
 ドロキシ-3-(2-ヒドロキシベンゾイル)フェノキシ]-3, 5-ジメチ
 ルマロンアニリド酸24mgを得た。

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.15 (6H, s), 3.52 (2H, s), 6.83-6.
 87 (1H, m), 6.93 (1H, brs), 7.01 (2H, brs), 7.02-7.08 (2H, m), 7.25 (2
 H, s), 7.46-7.54 (2H, m), 8.20 (1H, s), 10.05 (1H, s), 10.67 (1H, s)

(製造例10)

4-〔4-ヒドロキシ-3-〔2-(2-ヒドロキシフェニル)エチル〕フェノキシ〕-3, 5-ジメチルマロンアニリド酸 (化合物30)

- 4-〔4-メトキシ-3-〔2-(2-メトキシフェニル)エチル〕フェノキシ〕-3, 5-ジメチルマロンアニリド酸エチル 35 mg を塩化メチレン 2 mL に溶かし、-78℃にて1 M 三臭化ホウ素の塩化メチレン溶液 800 μL を滴下した後、室温にて一晩攪拌した。反応混合物にエタノール 20 mL を加えた後、減圧濃縮した。得られた残渣をメタノール 3 mL に溶かした後、1 mol/L 水酸化ナトリウム水溶液 3 mL を加え、60℃にて30分間攪拌した。反応混合物を減圧濃縮し、得られた残渣に水を加え、酢酸エチルで洗浄した。
- 10 水層に1 mol/L 塩酸、飽和食塩水を加え、酢酸エチルで抽出し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、4-〔4-ヒドロキシ-3-〔2-(2-ヒドロキシフェニル)エチル〕フェノキシ〕-3, 5-ジメチルマロンアニリド酸 28 mg を得た。

- ¹H-NMR (CDCl₃+CD₃OD) δ ppm: 2.09 (6H, s), 2.70-2.83 (4H, m), 3.46 (2H, s), 6.44-6.52 (2H, m), 6.72 (1H, d, J=8.4Hz), 6.78-6.85 (2H, m), 7.07-7.12 (2H, m), 7.26 (2H, s)
- 15

(製造例11)

- 4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸メチル (化合物31)
- 20

- 4-(4-アミノ-2, 6-ジメチルフェノキシ)-2-イソプロピルフェノール 188 mg とマロン酸ジメチル 520 mg を 110℃にて一晩攪拌した。反応混合物を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチル) にて精製し、4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸メチル 153 mg を得た。
- 25

¹H-NMR (CDCl₃) δ ppm: 1.21 (6H, d, J=6.9Hz), 2.10 (6H, s), 3.17 (1H, heptet, J=6.9Hz), 3.49 (s, 2H), 3.81 (s, 3H), 4.81 (s, 1H), 6.29 (1H, dd, J=3.0, 8.6Hz), 6.59 (1H, d, J=8.6Hz), 6.72 (1H, d, J

=3.0Hz), 7.28 (2H, s), 9.09 (1H, s)

(製造例 1 2)

製造例 1 1 と同様の方法により、以下の化合物を合成した。

- 5 4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3, 5-ジメチルマロンアニリド酸ベンジル (化合物 3 2)

¹H-NMR (CDCl₃) δ ppm: 1.21 (6H, d, J=6.9Hz), 2.10 (6H, s), 3.16 (1H, heptet, J=6.9Hz), 3.52 (2H, s), 4.55 (1H, s), 5.24 (2H, s), 6.30 (1H, dd, J=3.0, 8.6Hz), 6.59 (1H, d, J=8.6Hz), 6.72 (1H, d, J=3.0Hz), 7.26 (2H, s), 7.33-7.42 (5H, m)

4-[3-[3-(2-カルボキシエチル)ベンジル]-4-ヒドロキシフェノキシ]-3, 5-ジメチルマロンアニリド酸メチル (化合物 3 3)

15 ¹H-NMR (CDCl₃) δ ppm: 2.07 (6H, s), 2.61 (2H, t, J=7.8Hz), 2.89 (2H, t, J=7.8Hz), 3.48 (2H, s), 3.80 (3H, s), 3.86 (2H, s), 6.48 (1H, d, J=3.0Hz), 6.49 (1H, dd, J=3.0, 8.3Hz), 6.65 (1H, d, J=8.3Hz), 7.00-7.02 (3H, m), 7.16-7.21 (1H, m), 7.24 (2H, s), 9.09 (1H, s)

(製造例 1 3)

- 20 4-(4-ヒドロキシ-3-イソプロピルベンゾイル)-3, 5-ジメチルマロンアニリド酸エチル (化合物 3 4)

4-(4-ベンジルオキシ-3-イソプロピルベンゾイル)-3, 5-ジメチルマロンアニリド酸エチル 38mg を酢酸エチル 10mL に溶解し、10%パラジウム炭素触媒 (50%含水晶) 38mg を加え、室温にて水素雰囲気下
25 常圧で 3 時間攪拌した。不溶物をろ去後、ろ液を減圧濃縮し、4-(4-ヒドロキシ-3-イソプロピルベンゾイル)-3, 5-ジメチルマロンアニリド酸エチルを 28mg 得た。

¹H-NMR (CDCl₃) δ ppm: 1.25 (6H, d, J=6.9Hz), 1.34 (3H, t, J=7.1Hz), 2.08 (6H, s), 3.23 (1H, heptet, J=6.9Hz), 3.50 (2H, s), 4.2

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.20 (6H, d, $J=6.9\text{Hz}$), 1.32 (3H, t, $J=7.1\text{Hz}$), 3.20 (1H, heptet, $J=6.9\text{Hz}$), 3.49 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 4.80 (1H, brs), 6.35 (1H, dd, $J=3.0, 8.7\text{Hz}$), 6.64 (1H, d, $J=8.7\text{Hz}$), 6.78 (1H, d, $J=3.0\text{Hz}$), 7.86 (2H, s), 9.49 (1H, s)

5 (製造例 16)

(-) -4- [3- [(4-フルオロフェニル) ヒドロキシメチル] -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸エチル (化合物 37)

(-) -B-クロロジイソピノカンフェイルボラン 3.7 g をテトラヒドロフラン 6 mL に溶解し、 -15°C にて攪拌下、ピリジン 1.87 mL を滴下した。反応混合物に 4- [3- (4-フルオロベンゾイル) -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸エチル 2.28 g のテトラヒドロフラン溶液 6 mL を滴下し、室温にて 16 時間攪拌した。反応混合物を -15°C にて攪拌し、30% 過酸化水素水 6 mL を滴下した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を 10% 亜硫酸水素ナトリウム水溶液、水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー (溶出溶媒: ヘキサン-酢酸エチル) にて精製し、(-) -4- [3- [(4-フルオロフェニル) ヒドロキシメチル] -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸エチル 0.315 g を得た。

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 2.06 (6H, s), 3.45 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.87 (1H, s), 6.36 (1H, d, $J=3.2\text{Hz}$), 6.54 (1H, dd, $J=3.2, 8.8\text{Hz}$), 6.75 (1H, d, $J=8.8\text{Hz}$), 6.97-7.08 (2H, m), 7.22-7.39 (4H, m), 9.12 (1H, s)

25 (製造例 17)

製造例 16 と同様にして、(+)-B-クロロジイソピノカンフェイルボランを用いて以下の化合物を合成した。

(+) -4- [3- [(4-フルオロフェニル) ヒドロキシメチル] -4-ヒ

8 (2H, q, J=7.1Hz), 6.32 (1H, brs), 6.72 (1H, d, J=8.3Hz), 7.27 (2H, s), 7.32 (1H, brs), 7.86 (1H, brs), 9.30 (1H, s)

(製造例 14)

5 4-〔3-(4-フルオロベンジル)-4-ヒドロキシベンジル〕-3, 5-ジメチルマロンアニリド酸エチル (化合物 35)

4-〔3-(4-フルオロベンゾイル)-4-ヒドロキシベンジル〕-3, 5-ジメチルマロンアニリド酸エチル 9 mg を塩化メチレン 3 mL に溶かし、トリエチルシラン 15.5 μ L およびトリフルオロ酢酸 3 mL を加えた後、アルゴン雰囲気下室温にて一晩撹拌した。反応混合物に水 10 mL を加え、室温にて 15 分間撹拌した後、反応混合物を塩化メチレンで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー (展開溶媒: ヘキサン-酢酸エチル) にて精製して、4-〔3-(4-フルオロベンジル)-4-ヒドロキシベンジル〕-3, 5-ジメチルマロンアニリド酸エチル 4 mg を得た。

$^1\text{H-NMR}$ (CDCl₃) δ ppm: 1.33 (3H, t, J=7.1Hz), 2.20 (6H, s), 3.46 (2H, s), 3.87 (2H, s), 3.90 (2H, s), 4.26 (2H, q, J=7.1Hz), 4.52 (1H, s), 6.63 (1H, d, J=8.2Hz), 6.69 (1H, dd, J=2.1, 8.2Hz), 6.74 (1H, d, J=2.1Hz), 6.93-6.96 (2H, m), 7.09-7.13 (2H, m), 7.25 (2H, s), 9.07 (1H, brs)

(製造例 15)

3, 5-ジブromo-4-(4-ヒドロキシ-3-イソプロピルフェノキシ) マロンアニリド酸エチル (化合物 36)

4-(4-ベンジルオキシ-3-イソプロピルフェノキシ)-3, 5-ジブromoアニリン 400 mg を用い、製造例 1 及び製造例 3 と同様の方法により、N-(3, 5-ジブromo-4-(4-ヒドロキシ-3-イソプロピルフェノキシ) マロンアニリド酸エチル 119 mg を得た。

ドロキシフェノキシ] - 3, 5-ジメチルマロンアニリド酸エチル (化合物 38)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.33 (3H, t, $J=7.1\text{Hz}$), 2.06 (6H, s), 3.44 (2H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.87 (1H, s), 6.36 (1H, d, $J=3.2\text{Hz}$), 6.54 (1H, dd, $J=3.2, 8.8\text{Hz}$), 6.75 (1H, d, $J=8.8\text{Hz}$), 6.97-7.08 (2H, m), 7.22-7.39 (4H, m), 9.14 (1H, s)

(製造例 18)

4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル] - 4-ヒドロキシフェノキシ] - 3, 5-ジメチルマロンアニリド酸 (化合物 39)

4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル] - 4-ヒドロキシフェノキシ] - 3, 5-ジメチルマロンアニリド酸エチル 1.40 g にエタノール 20 mL と 1 mol/L 水酸化ナトリウム水溶液 20 mL を加え、アルゴン雰囲気下 60℃ にて 30 分間攪拌した。反応混合物を減圧濃縮し、得られた残渣に水を加え、ジエチルエーテルで洗浄した。水層に 1 mol/L 塩酸と飽和食塩水を加え、酢酸エチルで抽出した。有機層を無水硫酸マグネシウムで乾燥後、減圧濃縮し、4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル] - 4-ヒドロキシフェノキシ] - 3, 5-ジメチルマロンアニリド酸 1.31 g を得た。

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 2.01 (6H, s), 3.33 (2H, s), 5.70 (1H, d, $J=4.0\text{Hz}$), 5.87 (1H, d, $J=4.0\text{Hz}$), 6.40 (1H, dd, $J=3.2, 8.8\text{Hz}$), 6.64 (1H, d, $J=8.8\text{Hz}$), 6.84 (1H, d, $J=3.2\text{Hz}$), 7.01-7.13 (2H, m), 7.23-7.43 (4H, m), 9.07 (1H, s), 10.03 (1H, s), 12.60 (1H, brs)

25 (製造例 19)

製造例 18 と同様の方法により、以下の化合物を合成した。

2, 3, 5-トリフロロ-4-(4-ヒドロキシ-3-イソプロピルフェノキシ) マロンアニリド酸 (化合物 40)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.18 (6H, d, $J=6.9\text{Hz}$),

3.21 (1H, heptet, J=6.9Hz), 3.44 (2H, s), 6.26 (1H, dd, J=3.0, 8.7Hz),
6.55 (1H, d, J=8.7Hz), 6.80 (1H, d, J=3.0Hz), 8.40 (1H, brs)

3, 5-ジブロモ-4-(4-ヒドロキシ-3-イソプロピルフェノキシ) マ
5 ロンアニリド酸 (化合物41)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.20 (6H, d, J=6.9Hz),
3.22 (1H, heptet, J=6.9Hz), 3.47 (2H, s), 6.36 (1H, dd, J=3.0, 8.7Hz),
6.63 (1H, d, J=8.7Hz), 6.77 (1H, d, J=3.0Hz), 7.86 (2H, s)

10 4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-2, 3, 5-トリメ
チルマロンアニリド酸 (化合物42)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.19 (6H, d, J=6.9Hz),
2.07 (6H, s), 2.18 (3H, s), 3.24 (1H, heptet, J=6.9Hz), 3.49 (2H, s),
6.21 (1H, dd, J=3.0, 8.6Hz), 6.63 (1H, d, J=8.6Hz), 6.71 (1H, d, J=3.0
15 Hz), 7.40 (1H, s)

4-(4-ヒドロキシ-3-イソプロピル-2-メトキシフェノキシ)-3,
5-ジメチルマロンアニリド酸 (化合物43)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.39 (6H, d, J=7.1Hz),
20 2.09 (6H, s), 3.46 (2H, s), 3.55 (1H, heptet, J=7.1Hz), 3.96 (3H, s),
5.93 (1H, d, J=8.8Hz), 6.25 (1H, d, J=8.8Hz), 7.29 (2H, s)

2, 3, 5-トリクロロ-4-(4-ヒドロキシ-5, 6, 7, 8-テトラヒ
ドロ-1-ナフチルオキシ) マロンアニリド酸 (化合物44)

25 $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.70-1.85 (4H, m), 2.60
-2.72 (2H, m), 2.78-2.88 (2H, m), 3.42 (2H, s), 5.92 (1H, d, J=8.7Hz),
6.34 (1H, d, J=8.7Hz), 8.36 (1H, s)

4-[4-ヒドロキシ-3-(6-オキソ-1, 6-ジヒドロピリダジン-3

ーイルメチル) フェノキシ] - 3, 5-ジメチルマロンアニリド酸 (化合物 4 5)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.07 (6H, s), 3.45 (2H, s), 3.85 (2H, s), 6.46-6.53 (3H, m), 6.70 (1H, d, $J=8.6\text{Hz}$), 6.85 (1H, d, $J=9.7\text{Hz}$), 7.25-7.30 (3H, m)

4- [4-ヒドロキシ-3- [2- (4-テトラヒドロピラニル) エチル] フェノキシ] - 3, 5-ジメチルマロンアニリド酸 (化合物 4 6)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.23-1.34 (2H, m), 1.45-1.53 (3H, m), 1.61-1.68 (2H, m), 2.10 (6H, s), 2.51-2.57 (2H, m), 3.32-3.40 (2H, m), 3.46 (2H, s), 3.92-3.98 (2H, m), 6.38 (1H, dd, $J=3.0, 8.7\text{Hz}$), 6.52 (1H, d, $J=3.0\text{Hz}$), 6.61 (1H, d, $J=8.7\text{Hz}$), 7.29 (2H, s)

4- (4-ヒドロキシ-3-イソプロピルベンゾイル) - 3, 5-ジメチルマロンアニリド酸 (化合物 4 7)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.22 (6H, d, $J=6.9\text{Hz}$), 2.10 (6H, s), 3.27 (1H, heptet, $J=6.9\text{Hz}$), 3.46 (2H, s), 6.73 (1H, brd, $J=8.4\text{Hz}$), 7.28 (2H, s), 7.35 (1H, brs), 7.79 (1H, brs)

4- (4-ヒドロキシ-3-イソプロピルベンジル) - 3, 5-ジメチルマロンアニリド酸 (化合物 4 8)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.19 (6H, d, $J=6.9\text{Hz}$), 2.21 (6H, s), 3.19 (1H, heptet, $J=6.9\text{Hz}$), 3.46 (2H, s), 3.91 (2H, s), 6.51 (1H, dd, $J=2.0, 8.1\text{Hz}$), 6.58 (1H, d, $J=8.1\text{Hz}$), 6.91 (1H, d, $J=2.0\text{Hz}$), 7.23 (2H, s)

4- [3- (4-フルオロベンゾイル) - 4-ヒドロキシベンジル] - 3, 5-ジメチルマロンアニリド酸 (化合物 4 9)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.20 (6H, s), 3.53 (2H, s), 3.92

(2H, s), 6.97 (1H, d, J=8.5Hz), 7.07-7.17 (3H, m), 7.15-7.23 (3H, m),
7.53-7.62 (2H, m), 8.25 (1H, brs), 11.68 (1H, s)

4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシ
5 ベンジル〕-3, 5-ジメチルマロンアニリド酸 (化合物50)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.15 (6H, s), 3.43 (2H,
s), 3.85 (2H, s), 5.84 (1H, s), 6.51 (1H, d, J=1.4Hz), 6.72 (1H, d, J
=8.3Hz), 6.76 (1H, dd, J=1.4, 8.3Hz), 6.96-7.03 (2H, m), 7.20 (2H, s),
7.25-7.33 (2H, m)

10

4-〔3-(4-フルオロベンジル)-4-ヒドロキシベンジル〕-3, 5-
ジメチルマロンアニリド酸 (化合物51)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.19 (6H, s), 3.44 (2H,
s), 3.87 (4H, s), 6.63 (2H, s), 6.70 (1H, s), 6.90-6.96 (2H, m), 7.10
15 -7.17 (2H, m), 7.23 (2H, s)

4-〔3-(4-フルオロフェノキシ)-4-ヒドロキシフェノキシ〕-3,
5-ジメチルマロンアニリド酸 (化合物52)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.04 (6H, brs), 3.40 (2
20 H, brs), 6.27-6.38 (2H, m), 6.80-7.03 (5H, m), 7.20-7.30 (2H, brs)

4-〔〔3-(4-フルオロフェノキシ)-4-ヒドロキシフェニル〕 ヒドロ
キシメチル〕-3, 5-ジメチルマロンアニリド酸 (化合物53)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.23 (6H, s), 3.43 (2H,
25 s), 6.17 (1H, s), 6.76-6.79 (1H, m), 6.89-6.93 (4H, m), 6.93-7.01 (2H,
m), 7.19 (2H, s)

4-〔3-(4-フルオロフェノキシ)-4-ヒドロキシベンジル〕-3, 5-
ジメチルマロンアニリド酸 (化合物54)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 2.19 (6H, s), 3.42 (2H, s), 3.87 (2H, s), 6.55 (1H, d, $J=2.0\text{Hz}$), 6.60 (1H, dd, $J=2.0, 8.3\text{Hz}$), 6.86 (1H, d, $J=8.3\text{Hz}$), 6.86-6.92 (2H, m), 6.94-7.02 (2H, m), 7.22 (2H, s)

5

4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルオキシ)フェノキシ〕-3, 5-ジメチルマロンアニリド酸 (化合物55)

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ ppm: 1.73-1.84 (2H, m), 2.02-2.10 (2H, m), 2.11 (6H, s), 3.45 (2H, s), 3.54-3.61 (2H, m), 3.95-4.03 (2H, m), 4.38-4.47 (1H, m), 6.12 (1H, dd, $J=2.8, 8.7\text{Hz}$), 6.48 (1H, d, $J=2.8\text{Hz}$), 6.75 (1H, d, $J=8.7\text{Hz}$), 7.29 (2H, s)

10

4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルオキシ)ベンジル〕-3, 5-ジメチルマロンアニリド酸 (化合物56)

15 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.68-1.78 (2H, m), 1.93-2.02 (2H, m), 2.21 (6H, s), 3.45 (2H, s), 3.50-3.56 (2H, m), 3.92 (2H, s), 3.93-3.99 (2H, m), 4.33-4.38 (1H, m), 6.46 (1H, brd, $J=8.2\text{Hz}$), 6.52 (1H, br s), 6.78 (1H, d, $J=8.2\text{Hz}$), 7.26 (2H, s)

20

4-〔4-ヒドロキシ-3-(2-メトキシベンゾイル)フェノキシ〕-3, 5-ジメチルマロンアニリド酸 (化合物57)

$^1\text{H-NMR}$ (CD_3OD) δ ppm: 2.11 (6H, s), 3.41 (2H, s), 3.71 (3H, s), 6.68 (1H, d, $J=3.0\text{Hz}$), 6.78-7.00 (3H, m), 7.02-7.12 (1H, m), 7.23-7.37 (3H, m), 7.44-7.55 (1H, m)

25

4-〔3-〔3-(2-カルボキシエチル)ベンジル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸 (化合物58)

$^1\text{H-NMR}$ (CD_3OD) δ ppm: 2.02 (6H, s), 2.53 (2H, t, $J=7.7\text{Hz}$), 2.83 (2H, t, $J=7.7\text{Hz}$), 3.82 (2H, s), 6.31 (1H, d, $J=3.0\text{Hz}$), 6.41

(1H, dd, J=3.0, 8.6Hz), 6.67 (1H, d, J=8.6Hz), 6.93-7.05 (3H, m), 7.08-7.18 (1H, m), 7.26 (2H, s)

4- (4-ヒドロキシ-5, 6, 7, 8-テトラヒドロ-1-ナフチルオキシ) -3, 5-ジメチルマロンアニリド酸 (化合物59)

¹H-NMR (CD₃OD) δ ppm: 1.73-1.88 (4H, m), 2.05 (6H, s), 2.59-2.61 (2H, m), 2.78-2.88 (2H, m), 3.42 (2H, s), 5.86 (1H, d, J=8.7Hz), 6.35 (1H, d, J=8.7Hz), 7.30 (2H, s)

10 4- [3- (2-シクロヘキシルエチル) -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸 (化合物60)

¹H-NMR (CD₃OD) δ ppm: 0.81-0.98 (2H, m), 1.08-1.47 (6H, m), 1.56-1.80 (5H, m), 2.08 (6H, s), 2.51 (2H, t, J=7.8Hz), 3.43 (2H, s), 6.37 (1H, dd, J=3.0, 8.6Hz), 6.42 (1H, d, J=3.0Hz), 6.62 (1H, d, J=8.6Hz), 7.31 (2H, s)

4- [3- (4-フルオロベンジル) -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸 (化合物61)

20 ¹H-NMR (DMSO-d₆) δ ppm: 1.99 (6H, s), 3.32 (2H, s), 3.79 (2H, s), 6.32 (1H, dd, J=3.1, 8.6Hz), 6.53 (1H, d, J=3.1Hz), 6.68 (1H, d, J=8.6Hz), 7.00-7.13 (2H, m), 7.14-7.27 (2H, m), 7.32 (2H, s), 9.06 (1H, brs), 10.07 (1H, s)

25 4- [3- (4-フルオロベンゾイル) -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸 (化合物62)

¹H-NMR (DMSO-d₆) δ ppm: 2.05 (6H, s), 3.32 (2H, s), 6.62 (1H, d, J=2.7Hz), 6.80-6.95 (2H, m), 7.25-7.42 (4H, m), 7.68-7.82 (2H, m), 9.82 (1H, s), 10.04 (1H, s), 12.61 (1H, s)

4-〔3-(2-シクロヘキシル-1-ヒドロキシエチル)-4-ヒドロキシ
フェノキシ〕-3, 5-ジメチルマロンアニリド酸 (化合物63)

¹H-NMR (DMSO-d₆) δ ppm: 0.75-1.85 (13H, m), 2.02 (6H, s), 3.33 (2H, s), 4.78-4.93 (1H, m), 6.38 (1H, dd; J=3.2, 8.7Hz), 6.62
5 (1H, d, J=8.7Hz), 6.70 (1H, d, J=3.2Hz), 7.33 (2H, s), 8.86 (1H, s),
10.02 (1H, s), 12.61 (1H, brs)

2-フルオロ-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3,
5-ジメチルマロンアニリド酸 (化合物64)

10 ¹H-NMR (CD₃OD) δ ppm: 1.15 (6H, d, J=6.9Hz), 1.95-2.12
(6H, m), 3.23 (1H, heptet, J=6.9Hz), 3.51 (2H, s), 6.28 (1H, dd, J=3.0,
8.4Hz), 6.56-6.68 (2H, m), 7.69 (1H, d, J=8.6Hz)

4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルメチル)フェノキシ〕-3,
15 5-ジメチルマロンアニリド酸 (化合物65)

¹H-NMR (DMSO-d₆) δ ppm: 1.05-1.28 (2H, m), 1.37-1.50
(2H, m), 1.65-1.80 (1H, m), 2.02 (6H, s), 2.38 (2H, d, J=7.1Hz), 3.11-
3.26 (2H, m), 3.33 (2H, s), 3.70-3.85 (2H, m), 6.34 (1H, dd, J=3.1, 8.
7Hz), 6.42 (1H, d, J=3.1Hz), 6.66 (1H, d, J=8.7Hz), 7.33 (2H, s), 8.86
20 (1H, s), 10.03 (1H, s), 12.55 (1H, brs)

4-〔4-ヒドロキシ-3-〔2-(3-テトラヒドロフラン)エチル〕フェ
ノキシ〕-3, 5-ジメチルマロンアニリド酸 (化合物66)

¹H-NMR (DMSO-d₆) δ ppm: 1.35-1.61 (3H, m), 1.84-2.15
25 (8H, m), 2.30-2.65 (2H, m), 3.12-3.26 (1H, m), 3.33 (2H, s), 3.48-3.80
(3H, m), 6.32 (1H, dd, J=3.1, 8.7Hz), 6.48 (1H, d, J=3.1Hz), 6.65 (1H,
d, J=8.7Hz), 7.33 (2H, s), 8.83 (1H, s), 10.03 (1H, s), 12.63 (1H, br
s)

4-(4-ヒドロキシ-3-イソプロピルフェニルスルファニル)-3,5-ジメチルマロンアニリド酸(化合物67)

¹H-NMR (DMSO-d₆) δ ppm: 1.07 (6H, d, J=6.9Hz), 2.34 (6H, s), 3.11 (1H, heptet, J=6.9Hz), 3.35 (2H, s), 6.50 (1H, dd, J=2.4, 8.4Hz), 6.63 (1H, d, J=8.4Hz), 6.83 (1H, d, J=2.4Hz), 9.26 (1H, s), 10.16 (1H, s), 12.60 (1H, brs)

4-(4-ヒドロキシ-3-イソプロピルベンゼンスルホニル)-3,5-ジメチルマロンアニリド酸 (化合物68)

10 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 1.15 (6H, d, $J=6.9\text{Hz}$), 2.53 (6H, s), 3.20 (1H, heptet, $J=6.9\text{Hz}$), 3.36 (2H, s), 6.95 (1H, d, $J=8.5\text{Hz}$), 7.34-7.50 (3H, m), 7.55 (1H, d, $J=2.4\text{Hz}$), 10.37 (1H, s), 10.51 (1H, s), 12.65 (1H, brs)

15 4-(4-ヒドロキシ-3-イソプロピルフェノキシ)-3,5-ジメチルマ
ロンアニリド酸(化合物69)

¹H-NMR (CDCl₃+CD₃OD) δ ppm: 1.90 (6H, d, J=6.9Hz), 2.10 (6H, s), 3.21 (1H, heptet, J=6.9Hz), 3.46 (2H, s), 6.26 (1H, dd, J=3.0, 8.7Hz), 6.59 (1H, d, J=8.7Hz), 6.71 (1H, d, J=3.0Hz), 7.27 (2H, s)

(製造例 20)

4-〔3-〔(4-フルオロフェニル)ヒドロキシメチル]-4-ヒドロキシフェノキシ]-3,5-ジメチルマロンアニリド酸ナトリウム(化合物70)

25 4-〔3-〔(4-フルオロフェニル)ヒドロキシメチル]-4-ヒドロキシフェノキシ]-3,5-ジメチルマロンアニリド酸エチル2. 28gをメタノール20mLに溶解し、1mol/L水酸化ナトリウム水溶液20mLを加え、50℃で3時間攪拌した。反応混合物に水とジエチルエーテルを加え、水層を分取し、1mol/L塩酸を加えて中和し、酢酸エチルで抽出した。有機

層を無水硫酸マグネシウムで乾燥し、溶媒を減圧下に留去した。残渣に2m o
1/L水酸化ナトリウム水溶液4. 3mL加え、溶媒を減圧留去し、4-〔3
-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸ナトリウム1. 53gを得た。

- 5 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 1.99 (6H, s), 2.87 (2H, s), 5.
86 (1H, s), 6.37 (1H, dd, $J=3.0, 9.0\text{Hz}$), 6.64 (1H, d, $J=9.0\text{Hz}$), 6.80
(1H, d, $J=3.0\text{Hz}$), 6.98-7.12 (2H, m), 7.20-7.38 (4H, m), 12.23 (1H, s)

(製造例21)

- 10 製造例20と同様の方法により、以下の化合物を合成した。

4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシ
フェノキシ〕-3, 5-ジメチルマロンアニリド酸カリウム (化合物71)

- 15 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 1.99 (6H, s), 2.84 (2H, s), 5.
88 (1H, s), 6.38 (1H, dd, $J=3.1, 9.0\text{Hz}$), 6.67 (1H, d, $J=9.0\text{Hz}$), 6.84
(1H, d, $J=3.1\text{Hz}$), 7.00-7.15 (2H, m), 7.24-7.40 (4H, m), 12.48 (1H, s)

(-) -4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒ
ドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸ナトリウム (化合
物72)

- 20 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 1.99 (6H, s), 2.90 (2H, s), 5.
71 (1H, s), 5.87 (1H, s), 6.39 (1H, dd, $J=3.1, 8.6\text{Hz}$), 6.66 (1H, d, $J=$
8.6Hz), 6.84 (1H, d, $J=3.1\text{Hz}$), 7.00-7.15 (2H, m), 7.23-7.40 (4H, m), 9.
22 (1H, brs), 12.14 (1H, brs)

- 25 (+) -4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒ
ドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸ナトリウム (化合
物73)

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 1.99 (6H, s), 2.93 (2H, s), 5.
71 (1H, s), 5.87 (1H, s), 6.39 (1H, dd, $J=3.1, 8.6\text{Hz}$), 6.65 (1H, d, $J=$

8.6Hz), 6.84 (1H, d, J=3.1Hz), 7.00-7.15 (2H, m), 7.23-7.40 (4H, m), 9.18 (1H, brs), 11.99 (1H, brs)

(製造例 2 2)

- 5 ビス〔4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸〕カルシウム (化合物 7 4)

4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸 0.358 g と水酸化カルシウム 30 mg をメタノール 30 mL に加え、室温にて 2 時間攪拌した。反応混合物を減圧濃縮し、ビス〔4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸〕カルシウム 0.370 g を得た。

¹H-NMR (DMSO-d₆) δ ppm: 1.99 (6H, s), 3.04 (2H, s), 5.71 (1H, s), 5.87 (1H, s), 6.40 (1H, dd, J=3.1, 8.6Hz), 6.65 (1H, d, J=8.6Hz), 6.82 (1H, d, J=3.1Hz), 7.00-7.15 (2H, m), 7.23-7.43 (4H, m), 9.17 (1H, brs), 11.21 (1H, brs)

(製造例 2 3)

- 20 4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸メチル (化合物 7 5)

4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸ナトリウム 755 mg を 10 mL のメタノールに溶かし、ヨウ化メチル 0.123 mL を加え、40℃ にて一晩加熱攪拌した。反応混合物を水で希釈し、酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、減圧濃縮し、得られた残渣をシリカゲル薄層クロマトグラフィー (展開溶媒: ヘキサン-酢酸エチル) にて精製して、4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ

シ) - 3, 5-ジメチルマロンアニリド酸メチルを55mg得た。

¹H-NMR (CDCl₃) δ ppm: 2.04 (6H, s), 3.30 (1H, d, J=3.3Hz), 3.46 (2H, s), 3.81 (3H, s), 5.86 (1H, d, J=3.3Hz), 6.36 (1H, d, J=3.0Hz), 6.53 (1H, dd, J=3.0, 8.8Hz), 6.75 (1H, d, J=8.8Hz), 6.98-7.04
5 (2H, m), 7.26 (2H, s), 7.28-7.34 (2H, m), 7.38 (1H, s), 9.07 (1H, s)

(製造例24)

(+) - 4 - [3 - [(4-フルオロフェニル) ヒドロキシメチル] - 4 - ヒ
ドロキシフェノキシ] - 3, 5-ジメチルマロンアニリド酸L-チロシンアミ
10 ド塩 (化合物76)

(+) - 4 - [3 - [(4-フルオロフェニル) ヒドロキシメチル] - 4 -
ヒドロキシフェノキシ] - 3, 5-ジメチルマロンアニリド酸ナトリウム1.0
gおよびL-チロシンアミド塩酸塩0.51gを水20mLに懸濁させ、5
0℃にて溶解させた。室温にて放冷攪拌し、析出物をろ取して、(+) - 4 -
15 [3 - [(4-フルオロフェニル) ヒドロキシメチル] - 4 - ヒドロキシフェ
ノキシ] - 3, 5-ジメチルマロンアニリド酸L-チロシンアミド塩1.11
gを得た。

¹H-NMR (DMSO-d₆) δ ppm: 2.00 (6H, s), 2.60-2.70 (1H,
m), 2.81-2.92 (1H, m), 3.16 (2H, s), 3.45-3.57 (1H, m), 5.71 (1H, brs),
20 5.87 (1H, s), 6.39 (1H, dd, J=3.2, 8.6Hz), 6.60-6.80 (3H, m), 6.84 (1
H, d, J=3.2Hz), 6.97-7.44 (10H, m), 7.50 (1H, s), 9.14 (1H, brs), 10.8
3 (1H, brs)

(製造例25)

25 3, 5-ジプロモ-3' - (6-オキソ-1, 6-ジヒドロピリダジン-3
-イルメチル) - L-サイロニン (化合物77)

化合物77を、JP61/167643に記載された実施例33と同様にし
て製造した。

N- [4- [3- [(4-フルオロフェニル) ヒドロキシメチル] -4-ヒドロキシフェノキシ] -3, 5-ジメチルフェニル] オキサミド酸エチル (化合物78)

化合物78を、JP06/172275に記載された例20と同様にして製造した。

N- [3, 5-ジメチル-4- (4-ヒドロキシ-3-イソプロピルフェノキシ) ベンゾイル] グリシン (化合物79)

化合物79を、WO00/39077に記載された実施例211と同様にして製造した。

〔産業上の利用可能性〕

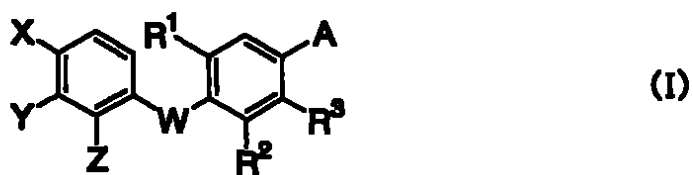
本発明の有効成分である甲状腺ホルモン受容体アゴニスト、特に前記一般式(I)で表される化合物またはそれらの薬理学的に許容される塩は、肝エストロゲンスルホトランスフェラーゼの発現を低下させる作用を有し、癌または前癌病変のマーカー酵素である胎盤型グルタチオンS-トランスフェラーゼ (GSTP) が発現した肝変異巣、および癌または前癌状態で増加する血中のマーカー酵素であるγ-グルタミルトランスフェラーゼ (GGT) を顕著に低下させ、優れた肝腫瘍抑制作用を有する。さらに当該化合物は、肝臓内グルタチオン含量を低下させ、肝癌細胞の増殖を抑制する作用を有する。さらに当該化合物は、甲状腺ホルモンに認められる副作用が軽微であり、極めて高い安全性を示す。従って当該化合物は、肝癌の予防または再発抑制剤として極めて有用である。

請求の範囲

1. 肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストを有効成分として含有する、肝癌の予防または再発抑制剤。

2. 前記甲状腺ホルモン受容体アゴニストが、さらに肝グルタチオン低下作用を有する、請求項1に記載の肝癌の予防または再発抑制剤。

3. 前記甲状腺ホルモン受容体アゴニストが、以下の一般式 (I) :



〔式中、

R^1 および R^2 は、それぞれ独立して、 C_{1-9} アルキル基、トリフルオロメチル基、ハロゲン原子またはシアノ基を表し；

R^3 は、水素原子、 C_{1-9} アルキル基、トリフルオロメチル基またはハロゲン原子を表し；

Wは、 $-O-$ 、 $-S-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、 $-CO-$ 、 $-SO-$ 、または $-SO_2-$ を表し；

Xは、水酸基、または一般式 $-NH-G-V$ で表される基を表し；

Gは、 $-CO-$ 、 $-SO-$ 、 $-SO_2-$ 、 $-CS-NH-$ または $-CO-NH-$ を表し；

Vは、 C_{1-10} アルキル基、 C_{3-8} シクロアルキル基、あるいは非置換または置換アリール基を表し；

Yは、 C_{1-10} アルキル基、トリフルオロメチル基、 C_{3-8} シクロアルキル基、非置換または置換アリール基、 $-S(O)_2NR^4R^5$ 、 $-C(O)NR^4R^5$ 、 $-S(O)_2R^6$ 、6-オキソ-1, 6-ジヒドロピリジン-3-イルメチル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基または一般

式-Q-Tで表される基を表すか、あるいはXとYが一緒になって、-NH-C=C(R⁷)-を形成し；

R⁴およびR⁵は、それぞれ独立して、水素原子、C₁₋₁₀アルキル基、C₃₋₈シクロアルキル基、C₃₋₈シクロアルキルC₁₋₈アルキル基、あるいは非置換または置換アリール基を表すか、あるいはR⁴およびR⁵が、それらが結合している窒素原子と一緒にあって5~7員の環状アミンを形成し；

R⁶は、C₁₋₁₀アルキル基、C₃₋₈シクロアルキル基、C₃₋₈シクロアルキルC₁₋₈アルキル基、あるいは非置換または置換アリール基を表し；

R⁷は、水素原子、またはC₁₋₈アルキル基を表し；

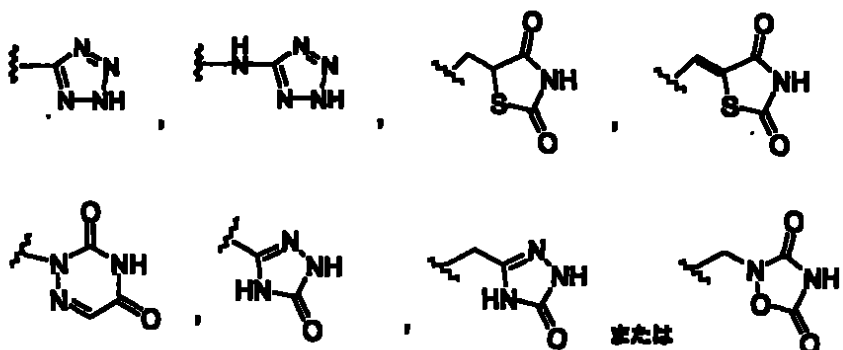
10 Qは、-O-、-CH₂-、-CH(OH)-、または-CO-を表し；

Tは、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよいC₃₋₈シクロアルキル基、あるいは環内に酸素原子を有してもよいC₃₋₈シクロアルキルメチル基を表し；

15 Zは、水素原子またはC₁₋₈アルコキシ基を表すか、あるいはYとZが、一緒になって-(CH₂)_m-を形成し；

mは、3~4の整数を表し；

Aは、-NHCO-Y¹-CO₂R⁸、-CONHCH₂CO₂R⁸、-CH₂CH(R⁹)NR¹⁰R¹¹、または-Y²-COR¹²を表すか、あるいは以下の式：



20 で表される基を表し；

Y¹は、結合、C₁₋₈アルキレン基、または-CH=CH-を表し；

R⁸は、水素原子、C₁₋₈アルキル基、またはアリールC₁₋₈アルキル基を表し；

R⁹は、カルボキシ基またはC₁₋₈アルコキシカルボニル基を表し；

R^{10} は、水素原子または C_{1-6} アルキル基を表し；

R^{11} は、水素原子、 C_{1-6} アルキル基または C_{1-4} アルカノイル基を表し；

Y^2 は、結合または C_{1-6} アルキレン基を表し；

R^{12} は、ヒドロキシ基または C_{1-6} アルコキシ基を表す]

- 5 で表される化合物またはそれらの薬理学的に許容される塩である、請求項1に記載の肝癌の予防または再発抑制剤。

4. R^1 および R^2 が、それぞれ独立して、 C_{1-6} アルキル基、トリフルオロメチル基、またはハロゲン原子であり；

- 10 Aが、 $-NHCO-Y^1-CO_2R^8$ 、 $-CONHCH_2CO_2R^8$ 、または $-CH_2CH(R^9)NH_2$ であり；

Y^1 が、結合、または $-CH_2-$ であり；

R^8 が、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基であり；

- 16 R^9 が、カルボキシ基または C_{1-6} アルコキシカルボニル基である、請求項3に記載の肝癌の予防または再発抑制剤。

5. Xが、水酸基であり；

- 20 Yが、 C_{1-6} アルキル基、トリフルオロメチル基、 $-S(O)_2R^6$ 、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基、または一般式 $-Q^1-T^1$ で表される基を表すか、あるいはXとYが一緒になって、 $-NH-C=C(R^7)-$ を形成し；

R^6 が、非置換または置換アリール基を表し；

R^7 が、水素原子、または C_{1-6} アルキル基を表し；

- 25 Q^1 が、 $-O-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、または $-CO-$ であり；

T^1 が、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよい C_{5-8} シクロアルキル基、あるいは環内に酸素原子を有してもよい C_{5-8} シクロアルキルメチル基である、請求項4に記載の肝癌の予防または再発抑制剤。

6. R^1 および R^2 が、それぞれ独立して、 C_{1-8} アルキル基またはハロゲン原子であり；

R^2 が、水素原子であり；

5 W が、 $-O-$ であり；

X が、水酸基であり；

Y が、一般式 $-Q^1-T^1$ で表される基であり；

Q^1 が、 $-CH(OH)-$ であり；

T^1 が、非置換または置換アリール基であり；

10 Z が、水素原子であり；

A が、 $-NHCOCO_2R^3$ であり；

R^3 が、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基である、請求項5に記載の肝癌の予防または再発抑制剤。

15 7. Y が、 C_{1-6} アルキル基、トリフルオロメチル基、6-オキソ-1,6-ジヒドロピリダジン-3-イルメチル基、または一般式 $-Q^1-T^1$ で表される基であり；

Q^1 が、 $-O-$ 、 $-CH_2-$ 、 $-CH(OH)-$ 、または $-CO-$ であり；

20 T^1 が、非置換または置換アリール基、非置換または置換アリールメチル基、環内に酸素原子を有してもよい C_{5-8} シクロアルキル基、あるいは環内に酸素原子を有してもよい C_{5-8} シクロアルキルメチル基であり；

Z が、水素原子または C_{1-8} アルコキシ基を表すか、あるいは Y と Z が、一緒になって $-(CH_2)_4-$ を形成し；

A が、 $-NHCOCH_2CO_2R^3$ であり；

25 R^3 が、水素原子、 C_{1-6} アルキル基、またはアリール C_{1-6} アルキル基である、請求項5に記載の肝癌の予防または再発抑制剤。

8. W が、 $-O-$ である、請求項7に記載の肝癌の予防または再発抑制剤。

9. R^1 および R^2 が、それぞれ独立して、 C_{1-3} アルキル基またはハロゲン原子であり；

R^2 が、水素原子であり；

Yが、 C_{1-6} アルキル基、6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル基、または一般式 $-Q^2-T^2$ で表される基であり；

Q^2 が、 $-CH_2-$ 、または $-CH(OH)-$ であり；

T^2 が、非置換または置換アリール基であり；

Zが水素原子である、請求項8に記載の肝癌の予防または再発抑制剤。

10 10. R^1 および R^2 が、それぞれ独立して、 C_{1-3} アルキル基であり；

Yが、一般式 $-Q^3-T^3$ で表される基であり；

Q^3 が、 $-CH(OH)-$ であり；

T^3 が、非置換または置換アリール基である、請求項9に記載の肝癌の予防または再発抑制剤。

15

11. 前記甲状腺ホルモン受容体アゴニストが、以下からなる群：

4-〔3-〔(4-フルオロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

20 4-〔3-〔(4-フルオロフェニル) メチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔3-〔(4-クロロフェニル) ヒドロキシメチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔3-〔(4-クロロフェニル) メチル〕-4-ヒドロキシフェノキシ〕-3, 5-ジメチルマロンアニリド酸；

25 4-〔4-ヒドロキシ-3-(6-オキソ-1, 6-ジヒドロピリダジン-3-イルメチル) フェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔4-ヒドロキシ-3-(4-テトラヒドロピラニルメチル) フェノキシ〕-3, 5-ジメチルマロンアニリド酸；

4-〔4-ヒドロキシ-3-〔2-(3-テトラヒドロフラン) エチル〕

フェノキシ] - 3, 5 - ジメチルマロンアニリド酸 ;

4 - (4 - ヒドロキシ - 3 - イソプロピルフェノキシ) - 3, 5 - ジメチルマロンアニリド酸 ;

5 4 - (4 - ヒドロキシ - 3 - イソプロピルフェノキシ) - 3, 5 - ジブロモマロンアニリド酸 ;

4 - (4 - ヒドロキシ - 3 - イソプロピルフェノキシ) - 3, 5 - ジクロロマロンアニリド酸 ;

N - { 4 - [3 - (4 - フルオロベンゼンスルホニル) - 4 - ヒドロキシフェノキシ] - 3, 5 - ジメチルフェニル } マロンアミド酸 ;

10 N - { 3 - クロロ - 4 - [3 - (4 - フルオロベンゼンスルホニル) - 4 - ヒドロキシフェノキシ] - 5 - メチルフェニル } マロンアミド酸 ;

N - { 3, 5 - ジクロロ - 4 - [3 - (4 - フルオロベンゼンスルホニル) - 4 - ヒドロキシフェノキシ] フェニル } オキサミド酸 ;

15 N - { 4 - [3 - (4 - フルオロベンゼンスルホニル) - 4 - ヒドロキシフェノキシ] - 3, 5 - ジメチルフェニル } オキサミド酸 ;

N - { 3 - クロロ - 4 - [3 - (4 - フルオロベンゼンスルホニル) - 4 - ヒドロキシフェノキシ] - 5 - メチルフェニル } オキサミド酸 ;

N - [4 - [3 - [(4 - フルオロフェニル) ヒドロキシメチル] - 4 - ヒドロキシフェノキシ] - 3, 5 - ジメチルフェニル] オキサミド酸 ;

20 N - [4 - (4 - ヒドロキシ - 3 - イソプロピルフェノキシ) - 3, 5 - ジメチルフェニル] オキサミド酸 ;

3, 5 - ジブロモ - 3' - (6 - オキソ - 1, 6 - ジヒドロピリダジン - 3 - イルメチル) - L - サイロニン ;

25 3, 5 - ジクロロ - 3' - (6 - オキソ - 1, 6 - ジヒドロピリダジン - 3 - イルメチル) - L - サイロニン ;

3, 5 - ジヨード - 3' - (6 - オキソ - 1, 6 - ジヒドロピリダジン - 3 - イルメチル) - L - サイロニン ;

3, 5 - ジブロモ - 3' - (6 - オキソ - 1, 6 - ジヒドロピリジン - 3 - イルメチル) - L - サイロニン ;

3, 5-ジクロロ-3'-(6-オキソ-1, 6-ジヒドロピリジン-3-イルメチル)-L-サイロニン;

3, 5-ジヨード-3'-(6-オキソ-1, 6-ジヒドロピリジン-3-イルメチル)-L-サイロニン;

5 N-[3, 5-ジメチル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

N-[3, 5-ジクロロ-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

10 N-[3, 5-ジブromo-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

N-[3, 5-ジブromo-2-トリフルオロメチル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

N-[3, 5-ジクロロ-2-トリフルオロメチル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

15 N-[3, 5-ジブromo-2-エチル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

N-[3, 5-ジクロロ-2-エチル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

20 N-[3, 5-ジブromo-2-プロピル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

N-[3, 5-ジクロロ-2-プロピル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

N-[3, 5-ジブromo-2-メチル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

25 N-[3, 5-ジクロロ-2-メチル-4-(4-ヒドロキシ-3-イソプロピルフェノキシ)ベンゾイル]グリシン;

N-[4-(1H-インドール-5-イルオキシ)-3, 5-ジメチルフェニル]オキサミド酸;

N-[4-(3-メチル-1H-インドール-5-イルオキシ)-3, 5-

ジメチルフェニル] オキサミド酸;

N- [4- (3-イソプロピル-1H-インドール-5-イルオキシ) -3, 5-ビス (トリフルオロメチル) フェニル] オキサミド酸;

5 N- [4- (3-エチル-1H-インドール-5-イルオキシ) -3, 5-ビス (トリフルオロメチル) フェニル] オキサミド酸;

N- [4- (1H-インドール-5-イルオキシ) -3, 5-ビス (トリフルオロメチル) フェニル] オキサミド酸、

から選択される化合物あるいはそれらのC₁₋₆アルキルエステルまたは薬理学的に許容される塩である、請求項3に記載の肝癌の予防または再発抑制剤。

10

1 2. 前記甲状腺ホルモン受容体アゴニストが、以下からなる群:

4- [3- [(4-フルオロフェニル) ヒドロキシメチル] -4-ヒドロキシフェノキシ] -3, 5-ジメチルマロンアニリド酸;

15 4- [4-ヒドロキシ-3- (6-オキソ-1, 6-ジヒドロピリダジーン-3-イルメチル) フェノキシ] -3, 5-ジメチルマロンアニリド酸;

4- (4-ヒドロキシ-3-イソプロピルフェノキシ) -3, 5-ジメチルマロンアニリド酸;

3, 5-ジブromo-3' - (6-オキソ-1, 6-ジヒドロピリダジーン-3-イルメチル) -L-サイロニン;

20 N- [4- [3- [(4-フルオロフェニル) ヒドロキシメチル] -4-ヒドロキシフェノキシ] -3, 5-ジメチルフェニル] オキサミド酸;

N- [3, 5-ジメチル-4- (4-ヒドロキシ-3-イソプロピルフェノキシ) ベンゾイル] グリシン;

25 N- [4- (3-メチル-1H-インドール-5-イルオキシ) -3, 5-ジメチルフェニル] オキサミド酸、

から選択される化合物あるいはそれらのC₁₋₆アルキルエステルまたは薬理学的に許容される塩である、請求項3に記載の肝癌の予防または再発抑制剤。

1 3. 前記甲状腺ホルモン受容体アゴニストが、4- [3- [(4-フルオ

ロフェニル) ヒドロキシメチル] - 4 - ヒドロキシフェノキシ] - 3, 5 - ジメチルマロンアニリド酸、あるいはそのC₁₋₆アルキルエステルまたは薬理学的に許容される塩である、請求項3に記載の肝癌の予防または再発抑制剤。

5 14. 外科手術、経皮的エタノール注入療法、肝動脈塞栓療法および経皮的マイクロ波凝固療法から選択される肝癌の根治治療後に使用される、請求項1に記載の肝癌の予防または再発抑制剤。

10 15. 肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストと、インターフェロン α 、NIK-333、およびウルソデオキシコール酸からなる群から選択される少なくとも1種とを組み合わせてなる肝癌の予防または再発抑制用の医薬。

15 16. 肝癌の予防または再発抑制剤を製造するための、肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストの使用。

20 17. 肝エストロゲンスルホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストの有効量を投与することからなる、肝癌の予防または再発抑制方法。

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/04601

A. CLASSIFICATION OF SUBJECT MATTERInt.Cl¹ A61K45/00, 31/197, A61P1/16, 35/00

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)

Int.Cl¹ A61K45/00, 31/197, A61P1/16, 35/00

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 practicable, search terms used)
CA(STN), REGISTRY(STN), MEDLINE(STN)**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Giovanna M. Ledda-Columbano et al., Cell Proliferation Induced by Triiodothyronine in Rat Liver is Associated with Nodule Regression and Reduction of Hepatocellular Carcinomas, Cancer Research, 2000, Vol.60, No.3, pages 603 to 609; full text	1-16
A	Naokata YOKOYAMA et al., Synthesis and Structure-Activity Relationships of Oxamic Acid and Acetic Acid Derivatives Related to L-Thyronine, J.Med.Chem, 1995, Vol.38, No.4, pages 695 to 707, full text	1-16
A	EP 580550 A (Ciba-Geigy A.-G), 26 January, 1994 (26.01.94), Full text & AU 667924 B2 & JP 06-172275 A & CA 2100817 A	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* "A" Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier document but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"Z" document member of the same patent family
"F" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
12 August, 2002 (12.08.02)Date of mailing of the international search report
27 August, 2002 (27.08.02)Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/04601

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

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17

because they relate to subject matter not required to be searched by this Authority, namely:

Claim 17 pertains to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of PCT Article 17(2)(a)(i) and Rule 39.1(iv), to search.

2. ☐ Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

Claims 1, 2, and 14-16 relate to preventive or recurrence-suppressive agents for liver cancer, containing as the active ingredient compounds defined by the desired property "thyroid hormone receptor agonists having an effect of inhibiting the expression of liver estrogen sulfotransferase", and claims 1, 2, and 14-16 include all of the compounds having the desired property. However, only a small part of the claimed compounds are supported by the description within the meaning of PCT Article 6 and disclosed within the meaning of PCT Article 5.

Further, the scope of the compounds having the property "thyroid hormone receptor agonists having an effect of inhibiting the expression of liver estrogen sulfotransferase" cannot be specified, though consideration has been given to the common general technical knowledge at the time of filing. Thus, claims 1, 2, and 14-16 do not comply with the requirement of clearness as provided for in PCT Article 6.

Additionally, claims 3-10 include extremely many compounds, but only a small part of the claimed compounds are supported by the description within the meaning of PCT Article 6 and disclosed within the meaning of PCT Article 5.

Accordingly, this search has been carried out on relationship between thyroid hormone receptor agonists having an effect of inhibiting the expression of liver estrogen sulfotransferase and liver cancer and on preventive or recurrence-suppressive agents for liver cancer containing as the active ingredient the compounds which are concretely disclosed in the description and specified in claims 11-13.

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国際調査報告

国際出願番号 PCT/JP02/04601

A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl⁷ A61K 45/00, 31/197, A61P 1/16, 35/00

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl⁷ A61K 45/00, 31/197, A61P 1/16, 35/00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で利用した電子データベース (データベースの名称、調査に利用した用語)

GA (STN)、REGISTRY (STN)、MEDLINE (STN)

C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
A	Giovanna M. Ledda-Columbano et al., Cell Proliferation Induced by Triiodothyronine in Rat Liver Is Associated with Nodule Regression and Reduction of Hepatocellular Carcinoma, Cancer Research, 2000, Vol.60, No.3, p.603-609, 全文	1-16
A	Naokata Yokoyama et al., Synthesis and Structure-Activity Relationships of Oxamic Acid and Acetic Acid Derivatives Related to L-Thyronine, J. Med.Chem, 1995, Vol.38, No.4, p.695-707, 全文	1-16

☒ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー

- 「A」に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に拠る提起する文献又は他の文献の発行日しくは他の特別な理由を確立するために引用する文献 (理由を付す)
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願

- の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日

12.08.02

国際調査報告の発送日

27.08.02

国際調査機関の名称及びあて先

日本国特許庁 (ISA/JP)

郵便番号100-8915

東京都千代田区霞が関三丁目4-3号

特許庁特許官 (権限のある職員)

八原 由美子



40 9261

電話番号 03-3581-1101 内線 3451

様式PCT/ISA/210 (英2ページ) (1998年7月)

C (続き) . 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
A	EP 580550 A (Ciba-Geigy A-G) 1994. 01. 26, 全文 &AU 667924 B2 & JP 06-172275 A &CA 2100817 A	1-16

様式PCT/ISA/210 (第2ページの続き) (1998年7月)

第I欄 請求の範囲の一部の調査ができないときの意見 (第1ページの2の続き)

法第8条第3項 (PCT第17条(2)(a)) の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1. ☒ 請求の範囲 17 は、この国際調査機関が調査をすることを要しない対象に係るものである。つまり、
請求の範囲17は、治療による人体の処置方法に関するものであって、PCT第17条(2)(a)(i)及びPCT規則39.1(iv)の規定により、この国際調査機関が国際調査を行うことを要しない対象に係るものである。
2. ☐ 請求の範囲 は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、
3. ☐ 請求の範囲 は、従属請求の範囲であってPCT規則6.4(a)の第2文及び第3文の規定に従って記載されていない。

第II欄 発明の単一性が欠如しているときの意見 (第1ページの3の続き)

次に述べるようにこの国際出願に二以上の発明があるところこの国際調査機関は認めた。

1. ☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。
2. ☐ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。
3. ☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。
4. ☐ 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意

- ☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。
☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。

様式PCT/ISA/210 (第1ページの続き (1)) (1998年7月)

請求の範囲 1、2、14-16 は、「肝エストロゲンスフホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニスト」という所望の性質により定義された化合物を有効成分とする肝癌の予防または再発抑制剤に関するものである。そして、請求の範囲 1、2、14-16 は、そのような性質を有するあらゆる化合物を包含するものであるが、PCT 6 条の意味において明細書に裏付けられ、また、PCT 5 条の意味において開示されているのは、クレームされた化合物のごくわずかな部分にすぎないものと認められる。

さらに、「肝エストロゲンスフホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニスト」は、出願時の技術常識を勘案してもそのような性質を有する化合物の範囲を特定できないから、請求の範囲 1、2、14-16 は、PCT 6 条における明確性の要件も欠いている。

また、請求の範囲 3-10 は、非常に多数の化合物を包含している。しかしながら、PCT 6 条の意味において明細書に裏付けられ、また、PCT 5 条の意味において開示されているのは、クレームされた化合物のごくわずかな部分にすぎない。

よって、調査は、肝エストロゲンスフホトランスフェラーゼ発現抑制作用を有する甲状腺ホルモン受容体アゴニストと肝癌との関係について、及び、明細書に具体的に記載され、請求の範囲 11-13 に特定されている化合物を有効成分とする肝癌の予防または再発抑制剤について行った。

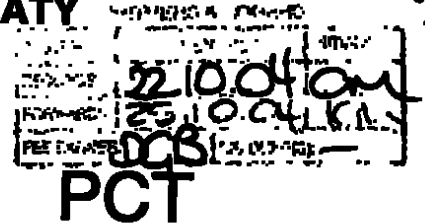
Synthesis of new derivatives of iodothyroacetic acid, the iodothyroacetylglucines. Jean Roche, Raymond Michel, and Gaetano Salvatore (Coll. de France, Paris). *Bull. Soc. Chim. France* 1959, 1547-50; cf. Harington and Pitt-Rivers, *CA* 48, 3303b. 3,5,4-I₃(*p*-HOC₆H₄O)C₆H₄CH₂COR (I) (R = NHCH₂CO₂H) (Ia) was prepd. from I (R = OH) (Ib) (3,5-diiodothyroacetic acid) in 5 steps. Ib (990 mg.) refluxed 10 min. in 22.5 ml. abs. EtOH while the mixt. was satd. with HCl gas, the mixt. filtered, and the filtrate taken to dryness *in vacuo* gave 950 mg. I (R = OEt) (Ic), needles; m. 157°, which did not migrate under electrophoresis. Similarly were prepd. the Et ester (II) of the 3'-iodo deriv. (III) of Ib, and the Me esters of Ib and III. Ic (708 mg.) in 7.2 ml. EtOH, refluxed 90 min. with 1.8 ml. 50% (NH₄)₂-HCl, acidified with 2N HCl to pH 3.5 gave 648 mg. I (R = NHNH₂) (IV), m. 275°. Similarly, II gave the hydrazide of III. IV (612 mg.) in 9.9 ml. HOAc and 2.1 ml. N HCl, treated at 0° with 4.8 ml. aq. 0.275M NaNO₂, gave 280 mg. I (R = N₂) (V), decompd. between 100 and 120°, sol. in EtOH, Me₂CO, or Et₂O-HOAc. EtO₂CCH₂NH₂, prepd. from 70 mg. of its HCl salt, in 2 ml. Me₂CO, treated with 260 mg. V in 8 ml. Me₂CO, the pH maintained at 7.5-8.5 24 hrs., the mixt. filtered, and the filtrate acidified to pH 4.5 with HCl gave 250 mg. I (R = NHCH₂CO₂Et) (VI), which was partially hydrolyzed. VI (200 mg.), heated 2 hrs. at 37° in 2 ml. EtOH and 2 ml. NaOH, acidified to pH 4 with 2N HCl, and kept several hrs. at 0° gave quant. impure Ia, which, purified several times by soln. in NH₄OH, pptn. in HCl, washing with 1% HOAc, recrystns. from abs. EtOH and abs. MeOH, gave 80 mg. Ia, m. 234-

5°. The overall yield of V to Ia was 32%. Ia, hydrolyzed with baryte, gave Ib and glycine. Ia was treated in NH₃ soln. with amts. of iodine enriched with I¹³¹, from 0.5 to 6 moles, and the mixts. chromatographed on paper to det. the optimum conditions for prepn. of III and the 3',5'-diiodo deriv. (VII) of Ib. Six moles of I produced the max. amt. of VII (80%) and the min. of III, while 1.5 moles of I produced the most III. III, m. 121-3° (EtOH) was prepd. in this manner. R_f values for Ia, III, and VII were given for 5 solvent mixts. Ia, III, and VII were displaced 5.0, 5.5, and 6 cm., resp., in 5 hrs. (25 ma., 500 v.) in paper electrophoresis with an 0.05M (NH₄)₂CO₃ buffer.

J. March

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



To:

BANNERMAN, David G.
WITHERS & ROGERS
Goldings House
2 Hays Lane
London SE1 2HW
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

18.10.2004

Applicant's or agent's file reference
KB523PCT/DGB

IMPORTANT NOTIFICATION

International application No.
PCT/EP 03/07333

International filing date (day/month/year)
08.07.2003

Priority date (day/month/year)
10.07.2002

Applicant
KARO BIO AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office - Gilchiner Str. 103
D-10958 Berlin
Tel. +49 30 25901 - 0
Fax: +49 30 25901 - 840

Authorized Officer

Koster, A

Tel. +49 30 25901-728



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B523PCT/DGB		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA16)	
International application No. PCT/EP 03/07333	International filing date (day/month/year) 08.07.2003	Priority date (day/month/year) 10.07.2002	
International Patent Classification (IPC) or both national classification and IPC C07C235/52			
Applicant KARO BIO AB et al.			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 38. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 6 sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 02.02.2004		Date of completion of this report 18.10.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office - Giltechiner Str. 103 D-10858 Berlin Tel. +49 30 25901 - 0 Fax +49 30 25901 - 840		Authorized Officer Rufet, J Telephone No. +49 30 25901-332 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/07333**

I. Basis of the report

1. ~~With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)).~~

Description, Pages

1-55 as originally filed

Claims, Numbers

1-30 filed with telefax on 27.09.2004

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/07333**

II. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 10-18 with respect to ind. applicability

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 10-18 with respect to ind. applicability

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-30
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-30
Industrial applicability (IA)	Yes: Claims	1-9,19-30
	No: Claims	10-18

2. Citations and explanations

see separate sheet

Re Item I

The new set of claims 1-30 filed with telefax dated 27 September 2004 is based on the examples and the claims as originally filed and is therefore acceptable.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 10-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1: WO 01 94293 A (2001-12-13)
- D2: WO 00 39077 A (2000-07-06)
- D3: WO 02 094319 A (2002-11-28)
- D4: CHEMICAL ABSTRACTS, vol. 57, no. 7, 1962, abstract no. 8493g

It should be noted that document D3 indicated in the search report as a P-document has not been taken into consideration for the evaluation of novelty and inventive step, because the priority document has been assumed to be valid (see Official Journal EPO, 11/2001, p. 539-542, especially item 13).

1. The documents D1, D2 and D4 refer to structurally very close thyroid hormone receptor ligands, which differ at least from the claimed compounds by the presence of 2 substituents on the phenoxy group instead of 3 for the claimed compounds; see especially D1, example 1 of p. 27 and D2, p. 7, l. 1-16 and claims 20-22.

2. According to the application (see especially page 2, last paragraph) the problem underlying the invention is to provide compounds which are thyroid hormone receptor ligands and useful in the treatment and prevention of diseases associated with thyroid hormone activity.

D2 and D1 are considered to represent equally the closest prior art, since those documents refer to structurally very close thyroid hormone receptor ligands.

In view of the information given in p. 55, l. 12-13 it is credible that the problem as defined above has actually been solved by the technical features of the claimed

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compounds.

However in view of the technical information given especially in D2 (see examples and claims 20-22) and D1 (see example 1) the proposed solution to the abovementioned problem is considered to be obvious.

From D2 (see claims 20-22) and D1 (example 1) the skilled person already knows that 4-hydroxyphenoxybenzamide derivatives or 4-hydroxyphenoxy phenyl acetamide derivatives having one substituent (isopropyl) in ortho position of the 4-hydroxyphenoxy group are thyroid hormone receptor ligands useful in the treatment and prevention of diseases associated with thyroid hormone activity.

The skilled person also knows from D1-D2 (see especially claim 1, the definition of R2, R3) that hydrogen atom, halogen atom and C1-C4 alkyl groups are equivalent substituents for a phenyl ring. He would have therefore, with expectation of success, considered the replacement of the hydrogen atom in ortho position of the 4-hydroxyphenoxy moiety by a C1-C4 alkyl group or a halogen atom as an alternative, if he wanted to produce further thyroid hormone receptor ligands. It is pointed out that such derivations belong to the common practice within the field of chemistry. In absence of truly comparative data showing an unexpected effect of the claimed compounds over the closest compounds of the prior art D1-D2 an inventive step for the claimed subject-matter cannot be acknowledged.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:
IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference DGB/KB523PCT	
International application No. PCT/EP03/07333	International filing date (day/month/year) 08/07/2003
(Earliest) Priority date (day/month/year) 10/07/2002	
Title of invention Novel Compounds	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Karo Bio AB Novum SE-141 57 Huddinge Sweden	
Telephone No.	
Facsimile No.	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: SE	State (that is, country) of residence: SE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Bristol-Myers Squibb Company P O Box 4000 Princeton NJ 08543-4000 USA	
State (that is, country) of nationality: US	State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
GARG, Neeraj Barkvägen 15 147 52 Tumba Sweden	
State (that is, country) of nationality:	State (that is, country) of residence: SE
☒ Further applicants are indicated on a continuation sheet.	

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Sheet No. 2.

International application No.
PCT/EP03/07333

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

GADIM, Mahmoud Rahimi
Gröndalsvägen 170, 5 tr
117 69 Stockholm
Sweden

State (that is, country) of nationality:

State (that is, country) of residence:

SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ERICSSON, Thomas Anders Wilson
Stjärna 1132
150 23 Enhörna
Sweden

State (that is, country) of nationality:

State (that is, country) of residence:

SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MALM, Lars Johan
Bridgevägen 9B
142 66 Trångsund
Sweden

State (that is, country) of nationality:

State (that is, country) of residence:

SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

RYONO, Denis Evan
28 Marion Road West
Princeton
New Jersey 08540
USA

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

☐ Further applicants are indicated on another continuation sheet.

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Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)

BANNERMAN, David Gardner
WITHERS & ROGERS
GOLDINGS HOUSE
2 HAYS LANE
LONDON, SE1 2HW
UNITED KINGDOM

Telephone No.

+44 (0) 20 7663 3500

Facsimile No.

+44 (0) 20 7663 3550

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).
4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- ☐ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

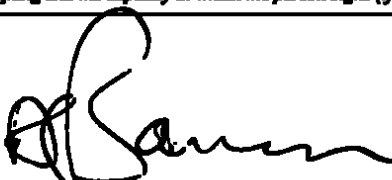
- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



David G. Bannerman - European Patent Attorney

28 January 2004

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP03/07333		For International Preliminary Examining Authority use only	
Applicant's or agent's file reference DGB/KB523PCT		Date stamp of the IPEA	
Applicant Karo Blo AB and Bristol-Myers Squibb Company			
CALCULATION OF PRESCRIBED FEES			
1. Preliminary examination fee		1530	P
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)		129	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box		€1659	
		TOTAL	
MODE OF PAYMENT			
☐ authorization to charge deposit account with the IPEA (see below)	☐ cash		
☐ cheque	☐ revenue stamps		
☐ postal money order	☐ coupons		
☐ bank draft	☒ other (specify): Being paid into Cash Ac's Munich		
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs)			
☐ Authorization to charge the total fees indicated above.		IPEA/	
☐ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.		Deposit Account No.:	
		Date:	
		Name:	
		Signature:	

2 8 SEP 2004

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5 CLAIMS:

1. N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine
(E1);
N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
10 (E2);
N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E3);
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E4);
15 N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E5);
N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
(E6).
N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]
20 glycine (E7).
L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl]
valine (E10)
D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl]
phenylglycine (E11)
25 L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl]
valine (E12)
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenyl-
acetyl]phenylglycine (E13)
L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]-
30 phenylglycine (E14)
N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]
glycine (E8).
N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl]
35 glycine (E9).
2. A compound according to claim 1 for use in medical therapy.

agx

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3. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.

- 10 4. A process for making a pharmaceutical composition comprising combining a compound according to claim 1 and a pharmaceutically acceptable carrier.

- 15 5. A pharmaceutical composition comprising a compound according to claim 1 and at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, 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, cholesterol/lipid lowering agents, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.

- 20 6. The pharmaceutical composition of claim 5 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of a biguanide, a glucosidase inhibitor, a meglitinide, a sulfonylurea, a thiazolidinedione, a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR alpha/gamma dual agonist, an SGLT2 inhibitor, a glycogen phosphorylase inhibitor, an α 2 inhibitor, a glucagon-like peptide-1 (GLP-1), a dipeptidyl peptidase IV inhibitor and insulin.

- 30 7. The pharmaceutical composition of claim 5 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of metformin, glyburide, glimepiride, glipyrice, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, pioglitazone, englitazone, darglitazone, rosiglitazone and insulin.

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8. The pharmaceutical composition of claim 5 wherein said additional therapeutic agent is an anti-obesity agent is selected from the group consisting of an α 2

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- 5 inhibitor, a PPAR gamma antagonist, a PPAR delta agonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake inhibitor, a cannabinoid-1 receptor antagonist and an anorectic agent.
9. The pharmaceutical composition of claim 5 wherein said additional therapeutic
10 agent is a hypolipidemic agent selected from the group consisting of a thiazolidinedione, an MTP inhibitor, a squalene synthetase inhibitor, an HMG CoA reductase inhibitor, a fibric acid derivative, an ACAT inhibitor, a cholesterol absorption inhibitor, an ileal Na^+ /bile cotransporter inhibitor, a bile acid sequestrant and a nicotinic acid or a derivative thereof.
- 15 10. A method for preventing, inhibiting or treating a disease which is dependent on the expression of a T_3 regulated gene or associated with metabolic dysfunction, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.
- 20 11. A method for treating or delaying the progression or onset of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass, density or growth, eating disorders, reduced cognitive function, thyroid cancer,
25 glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or disease, which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.
12. The method as defined in claim 10 wherein the said disease is obesity,
30 hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.
13. The method according to claim 11 wherein the skin disorder or disease is dermal
35 atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis,

- 5 Dermier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
14. The method according to claim 10 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional
10 therapeutic agent selected from the group consisting of other compounds of formula I, 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, cholesterol/lipid
15 lowering agents, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.
15. A method of treating or delaying the progression or onset of a skin disorder or disease which comprises administering to a mammalian patient a therapeutically effective amount of a compound as defined in claim 1 in combination with a
20 retinoid or a vitamin D analog.
16. A method for treating or delaying the progression or onset of obesity which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.
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17. A method according to claim 16 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.
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18. A method according to claim 17 wherein said anti-obesity agent is selected from the group consisting of α 2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-1 receptor antagonists, other thyroid receptor
35 agents and anorectic agents.

- 5 19. The use of a compound according to claim 1 in the preparation of a medicament to inhibit or treat a disease which is dependent on the expression of a T₃ regulated gene or associated with metabolic dysfunction.
- 10 20. The use according to claim 19, wherein said disease is selected from obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass density or growth, eating disorders, reduced cognitive function, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or disease.
- 15 21. The use according to claim 20, wherein the skin disorder or disease is selected from dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis, Demier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
- 20 22. Use according to claim 19 in combination with at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, 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, cholesterol/lipid lowering agents, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.
- 25 23. Use according to claim 19 in combination with a retinoid or a vitamin D analog wherein said disease is a skin disorder or disease.
24. Use according to claim 19 wherein said disease is obesity.
- 30 25. Use according to claim 24 in combination with at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.

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26. Use according to claim 25 wherein said anti-obesity agent is selected from the group consisting of ~~ap2~~ inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-1 receptor antagonists, other thyroid receptor agents and anorectic agents.

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30. A pharmaceutical composition which functions as a selective agonist of the thyroid hormone receptor comprising a compound as defined in claim 1.

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PAGINA ENMENDADA

28 SEP 2004

REIVINDICACIONES (enmendadas)

1. N-[3,5-Dicloro-4-(4-hidroxi-3-isopropil-5-metilfenoxi)benzoil] glicina (E1);
N-[3,5-Dicloro-4-(3-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E2);
N-[3,5-Dicloro-4-(2-bromo-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E3);
N-[3,5-Dicloro-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E4);
N-[3,5-Dicloro-4-(3-ciano-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E5);
N-[3,5-Dicloro-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E6);
N-[3,5-Dicloro-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E7);
L-N-[3,5-Dibromo-4-(3-fluoro-4-hidroxi-5-isopropilfenoxi)fenilacetil] valina (E10);
D-N-[3,5-Dibromo-4-(3-cloro-4-hidroxi-5-isopropilfenoxi)fenilacetil] fenilglicina (E11);
L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] valina (E12);
L-N-[3,5-Dibromo-4-(4-hidroxi-3-isopropil-5-metilfenoxi)fenilacetil] fenilglicina (E13);
L-N-[3,5-Dibromo-4-(3,5-dimetil-4-hidroxifenoxi)fenilacetil] fenilglicina (E14);
N-[3,5-Dibromo-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E8);
N-[3,5-Dimetil-2-metil-4-(3-metil-4-hidroxi-5-isopropilfenoxi)benzoil] glicina (E9);
2. Un compuesto acorde con la reivindicación 1 para uso en terapia médica.

3. Una formulación farmacéutica que contiene una cantidad efectiva de un compuesto acorde con las reivindicación 1 o una sal farmacéuticamente efectiva de este, junto con un vehículo farmacéuticamente aceptable.
4. Un proceso para elaborar una formulación farmacéutica que contiene la combinación de un compuesto acorde con la reivindicación 1 y un vehículo farmacéuticamente aceptable.
5. Una formulación farmacéutica que contiene un compuesto acorde con la reivindicación 1 y al menos un agente terapéutico adicional seleccionado del grupo que consta de otros compuestos con la formula 1, agentes anti-diabéticos, agentes anti-osteoporosis, agentes anti-obesidad, agentes promotores de crecimiento, agentes anti-inflamatorios, agentes anti-ansiedad, anti-depresivos, agentes anti-hipertensivos, glicósidos cardíacos, agentes reductores de colesterol/lípido, supresores de apetito, inhibidores de la resorción ósea, miméticos tiroideos, agentes anabólicos, agentes antitumorales y retinoides.
6. La formulación farmacéutica de la reivindicación 5 en donde dicho agente terapéutico adicional es un agente anti-diabético seleccionado del grupo que consta de una biguanida, un inhibidor de la glucosidasa, una meglitinida, una sulfonilurea, una tiazolidindiona, un agonista de la PPAR-alfa, un agonista de la PPAR-gama, un agonista dual PPAR alfa/gama, un inhibidor del SGLT2, un

inhibidor de la glicógeno fosforilasa, un inhibidor de la α P2, un péptido-1 similar al glucagón (GLP-1), un inhibidor de la dipeptidil peptidasa IV e insulina.

7. La formulación farmacéutica de la reivindicación 5 en donde dicho agente terapéutico adicional es un agente anti-diabético seleccionado del grupo que consta de metformina, gliburida, glimepirida, glipirida, glipizida, clorpropamida, gliclazida, acarbosa, miglitol, troglitazona, pioglitazona, englitazona, darglitazona, rosiglitazona e insulina.
8. La formulación farmacéutica de la reivindicación 5 en donde dicho agente terapéutico adicional es un agente anti-obesidad seleccionado del grupo que consta de un inhibidor de la α P2, un antagonista de la PPAR gama, un agonista de la PPAR delta, un agonista de los adrenérgicos beta 3, un inhibidor de la lipasa, un inhibidor de la recaptación de la serotonina, un antagonista del receptor canabinoide-1 y un agente anoréxico.
9. La formulación farmacéutica de la reivindicación 5 en donde dicho agente terapéutico adicional es un agente hipolipidémico seleccionado del grupo que consta de una tiazolidindiona, un inhibidor de la MTP, un inhibidor de la escualeno sintetasa, un inhibidor de la HMG-CoA reductasa, un derivado del ácido fibríco, un inhibidor de la ACAT, un inhibidor de la absorción del colesterol,

un inhibidor del co-transportador ileal de Na⁺/ácido biliar, un secuestrante de ácido biliar y un ácido nicotínico o un derivado de este.

10. Un método para prevenir, inhibir o tratar una enfermedad que depende de la expresión de un gen regulado por T₃ o asociada con una disfunción del metabolismo, que consiste en administrar a un paciente que requiera de tratamiento una cantidad terapéuticamente efectiva de un compuesto como los definidos en la reivindicación 1.
11. Un método para tratar o retrasar la progresión o el inicio de obesidad, hipercolesterolemia, aterosclerosis, depresión, osteoporosis, hipotiroidismo, hipertiroidismo subclínico, bocio no tóxico, cáncer de tiroides, masa, densidad o crecimiento óseo reducido, trastornos alimenticios, función cognoscitiva reducida, cáncer de tiroides, glaucoma, arritmia cardíaca, insuficiencia cardíaca congestiva, o trastornos o enfermedades de piel, el cual consiste en administrar a un paciente mamífero que requiera de tratamiento una cantidad terapéuticamente efectiva de un compuesto como los definidos en la reivindicación 1.
12. El método que fue definido en la reivindicación 10, en donde dicha enfermedad es obesidad, hipercolesterolemia, aterosclerosis, depresión, osteoporosis,

hipotiroidismo, bocio, cáncer de tiroides, glaucoma, arritmia cardíaca, insuficiencia cardíaca congestiva o trastornos de piel.

13. El método acorde con la reivindicación 11, en donde el trastorno o la enfermedad de la piel es atrofia dérmica, lesión post quirúrgica causada por resurfacing láser, queloides, estría, celulitis, piel áspera, daño actínico de la piel, liquen plano, ictiosis, acné, soriasis, la enfermedad de Demier, eccema, dermatitis atópica, cloracne, pitiriasis y cicatrices en la piel.
14. El método acorde con la reivindicación 10 que además incluye la administración, concurrente o secuencialmente, de una cantidad terapéuticamente efectiva de al menos un agente terapéutico adicional seleccionado del grupo que consta de otros compuestos con la formula I, agentes anti-diabéticos, agentes anti-osteoporosis, agentes anti-obesidad, agentes promotores de crecimiento, agentes anti-inflamatorios, agentes anti-ansiedad, anti-depresivos, agentes anti-hipertensivos, glicósidos cardíacos, agentes reductores de colesterol/lípido, supresores de apetito, inhibidores de la resorción ósea, miméticos tiroideos, agentes anabólicos, agentes antitumorales y retinoides.
15. Un método para tratar o retrasar la progresión o el inicio de un trastorno o enfermedad de la piel el cual consiste en administrar a un paciente mamífero una

cantidad terapéuticamente efectiva de un compuesto como los definidos en la reivindicación 1 en combinación con un retinoide o un análogo de la vitamina D.

- 16. Un método para tratar o retrasar la progresión o el inicio de obesidad el cual consiste en administrar a un paciente mamífero una cantidad terapéuticamente efectiva de un compuesto como los definidos en la reivindicación 1.**
- 17. Un método acorde con la reivindicación 16 que además incluye la administración, concurrente o secuencialmente, de una cantidad terapéuticamente efectiva de al menos un agente terapéutico adicional seleccionado del grupo que consta de un agente anti-obesidad y un supresor de apetito.**
- 18. Un método acorde con la reivindicación 17 en donde dicho agente anti-obesidad es seleccionado del grupo que consta de inhibidor de la α P2, antagonista de la PPAR gama, agonista de la PPAR delta, un agonista de los adrenérgicos beta 3, inhibidor de la lipasa, inhibidor de la recaptación de la serotonina (y dopamina), antagonista del receptor canabinoide-1, otro agente receptor tiroideo y agente anoréxico.**

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19. El uso de un compuesto acorde con la reivindicación 1 en la preparación de un medicamento para inhibir o tratar una enfermedad que depende de la expresión de un gen regulado por T_3 o asociada con una disfunción del metabolismo.
20. El uso acorde con la reivindicación 19, en donde dicha enfermedad es seleccionada entre obesidad, hipercolesterolemia, aterosclerosis, depresión, osteoporosis, hipotiroidismo, hipertiroidismo subclínico, bocio no tóxico, cáncer de tiroides, masa, densidad o crecimiento óseo reducido, trastornos alimenticios, función cognoscitiva reducida, cáncer de tiroides, glaucoma, arritmia cardíaca, insuficiencia cardíaca congestiva, o trastornos o enfermedades de piel.
21. El uso acorde con la reivindicación 20, en donde el trastorno o enfermedad de la piel es seleccionado entre atrofia dérmica, lesión post quirúrgica causada por resurfacing láser, queloides, estría, celulitis, piel áspera, daño actínico de la piel, liquen plano, ictiosis, acné, soriasis, la enfermedad de Demier, eccema, dermatitis atópica, cloracne, pitiriasis y cicatrices en la piel.
22. Uso acorde con la reivindicación 19 en combinación con al menos un agente terapéutico adicional seleccionado del grupo que consta de otros compuestos con la fórmula I, agentes anti-diabéticos, agentes anti-osteoporosis, agentes anti-obesidad, agentes promotores de crecimiento, agentes anti-inflamatorios, agentes anti-ansiedad, anti-depresivos, agentes anti-hipertensivos, glicósidos cardíacos, agentes reductores de colesterol/lípido, supresores de apetito,

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inhibidores de la resorción ósea, miméticos tiroideos, agentes anabólicos, agentes antitumorales y retinoides.

- 23. Uso acorde con la reivindicación 19 en combinación con un retinoide o un análogo de la vitamina D en donde dicha enfermedad es un trastorno o enfermedad de la piel.**
- 24. Uso acorde con la reivindicación 19 en donde dicha enfermedad es obesidad.**
- 25. Uso acorde con la reivindicación 24 en combinación con al menos un agente terapéutico adicional seleccionado del grupo que consta de un agente anti-obesidad y un supresor de apetito.**
- 26. Uso acorde con la reivindicación 25, en donde dicho agente anti-obesidad es seleccionado del grupo que consta de inhibidor de la α P2, antagonista de la PPAR gama, agonista de la PPAR delta, agonista de los adrenérgicos beta 3, inhibidor de la lipasa, inhibidor de la recaptación de la serotonina (y dopamina), un antagonista del receptor canabinoide-1, otro agente receptor tiroideo y un agente anoréxico.**

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30. Una formulación farmacéutica la cual funciona como un agonista selectivo del receptor de la hormona tiroidea que contiene un compuesto como los definidos en la reivindicación 1.

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
Indicación de que se solicita la concesión de una patente.	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
Descripción de la invención.	()	()
Dibujos de ser estos pertinentes.	()	()
Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA ()

INCOMPLETA () ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()

COMPLETA ()

INCOMPLETA () ()

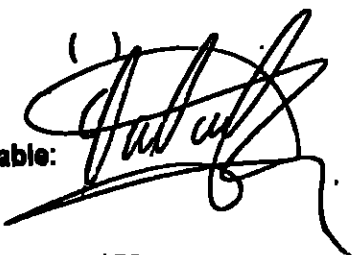
ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA ()

INCOMPLETA () ()

Firma Responsable:



SUPERINDUSTRIA Y COMERCIO

Fecha: Radicación : 05001416 00000000 Folios: 320
 Fecha (AMB): 2005-01-11 15:49:20
 Trámite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTAC
 Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

2020
Bogotá D C

Doctor(a)
DILIA MARIA RODRIGUEZ D'ALEMAN
Apoderado(a)
KARO BIO AB
BRISTOL – MYERS SQUIBB COMPANY

Oficio N° **11966**

ASUNTO:

Radicación N°	05 - 1416
Solicitud internacional	PCT/EP2003/007333
Fecha inicio fase nacional	10/02/2005
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica.
- El solicitante debe presentar un nuevo título, que permita identificar la materia de la cual trata la solicitud, ya que el relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente (Regla 4.3 PCT, Art. 27, 27 Decisión 486, Circular Única 5.2.9).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
28 ENE 2005

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