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N-ACYL SULFAMIC ACID ESTERS (OR THIOESTERS), N-ACYL SULFONAMIDES, AND N-SULFONYL CARBAMIC ACID ESTERS (OR THIOESTERS) AS HYPERCHOLESTEROLEMIC AGENTS

5 This is a continuation-in-part of United States
Serial No. 081,062,515 filed May 14, 1993.

BACKGROUND OF INVENTION

10

This invention relates to chemical compounds having pharmacological activity, to pharmaceutical compositions which include these compounds, and to a pharmaceutical method of treatment. More particularly, 15 this invention concerns certain N-acyl sulfamic acid esters (or thioesters), N-acyl sulfonamides, and N-sulfonyl carbamic acid esters (or thioesters) which inhibit the enzyme, acyl-coenzyme A:cholesterol acyltransferase (ACAT), pharmaceutical compositions 20 containing these compounds, and a method of treating hypercholesterolemia and atherosclerosis.

The compounds of the instant invention show increased chemical stability over those of United States Patent No. 5,245,068.

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In recent years the role which elevated blood plasma levels of cholesterol plays in pathological conditions in man has received much attention. Deposits of cholesterol in the vascular system have been indicated as causative of a variety of 30 pathological conditions including coronary heart disease.

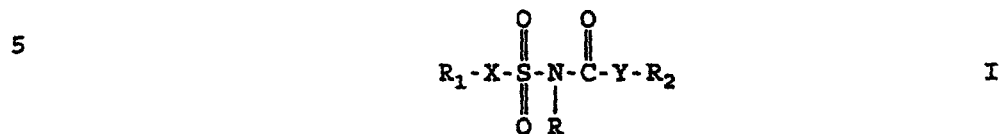
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Initially, studies of this problem were directed toward finding therapeutic agents which would be effective in lowering total serum cholesterol levels. 35 It is now known that cholesterol is transported in the blood in the form of complex particles consisting of a

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The first aspect of the invention is a compound of
Formula I



- 10 or a pharmaceutically acceptable salt thereof wherein:
X and Y are selected from oxygen, sulfur and (CR'R")_n,
wherein n is an integer of from 1 to 4 and R' and
R" are each independently hydrogen, alkyl, alkoxy,
halogen, hydroxy, acyloxy, cycloalkyl, phenyl
15 optionally substituted or R' and R" together form
a spirocycloalkyl or a carbonyl;
with the proviso at least one of X and Y is
-(CR'R")_n- and with the further proviso when
X and Y are both (CR'R")_n and R' and R" are
20 hydrogen and n is one, R₁ and R₂ are aryl;
R is hydrogen, a straight or branched alkyl of from
1 to 8 carbon atoms or benzyl;
R₁ and R₂ are each independently selected from
(a) phenyl or phenoxy each of which is
25 unsubstituted or is substituted with 1 to
5 substituents selected from
phenyl,
an alkyl group having from 1 to 6 carbon atoms and
which is straight or branched,
30 an alkoxy group having from 1 to 6 carbon atoms
and which is straight or branched;
phenoxy,
hydroxy,
fluorine,
35 chlorine,
bromine,
nitro,
trifluoromethyl,

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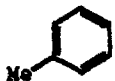
- COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,
5 $-(CH_2)_pNR_3R_4$ wherein p is zero or one, and each of R_3 and R_4 is selected from hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;
(b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to 3 substituents selected from
10 phenyl,
 an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,
 an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;
15 hydroxy,
 phenoxy,
 fluorine,
 chlorine,
 bromine,
20 nitro,
 trifluoromethyl,
 -COOH,
 -COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,
25 $-(CH_2)_pNR_3R_4$ wherein p, R_3 and R_4 have the meanings defined above;
(c) arylalkyl;
(d) a straight or branched alkyl chain having from 1 to 20 carbon atoms and which is saturated or
30 contains from 1 to 3 double bonds; or
(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 6 carbon atoms;
with the provisos:
(i) where X is $(CH_2)_n$, Y is oxygen, and R_1 is a
35 substituted phenyl, then R_2 is a substituted phenyl;

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- (ii) where Y is oxygen, X is $(CH_2)_n$, R^2 is phenyl or naphthyl, then R^1 is not a straight or branched alkyl chain; and
 (iii) the following compounds are excluded:

5

X	Y	R	R_1	R_2
CH_2	O	H	$(CH_2)_2CH_3$	Ph
CH_2	O	H	CH_3	Ph
CH_2	O	H		i-Pr

10

Preferred compounds of the instant invention are those of Formula I:

15 wherein R_1 is phenyl or is phenyl disubstituted in the 2,6-positions,

wherein R_2 is phenyl or is phenyl disubstituted in the 2,6-positions,

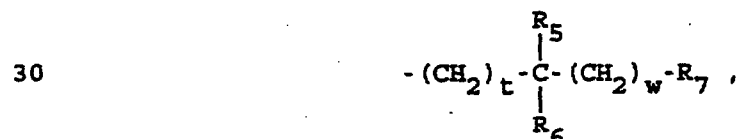
wherein each of R_1 and R_2 is phenyl,

20 wherein each phenyl is disubstituted in the 2,6-position,

wherein R_1 is phenyl disubstituted in the 2,6-positions and R_2 is phenyl trisubstituted in the 2,4,6-positions,

25 wherein R_1 is 2,6-bis(1-methylethyl)phenyl and R_2 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl,

wherein one of R_1 and R_2 is the group



35 wherein t is zero or 1 to 4; w is zero or 1 to 4 with the proviso that the sum of t and w is not greater than 5; R_5 and R_6 are each independently selected from

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hydrogen or alkyl having from 1 to 6 carbon atoms, or
when R_5 is hydrogen, R_6 can be selected from the groups
defined for R_7 ; and R_7 is phenyl or phenyl substituted
with from 1 to 3 substituents selected from a straight
5 or branched alkyl group having from 1 to 6 carbon
atoms, straight or branched alkoxy group having from
1 to 6 carbon atoms, phenoxy, hydroxy, fluorine,
chlorine, bromine, nitro, trifluoromethyl, $-COOH$,
 $COOalkyl$ wherein alkyl has from 1 to 4 carbon atoms, or
10 $-(CH_2)_pNR_3R_4$ wherein P , R_3 and R_4 have the meanings
defined above.

Also preferred compounds of the instant invention
are those of Formula I wherein
X is oxygen, sulfur or $(CR'R'')_n$;
15 Y is oxygen, sulfur or $(CR'R'')_n$, with the proviso that
at least one of X or Y is $(CR'R'')_n$ wherein n is an
integer of from 1 to 4 and R' and R'' are each
independently hydrogen, straight or branched alkyl
of from 1 to 6 carbons, optionally substituted
20 phenyl, halogen, hydroxy, alkoxy, acyloxy,
cycloalkyl, or R' and R'' taken together form a
carbonyl or a spirocycloalkyl group of from 3 to
10 carbons;
R is hydrogen;
25 R_1 is phenyl optionally substituted, straight or
branched alkyl of from 1 to 10 carbon atoms,
cycloalkyl of from 3 to 10 carbon atoms;
 R_2 is phenyl optionally substituted, straight or
branched alkyl of from 1 to 10 carbon atoms,
30 cycloalkyl of from 3 to 8 carbon atoms, phenoxy
optionally substituted with the proviso that only
if X is $(CR'R'')_n$ can R_1 be optionally substituted
phenoxy and only if Y is $(CR'R'')_n$ can R_2 be
optionally substituted phenoxy, and with the
35 further proviso that at least one of R_1 and R_2 is
optionally substituted phenyl or phenoxy.

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More preferred compounds of the instant invention are those of Formula I wherein

X is oxygen;

Y is $(CR'R'')_n$ wherein n is an integer of from 1 to 2;

5 R is hydrogen;

R₁ is optionally substituted phenyl;

R₂ is optionally substituted phenyl or phenoxy,

straight or branched alkyl of from 1 to

10 carbons, or cycloalkyl of from 3 to 10 carbons;

10 and

R' and R'' are each independently hydrogen, straight or branched alkyl of from 1 to 6 carbons, optionally substituted phenyl, halogen, hydroxy, alkoxy, acyloxy, cycloalkyl, or R' and R'' taken together
15 form a carbonyl or a spirocycloalkyl.

The present invention also provides a pharmaceutical composition for regulating plasma cholesterol concentrations comprising a therapeutically
20 effective amount of one or more compounds of Formula I. It further provides a method of treating hypercholesterolemia and for treating atherosclerosis comprising administering to a patient an effective amount of one or more compounds of Formula I with a
25 pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

30 The compounds of the present invention provide a novel class of N-acyl sulfamic acid esters (or thioesters), N-acyl sulfonamides, and N-sulfonyl carbamic acid esters (or thioesters) which are ACAT inhibitors, rendering them useful in treating
35 hypercholesterolemia and atherosclerosis.

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In Formula I above, illustrative examples of straight or branched saturated hydrocarbon chains having from 1 to 20 carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-undecyl, n-dodecyl, n-hexadecyl, 2,2-dimethyldodecyl, 2-tetradecyl, and n-octadecyl groups.

Illustrative examples of straight or branched hydrocarbon chains having from 1 to 20 carbon atoms and having from 1 to 3 double bonds include ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and hexadecenyl.

Straight or branched alkoxy groups having from 1 to 6 carbon atoms include, for example, methoxy, ethoxy, n-propoxy, t-butoxy, and pentyloxy.

Illustrative examples of straight or branched alkyl groups having from 1 to 6 carbon atoms as used in Formula I include methyl, ethyl, n-propyl, isopropyl, n-pentyl, n-butyl, and tert-butyl.

Illustrative examples of cycloalkyl groups, as used in Formula I, include cyclopentyl, cyclohexyl, cyclooctyl, tetrahydronaphthyl, and 1- or 2-adamantyl.

Spirocycloalkyl groups are, for example, spirocyclopropyl, spirocyclobutyl, spirocyclopentyl, and spirocyclohexyl.

Illustrative examples of arylalkyl groups are: benzyl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl, 2-phenylbutyl, 3-phenylbutyl, benzhydryl, 2,2-diphenylethyl, and 3,3-diphenylpropyl.

Pharmaceutically acceptable salts of the compounds of Formula I are also included as a part of the present invention.

The base salts may be generated from compounds of Formula I by reaction of the latter with one equivalent

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of a suitable nontoxic, pharmaceutically acceptable base followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The compounds of Formula I may be recovered
5 from the base salt by reaction of the salt with an aqueous solution of a suitable acid such as hydrobromic, hydrochloric, or acetic acid.

Suitable bases for forming base salts of the compounds of this invention include amines such as
10 triethylamine or dibutylamine, or alkali metal bases and alkaline earth metal bases. Preferred alkali metal hydroxides and alkaline earth metal hydroxides as salt formers are the hydroxides of lithium, sodium, potassium, magnesium, or calcium. The class of bases
15 suitable for the formation of nontoxic, pharmaceutically acceptable salts is well known to practitioners of the pharmaceutical formulation arts. See, for example, Berge SN, et al, J Pharm Sci 1977;66:1-19.

20 Suitable acids for forming acid salts of the compounds of this invention containing a basic group include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic,
25 glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The acid addition salts are formed by procedures well known in the art.

The compounds of the present invention may also
30 exist in different stereoisomeric forms by virtue of the presence of asymmetric centers in the compound. The present invention contemplates all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures.

35 Further, the compounds of this invention may exist in unsolvated as well as solvated forms with

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pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

5 Preferred compounds of the present invention are those wherein one of R_1 and R_2 is phenyl, and more preferably wherein one of R_1 and R_2 is substituted phenyl, and still more preferably wherein one of R_1 and R_2 is phenyl disubstituted in the 2,6-positions.

10 In one preferred embodiment both R_1 and R_2 are phenyl disubstituted in the 2,6-positions. In another preferred embodiment R_1 is phenyl disubstituted in the 2,6-position and R_2 is trisubstituted in the 2,4,6-positions.

15 In another preferred embodiment of the present invention, R_1 is 2,6-bis(1-methylethyl)phenyl; and R_2 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl.

20 Preferred compounds of Formula I include, but are not limited to the following:

Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

30 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

35 Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

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Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)-phenyl ester,

Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

5 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl]benzeneacetamide,

2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris-(1-methylethyl)phenyl]methyl]sulfonyl]benzeneacetamide-sodium salt,

10 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl]methyl]sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl]methyl]sulfonyl]carbamate-sodium salt,

15 Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-

2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-

20 2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid trans-[(2-phenylcyclopropyl)-carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-

2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-

2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-

2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-thiophenyl(acetyl)]-

30 2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [3-thiophenyl(acetyl)]-

2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-methoxyphenyl(acetyl)]-

2,6-bis(1-methylethyl)phenyl ester,

35 Sulfamic acid (oxophenylacetyl)-

2,6-bis(1-methylethyl)phenyl ester,

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- Sulfamic acid [2-trifluoromethylphenyl(acetyl)] -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2-phenylpropyl) -
2,6-bis(1-methylethyl)phenyl ester,
5 Sulfamic acid (cyclopentylphenylacetyl) -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (cyclohexylacetyl) -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (diphenylacetyl) -
10 2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (triphenylacetyl) -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [(1-phenylcyclopentyl)carbonyl] -
2,6-bis(1-methylethyl)phenyl ester,
15 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl) -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2-phenylbutyl) -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (cyclohexylphenylacetyl) -
20 2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2,2-diphenylpropyl) -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [(9H-fluoren-9-yl)carbonyl] -
2,6-bis(1-methylethyl)phenyl ester,
25 Sulfamic acid (1-oxo-3-phenylpropyl) -
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)-
phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)-
30 phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [(acetyloxy) [2,4,6-tris(1-methyl-
ethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl
ester,
Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)-
35 phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)-phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

5 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]-acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]-acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

10 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,6-bis(phenyl)phenyl ester.

As shown by the data presented below in Table 1, the compounds of the present invention are inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT), and are thus effective in inhibiting the esterification and transport of cholesterol across the intestinal cell wall. The compounds of the present invention are thus useful in pharmaceutical formulations for the treatment of hypercholesterolemia or atherosclerosis.

20 The ability of representative compounds of the present invention to inhibit ACAT was measured using an in vitro test more fully described in Field FJ, Salone RG, Biochemica et Biophysica, 1982;712:557-570. The test assesses the ability of a test compound to inhibit the acylation of cholesterol by oleic acid by measuring the amount of radiolabeled cholesterol oleate formed from radiolabeled oleic acid in a tissue preparation containing rat liver microsomes.

25 The data appear in Table 1 where they are expressed in IC_{50} values; i.e., the concentration of test compound required to inhibit the activity of the enzyme by 50%.

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TABLE 1

	Example	LAI IC ₅₀ (μM)
	1	9.7
	2	12
5	3	11
	4	13
	5	12
	6	12
	7	47
10	8	21
	10	>5
	11	>10
	13	25
	14	33
15	15	34
	16	36
	17	>50
	18	22
	19	>50
20	20	>50
	21	55
	22	50
	23	12
	24	26
25	25	7.2
	26	28
	27	12
	28	6
	29	15
30	30	4.1
	31	3.3
	32	8.9
	33	9.3

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TABLE 1 (cont.)

	Example	LAI
		IC ₅₀ (μM)
5	34	7.7
	35	8.9
	36	22
	37	16
	38	31
10	39	32
	40	32
	41	28
	42	7
	43	31
15	44	9.4
	45	5.6
	46	34
	47	38
	48	8.3

20 In one in vivo screen designated APCC, male
Sprague-Dawley rats (200 to 225 g) were randomly
divided into treatment groups and dosed at 4 PM with
either vehicle (CMC/Tween) or suspensions of compounds
in vehicle. The normal chow diet was then replaced
25 with a high fat, high cholesterol diet (designated PCC)
containing 0.5% cholic acid. The rats consumed this
diet ad libitum during the night and were sacrificed at
8 AM to obtain blood samples for cholesterol analysis
using standard procedures. Statistical differences
30 between mean cholesterol values for the same vehicle
were determined using analysis of variance followed by
Fisher's least significant test. The results of this
trial for representative compounds of the present
invention appear in Table 2.

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TABLE 2

	Compound of Example	% Change (mg/dl)
	1	-63
5	2	-62
	3	-79
	4	-47
	5	-73
	6	-75
10	7	-17
	8	-66
	10	-26
	11	-8
	12	-5
15	13	-31
	14	-12
	15	-14
	16	+10
	17	-40
20	18	-47
	19	-20
	20	-19
	21	-16
	22	-23
25	23	-19
	24	-24
	25	-71
	26	-26
	27	-72
30	28	-30
	29	-9
	30	-40
	31	-30
	32	-48

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TABLE 2 (cont.)

Example	% Change (mg/dl)
33	-63
34	-67
5	35
	-9
	36
	-6
	37
	-50
	38
	-16
	39
	+5
10	40
	-54
	41
	-73
	42
	-25
	43
	-45
	44
	-74
15	45
	-63
	46
	-57
	47
	-46
	48
	-73

20

In therapeutic use as agents for treating hypercholesterolemia or atherosclerosis, the compounds of Formulas I or II or pharmaceutically acceptable salts thereof are administered to the patient at dosage levels of from 250 to 3000 mg per day. For a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 5 to 40 mg/kg of body weight per day. The specific dosages employed, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

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For preparing the pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, and cachets.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers are magnesium dicarbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner cachets or transdermal systems are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions, or emulsions suitable for oral administration. Aqueous solutions for oral

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administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made
5 by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethylcellulose, and other suspending agents known to the pharmaceutical formulation art.

10 Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation containing discrete
15 quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of these packaged forms.

20 Some of the preferred compounds of the present invention are prepared as set forth in Chart I hereof wherein R, R₁ and R₂ have the meanings defined in Formula I; and Z represents a halogen.

In Route 1, a solution of a halide of the
25 Formula R₂Z in ether is added to a suspension of Li powder in ether heated under reflux. The solution is cooled to 0°C. The resulting lithium compound is then poured into the liquid ethylene oxide precooled to -78°C. The mixture is allowed to warm up to room
30 temperature. After work-up with saturated NH₄Cl, the product (3) is extracted with ethyl acetate. The alcohol (3) is oxidized to the acid (4) by Jones reagent (K₂Cr₂O₇/H₂SO₄) in acetone at 0°C.

Alternatively, the acid (4) can be arrived at
35 using a method similar to Org. Syn. Coll., 3:557 in which a substituted benzene is chloromethylated

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(as arrived at by Routes 2 or 3, respectively) with a base and then RZ.

The halides RZ, R₂Z, and R₁Z used in preparing the compounds of this invention are known in the art or
5 prepared by procedures generally known in the art.

Whereas the preferred compounds of the present invention are prepared as set forth in Charts I and II, it should be understood that the compounds of the present invention can be prepared as set forth
10 generally as follows.

N-acyl sulfamic acid esters (or thioesters) having the formula of Compound 9 in Chart I Route 1 can be prepared by reacting an acyl chloride and a sulfamate having the formula of Compounds 5 and 8, respectively,
15 in Route 1. The resulting ester (or thioester) can optionally be reacted with a base, followed by an aryl halide.

Alternatively, N-acyl sulfamic acid esters (or thioesters) having the formula of Compound 9 in Chart I
20 Route 1A can be prepared by reacting an oxysulfonyl isocyanate and a grignard agent having the formula of Compounds 7 and 15, respectively, in Route 1A. The resulting ester (or thioester) can optionally be reacted with a base, followed by an aryl halide.

25 N-acyl sulfonamides having the formula of Compound 21 in Chart II Route 2 can be prepared by reacting an acid chloride and a sulfonamide having the formula of Compounds 5 and 18, respectively, in Route 2. The resulting sulfonamide can optionally be
30 reacted with a base, followed by an aryl halide.

N-sulfonyl carbamic acid esters (or thioesters) having the formula of Compound 23 in Chart II Route 3 can be prepared by reacting a sulfonamide and a chloroformate having the formula of Compounds 18
35 and 22, respectively, in Route 3. The resulting ester

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(or thioester) can optionally be reacted with a base, followed by an aryl halide.

5

EXAMPLES

10 The following examples illustrate techniques discovered by the inventors for the preparation of the compounds of the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent laboratory techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to constitute preferred modes for this practice. Those of skill in the art should, however, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention. In other words, the following examples are given to illustrate particular compositions and methods within the scope of the present invention and are not intended to limit the scope of the present invention.

25

EXAMPLE 1

Synthesis of sulfamic acid[[2,6-bis(1-methylethyl)-phenylacetyl]-2,6-bis(1-methylethyl)phenyl ester

(a) 2,6-Diisopropylphenylethanol

30 2,6 diisopropylbromobenzene (see J. Org. Chem., 42(14):2426-2431 (1977) for preparation) (30 g, 124.4 mmol) was added to a suspension of Li powder (1.9 g, 273.6 mmol) in ether (100 mL) heated under reflux, the heating was continued for another 4 hours, cooled, and the mixture was poured into ethylene oxide
35 which was precooled to -78°C. The mixture was warmed

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slowly to room temperature, saturated NH_4Cl solution was added slowly with caution, the ether layer was separated and washed with brine, dried over MgSO_4 , filtered, and the solvent was evaporated to dryness.

5 After column chromatography (3:1 hexane:ethyl acetate) pure 2,6-diisopropylphenylethanol was obtained (17 g, 66.3%);

NMR (CDCl_3): δ 1.2-1.3 (m, 12H), 3.05 (t, 2H), 3.15-3.35 (m, 2H), 3.7-3.8 (t, 2H), 7.1-7.3 (m, 3H) ppm.

(b) 2,6-Diisopropylacetic acid

Jones reagent (94 mL, 2 M, 188 mmol) was added to a solution of 2,6-diisopropylphenylethanol (19.2 g, 93.05 mmol) in acetone (600 mL) at 0°C over 2 hours. The mixture was stirred for another 0.5 hour. The reaction mixture was poured into ether (1 L), washed with brine, and the product was extracted by 1N NaOH. The basic extract was acidified with concentrated HCl, the liberated acid was removed by ether extraction (200 mL $\times$ 5). The combined ether extract was dried over MgSO_4 , filtered, and then evaporated. The residue was used for the next step without further purification (18.47 g, 90%);

25 NMR (CDCl_3): δ 1.15-1.35 (m, 12H), 3.05-3.25 (m, 2H), 3.85 (s, 2H), 7.1-7.35 (m, 3H) ppm.

(c) Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester

30 2,6-Diisopropylacetic acid (200 mg, 0.91 mmol) and oxalyl chloride (253.9 mg, 2 mmol) were mixed together in 20 mL of toluene at room temperature under N_2 with a few drops of DMF as catalyst. The mixture was stirred for 16 hours, the solvent and the excess oxalyl chloride were then removed in vacuo, and the acyl chloride was redissolved in 20 mL of dry THF.



2,6-Diisopropylphenyl sulfamate (257 mg, 1 mmol, see
Phos. and Sulf., 19:167 (1984) for preparation) and
Et₃N (139 μ L, 1 mmol) were added to the solution under
N₂ and the mixture was stirred at room temperature for
3 hours. The solvent was removed and the residue was
distributed between ethyl acetate and 1N HCl. The
organic layer was dried over MgSO₄, filtered, and
evaporated, and the pure product was isolated by column
chromatography (1:1 hexane:EtOAc, 300 mg, 72%),
mp 166-168°C.

EXAMPLE 2

Synthesis of sulfamic acid[[2,6-bis(1-methylethyl)-
phenyllacetyl]-2,6-bis(1-methylethyl)phenyl ester
sodium salt

The sodium salt of the title compound of Example 1
was prepared by dissolving the title compound of
Example 1 (1 g, 2.18 mmol) in THF (10 mL), and one
equivalent of NaH (87 mg, 2.18 mmol) was added to the
solution and this was then stirred for 0.5 hour. The
solvent was evaporated and product was obtained by
trituration with hexane (0.63 g, 60%), mp 242-244°C.

EXAMPLE 3

Synthesis of sulfamic acid[[2,6-bis(1-methylethyl)-
phenyllacetyl]-2,4,6-tris(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenyl sulfamate was replaced with
2,4,6-triisopropylphenyl sulfamate, mp 152-155°C.

EXAMPLE 4

Synthesis of sulfamic acid[adamantaneacetyl]-2,6-bis-
[1-methylethyl]phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that

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2,6-diisopropylphenylacetyl chloride was replaced with adamantaneacetyl chloride;

^1H NMR(CDCl_3): 1.21 (d, 12H), 1.6-2.0 (m, 15H), 2.15 (s, 2H), 3.4 (m, 2H), 7.15-7.25 (m, 3H) ppm.

5

EXAMPLE 5

Synthesis of Sulfamic acid[[2,4,6-tris(1-methylethyl)-phenylacetyl]-2,6-bis(1-methylethyl)phenyl ester

(a) 2,4,6-Triisopropylbenzyl alcohol

10 A solution of commercially available 2,4,6-triisopropylbenzoyl chloride (35 g, 131.2 mmol) in 400 mL ether was added slowly to a suspension of lithium aluminum hydride (LAH) (4.89 g, 131.2 mmol) in ether (300 mL) at -15°C . The mixture was slowly warmed to
15 room temperature over 18 hours. Saturated Na_2SO_4 solution was added slowly and the ether layer was separated, dried over MgSO_4 , and evaporated to dryness. The compound was used in the next step without further purification;

20 NMR (CDCl_3): δ 1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.3-3.5 (m, 2H), 4.8 (s, 2H), 7.1 (s, 2H) ppm.

(b) 2,4,6-Triisopropylbenzyl bromide

25 A solution of PBr_3 (2.7 g, 10 mmol) in ether (10 mL) was added slowly to a solution of 2,4,6-triisopropylbenzyl alcohol (4.68 g, 20 mmol) in 20 mL of ether at room temperature. The mixture was stirred for 1 hour, 5 mL of absolute EtOH was added, and stirring was continued for another 0.5 hour. The solvent was
30 removed and the residue distributed between EtOAc and saturated Na_2CO_3 . The EtOAc layer was separated, washed with brine, and dried over MgSO_4 . The solvent was evaporated and the pure product was isolated by column chromatography (100% CH_2Cl_2 , 3.5 g, 59%);

35 NMR (CDCl_3): δ 1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.2-3.45 (m, 2H), 4.7 (s, 2H), 7.04 (s, 2H) ppm.

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(c) Sulfamic acid[2,4,6-tris(1-methylethyl)phenyl]-
acetyl[2,6-bis(1-methylethyl)phenyl ester

5 A solution of 2,4,6-triisopropylbenzyl bromide
(12 g, 40.4 mmol) in dry THF (160 mL) was added to a
suspension of Mg powder (1.96 g, 80.8 mmol) (4 hours)
in THF (20 mL) heated under reflux. 2,6-Diisopropyl-
phenoxy sulfonyl isocyanate (ROSO₂NCO) (see Phos. and
Sulf., 19:167 (1984) for preparation) (11.45 g,
40.4 mmol) was added neat, and after the addition was
10 completed, the reflux was continued for another
2 hours. The reaction was stirred at room temperature
for 16 hours. Saturated NH₄Cl and EtOAc were added.
The EtOAc layer was separated, dried over MgSO₄,
filtered, and evaporated to dryness. After
15 purification by column chromatography (4:1
hexane:EtOAc), the compound was isolated as white solid
(13.5 g, 67%), mp 178-180°C.

EXAMPLE 6

20 Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-
phenylacetyl]-2,6-bis(1-methylethyl)phenyl ester
sodium salt

This compound was prepared in the same manner as
for the title compound of Example 2, except that the
25 title compound of Example 1 was replaced with the title
compound of Example 5, mp 250-252°C.

EXAMPLE 7

30 Synthesis of sulfamic acid(phenylacetyl)-2,6-bis-
(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
the title compound of Example 5, except that
2,4,6-triisopropylbenzyl magnesium bromide was replaced
with benzylmagnesium chloride (commercially available),
35 mp 150-152°C.

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EXAMPLE 8

Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-phenyllacetyl]-2,4,6-tris(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as the title compound of Example 5, except that 2,6-diisopropylphenoxy sulfonyl isocyanate was replaced with 2,4,6-triisopropylphenoxy sulfonyl isocyanate, mp 178-180°C.

EXAMPLE 9

10 Synthesis of 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl]benzeneacetamide

(a) S-2,4,6-Triisopropylbenzylisothiurea

15 A mixture of 2,4,6-triisopropylbenzyl bromide (6.0 g, 20 mmol) and thiourea (1.536 g, 20.1 mmol) in 180 mL of absolute EtOH was heated under reflux for 3 hours. The reaction was cooled and evaporated. The white powder (7.1 g, 95%) was used for next step without further purification, mp 200-205°C.

20 (b) 2,4,6-Triisopropylbenzylsulfonamide

Chlorine gas was bubbled through a suspension of S-2,4,6-triisopropylbenzylisothiurea hydrobromide (2.5 g, 8.56 mmol) in H₂O (100 mL) at 0°C for 1 hour. 25 The solid was extracted into EtOAc (50 mL) and NH₃(g) was bubbled through the EtOAc solution at 0°C for 0.5 hour and the solution was further stirred at room temperature for 2 hours. 2,4,6-Triisopropylbenzylsulfonamide was isolated as white powder (100 mg) by 30 column chromatography (4:1 hexane:EtOAc);
NMR (CDCl₃): δ 1.2-1.6 (m, 18H), 2.8-3.0 (m, 2H), 3.25-3.4 (m, 2H), 4.75 (s, 2H), 7.0 (s, 2H), ppm.



EXAMPLE 12

Synthesis of sulfamic acid[1-adamantyl(carbonyl)]-
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
1-adamantecarboxylic acid, mp 165-167°C.

EXAMPLE 13

10 Synthesis of sulfamic acid(1-oxo-3,3-diphenylpropyl)-
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
15 3,3-diphenylpropionic acid, mp 149-152°C.

EXAMPLE 14

Synthesis of sulfamic acid[2,6-dichlorophenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
2,6-dichlorophenylacetic acid, mp 203-205°C.

EXAMPLE 15

25 Synthesis of sulfamic acid trans-[(2-phenylcyclo-
propyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
30 2,6-diisopropylphenylacetic acid was replaced with
trans-2-phenylcyclopropylcarboxylic acid, mp 166-168°C.

30 2,6-diisopropylphenylacetic acid was replaced with
2-thiopheneacetic acid, mp 133-136°C.



EXAMPLE 20

Synthesis of sulfamic acid[3-thiophenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
3-thiopheneacetic acid, mp 136-138°C.

EXAMPLE 21

10 Synthesis of sulfamic acid[2-methoxyphenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
15 2-methoxyphenylacetic acid, mp 159-161°C.

EXAMPLE 22

Synthesis of sulfamic acid(oxophenylacetyl)-
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
benzoylformic acid, mp 106-109°C.

EXAMPLE 23

25 Synthesis of sulfamic acid[2-trifluoromethylphenyl-
(acetyl)]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
30 2,6-diisopropylphenylacetic acid was replaced with
2-trifluoromethylphenylacetic acid, mp 144-149°C.

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EXAMPLE 24

Synthesis of sulfamic acid(1-oxo-2-phenylpropyl)-
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
2-phenylpropionic acid, mp 142-144°C.

EXAMPLE 25

10 Synthesis of sulfamic acid(cyclopentylphenylacetyl)-
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
15 α -phenylcyclopentanecarboxylic acid, mp 142-143°C.

EXAMPLE 26

Synthesis of sulfamic acid(cyclohexylacetyl)-
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
cyclohexylacetic acid;
 ^1H NMR (CDCl_3): δ 8.35 (s, 1H), 7.1-7.3 (m, 3H),
25 3.3-3.45 (m, 2H), 2.35 (d, 2H), 1.55-1.95 (m, 8H), 1.22
(d, 12H), 0.9-1.1 (m, 2H), ppm.

EXAMPLE 27

30 Synthesis of sulfamic acid(diphenylacetyl)-
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
diphenylacetic acid, mp 164-166°C.

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EXAMPLE 36

Synthesis of sulfamic acid[(9H-xanthen-9-yl)carbonyl]-
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
xanthene-9-carboxylic acid, mp 180-181°C.

EXAMPLE 37

10 Synthesis of sulfamic acid[(9H-fluoren-9-yl)carbonyl]-
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
15 9-fluorene-carboxylic acid, mp 146-147°C.

EXAMPLE 38

Synthesis of sulfamic acid(1-oxo-3-phenylpropyl)-
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
hydrocinnamic acid, mp 121-124°C.

EXAMPLE 39

25 Synthesis of sulfamic acid[bromo(phenyl)acetyl]-
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
30 2,6-diisopropylphenylacetic acid was replaced with
 α -bromophenylacetic acid, mp 155-159°C.

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EXAMPLE 40

Synthesis of sulfamic acid[1-oxo-3-[2,4,6-tris-
(1-methylethyl)phenyl]-2-propenyl]-2,6-bis-
(1-methylethyl)phenyl ester

- 5 (a) 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl
carboxylic acid, methyl ester

A mixture of methyl acrylate (15.9 mL, 176 mmol) and bis(triphenylphosphine)palladium (II) chloride (0.99 g, 1.4 mmol) in 125 mL dimethylformamide and
10 125 mL triethylamine was heated to reflux for 1 hour and then 2,4,6-triisopropylbromobenzene (10.0 g, 35 mmol) was added. Reflux was continued for 6 hours and then stirred at room temperature for 16 hours. Partitioned the reaction between water and diethyl
15 ether. The ether layer was dried with MgSO_4 , filtered, and concentrated to give a brown oil. Chromatography (SiO_2 , eluant = 5% ethyl acetate in hexanes) gave 3.80 g of 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, methyl ester as an off-
20 white solid, mp 61-63°C.

- (b) 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl
carboxylic acid

Sodium hydroxide (0.23 g, 5.7 mmol) was added to a
25 solution of 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, methyl ester (1.5 g, 5.2 mmol) in 100 mL methanol and 10 mL water. Stirred at room temperature for 48 hours and concentrated to dryness. Partitioned the residue between water and
30 diethyl ether. The aqueous layer was acidified with concentrated HCl and extracted with dichloromethane. The organic extract was dried over MgSO_4 , filtered, and concentrated to give 1.33 g of 3-[2,4,6-tris-(1-methylethyl)phenyl]-2-propenyl carboxylic acid as a
35 white solid, mp 201-203°C.

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(c) Sulfamic acid[1-oxo-3-[2,4,6-tris(1-methylethyl)-phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetic acid was replaced with 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, mp 144-148°C.

10 EXAMPLE 41

Synthesis of sulfamic acid[1-oxo-3-[2,4,6-tris-(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)-phenyl ester

15 (a) 3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid, methyl ester

3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, methyl ester (2.20 g, 7.6 mmol, from Example 40(a)) was dissolved in 100 mL methanol. 0.5 g of 20% palladium on carbon was added and the mixture was charged with 50 psi of hydrogen gas. After 5 hours at room temperature, the reaction was filtered and concentrated to give 2.37 g of 3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid, methyl ester as an off-white solid, mp 45-47°C.

25 (b) 3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid
3-[2,4,6-Tris(1-methylethyl)phenyl]propionic acid, methyl ester (2.12 g, 7.3 mmol) was dissolved in 100 mL methanol and 10 mL water. Sodium hydroxide (0.32 g, 8.0 mmol) was added and the resulting solution was stirred at room temperature for 4 hours. Concentrated in vacuo and partitioned the residue between water and diethyl ether. The aqueous layer was acidified with concentrated HCl and extracted with dichloromethane.
30 The organic extract was dried over MgSO₄, filtered, and concentrated to give 1.87 g of 3-[2,4,6-tris(1-methyl-

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ethyl)phenyl]propionic acid as a white solid,
mp 194-196°C.

- 5 (c) Sulfamic acid[1-oxo-3-[2,4,6-tris(1-methylethyl)-
phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
2,6-diisopropylphenylacetic acid was replaced with
3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid,
10 mp 138-141°C.

EXAMPLE 42

- Synthesis of sulfamic acid[(acetyloxy)[2,4,6-tris-
(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-
15 phenyl ester

- (a) Acetyloxy[2,4,6-tris(1-methylethyl)phenyl]acetic
acid

Glyoxylic acid (1.99 g, 27 mmol) and 1,3,5-triisopropylbenzene (5.0 g, 24.5 mmol) were mixed in 30 mL
20 glacial acetic acid and 2 mL concentrated sulfuric acid. The resulting solution was heated to reflux for 5 hours and then stirred at room temperature for 16 hours. The reaction mixture was poured into 100 g ice and the resulting mixture was extracted with
25 diethyl ether. The organic layer was dried over MgSO_4 , filtered, and concentrated to give an oily solid which was recrystallized from hexanes to give 3.29 g of acetyloxy[2,4,6-tris(1-methylethyl)phenyl]acetic acid,
mp 166-169°C.

- 30 (b) [(Acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]-
acetyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as
for the title compound of Example 1, except that
35 2,6-diisopropylphenylacetic acid was replaced with

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acetyloxy[2,4,6-tris(1-methylethyl)phenyl]acetic acid,
mp 140-146°C.

EXAMPLE 43

5 Synthesis of sulfamic acid[hydroxy[2,4,6-tris-
 (1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-
 phenyl ester

 [(Acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]-
 acetyl]-2,6-bis(1-methylethyl)phenyl ester (1.50 g,
10 2.7 mmol) was dissolved in 75 mL methanol and 25 mL
 water. Sodium hydroxide (0.22 g, 5.5 mmol) was added
 and the resulting solution was stirred at room
 temperature for 16 hours. Concentrated in vacuo,
 redissolved the residue in water, acidified to pH 4.0
15 with concentrated HCl and extracted with diethyl ether.
 The organic extract was dried over MgSO₄, filtered, and
 concentrated to give an oil. Triturated with hexanes
 to give 0.56 g of sulfamic acid [hydroxy[2,4,6-tris-
 (1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-
20 phenyl ester, mp 96-101°C.

EXAMPLE 44

Synthesis of sulfamic acid[fluoro[2,4,6-tris-
 (1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-
25 phenyl ester

 [Hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
 2,6-bis(1-methylethyl)phenyl ester (0.73 g, 1.4 mmol)
 was dissolved in 20 mL dichloromethane and added
 dropwise to a solution of diethylaminosulfur
30 trifluoride (0.19 mL, 1.4 mmol) in 10 mL
 dichloromethane at -8°C. Gradually warmed to room
 temperature and stirred for 16 hours. Concentrated
 in vacuo and partitioned the residue between water and
 ethyl acetate. The organic extract was dried over
35 MgSO₄, filtered, and concentrated to give a yellow oil.
 Triturated with hexanes to give 0.39 g of sulfamic acid

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[fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester, mp 130-132°C.

EXAMPLE 45

5 Synthesis of sulfamic acid(3-methyl-1-oxo-2-phenyl-
 pentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt

 This compound was prepared in the same manner as
 for the title compound of Example 2, except that the
10 title compound of Example 1 was replaced with the title
 compound of Example 31, mp 275-277°C.

EXAMPLE 46

Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-
 phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester

15 (a) [2,4,6-tris(1-methylethyl)phenoxy]acetic acid

 A solution of 2,4,6-triisopropylphenol (4.0 g,
 18 mmol) in 50 mL tetrahydrofuran was added dropwise to
 a suspension of sodium hydride (1.52 g, 38 mmol) in
20 25 mL tetrahydrofuran. The resulting pale green
 suspension was stirred for 30 minutes before a solution
 of bromoacetic acid (2.52 g, 18 mmol) in 50 mL
 tetrahydrofuran was added dropwise. The resulting
 thick suspension was stirred for 16 hours and then
25 concentrated in vacuo. The residue was partitioned
 between 1N HCl and dichloromethane, the organic extract
 was dried over MgSO₄, filtered, and concentrated to
 give a yellow solid. Recrystallized from hexanes to
 give 3.1 g of [2,4,6-tris(1-methylethyl)phenoxy]acetic
 acid, mp 105-108°C.

30

 (b) Sulfamic acid[[2,4,6-tris(1-methylethyl)phenoxy]-
 acetyl]-2,6-bis(1-methylethyl)phenyl ester

 This compound was prepared in the same manner as
 for the title compound of Example 1, except that
35 2,6-diisopropylphenylacetic acid was replaced with

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[2,4,6-tris(1-methylethyl)phenoxy]acetic acid,
mp 126-128°C.

EXAMPLE 47

5 Synthesis of sulfamic acid[[2,6-bis(1-methylethyl)-
 phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester

 This compound was prepared in the same manner as
 for the title compound of Example 46, except that
 2,4,6-triisopropylphenol was replaced with
10 2,6-diisopropylphenol, mp 108-110°C.

EXAMPLE 48

Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-
 phenyl]acetyl]-2,6-bis(phenyl)phenyl ester

15 (a) 2,6-Bis(phenyl)phenyl sulfamate

 A solution of chlorosulfonyl isocyanate (5.57 mL,
 64 mmol) in 50 mL toluene was added dropwise to a
 solution of 2,6-diphenylphenol (15.0 g, 61 mmol) in
 200 mL toluene at 50°C. The resulting white suspension
20 was heated to reflux for 16 hours. Concentrated
 in vacuo and carefully partitioned the residue between
 water and diethyl ether. The ether layer was dried
 over MgSO₄, filtered, and concentrated to give an off-
 white solid. Recrystallized from hexanes to give
25 2,6-bis(phenyl)phenyl sulfamate as a white solid,
 mp 145-147°C.

 (b) Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]-
 acetyl]-2,6-bis(phenyl)phenyl ester

30 This compound was prepared in the same manner as
 for the title compound of Example 1, except that
 2,6-diisopropylphenyl sulfamate was replaced with
 2,6-bis(phenyl)phenyl sulfamate, mp 129-132°C.

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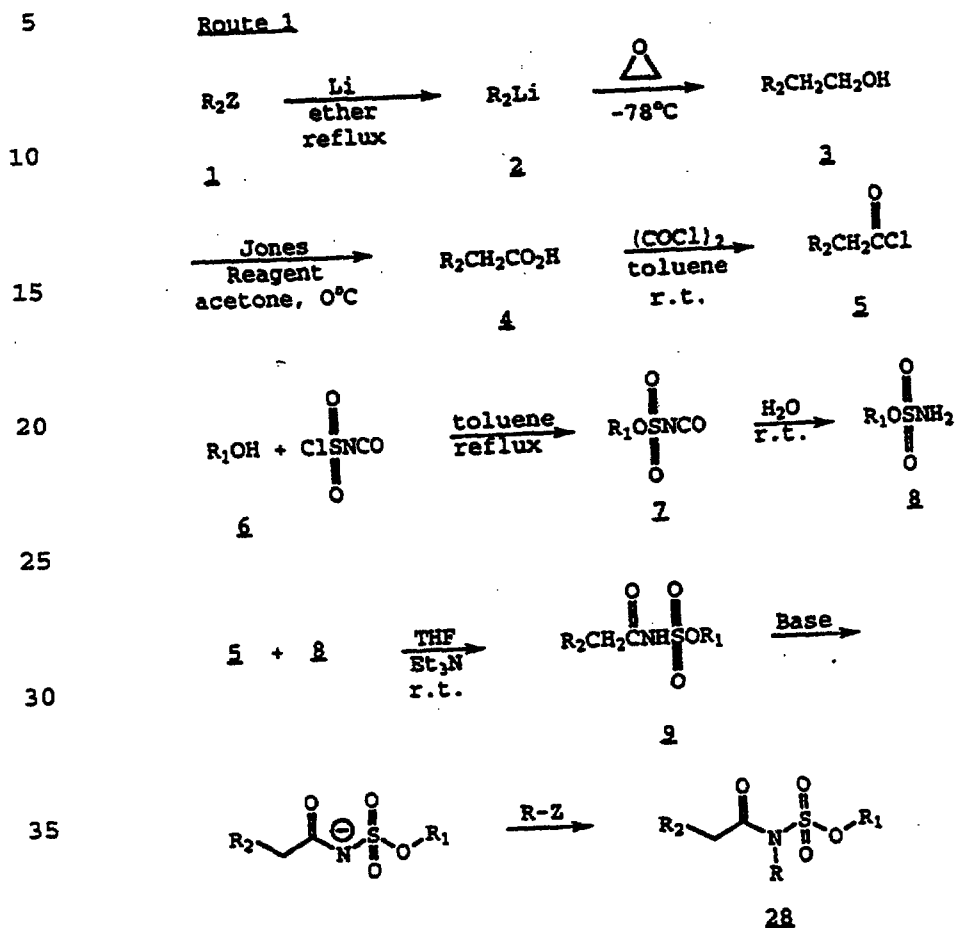
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CHART I

(R, R₁, and R₂ have the meanings defined in Formula I;
and Z represents a halogen)

Route 1



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CHART I (continued)

(R, R₁, and R₂ have the meanings defined in Formula I;
and Z represents a halogen)

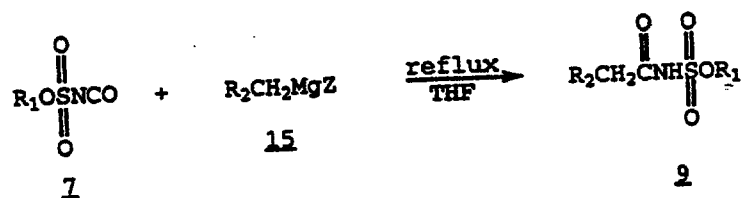
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Route 1A

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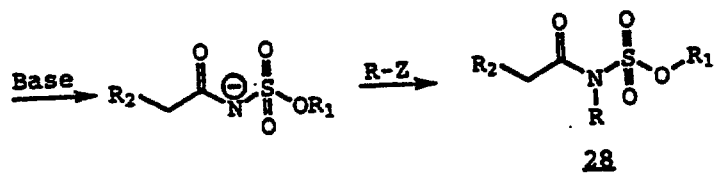


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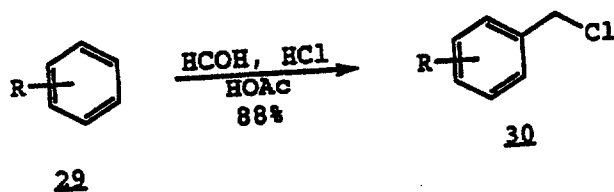


CHART I (continued)
(R, R₁, and R₂ have the meanings defined in Formula I;
and Z represents a halogen)

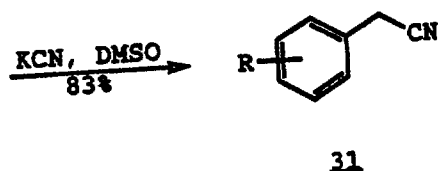
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Route 1B

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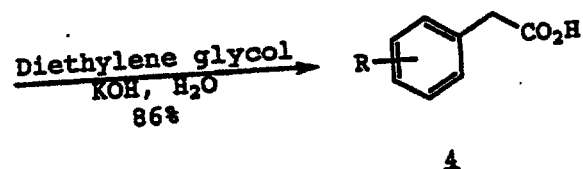


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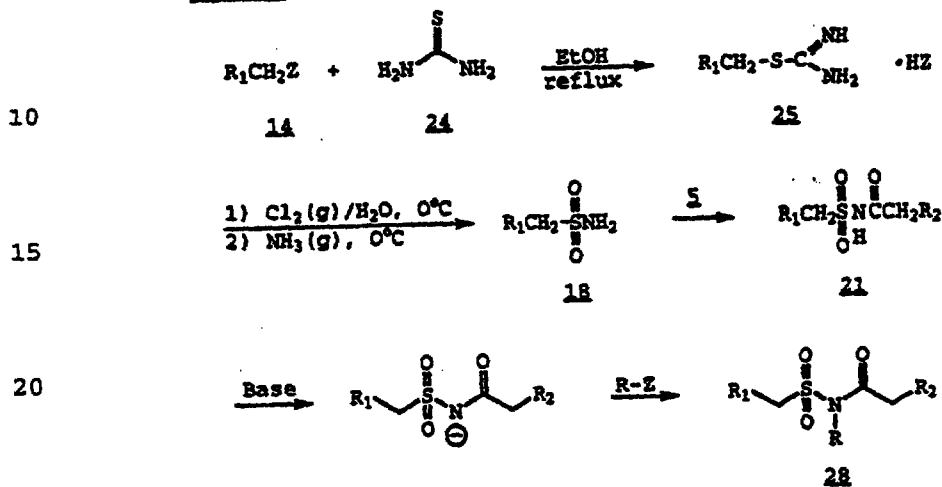


CHART II

(R, R₁, and R₂ have the meanings defined in Formula I;
and Z represents a halogen)

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Route 2



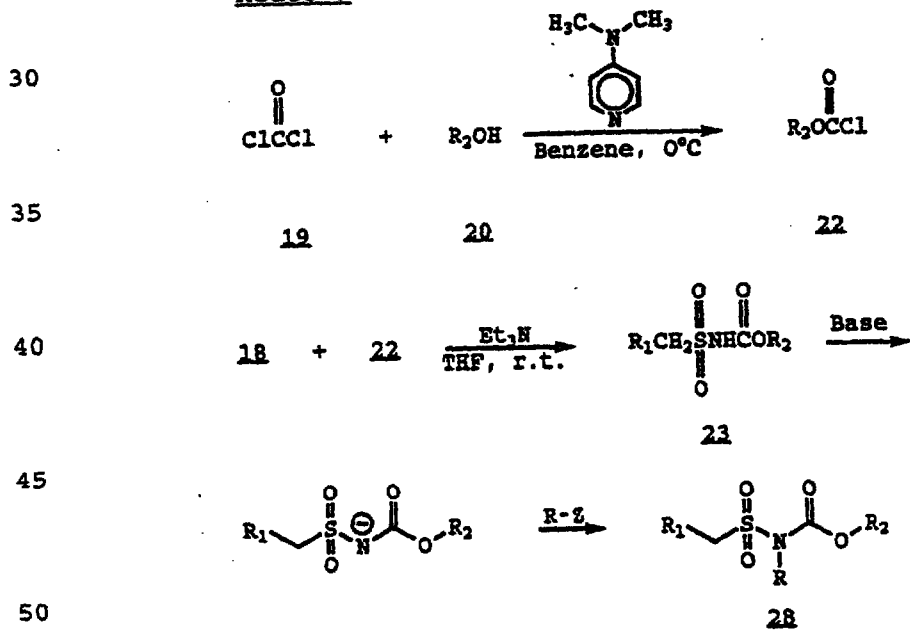
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Route 3



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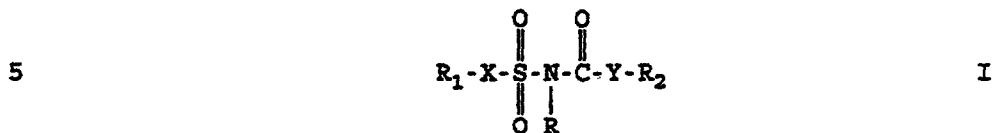
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CLAIMS

1. A compound of the formula



or a pharmaceutically acceptable salt thereof
wherein:

X and Y are selected from oxygen, sulfur and
(CR'R")_n wherein n is an integer of from
1 to 4 and R' and R" are each independently
hydrogen, alkyl, alkoxy, halogen, hydroxy,
acyloxy, cycloalkyl, phenyl optionally
substituted or R' and R" together form a
spirocycloalkyl or a carbonyl;
with the proviso at least one of X and Y is
(CR'R")_n and with the further proviso when
X and Y are both (CR'R")_n and R' and R" are
hydrogen and n is one, R₁ and R₂ are aryl;
R is hydrogen, a straight or branched alkyl of
from 1 to 8 carbon atoms or benzyl;
R₁ and R₂ are each independently selected from
(a) phenyl or phenoxy each of which is
unsubstituted or is substituted with 1 to
5 substituents selected from
phenyl,
an alkyl group having from 1 to 6 carbon
atoms and which is straight or branched,
an alkoxy group having from 1 to 6 carbon
atoms and which is straight or branched;
phenoxy,
hydroxy,
fluorine,
chlorine,

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- bromine,
nitro,
trifluoromethyl,
40 -COOH,
-COOalkyl wherein alkyl has from 1 to
4 carbon atoms and is straight or
branched,
- (CH₂)_pNR₃R₄ wherein p is zero or one, and
45 each of R₃ and R₄ is selected from
hydrogen or a straight or branched alkyl
group having 1 to 4 carbon atoms;
(b) 1- or 2-naphthyl unsubstituted or
substituted with from 1 to 3 substituents selected
50 from
phenyl,
an alkyl group having from 1 to 6 carbon
atoms and which is straight or branched,
an alkoxy group having from 1 to 6 carbon
55 atoms and which is straight or branched;
hydroxy,
phenoxy,
fluorine,
chlorine,
60 bromine,
nitro,
trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to
65 4 carbon atoms and is straight or
branched,
- (CH₂)_pNR₃R₄ wherein p, R₃ and R₄ have the
meanings defined above;
(c) arylalkyl;
70 (d) a straight or branched alkyl chain
having from 1 to 20 carbon atoms and which is
saturated or contains from 1 to 3 double bonds; or

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(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 6 carbon atoms;

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with the provisos:

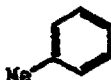
(i) where X is $(CH_2)_n$, Y is oxygen, and R_1 is a substituted phenyl, then R_2 is a substituted phenyl;

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(ii) where Y is oxygen, X is $(CH_2)_n$, R^2 is phenyl or naphthyl, then R^1 is not a straight or branched alkyl chain; and

(iii) the following compounds are excluded:

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X	Y	R	R_1	R_2
CH_2	O	H	$(CH_2)_2CH_3$	Ph
CH_2	O	H	CH_3	Ph
CH_2	O	H		i-Pr

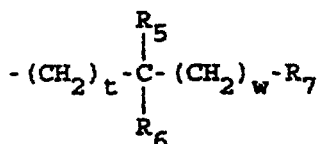
2. A compound of Claim 1 wherein R_1 is phenyl.
3. A compound of Claim 2 wherein R_1 is phenyl disubstituted in the 2,6-positions.
4. A compound of Claim 1 wherein R_2 is phenyl.
5. A compound of Claim 4 wherein R_2 is phenyl disubstituted in the 2,6-positions.
6. A compound of Claim 1 wherein each of R_1 and R_2 is phenyl.
7. A compound of Claim 6 wherein each phenyl is disubstituted in the 2,6-positions.

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8. A compound of Claim 1 wherein R_1 is phenyl disubstituted in the 2,6-positions and R_2 is phenyl trisubstituted in the 2,4,6-positions.
9. A compound of Claim 1 wherein R_1 is 2,6-bis-(1-methylethyl)phenyl and R_2 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl.
10. A compound of Claim 1 wherein R_1 is phenyl or isophenyl disubstituted in the 2,6-positions, wherein R_2 is phenyl or is phenyl disubstituted in the 2,6-positions, wherein each of R_1 and R_2 is phenyl, wherein each phenyl is disubstituted in the 2,6-position, wherein R_1 is phenyl disubstituted in the 2,6-positions and R_2 is phenyl trisubstituted in the 2,4,6-positions, wherein R_1 is 2,6-bis(1-methylethyl)phenyl and R_2 is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl, wherein one of R_1 and R_2 is the group



- wherein t is zero or 1 to 4; w is zero or 1 to 4 with the proviso that the sum of t and w is not greater than 5; R_5 and R_6 are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R_5 is hydrogen, R_6 can be selected from the groups defined for R_7 ; and R_7 is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy,

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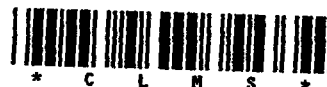
fluorine, chlorine, bromine, nitro,
trifluoromethyl, -COOH, COOalkyl wherein alkyl has
from 1 to 4 carbon atoms, or $-(CH_2)_pNR_3R_4$ wherein
P, R_3 and R_4 have the meanings defined above.

11. A compound according to Claim 1 wherein
X is oxygen, sulfur or $(CR'R'')_n$;
Y is oxygen, sulfur or $(CR'R'')_n$ with the proviso
that at least one of X or Y is $(CR'R'')_n$
wherein n is an integer of from 1 to 4 and R'
5 and R'' are each independently hydrogen,
straight or branched alkyl of from 1 to
6 carbons, optionally substituted phenyl,
halogen, hydroxy, alkoxy, acyloxy,
cycloalkyl, or R' and R'' taken together form
10 a carbonyl or a spirocycloalkyl group of from
3 to 10 carbons;
R is hydrogen;
R₁ is phenyl optionally substituted, straight or
branched alkyl of from 1 to 10 carbon atoms,
15 cycloalkyl of from 3 to 10 carbon atoms;
R₂ is phenyl optionally substituted, straight or
branched alkyl of from 1 to 10 carbon atoms,
cycloalkyl of from 3 to 8 carbon atoms,
phenoxy optionally substituted with the
20 proviso that only if X is $(CR'R'')_n$ can R₁ be
optionally substituted phenoxy and only if Y
is $(CR'R'')_n$ can R₂ be optionally substituted
phenoxy, and with the further proviso that at
least one of R₁ and R₂ is optionally
25 substituted phenyl or phenoxy.

12. A compound according to Claim 1 wherein
X is oxygen;
Y is $(CR'R'')_n$ wherein n is an integer of from
1 to 2;

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5 R is hydrogen;
R₁ is optionally substituted phenyl;
R₂ is optionally substituted phenyl or phenoxy,
straight or branched alkyl of from 1 to
10 carbons, or cycloalkyl of from 3 to
10 carbons;
R' and R" are each independently hydrogen,
straight or branched alkyl of from 1 to
6 carbons, optionally substituted phenyl,
halogen, hydroxy, alkoxy, acyloxy,
15 cycloalkyl, or R' and R" taken together form
a carbonyl or a spirocycloalkyl.

13. A compound named sulfamic acid[[2,4,6-tris-(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester.

14. A compound of Claim 1 selected from:

Sulfamic acid (phenylacetyl)-2,6-bis-(1-methylethyl)phenyl ester,

5 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)-phenyl]acetyl-2,4,6-tris(1-methylethyl)phenyl ester,

10 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis-[1-methylethyl)phenyl ester,

15 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid[[2,4,6-tris(1-methylethyl)-phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

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- 20 Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris-(1-methylethyl)phenyl]methyl]sulfonyl]benzene-
25 acetamide,
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris-(1-methylethyl)phenyl]methyl]sulfonyl]benzene-
acetamide-sodium salt,
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl]methyl]sulfonyl]carbamate,
30 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl]methyl]sulfonyl]carbamate-
sodium salt,
Sulfamic acid (1-oxo-3,3-diphenylpropyl)-
35 2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester,
40 Sulfamic acid trans-[(2-phenylcyclopropyl)-
carbonyl]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,4,6-trimethoxyphenyl-
45 (acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2,4,6-trimethylphenyl-
(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2-thiophenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester,
50 Sulfamic acid [3-thiophenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2-methoxyphenyl(acetyl)]-
2,6-bis(1-methylethyl)phenyl ester,

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- 55 Sulfamic acid (oxophenylacetyl)-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [2-trifluoromethylphenyl-
(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2-phenylpropyl)-
2,6-bis(1-methylethyl)phenyl ester,
60 Sulfamic acid (cyclopentylphenylacetyl)-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (cyclohexylacetyl)-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (diphenylacetyl)-
65 2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (triphenylacetyl)-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [(1-phenylcyclopentyl)-
carbonyl]-2,6-bis(1-methylethyl)phenyl ester,
70 Sulfamic acid (3-methyl-1-oxo-
2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl
ester,
Sulfamic acid (1-oxo-2-phenylbutyl)-
2,6-bis(1-methylethyl)phenyl ester,
75 Sulfamic acid (cyclohexylphenylacetyl)-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-2,2-diphenylpropyl)-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-
80 2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid (1-oxo-3-phenylpropyl)-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [1-oxo-3-[2,4,6-tris-
(1-methylethyl)phenyl]-2-propenyl]-2,6-bis-
85 (1-methylethyl)phenyl ester,
Sulfamic acid [1-oxo-3-[2,4,6-tris-
(1-methylethyl)phenyl]propyl]-2,6-bis(1-methyl-
ethyl)phenyl ester,

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- 90 Sulfamic acid [(acetyloxy) [2,4,6-tris-(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- 95 Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,
- 100 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and
- 105 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.
- 110 15. A pharmaceutical composition for regulating plasma cholesterol concentrations comprising an effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.
16. A method of treating hypercholesterolemia comprising administering to a patient a therapeutically effective amount of a compound of Claim 1.
17. A method of treating atherosclerosis comprising administering to a patient a therapeutically effective amount of a compound of Claim 1.

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