



**NOVEL 2-SACCHARINYLMETHYL PHOSPHATES, PHOSPHONATES
AND PHOSPHINATES USEFUL AS PROTEOLYTIC ENZYME
INHIBITORS AND COMPOSITIONS AND METHOD OF USE
THEREOF**

5

FIELD OF THE INVENTION

This invention relates to novel 2-saccharinylmethyl phosphates, phosphonates and phosphinates which inhibit the enzymatic activity of proteolytic enzymes, to compositions containing the same, to the method of use thereof in the treatment of degenerative diseases and to processes for their preparation.

BACKGROUND OF THE INVENTION

15 The inhibition of proteolytic enzymes by nontoxic reagents is useful in the treatment of degenerative disorders, such as emphysema, rheumatoid arthritis and pancreatitis, in which proteolysis is a substantive element. Protease inhibitors are widely utilized in
20 biomedical research. Serine proteases are the most widely distributed class of proteolytic enzymes. Some serine proteases are characterized as chymotrypsin-like or elastase-like based upon their substrate specificity.

Chymotrypsin and chymotrypsin-like enzymes normally
25 cleave peptide bonds in proteins at a site at which the amino acid residue on the carboxyl side is typically Trp, Tyr, Phe, Met, Leu or another amino acid residue which contains aromatic or large alkyl side chains. Elastase and elastase-like enzymes normally cleave peptide bonds at
30 a site at which the amino acid residue on the carboxyl side of the bond is typically Ala, Val, Ser, Leu or other similar, smaller amino acids. Both chymotrypsin-like and elastase-like enzymes are found in leukocytes, mast cells

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and pancreatic juice in higher organisms, and are secreted by many types of bacteria, yeast and parasites.

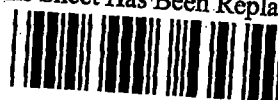
Japanese Patent Publication 72/00419 discloses a number of 2-saccharinylmethyl benzoates, including
5 2-saccharinylmethyl benzoate per se and 2-saccharinylmethyl 2,4-dichlorobenzoate and 4-nitrobenzoate. The compounds are said to have strong activity against rice blast, rice sheath blight, rice helminthosporium leaf spot and rice bacterial leaf blight disease.

10 Sunkel et al., J. Med. Chem., 31, 1886-1890 (1988) disclose a series of 2-saccharinyl-lower-alkyl-1,4-dihydropyridine-3-carboxylates having platelet aggregation inhibitory and anti-thrombotic activities.

Chen U.S. Patent 4,263,393 discloses various 2-aroysl-
15 methylsaccharins useful as photographic elements and film units.

Mulvey et al. U.S. Patent 4,195,023 discloses R_1 -2- R_2 CO-1,2-benzisothiazol-3-ones, where R_1 is halogen, alkoxy, alkylamino, dialkylamino, alkoxycarbonyl, amino,
20 nitro or hydrogen in the benzenoid ring and R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, halophenyl, heteroaryl or substituted heteroaryl, and R_1 -2-A-CO saccharins, where R_1 has the same meanings as the benzenoid ring substituents in the 1,2-benzisothiazol-
25 3-ones and A is alkyl, alkenyl, alkynyl, cycloalkyl, fluorophenyl, heteroaryl or substituted-heteroaryl. The compounds are said to have elastase inhibitory activity and to be useful in the treatment of emphysema.

Zimmerman et al., J. Biol. Chem., 255(20), 9848-9851
30 (1980) disclose N-acylsaccharins, where the acyl group is furoyl, thenoyl, benzoyl, cyclopropanoyl, ethylbutyryl and acryloyl, having serine protease inhibitory activity.



Chemical Abstracts 81, 22249n (1974) discloses 4-methylphenyl 2-saccharinylcarboxylate which is said to have bactericidal and fungicidal activities.

Several classes of compounds are known to be serine protease inhibitors. For example Powers in U.S. Patent 4,659,855 discloses arylsulfonyl fluoride derivatives useful as elastase inhibitors. Doherty et al. in U.S. Patents 4,547,371 and 4,623,645 disclose cephalosporin sulfones and sulfoxides, respectively, which are stated to be potent elastase inhibitors useful in the treatment of inflammatory conditions, especially arthritis and emphysema.

Teshima et al., J. Biol. Chem., 257(9), 5085-5091 (1982) report the results of studies on serine proteases (human leukocyte elastase, porcine pancreatic elastase, cathepsin G and bovine chymotrypsin A₂) with 4-nitrophenylesters and thioesters of N-trifluoroacetyl-anthranilates, 2-substituted-4H-3,1-benzoxazin-4-ones, 2-substituted-4-quinazolinones and 2-substituted-4-chloroquinazolines.

Cha, Biochem. Pharmacol., 24, 2177-2185 (1975) discusses kinetic approaches to the study of the binding of inhibitors to macromolecules, such as enzymes, and methods for determination of such parameters as the inhibition constants, reaction rates and bound and unbound enzyme concentrations.

Jones et al., U.S. Patent 4,276,298 discloses 2-R-1,2-benzisothiazolinone-1,1-dioxides, where R is phenyl substituted by fluoro, dinitro, trifluoromethyl, cyano, alkoxycarbonyl, alkylcarbonyl, carboxyl, carbamoyl, alkylacylamino, alkylsulfonyl, N,N-dialkylsulfamoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfonyl and trifluoromethylsulfinyl, or pyridyl



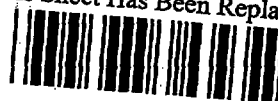
substituted the same as R when R is phenyl except that pyridyl may also be mono-nitro substituted. The compounds are said to have protease enzyme inhibitory activity, especially elastase inhibitory activity, and to be useful
5 in the treatment of emphysema, rheumatoid arthritis and other inflammatory diseases.

Powers et al., Biochem., 24, 2048-2058 (1985) discloses studies of the inhibitions of four chymotrypsin-like enzymes, cathepsin G, rat mast cell proteases I and
10 II, human skin chymase and chymotrypsin A_a, by N-furoyl-saccharin and N-(2,4-dicyanophenyl)saccharin.

Svoboda et al., Coll. Czech. Chem. Commun., 51, 1133-1139 (1986) disclose the preparation of 4-hydroxy-2H-1,2-benzothiazine-3-carboxylates by intramolecular
15 Dieckmann condensation of 2H-1,2-benzisothiazol-3-one-2-acetate-1,1-dioxide esters.

Reczek et al. U.S. Patents 4,350,752 and 4,363,865 and Vanmeter et al. U.S. Patent 4,410,618 relate to photographic reagents (Reczek 4,350,752 and Vanmeter.
20 et al.) and photographic dyes (Reczek 4,363,865) and disclose various 2-substituted saccharins useful for such applications, for example photographic reagents bound through a heteroatom to an imidomethyl blocking group (Reczek 4,350,752), carrier-diffusible photographic dyes
25 bound to the nitrogen atom of an imide through a 1,1-alkylene group (Reczek 4,363,865) and N-acylmethyl-imides which are described as blocked photographic reagents and which have a residue of an organic photographic reagent containing a hetero atom through
30 which it is bound to the blocking group (Vannmeter).

Freed et al. U.S. Patent 3,314,960 discloses 2-(1,1,3-trioxo-1,2-benzisothiazol-2-yl)glutarimides which are stated to be useful as sedatives.



2-Chloromethylsaccharin is disclosed in French Patent 1,451,417 as an intermediate for the preparation of N-methylsaccharin d,l-trans-chrysanthemate, useful as an insecticide, and Lo U.S. Patent 3,002,884 discloses 2-chloro, 2-bromo and 2-iodomethylsaccharins, useful as fungicidal agents.

Dunlap et al. PCT application WO 90/13549 discloses a series of 2-substituted saccharin derivatives useful as proteolytic enzyme inhibitors.

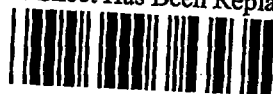
SUMMARY OF THE INVENTION

The present invention relates to 4-R₁-R₂-R₃-2-saccharinylmethyl phosphates, phosphonates and phosphinates of formula I hereinbelow which have protease enzyme inhibitory activity and which are useful in the treatment of degenerative diseases.

The invention also relates to compositions for the treatment of degenerative diseases which comprise a pharmaceutical carrier and an effective proteolytic enzyme inhibiting amount of a compound of formula I.

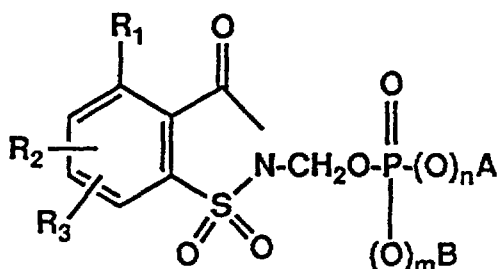
The invention further relates to a method of use of a compound of formula I in the treatment of degenerative diseases which comprises administering to a patient in need of such treatment a medicament containing an effective proteolytic enzyme inhibiting amount of the compound of formula I.

The invention also relates to a process for the preparation of a compound of formula I which comprises reacting a 4-R₁-R₂-R₃-2-halomethylsaccharin with a phosphate, phosphonate or phosphinic acid of formula III hereinbelow in the presence of an acid-acceptor.



DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

More specifically this invention relates to 4-R₁-R₂-R₃-2-saccharinylmethylphosphates, phosphonates and phosphinates having the formula:



Formula I

wherein A):

R₁ is hydrogen, halogen, lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, lower-alkenyl, lower-alkynyl, cyano, amino, lower-alkylamino, di-lower-alkyl-amino, carboxamido, lower-alkoxy, benzyloxy, hydroxy, lower-alkoxycarbonyl or phenyl;

R₂ is a substituent in any of the available 5-, 6- or 7-positions selected from the group consisting of benzyloxy-lower-alkoxy, -O-(CH₂)_jOC(O)(CH₂)_k-N=B,

-O-(CH₂)_j-[5-(CH₂)_k-N=B-2-furanyl],

-O-(CH₂)_j-C≡C-(CH₂)_k-N=B', -O-(CH₂)_j-CH=CH-(CH₂)_k-N=B',

where -N=B in each instance is amino, lower-alkylamino, di-lower-alkylamino, 1-azetidiny, 1-pyrrolidinyl,

1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-

alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl

or (carboxy-lower-alkyl)amino, N=B' is amino, lower-

alkylamino, di-lower-alkylamino, dibenzylamino,

1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl,

4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl,

4-benzyl-1-piperazinyl, 1-imidazolyl, or

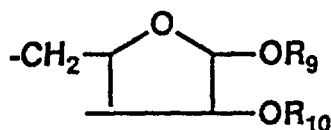
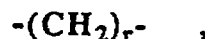
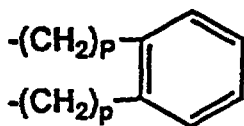
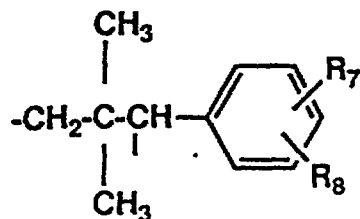


$-NR'(C_{2-10}\text{-alkylene})-N(\text{alkyl})_2$ wherein R' is hydrogen or lower-alkyl, and j and k are independently an integer from 1 to 4;

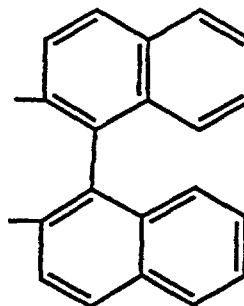
R_3 is hydrogen or a substituent in any of the
 5 available 5-, 6- or 7-positions selected from the group consisting of halogen, cyano, nitro, $N=B$, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, polyfluoro-lower-alkyl-sulfonylamino, polychloro-lower-alkylsulfonylamino, aminosulfonyl, lower-alkyl, polyfluoro-lower-alkyl,
 10 polychloro-lower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxy-lower-alkyl, formyl, amino-methyl, polyfluoro-lower-alkylsulfonyl, polychloro-lower-alkyl-sulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxy-poly-lower-alkyleneoxy, cycloalkyloxy, hydroxy-
 15 lower-alkoxy, benzyloxy-lower-alkoxy, polyhydroxyalkoxy, or acetal or ketal thereof, polyalkoxyalkoxy, (lower-alkoxy) $_2P(O)O-$, $-SR$, $-SOR$, $-SO_2R$, $-OCOR$, $-O-(C_{1-10}\text{-alkylene})-COOR$, $-O-(C_{1-10}\text{-alkylene})-COOH$, $-O-(C_{2-10}\text{-alkylene})-N=B$, $-O-(CH_2)_jOC(O)(CH_2)_k-N=B$,
 20 $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2\text{-furanyl}]$, $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$, $-O-(CH_2)_j-CH=CH-(CH_2)_k-N=B'$, where R is lower-alkyl, phenyl, benzyl or naphthyl, or phenyl or naphthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy or
 25 halogen, $-N=B$, $N=B'$ and j and k are as defined above for R_2

m and n are independently 0 or 1;

when m and n are 1, A and B are independently
 hydrogen, lower-alkyl, phenyl, lower-alkoxyphenyl or
 30 benzyl, or, taken together, represent:



or



where R_7 and R_8 are independently hydrogen or chlorine, R_9 and R_{10} each is hydrogen or together represent isopropylidene, p is 0 or 1 and r is 2, 3 or 4;

5 when m is 1 and n is 0, A and B are independently lower-alkyl, phenyl, benzyl or 2-pyridinyl; and

when m and n are 0, A and B are independently lower-alkyl, phenyl or lower-alkoxyphenyl; or

B)

10 R_1 is hydrogen, isopropyl, sec-butyl, methoxy or ethoxy;

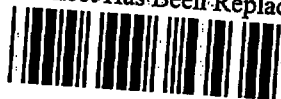
R_2 is 2-hydroxyethoxy, 2-(benzyloxycarbonylmethoxy), or 2-(hydroxycarbonylmethoxy), or dimethylketal thereof;

R_3 is hydrogen;

15 m and n are independently 0 or 1;

when m and n are 1, A and B are independently hydrogen, methyl, ethyl, isopropyl, butyl, phenyl or benzyl; and

20 when m and n are 0, A and B are independently butyl, phenyl or 4-methoxyphenyl.



Preferred compounds of formula I within part A) are those wherein R_1 is lower-alkyl; R_2 is benzyloxy-lower-alkoxy; $-O-(CH_2)_j-OC(O)(CH_2)_k-N=B$;
 $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2-furanyl]$;
5 $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$ or $-O-(CH_2)_j-CH=CH-(CH_2)_k-N=B'$;
 R_3 is hydrogen and m , n , A and B are as defined hereinabove in relation to formula I part A).

Particularly preferred compounds within this group are those wherein R_2 is 2-benzyloxyethoxy or those wherein
10 in the structures above, j and k each is 1, especially when $N=B$ and $N=B'$ each is di-lower-alkylamino, m and n each is 1 and A and B each is lower-alkyl. An especially preferred compound is diisopropyl 6-(2-benzyloxyethoxy)-4-isopropylsaccharinylmethyl phosphate.

15 Particularly preferred compounds within group B) are those wherein R_1 , A and B are each isopropyl, m and n are each 1 and R_2 is 2-hydroxyethoxy, 2-(benzyloxycarbonylmethoxy), or 2-(hydroxycarbonylmethoxy).

It should be understood that the compounds having the
20 general structural formula I are usually named in the chemical literature as 1,2-benzisothiazol-3(2H)-one 1,1-dioxides. However for the sake of brevity, such compounds are frequently named as saccharin derivatives, and that nomenclature will be used hereinafter in
25 describing the compounds of the invention and their biological properties.

As used herein the terms lower-alkyl, lower-alkoxy, and lower-alkane mean monovalent aliphatic radicals, including branched chain radicals, of from one to ten
30 carbon atoms. Thus the lower-alkyl (or lower-alkane) moiety of such groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl,



2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methyl-pentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, 1,1,3,3-tetramethylpentyl, 1,1-dimethyloctyl and the like.

- 5 As used herein the terms cycloalkyl and cycloalkyloxy mean such radicals having from three to seven carbon atoms illustrated by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cycloheptyloxy.

- 10 As used herein the term halogen (or halo) means fluorine, chlorine, bromine or iodine.

- As used herein the terms lower-alkenyl and lower-alkynyl mean monovalent, unsaturated radicals, including branched chain radicals, of from two to ten carbon atoms and thus include 1-ethenyl, 1-(2-propenyl), 1-(2-butenyl), 15 1-(1-methyl-2-propenyl), 1-(4-methyl-2-pentenyl), 4,4,6-trimethyl-2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butylnyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentylnyl), and the like.

- 20 As used herein, the term C₂₋₁₀-alkylene means divalent, saturated radicals, including branched chain radicals, of from two to ten carbon atoms having their free valences on different carbon atoms; and the term C₁₋₁₀-alkylene means divalent, saturated radicals, 25 including branched chain radicals, of from one to ten carbon atoms having their free valences on the same or different carbon atoms. Such terms thus include 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1-methyl-1,2-ethylene, 1,8-octylene and the like and in the case 30 only of C₁₋₁₀, also methylene, ethylidene, propylidene and the like.

 As used herein, the term lower-alkoxy-poly-lower-alkyleneoxy means such radicals in which lower-alkoxy has



the meaning given above, poly means 2 to 4, and lower-alkylene in lower-alkyleneoxy means divalent saturated radicals, including branched radicals, of from two to five carbon atoms. That term thus includes $\text{CH}_3(\text{OCH}_2\text{CH}_2)_p\text{O}-$,
5 $\text{CH}_3\text{CH}_2[\text{OCH}_2\text{CH}(\text{CH}_3)]_p\text{O}-$. where $p = 2-4$, and the like.

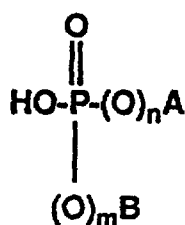
As used herein, hydroxy-lower-alkoxy means lower-alkoxy as defined above substituted by a hydroxy group other than on the C-1 carbon atom and thus includes 2-hydroxyethoxy and the like.

10 As used herein, the term polyhydroxyalkoxy means such a group wherein alkoxy is a monovalent aliphatic radical of from two to five carbon atoms substituted by from two to four hydroxy groups none of which are attached to the same or the C-1 carbon atom and thus includes 2,3-di-
15 hydroxypropoxy, 2,3,4,5-tetrahydroxypentoxy and the like.

As used herein, the term polyalkoxyalkoxy means monovalent aliphatic alkoxy radicals of from three to five carbon atoms substituted by from two to four methoxy or ethoxy groups none of which are attached to the same or
20 the C-1 carbon atom.

The compounds of the present invention inhibit the activity of serine proteases, specifically human leukocyte elastase and the chymotrypsin-like enzymes, and are thus useful in the treatment of degenerative disease conditions
25 such as emphysema, rheumatoid arthritis, pancreatitis, cystic fibrosis, chronic bronchitis, adult respiratory distress syndrome, inflammatory bowel disease, psoriasis, bullous pemphigous and alpha-1-antitrypsin deficiency.

The compounds of formula I are prepared by reaction
30 of a 4- R_1 - R_2 - R_3 -2-halomethylsaccharin with an appropriate phosphoric acid di-ester, phosphonic acid mono-ester or phosphinic acid of the formula



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III

where A, B, m and n have the meanings given hereinabove except that when m and n are 1, A and B are other than hydrogen. The reaction can be carried out in the presence of an acid-acceptor, such as an alkali metal carbonate, a tri-lower-alkylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, hereinafter DBU. Alternatively, the alkali metal salt, especially cesium salt, of the compound of formula III can be used (prepared by reaction of the compound of formula III with an alkali metal carbonate). The reaction is carried out in an organic solvent inert under the conditions of the reaction, for example acetone, methyl-ethylketone (MEK), acetonitrile, tetrahydrofuran (THF), diethylether, dimethylformamide (DMF), N-methyl-pyrrolidinone, methylene dichloride (MDC), xylene, toluene or lower-alkanols, at a temperature in the range from ambient up to the boiling point of the solvent used.

The compounds of formula I wherein R₃ is lower-alkoxy, lower-alkoxy-poly-lower-alkyleneoxy, cycloalkyloxy, acetal or ketal of polyhydroxyalkoxy, polyalkoxyalkoxy, (lower-alkoxy)₂P(O)O-, -O-(C₂₋₁₀-alkylene)-N=B and wherein R₂ and/or R₃ is -O-(C₁₋₁₀-alkylene)-COOR, benzyl-oxy-lower-alkoxy, -O-(CH₂)_j-OC(O)-(CH₂)_k-N=B, -O-(CH₂)_j-[5-(CH₂)_k-N=B-2-furanyl] or -O-(CH₂)_j-C≡C-(CH₂)_k-N=B' can also be prepared by the Mitsunobu reaction, i.e. by reaction of a starting



material of or equivalent to formula I where R_2 and/or R_3 is hydroxy with an excess of a corresponding alcohol of the R_2 and/or R_3 radical (for example, when the R_2 radical is ethoxy, the corresponding alcohol is ethyl alcohol) in the presence of an excess of a triarylphosphine, such as triphenylphosphine, or trialkylphosphine, such as tri-
5 butylphosphine, and an excess of a di-lower-alkyl azodicarboxylate, preferably diethyl azodicarboxylate, in a suitable solvent, such as THF, at about room temperature
10 or above, preferably at about room temperature.

The compound of formula I wherein R_2 and/or R_3 is $-O-(CH_2)_j-CH=CH-(CH_2)_k-N=B'$ can be prepared by partial reduction of the corresponding compound wherein R_2 and/or R_3 is $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$ over palladium on barium
15 sulfate which has been poisoned by addition of quinoline.

The compound of formula I wherein R_2 and/or R_3 is hydroxy-lower-alkoxy can also be prepared by debenzylation of a corresponding compound of formula I wherein R_2 and/or R_3 is benzyloxy-lower-alkoxy, e.g. by hydrogenation of the
20 benzyloxy-lower-alkoxy compound over palladium-on-carbon.

The compound of formula I wherein R_3 is polyhydroxy-alkoxy can be prepared by acidic hydrolysis of a corresponding compound of formula I wherein R_3 is the acetal or ketal of polyhydroxyalkoxy. The hydrolysis can
25 be carried out by reacting the acetal or ketal in a suitable solvent such as methanol with an equivalent amount of p-toluenesulfonic acid monohydrate at about room temperature.

The compounds of formula I wherein R_2 and/or R_3 is $-O-(CH_2)_j-OC(O)-(CH_2)_k-N=B$ can also be prepared by reacting
30 a corresponding compound wherein R_2 and/or R_3 is hydroxy-lower-alkoxy with an amino acid of the formula $HOC(O)-(CH_2)_k-N=B$ in the presence of a coupling agent,



e.g. dicyclohexylcarbodiimide, in a suitable solvent,
e.g. MDC, at about room temperature.

The compounds of formula I wherein R_2 and/or R_3 is benzyloxy-lower-alkoxy, $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2-furanyl]$ or $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$ can also be prepared from a
5 $R_1-R_2-R_3$ -2-phenylthiomethylsaccharin wherein R_2 and/or R_3 is hydroxy by reaction with a corresponding alcohol of the R_2 and/or R_3 radical using the Mitsunobu reaction as described above to give the corresponding 2-phenylthio-
10 methyl compound wherein R_2 and/or R_3 is benzyloxy-lower-alkoxy, $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2-furanyl]$ or $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$ and, using procedures described hereinbefore, converting the 2-phenylthio compound to the corresponding 2-halomethyl compound and the latter to the
15 corresponding phosphate, phosphonate or phosphinate.

The compounds of formula I wherein R_2 and/or R_3 is $-O-(C_{1-10}\text{-alkylene})-COOR$ can also be prepared by reacting a starting material of or equivalent to formula I wherein R_2 and/or R_3 is hydroxy with a compound of the formula
20 $X-(C_{1-10}\text{-alkylene})-COOR$ in the presence of a suitable base, e.g. potassium carbonate, in a suitable solvent, e.g. acetone, at about room temperature.

The compounds of formula I wherein R_2 and/or R_3 is $-O-(C_{1-10}\text{-alkylene})-COOH$ can be prepared by debenzylation
25 of the corresponding benzyl ester by hydrogenation over palladium-on-carbon.

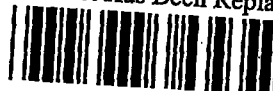
The compounds of formula I wherein m and n are 1 and A and B are hydrogen are prepared by hydrogenolysis of the corresponding compounds wherein m and n are 1 and A and B
30 are benzyl.

The 4- R_1 - R_2 - R_3 -2-halomethylsaccharins required for the preparation of the compounds of formula I are prepared by the methods described by D'Alelio *et al.*, J. Macromol.



Sci-Chem., A3(5), 941 (1969) and Saari et al., J. Het. Chem., 23, 1253 (1986). In the method described by Saari et al., a methyl ester of an appropriate anthranilic acid is prepared by conventional means from the substituted
5 anthranilic acid and the ester diazotized. The diazonium salt is then reacted with sulfur dioxide and cupric chloride to produce a sulfonyl chloride which is then reacted with concentrated ammonium hydroxide to produce the substituted saccharin derivatives of formula IV. The
10 latter, on reaction with formaldehyde in a lower-alkanol solvent, affords the 4-R₁-R₂-R₃-2-hydroxymethylsaccharins of formula V, which, on reaction with a thionyl halide or a phosphorus trihalide, afford the corresponding
15 4-R₁-R₂-R₃-2-halomethylsaccharin derivatives of formula VI.

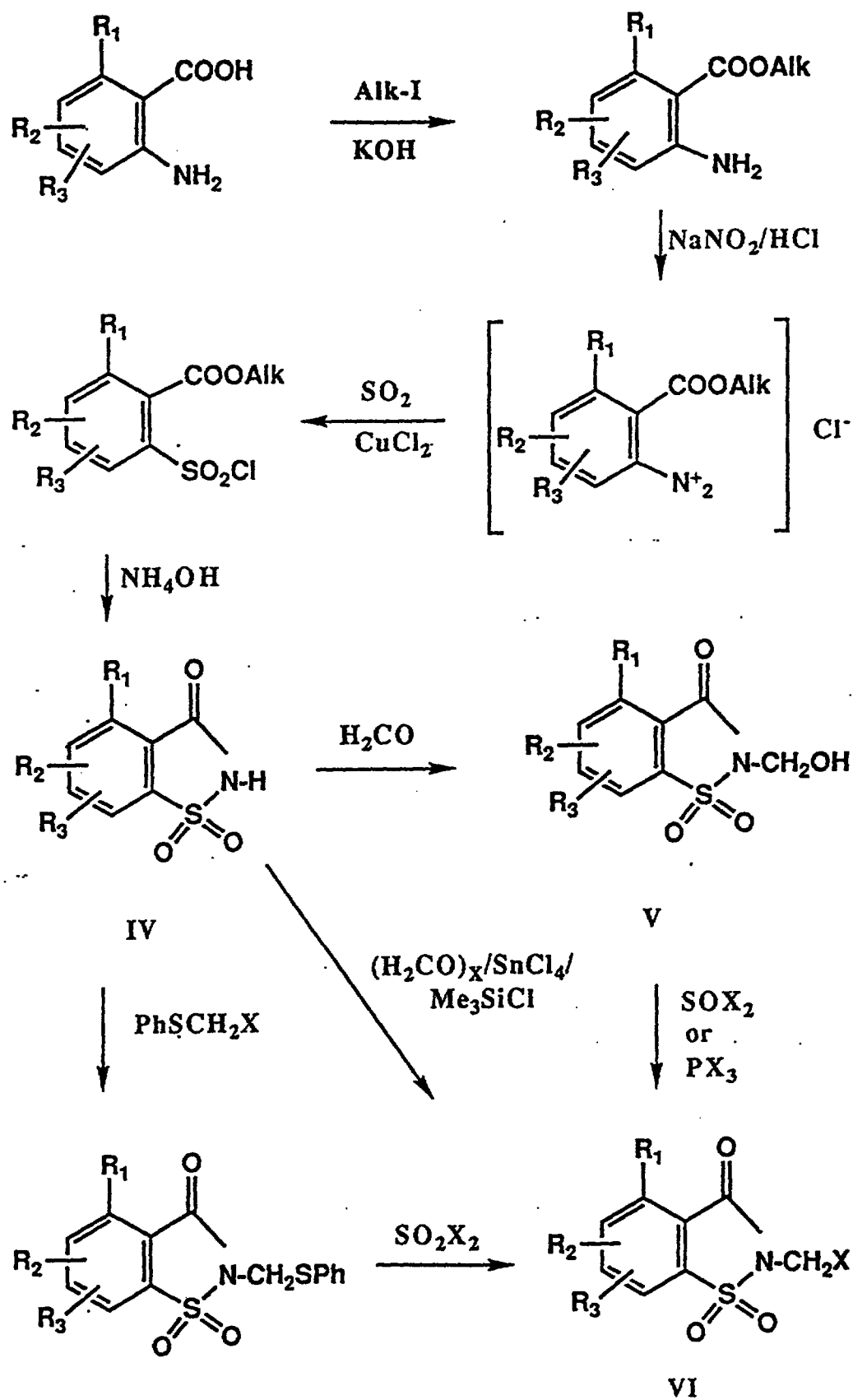
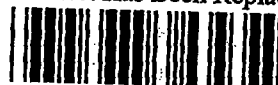
The 4-R₁-R₂-R₃-2-halomethylsaccharins of formula VI, where R₁, R₂, R₃ have the meanings given above and X is chlorine or bromine, can also be prepared by reaction of a
20 corresponding 4-R₁-R₂-R₃-2-phenylthiomethylsaccharin with a sulfonyl halide in an inert organic solvent, for example MDC, ethylene dichloride (EDC) or carbon tetrachloride, at a temperature from around 0°C to around 30°C. The
4-R₁-R₂-R₃-2-phenylthiomethylsaccharins are in turn prepared by reaction of a 4-R₁-R₂-R₃-saccharin of formula
25 IV with a halomethylphenyl sulfide in an inert organic solvent, such as toluene, xylene, DMF or MDC at a temperature in the range from ambient up to the boiling point of the solvent used. The reaction can be carried
30 out by reaction of the halomethyl phenyl sulfide with either the thallium salt of the saccharin derivative of formula IV (prepared by reaction of the saccharin derivative with a thallium lower-alkoxide in a lower-alkanol); or with a di-lower-alkyl ammonium salt of the



saccharin derivative (prepared as described below) in the presence of a tetra-lower-alkyl ammonium halide, such as tetrabutyl ammonium bromide (hereinafter TBAB); or with the saccharin derivative of formula IV per se in the
5 presence of a tetra-lower-alkyl ammonium halide; or with the saccharin derivative of formula IV per se in the presence of a tetra-lower-alkyl ammonium halide and an alkali metal lower-alkoxide, such as potassium t-butoxide.

The saccharins of formula IV may also be converted to
10 the chloromethyl saccharins of formula VI, wherein X is Cl, in one step by reaction with an excess of formaldehyde or a formaldehyde equivalent, such as paraformaldehyde or 1,3,5-trioxane, and a chlorosilane, preferably chlorotri-methylsilane, in the presence of a Lewis acid, preferably
15 a catalytic amount of stannic chloride, in an inert solvent, preferably 1,2-dichloroethane (ethylene dichloride, EDC).

These approaches are illustrated as follows, where
R₁, R₂ and R₃ have the meanings given above, Alk is lower-
20 alkyl, X is halogen and Ph is phenyl.





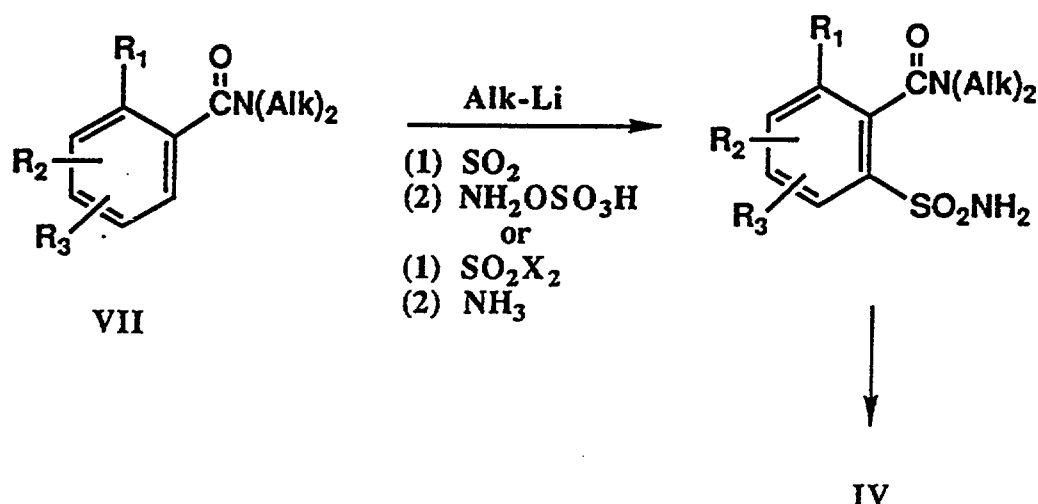
The compounds of formula IV can also be prepared by reaction of a 2-R₁-R₂-R₃-N,N-di-lower-alkylbenzamide of formula VII with one molar equivalent of a lower-alkyl alkali metal, such as lithium, optionally in the presence of a tetra-lower-alkylethylenediamine in an inert organic solvent, for example THF, and reaction of the resulting alkali metal salt either with sulfur dioxide at a temperature in the range from -50°C to -80°C followed by reaction of the resulting alkali metal sulfinat

5 hydroxylamine-O-sulfonic acid in the presence of aqueous base, or with a sulfonyl halide followed by ammonia. When the sulfur dioxide-hydroxylamine-O-sulfonic acid route is used, it is particularly advantageous to neutralize the hydroxylamine-O-sulfonic acid with one equivalent of

10 aqueous sodium hydroxide prior to addition of the alkali metal sulfinat. The resulting 2-R₁-R₂-R₃-6-aminosulfonyl-N,N-di-lower-alkyl-benzamide is thereafter heated in an acid medium to effect cyclization of the latter to produce the di-lower-alkyl ammonium salt of the desired

15 2-R₁-R₂-R₃-saccharin of formula IV, which can be used as such in the subsequent reaction or, if desired, can be hydrolyzed in dilute acid and the free saccharin isolated. It is preferred to carry out the cyclization in refluxing glacial acetic acid. The method is illustrated as follows

20 where R₁, R₂, R₃ and Alk have the meanings given above, and the alkali metal is lithium.



The compounds of formula IV where R_1 is either primary or secondary lower-alkyl, and which are useful as intermediates for the preparation of the compounds of formula I as described above, are prepared by one of the following methods.

The compounds of formula IV where R_1 is primary lower-alkyl are prepared by reacting a 4-methyl- R_2 - R_3 -saccharin (formula IV, R_1 is CH_3) with two molar equivalents of a lower-alkyl lithium in an inert organic solvent, for example THF, and reacting the resulting lithium salt with one molar equivalent of a lower-alkyl halide, both reactions being carried out at a temperature in the range from about $-50^\circ C$ to $-80^\circ C$.

The compounds of formula IV where R_1 is primary lower-alkyl and R_2 and R_3 are other than hydrogen, or R_1 is secondary lower-alkyl and R_2 and R_3 are as defined for formula I comprises reaction of a 2-primary-lower-alkyl- R_2 - R_3 -N,N-di-lower-alkylbenzamide (formula VII, R_1 is primary-lower-alkyl) with one molar equivalent of either a lower-alkyl lithium in the presence of a tetra-lower-alkylethylenediamine or a lithium di-lower-alkylamide, optionally in the presence of a tetra-lower-alkylethylene-

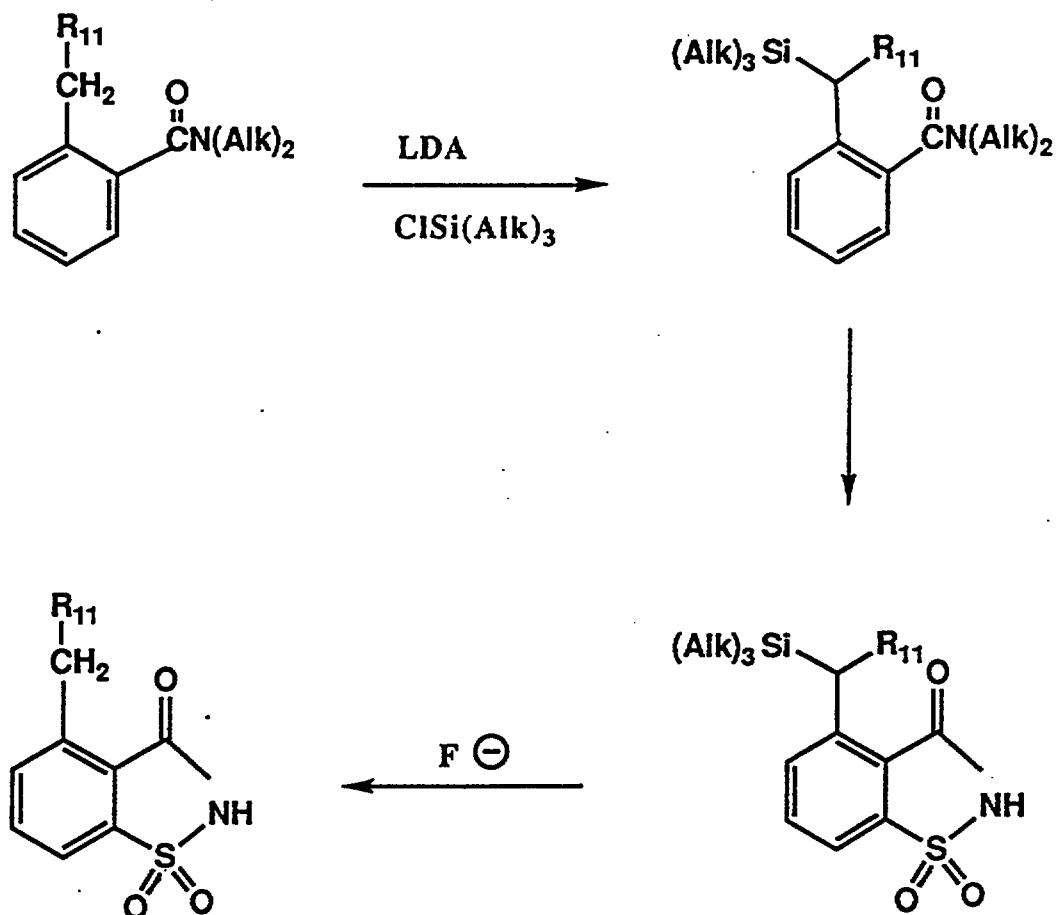


diamine, in an inert organic solvent, for example THF, and reaction of the resulting lithium salt with one molar equivalent of a lower-alkyl halide at a temperature in the range from about -50°C to -80°C . The resulting 2-primary or secondary-lower-alkyl- $\text{R}_2\text{-R}_3\text{-N,N-di-lower-alkyl-}$ benzamide is thereafter converted to the compounds of formula IV, where R_1 is primary or secondary lower-alkyl, by the same sequence of reactions described above, i.e. by reaction of the 2-primary or secondary-lower-alkyl- $\text{R}_2\text{-R}_3\text{-N,N-di-lower-alkylbenzamide}$ with one molar equivalent of a lower-alkyl lithium; reaction of the resulting lithium salt either with sulfur dioxide followed by hydroxylamine-O-sulfonic acid in the presence of base or with a sulfonyl halide followed by ammonia; and cyclization of the product to the desired 4-primary or secondary-lower-alkyl- $\text{R}_2\text{-R}_3\text{-saccharin}$ of formula IV.

When the 2-lower-alkyl group in the 2-lower-alkyl- $\text{R}_2\text{-R}_3\text{-N,N-di-lower-alkylbenzamide}$ starting material is methyl, alkylation affords species where the 2-lower-alkyl group is either straight or branched depending upon whether a straight or branched chain lower-alkyl halide is used for the alkylation. On the other hand, when the 2-lower-alkyl group in the starting material contains more than one carbon atom, alkylation takes place on the carbon atom adjacent the benzene ring and affords products having a sec.-lower-alkyl group at the 2-position.

A particularly useful method for the preparation of compounds IV where R_1 is n-lower-alkyl and R_2 and R_3 are hydrogen involves the protection of the benzylic protons of the starting material VII with a trialkylsilyl group, thereby permitting lithiation at the 6-position and formation of the sulfonamide as described above. This

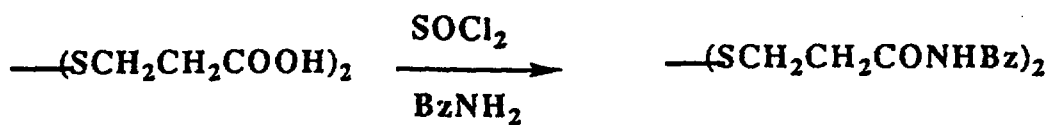
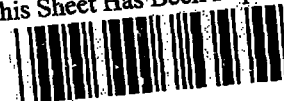
approach is illustrated as follows wherein $R_{11}-CH_2$ is n-lower-alkyl.



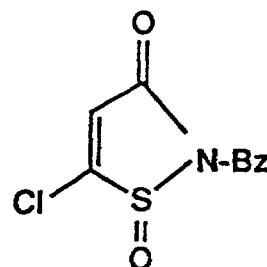
5 A 2-n-lower-alkylbenzamide is silylated by forming
the benzylic anion using an alkyl lithium or, preferably,
a lithium dialkylamide (LDA) in an inert solvent,
preferably THF, and treating with a suitable chlorotri-
alkylsilane, preferably chlorotrimethylsilane. The
saccharin is synthesized as before, and the silyl group is
10 removed by treatment with a source of fluoride anion,
preferably cesium fluoride in DMF or tetra-n-butylammonium
fluoride in an inert solvent.



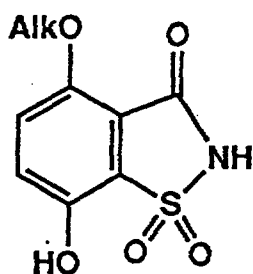
Access to certain of the required saccharin and tetrahydrosaccharin intermediates in some cases requires building up the two rings making up the saccharin nucleus. Thus to prepare saccharins of formula IV where R_1 is lower-alkoxy, R_2 is 7-hydroxy and R_3 is hydrogen, 3,3-dithiobispropionic acid is converted to the bis acid chloride by reaction of the acid with thionyl chloride, and the acid chloride is then reacted with two molar equivalents of benzylamine to produce the bis N-benzylamide. The latter, on reaction with sulfuryl chloride in an organic solvent, such as MDC, EDC or carbon tetrachloride, affords 5-chloro-2-benzyl-2H-isothiazol-3-one, which is oxidized with one molar equivalent of a peracid, such as perbenzoic acid or 3-chloroperbenzoic acid, to 5-chloro-2-benzyl-3(2H)-isothiazolone 1-oxide. The latter, on heating under pressure with a 2-lower-alkoxyfuran in an organic solvent, such as benzene, toluene or xylene, affords a 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzisothiazol-3(2H)-one 1-oxide. The 7-hydroxy group can, if desired, then be reacted with a lower-alkyl halide or a lower-alkyl-(O-lower-alkylene)_p-halide, where halide is bromide, chloride or iodide, to give the corresponding 4,7-di-lower-alkoxy or 4-lower-alkoxy-7-[lower-alkyl-(O-lower-alkylene)_p-O]-2-benzyl-1,2-benzisothiazol-3(2H)-one 1-oxide. Further oxidation of the product with one molar equivalent of a peracid as described above followed by catalytic debenzylation affords the corresponding 4-lower-alkoxy-7-hydroxy-saccharins. The method is illustrated as follows where Bz is benzyl:



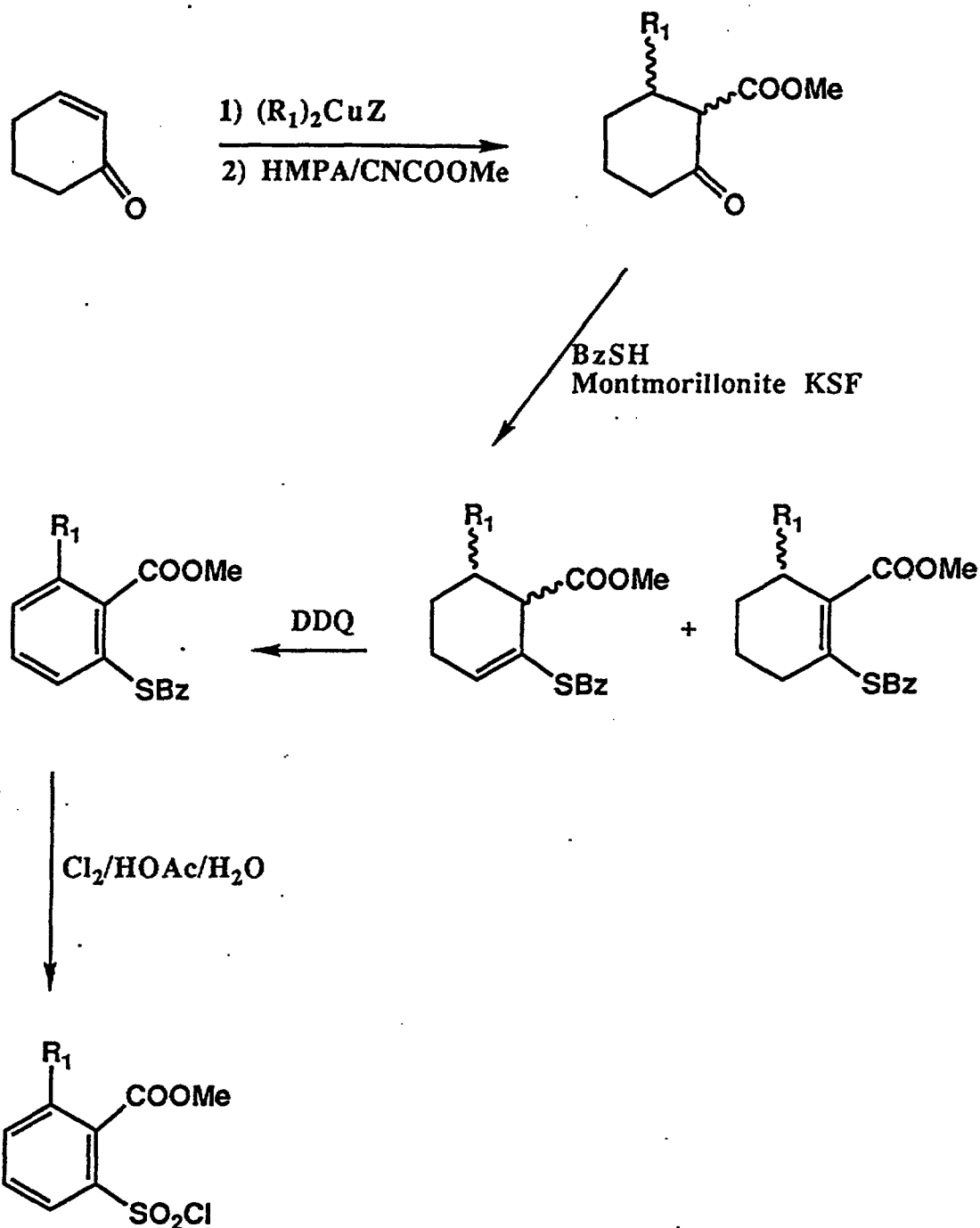
(1) SO_2Cl_2
(2) peracid



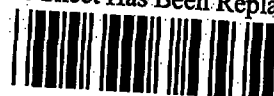
(1) 
(2) peracid
(3) [H]



Compounds of formula I wherein R_1 is lower-alkyl or phenyl and R_2 and R_3 are hydrogen may be synthesized by an alternate route from 2-cyclohexenone:



2-Cyclohexenone is reacted with the cuprate $(R_1)_2CuZ$,
 where Z is lithium or $Mg(X')_2$, where X' is bromide,
 5 chloride or iodide, followed by methyl cyanoformate and



hexamethylphosphoramide (HMPA) according to the method of Winkler *et al.* [Tet. Lett. 1987, 1051 and J. Org. Chem. 54, 4491 (1989)]. The resulting β -ketoester is reacted with benzylmercaptan in the presence of the acidic clay Montmorillonite KSF to produce a mixture of regioisomers of the benzylthioenol ether. The mixture is aromatized by treatment with dichlorodicyanobenzoquinone (DDQ) and oxidized with chlorine gas in aqueous acid to provide the sulfonyl chloride ester, which may then be converted to the corresponding intermediate VI as shown earlier.

The phosphates, phosphonates and phosphinic acids of formula III belong to well known classes of phosphorus compounds. References disclosing such classes of phosphorus compounds and methods for their preparation are numerous, for example, M. Regitz, *Organische Phosphor-Verbindungen I and II*, Hauben-Weyl, *Methoden Der Organischen Chemie*, Vierte Auflage, Erweiterungs-Und-Folge-Bande, Bande E1 and E2, Georg Thieme Verlag Stuttgart-New York, 1982; Robert Engel, Ph.D., *Synthesis of Carbon-Phosphorus Bonds*, CRC Press, Inc., Boca Raton, Florida, 1988; J. Jankowska *et al.*, *Synthesis* (1984), 408; K. Nagasawa, *Chem. and Pharm. Bull.* 7, 397 (1959); and J.G. Moffatt *et al.*, *J. Am. Chem. Soc.* 79, 1194 (1957).

Simple chemical transformations which are conventional and well known to those skilled in the art of chemistry can be used for effecting changes in functional groups in the compounds of the invention. For example, catalytic reduction of nitro groups to produce the corresponding amino substituted compounds, oxidation of sulfides or sulfoxides to prepare the corresponding, respective sulfoxides or sulfones, saponification of esters to produce corresponding carboxylic acids, catalytic debenzylation of benzyl ethers, benzylamines or

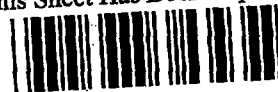


benzyl phosphates to produce the corresponding alcohols, debenzylated amines and debenzylated phosphates, reaction of phenols with an alkylating agent in the presence of base or an alcohol in the presence of a coupling agent to produce ethers, or coupling of alcohols with acids in the presence of a coupling agent to produce the corresponding esters, as desired, can be carried out. It will also be appreciated that these simple chemical transformations are equally applicable for effecting changes in functional groups of the intermediates which are useful in the preparation of the final products of the invention.

The compounds of formula I can also be prepared according to the methods of U.S. patent 5,187,173 entitled "Novel 2-Saccharinylmethyl and 4,5,6,7-Tetrahydro-2-saccharinylmethyl Phosphates, Phosphonates And Phosphinates Useful As Proteolytic Enzyme Inhibitors And Compositions And Method Of Use Thereof" or in the specification of published European application EP-A 0549073.

In standard biological test procedures, representative examples of compounds of the invention have been found to possess human leukocyte elastase (HLE) inhibitory activity, and are thus useful in the treatment of degenerative diseases, such as emphysema, rheumatoid arthritis, pancreatitis, cystic fibrosis, chronic bronchitis, adult respiratory distress syndrome, inflammatory bowel disease, psoriasis, bullous pemphigous and alpha-1-antitrypsin deficiency.

The compounds of the invention having basic functions can be converted to the acid-addition salt form by interaction of the base with an acid. In like manner, the free base can be regenerated from the acid-addition salt form in conventional manner, that is by treating the salts



with cold, weak aqueous bases, for example alkali metal carbonates and alkali metal bicarbonates. The bases thus regenerated can be interacted with the same or a different acid to give back the same or a different acid-addition salt. Thus the bases and all of their acid-addition salts are readily interconvertible.

Likewise compounds of the invention having acid, i.e. carboxylic acid and phosphate, functions can be converted to salt forms thereof by reaction of the acid or phosphate with a base, such as alkali metal or ammonium hydroxides or with organic bases such as alkyl, dialkyl or trialkylamines, and the acids and phosphates can be regenerated from the salts by treatment of the salts with aqueous acids.

The compounds of the invention and their salts have inherent pharmacological activity of a type to be more fully described hereinbelow. This inherent pharmacological activity can be enjoyed in useful form for pharmaceutical purposes by employing the free bases or free acids themselves or the salts formed from pharmaceutically acceptable acids and bases; that is, acids or bases whose anions or cations are innocuous to the animal organism in effective doses of the salts so that beneficial properties inherent in the common structural entity represented by the free bases and free acids are not vitiated by side effects ascribable to the anions or cations.

In utilizing this pharmacological activity of the salt, it is preferred, of course, to use pharmaceutically acceptable salts. Although water insolubility, high toxicity or lack of crystalline character may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the



water-insoluble or toxic salts can be converted to the corresponding pharmaceutically acceptable bases by decomposition of the salts with aqueous base or aqueous acid as explained above, or alternatively they can be converted to any desired pharmaceutically acceptable salt by double decomposition reactions involving the anion or cation, for example by ion-exchange procedures.

Moreover, apart from their usefulness in pharmaceutical applications, the salts are useful as characterizing or identifying derivatives of the free bases or free acids or in isolation or purification procedures. Like all of the salts, such characterization or purification salt derivatives can, if desired, be used to regenerate the pharmaceutically acceptable free bases or free acids by reaction of the salts with aqueous base or aqueous acid, or alternatively they can be converted to a pharmaceutically acceptable salt by, for example, ion-exchange procedures.

The novel feature of the compounds then resides in the concept of the free bases and acids and the cationic and anionic forms of those compounds having basic and/or acid functions and not in any particular acid or base moiety or acid anion or base cation associated with the salt forms of the compounds; rather, the acid or base moieties or the anions or cations which can be associated with the salt forms are in themselves neither novel nor critical and therefore can be any acid anion or base cation capable of salt formation with the bases or acids.

The compounds of the invention can be prepared for pharmaceutical use by incorporating them in unit dosage form as tablets or capsules for oral administration either alone or in combination with suitable adjuvants such as calcium carbonate, starch, lactose, talc, magnesium



5 stearate, gum acacia and the like. Still further, the compounds can be formulated for oral, parenteral or aerosol inhalation administration either in aqueous solutions of water soluble salts of the compounds or in aqueous alcohol, glycol or oil solutions or oil-water emulsions in the same manner as conventional medicinal substances are prepared.

10 The percentages of active component in such compositions may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is variable, depending upon the clinician's judgment using as criteria: the route of administration, the duration of treatment, the size and physical condition of the patient, the potency of the active component and the patient's
15 response thereto. An effective dosage amount of the active component can thus readily be determined by the clinician after a consideration of all criteria and using his best judgment on the patient's behalf.

20 The molecular structures of the compounds of the invention were assigned on the basis of study of their infrared and NMR spectra. The structures were confirmed by the correspondence between calculated and found values for elementary analyses for the elements. All melting points are uncorrected.

25 The invention will now be more particularly described with reference to the following examples which in no way are to be construed as limiting the scope of the invention.

preparation A

diisopropyl 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy-
4-isopropyl-2-saccharinylmethyl phosphate (I)

Diethyl azodicarboxylate (0.96 g, 5.55 mmol) was added to
a mixture of diisopropyl 6-hydroxy-4-isopropyl-
2-saccharinylmethyl phosphate (I) (2.37 g, 5.44 mmol),
triphenylphosphine (1.44 g, 5.5 mmol) and glycerol
dimethylketal (2,2-dimethyl-1,3-dioxolane-4-methanol)
(0.79 g, 5.98 mmol) in 40 ml THF and the mixture was
stirred for 15 hr at RT. Excess solvent was removed under
reduced pressure and the residue was flash chromatographed
(SiO₂; ethyl acetate-MDC) to give a first fraction
yielding 0.49 g (19.7%) of the title compound as a thick
oil, and a second fraction yielding 2.0 g of a mixture
containing about 85% of the title compound.

Preparation B

2-chloromethyl-4-bromosaccharin (VI)

A mixture of 3.22 g (0.012 mol) 4-bromosaccharin (IV)
[Japanese Pat. Disclosure 58/79,034; C.A. 100, 7773w
(1984)], 1.63 g (0.015 mol) potassium t-butoxide, 0.39 g
(0.0012 mol) TBAB and 3.0 ml (0.022 mol) chloro-
methylphenyl sulfide in 100 ml toluene was heated under
reflux under a nitrogen atmosphere for eight hours and
then stirred at ambient temperature for about sixteen
hours. The reaction mixture was then diluted with ethyl
acetate, and the organic layer was washed with dilute
potassium carbonate, water and brine, dried over magnesium
sulfate and taken to dryness in *vacuo*. The residual solid
was recrystallized from toluene-hexane to give 3.86 g
(84%) of 4-bromo-2-phenylthiomethylsaccharin,
mp 174.5-178°C.



To a solution of the latter (3.27 g, 0.0085 mol) in 85 ml MDC was added, dropwise with stirring, 1.02 ml (0.0127 mol) sulfuryl chloride. The mixture was stirred at ambient temperature for an hour and a half, concentrated in vacuo and the residue triturated with hexane and filtered to give 2.61 g of crude product which was recrystallized from toluene-hexane to give 2.24 g (85%) of the desired product, mp 157-159°C.

Preparation C

Diethyl 4-ethoxy-2-saccharinylmethyl phosphate (I)

A solution of 2-chloromethyl-4-ethoxysaccharin (VI) (2.0 g, 7.3 mmol), diethyl phosphate (1.68 g, 10.9 mmol), and triethylamine (1.53 ml, 10.9 mmol) in 25 ml methylene chloride was refluxed for 58 hr. On cooling, the reaction mixture was concentrated and the residue flash chromatographed on silica gel eluting with ethyl acetate-hexanes to give 2.0 g (73%) of the desired product as a colorless oil.

Preparation 1

It is contemplated that there can be prepared various alcohols of the formula $\text{HO}-(\text{CH}_2)_j-[5-(\text{CH}_2)_k-\text{N}=\text{B}-2\text{-furanyl}]$ by treatment of an appropriate aldehyde of formula $\text{HO}-(\text{CH}_2)_j-[5-(\text{CH}_2)_k-\text{CHO}-2\text{-furanyl}]$ with an appropriate compound of formula $\text{HN}=\text{B}$, followed by reduction of the imine thus formed with sodium borohydride.

Preparation 2

It is contemplated that various alcohols of the formula $\text{HO}-(\text{CH}_2)_j-\text{C}\equiv\text{C}-(\text{CH}_2)_k-\text{N}=\text{B}'$ can be prepared by the treatment of an alcohol of the formula $\text{HO}-(\text{CH}_2)_j-\text{C}\equiv\text{C}-\text{H}$



with an excess of sodium amide, followed by treatment of the anion thus formed with a compound of the formula $X(CH_2)_k-N=B'$ where X is halogen.

Preparation 3

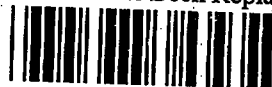
5 6-(2-benzyloxyethoxy)-2-chloromethyl-4-isopropylsaccharin (VI)

Following a procedure analogous to that described in Preparation A hereinbefore and using 2.0 g (5.5 mmol) 6-hydroxy-4-isopropyl-2-phenylthiomethylsaccharin,
 10 0.99 g (5.68 mmol) diethyl azodicarboxylate, 1.46 g (5.56 mmol) triphenylphosphine, 0.87 g (5.71 mmol) of 2-benzyloxyethyl alcohol and 40 ml THF, there was obtained 2.1 g (77%) of 6-(2-benzyloxyethoxy)-4-isopropyl-2-phenylthiomethylsaccharin, mp 98-99°C, which, on reaction with
 15 0.63 g (4.65 mmol) sulfuryl chloride in MDC for 3 hours by a procedure analogous to that described in Preparation B hereinbefore, yielded 1.67 g (93%) of the desired product, mp 101-102°C.

20 Preparation 4

2-Chloromethyl-6-{5-[(dimethylamino)methyl]furan-2-yl-methoxy}-4-isopropylsaccharin (VI)

Following procedures analogous to those described in Preparation 3 but substituting 2-hydroxymethyl-5-(dimethylamino)methylfuran for 2-benzyloxyethyl alcohol there
 25 can be obtained 6-{5-[(dimethylamino)methyl]furan-2-yl-methoxy}-4-isopropyl-2-phenylthiomethylsaccharin which can be converted to the desired product on reaction with sulfuryl chloride.

Preparation 5

2-chloromethyl-6-[4-(diethylamino)-2-butyne-1-oxyl]-4-isopropylsaccharin. (VI)

Following procedures analogous to those described in Preparation 3 but substituting 4-(diethylamino)-2-butyne-1-ol for 2-benzyloxyethyl alcohol there can be obtained 6-[4-(diethylamino)-2-butyne-1-oxyl]-4-isopropyl-2-phenylthiomethylsaccharin which can be converted to the desired product on reaction with sulfuryl chloride.

Example 1

Diisopropyl 6-(2-benzyloxyethoxy)-4-isopropylsaccharinylmethyl phosphate (I)

Cesium carbonate (0.92 g, 2.83 mmol) was added to a solution of diisopropyl phosphate (III) (1.03 g, 5.67 mmol) in methyl alcohol (30 ml) at room temperature. The solution was stirred for 2 hr at room temperature, the methyl alcohol was removed under reduced pressure and the resulting residue was dried under high vacuum for 3 to 4 hours and suspended in DMF (25-30 ml). To this suspension was added 6-(2-benzyloxyethoxy)-2-chloromethyl-4-isopropylsaccharin (VI) (1.6 g, 3.75 mmol) and the mixture was stirred at room temperature for 5 days, poured over ice-water and extracted with ethyl acetate. The extract was washed with water (3 x) and brine and dried. The solvent was removed and the resulting residue was subjected to flash chromatography (30-60% ethyl acetate-hexane) to give 1.12 g of the desired product (52%) as an oil.

Example 2

Diisopropyl 6-(2-hydroxyethoxy)-4-isopropylsaccharinyl-
methyl phosphate (I).

Diisopropyl 6-(2-benzyloxyethoxy)-4-isopropyl-
5 saccharinylmethyl phosphate (I) (1.04 g) in ethyl acetate
(150 ml) was subjected to hydrogenation using 10% Pd-C
(0.42 g) at 40 psig. After 4 hr, additional catalyst
(0.2 g) was added and hydrogenation was continued at
10 50 psig for 4 hr. The mixture was filtered through celite
and concentrated under reduced pressure. The resulting
residue was subjected to flash chromatography (60%:70%
ethyl acetate:hexane) to give 0.63 g of the desired
product (72%) as a thick oil.

Example 3

Diisopropyl 6-{2-[(dimethylamino)methylcarbonyloxy]-
ethoxy}-4-isopropylsaccharinylmethyl phosphate (I)

By coupling diisopropyl 6-(2-hydroxyethoxy)-4-iso-
propylsaccharinylmethyl phosphate (I) with N,N-dimethyl-
20 aminoglycine in the presence of the coupling agent
dicyclohexylcarbodiimide the desired product can be
obtained.

Example 4

25 Diisopropyl 6-{5-[(dimethylamino)methyl]furan-2-yl-
methoxy}-4-isopropylsaccharinylmethyl phosphate (I)

Following a procedure analogous to that described in
Preparation C but reacting 2-chloromethyl-6-{5-[(dimethyl-
amino)methyl]furan-2-ylmethoxy}-4-isopropylsaccharin (VI)
30 and diisopropyl phosphate (III) the desired product can be
obtained.

Example 5

Diisopropyl 6-[4-(diethylamino)-2-butyne-1-oxy]-4-isopropylsaccharinylmethyl phosphate. (I)

Following a procedure analogous to that described in Preparation C but reacting 2-chloromethyl-6-[4-(diethylamino)-2-butyne-1-oxy]-4-isopropylsaccharin (VI) and diisopropyl phosphate (III) the desired product can be obtained.

10 Example 6

Diisopropyl 6-[4-(diethylamino)-2-buten-1-oxy]-4-isopropylsaccharinylmethyl phosphate (I)

By partial hydrogenation of diisopropyl 6-[4-(diethylamino)-2-butyne-1-oxy]-4-isopropylsaccharinylmethyl phosphate (I) over 5% palladium on barium sulfate which has been poisoned with quinoline the desired product can be obtained.

Example 7

20 Diisopropyl 6-(benzyloxycarbonylmethoxy)-4-isopropylsaccharinylmethyl phosphate (I)

To a solution of diisopropyl 6-hydroxy-4-isopropylsaccharinylmethyl phosphate (I) (1.06 g, 2.44 mmol) in 30 ml acetone was added potassium carbonate (0.67 g, 4.85 mmol) followed by benzyl bromoacetate. The mixture was stirred at room temperature for 15 hours, filtered and the filtrate was concentrated. The residue was flash chromatographed (SiO₂; 40% ethyl acetate-hexane) to give (0.87 g, 61%) of the desired product, mp 93-94°C.

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Example 8

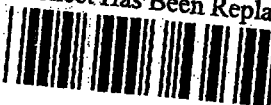
Diisopropyl 6-(hydroxycarbonylmethoxy)-4-isopropyl-
saccharinylmethyl phosphate (I).

Diisopropyl 6-(benzyloxycarbonylmethoxy)-4-isopropyl-
5 saccharinylmethyl phosphate (I) (0.82 g) in 35 ml ethyl
acetate was hydrogenated over palladium-on-carbon at
1 atmosphere for 3-4 hours. The mixture was filtered
through Celite and the filtrate was concentrated under
reduced pressure. The residue was dried under high vacuum
10 to give the desired product (0.61 g, 88%), mp 118-125°C
(shrinks at 114°C and opaque at 118°C).

BIOLOGICAL TEST RESULTS

Measurement of the inhibition constant, K_i , of a
15 HLE-inhibitor complex has been described for truly
reversible inhibition constants usually concerning
competitive inhibitors [Cha, Biochem. Pharmacol., 24,
2177-2185 (1975)]. The compounds of the present
invention, however, do not form truly reversible inhibitor
20 complexes but are consumed by the enzyme to some extent.
Thus, instead of measuring a K_i , a K_i^* is calculated which
is defined as the ratio of the k_{off}/k_{on} , the rate of
reactivation of the enzyme to the rate of inactivation of
the enzyme. The values of k_{off} and k_{on} are measured and
25 K_i^* is then calculated.

The rate of inactivation, k_{on} , of enzymatic activity
was determined for the compounds tested by measuring the
enzyme activity of an aliquot of the respective enzyme as
a function of time after addition of the test compound.
30 By plotting the log of the enzyme activity against time,
an observed rate of inactivation, k_{obs} , is obtained which
can be represented as $k_{obs} = \ln 2/t_{1/2}$ where $t_{1/2}$ is the



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time required for the enzyme activity to drop by 50%. The rate of inactivation is then equal to

$$k_{on} = \frac{k_{obs}}{[I]}$$

where [I] is the concentration of the inhibiting compound.

5 The reactivation constant, k_{off} , is similarly determined, and the inhibition constant, K_i^* , is then calculated as

$$K_i^* = k_{off}/k_{on}$$

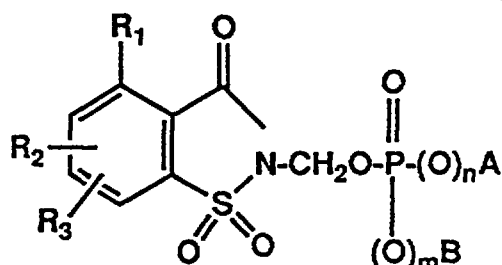
10 The K_i^* values determined for the compounds are as follows:

Compound of Example No.	K_i^*
1	0.068 nM
2	0.040 nM
7	0.19 nM
8	0.14 nM



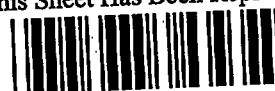
CLAIMS:

1. A compound having the formula



wherein A):

- R₁ is hydrogen, halogen, lower-alkyl, perfluoro-
 5 lower-alkyl, perchloro-lower-alkyl, lower-alkenyl, lower-alkynyl, cyano, amino, lower-alkylamino, di-lower-alkyl-amino, carboxamido, lower-alkoxy, benzyloxy, hydroxy, lower-alkoxycarbonyl or phenyl;
 R₂ is a substituent in any of the available
 10 5-, 6- or 7-positions selected from the group consisting of benzyloxy-lower-alkoxy, -O-(CH₂)_jOC(O)(CH₂)_k-N=B,
 -O-(CH₂)_j-[5-(CH₂)_k-N=B-2-furanyl],
 -O-(CH₂)_j-C≡C-(CH₂)_k-N=B', -O-(CH₂)_j-CH=CH-(CH₂)_k-N=B',
 where -N=B in each instance is amino, lower-alkylamino,
 15 di-lower-alkylamino, 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl or (carboxy-lower-alkyl)amino, N=B' is amino, lower-alkylamino, di-lower-alkylamino, dibenzylamino,
 20 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, or
 -NR'(C₂₋₁₀-alkylene)-N(alkyl)₂ wherein R' is hydrogen or lower-alkyl, and j and k are independently an integer from
 25 1 to 4;

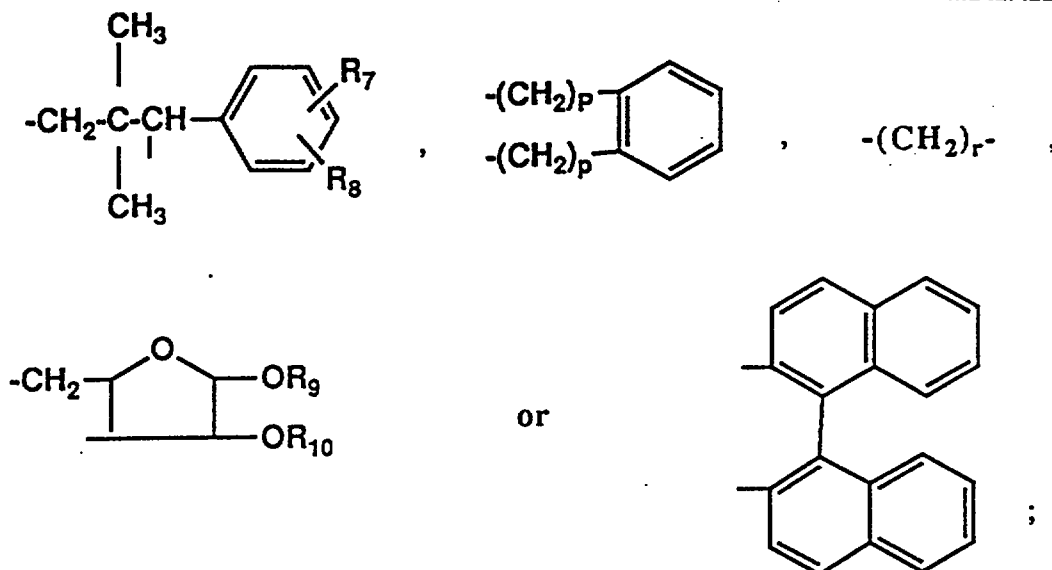


R_3 is hydrogen or a substituent in any of the available 5-, 6- or 7-positions selected from the group consisting of halogen, cyano, nitro, $N=B$, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, polyfluoro-lower-alkyl-sulfonylamino, polychloro-lower-alkylsulfonylamino, 5
 aminosulfonyl, lower-alkyl, polyfluoro-lower-alkyl, polychloro-lower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxy-lower-alkyl, formyl, amino-methyl, polyfluoro-lower-alkylsulfonyl, polychloro-lower-alkyl-sulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxy-poly-lower-alkyleneoxy, cycloalkyloxy, hydroxy-lower-alkoxy, benzyloxy-lower-alkoxy, polyhydroxyalkoxy, or acetal or ketal thereof, polyalkoxyalkoxy, (lower-alkoxy) $_2P(O)O-$, $-SR$, $-SOR$, $-SO_2R$, $-OCOR$,
 10 $-O-(C_{1-10}\text{-alkylene})-COOR$, $-O-(C_{1-10}\text{-alkylene})-COOH$, $-O-(C_{2-10}\text{-alkylene})-N=B$, $-O-(CH_2)_jOC(O)(CH_2)_k-N=B$, $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2\text{-furanyl}]$, $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$, $-O-(CH_2)_j-CH=CH-(CH_2)_k-N=B'$, where R is lower-alkyl, phenyl, benzyl or naphthyl, or
 20 phenyl or naphthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy or halogen, $-N=B$, $N=B'$ and j and k are as defined above for R_2

m and n are independently 0 or 1;

25 when m and n are 1, A and B are independently hydrogen, lower-alkyl, phenyl, lower-alkoxyphenyl or benzyl, or, taken together, represent:





where R₇ and R₈ are independently hydrogen or chlorine, R₉ and R₁₀ each is hydrogen or together represent isopropylidene, p is 0 or 1 and r is 2, 3 or 4;

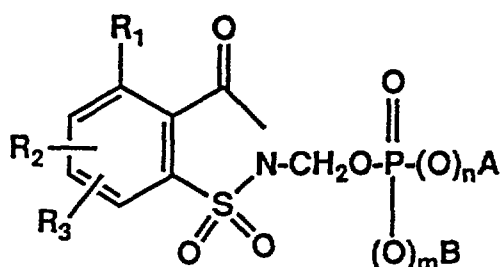
- 5 when m is 1 and n is 0, A and B are independently lower-alkyl, phenyl, benzyl or 2-pyridinyl; and
 when m and n are 0, A and B are independently lower-alkyl, phenyl or lower-alkoxyphenyl; or

B)

- 10 R₁ is hydrogen, isopropyl, sec-butyl, methoxy or ethoxy;
 R₂ is 2-hydroxyethoxy, 2-(benzyloxycarbonylmethoxy), or 2-(hydroxycarbonylmethoxy), or dimethylketal thereof;
 R₃ is hydrogen;
 15 m and n are independently 0 or 1;
 when m and n are 1, A and B are independently hydrogen, methyl, ethyl, isopropyl, butyl, phenyl or benzyl; and
 when m and n are 0, A and B are independently butyl,
 20 phenyl or 4-methoxyphenyl;
 or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.



2. A compound as claimed in claim 1 having the formula



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wherein :

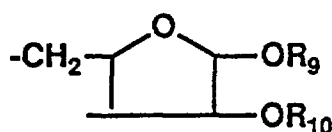
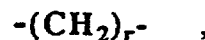
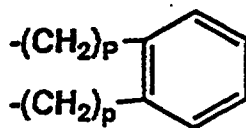
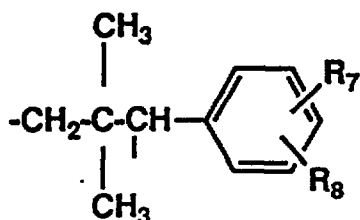
- 5 R_1 is hydrogen, halogen, lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, lower-alkenyl, lower-alkynyl, cyano, amino, lower-alkylamino, di-lower-alkyl-amino, carboxamido, lower-alkoxy, benzyloxy, hydroxy, lower-alkoxycarbonyl or phenyl;
- 10 R_2 is a substituent in any of the available 5-, 6- or 7-positions selected from the group consisting of benzyloxy-lower-alkoxy, $-O-(CH_2)_jOC(O)(CH_2)_k-N=B$, $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2-furanyl]$, $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$; $-O-(CH_2)_j-CH=CH-(CH_2)_k-N=B'$,
- 15 where $-N=B$ in each instance is amino, lower-alkylamino, di-lower-alkylamino, 1-azetidiny, 1-pyrrolidiny, 1-piperidiny, 4-morpholiny, 1-piperaziny, 4-lower-alkyl-1-piperaziny, 4-benzyl-1-piperaziny, 1-imidazolyl or (carboxy-lower-alkyl)amino, $N=B'$ is amino, lower-
- 20 alkylamino, di-lower-alkylamino, dibenzylamino, 1-azetidiny, 1-pyrrolidiny, 1-piperidiny, 4-morpholiny, 1-piperaziny, 4-lower-alkyl-1-piperaziny, 4-benzyl-1-piperaziny, 1-imidazolyl, or $-NR'(C_{2-10}\text{-alkylene})-N(alkyl)_2$ wherein R' is hydrogen or
- 25 lower-alkyl, and j and k are independently an integer from 1 to 4;



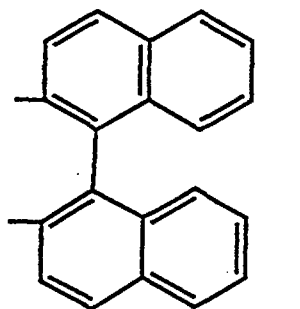


- R_3 is hydrogen or a substituent in any of the available 5-, 6- or 7-positions selected from the group consisting of halogen, cyano, nitro, $N=B$, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, polyfluoro-lower-alkyl-sulfonylamino, polychloro-lower-alkylsulfonylamino, aminosulfonyl, lower-alkyl, polyfluoro-lower-alkyl, polychloro-lower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxy-lower-alkyl, formyl, amino-methyl, polyfluoro-lower-alkylsulfonyl, polychloro-lower-alkyl-sulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxy-poly-lower-alkyleneoxy, cycloalkyloxy, hydroxy-lower-alkoxy, benzyloxy-lower-alkoxy, polyhydroxyalkoxy, or acetal or ketal thereof, polyalkoxyalkoxy, (lower-alkoxy) $_2P(O)O-$, $-SR$, $-SOR$, $-SO_2R$, $-OCOR$, $-O-(C_{1-10}\text{-alkylene})-COOR$, $-O-(C_{1-10}\text{-alkylene})-COOH$, $-O-(C_{2-10}\text{-alkylene})-N=B$, $-O-(CH_2)_jOC(O)(CH_2)_k-N=B$, $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2\text{-furanyl}]$, $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$, $-O-(CH_2)_j-CH=CH-(CH_2)_k-N=B'$, where R is lower-alkyl, phenyl, benzyl or naphthyl, or phenyl or naphthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy or halogen, $-N=B$, $N=B'$ and j and k are as defined above for R_2
- m and n are independently 0 or 1;
- when m and n are 1, A and B are independently hydrogen, lower-alkyl, phenyl, lower-alkoxyphenyl or benzyl, or, taken together, represent:





or



where R_7 and R_8 are independently hydrogen or chlorine, R_9 and R_{10} each is hydrogen or together represent isopropylidene, p is 0 or 1 and r is 2, 3 or 4;

5 when m is 1 and n is 0, A and B are independently lower-alkyl, phenyl, benzyl or 2-pyridinyl; and

when m and n are 0, A and B are independently lower-alkyl, phenyl or lower-alkoxyphenyl; or

10 or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.

3. A compound as claimed in claim 2 wherein:

R_1 is lower-alkyl;

15 R_2 is selected from the group consisting of benzyloxy-lower-alkoxy, $-O-(CH_2)_jOC(O)(CH_2)_k-N=B$, $-O-(CH_2)_j-[5-(CH_2)_k-N=B-2-furanyl]$, $-O-(CH_2)_j-C\equiv C-(CH_2)_k-N=B'$ and $-O-(CH_2)_j-CH=CH-(CH_2)_k-N=B'$; and R_3 is hydrogen.

4. A compound as claimed in claim 3 wherein j and k each is 1.

20 5. A compound as claimed in claim 4 wherein $N=B$ and $N=B'$ each is di-lower-alkylamino, m and n each is 1 and A and B each is lower-alkyl.

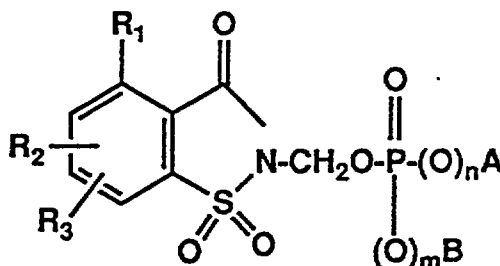




6. A compound as claimed in claim 5 wherein R_2 is 2-benzyloxyethoxy.

7. Diisopropyl 6-(2-benzyloxyethoxy)-4-isopropylsaccharinylmethyl phosphate.

5 8. A compound as claimed in claim 1 having the formula



wherein:

10 R_1 is hydrogen, isopropyl, sec-butyl, methoxy or ethoxy;

R_2 is 2-hydroxyethoxy, 2-(benzyloxycarbonylmethoxy), or 2-(hydroxy-carbonylmethoxy), or dimethyl ketal thereof;

R_3 is hydrogen;

m and n are independently 0 or 1;

15 when m and n are 1, A and B are independently hydrogen, methyl, ethyl, isopropyl, butyl, phenyl or benzyl; and

when m and n are 0, A and B are independently butyl, phenyl or 4-methoxyphenyl;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.





9. A compound as claimed in claim 8 selected from the group consisting of the compounds wherein R_3 in each case is hydrogen and R_1 , R_2 , m , n , A and B are as follows:

R_1	R_2	$m=n=$	$A=B=$
$\text{CH}(\text{CH}_3)_2$	$6\text{-OCH}_2\text{CH}_2\text{OH}$	1	$\text{CH}(\text{CH}_3)_2$
$\text{CH}(\text{CH}_3)_2$	$6\text{-OCH}_2\text{COOBz}$	1	$\text{CH}(\text{CH}_3)_2$
$\text{CH}(\text{CH}_3)_2$	$6\text{-OCH}_2\text{COOH}$	1	$\text{CH}(\text{CH}_3)_2$

10. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims together with a pharmaceutical carrier.

5 11. The use in the manufacture of a medicament for treatment of degenerative diseases of a compound as claimed in any one of the preceding claims.

