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SUPERINDUSTRIA Y COMERCIO

Radicacion : 00014834 00000003

Folios: 2

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Tramite : 002 PATENTES 0 1 REGISTRO/ 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 37,040
FECHA : JUNIO 7 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	9226066	07/06/2002	28,841,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	05-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
TOTAL :			\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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140

375
2005-01-13

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctor
Carlos R. Olarte
Apoderado

Oficio N°
11829

REFERENCIA	Radicación	00 14834
	Trámite	002
	Evento	001
	Actuación	430
	Folios	021

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 14834, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 64-87
- . Ejemplos: folios 87-89
- . Capítulo reivindicatorio estudiado: folios 117-128
- . Se reivindica prioridad, presentada en Estados Unidos el 01.03.99, bajo el número 60/122015

Objeto de la invención

Según las reivindicaciones 1 a 44 de la presente solicitud, se refiere a el uso de agentes tiromiméticos de fórmula (I), cuyos sustituyentes se revelan en la descripción para la fabricación de un medicamento para el tratamiento de la obesidad.

Clasificación internacional de patentes A 61 K 31/24

HH

Claridad de la solicitud

El artículo 30 de la decisión 486 establece que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

La reivindicación 5 aparece incompleta.

En las reivindicaciones 16-42 se describe el uso de un agente de la fórmula (I) y un agente anoréxico en una composición terapéutica, sin embargo no se describe a lo largo de la descripción composiciones que contengan tales compuestos dentro de una única forma de presentación, por el contrario, se describen "kits" o una administración secuencial de los compuestos en cuestión, en adición a lo anterior, en la parte experimental se describe únicamente la acción antiobesidad de los compuestos de fórmula (I) y no se encuentra por ninguna parte pruebas y resultados donde se describa la acción combinada de los compuestos de fórmula (I) con agentes anoréxicos; por lo tanto, tales composiciones no se encuentran enteramente sustentadas por la descripción.

Las reivindicaciones 30-42 se refieren al uso de un compuesto según la reivindicación 28 cuando dicha reivindicación se refiere a una combinación de dos compuestos.

Las reivindicaciones 43-45 se refieren a combinaciones de dos medicamentos presentados de manera independiente, lo cual no tiene unidad de invención, puesto que se tratan de entidades químicas diferentes. Si el solicitante pretende proteger el "kit", éste se relaciona con métodos de tratamiento que no son patentables a la luz de la legislación vigente

Favor hacer las aclaraciones y correcciones del caso.

Excepciones a la patentabilidad

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 1-42, que trata de "El uso de un compuesto de fórmula (I)..." no es patentable, debido a que la legislación vigente contempla únicamente como objeto de patente a los productos y procedimientos.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 01.03.99-, relacionados con la materia de la presente solicitud:

WZ

Nº	Documento	Título	Fecha de Publicación
1	US 5401772	"Derivados de ácido heteroacético"	28.03.95
2	US 5569674	"Derivados de ácido heteroacético"	29.10.96
3		"The Merck Index"	31.12.96

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 dispone *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

Las patentes US 5401772 y US 5569674 se relacionan con compuestos de fórmula (I), su procedimiento de síntesis y composiciones farmacéuticas que los contienen. Se dice que son agentes tiromiméticos.

Comparando elemento por elemento, los compuestos de la anterioridad citada son iguales a los que aparecen en las reivindicaciones 1-15 y pueden afectar la novedad de la presente solicitud.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

Las patentes US 5401772 y US 5569674 se relacionan con compuestos de fórmula (I), su procedimiento de síntesis y composiciones farmacéuticas que los contienen. Se dice que son agentes tiromiméticos

El libro "The Merck Index" presenta diferentes compuestos de carácter químico y medicinal, entre estos compuestos se revelan diferentes compuestos anoréxicos como sibutramina, fentermina y fenfluramina

Teniendo en cuenta el objeto de la solicitud, el cual es proporcionar composiciones de tiromiméticos y anoréxicos, se aprecia que es una derivación evidente del estado de la técnica ya que la combinación de los documentos citados enseñan composiciones similares que tienen el mismo propósito.

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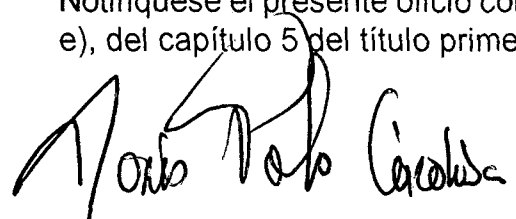
Finalmente, no se muestran pruebas ni resultados en donde se demuestre la efectividad de las composiciones en cuestión

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5401772	1-15	Novedad
		16-44	Nivel Inventivo
2	US 5569674	1-15	Novedad
		16-44	Nivel Inventivo
3	"The Merck Index"	16-44	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001


Doris Polo Córdoba
Jefe de la División de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 13 ENE. 2005

CONCEPTO TÉCNICO Número 1712	EXAMINADOR TÉCNICO Código 202024
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US005401772A

United States Patent [19][11] **Patent Number:** 5,401,772

Yokoyama, deceased et al.

[45] **Date of Patent:** Mar. 28, 1995[54] **HETEROACETIC ACID DERIVATIVES**

[75] **Inventors:** Naokata Yokoyama, deceased, late of Cliffside Park, by Rina Yokoyama, administrator; Gordon N. Walker, Morristown; Alan J. Main, Basking Ridge, all of N.J.

[73] **Assignee:** Ciba-Geigy Corporation, Ardsley, N.Y.

[21] **Appl. No.:** 154,203

[22] **Filed:** Nov. 18, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 918,544, Jul. 21, 1992, abandoned.

[51] **Int. Cl.⁶** A61K 31/24

[52] **U.S. Cl.** 514/539; 514/616; 514/619; 514/563

[58] **Field of Search** 514/534, 563, 616, 619, 514/539

[56] **References Cited****U.S. PATENT DOCUMENTS**

3,903,053	9/1975	Iwata	548/314.1
3,969,290	7/1976	Kraft et al.	260/2.5
4,036,837	7/1977	Sellstedt et al.	260/250
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4,154,961	5/1979	Sellstedt et al.	562/438
4,227,009	10/1980	Koch et al.	560/61
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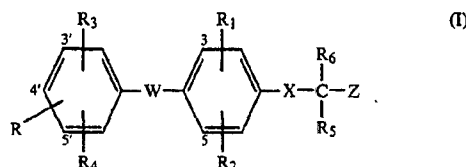
Primary Examiner—José G. Dees

Assistant Examiner—Samuel Barts

Attorney, Agent, or Firm—Norbert Gruenfeld

[57] **ABSTRACT**

Disclosed are compounds of formula



wherein

R is hydroxy, esterified hydroxy or etherified hydroxy;

R₁ is halogen, trifluoromethyl or lower alkyl;

R₂ is halogen, trifluoromethyl or lower alkyl;

R₃ is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl;

or

R₃ is the radical



wherein R₈ is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R₉ is hydroxy or acyloxy; R₁₀ represents hydrogen or lower alkyl; or R₉ and R₁₀ together represent oxo;

HETEROACETIC ACID DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 07/918,544, filed Jul. 21, 1992, now abandoned which is incorporated herein by reference.

SUMMARY OF THE INVENTION

The invention relates to the heteroacetic acid derivatives as defined herein which are particularly useful as potent lipid lowering agents, methods for preparation thereof, pharmaceutical compositions comprising said compounds, and a method of treating hyperlipidemia, in particular hypercholesterolemia and related conditions in mammals, by administering said compounds or pharmaceutical compositions comprising said compounds.

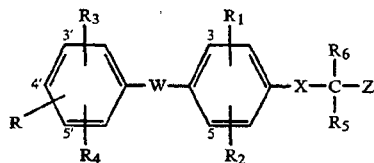
The compounds of the invention are selective thyromimetic hypolipidemic agents which enhance the clearance of cholesterol from the circulation, particularly the clearance of cholesterol in the form of low density lipoproteins (LDL). They, inter alia, upregulate (increase) hepatic LDL receptor function in mammals.

Thus, the compounds of the instant invention are primarily useful for reducing total cholesterol plasma levels in mammals, in particular for reducing levels of LDL-cholesterol.

The compounds of the invention are therefore expected to be useful for the prevention and/or treatment of occlusive cardiovascular conditions in which hyperlipidemia and hyperlipoproteinemia are implicated, such as atherosclerosis and coronary heart disease (myocardial infarctions) in mammals.

DETAILED DESCRIPTION OF THE INVENTION

More particularly, the invention relates to the compounds of formula I



wherein

R is hydroxy, esterified hydroxy or etherified hydroxy;

R₁ is halogen, trifluoromethyl or lower alkyl;

R₂ is halogen, trifluoromethyl or lower alkyl;

R₃ is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl;

or

R₃ is the radical



wherein R₈ is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R₉ is hydroxy or acyloxy; R₁₀ represents hydrogen or lower alkyl; or R₉ and R₁₀ together represent oxo;

R₄ is hydrogen, halogen, trifluoromethyl or lower alkyl;

X is —NR₇, S or O;

W is O or S;

R₅ represents hydrogen, lower alkyl or aryl-lower alkyl; and

R₆ represents hydrogen; or

R₅ and R₆ together represent oxo provided that X represents —NR₇;

R₇ represents hydrogen or lower alkyl;

Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; and pharmaceutically acceptable salts thereof.

Particular embodiments of the invention relate to the compounds of formula I wherein

(a) R is located at the 4'-position; R₁ and R₂ are located at the 3 and 5 positions, and R₃ and R₄ are located at the 3' and 5'-positions;

(b) X and W represent O; or

(c) X represents —NR₇, and W represents O; or

(d) X represents S, and W represents O;

(e) R₄ is hydrogen;

(f) Z is carboxyl or carboxyl esterified as a pharmaceutically acceptable ester,

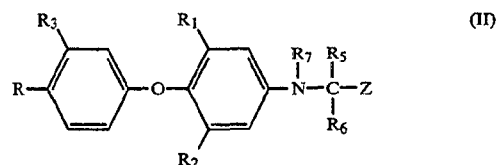
(g) R₅ and R₆ together represent oxo and X represents NR₇;

(h) R₃ represents the radical



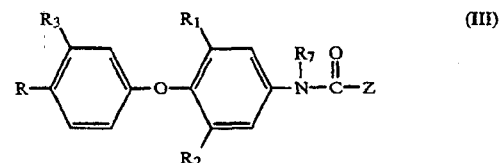
lower alkyl, aryl-lower alkyl or cycloalkyl-lower alkyl.

A preferred embodiment of the invention relates to the compounds of formula II



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ and R₂ independently represent halogen, trifluoromethyl or C₁-C₃alkyl; R₃ represents lower alkyl, lower alkanoyl, hydroxy-lower alkyl, carbocyclic arylmethyl, carbocyclic aroyl or carbocyclic aryl-hydroxymethyl; R₅ and R₆ together represent oxo; R₇ represents hydrogen or lower alkyl; and Z represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

A further preferred embodiment relates to the compounds of formula III



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ represents halogen, trifluoromethyl or C₁-C₃alkyl; R₂ represents halogen, trifluoromethyl or C₁-C₃alkyl; R₃ represents lower alkyl, carbocyclic aryl, carbocyclic arylmethyl or carbocyclic aryl-hydroxymethyl; R₇ represents hydrogen or lower alkyl; Z represents carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

Advantageously Z represents carboxyl or carboxyl esterified as a pharmaceutically acceptable ester.

Preferred are said compounds of formula III wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R₁ and R₂ are advantageously identical and represent halogen or C₁-C₃alkyl; R₃ is C₁-C₃alkyl or monocyclic carbocyclic arylmethyl; R₇ is hydrogen or C₁-C₂alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

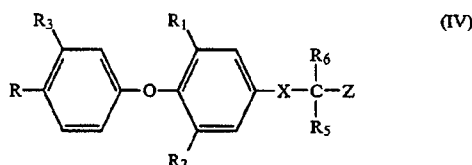
A further preferred embodiment relates to compounds of formula III wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R₁ and R₂ are advantageously identical and represent halogen or C₁-C₃alkyl; R₃ is carbocyclic aryl or carbocyclic aryl-hydroxymethyl; R₇ is hydrogen or C₁-C₂alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

Further preferred are said compounds of formula III wherein R is hydroxy; R₁ and R₂ are advantageously identical and represent chloro or methyl; R₃ is isopropyl, benzyl or benzyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R₇ is hydrogen; Z is carboxyl or lower alkoxycarbonyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are also compounds of formula III wherein R is hydroxy; R₁ and R₂ are identical and represent chloro or methyl; R₃ is phenyl-hydroxymethyl or phenyl-hydroxymethyl substituted on phenyl by halogen, lower alkyl, lower alkoxy or trifluoromethyl; or R₃ is benzoyl or benzoyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R₇ is hydrogen; Z is carboxyl or lower alkoxycarbonyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are also compounds of formula III wherein R is hydroxy; R₁ and R₂ are identical and represent methyl or chloro; R₃ is isopropyl or 4-halophenyl-hydroxymethyl in which halo represents fluoro or chloro; R₇ is hydrogen; and Z represents carboxy or lower alkoxycarbonyl; and pharmaceutically acceptable salts thereof.

Another particular embodiment of the invention relates to the compounds of formula IV



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ and R₂ independently represent halogen, trifluoromethyl or C₁-C₃alkyl; R₃ represents lower alkyl, carbocyclic arylmethyl, carbocyclic aryl, or carbocyclic aryl-hydroxymethyl; X represents NR₇, S or O; R₅, R₆ and R₇ independently represent hydrogen or lower alkyl; Z represents carboxyl or carboxyl

derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; and pharmaceutically acceptable salts thereof.

Preferred are said compounds wherein R₅, R₆ and R₇ represent hydrogen; also said compounds wherein Z represents carboxyl or carboxyl esterified as a pharmaceutically acceptable ester, and pharmaceutically acceptable salts thereof.

Certain compounds of the invention which have one or more asymmetric centers can exist in the form of racemates, enantiomers and mixtures thereof, all of which are within the scope of the invention.

The definitions used herein, unless denoted otherwise, have the following meanings within the scope of the present invention.

Aryl represents carbocyclic or heterocyclic aryl.

Carbocyclic aryl represents optionally substituted phenyl or optionally substituted naphthyl.

Optionally substituted phenyl represents preferably phenyl or phenyl substituted by one to three substituents, such being advantageously lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, cyano, trifluoromethyl, lower alkanoylamino or lower alkoxycarbonyl.

Optionally substituted naphthyl represents 1- or 2-naphthyl or 1- or 2-naphthyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Heterocyclic aryl represents preferably monocyclic heterocyclic aryl such as optionally substituted thienyl, furanyl, pyridyl, pyrrolyl or N-lower alkylpyrrolyl.

Optionally substituted furanyl represents 2- or 3-furanyl or 2- or 3-furanyl preferably substituted by lower alkyl.

Optionally substituted pyridyl represents 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl preferably substituted by lower alkyl or halogen.

Optionally substituted thienyl represents 2- or 3-thienyl or 2- or 3-thienyl preferably substituted by lower alkyl.

Aryl as in aryl-lower and the like is preferably phenyl or phenyl substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano, lower alkanoylamino or lower alkoxycarbonyl.

Aryl-lower alkyl is advantageously benzyl or phenethyl optionally substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms. Such may be straight chain or branched.

A lower alkyl group preferably contains 1-4 carbon atoms and represents for example ethyl, propyl, butyl or advantageously methyl.

A lower alkoxy group preferably contains 1-4 carbon atoms and represents for example methoxy, propoxy, isopropoxy or advantageously ethoxy.

Cycloalkyl represents a saturated cyclic hydrocarbon radical, preferably C₅-C₇-cycloalkyl which contains 5 to 7 ring carbons and is, advantageously cyclopentyl or cyclohexyl.

Cycloalkyl-lower alkyl represents preferably 1- or 2-(cyclopentyl or cyclohexyl)ethyl, 1-, 2- or 3-(cyclopentyl or cyclohexyl)propyl, or 1-, 2-, 3- or 4-(cyclopentyl or cyclohexyl)-butyl.

Lower alkenyloxy represents preferably alkyloxy. Di-lower alkylamino preferably contains 1-4 carbon atoms in each lower alkyl portion and represents, for example, N,N-dimethylamino, N-methyl-N-ethylamino and advantageously N,N-diethylamino.

Lower alkoxy-carbonyl preferably contains 1 to 4 carbon atoms in the alkoxy portion and represents, for example, methoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl or advantageously ethoxycarbonyl.

Hydroxy-lower alkyl is preferably hydroxymethyl.

Halogen (halo) preferably represents fluoro or chloro, but may also be bromo or iodo.

Lower alkanoyl is preferably acetyl, propionyl, butyryl, or pivaloyl.

Lower alkanoyloxy is preferably acetoxy, pivaloyloxy or propionyloxy.

Acylamino represents preferably lower alkanoylamino, aroylamino, or aryl-lower alkoxy-carbonylamino such as benzyloxycarbonylamino.

Lower alkanoylamino is preferably acetamido or propionamido.

Aroyl is preferably benzoyl or benzoyl substituted on the benzene ring by lower alkyl, lower alkoxy, halogen or trifluoromethyl.

Acyl represents preferably lower alkanoyl, carbocyclic aryl-lower alkanoyl or carbocyclic aroyl.

Carboxyl derivatized as a pharmaceutically acceptable ester represents esterified carboxyl, advantageously a prodrug ester that may be convertible by solvolysis or under physiological conditions to the free carboxylic acid, such being preferably lower alkoxy-carbonyl; (amino, acylamino, mono- or di-lower alkylamino)-lower alkoxy-carbonyl; carboxy-lower alkoxy-carbonyl, e.g. alpha-carboxy-lower alkoxy-carbonyl; lower alkoxy-carbonyl-lower alkoxy-carbonyl, e.g. alpha-lower alkoxy-carbonyl-lower alkoxy-carbonyl; alpha-(di-lower alkylamino, amino, mono-lower alkylamino, morpholino, piperidino, pyrrolidino, 1-lower alkyl-piperazino)-carbonyl-lower alkoxy-carbonyl; carbocyclic or heterocyclic aryl-lower alkoxy-carbonyl, preferably optionally (halo, lower alkyl or lower alkoxy)-substituted benzyloxycarbonyl, or pyridylmethoxycarbonyl; 1-(hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxy-carbonyl, e.g. pivaloyloxymethoxycarbonyl; (hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxy-methoxycarbonyl; 1-(lower alkoxy-carbonyloxy)-lower alkoxy-carbonyl; 5-indanyloxycarbonyl; 3-phthalidoxycarbonyl and (lower alkyl, lower alkoxy or halo)-substituted 3-phthalidoxycarbonyl; dihydroxy-propyloxycarbonyl wherein hydroxy groups are free or are protected in the form of ketals, e.g. a lower alkylidene, a benzylidene or a 5- or 6-membered cycloalkylidene derivative, advantageously being (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl.

Carboxyl derivatized as a pharmaceutically acceptable prodrug ester represents most advantageously C₁-C₄-alkoxy-carbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, 1-(C₂-C₄-alkanoyloxy)-ethoxycarbonyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, 5-indanyloxycarbonyl, 1-(C₁-C₄-alkoxy-carbonyloxy)-ethoxycarbonyl or 3-pyridylmethoxycarbonyl.

Carboxyl derivatized as a pharmaceutically acceptable amide represents preferably carbamoyl or N-substituted carbamoyl, advantageously [lower alkylamino, arylamino, di-lower alkylamino, morpholino, N-lower alkylpiperazino, pyrrolidino, piperidino, (amino or

acylamino)-lower alkylamino or aryl-lower alkylamino]-carbonyl.

Esterified hydroxy represents acyloxy, e.g. acyloxy derived from an organic carboxylic acid, preferably lower alkanoyloxy, aroyloxy, or aryl-lower alkanoyloxy; also 3,7,12(3 α ,5 β ,7 α ,12 α)-trihydroxy-cholan-24-oyloxy (derived from cholic acid), and the like.

Etherified hydroxy represents preferably lower alkoxy, lower alkenyloxy, C₅-C₇-cycloalkyloxy, carbocyclic aryl-lower alkoxy, tetrahydropyraniloxy, C₅-C₇-cycloalkyl-lower alkoxy, and the like.

Pharmaceutically acceptable salts are either pharmaceutically acceptable acid addition salts for any basic compounds of the invention or salts derived from pharmaceutically acceptable bases for any acidic compounds of the invention.

Pharmaceutically acceptable salts of any basic compounds of the invention are acid addition salts, which are preferably such of therapeutically acceptable inorganic or organic acids, such as strong mineral acids, for example hydrohalic, e.g. hydrochloric, hydrobromic, sulfuric or phosphoric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. acetic, propionic, succinic, glycollic, lactic, malic, tartaric, gluconic, citric, maleic, fumaric, pyruvic, phenylacetic, benzoic, pantoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, 1,2-ethanedithionyl, benzenesulfonic, p-toluenesulfonic or naphthalenesulfonic acid; or ascorbic acid.

Pharmaceutically acceptable salts of the acidic compounds of the invention, e.g. those having a carboxyl group are salts formed with pharmaceutically acceptable bases, e.g. alkali metal salts (e.g. sodium, potassium salts), alkaline earth metal salts (e.g. magnesium, calcium salts), amine salts (e.g. ethanolamine, diethanolamine, triethanolamine, trimethylamino salts).

The novel compounds of the invention have valuable pharmacological properties. They are pharmacologically potent hypolipidemic agents which reduce plasma cholesterol levels in mammals. The compounds of the invention demonstrate potent binding to the triiodothyronine (T₃) nuclear receptor which is indicative of upregulation of LDL receptor activity and enhancement of the clearance of LDL-cholesterol from the circulation.

The compounds of the invention are thus particularly useful in mammals as hypocholesteremic agents for the treatment and prevention of occlusive cardiovascular conditions in which hypercholesteremia are implicated, by reducing plasma levels of total and LDL-cholesterol.

The above-cited properties are demonstrable in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally, parentally, advantageously intravenously, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10⁻⁷ molar and 10⁻¹¹ molar concentrations. The dosage in vivo may range depending on the route of administration, between about 0.1 and 300 micrograms/Kg, preferably between about 0.5 and 100 micrograms/Kg, advantageously between about 1 and 100 micrograms/Kg.

The in vitro binding to T₃ nuclear receptors is determined as follows:

for example trimethylamine, triethylamine or ethyl-di-isopropylamine, an N,N-di-lower-alkyl-aniline, for example N,N-di-methylaniline, a cyclic tertiary amine, such as an N-lower-alcylated morpholine, for example N-methyl-morpholine, a base of the pyridine type, for example pyridine, an inorganic base, for example hydroxides, carbonates, or hydrogen carbonates of alkali metals or alkaline-earth metals, for example sodium, potassium or calcium hydroxide, carbonate or hydrogen carbonate, or a quaternary ammonium base, such as a tetraalkylammonium hydroxide, carbonate or hydrogen carbonate, for example in which alkyl is e.g. methyl, ethyl, propyl, isopropyl, butyl, or the like, or an alkali metal salt of bis-trialkylsilylamide (e.g. trimethyl) optionally in the presence of a crown ether such as 18-crown-6 in a suitable inert solvent or solvent mixture, e.g. acetonitrile, toluene, and the like.

Esterification of a compound with a free carboxyl group using in excess an alcohol of formula XIII (wherein Y represents hydroxy) is carried out in a manner known per se, e.g. in the presence of an acid catalyst e.g. sulfuric acid or boron trifluoride etherate, preferably at an elevated temperature, advantageously ranging from about 40° C. to 100° C. Alternatively, the esterification of a compound with a free carboxyl group can be carried out with at least an equimolar amount of the alcohol in the presence of a condensing agent such as dicyclohexylcarbodiimide or N-(3-dimethylamino-propyl)-N'-ethylcarbodiimide in a polar solvent such as methylene chloride, in the presence of a base if required, e.g. such as 4-(dimethylamino)pyridine.

Similarly, the free carboxylic acids can be converted to amides using methods well known in the art, e.g. in the presence of a condensing agent such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline

Conversely, carboxylic acid esters can be converted to compounds of the invention with a free carboxy group using the methods and conditions generally known in the art and illustrated herein. Depending on type of ester involved, useful reagents include aqueous acids or bases. Any benzyl esters can be selectively hydrogenolyzed with e.g. hydrogen in the presence of a catalyst such as palladium on charcoal.

Compounds wherein R represents esterified hydroxy or etherified hydroxy can be converted to the compounds wherein R represents hydroxy using methods well-known in the art.

For example, compounds wherein R represents e.g. methoxy can be treated with boron tribromide or boron trichloride in e.g. dichloromethane to obtain compounds wherein R is hydroxy. Also, if R represents benzyloxy, such can be debenzylated by hydrogenolysis with hydrogen in the presence of e.g. palladium catalyst. In the case of esterified hydroxy such can be deesterified with e.g. aqueous acid or base, such as lithium or sodium hydroxide.

In the case mixtures of stereoisomers or optical isomers are obtained, these can be separated into the single isomers by methods in themselves known, e.g., by fractional distillation, crystallization and/or chromatography. Racetalc products or intermediates can be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g. for basic compounds by the fractional crystallization of d- or l-(tartrate, mandelate or camphorsulfonate) salts, or for acidic compounds by fractional crystallization of d- or l-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine,

brucine or strychnine)-salts. Racetalc products can also be resolved by chiral chromatography, e.g. high pressure liquid chromatography using a chiral adsorbent.

The above-mentioned transformations are carried out according to standard methods for the reactions involved, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, alkaline or acidic condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably near the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The present invention additionally relates to the use in mammals for the treatment of hypercholesterolemia of the compounds of the invention or pharmaceutical compositions thereof, e.g. as cholesterol lowering agents, e.g. for lowering LDL-cholesterol, by administration to a mammal in need thereof of a therapeutically effective amount of a said compound.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, for the treatment of hypercholesterolemia, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application.

Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salts and/or polyethyleneglycol; for tablets also c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, the compositions may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with a carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound, optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate

EXAMPLE 28

A slurry of Raney nickel (10 ml) is washed with water (3×25 ml), ethanol (2×25 ml) and added to a solution of 1.4 g (3.1 mmol) of ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate in 20 ml ethyl acetate diluted with 80 ml ethanol. The reaction mixture is hydrogenated on a Parr apparatus for 2 hours at 45 psi and room temperature, then filtered and evaporated. The residue is recrystallized from ether-petroleum ether to give ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate, m.p. 146°-148°.

EXAMPLE 29

A solution of 900 mg (2.0 mmol) of ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate in 20 ml of ethanol and 2.5 ml (2.5 mmol) of 1.0 N aqueous sodium hydroxide is refluxed 2 hours, then evaporated. The residue is dissolved in water and the aqueous solution is washed with ethyl acetate, acidified with 6 N aqueous hydrochloric acid and extracted with ether. The ether layer is washed with water, dried (CaSO₄) and evaporated. Recrystallization from methylene chloride-petroleum ether gives N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 160°-162° dec.

EXAMPLE 30

The following compounds are prepared using essentially the same procedure as described in the above examples for N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, via the corresponding ethyl ester.

- (a) N-[3,5-dichloro-4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]phenyl]oxamic acid, m.p. 196°;
- (b) N-[3,5-dichloro-4-[3'-(4-chlorobenzoyl)-4'-hydroxyphenoxy]phenyl]oxamic acid, m.p. 199°;
- (c) N-[4-[3'-(4-chlorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 188°;
- (d) N-[3,5-dichloro-4-[4'-hydroxy-3'-(1-oxobutyl)-phenoxy]phenyl]oxamic acid, m.p. 183°;
- (e) N-[4-[3'-(benzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid.

EXAMPLE 31

To a solution of 300 mg (0.71 mmol) of N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid in 10 ml methanol is added 130 mg (3.5 mmol) of sodium borohydride. The reaction mixture is stirred at room temperature for 15 minutes, then diluted with water, acidified with 6 N aqueous hydrochloric acid and extracted with ether. The ether layer is washed with water, dried (CaSO₄) and evaporated. The residue is taken up in methylene chloride, filtered and evaporated. Recrystallization from methylene chloride-petroleum ether gives N-[4-[3'-(4-fluorophenyl)-hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 142°-147° dec.

EXAMPLE 32

The following compounds are prepared using essentially the same procedure as described above for N-[4-[3'-(4-fluorophenyl)-hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid.

- (a) N-[3,5-dichloro-4-[3'-(4-chlorophenyl)-hydroxymethyl]-4'-hydroxyphenoxy]phenyl]oxamic acid, m.p. 155°;

- (b) N-[4-[3'-(4-chlorophenyl)-hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 123°.

EXAMPLE 33

A solution of 660 mg (1.96 mmol) of 4-(4-amino-2,6-dimethylphenoxy)-2-[(4-fluorophenyl)methyl]phenol in 5 ml diethyl oxalate is heated at 100° for 1.25 hours. The excess diethyl oxalate is evaporated with a nitrogen stream and the residue is triturated with petroleum ether and filtered. Flash chromatography gives ethyl N-[4-[3'-(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate, m.p. 153°-156°.

The starting material is prepared as follows:

To a solution of 2.2 g (5.55 mmol) of (4-fluorophenyl)[2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)phenyl]methanone in 10 ml methylene chloride and 3 ml trifluoroacetic acid is added 2.1 g (18.0 mmol) of triethylsilane. The solution is stirred overnight at room temperature, then diluted with ether (100 ml) and washed with water, 5% aqueous sodium carbonate, water, dried (CaSO₄) and evaporated. The residual oil is flash chromatographed to give 1-[(4-fluorophenyl)methyl]-2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)benzene, m.p. 105°-110°.

To a solution of 1.7 g (4.5 mmol) of 1-[(4-fluorophenyl)methyl]-2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)benzene in 100 ml methylene chloride is added 13.5 ml (13.5 mmol) 1.0 N boron tribromide in methylene chloride. The solution is stirred overnight at room temperature, poured into ice water (300 ml) and stirred 1 hour. The organic layer is separated, washed with water, dried (CaSO₄) and evaporated. Flash chromatography of the residue gives 2-[(4-fluorophenyl)methyl]-4-(2,6-dimethyl-4-nitrophenoxy)phenol, m.p. 127°-132°.

A slurry of Raney nickel (10 ml) is washed with water (2×25 ml), ethanol (2×25 ml) and added to a solution of 2-[(4-fluorophenyl)methyl]-4-(2,6-dimethyl-4-nitrophenoxy)phenol in 100 ml ethanol. The reaction mixture is hydrogenated on a Parr apparatus for 1.5 hours at 45 psi and room temperature, filtered and evaporated. Recrystallization from ether-petroleum ether gives 4-(4-amino-2,6-dimethylphenoxy)-2-[(4-fluorophenyl)methyl]phenol, m.p. 179°-182°.

EXAMPLE 34

A solution of 440 mg (1.0 mmol) of ethyl N-[4-[3'-(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate in 20 ml ethanol and 1.2 ml (1.2 mmol) 1.0 N aqueous sodium hydroxide is refluxed for 1 hour, then evaporated. The residue is dissolved in water, and the solution is washed with ether, acidified with 6 N aqueous hydrochloric acid and extracted with ether. The ether layer is washed with water, dried (CaSO₄) and evaporated. The residue is recrystallized from methylene chloride to give N-[4-[3'-(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 182°-184° dec.

EXAMPLE 35

The following examples are prepared using essentially the same procedure as described above for N-[4-[3'-(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid.

- (a) N-[3,5-dichloro-4-[3'-(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]phenyl]oxamic acid, m.p. 180°;

magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 250 ml of water. The paste formed is added to the powders, which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35° C. broken on a screen with 1.2 mm openings and compressed into tablets, using concave punches uppers bisected.

Analogously tablets are prepared, containing about 0.01-10 mg of one of the other compounds disclosed and exemplified herein.

EXAMPLE 46

Preparation of 1,000 capsules each containing 0.05 mg of the active ingredient, for example, ethyl N-[4-[3'-(4-fluorophenyl) hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate

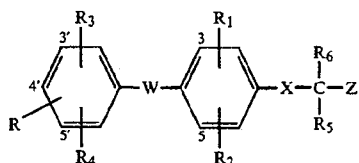
Active ingredient	0.05 g
Lactose	217.00 g
Modified starch	80.00 g
Magnesium stearate	3.00 g

Procedure: All the powders are passed through a screen with openings of 0.6 mm. The drug substance is placed in a suitable mixer and mixed first with the magnesium stearate, then with the lactose and starch until homogeneous. No. 2 hard gelatin capsules are filled with 300 mg of said mixture each, using a capsule filling machine.

Analogously capsules are prepared, containing about 0.01-10 mg of the other compounds disclosed and exemplified herein.

What is claimed is:

1. A method of treating hypercholesterolemia in mammals which comprises administering to a mammal in need of such treatment an effective cholesterol-lowering amount of a compound of the formula



wherein

R is hydroxy, esterified hydroxy or etherified hydroxy;

R₁ is halogen, trifluoromethyl or lower alkyl;

R₂ is halogen, trifluoromethyl or lower alkyl;

R₃ is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or

R₃ is the radical



wherein R₈ is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R₉ is hydroxy or acyloxy; R₁₀ represents hydrogen or lower alkyl; or R₉ and R₁₀ together represent oxo;

R₄ is hydrogen, halogen, trifluoromethyl or lower alkyl;

X is —NR₇;

W is O or S;

R₅ and R₆ together represent oxo;

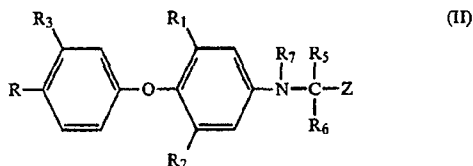
R₇ represents hydrogen or lower alkyl;

Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; and aryl in any of the above definitions represents carbocyclic aryl; or a pharmaceutically acceptable salt thereof.

2. A method according to claim 1 which comprises administering a compound of formula I wherein R is located at the 4'-position, R₁ and R₂ are located at the 3 and 5 positions, and R₃ and R₄ are located at the 3' and 5'-positions; or a pharmaceutically acceptable salt thereof.

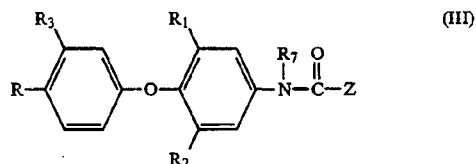
3. A method according to claim 1 which comprises administering a compound of formula I wherein X and W represent O.

4. A method according to claim 1 which comprises administering a compound of the formula



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ and R₂ independently represent halogen, trifluoromethyl or C₁-C₃alkyl; R₃ represents lower alkyl, lower alkanoyl, hydroxy-lower alkyl, carbocyclic arylmethyl, carbocyclic aroyl or carbocyclic aryl-hydroxymethyl; R₅ and R₆ together represent oxo; R₇ represents hydrogen or lower alkyl; and Z represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

5. A method of treating hypercholesterolemia in mammals which comprises administering to a mammal in need of such treatment an effective cholesterol-lowering amount of a compound of the formula



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ represents halogen, trifluoromethyl or C₁-C₃alkyl; R₂ represents halogen, trifluoromethyl or C₁-C₃alkyl; R₃ represents lower alkyl, carbocyclic aroyl, carbocyclic arylmethyl or carbocyclic aryl-hydroxymethyl; R₇ represents hydrogen or lower alkyl; Z represents carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

6. A method according to claim 5 which comprises administering a compound of formula III wherein R represents hydroxy, acyloxy, lower alkoxy or tetrahydropyranyloxy; or of a pharmaceutically acceptable salt thereof.

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7. A method according to claim 5 which comprises administering a compound of formula III wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R₁ and R₂ represent halo or C₁-C₃-alkyl; R₃ is C₁-C₃-alkyl or monocyclic carbocyclic arylmethyl; R₇ is hydrogen or C₁-C₂-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

8. A method according to claim 5 which comprises administering a compound of formula III wherein Z is carboxyl or carboxyl esterified as a pharmaceutically acceptable ester; or a pharmaceutically acceptable salt thereof.

9. A method according to claim 5 which comprises administering a compound of formula III wherein R₁ and R₂ represent chloro or methyl; R₃ is isopropyl, benzyl or benzyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R₇ is hydrogen; Z is carboxyl or lower alkoxy carbonyl; or a pharmaceutically acceptable salt thereof.

10. A method according to claim 9 which comprises administering N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamic acid or a pharmaceutically acceptable salt thereof.

11. A method according to claim 9 which comprises administering N-[3,5-dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamic acid or a pharmaceutically acceptable salt thereof.

12. A method according to claim 5 which comprises administering a compound of formula III wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R₁ and R₂ represent halo or C₁-C₃-alkyl; R₃ is carbocyclic aroyl or carbocyclic arylhydroxymethyl; R₇ is hydrogen or C₁-C₂-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

13. A method according to claim 5 which comprises administering a compound of formula III wherein R is hydroxy; R₁ and R₂ represent chloro or methyl; R₃ is phenyl-hydroxymethyl or phenyl-hydroxymethyl substituted on phenyl by halogen, lower alkyl, lower alkoxy or trifluoromethyl; or R₃ is benzoyl or benzoyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R₇ is hydrogen; Z is carboxyl or lower alkoxy carbonyl; or a pharmaceutically acceptable salt thereof.

14. A method according to claim 13 which comprises administering ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate or an enantiomer thereof.

15. A method according to claim 13 which comprises administering N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, an enantiomer thereof or a pharmaceutically acceptable salt thereof.

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US005569674A

United States Patent [19]

Yokoyama et al.

[11] **Patent Number:** 5,569,674[45] **Date of Patent:** Oct. 29, 1996[54] **HETEROACETIC ACID DERIVATIVES**

[75] Inventors: **Naokato Yokoyama**, deceased, late of Cliffside Park, by Rina Yokoyama, administrator; **Gordon N. Walker**, Mt. Kemble Lake; **Alan J. Main**, Basking Ridge, all of N.J.

[73] Assignee: **Ciba-Geigy Corporation**, Tarrytown, N.Y.

[21] Appl. No.: **358,130**

[22] Filed: **Dec. 16, 1994**

Related U.S. Application Data

[60] Division of Ser. No. 154,203, Nov. 18, 1993, Pat. No. 5,401,772, which is a continuation-in-part of Ser. No. 918,544, Jul. 21, 1992, abandoned.

[51] **Int. Cl.⁶** **A61K 31/24**

[52] **U.S. Cl.** **514/539; 514/563; 514/619; 514/459; 549/416; 560/43; 562/455; 564/167**

[58] **Field of Search** **560/43; 562/455; 564/167; 514/539, 563, 619, 459; 549/416**

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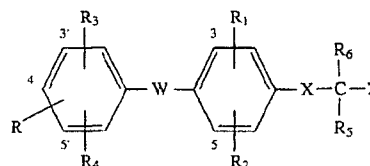
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Primary Examiner—Samuel Barts

Attorney, Agent, or Firm—Norbert Gruenfeld

[57] **ABSTRACT**

Disclosed are compounds of formula



wherein

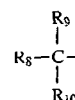
R is hydroxy, esterified hydroxy or etherified hydroxy;

R₁ is halogen, trifluoromethyl or lower alkyl;

R₂ is halogen, trifluoromethyl or lower alkyl;

R₃ is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or

R₃ is the radical



wherein R₈ is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R₉ is hydroxy or acyloxy; R₁₀ represents hydrogen or lower alkyl; or R₉ and R₁₀ together represent oxo;

R₄ is hydrogen, halogen, trifluoromethyl or lower alkyl;

X is —NR₇, S or O;

W is O or S;

R₅ represents hydrogen, lower alkyl or aryl-lower alkyl; and

R₆ represents hydrogen; or

R₅ and R₆ together represent oxo provided that X represents —NR₇;

R₇ represents hydrogen or lower alkyl;

Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; and pharmaceutically acceptable salts thereof; which are useful as hypocholesteremic agents.

16 Claims, No Drawings

HETEROACETIC ACID DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a Divisional of Ser. No. 08/154,203, filed Nov. 18, 1993, now U.S. Pat. No. 5,401,772 which is a continuation-in-part of Ser. No. 07/918,544, filed Jul. 21, 1992, now abandoned.

SUMMARY OF THE INVENTION

The invention relates to the heteroacetic acid derivatives as defined herein which are particularly useful as potent lipid lowering agents, methods for preparation thereof, pharmaceutical compositions comprising said compounds, and a method of treating hyperlipidemia, in particular hypercholesterolemia and related conditions in mammals, by administering said compounds or pharmaceutical compositions comprising said compounds.

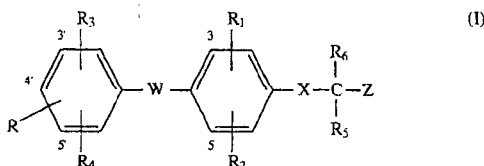
The compounds of the invention are selective thyromimetic hypolipidemic agents which enhance the clearance of cholesterol from the circulation, particularly the clearance of cholesterol in the form of low density lipoproteins (LDL). They, *inter alia*, upregulate (increase) hepatic LDL receptor function in mammals.

Thus, the compounds of the instant invention are primarily useful for reducing total cholesterol plasma levels in mammals, in particular for reducing levels of LDL-cholesterol.

The compounds of the invention are therefore expected to be useful for the prevention and/or treatment of occlusive cardiovascular conditions in which hyperlipidemia and hyperlipoproteinemia are implicated, such as atherosclerosis and coronary heart disease (myocardial infarctions) in mammals.

DETAILED DESCRIPTION OF THE INVENTION

More particularly, the invention relates to the compounds of formula I



wherein

- R is hydroxy, esterified hydroxy or etherified hydroxy;
- R₁ is halogen, trifluoromethyl or lower alkyl;
- R₂ is halogen, trifluoromethyl or lower alkyl;
- R₃ is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or
- R₃ is the radical



wherein R₈ is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R₉ is hydroxy or acyloxy; R₁₀ represents hydrogen or lower alkyl; or R₉ and R₁₀ together represent oxo;

R₄ is hydrogen, halogen, trifluoromethyl or lower alkyl;

X is —NR₇, S or O;

W is O or S;

R₅ represents hydrogen, lower alkyl or aryl-lower alkyl; and

R₆ represents hydrogen; or

R₅ and R₆ together represent oxo provided that X represents —NR₇;

R₇ represents hydrogen or lower alkyl;

Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; and pharmaceutically acceptable salts thereof.

Particular embodiments of the invention relate to the compounds of formula I wherein

(a) R is located at the 4'-position; R₁ and R₂ are located at the 3 and 5 positions, and R₃ and R₄ are located at the 3' and 5'-positions;

(b) X and W represent O; or

(c) X represents —NR₇, and W represents O; or

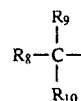
(d) X represents S, and W represents O;

(e) R₄ is hydrogen;

(f) Z is carboxyl or carboxyl esterified as a pharmaceutically acceptable ester;

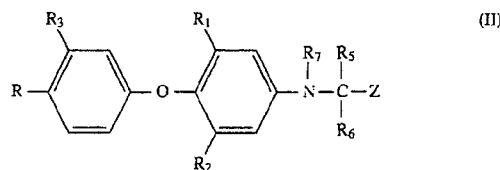
(g) R₅ and R₆ together represent oxo and X represents NR₇;

(h) R₃ represents the radical



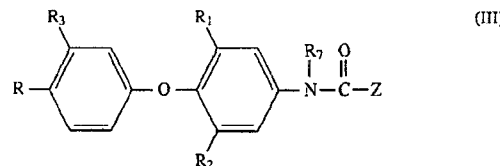
lower alkyl, aryl-lower alkyl or cycloalkyl-lower alkyl.

A preferred embodiment of the invention relates to the compounds of formula II



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ and R₂ independently represent halogen, trifluoromethyl or C₁–C₃alkyl; R₃ represents lower alkyl, lower alkanoyl, hydroxy-lower alkyl, carbocyclic arylmethyl, carbocyclic aroyl or carbocyclic aryl-hydroxymethyl; R₅ and R₆ together represent oxo; R₇ represents hydrogen or lower alkyl; and Z represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

A further preferred embodiment relates to the compounds of formula III



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ represents halogen, trifluoromethyl or C₁–C₃alkyl; R₂ represents halogen, trifluoromethyl or C₁–C₃alkyl; R₃ represents lower alkyl, carbocyclic aroyl,

33

- (b) ethyl N-[4-[3'-[(4-chlorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate;
 (c) ethyl N-4-[3'-(phenyl-hydroxymethyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate;
 (d) ethyl N-[4-[3'-[(4-tolyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate;
 (e) ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-methoxyphenoxy]-3,5-dimethylphenyl]oxamate, m.p. 155°-156°.

EXAMPLE 44

Ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate according to Example 42 is resolved by high pressure liquid chromatography (HPLC) on a chiral OD (Daicel) column (cellulose para-methylbenzoate coated on silica gel) during with 80:20 hexane/ethanol to give isomer A (retention time 115 minutes), $\alpha_D = +23.1^\circ$ C. (c=0.64 in acetonitrile), m.p. 150°-152° C.; and isomer B (retention time 150 minutes), $\alpha_D = -21.7^\circ$ C. (c=0.47 in acetonitrile), m.p. 147°-150° C.

EXAMPLE 45

Preparation of 10,000 tablets each containing 0.2 mg of the active ingredient, for example, N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid,

Active ingredient	2.00 g
Lactose	2,535.00 g
Corn starch	125.00 g
Polyethylene glycol 6,000	150.00 g
Magnesium stearate	40.00 g
Purified water	q.s.

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. The drug substance, lactose, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 250 ml of water. The paste formed is added to the powders, which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35° C. broken on a screen with 1.2 mm openings and compressed into tablets, using concave punches uppers bisected.

Analogously tablets are prepared, containing about 0.01-10 mg of one of the other compounds disclosed and exemplified herein.

EXAMPLE 46

Preparation of 1,000 capsules each containing 0.05 mg of the active ingredient, for example, ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate

Active ingredient	0.05 g
Lactose	217.00 g
Modified starch	80.00 g
Magnesium stearate	3.00 g

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. The drug substance is placed in a suitable mixer and mixed first with the magnesium stearate, then with the lactose and starch until homogenous. No. 2 hard

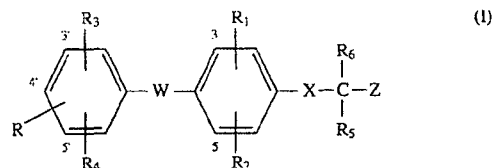
34

gelatin capsules are filled with 300 mg of said mixture each, using a capsule filling machine.

Analogously capsules are prepared, containing about 0.01-10 mg of the other compounds disclosed and exemplified herein.

What is claimed is:

1. A compound of the formula



wherein

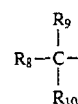
R is hydroxy, esterified hydroxy or etherified hydroxy;

R₁ is halogen, trifluoromethyl or lower alkyl;

R₂ is halogen, trifluoromethyl or lower alkyl;

R₃ is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or

R₃ is the radical



wherein R₈ is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R₉ is hydroxy or acyloxy; R₁₀ represents hydrogen or lower alkyl; or R₉ and R₁₀ together represent oxo;

R₄ is hydrogen, halogen, trifluoromethyl or lower alkyl;

X is —NR₇;

W is O or S;

R₅ and R₆ together represent oxo;

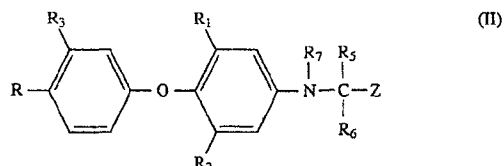
R₇ represents hydrogen or lower alkyl;

Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R is located at the 4'-position, R₁ and R₂ are located at the 3 and 5 positions, and R₃ and R₄ are located at the 3' and 5'-positions.

3. A compound according to claim 1 wherein W is O.

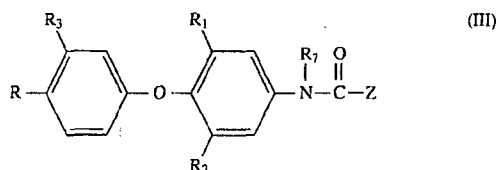
4. A compound according to claim 1 of the formula



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ and R₂ independently represent halogen, trifluoromethyl or C₁-C₃alkyl; R₃ represents lower alkyl, lower alkanoyl, hydroxy-lower alkyl, carbocyclic arylmethyl, carbocyclic aryl or carbocyclic aryl-hydroxymethyl; R₅ and R₆ together represent oxo; R₇ represents hydrogen or lower alkyl; and Z represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

35

5. A compound according to claim 4 of the formula



wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R₁ represents halogen, trifluoromethyl or C₁-C₃alkyl; R₂ represents halogen, trifluoromethyl or C₁-C₃alkyl; R₃ represents lower alkyl, carbocyclic aryl, carbocyclic arylmethyl or carbocyclic aryl-hydroxymethyl; R₇ represents hydrogen or lower alkyl; Z represents carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 5 wherein R represents hydroxy, acyloxy, lower alkoxy or tetrahydropyranyloxy.

7. A compound according to claim 5 wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R₁ and R₂ represent halo or C₁-C₃-alkyl; R₃ is C₁-C₃-alkyl or monocyclic carbocyclic arylmethyl; R₇ is hydrogen or C₁-C₂-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 5 wherein Z is carboxyl or carboxyl esterified as a pharmaceutically acceptable ester.

9. A compound according to claim 7 wherein R₁ and R₂ represent chloro or methyl; R₃ is isopropyl, benzyl or benzyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R₇ is hydrogen; Z is carboxyl or lower alkoxy-carbonyl; or a pharmaceutically acceptable salt thereof.

36

10. A compound according to claim 5 wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R₁ and R₂ represent halo or C₁-C₃-alkyl; R₃ is carbocyclic aryl or carbocyclic aryl-hydroxymethyl; R₇ is hydrogen or C₁-C₂-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 5 wherein R is hydroxy; R₁ and R₂ represent chloro or methyl; R₃ is phenyl-hydroxymethyl or phenyl-hydroxymethyl substituted on phenyl by halogen, lower alkyl, lower alkoxy or trifluoromethyl; or R₃ is benzoyl or benzoyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R₇ is hydrogen; Z is carboxyl or lower alkoxy-carbonyl; or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 9 which is N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamic acid or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 9 which is N-[3,5-dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamic acid or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 11 which is ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate or an enantiomer thereof.

15. A compound according to claim 11 which is N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, an enantiomer thereof or a pharmaceutically acceptable salt thereof.

16. A cholesterol-lowering pharmaceutical composition comprising an effective cholesterol-lowering amount of a compound of claim 1 in combination with one or more pharmaceutically acceptable carriers.

* * * * *

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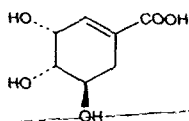
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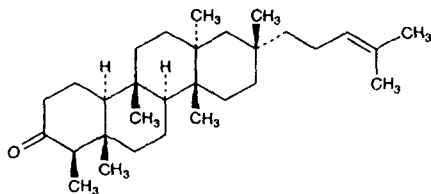
148



Needles from methanol/ethyl acetate, mp 183-184.5°. Sublimes. $[\alpha]_D^{25} -161^\circ$ (c = 0.57 in methanol). $[\alpha]_D^{25} -183.8^\circ$ (c = 4.03 in water). uv max (alcohol): 213 nm (ϵ 8900). K at $14.1^\circ = 7.1 \times 10^{-5}$. Soly in water about 18 g/100 ml. Soly at 23° (g/100 m): 2.25 in abs alcohol; 0.015 in anhyd ether. Practically insol in chloroform, benzene, petr ether. LD₅₀ i.p. in mice: 1000 mg/kg (Evans, Osman).

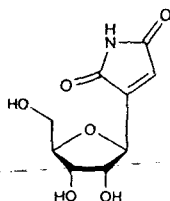
(±)-Form, needles from methanol/ethyl acetate, mp 191-192°. uv max (ethanol): 212 nm (ϵ 8200).

8626. Shionone. *D:A-Friedo-18,19-secolup-19-en-3-one; 3β,5α,8,17β-tetramethyl-3-(4-methyl-3-pentenyl)-D-homoandrostan-17-one.* C₃₀H₅₀O; mol wt 426.73. C 84.44%, H 11.81%, O 3.75%. From *Aster tartaricus* L., *Compositae*: Nakaoki, *J. Pharm. Soc. Japan* 52, 499 (1932); C.A. 26, 4821⁴ (1932); Takahashi et al., *ibid.* 79, 1281 (1959); C.A. 54, 4667g (1960). Structure: Y. Tanahashi et al., *Bull. Soc. Chim. France* 1966, 1670. Conformation: Y. Moriyama et al., *ibid.* 1968, 2890.



Crystals from alc, mp 161-162°. $[\alpha]_D^{25} -56.1^\circ$ (c = 1.07 in chloroform). uv max (chloroform): 290 nm (log ϵ 1.47).

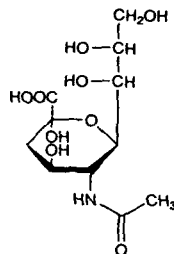
8627. Showdomycin. *3-β-D-Ribofuranosyl-1H-pyrrole-2,5-dione; 2-β-D-ribofuranosylmaleimide.* C₉H₁₁NO₆; mol wt 229.19. C 47.17%, H 4.84%, N 6.11%, O 41.89%. Nucleoside antibiotic isolated from *Streptomyces showdoensis*: Nishimura et al., *J. Antibiot.* 17A, 148 (1964); Nishimura, Fr. pat. M2751 corresp to U.S. pat. 3,316,149 (1964, 1967, both to Shionogi). Structure: Nakagawa et al., *Tetrahedron Letters* 1967, 4105; Darnall et al., *Proc. Nat. Acad. Sci. USA* 57, 548 (1967). Synthesis: Kalvoda et al., *Tetrahedron Letters* 1970, 2297; Trummelitz, Moffatt, *J. Org. Chem.* 38, 1841 (1973); T. Sato et al., *Tetrahedron Letters* 1978, 1829; J. G. Buchanan et al., *J. Chem. Soc. Perkin Trans. I* 1979, 225; T. Inoue, I. Kuwajima, *Chem. Commun.* 1980, 251; A. P. Kozikowski, A. Ames, *J. Am. Chem. Soc.* 103, 3923 (1981); Y. Araki et al., *Tetrahedron Letters* 29, 351 (1988). Exhibits antitumor activity: Shinzo et al., *J. Antibiot.* 17A, 234 (1964). Review: D. W. Visser, S. Roy-Burman in *Antibiotics* vol. 5 (pt. 2), F. E. Hahn, Ed. (Springer-Verlag, New York, 1979) pp 363-371.



Leaflets from acetone + benzene, mp 153-154°. $[\alpha]_D^{25} +49.9^\circ$ (H₂O). uv max: 220-221 nm ($\epsilon_{1\text{cm}}^{1\%}$ 422). Sol in

alkaline. LD₅₀ in mice (mg/kg): 25 i.p.; 18 s.c. (Nishimura).

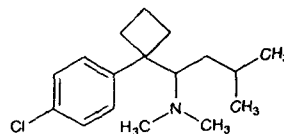
8628. Sialic A Nonulosaminic acids. Five amino sugars contg 9 or more carbon atoms. Found as substituted derivatives of neuraminic acid, q.v. Widely distributed throughout the animal kingdom; appear to be major components of all types of mucoproteins, mucopolysaccharides and certain mucolipids. Bovine and ovine salivary gland sialic acids are diacetyl derivs. Pig submaxillary mucin, and pig, horse, and ox erythrocytes contain sialic acids having an *N*-glycolyl group. Reviews: A. Gottschalk, *The Chemistry and Biology of Sialic Acids and Related Substances* (Cambridge U. Press, 1960); *idem*, *Rev. Pure Appl. Chem.* 12, 46 (1962). Books: *Biological Roles of Sialic Acid*, A. Rosenberg, C.-L. Schengrund, Eds. (Plenum Press, New York, 1976) 393 pp; *Sialic Acids: Chemistry, Metabolism & Function*, R. Schauer, Ed. (Springer-Verlag, New York, 1983) 346 pp.



N-Acetylneuraminic acid

N-Acetylneuraminic acid, C₁₁H₁₉NO₉, 5-(acetylamine)-1,4,6-dideoxy-D-glycero-D-galacto-2-nonulosonic acid, *NAN*, *NANA*, lactaminic acid, *O*-sialic acid. mol wt 309.27. The most important of the 5 sialic acids. Isoln: Klenk, Faillard, *J. Physiol. Chem.* 298, 230 (1954). Prep'n from sheep submaxillary mucins: Blix, *Methods Carbohydr. Chem.* 1, 244 (1962). Synthesis: Cornforth et al., *Biochem. J.* 68, 91 (1958); R. Csuk et al., *Helv. Chim. Acta* 71, 609 (1988). First synthesis from non-carbohydrate sources: M. P. De Ninnio, S. J. Danishevsky, *J. Org. Chem.* 51, 2615 (1986). Configuration: Kuhn, Brossmer, *Angew. Chem. Int. Ed.* 1, 218 (1962). Crystals from water/acetic acid (0.8:12) at T , mp 180-182° (dec). $[\alpha]_D^{25} -33.1^\circ$ (c = 0.9 in water).

8629. Sibutramine. *1-(4-Chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)cyclobutanemethanamine; N-1-(4-chlorophenyl)cyclobutyl-3-methylbutyl-N,N-dimethylamine.* C₁₇H₂₅ClN; mol wt 279.85. C 72.96%, H 9.36%, Cl 12.67%, N 5.01%. Monoamine reuptake inhibitor. Prep'n: J. E. Jeffery et al., Ger. pat. 3,212,682 (1982 to Boots). J. E. Jeffery, D. Whybrow, Brit. pat. 2,184,122; J. E. Jeffery, U.S. pat. 4,929,629 (1987, 1990 both to Boots). Pharmacology of sibutramine and its metabolites: G. P. Luscombe et al., *Neuropharmacology* 28, 129 (1989). Clinical pharmacology: D. J. King, N. Devaney, *Brit. J. Clin. Pharmacol.* 26, 607 (1988). Clinical efficacy in weight control: M. W. Traub et al., *Clin. Pharmacol. Ther.* 50, 330 (1991).

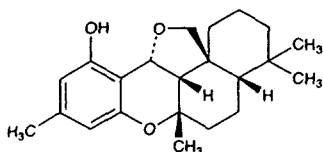


Hydrochloride monohydrate, C₁₇H₂₅ClN·HCl·H₂O. **54524.** *Reduicil, Meridia.* Crystals from water, mp 191.5°.

THERAP CAT: Anorexic.

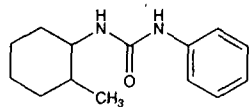
8630. Siccanin. *[4aS-(4α,6α,11b,13aR*,13bS*)-1,2,3,4a,5,6,6a,11b,13b-Decahydro-4,4,6a,9-tetramethyl-13H-benzofuro[2,3,4-m]xanthen-11-ol.* Tackle. C₂₂H₂₈O₂.

... a parasitic organism of (ye. grass (*Lottum*...
 ... (Isôin: K... (shi, Japan. pat. 62 3548
 ... Sankyo). idem. *J. A...* 15A, 161 (1962). The
 ... of the decahydro... nthalene system may be
 ... example of the naturally occurring drimane skele-
 ... K. Hirai et al., *Tetrahedron Letters* 1967,
 ... Structure. *Tetrahedron* 27, 6057 (1971). Ap-
 ... K. Hirai et al., *Chem. Pharm. Bull.* 20,
 ... to synthesis: H. Oida et al., *Chem. Pharm. Bull.* 20,
 ... (1972); T. Yoshida et al., *ibid.* 2642. Total synthesis of
 ... M. Kato et al., *J. Am. Chem. Soc.* 103, 2434
 ... *Tetrahedron* 43, 711 (1987). CD spectral
 ... idem. *Tetrahedron* 30, 2773 (1974). In vitro
 ... S. Nozoe et al., *Antimicrob. Ag. Chemother.*
 ... 247; M. G. Bellotti, L. Riviera, *Chemioterapia* 4, 431
 ... in vivo studies: S. Sugarwara, *Antimicrob. Ag.*
 ... 1969, 253. Toxicology: Y. Suzuki et al., *Sankyo*
 ... *Nempo* 21, 120 (1969), C.A. 72, 130939k (1970).
 ... of action: K. Nose, A. Endo, *J. Bacteriol.* 105, 176
 ... Biosynthesis: K. Suzuki et al., *Bioorg. Chem.* 3, 72
 ... Clinical evaluation in surface mycosis: D. Crippa et
 ... *Ital. Dermatol. Venereol.* 120, 57 (1985).



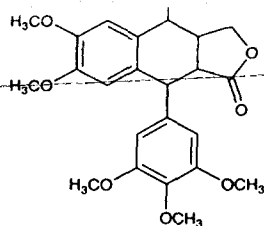
White to pale yellow odorless crystals, mp 139-140°. $[\alpha]_D^{20}$
 -136° (c = 2 in chloroform). uv max (ethanol): 210, 285
 (45690, 1717). pK 10.9. Very sol in chloroform,
 dimethylformamide, benzene; freely sol in acetone, ether,
 ethyl acetate; sol in alcohol. Practically insol in water.
 LD₅₀ in mice, rats (mg/kg): > 6000, > 1000 orally; > 3000,
 > 600 s.c. or i.p. (Suzuki).
 THERAP CAT: Antifungal.

8631. Siduron. *N*-(2-Methylcyclohexyl)-*N'*-phenylurea;
 Hyperm. $C_{14}H_{20}N_2O$; mol wt 232.33. C 72.38%, H 8.68%,
 N 12.06%, O 6.89%. Prepn: Luckenbaugh, Belg. pat. 631,
 (1963 to du Pont), C.A. 60, 15775h (1964), corresp to
 Brit. pat. 1,028,818. Prepn of trans-form: Hayman et al., *J.*
Pharm. Pharmacol. 16, 538 (1964).



Solid, mp 133-138°. Sol in water (18 ppm); sol to the
 extent of 10% or more in ethanol, dimethylacetamide,
 dimethylformamide, methylene chloride.
 Trans-Form, crystals, mp 157-159°.
 USE: Herbicide.

8632. Sikkimotoin. 3a,4,9,9a-Tetrahydro-4-hydroxy-
 7-dimethoxy-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-c]-
 furo[1,3H]-one, 1-hydroxy-2-hydroxymethyl-6,7-dimeth-
 oxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaph-
 thene-3-carboxylic acid lactone. $C_{23}H_{26}O_8$; mol wt 430.45.
 C 64.18%, H 6.09%, O 29.73%. Isoln from roots and rhi-
 zomes of *Podophyllum sikkimensis* R. Chatterjee et Muker-
 jee, *Berberidaceae*: Chatterjee, Datta, *Indian J. Physiol.*
Med Sci. 4, 61 (1950). Structure: Chatterjee, Chakravarti,
J. Am. Pharm. Assoc. Sci. Ed. 41, 415 (1952); Schreier, *Helv.*
Chim. Acta 47, 1529 (1964).



Crystals from ethanol + benzene, mp 120°. $[\alpha]_D^{25}$ -91.8°.
 Freely sol in ethanol, methanol, chloroform. Sparingly sol
 in benzene. Practically insol in water and petr ether.

8633. Silane. Silicon tetrahydride; silicane; monosila-
 ne. H_4Si ; mol wt 32.12. H 12.55%, Si 87.45%. SiH_4 .
 Prepd from aluminum silicide and hydrochloric acid or by
 electrolysis of an aq soln of sodium, ammonium, manga-
 nese, or ferrous chloride using an aluminum-silicon alloy as
 the positive pole: Buff, Wöhler, *Ann.* 102, 128 (1857); from
 magnesium silicide and HCl: Wöhler, *ibid.* 106, 56 (1858);
 Stock, Somiesky, *Ber.* 49, 111 (1916); from zinc silicide and
 acid: Deville, Caron, *Compt. Rend.* 45, 163 (1857); from
 lithium silicide and acid: Moissan, *ibid.* 135, 1284 (1902);
 from magnesium silicide and ammonium bromide or chlo-
 ride in liquid ammonia: Johnson, Isenberg, *J. Am. Chem.*
Soc. 57, 1349 (1935); Clasen, Ger. pat. 926,069 (1952);
Angew. Chem. 70, 179 (1958); from lithium aluminum hy-
 dride in ether and silicon tetrachloride: Finholt et al., *J.*
Am. Chem. Soc. 69, 2692 (1947); from silica gel, aluminum
 oxide and hydrogen: Jackson, U.S. pat. 3,068,069 (1962 to
 du Pont); from silicon tetrachloride and sodium aluminum
 hydride: Mason, Kelly, U.S. pat. 3,043,664 (1962 to Allied
 Chem.). Purification: Jacob, Trenner, U.S. pat. 3,019,087
 (1962 to Merck & Co.); Shoemaker, Sumrell, U.S. pat.
 3,041,141 (1962 to Baker Chem.).

Gas, repulsive odor. d_{-185}^{25} (liq) 0.68. Solidifies at approx
 -200°. mp -185°; bp -112°. Stable at ordinary temps;
 completely dec ~400° into silicon and hydrogen; dec by an
 electric discharge; ignites in an atm of chlorine; ignites in air
 by raising the temp. Slowly dec in water; practically insol
 in alc, ether, benzene, chloroform, silicichloroform and sili-
 con tetrachloride. Dec in potassium hydroxide solns.

Caution: Irritating to respiratory tract.

USE: Source of hyperpure silicon for semiconductors.

8634. Silicic Acid. Precipitated silica. Approx
 H_2SiO_3 . Occurs in nature as opal. Monograph: E. A.
 Hauser, *Silicic Science* (Van Nostrand, Princeton, 1958).
 Short review of chemistry: S. A. Greenberg, *J. Chem. Ed.*
 36, 218-219 (1959).

White, amorphous powder. Insol in water or acids except
 hydrofluoric (see under Silicon Dioxide); sol in hot fixed alk
 hydroxide solns.

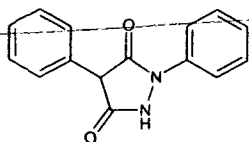
Silica gel, Dri-Die. Pptd silicic acid in form of lustrous
 granules, esp prepd and adapted for absorption of various
 vapors.

USE: Silica gel as insecticide.

8635. Silicon. Si; at. wt 28.0855; at. no. 14; valence 4,
 also 2. Three naturally occurring isotopes: 28 (92.18%); 29
 (4.71%); 30 (3.12%); artificial isotopes: 25-27; 31; 32. Does
 not occur free in nature; found as silica (quartz, sand, sand-
 stone) or as silicate (feldspar or orthoclase, kaolinite, anor-
 thite, etc.). Constitutes about 27.6% of the earth's crust;
 second most abundant element on earth, oxygen being first.
 Prepd industrially by carbon reduction of silica in an elec-
 tric arc furnace. Purification by zone refining (see ref. under
 Germanium). Very pure silicon is obtained by decompn of
 silicon tetraiodide: Litton, Anderson, *J. Electrochem. Soc.*
 101, 287 (1954); *Chem. & Eng. News* 34, 5007 (1956). From
 silicon tetrachloride: Lyon et al., *Trans. Electrochem. Soc.*
 96, 359 (1949); Klyuchnikov, *J. Appl. Chem. USSR* 29, 139
 (1956). By thermal decompn of a chlorosilane: Schering,
 U.S. pat. 3,041,144 (1962 to Siemens-Schuckertwerke). Re-
 view of silicon and its compounds: Rochow, "Silicon" in

THERAP CAT: Analgesic (narcotic).

7401. Phenopyrazone. 1,4-Diphenyl-3,5-pyrazolidine-dione; 1,4-diphenyl-3,5-dioxypyrazolidine. $C_{15}H_{12}N_2O_2$; mol wt 252.27. C 71.42%, H 4.79%, N 11.10%, O 12.68%. Prepn: Kraft, U.S. pat. 2,909,465 (1959 to Knoll).

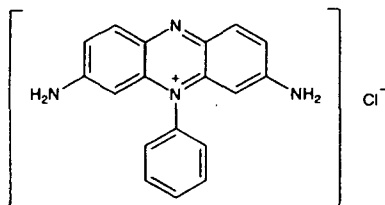


Crystals, mp 233-234°. May be recrystallized from dioxane or ethyl acetate.

2-Diethylaminoethanol salt, component of *Osadrin*.

THERAP CAT: Analgesic, antipyretic.

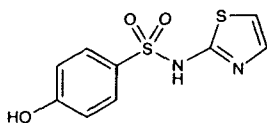
7402. Phenosafranin. 3,7-Diamino-5-phenylphenazinium chloride; C.I. 50200; Safranin B Extra. $C_{18}H_{15}ClN_4$; mol wt 322.80. C 66.98%, H 4.68%, Cl 10.98%, N 17.36%. Prepd by dichromate oxidation of 1 mol *p*-phenylenediamine hydrochloride and 2 mols aniline hydrochloride: Witt, *Ber.* 12, 939 (1879); 19, 3121 (1886). See also *Colour Index* vol. 4 (3rd ed., 1971) p 4449.



Green, lustrous needles from dil HCl. Freely sol in water, also sol in alc. Aq and alcoholic solns are purplish-red and have a greenish-yellow fluorescence. Absorption max ~530 nm.

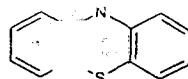
USE: Biological stain.

7403. Phenosulfazole. 4-Hydroxy-*N*-2-thiazolylbenzenesulfonamide; *N*-(2-thiazolyl)-1-phenol-4-sulfonamide; Virazene. $C_9H_8N_2O_3S_2$; mol wt 256.31. C 42.18%, H 3.15%, N 10.93%, O 18.73%, S 25.02%. Refs: Sanders *et al.*, *Tex. Rep. Biol. Med.* 6, 385 (1948); *Chem. & Eng. News* 26, 2710 (1948); Jungeblut, *Proc. Soc. Exp. Biol. Med.* 70, 371 (1949); LoGrippe *et al.*, *ibid.* 528; Cox *et al.*, *ibid.* 530; Weil, Warren, *ibid.* 534; Francis, Brown, *ibid.* 535.



Crystals, insol in water. Forms a water-sol sodium salt. THERAP CAT: Formerly in poliomyelitis.

7404. Phenothiazine. 10*H*-Phenothiazine; thiodiphenylamine; dibenzothiazine; AFI-Tiazin; Antiverm; Fentiazin; Helmetina; Lethelmin; Nemazine; Orimon; Phénégic; Phenoverm; Phenovis; Phenoxur; Reconox; Souframine; Vermitin. $C_{12}H_9NS$; mol wt 199.28. C 72.33%, H 4.55%, N 7.03%, S 16.09%. Prepd by fusing diphenylamine with sulfur: Bernthsen, *Ber.* 16, 2896 (1883); *Ann.* 230, 73 (1885); Ger. pat. 25,150 (1883); *Frdl.* 1, 252. Improved yields with iodine as catalyst: Knoevenagel, *J. Prakt. Chem.* [2] 89, 11 (1914); Mitchell, Webb, U.S. pat. 2,415,363 (1947 to Koppers). Purification: Vierling, U.S. pat. 2,887,482 (1959); Rigby, U.S. pat. 3,000,887 (1961 to Shell Oil). Crystal structure: J D. Bell *et al.*, *Chem. Commun.* 1968, 1656.

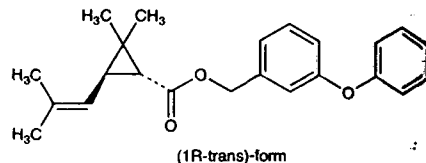


Yellow, rhombic leaflets or diamond-shaped plates from toluene or butanol, mp 185.1°. Sublimes at 130° at 1 mm bp₇₆₀ 371°; bp₄₀ 290°. Freely sol in benzene; sol in chloroform, hot acetic acid; slightly sol in alcohol and in mineral oil. Practically insol in petr ether, chloroform, water. Oxidized by sunlight or when in presence of a finely divided inert carrier, acquiring a greenish-brown tint. This can be prevented by the admixture of 0.3-1.0% methenamine.

USE: Insecticide; manuf pharmaceuticals.

THERAP CAT (VET): Anthelmintic.

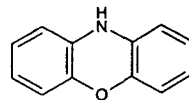
7405. Phenothrin. 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid (3-phenoxyphenyl)amide ester; 2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylic acid *m*-phenoxybenzyl ester; 3-phenoxybenzyl chrysanthemate; S-2539; Sumithrin. $C_{21}H_{24}O_3$; mol wt 350.46. C 78.83%, H 7.48%, O 13.70%. Potent synthetic pyrethroid insecticide. Prepn of racemic mixture: N. Imai *et al.*, Ger. pat. 1,926,433 corresp to U.S. pat. 3,664,589 (1969, 1972 to Sumitomo). Comparative activity of isomers: K. Fujimoto *et al.*, *Agr. Biol. Chem.* 37, 2681 (1973). Y. Okuno *et al.*, Ger. pat. 2,348,930 corresp to U.S. pat. 3,934,023 (1973, 1976 to Sumitomo). Analysis: Y. Takimoto *et al.*, *Anal. Methods Pestic. Plant Growth Regul.* 13, 133-146 (1984).



The commercial product is a mixture of isomers. Colorless liquid. d_{25}^{25} 1.06; n_D^{25} 1.5483. Sol in acetone, xylene; insol in water.

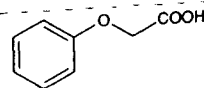
USE: Insecticide.

7406. Phenoxazine. Phenazoxine. $C_{12}H_9NO$; mol wt 183.21. C 78.67%, H 4.95%, N 7.65%, O 8.73%. Prepd from 2-aminophenol and 2-aminophenol-HCl: Kehrman, Neil, *Ber.* 47, 3107 (1903); de Antoni, *Bull. Soc. Chim. France* 1963, 2871; by heating 2-amino-2'-hydroxydiphenyl ether in a sealed tube at 270-280° for 40 hrs: Cullinan *et al.*, *J. Chem. Soc.* 1934, 718.



Leaflets from alc, mp 156°. Freely sol in abs methanol, ethanol, ether, $CHCl_3$, benzene. Sparingly sol in petr ether. 10-Acetylphenoxazine, $C_{14}H_{11}NO_2$, prisms, mp 147°. Sparingly sol in hot water; sol in alc; freely sol in glacial acetic acid.

7407. Phenoxyacetic Acid. Phenoxyethanoic acid. O-phenylglycolic acid; phenyl ether glycolic acid; Phenoxym. $C_8H_7O_3$; mol wt 152.15. C 63.15%, H 5.30%, O 31.55%. Prepared from phenol and monochloroacetic acid: Giacomini, *Prakt. Chem.* [2] 19, 396 (1879); van Alphen, *Rec Trav. Chim.* 46, 148 (1927).

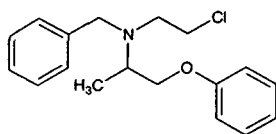


Needles from water, mp 98°; bp 285° (some decomposition) at 25° = 7.54×10^{-4} . One gram dissolves in ~2 ml

Mild irritant.
Fungicide: keratin e
calluses, corns, and oth
blisters, pads or in liquids).

Phenoxyacetyl Cellulose. *Cellulose phenoxyace-*
tate. **Exorb-A.** Support used to immobilize proteins, en-
zymes and microsomes by hydrophobic adsorption. The
attractive forces between the hydrophobic phenoxyacetate
groups of the support and the hydrophobic surface areas of
the molecules arise from the common repulsion of the
aqueous medium. Prepn and properties: L. G. Butler,
Biochem. Biophys. 171, 645 (1975). Applications: J.
G. Butler *et al.*, *Biotechnol. Bioeng.* 21, 2113 (1979).
Soluble in dry form; slowly hydrolyzed in aq media above
pH 6. Resistant to enzymatic hydrolysis.
Use in enzyme immobilization.

7409. Phenoxybenzamine. *N-(2-Chloroethyl)-N-(1-
phenoxyethyl)benzenemethanamine; N-(2-chloroeth-
yl)-N-(1-methyl-2-phenoxyethyl)benzylamine; N-phenoxyiso-
propyl-N-benzyl-β-chloroethylaniline; benzyl; 688-A.* $C_{18}H_{19}ClNO$; mol wt 303.83. C 71.16%, H 7.30%, Cl 11.67%,
N 4.61%, O 5.27%. Prepn: Kerwin, Ulliyot, U.S. pat.
2,800,800 (1952 to SK&F).



Crystals from petr ether, mp 38-40°. Sol in benzene.
Hydrochloride, $C_{18}H_{22}ClNO \cdot HCl$, *Dibenzyline, Dibenzylin,*
Dibenzylran. Crystals from alcohol + ether, mp 137.5-140°.
Sol in alcohol, propylene glycol. Very sparingly sol in
water. Solutions in propylene glycol should be sterilized by
autoclaving.

Note: The hydrochloride may reasonably be anticipated
to be a carcinogen: *Seventh Annual Report on Carcinogens*
9795-109781, 1994) p 318.

THERAP CAT: Antihypertensive.

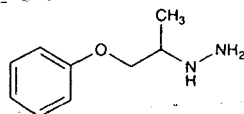
7410. 2-Phenoxyethanol. 1-Hydroxy-2-phenoxyeth-
ane. ethylene glycol monophenyl ether; β-hydroxyethyl
phenyl ether; Phenoxtol; Phenoxtol; Phenyl Cellosolve.
 $C_{10}H_{12}O$; mol wt 138.17. C 69.55%, H 7.30%, O 23.16%.
 $CH_3OCH_2CH_2OH$. Obtained by treating phenol with
ethylene oxide in an alkaline medium: Becker, Barthell,
Monatsh. 77, 80 (1947); see also Roithner, *ibid.* 15, 674, 678
(1944); Rindfusz, *J. Am. Chem. Soc.* 41, 669 (1919). Toxic-
ity study: H. F. Smyth *et al.*, *J. Ind. Hyg. Toxicol.* 23, 259
(1941).

Oily liquid. Faint aromatic odor. Burning taste. d_{20}^{20}
1.044, d_4^{25} 1.102; mp 14°; bp₇₆₀ 245.2°; bp₂₅ 137°;
128-130°. n_D^{20} 1.534. Flash pt 250°F. Soly in water:
16 g/100 ml. Freely sol in alcohol, ether, NaOH solns.
LD₅₀ orally in rats: 1.26 g/kg (Smyth).

Acetate, $C_{10}H_{12}O_3$, liquid, bp 243°.
Use: Fixative for perfumes, in org synthesis; as bactericide
in conjunction with quaternary ammonium compds; as in-
sect repellent.

THERAP CAT: Antiseptic (topical).

7411. Phenoxypropazine. (1-Methyl-2-phenoxyethyl)-
phenylamine; phenoxypropazine. $C_9H_{14}N_2O$; mol wt 166.22. C
69.7%, H 8.49%, N 16.85%, O 9.63%. Prepn: Drain *et al.*,
J. Med. Chem. 6, 63 (1963).



in ethanol, isopropanol.

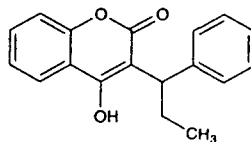
THERAP CAT: Formerly as monoamine oxidase inhibitor.

7412. Phenprobamate. *Benzenepropanol-carbamate;
carbamate acid-3-phenylpropyl ester;* 1-carbamoyloxy-3-phen-
ylpropane; γ-phenylpropyl carbamate; proformiphen; MH-
532; Extacol; Palmita; Spantol; Ansepron; Gamaquil; Qua-
maquil. $C_{10}H_{13}NO_3$; mol wt 179.22. C 67.02%, H 7.31%, N
7.82%, O 17.85%. $H_2NCOOCH_2CH_2CH_2C_6H_5$. Prepn:
Brit. pat. 837,718 (1960 to Siegfried AG). Pharmacology:
G. Stille, *Arzneimittel-Forsch.* 12, 340 (1962).

Shiny leaflets from aq ethanol, mp 101-104°. Slightly
bitter, somewhat burning taste. Numbs the tongue slightly
afterwards. Soluble in abs ethanol, chloroform, propylene
glycol, ethylenediamine, dimethylformamide; sparingly sol
in ether, 50% ethanol. Practically insol in water. LD₅₀
orally in mice: 840 mg/kg (Stille).

THERAP CAT: Anxiolytic, muscle relaxant (skeletal).

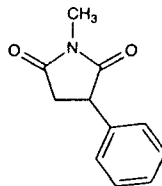
7413. Phenprocoumon. 4-Hydroxy-3-(1-phenylpropyl)-
2H-1-benzopyran-2-one; 3-(α-ethylbenzyl)-4-hydroxycouma-
rin; 3-(1-phenylpropyl)-4-hydroxycoumarin; Falithrom;
Marcoumar; Marcumar; Liquamar. $C_{18}H_{16}O_3$; mol wt
280.32. C 77.12%, H 5.75%, O 17.12%. Prepn: Grüssner,
Balthasar, U.S. pat. 2,723,276 (1955 to Hoffmann-La
Roche); Junck, Ziegler, *Monatsh.* 87, 218 (1956); Schroeder,
Link, *J. Am. Chem. Soc.* 79, 3291 (1957); U.S. pat. 2,872,-
457 (1959 to Wisconsin Alumni Res. Found.); Brit. pat.
805,748 (1958 to Geigy); L. R. Pohl, *J. Med. Chem.* 18, 513
(1975). Resolution: Preis *et al.*, U.S. pat. 3,239,529 (1966
to Wisconsin Alumni Res. Found.). Conformation in soln:
E. J. Valente *et al.*, *J. Med. Chem.* 21, 141, 231 (1978).



Crystals or prisms from dil methanol, mp 179-180°.

THERAP CAT: Anticoagulant.

7414. Phensuximide. 1-Methyl-3-phenyl-2,5-pyrroli-
dinedione; N-methyl-2-phenylsuccinimide; N-methyl-α-phen-
ylsuccinimide; Lifene; Milontin; Mironin; Succinimal. $C_{11}H_{11}NO_2$; mol wt 189.21. C 69.83%, H 5.86%, N 7.40%, O
16.91%. Prepd by the action of methylamine on phenylsuc-
cinic acid: Miller, Long, *J. Am. Chem. Soc.* 73, 4895 (1951);
U.S. pat. 2,643,258 (1953 to Parke, Davis). Toxicity study:
Chen, Ensor, *J. Lab. Clin. Med.* 41, 78 (1953).

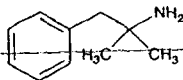


Fine crystals from hot 95% ethanol, mp 71-73°. Slightly
sol in water (about 4.2 mg/ml at 25°). Readily sol in meth-
anol, ethanol. Aq solns are fairly stable at pH 2-8, but
hydrolysis sets in under more alkaline conditions. LD₅₀
orally in mice: 960 mg/kg (Chen, Ensor).

THERAP CAT: Anticonvulsant.

7415. Phentermine. α,α-Dimethylbenzeneethanamine;
α,α-dimethylphenethylamine; phenyl-tert-butylamine; α-
benzylisopropylamine. $C_{10}H_{15}N$; mol wt 149.24. C 80.48%,
H 10.13%, N 9.39%. Prepn: Shelton, Van Campen, U.S.
pat. 2,408,345 (1946 to Wm. S. Merrell); Abell *et al.*, U.S.
pat. 2,590,079 (1952 to Wyeth).

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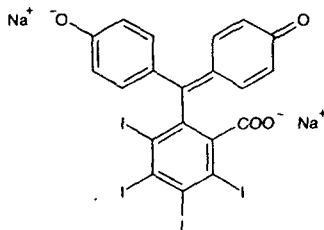


Oily liquid. bp_{750} 205°; bp_{21} 100°. Hydrochloride, $C_{10}H_{15}N.HCl$, *Adipex-P*, *Fastin*, *Wilpo*. Crystals, mp 198°. Ion exchange resin complex, *Duromine*, *Ionamin*, *Linyl*, *Mirapront*, *Omnibex*.

Note: This is a controlled substance (stimulant) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.14 (1995).

THERAP CAT: Anorexic.

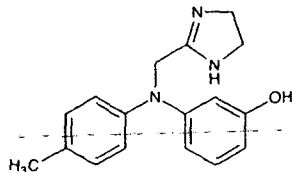
7416. Phentetiothalein Sodium. 4,5,6,7-Tetraiodophenolphthalein sodium; 3,3-bis(4-hydroxyphenyl)-4,5,6,7-tetraiodo-1(3*H*)-isobenzofuranone disodium salt; 3,4,5,6-tetraiodophenolphthalein disodium salt; phenoltetraiodophthalein sodium; Iso-Iodeikon. $C_{20}H_8I_4Na_2O_6$; mol wt 865.88. C 27.74%, H 0.93%, I 58.62%, Na 5.31%, O 7.39%. Prep'd by the condensation of phenol and tetraiodophthalic acid or its anhydride: Orndorff, Black, *Am. Chem. J.* 41, 349 (1909); Zalkind, Belikova, *Zh. Prikl. Khim. (Leningrad)* 8, 1210 (1935). Isomeric with iodophthalein sodium, *q. v.*



Bronze-purple, odorless, slightly hygroscopic granules. Dec on exposure becoming incompletely sol. Sol in water, alcohol. Keep tightly closed.

THERAP CAT: Diagnostic aid (radiopaque medium—cholecystography and hepatic function).

7417. Phentolamine. 3-[[4,5-Dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol; 2-[*N*-(*m*-hydroxyphenyl)-*p*-toluidinomethyl]imidazoline; 2-(*m*-hydroxy-*N*-*p*-tolylanilinomethyl)-2-imidazoline; 2-(*N*'-*p*-tolyl-*N*'-*m*-hydroxyphenylaminomethyl)-2-imidazoline; C-7337. $C_{17}H_{19}N_3O$; mol wt 281.36. C 72.57%, H 6.81%, N 14.93%, O 5.69%. α -Adrenergic blocker. Prep'n: K. Miescher *et al.*, U.S. pat. 2,503,059 (1950 to Ciba); E. Urech *et al.*, *Helv. Chim. Acta* 33, 1386 (1950). Pharmacology and toxicity: R. Meier *et al.*, *Proc. Soc. Exp. Biol. Med.* 71, 70 (1949). HPLC determ'n in biological samples: B. D. Kerger *et al.*, *Anal. Biochem.* 170, 145 (1988). Diagnostic use: G. Spergel *et al.*, *J. Am. Med. Assoc.* 211, 266 (1970). Review of pharmacology and therapeutic applications: L. Gould, C. V. R. Reddy, *Am. Heart J.* 92, 397-402 (1976).



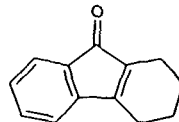
Crystals, mp 174-175°.

Hydrochloride, $C_{17}H_{19}N_3O.HCl$, bitter crystals, mp 239-240°. One gram dissolves in 50 ml water, in 70 ml alcohol. Very slightly sol in chloroform. Practically insol in acetone.

reform. pH of 1% aq soln 4.5-5.5. Aq solns cannot be stored.

THERAP CAT: Antihypertensive; treatment of pheochromocytoma; diagnostic aid (pheochromocytoma).

7418. Phenthyrone. 1,2,3,4-Tetrahydro-9-fluorenone. THF. $C_{13}H_{12}O$; mol wt 184.24. C 84.75%, H 6.57%, O 8.68%. Prep'n: Beyerman, Veer, U.S. pat. 2,692,898 (1954 to Organon); House *et al.*, *J. Am. Chem. Soc.* 82, 1457 (1960).



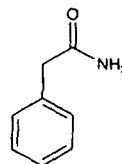
Light yellow needles or prisms from pentane, mp 81-82° (Beyerman); golden yellow prisms from petr ether, mp 41.5-42.5° (House). $bp_{0.05}$ 139-140°. uv max (alcoholic moln soln): 265, 232 nm ($\log \epsilon$ 4.48, 3.62); (carbon tetrachloride) 238, 245, 317 nm (ϵ 39700, 46900, 960). LD_{50} s.c. in mice 1-1.3 g/kg.

7419. Phenylacetaldehyde. *Benzeneacetaldehyde*; α -toluic aldehyde; α -tolualdehyde; *Hyacinthin*. C_8H_8O ; mol wt 120.15. C 79.97%, H 6.71%, O 13.32%. $C_6H_5CH_2CHO$. Prep'd by oxidizing phenylethyl alcohol with chromic acid. High-yield synthesis from styrene oxide or styrene glycol: G. Paparatto, G. Gregorio, *Tetrahedron Letters* 29, 1471 (1988).

Oily, colorless liq which polymerizes and grows more viscous on standing. Odor reminiscent of lilac and hyacinth. (Has been crystallized, mp 33-34°). d_{25}^{25} 1.023-1.030; bp_{10} 195°; bp_{18} 88°; bp_{10} 78°; n_D^{20} 1.524-1.528. Slightly sol in water. Soluble in alcohol, ether. One part is sol in 2 parts of 80% alc forming a clear solution.

USE: In perfumery; intermediate in organic syntheses.

7420. α -Phenylacetamide. *Benzeneacetamide*; α -toluamide. C_8H_9NO ; mol wt 135.17. C 71.09%, H 6.71%, N 10.36%, O 11.84%. The amide of phenylacetic acid, not to be confused with *N*-phenylacetamide which is acetanilide. Prep'd by Willgerodt reaction from acetophenone or from styrene. Review and lab procedures: Carmack, Spidman *in Org. Reactions* II (New York, 1946) p 83. Has also been prep'd by heating the ammonium salt of phenylacetic acid: Menschutkin, *Ber.* 31, 1429 (1898). Lab procedure from benzyl cyanide: Wenner, *Org. Syn. coll. vol. IV*, 760 (1963).



Bimorphous plates, leaflets. mp 155°. Distills in vacuo. Freely sol in alc. Slightly sol in water, ether, benzene. USE: In manuf of penicillin G.

7421. Phenyl Acetate. *Acetic acid phenyl ester*, *acetophenol*. $C_8H_8O_2$; mol wt 136.15. C 70.57%, H 5.97%, O 23.50%. $C_6H_5OOCCH_3$. Prep'd from phenol and acetic chloride.

Colorless, mobile, highly refractive liquid; phenolic odor. d_4^{20} 1.073; bp 195-196°. n_D^{20} 1.5030 (almost the same as glass). Practically insol in water. Miscible with alc, chloroform, ether; sol in glacial acetic acid. LD_{50} orally in mice 1.63 ml/kg. H: F. Smyth *et al.*, *Am. Ind. Hyg. Assoc. J.* 470 (1969).

7422. Phenylacetic Acid. *Benzeneacetic acid*; α -toluic acid. $C_8H_8O_2$; mol wt 136.15. C 70.57%, H 5.97%, O 23.50%.

Leaflets on distillation *in vacuo*: plates, tablets from petr ether: mp 76.5°. bp₇₆₀ 265.5°; bp₁₀₀ 198.2°; bp₄₀ 173.6°; bp₁₂₇ 97°. d₄²⁵ 1.091. pK (25°): 4.25. Slightly sol in cold, freely in hot water. The aq soln satd at 25° is 0.131N. Sol in alcohol, ether. Sol at 25° in chloroform (moles/l): 4.422; in carbon tetrachloride: 1.842; in acetylene tetrachloride: 4.513; in trichlorethylene: 3.299; in tetrachlorethylene: 1.558; in pentachloroethane: 3.252. Methyl ester, C₉H₁₀O₂, liquid, bp 215°. Ethyl ester, see Ethyl phenylacetate. USE: Starting material in manuf synthetic perfumes, condensation products with aldehydes.

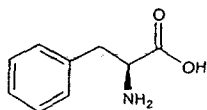
7423. Phenylacetone. 1-Phenyl-2-propanone; benzyl methyl ketone. C₉H₁₀O; mol wt 134.18. C 80.56%, H 7.51%, O 11.92%. C₆H₅CH₂COCH₃. Prepn from phenylacetic and acetic acids: R. H. Pickard, J. Kenyon, *J. Chem. Soc.* 105, 1124 (1914); R. M. Herbst, R. H. Manske, *Org. Syn. coll. vol. II*, 389 (1943); from α -phenylacetoacetonitrile: P. L. Julian, J. J. Oliver, *ibid.* 391; from α -methyl- α -phenylethylene oxide: S. Danilow, E. Venus-Danilowa, *Ber.* 48, 1050 (1927); from diethyl malonate: H. G. Walker, C. R. Hauser, *J. Am. Chem. Soc.* 68, 1386 (1946). Conformational calculations: M. Hirota *et al.*, *Tetrahedron* 39, 3091 (1983). Use as prochiral ketone in enantioselective hydroxylation: B. Brenner *et al.*, *Ber.* 117, 1330 (1984). Oil, mp -16° to -15°. bp₇₆₀ 214°; bp₁₄ 100-101°. d₄²⁰ 1.0157. n_D 1.5174. uv max (ethanol): 258, 283 nm (ϵ 255, 150).

Note: This is a controlled substance listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.12 (1995). USE: In organic synthesis; production of benzyl radicals by photolysis.

7424. Phenyl Acetylsalicylate. 2-(Acetyloxy)benzoic acid phenyl ester; acetylphenylsalicylate; Acetylsalol; Spiroform; Vesipyrin. C₁₅H₁₁O₄; mol wt 256.26. C 70.31%, H 4.72%, O 24.97%. CH₃COOC₆H₄COOC₆H₅. White, crystalline powder. mp 97°; bp₁₁ 198°. Insol in water. Sol in alcohol, ether.

INFRACAT: Analgesic, antipyretic, anti-inflammatory.

7425. Phenylalanine. L-Phenylalanine; Phe; F; β -phenylalanine; α -aminohydrocinnamic acid; (S)-2-amino-3-phenylpropanoic acid; α -amino- β -phenylpropionic acid. C₉H₉NO₂; mol wt 165.19. C 65.44%, H 6.71%, N 8.48%, O 19.37%. Essential amino acid for human development. Originally isolated from the sprouts of lupine: E. Schulze, *J. Berber.* 12, 1924 (1879). Early chemistry and biochemistry: *Amino Acids and Proteins*, D. M. Greenberg, Ed. Charles C. Thomas, Springfield, IL, 1951) 950 pp. *passim*; I. P. Greenstein, M. Winitz, *Chemistry of the Amino Acids*, vol. 1-3 (John Wiley and Sons, Inc., New York, 1961) pp. 216-2177, *passim*. Synthesis from L-tyrosine: V. Viswanatha, V. J. Hruba, *J. Org. Chem.* 45, 2010 (1980). Colorimetric determin in blood: R. S. Campbell *et al.*, *Ann. Clin. Biochem.* 31, 140 (1994). Effects on food intake: G. H. Anderson, L. A. Leiter, *Appetite* 11, Suppl. 48 (1988); P. J. Rogers, J. E. Blundell, *Physiol. Behav.* 56, 247 (1994). Clinical trial in vitiligo: C. Antoniou *et al.*, *Int. J. Dermatol.* 28, 343 (1989); A. H. Siddiqui *et al.*, *Dermatology* 188, 215 (1994). Review of metabolism: H. N. Munro, *J. Toxicol. Environ. Health* 2, 189-206 (1976). Review of role in phenylketonuria: S. P. Bessman, *Nutr. Rev.* 37, 209-220 (1979); P. Ostler, *Acta Paediatr. Scand.* 73, 705-716 (1984). Review of microbial production: T.-K. Maiti, S. P. Chatterjee, *Antibiot. Bull.* 32, 3-26 (1990).

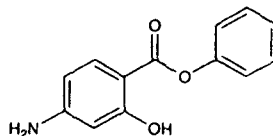


D-Form, (R)-phenylalanine, Sabiden. Occurs naturally in microbial products such as tyrocidine, q.v.: A. H. Gordon *et al.*, *Biochem. J.* 37, 1313 (1943). May be used as a source for L-form in man. Biotransformation: S. Tokuhisa *et al.*, *Chem. Pharm. Bull.* 29, 514 (1981). Evaluation of D-form in multiple sclerosis: A. Winter, *Neurol. Orthopaed. J. Med. Surg.* 5, 39 (1984). Leaflets from water, dec 285°. [α]_D²⁰ +35.0° (c = 2.04); [α]_D²⁰ +7.1° (c = 3.8 in 18% HCl). One gram dissolves in 35.5 ml water at 16°. Sparingly sol in methanol.

DL-Form, monoclinic leaflets or prisms from water or alcohol, sweetish taste. Dec 271-273°. Sublimes *in vacuo*. pK₁ 2.58; pK₂ 9.24. Sol in water (g/l): 9.97 at 0°; 14.11 at 25°; 21.87 at 50°; 37.08 at 75°; 68.9 at 100°.

USE: Component of the artificial sweetener aspartame, q.v.; nutrient.

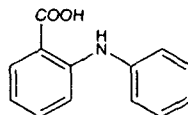
7426. Phenyl Aminosalicylate. 4-Amino-2-hydroxybenzoic acid phenyl ester; p-aminosalicylic acid phenyl ester; phenyl p-aminosalicylic acid; p-aminosalol; fenamisol; Phenyl PAS; Phenyl-PAS-Tebamin; Tebamin; Tebanyl. C₁₅H₁₁NO₃; mol wt 229.24. C 68.11%, H 4.84%, N 6.11%, O 20.94%. Description of properties: Meyer, *Antibiot. Ann.* 1957-1958, 614. Prepd by Raney nickel reduction of the corresp nitro ester in ethyl acetate: Friere, U.S. pat. 2,604,488 (1952 to Rhône-Poulenc).



Crystals from isopropanol, mp 153°. Sol in water: 0.7 mg/100 ml; in serum: 12 mg/100 ml. One gram of phenyl PAS is equivalent to 0.67 g PAS.

THERAP CAT: Antibacterial (tuberculostatic).

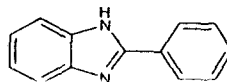
7427. N-Phenylanthranilic Acid. 2-(Phenylamino)benzoic acid; 2-anilinobenzoic acid; diphenylamine-2-carboxylic acid. C₁₅H₁₁NO₂; mol wt 213.24. C 73.23%, H 5.20%, N 6.57%, O 15.01%. Prepd from o-chlorobenzoic acid and aniline: Ullmann, Dieterle, *Ann.* 365, 322 (1907); Ullmann, *Ber.* 36, 2382 (1907); from 2-iodobenzoic acid and phenylhydroxylamine: Wieland, Roseau, *Ber.* 48, 1120 (1915). Use: Adamovich, Zagorulkov, *Zavodskaya Lab.* 9, 465 (1940), *C.A.* 37, 1346 (1943).



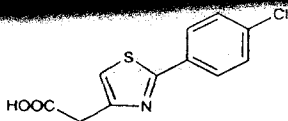
Leaflets from alcohol, dec 183-184°. Sol in hot alcohol. Very slightly sol in hot water, hot benzene, ether.

USE: Detection of vanadium in steel.

7428. 2-Phenyl-1H-benzimidazole. N,N'-Benzoyl-o-phenylenediamine; phenzidole; Gainex. C₁₅H₁₀N₂; mol wt 194.24. C 80.39%, H 5.19%, N 14.42%. Prepn from N-benzoyl-o-phenylenediamine: v. Auwers, Frese, *Ber.* 59, 548 (1926); from o-phenylenediamine and benzonitrile: Hölljes, Wagner, *J. Org. Chem.* 9, 31 (1944). Anthelmintic in sheep: Forsyth, *Australian Vet. J.* 38, 398 (1962).



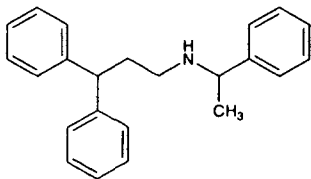
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Colorless crystalline solid from ethyl acetate, mp 155-156°. Soluble in most organic solvents; sparingly sol in water. LD₅₀ in rats, mice (mg/kg): 850, 1000 orally; 250, 300 i.v. (Hepworth).

THERAP CAT: Anti-inflammatory.

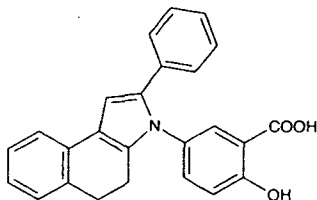
4011. Fendiline. γ -Phenyl-N-(1-phenylethyl)benzene-propanamine; N-(3,3-diphenylpropyl)- α -methylbenzylamine; N-(1-phenylethyl)-3,3-diphenylpropylamine. C₂₃H₂₅N; mol wt 315.46. C 87.57%, H 7.99%, N 4.44%. Calcium blocking agent. Prepn: Belg. pat. 621,300; Harsányi *et al.*, U.S. pat. 3,262,977 (1962, 1966 both to Chinoi); *idem*, *J. Med. Chem.* 7, 623 (1964); Klosa, *J. Prakt. Chem.* 34, 312 (1966). Prepn and studies of the labelled compound: Volford, Harsányi, *J. Label. Compounds* 9, 219 (1973). Structure-activity studies: Leszkovszky *et al.*, *Acta Physiol. Acad. Sci. Hung.* 29, 283 (1966). Pharmacologic properties: W. R. Kukovetz *et al.*, *Arzneimittel-Forsch.* 26, 1321 (1976); A. Fleckenstein *et al.*, *ibid.* 27, 562 (1977). Pharmacokinetics and tolerance: R. Weyhenmeyer *et al.*, *ibid.* 37, 58 (1987). Use in ischemic heart disease: Z. Antaloczy, I. Preda, *Ther. Hung.* 27, 71 (1979). Assessment of Ca²⁺-antagonist effects: M. Spedding, *Arch. Pharmacol.* 318, 234 (1982).



bp_{0.3} 206-210°. Hydrochloride, C₂₃H₂₅N.HCl, HK-137, Cordan, Fendilar, Sensit. Almost white or slightly pink powder, mp 204-205°. Very slightly sol in water; easily sol in methanol, ethanol, chloroform. LD₅₀ in mice (mg/kg): 14.5 i.v.; 950 orally (Harsányi).

THERAP CAT: Vasodilator (coronary).

4012. Fendosal. 5-(4,5-Dihydro-2-phenyl-3H-benz[e]indol-3-yl)-2-hydroxybenzoic acid; 5-(4,5-dihydro-2-phenyl-3H-benz[e]indol-3-yl)salicylic acid; 3-(3-carboxy-4-hydroxyphenyl)-2-phenyl-4,5-dihydro-3H-benz[e]indole; HP-129; P-71-0129; Alnovin. C₂₅H₁₉NO₃; mol wt 381.43. C 78.72%, H 5.02%, N 3.67%, O 12.58%. Prepn: R. C. Allen, B. Anderson, Ger. pat. 2,407,671 corresp to U.S. pat. 3,878,225 (1974, 1975, both to Hoechst); V. B. Anderson *et al.*, *J. Med. Chem.* 19, 318 (1976). Pharmacology: H. B. Lassman *et al.*, *Agents Actions* 8, 209 (1978). Clinical study: S. S. Bloomfield *et al.*, *Clin. Pharmacol. Ther.* 23, 390 (1978).

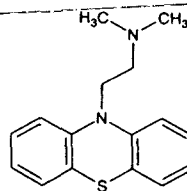


Crystals from acetic acid, mp 223-225° (dec). -LD₅₀ in mice, rats: 740, 450 mg/kg orally.

THERAP CAT: Anti-inflammatory.

4013. Fenethazine. N,N-Dimethyl-10H-phenothiazine-10-ethanamine; 10-(2-dimethylaminoethyl)phenothiazine; 10-(β -dimethylaminoethyl)phenothiazine; RP-3015; SC-1627; Anergan; Anergen; Ethisine; Etisine; Lisergan; Lysergan;

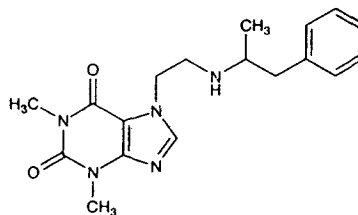
71.07%, H 6.71%, N 10.30%, S 11.80%. Prepd by the condensation of phenothiazine, dimethylaminoethyl chloride; Charpentier, U.S. pat. 19,886 (1950 to Rhône-Poulenc).



bp₁ 183-187°. Hydrochloride, C₁₆H₁₈N₂S.HCl, mp 201-201.5°. LD₅₀ i.p. in mice: 115-120 mg/kg.

THERAP CAT: Antihistaminic.

4014. Fenethylamine. 3,7-Dihydro-1,3-dimethyl-7-[2-[(1-methyl-2-phenylethyl)amino]ethyl]-1H-purine-2,6-dione; 7-[2-[(α -methylphenethyl)amino]ethyl]theophylline; 7-[β -(α -methyl- β -phenylethylamino)ethyl]theophylline; 7-(phenylisopropylaminoethyl)theophylline; 7-(3-phenyl-2-propylaminoethyl)theophylline; theophyllineethylamphetamine. C₁₈H₂₀N₂O₂; mol wt 341.41. C 63.32%, H 6.79%, N 20.51%, O 9.37%. Prepn from 7-(β -chloroethyl)theophylline and amphetamine; Kholstaedt, Klinger, Ger. pat. 1,123,329 (1962 to Degussa), C.A. 57, 5933c (1962). Metabolism in man: T. Ellison *et al.*, *Eur. J. Pharmacol.* 13, 123 (1970).

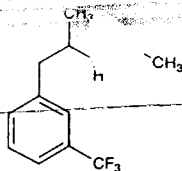


Hydrochloride, C₁₈H₂₂N₂O₂.HCl, H-814, Captagon. Crystals, two different modifications, mp 227-229° and 237-239°. d-Form hydrochloride, crystals, mp 246-247°. l-Form hydrochloride, crystals, mp 246-247°.

Note: This is a controlled substance (stimulant) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.11 (1995).

THERAP CAT: CNS stimulant.

4015. Fenfluramine. N-Ethyl- α -methyl-3-(trifluoromethyl)benzeneethanamine; N-ethyl- α -methyl-m-(trifluoromethyl)phenethylamine; 2-ethylamine-1-(3-(trifluoromethyl)phenyl)propane; S-768. C₁₇H₁₆F₃N; mol wt 231.26. C 62.32%, H 6.97%, F 24.65%, N 6.06%. Prepn: L. G. Beregi *et al.*, Fr. pat. M1658; *idem*, U.S. pat. 3,198,833 (1963, 1965 both to Sci. Union et Cie Soc. Franc. Recherche Méd.). Prepn of optical isomers: *idem*, U.S. pat. 3,198,834 (1965 to Sci. Union et Cie Soc. Franc. Recherche Méd.). -Pharmacology: *Presse Med.* 71, 181 (1963). Pharmacology and toxicity of isomers and racemate: J. C. Le Douarec *et al.*, *Arch. Int. Pharmacodyn. Ther.* 161, 206 (1966). Pharmacokinetics: S. Caccia *et al.*, *Eur. J. Clin. Pharmacol.* 29, 221 (1985). Clinical trial of dextrofenfluramine in refractory obesity: N. Finer *et al.*, *Curr. Ther. Res.* 38, 847 (1985). Comprehensive review: Pinder *et al.*, *Drugs* 10, 241-323 (1975).



bp₁₂ 108-112°. LD₅₀ i.p. in mice: 144 mg/kg (U.S. pat. 3,102,833).

Hydrochloride, C₁₂H₁₆F₃N.HCl, Acino, Adipomin, Obeflex, Psoas, Ponderal, Ponderax, Ponderex, Pondimin, Roton-din. Crystals from ethanol + ether, mp 166°.

d-Form. dexfenfluramine, dextrofenfluramine. [α]_D²⁵ +9.5° (c = 8 in ethanol). LD₅₀ orally in rats: 114.6 mg/kg (Le Douarec).

d-Form hydrochloride, Adifax, Glypolix, Isomeride. Crystals from ethyl acetate, mp 160-161°.

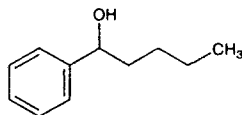
l-Form. [α]_D²⁵ -9.6° (c = 8 in ethanol). LD₅₀ orally in rats: 195 mg/kg (Le Douarec).

l-Form hydrochloride, crystals from ethyl acetate, mp 160-161°.

Note: This is a controlled substance listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.14 (1995).

THERAP CAT: Anorexic.

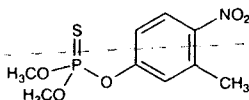
4016. Fenipentol. α-Butylbenzenemethanol; α-butylbenzyl alcohol; phenylbutylcarbinol; 1-phenyl-1-hydroxypentane; phenylpentanol; PC 1; Ph BC; Pancoral. C₁₁H₁₆O; mol wt 164.25. C 80.44%, H 9.82%, O 9.74%. Synthesis: Pournau, Puyal, *An. Soc. Espan. Fis. Quim.* 18, 323 (1920); Adams, Vander Werf, *J. Am. Chem. Soc.* 72, 4368 (1950); Proiva et al., *Chem. Listy* 46, 37 (1952). Prepn of the drug: Scheffler, Engelhorn, *Brit. pat.* 915,815 corresp to U.S. pat. 3,084,100 (both 1963 to Thomae). Pharmacology: Engelhorn, *Arzneimittel-Forsch.* 10, 255 (1960); Beck, Bierwisch, *ibid.* 20, 693 (1970). Metabolism: Koss et al., *ibid.* 14, 195 (1964).



Colorless or slightly yellow liquid. bp₁₂ 123-124°. n_D²⁰ 1.5112. Miscible with organic liquids. Practically insol in water. LD₅₀ in mice: 1.03 g/kg i.p.; 3.10 g/kg orally.

THERAP CAT: Choleric. Also used in treatment of mild chronic pancreatitis.

4017. Fenitrothion. Phosphorothioic acid O,O-dimethyl O-(3-methyl-4-nitrophenyl) ester; O,O-dimethyl O-4-nitro-m-tolyl phosphorothioate; O,O-dimethyl O-(3-methyl-4-nitrophenyl) phosphorothioate; O,O-dimethyl O-4-nitro-m-tolyl thiophosphate; MEP; metathion; Bayer 41831; Bayer S 5660; ENT-25715; OMS-45; AC-47300; Accothion; Cyten; Cyfen; Folithion; Sumithion. C₉H₁₁NO₃PS; mol wt 277.24. C 38.99%, H 4.36%, N 5.05%, O 28.86%, P 11.17%, S 11.57%. Prepn: Belg. pat. 594,669 (1960 to Sumitomo); Belg. pat. 596,091 (1960 to Bayer). Activity: Y. Nishizawa et al., *Agr. Biol. Chem.* 25, 605 (1961). Toxicity study: G. Schrader, *Angew. Chem.* 73, 331 (1961).

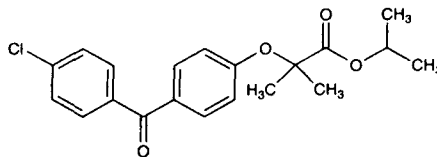


Yellow oil. bp_{0.05} 118°. n_D²⁵ 1.5528. d₄²⁵ 1.3227. Vapor press at 20°: 6 × 10⁻⁶ mm Hg. uv max: 269.5 nm (ε 6756). Practically insol in water. Low sol in aliphatic hydrocarbons; sol in most organic solvents. LD₅₀ orally in rats: 250 mg/kg (Schrader).

USE: Insecticide.

4018. Fennel. Large fennel; sweet fennel. Dried, ripe fruit of cultivated varieties of *Foeniculum vulgare* Mill., *Umbelliferae*. Habit.—Southern Europe, Western Asia, widely cultivated. Contains 3-4% volatile oil.

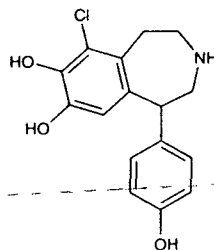
4019. Fenofibrate. 2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid 1-methylethyl ester; isopropyl [4-(p-chlorobenzoyl)-2-phenoxy-2-methyl]propionate; procetofen; procetofene; LF-178; Ankebin; Elastarin; Fenofibrate; Fenotard; Lipanthyl; Lipantil; Lipidil; Lipoclar; Lipofene; Liposit; Lipsin; Nolipax; Procetoken; Protolipan; Secalip. C₂₀H₂₁ClO₄; mol wt 360.84. C 66.57%, H 5.87%, Cl 9.83%, O 17.74%. Prepn: A. Merville, *Ger. pat.* 2,250,327 (1973 to Orchimed), C.A. 79, 53029 (1973), addn to *Ger. pat.* 2,003,430; *eidem*, U.S. pat. 4,058,552 (1970, 1977 both to Orchimed). Series of articles on synthesis, metabolism, pharmacology and clinical trials: *Arzneimittel-Forsch.* 26, 885-909 (1976). Toxicity data: R. Sornay et al., *ibid.* 885. GC-MS of major metabolite in humans: L. F. Elsom et al., *J. Chromatog.* 123, 463 (1976). Efficacy in hyperlipidemias: H. B. Stähelin et al., *Praxis* 68, 24 (1979). Effect on human biliary lipids: E. M. Grandjean et al., *Schweiz. Med. Wochenschr.* 109, 601 (1979). Mechanism of action: W. Wülfert et al., *Artery* 9, 120 (1981).



Crystals from isopropanol, mp 80-81°. Practically insol in water. Slightly sol in methanol, ethanol. Sol in acetone, ether, benzene, chloroform. LD₅₀ in mice: 1600 mg/kg orally (Sornay).

THERAP CAT: Antihyperlipoproteinemic.

4020. Fenoldopam. 6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol; 6-chloro-7,8-dihydroxy-1-p-hydroxyphenyl-2,3,4,5-tetrahydro-1H-3-benzazepine; SKF-82526. C₁₆H₁₆ClNO₃; mol wt 305.76. C 62.85%, H 5.27%, Cl 11.59%, N 4.58%, O 15.70%. Dopamine D₁-receptor agonist. Prepn: J. Weinstock, *Ger. pat.* 2,751,258; *idem*, U.S. pat. 4,197,297 (1978, 1980 both to SmithKline); J. Weinstock et al., *J. Med. Chem.* 23, 973 (1980). HPLC determ in urine and plasma: V. K. Boppana et al., *J. Chromatog.* 317, 463 (1984). Clinical pharmacology: R. M. Stote et al., *Clin. Pharmacol. Ther.* 34, 309 (1983); R. M. Carey et al., *J. Clin. Invest.* 74, 2198 (1984). Hemodynamic effects in hypertension: H. O. Ventura et al., *Circulation* 69, 1142 (1984); M. P. Caruana et al., *Brit. J. Clin. Pharmacol.* 24, 721 (1987). Clinical evaluation in congestive heart failure: G. S. Francis et al., *Am. Heart J.* 116, 473 (1988).



Hydrobromide, C₁₆H₁₆ClNO₃.HBr, mp 277° (dec). Monomethanesulfonate, C₁₆H₁₆ClNO₃.CH₃SO₃, fenoldopam mesylate, SKF-82526 J. Corlopam. mp 274° (dec). THERAP CAT: Antihypertensive.

4021. Fenopropfen. (±)-α-Methyl-3-phenylbenzeneacetic acid; (±)-m-phenoxyhydratropic acid; α-d. 2-(3-phenyl-

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-14834

EDICTO No. 5996

**LA SECRETARÍA GENERAL AD-HOC
HACE SABER:**

Que esta Superintendencia profirió **Resolución No. 9679 de 29-ABR-2005**. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "AGENTES TIROMIMETICOS ANTI OBESIDAD DERIVADOS DE ACIDOS

HETEROACETICOS Y COMPOSICIONES QUE LOS CONTIENEN".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos R. Olarte, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

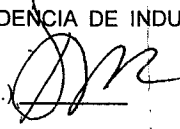
NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los **29 ABR. 2005**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIME RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **23-MAY-2005**  Este edicto se desfija hoy **07-JUN-2005** a las cinco (5:00 p.m.) 
Secretaría General Ad-Hoc
EDICTO No. 5996