NOVEL 2-SACCHARINYLMETHYL HETEROCYCLIC CARBOXYLATES USEFUL AS PROTEOLYTIC ENZYME INHIBITORS AND COMPOSITIONS AND METHOD OF USE THEREOF

This invention relates to novel 2-saccharinyl-methyl heterocyclic carboxylates, 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.

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 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 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 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 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-RZ-methylsaccharins, stated to have strong activity against rice blast, rice sheath blight, rice helminthosporium leaf spot and rice bacterial leaf blight disease, wherein RZ is lower-alkoxy, butoxyethoxy, ethylthioethoxy, di-lower-alkylamino-ethoxy, ethylthio, 2-chloroethoxy, 1-(2-propenyloxy),1-(2-propynyloxy),

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2-saccharinylmethoxy, phenoxy (or phenoxy substituted by chlorine, methyl, nitro or methylthio), phenylthio, chlorophenylthio, benzylthio (or chlorobenzylthio), acetoxy, dichloroacetoxy, benzoyloxy (or benzoyloxy substituted by chlorine or nitro), acetylthio, dichloroacetyloxy, chlorobenzoylthio, methyl or ethylcarbamyloxy, dimethylcarbamyloxy, phenylcarbamyloxy, ethylcarbamylthio, phenylcarbamyl-thio, dimethylthioylcarbamothioyl, ethylthiothioylthio, ethoxycarbonylthio, ethoxythioylthio and ethylthio-carbonylthio.

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-aroylmethylsaccharins useful as photographic elements and film units.

Mulvey et al. U.S. Patent 4,195,023, discloses R_1-2-R_2CO-1,2-benzisothiazol-3-ones, where R_1 is halogen, alkoxy, alkylamino, dialkylamino, alkoxycarbonyl, amino, 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-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 (1980) disclose N-acylsaccharins, where the acyl group is furoyl, thenoyl, benzoyl, cyclopropanoyl, ethylbutyryl and acryloyl, having serine protease inhibitory activity.

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

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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. 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 A_a) with 4-nitrophenylesters and thioesters of N-trifluoroacetylanthranilates, 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, alkoxyarbonyl, 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 mononitro substituted. The compounds are said to have protease enzyme inhibitory activity, especially elastase inhibitory activity, and to be useful 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

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enzymes, cathepsin G, rat mast cell proteases I and II, human skin chymase and chymotrypsin A_a, by N-furoylsaccharin 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 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 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 bound to the nitrogen atom of an imide through a 1,1-alkylene group (Reczek 4,363,865) and N-acylmethylimides which are described as blocked photographic reagents and which have a residue of an organic photographic reagent containing a hetero atom through which it is bound to the blocking group (Vanmeter).

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.

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The present invention relates to 4-R^4-R^5-2-saccharinylmethyl heterocyclic carboxylates and 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylates which have protease enzyme inhibitory activity and which are useful in the treatment of degenerative diseases.

The invention further relates to compositions for the treatment of degenerative diseases which comprise a pharmaceutical carrier and an effective proteolytic enzyme inhibiting amount of a 4-R^4-R^5-2-saccharinylmethyl heterocyclic carboxylate or a 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylate.

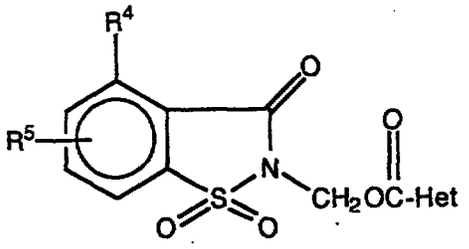
The invention further relates to a method of use of said 2-saccharinylmethyl heterocyclic carboxylates in the treatment of degenerative diseases which comprises administering to a patient in need of such treatment a medicament containing an effective proteolytic enzyme inhibiting amount of a 4-R^4-R^5-2-saccharinylmethyl heterocyclic carboxylate or a 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylate.

The invention further relates to processes for the preparation of said 4-R^4-R^5-2-saccharinylmethyl heterocyclic carboxylates and 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylates which comprises reacting (1) a 2-halomethylsaccharin with a heterocyclic carboxylic acid in the presence of an acid-acceptor, or (2) reacting an alkali metal salt of the appropriate acid with the appropriate halomethyl species.

More specifically this invention relates to 4-R^4-R^5-2-saccharinylmethyl heterocyclic carboxylates having the formula:

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I

wherein:

Het is a 5- or 6-membered monocyclic heterocycle, or a 9- or 10-membered bicyclic heterocycle containing from 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur, or said heterocycles substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, oxo, phenyl, halogen, and -O-(C_2-C_{10} alkylene)-N=B where N=B is dilower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, or 4-lower-alkyl-1-piperazinyl;

R^4 is hydrogen, halogen, lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, lower-alkenyl, lower-alkynyl, cyano, carboxamido, amino, lower-alkylamino, dilower-alkylamino, lower-alkoxy, benzyloxy, lower-alkoxycarbonyl, hydroxy or phenyl; and

R^5 is hydrogen or from one to two substituents in any of the 5-, 6- or 7-positions selected from halogen, cyano, nitro, N=B', lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, polyfluorolower-alkylsulfonylamino, polychloroloweralkylsulfonylamino, aminosulfonyl, lower-alkyl, polyfluoro-lower-alkyl, polychlorolower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxylower-alkyl, methylenedioxy, cycloalkyloxy, formyl, aminomethyl, polyfluoroloweralkylsulfonyl, polychlorolower-alkylsulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxycarbonyl-lower-alkylamino, lower-alkylcarbonylamino, di(lower-alkyl)phosphonoxy, lower-alkoxy-poly-lower-alkyleneoxy, hydroxy-lower-alkoxy,

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polyhydroxy-alkoxy, or acetal or ketal thereof, polyalkoxy-alkoxy, -SR, -SOR, -SO_2R, -OCOR, -O-(C_1-C_{10} alkylene)-COOR, -O-(C_2-C_{10} alkylene)-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 and where N=B' is amino, lower-alkylamino, dilower-alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl or (carboxy-lower-alkyl)amino; or R^5 is a 5- or 6-membered saturated ring fused to the saccharin ring at the 5,6 or 6,7 positions, said ring containing two heteroatoms chosen from the group consisting of nitrogen, oxygen and sulfur or a methylated derivative of said ring;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof, with the proviso that, when R^4 and R^5 are both hydrogen, Het cannot be a dihydropyridine.

Preferred compounds of formula I above are those wherein:

R^4 is hydrogen, halogen, lower-alkyl or lower-alkoxy and R^5 is hydrogen, lower-alkoxy, methylenedioxy, cycloalkyloxy, hydroxylower-alkoxy, polyhydroxy-alkoxy or acetal or ketal thereof, polyalkoxy-alkoxy, -O-(C_1-C_{10} alkylene) -COOR, or -O-(C_2-C_{10} alkylene)-N=B'.

Particularly preferred compounds of formula I above are those wherein:

Het is substituted or unsubstituted pyridinyl, preferably 4-pyridinyl, 3,5-dichloro-4-pyridinyl, 2,4-dimethyl-3-pyridinyl, or 3,5-dichloro-2-[O-(C_2-C_{10} alkylene)-N=B]-4-pyridinyl, in particular 3,5-dichloro-2-[2-(4-morpholinyl)-ethoxy]-4-pyridinyl or 3,5-dichloro-2-[2-dimethylamino)-ethoxy]-4-pyridinyl;:

R^4 is hydrogen or lower-alkyl, preferably hydrogen or isopropyl; and

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R^5 is hydrogen, lower alkoxy, or polyalkoxyalkoxy, preferably hydrogen or methoxy.

Other preferred compounds of formula I above are those wherein:

Het is thienyl unsubstituted or substituted with lower-alkyl, perfluorolower-alkyl, lower-alkoxy and halogen; or isoxazolyl or (lower-alkyl)-substituted isoxazolyl, most preferably thienyl, methylthienyl, chlorothienyl, 3-methyl-5-isoxazolyl or 3,5-dimethyl-4-isoxazolyl;

R^4 is lower alkyl; and

R^5 is lower alkoxy or polyalkoxyalkoxy

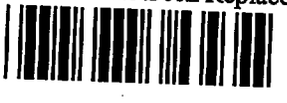
Particularly preferred are compounds wherein Het is thienyl, methylthienyl, chlorothienyl, 3-methyl-5-isoxazolyl or 3,5 dimethyl-4-isoxazolyl, R^4 is isopropyl and R^5 is methoxy.

Other preferred compounds of formula I above are those wherein:

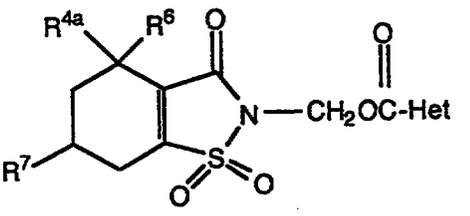
Het is pyrrolyl or pyrrolidinyl unsubstituted or substituted with lower-alkyl, perfluorolower-alkyl, lower-alkoxy, oxo and halogen; and pyrazolyl or imidazolyl unsubstituted or substituted with lower-alkyl, perfluorolower-alkyl, lower-alkoxy, phenyl or halogen.

Further preferred compounds of formula I are those wherein Het is a 9- or 10-membered bicyclic heterocycle, preferably indolyl unsubstituted or substituted with lower-alkyl, perfluorolower-alkyl, lower-alkoxy or halogen.

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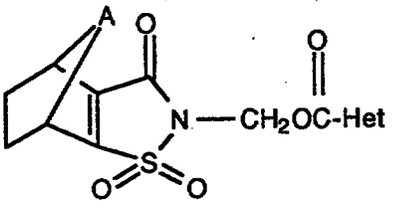
The invention also relates to 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylates of formula VI



VI

wherein R^{4a} is hydrogen, lower-alkyl or phenyl; R^6 is hydrogen or primary lower-alkyl or R^{4a} and R^6 together form a spirocyclopropyl ring; and R^7 is hydrogen or lower-alkoxy, and Het is as defined for formula I.

The tetrahydrosaccharin may contain a 4,7-alkylene bridge and hence the invention also relates to compounds of the formula



wherein A is methylene, ethylene or dimethylmethylene and Het is as defined for formula I.

It should be understood that the compounds having the 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 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,

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including branched chain radicals, of from one to ten 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-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, 1,1,3,3-tetramethylpentyl, 1,1-dimethyloctyl and the like.

As used herein, the term C_1-C_{10} alkylene means divalent, saturated radicals, including branched chain radicals, of from one to ten carbon atoms and having their free valences on the same or different carbon atoms and thus includes methylene, 1,2-ethylene, ethylidene, 1,3-propylene, proylidene 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. The term thus includes $CH_3(OCH_2CH_2)_p$-O-, $CH_3CH_2[OCH_2CH(CH_3)]_p$-O-, where p=2-4, and the like.

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

As used herein, the term polyhydroxy-alkoxy 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-dihydroxy-propoxy, 2,3,4,5-tetrahydroxypentoxy and the like.

As used herein, the term polyalkoxy-alkoxy means monovalent aliphatic alkoxy radicals of from three to five carbon atoms substituted by from two to four methoxy or

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ethoxy groups none of which are attached to the same or the C-1 carbon atom.

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), 1-(1-methyl-2-propenyl), 1-(4-methyl-2-pentenyl), 4,4,6-trimethyl-2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butynyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentynyl), and the like.

As used herein, the term C_2-C_{10} alkylene means divalent, saturated radicals, including branched chain radicals, of from two to ten carbon atoms and having their free valences on different carbon atoms and thus includes 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1-methyl-1,2-ethylene, 1,8-octylene and the like.

As used herein cycloalkyl means C_3 through C_7 saturated monocyclic hydrocarbon residues and thus includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

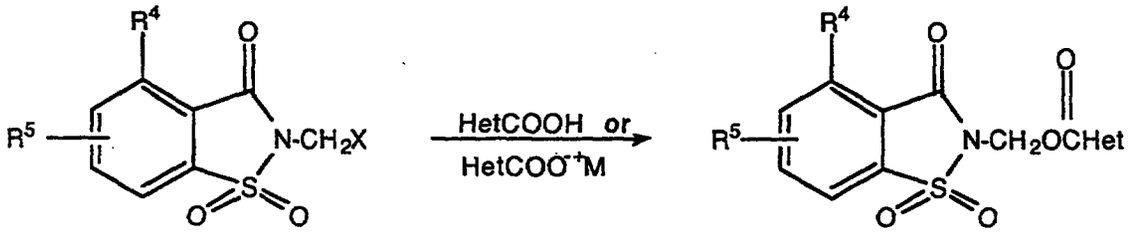
The compounds of the present invention inhibit the activity of serine proteases, specifically human leukocyte elastase and the chymotrypsin-like enzymes, and are thus useful in the treatment of degenerative disease conditions such as emphysema, rheumatoid arthritis, pancreatitis, cystic fibrosis, chronic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

The compounds of formula I and formula VI can be prepared by reaction of a 2-halomethylsaccharin or 2-halomethyl-4,5,6,7-tetrahydrosaccharin with an appropriate heterocyclic carboxylic acid, HetCOOH, in the presence of an acid-acceptor, such as an alkali metal carbonate or a trilower-

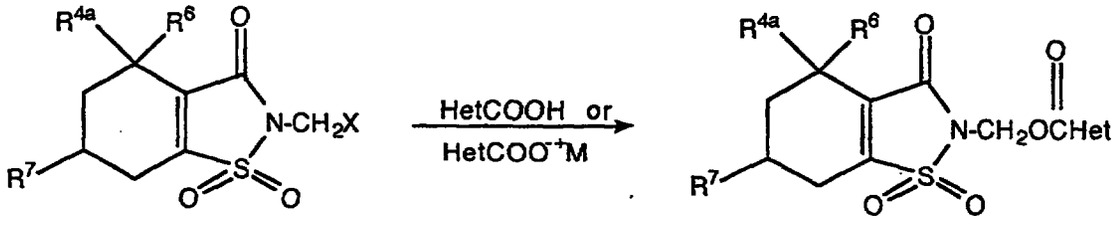
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alkylamine. Alternatively an alkali metal salt, especially a cesium salt, of the heterocyclic carboxylic acid, $HetCOO^{-+}M$, (prepared by reaction of the acid with an alkali metal carbonate) can be reacted with the 2-halomethyl compound. These reactions can also be optionally run in the presence of tetrabutylammonium bromide (TBAB). These reactions can be carried out in an inert organic solvent such as xylene, acetonitrile, methylene dichloride (MDC), N-methyl-2-pyrrolidinone, or dimethylformamide (DMF) at a temperature in the range from ambient up to the boiling point of the solvent used. The reactions are illustrated as follows where X is chloro, bromo or iodo.



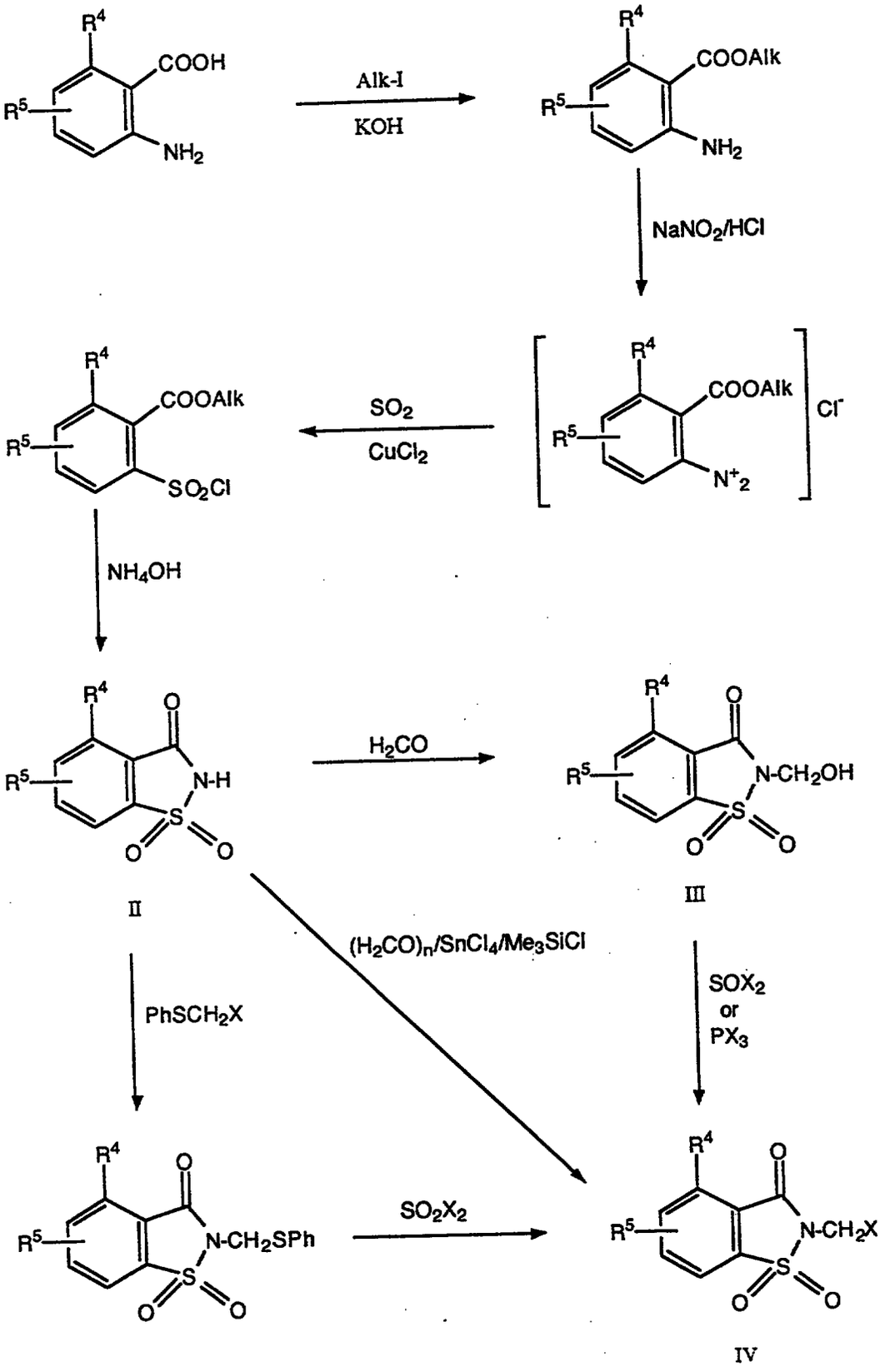
IV I



VIII VI

The 4-R^4-R^5-2-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) as shown below where Alk is lower alkyl.

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In the method described by Saari, an ester of an appropriate anthranilic acid is prepared by conventional means from the substituted 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 II. The latter, on reaction with formaldehyde in a lower-alkanol solvent, affords the 4-R^4-R^5-2-hydroxymethylsaccharins of formula III, which, on reaction with a thionyl halide or a phosphorus trihalide, afford the corresponding 4-R^4-R^5-2-halomethylsaccharin derivatives of formula IV.

The 4-R^4-R^5-2-halomethylsaccharins of formula IV, where R^4, R^5 and X have the meanings given above, can also be prepared by reaction of a corresponding 4-R^4-R^5-2-phenylthiomethylsaccharin with a sulfuryl halide in an inert organic solvent, for example methylene dichloride (MDC), ethylene dichloride (EDC) or carbon tetrachloride, at a temperature from around 0°C to around 30°C. The 4-R^4-R^5-2-phenylthiomethylsaccharins are in turn prepared by reaction of a 4-R^4-R^5-saccharin of formula II with a halomethyl phenyl 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 out by reaction of the halomethyl phenyl sulfide with either the thallium salt of the saccharin derivative of formula II (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 derivatives (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 II per se in the presence of a tetralower-alkyl ammonium halide; or with the saccharin derivative of formula II per se in the presence of a tetralower-alkyl

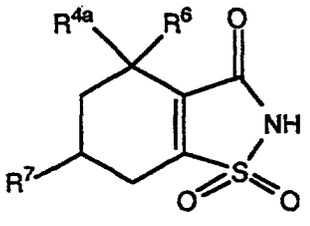
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ammonium halide and an alkali metal lower-alkoxide, such as potassium t-butoxide.

The saccharins of formula II may also be converted to the chloromethyl saccharins of formula IV, 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 chlorotrimethylsilane in the presence of a Lewis acid, preferably a catalytic amount of stannic chloride in an inert solvent, preferably 1,2-dichloroethane (ethylene dichloride, EDC).

It will be appreciated that all of the conversions of the saccharins II to the 2-chloromethyl saccharins IV are equally applicable to the conversion of tetrahydrosaccharins VII to 2-chloromethyl tetrahydrosaccharins VIII.



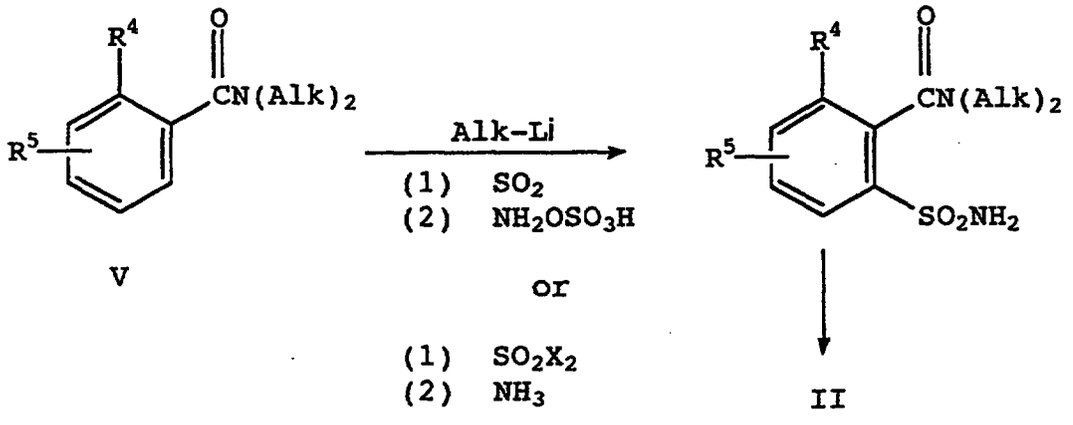
VII

The compounds of formula II can also be prepared by reaction of a 2-R^4-R^5-N,N-di-lower-alkylbenzamide of formula V with one molar equivalent of a lower-alkyl alkali metal, such as a lower-alkyl lithium, optionally in the presence of a tetralower-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 sulfinate with hydroxylamine-O-sulfonic acid in the presence of base, or with a sulfuryl 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 a base, preferably

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with one equivalent of sodium hydroxide, prior to addition of the alkali metal sulfinate. The resulting 2-R^4-R^5-6-aminosulfonyl-N,N-dilower-alkylbenzamide is thereafter heated in an acid medium to effect cyclization of the latter to produce the dilower-alkyl ammonium salt of the desired 4-R^4-R^5-saccharin of formula II, 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 where R^4, R^5 and Alk have the meanings given above.



V II

The compounds of formula II where R^4 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 II where R^4 is primary lower-alkyl are prepared by reacting a 4-methyl-R^5-saccharin (formula II, R^4 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°C to -80°C.

The compounds of formula II where R^4 is primary lower-alkyl and R^5 is other than hydrogen, or R^4 is secondary

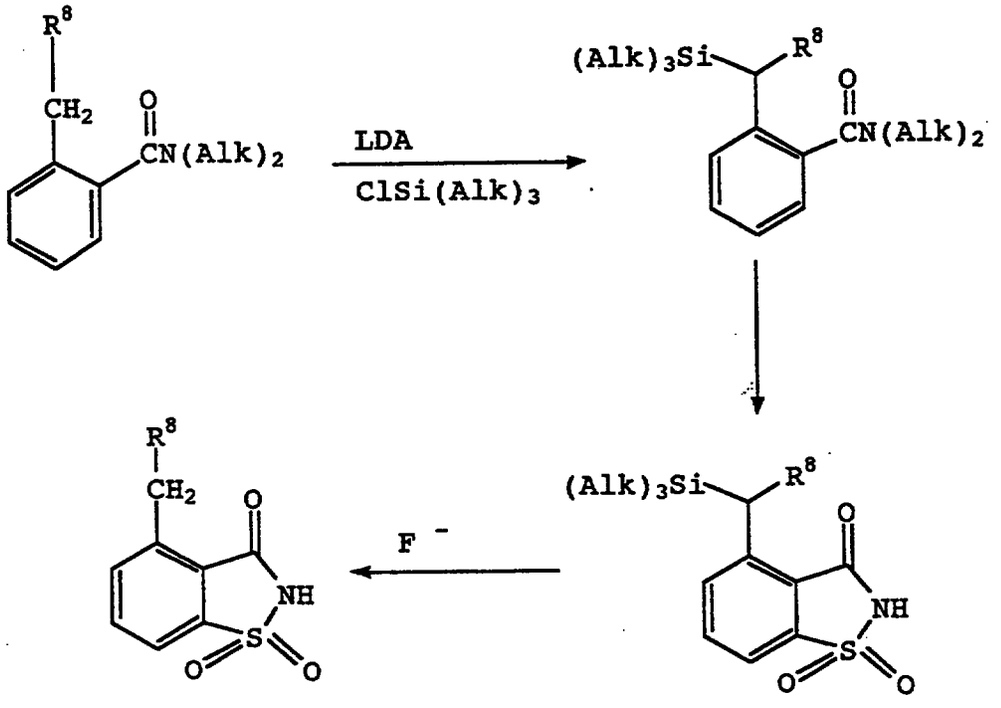
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lower-alkyl and R^5 is as defined for formula I comprises reaction of a 2-primary-lower-alkyl-R^5-N,N-di-lower-alkyl-benzamide (formula V, R^4 is primary-lower-alkyl) with one molar equivalent of a lower-alkyl lithium or a lithium dilower-alkylamide, optionally in the presence of a tetralower-alkyl-ethylenediamine, 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-R^5-N,N-di-lower-alkyl-benzamide is thereafter converted to the compounds of formula II, where R^4 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-R^5-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 sulfuryl halide followed by ammonia; and cyclization of the product to the desired 4-primary or secondary-lower-alkyl-R^5-saccharin of formula II. When the 2-lower-alkyl group in the 2-lower-alkyl-R^5-N,N-di-lower-alkyl-benzamide 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 II where R^4 is n-lower-alkyl and R^5 is hydrogen involves the protection of the benzylic protons of the starting material V with a trialkylsilyl group, thereby permitting lithiation at the 6-position and formation of the sulfonamide as described above.

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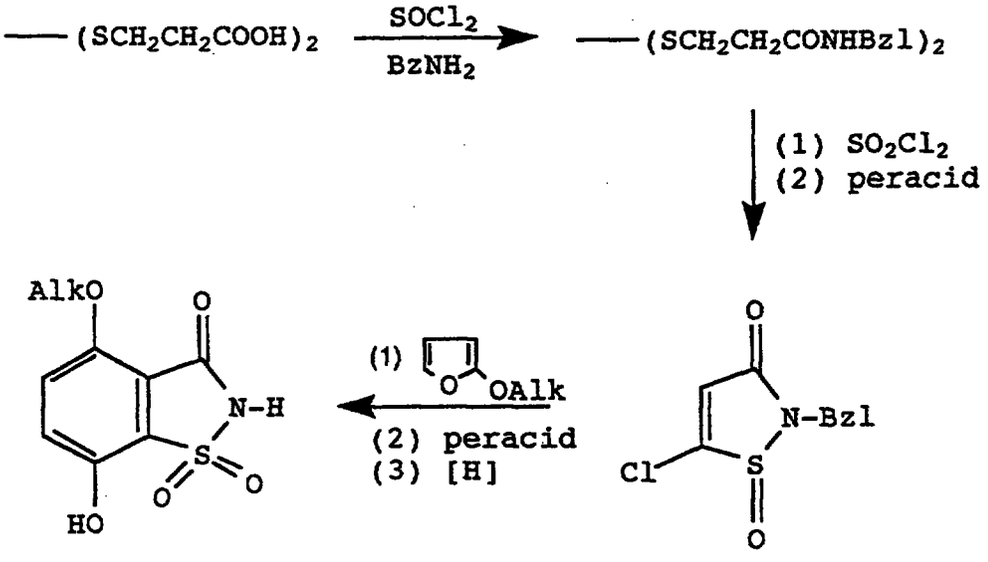




A 2-n-lower-alkylbenzamide wherein R^8 is lower-alkyl is silylated by forming the benzylic anion using an alkyllithium or, preferably, a lithium dialkylamide (i.e. LDA) in an inert solvent, preferably THF, and treating with a suitable chlorotrialkylsilane, preferably chlorotrimethylsilane. The saccharin is synthesized as before, and the silyl group is 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 intermediates in some cases requires building up the two rings making up the saccharin nucleus. Thus to prepare saccharins where R^4 is lower-alkoxy and R^5 is 7-hydroxy, or tetrahydrosaccharins where R^7 is lower-alkoxy, the following synthesis may be used:

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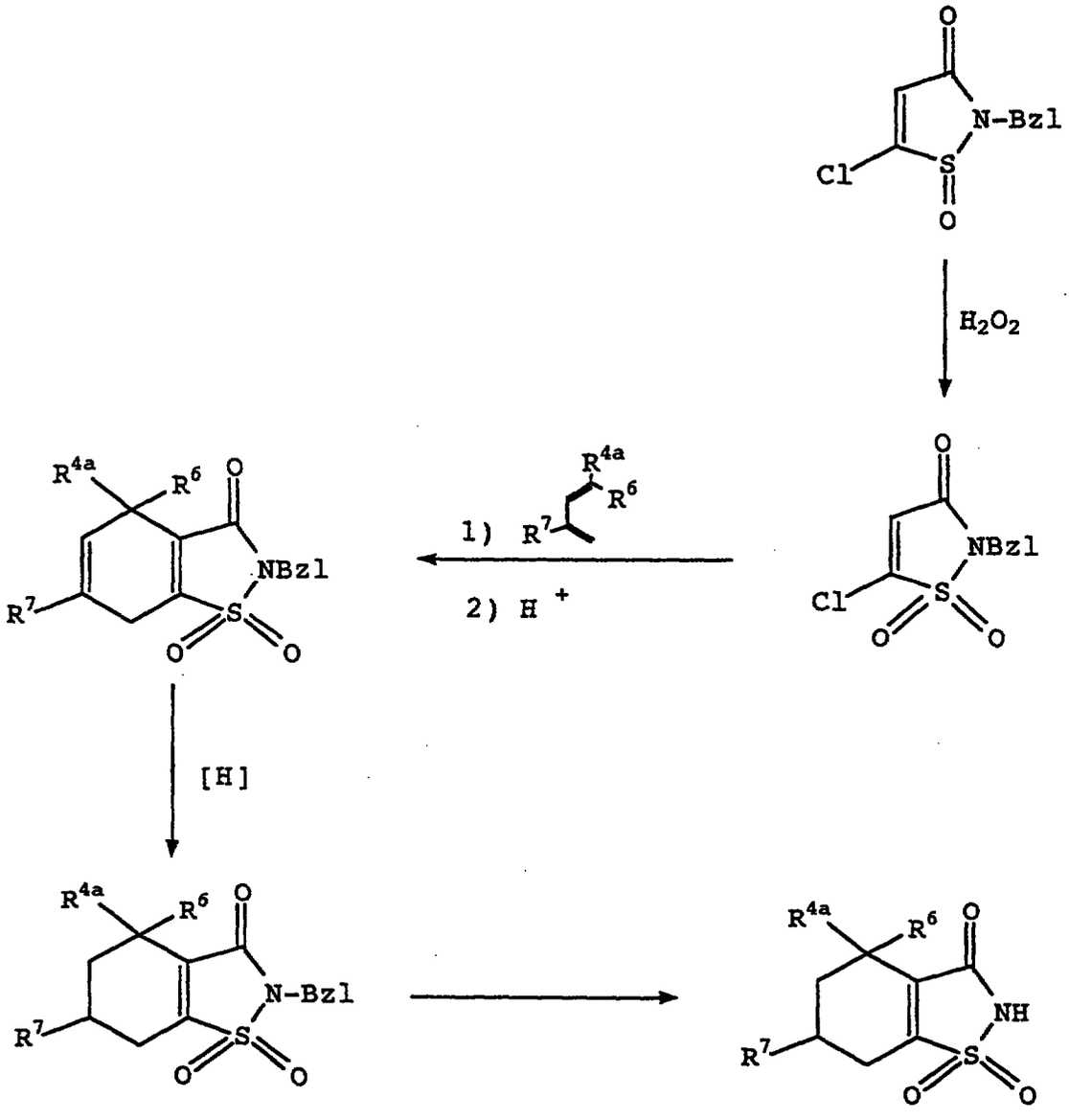
3,3-Dithiobispropionic acid is converted to the bis acid chloride by reaction of the acid with thionyl chloride, and the acid chloride is then reacted with two molar equivalents of benzylamine to produce the bis N-benzylamide. The latter, on reaction with sulfuryl chloride in an organic solvent, such 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-chloro-perbenzoic acid, to 5-chloro-2-benzyl-2H-isothiazol-3-one-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-benzsothiazol-2H-3-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 the halide is a chloride, bromide 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-2H-3-one-1-oxide. Further oxidation of the product with one molar equivalent of a peracid as described above followed by catalytic

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debenzylation by transfer hydrogenation affords the corresponding 4-lower-alkoxy-7-hydroxysaccharins.

When a tetrahydrosaccharin is desired, the following modification is used:

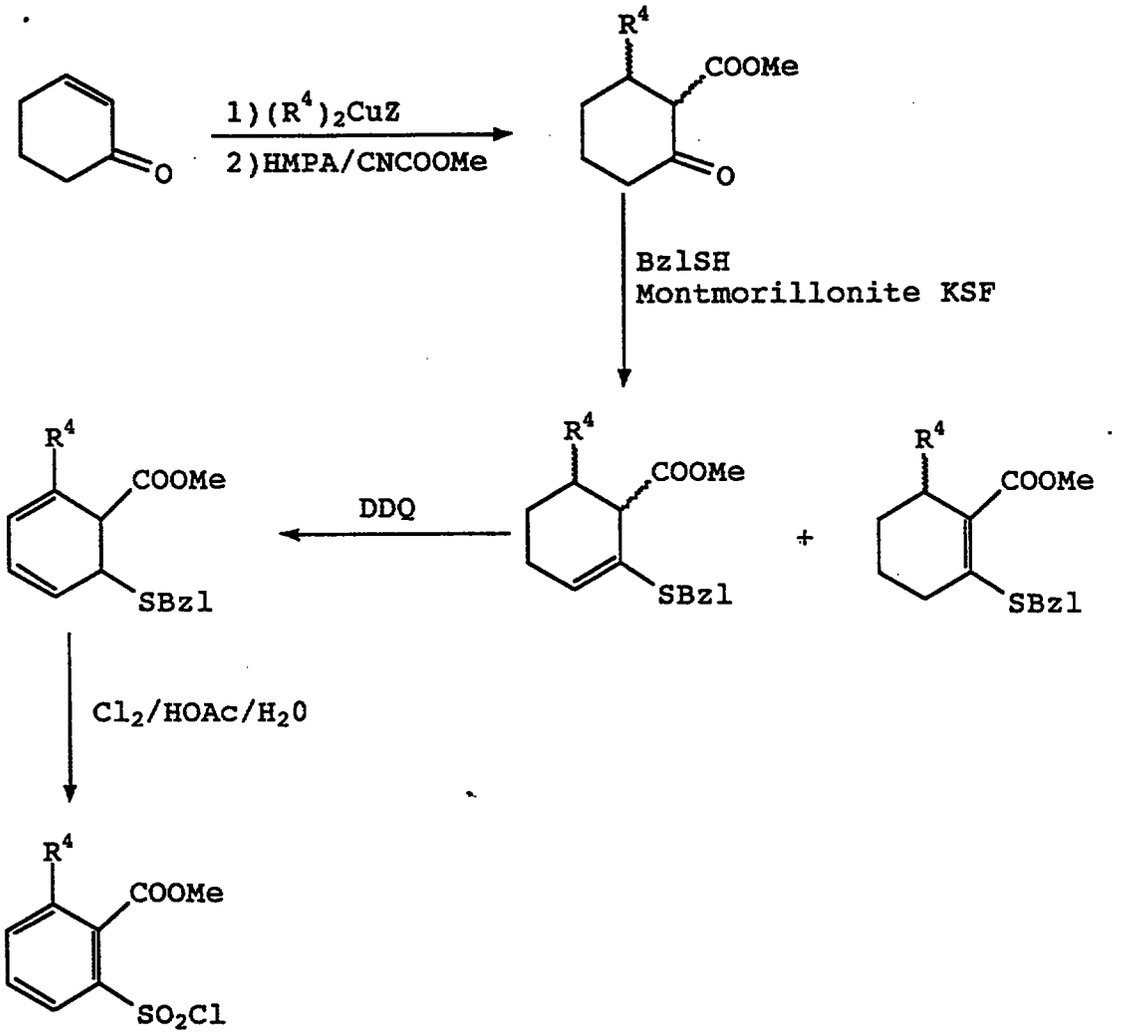


The 5-chloro-2-benzyl-2H-isothiazole-3-one-1-oxide may be oxidized with a suitable oxidizing agent, preferably hydrogen peroxide in acetic acid, to the 1,1-dioxide

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which is then reacted under typical Diels Alder conditions with the appropriate diene and reduced to provide the 2-benzyl tetrahydrosaccharin which is hydrogenolyzed as before to the tetrahydrosaccharin.

Compounds of formula II wherein R^4 is lower-alkyl or phenyl and R_5 is hydrogen may be synthesized by an alternate route from 2-cyclohexenone:



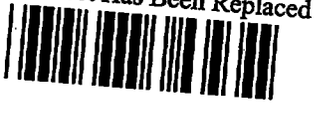
2-Cyclohexenone is reacted with the appropriate cuprate, $(R^4)_2CuZ$ wherein Z is lithium or $Mg(X')_2$ and X' is a chloride, bromide or iodide, followed by methyl cyanoformate and hexamethylphosphoramide (HMPA) according to the method of Winkler et al. [Tet. Lett. 1987, 1051

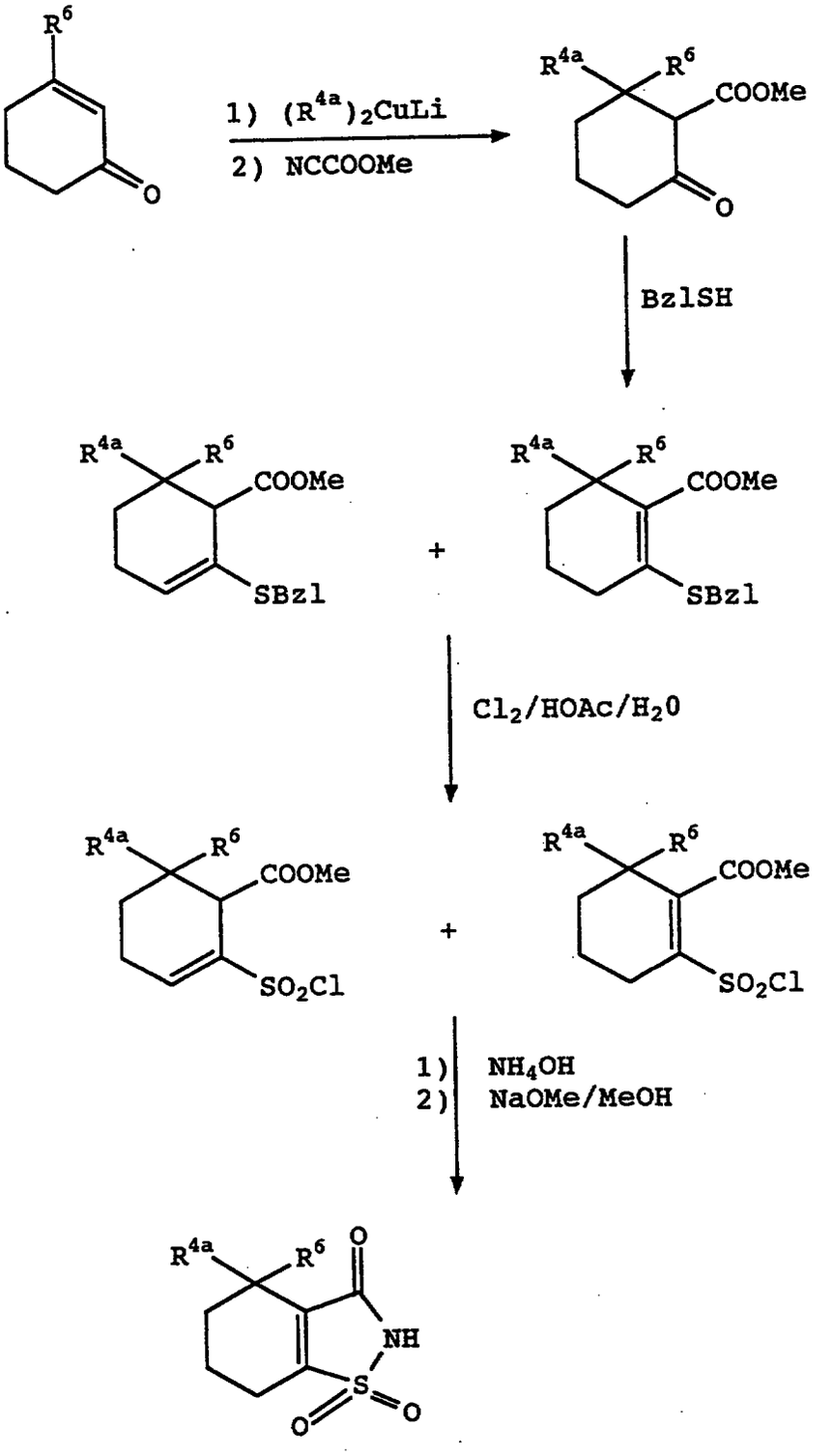
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and J. Org. Chem. 54, 4491 (1989)]. The resulting ß-ketoester is reacted with benzylmercaptan in the presence of the acidic clay Montmorillonite KSF to produce a mixture of regioisomers of the benzylthioenol ether. The mixture is aromatized by treatment with dichlorodicyano-benzoquinone (DDQ) and oxidized with chlorine gas in aqueous acid to provide the sulfonyl chloride ester, which may then be converted to the intermediate II as shown earlier.

The 4,5,6,7-tetrahydrosaccharins which are the starting materials for the compounds of formula VI wherein R^7 is hydrogen are synthesized by a route similar to the preceding one:

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A 3-alkyl-2-cyclohexenone is reacted with the appropriate alkyl lithium cuprate in an ethereal solvent, preferably diethyl ether, at -50 to +20°, preferably about 0°, and the resulting adduct is treated in situ with methyl cyanoformate and hexamethylphosphoramide. The 6,6-dialkyl-2-oxocyclohexane carboxylate so produced is reacted with benzyl mercaptan as described above and the mixture of 2-(benzylthio)cyclohexane carboxylates is oxidatively chlorinated as described above to provide a mixture of chlorosulfonyl esters that are treated with ammonia as before to yield the desired 4,4-dialkyl-4,5,6,7-tetrahydrosaccharins.

The heterocyclic carboxylic acids, HetCOOH used to prepare the final products of formula I are either commercially available or are members of a known class and can be prepared by well-known, conventional synthetic methods.

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, acylation of amino-substituted species to prepare the corresponding amides, oxidation of sulfides or sulfoxides to prepare the corresponding, respective sulfoxides or sulfones, saponification of esters to produce the corresponding carboxylic acids, catalytic debenzylation of phenolic ethers or of benzylamines to produce the corresponding phenols or debenzylated amines or reaction of phenols with an alkylating agent in the presence of base to produce ethers as desired can be carried out.

In standard biological test procedures, representative examples of the 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

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arthritis, pancreatitis, cystic fibrosis, chronic bronchitis, adult respiratory distress syndrome, inflammatory bowel disease, psoriasis, bullous pemphigoid 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 the compounds of the invention having acid, i.e. carboxylic acid, functions can be converted to salt forms thereof by reaction of the acid with a base, such as alkali metal or ammonium hydroxides or with organic bases such as alkyl, dialkyl or trialkylamines, and the acids can be regenerated from the salts by treatment of the salts with aqueous acids.

The pharmacological activity of the compounds of the invention 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 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

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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 2-saccharinylmethyl heterocyclic carboxylates not in any particular acid or base moiety or acid anion or base cation associated with the salt forms of the compounds.

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 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.

The percentages of active component in such compositions may be varied so that a suitable dosage is

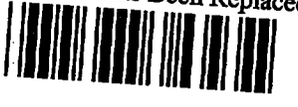
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obtained. The dosage administered to a particular patient is variable, depending upon the clinician's judgment using as criteria: the route of administration, the duration of treatment, the size and physical condition of the patient, the potency of the active component and the patient's 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.

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 or by analysis of the high-resolution mass spectra.

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The invention will be described with reference to the following examples without however limiting it thereto. All melting points are in °C and are uncorrected.

Preparation of Starting Materials

Preparation 1

Powdered potassium hydroxide (7.4 g, 0.132 mol) was admixed with dimethylsulfoxide (DMSO) (100 ml), and the mixture was stirred for 5 minutes. 6-Methylanthranilic acid (10.0 g, 0.066 mol) was then added to the mixture and iodomethane (4.52 ml, 0.073 mol) added dropwise. The reaction mixture was stirred for 30 minutes at room temperature, then diluted with 250 ml ether, washed with water (3 x 100 ml), dried over magnesium sulfate and concentrated. The crude product was filtered through a pad of flash grade (32-63) silica gel and eluted with 1:9 ether:hexane to afford 4.23 g (39%) of methyl 6-methylanthranilate as an oil.

The methyl 6-methylanthranilate so prepared (4.23 g, 0.026 mol) was dissolved in 25 ml acetic acid and the solution cooled to 0°C. Concentrated hydrochloric acid (45 ml) was added to produce a tan slurry. A solution of 1.89 g (0.027 mol) sodium nitrite in 8 ml water was added dropwise with stirring, the resulting orange solution was stirred at 0°C for 1 hour and then added in 6 portions to a mixture of 2.18 g (0.013 mol) cupric chloride dihydrate and sulfur dioxide (6.3 g) in 33 ml acetic acid and 6 ml water at 0°C. The dark green solution was stirred at room temperature overnight, poured into 300 ml ice-water, and the solid which separated was collected and dried by suction to provide 1.11 g methyl 2-chlorosulfonyl-6-methylbenzoate which was immediately added to 100 ml ice cold ammonium hydroxide and stirred at room temperature overnight. The solution was acidified to pH 1 with concentrated hydrochloric acid, and the resulting precipitate was collected and air-dried to provide 729 mg (12%) of 4-methylsaccharin, mp 224-226°C.

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A mixture of 1.0 g (0.005 mol) 4-methylsaccharin, 0.33 g (0.001 mol) TBAB and 1.2 g (0.0075 mol) chloromethyl phenyl sulfide in 25 ml toluene was heated under reflux for about sixteen hours and then cooled, diluted with ethyl acetate and the solution washed with aqueous bicarbonate and water. The organic layer was dried and taken to dryness to give 0.74 g of 2-phenylthiomethyl-4-methylsaccharin.

The latter (0.74 g, 0.002 mol) was dissolved in 25 ml MDC and the solution treated dropwise over a period of about two hours with stirring with a solution of 0.47 g (0.003 mol) sulfuryl chloride in MDC and the reaction mixture taken to dryness. The yellow residual solid was triturated with hexane and filtered and dried to give 0.46 g of 2-chloro-methyl-4-methylsaccharin as a pale yellow solid.

Preparation 2

Using the procedure described above in Preparation 1, 5.0 g (0.029 mol) 6-chloroanthranilic acid and 2.75 ml (0.044 mol) iodomethane were reacted in the presence of 4.08 g (0.073 mol) powdered potassium hydroxide to give 4.22 g (78%) of methyl 6-chloroanthranilate as an oil.

4-Chlorosaccharin was prepared by the same method as used for the preparation of 4-methylsaccharin using 4.22 g (0.023 mol) methyl 6-chloroanthranilate in 22 ml acetic acid and 40 ml concentrated hydrochloric acid and 1.68 g (0.024 mol) sodium nitrite in 7 ml water to prepare the diazonium salt which was added to 1.93 g (0.011 mol) cupric chloride dihydrate and 6.5 g sulfur dioxide in 30 ml acetic acid and 5 ml water. The resulting methyl 2-chloro-sulfonyl-6-chlorobenzoate was treated with 150 ml ammonium hydroxide as described above to afford 3.07 g (62%) of 4-chlorosaccharin as a pale yellow solid, mp 245-246°C.

2-Hydroxymethyl-4-chlorosaccharin was prepared by heating a solution of 1.00 g (0.0046 mol) 4-chlorosaccharin and 3.22 ml aqueous 37% formalin in ethanol. All attempts to crystallize the viscous oily product resulted in decomposition

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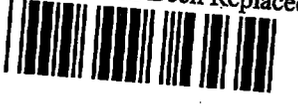
to the starting material, and the product was thus used in the next step without characterization.

The crude 2-hydroxymethyl-4-chlorosaccharin so prepared (609 mg, 0.0025 mol) was admixed with 5 ml diethyl ether, and 3 ml thionyl chloride was added. The resulting mixture was heated to effect complete solution, stirred at room temperature overnight, diluted with 20 ml ether and filtered through a pad of celite topped with sand and eluted with ether. Removal of the solvent afforded 430 mg crude chloromethyl derivative. A portion (225 mg) was removed for further reactions. The remainder (205 mg) was flash chromatographed on silica gel and eluted with 40% ether/-pentane to provide 137 mg of 2-chloromethyl-4-chloro-saccharin, mp 135-136°C.

Preparation 3A

To a suspension of 6.0 g (0.03 mol) cuprous iodide in 100 ml THF was added 25 ml dimethyl sulfide, and the resulting yellow solution was cooled to -78°C and treated dropwise with a solution of 23 ml (0.06 mol) 3.0 M solution of phenyl magnesium bromide in diethylether. The resulting pale yellow-orange solution was stirred at -78°C under nitrogen for one hour and then treated with 3.02 g (0.03 mol) 2-cyclohexenone in 10 ml THF. The resulting mixture was allowed to warm to 0°C over a two hour period, recooled to -78°C, treated with 15 ml hexamethylphosphoramide, stirred for thirty minutes, treated with 8.0 g (0.09 mol) methyl cyanoformate and allowed to warm to ambient temperature overnight. The reaction mixture was poured into 100 ml 2N hydrochloric acid, and the organic phase was separated and the aqueous phase back-extracted with MDC. The combined organic extracts were taken to dryness in vacuo and the residue triturated with saturated ammonium chloride, then with water, then with brine and taken to dryness once again to give 3.2 g of methyl 2-phenylcyclohexan-6-one carboxylate as an oil.

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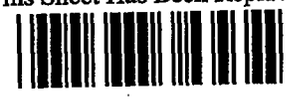


The latter (3.0 g, 0.013 mol), 4.8 g (0.039 mol) benzyl mercaptan and 1.0 g Amberlyst®-15 resin (Rohm and Haas) in chloroform was heated under reflux for twenty hours, the mixture treated with an additional 1.5 g of the resin and heated for an additional four hours. The mixture was then cooled to ambient temperature, filtered, the filtrate taken to dryness in vacuo, the residue triturated with hexane and the solid collected by filtration to give 0.85 g (19%) of a mixture of methyl 2-benzylthio-6-phenylcyclohex-2-ene carboxylate and methyl 2-benzylthio-6-phenylcyclohex-1-ene carboxylate, 0.6 g (0.0018 mol) of which was heated with 2.0 g 2,3-dichloro-5,6-dicyanobenzoquinone in 25 ml toluene with stirring under nitrogen for twenty-four hours. The mixture was filtered through a pad of silica gel, eluting with 2:1 MDC:hexane, and the eluate was taken to dryness to give 0.3 g (67%) of methyl 2-benzylthio-6-phenylbenzoate.

The latter (0.52 g, 0.0016 mol) dissolved in 10 ml MDC was diluted with 20 ml acetic acid and 5 ml water, the mixture cooled to -10°C, and chlorine gas was bubbled through the mixture until the exothermic reaction subsided. The mixture was then stirred for ten minutes and taken to dryness in vacuo to give 0.41 g (85%) of methyl 2-chlorosulfonyl-6-phenylbenzoate which was dissolved in 10 ml THF and added to 25 ml of a solution of concentrated ammonium hydroxide while cooling in an ice/acetone bath. The reaction mixture was extracted with MDC, the organic phase discarded, and the aqueous layer acidified to pH 1 with concentrated hydrochloric acid and extracted with MDC. The organic extracts, on washing with brine, drying and evaporation to dryness, afforded 0.33 g (97%) of 4-phenylsaccharin.

Following a procedure similar to that described in Preparation 1, the latter (0.33 g, 0.0012 mol) was reacted with 0.3 g (0.0019 mol) chloromethyl phenyl sulfide in 15 ml toluene in the presence of 0.08 g (0.0025 mol) TBAB and the product, 2-phenylthiomethyl-4-phenylsaccharin

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(0.48 g, 100%), treated with sulfuryl chloride in MDC to give 0.36 g (95%) of 2-chloromethyl-4-phenylsaccharin.

Preparation 3B

To a suspension of anhydrous CuCN (2.16 g, 0.025 mol) in anhydrous ether (100 ml) at -78°C was added t-butyllithium (29.0 ml 1.7 M solution in pentane, 0.05 mol). After being stirred at -78°C for 1 hr and at -45°C for 30 minutes, the reaction mixture was recooled to -78°C. A solution of cyclohexenone (2.4 g, 0.025 mol) in ether (25 ml) was added and stirring continued for 15 minutes at -78°C and at -45°C for 30 minutes. The resulting mixture was recooled to -78°C, and HMPA (10 ml) in ether (25 ml) was added. After 5 min, methyl cyanoformate (2.55 g, 0.03 mol) in ether (25 ml) was added and the reaction warmed to 0°C over a 2 hr period. The resulting mixture was quenched with 2N HCl (100 ml), the layers separated, and the organic phase washed with saturated NH_4Cl solution (3 x 50 ml), water (2 x 50 ml), brine (1 x 50 ml) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification by Kugelrohr distillation (bath temperature 100-115°C at 0.6 mm) afforded 4.7 g (88%) of methyl-2-(1,1-dimethylethyl)cyclohexan-6-one carboxylate.

The cyclohexanone (4.6 g, 0.022 mol) was mixed with benzylmercaptan (2.95 g, 0.024 mol) and the acidic clay montmorillonite, KSF (7.5 g) in anhydrous toluene (7.5 ml). The mixture was refluxed under nitrogen with azeotropic removal of water for 6 hr, cooled to room temperature and let stand overnight. The solids were filtered off and washed with ether. The combined filtrate was washed with 10% Na_2CO_3, water, brine and dried. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (10% ether in hexanes) gave 4.4 g (66%) of a mixture of methyl 2-benzylthio-6-(1,1-dimethylethyl)cyclohex-2-ene carboxylate and 2-benzylthio-6-(1,1-dimethylethyl)cyclohex-1-ene carboxylate, which was stirred with DDQ (17.5 g,

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0.077 mol) in toluene (50 ml) for 16 hr. The red reaction mixture was filtered through a 15 cm pad of silica gel, eluting with 6:3:1 hexanes:MDC:ether (1000 ml). The eluates were washed with 10% NaOH solution, water, brine and dried. Removal of the solvent in vacuo and purification by chromatography on silica gel (5% ether in hexanes) gave 1.6 g (40%) of methyl 2-benzylthio-6-(1,1-dimethyl)benzoate.

The benzylthiobenzoate (1.3 g, 0.004 mol) dissolved in MDC (5 ml) was diluted with acetic acid (25 ml) and water (2 ml), the mixture cooled to -10°C, and chlorine gas was bubbled until the exothermic reaction subsided. The mixture was then stirred for 10 minutes and taken to dryness in vacuo. Purification of the residue by flash chromatography on silica gel (1:1 hexanes:MDC) gave 0.8 g (67%) of methyl 2-chloro-sulfonyl-6-(1,1-dimethylethyl)benzoate, which was dissolved in THF (5 ml) and added to a solution of concentrated ammonium hydroxide (25 ml) while cooling in an ice/acetone bath. After stirring at room temperature for 16 hr, the reaction mixture was concentrated in vacuo and acidified to pH 1 with 2N HCl. The separated solids were collected by filtration and crystallized from ether to give 0.64 g (95%) of 4-(1,1-dimethylethyl)saccharin, mp 185-187°C.

The 4-(1,1-dimethylethyl)saccharin (0.025 g, 1.0 mmol) was mixed with chloromethyl phenyl sulifde (0.25 g, 1.5 mmol) and tetrabutyl ammonium bromide (0.2 g, 0.6 mmol) in toluene (25 ml) and refluxed under nitrogen for 16 hr. The resulting mixture was cooled to room temperature, evaporated to dryness and purified by chromatography on silica gel (80%) MDC in hexanes to give 0.35 g (98%) of 2-phenylthiomethyl-4-(1,1-dimethylethyl)-saccharin, which was treated with sulfuryl chloride (0.25 g, 1.8 mmol) in MDC to give 0.21 g (75%) of 2-chloro-methyl-4-(1,1-dimethylethyl)-saccharin.

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Preparation 4

A mixture of 3.22 g (0.012 mol) of 4-bromo-saccharin [Japanese Pat. Publication 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) chloromethyl phenyl 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-phenylthiomethyl-saccharin, 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 2-chloromethyl-4-bromo-saccharin, mp 157-159°C.

Preparation 5

To a solution of 8.0 ml (0.053 mol) tetramethyl-ethylenediamine (TMEDA) in 350 ml THF at -70°C was added 42 ml (0.055 mol) of a 1.3 M solution of s-butyl lithium in cyclohexane and the mixture was stirred for fifteen minutes. To the solution was added dropwise with stirring a solution of 10.36 g (0.050 mol) 2-methoxy-N,N-diethylbenzamide in 150 ml THF while maintaining the temperature at -60°C or below. After stirring for 20 minutes sulfur dioxide was bubbled into the reaction mixture, keeping the reaction temperature below -50°C, until the reaction mixture was acid to wet litmus paper. The mixture was stirred at ambient temperature for two hours, diluted with 450 ml hexane, and

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the solid material which had separated was collected, dissolved in 200 ml water and the mixture treated with 65 g sodium acetate and 21.5 g (0.19 mol) hydroxylamine-O-sulfonic acid in portions with stirring. The white solid which separated was collected and dried to give 7.04 g (49%) of 2-aminosulfonyl-6-methoxy-N,N-diethylbenzamide, mp 190-194.5°C.

A mixture of the product (4.3 g, 0.015 mol) in 75 ml dioxane and 25 ml concentrated hydrochloric acid was heated on a steam bath for 70 hours, then cooled, concentrated in vacuo, diluted with water and ice and rendered strongly basic with concentrated sodium hydroxide. The mixture was washed with MDC, and the aqueous layer was acidified with dilute hydrochloric acid and extracted with MDC. The extracts were dried over magnesium sulfate and taken to dryness to give 1.29 g (40%) of 4-methoxysaccharin. In an alternative, and preferred, procedure, cyclization of 2-aminosulfonyl-6-methoxy-N,N-diethylbenzamide to 4-methoxysaccharin in 65% yield was carried out in refluxing glacial acetic acid for six and a half hours.

Following a procedure similar to that described in Preparation 4 above, 1.14 g (0.0053 mol) of the latter was reacted with 1.31 ml (0.0097 mol) chloromethyl phenyl sulfide in toluene in the presence of 0.72 g (0.0064 mol) potassium t-butoxide and 174 mg (0.00054 mol) tetrabutylammonium bromide to give 1.23 g (69%) of 4-methoxy-2-phenylthio-methylsaccharin, mp 152.5-154.5°C (from ethyl acetate-hexane), 1.02 g (0.003 mol) of which was treated with 0.36 ml (0.0045 mol) sulfuryl chloride in MDC to give 282 mg (36%) of 2-chloromethyl-4-methoxysaccharin, mp 169-174°C.

Preparation 6A

To a solution of 4.74 ml (0.031 mol) tetramethyl-ethylenediamine in 300 ml THF (passed through alumina prior to use) was added 5.8 g (0.03 mol) 2-ethyl-N,N-diethyl-

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benzamide. The solution was cooled to -78°C and treated with a solution of 34.9 ml (0.031 mol) of a 0.9 M solution of s-butyl lithium in cyclohexane. When addition was complete, the mixture was stirred for twenty minutes and then treated with a solution of 3.2 ml (0.04 mol) ethyl iodide while maintaining the temperature at -78°C. The temperature was then allowed to rise to ambient temperature and the mixture stirred for about sixteen hours and then poured into water. The resulting oil was separated and chromatographed on silica gel, eluting with 10% ethyl acetate/hexane to give 2.86 g (43%) of 2-sec.-butyl-N,N-diethylbenzamide as a yellow oil.

Following a procedure similar to that described in Preparation 5 above, the latter (10.45 g, 0.045 mol), dissolved in 70 ml THF, was added to a solution of 39.2 ml (0.047 mol) of a 1.2 M solution of s-butyl lithium in cyclohexane and 7.1 ml (0.047 mol) tetramethylethylenediamine in 250 ml THF while maintaining the temperature at -78°C. When addition was complete the mixture was stirred for an additional one half hour at -78°C and then treated with sulfur dioxide at -70°C and then allowed to warm to room temperature. The mixture was taken to dryness in vacuo, and the residue was dissolved in water and added with stirring to a cold solution of 15.2 g (0.134 mol) of hydroxylamine-O-sulfonic acid and 15.4 ml (0.134 mol) 35% sodium hydroxide to give 10.1 g (72%) of 2-aminosulfonyl-6-sec.-butyl-N,N-diethylbenzamide.

The latter (6.83 g, 0.22 mol) was dissolved in 100 ml glacial acetic acid and the solution heated under reflux for thirteen hours and then taken to dryness. The residue was triturated with diethyl ether and collected by filtration to give 5.7 g (83%) of the diethylammonium salt of 4-sec.-butyl-saccharin.

The latter (3.0 g, 0.0096 mol), on reaction with 1.13 ml (0.012 mol) chloromethyl phenyl sulfide in toluene, afforded 3.47 g (100%) of 2-phenylthiomethyl-4-sec.-butyl-saccharin.

Reaction of the latter (3.2 g. 0.0097 mol) with

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2.3 ml (0.029 mol) sulfuryl chloride in 20 ml MDC afforded 2.4 g (87%) of 2-chloromethyl-4-sec.-butylsaccharin.

Preparation 6B

By a procedure analogous to that described for Preparation 6A, 9.2 g (32.9 mmol) 3,4-dimethoxy-2-propyl-N,N-diethylbenzamide was reacted with sulfur dioxide and 5.6 g (49.4 mmol) hydroxylamine-O-sulfonic acid to provide 7.4 g (63%) of 2-aminosulfonyl-4,5-dimethoxy-6-propyl-N,N-diethylbenzamide which was cyclized in quantitative yield in acetic acid and phenylthiomethylated with 1.42 ml (15 mmol) chloromethyl phenyl sulfide to provide 4.07 g of 5,6-dimethoxy-2-phenylthio-4-propylsaccharin. Reaction of 3.59 g (8.8 mmol) of the phenylthioether with 2.12 ml (26.4 mmol) sulfuryl chloride provided 2.84 g (97%) of 2-chloromethyl-5,6-dimethoxy-4-propylsaccharin.

The 3,4-dimethoxy-2-propyl-N,N-diethyl-benzamide was obtained by the following procedure:

To a solution of 0.216 moles n-butyllithium in 250 ml ether at ambient temperature was added dropwise 138.2 g (0.216 mol) veratrol in 100 ml ether and 32.6 ml (0.216 mol) of TMEDA. The reaction was stirred at ambient temperature for 14 hours and 21.9 ml (0.225 mol) n-propyl 1 hour at room temperature and worked up with aqueous 1N HCl to give 14 g (36%) of 2,3-dimethoxy-benzenepropane which was brominated with 14.52 g (81.6 mmol) N-bromo-succinimide on 36 g Kieselgel in 400 ml CCl_4 according to the method of Hisatoshi et al. [Bull. Chem. Soc. Jap. 32, 591-593 (1989)] to give 19.6 g (98%) of 6-bromo-2,3-dimethoxy-benzenepropane.

The bromobenzene (14.2 g, 54.8 mmol) was dissolved in 200 ml ether, cooled to -78°C, and 25.2 ml (63 mmol) of 2.5 N n-butyllithium in hexane was added. The reaction was warmed to 0°C, held for an hour, and cooled to -70°C, and 9 ml (71.2 mmol) of diethyl carbamyl chloride was added. The reaction was allowed to come to room temperature and was

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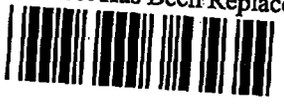
quenched with saturated ammonium chloride. After extraction and drying, the product was crystallized from hexane to provide 9.5 g (62%) of 3,4-dimethoxy-2-propyl-N,N-diethylbenzamide, mp 65-67°C.

Preparation 6C

By a process analogous to that of Preparation 6B, 10.75 g (30 mmol) 2-aminosulfonyl-4,5-dimethoxy-6-isopropyl-N,N-diethylbenzamide was cyclized to provide 6.43 g of 5,6-dimethoxy-4-isopropylsaccharin (mp 186-188°C from ether-hexane), 5 g (17.5 mmol) of which was phenylthiomethylated with 2.48 ml (26.3 mmol) of phenylthiomethylchloride according to the procedure of Preparation 5, and chlorinated with 3 equivalents of sulfuryl chloride to provide an 85% yield of 2-chloromethyl-5,6-dimethoxy-4-isopropylsaccharin, mp 117-119°C from ethyl acetate-hexane.

The requisite benzamide was obtained from 2,3-dimethoxy-α-methylbenzeneethane by bromination followed by carbamylation as in Preparation 6B, to provide the intermediate 3,4-dimethoxy-2-isopropyl-N,N-diethylbenzamide. A solution of 66 ml 0.96M sec-butyllithium was added to 16.1 g (57.6 mmol) of the benzamide in 400 ml THF at -78°C under nitrogen. After stirring 2 hours the orange anion was cannulated into excess sulfur dioxide at -60°C. The reaction was allowed to come to room temperature and stirred for 18 hrs to remove SO_2. 10 ml sulfuryl chloride was added at 0°C and the reaction was stripped. The sulfonyl chloride was extracted into EtOAc-ether, washed with water, dried and stripped. The residue was dissolved in 80 ml THF and 17 ml conc. NH_4OH was added at 0°C. The reaction was stirred briefly at room temperature, stripped, and triturated in 2:1 ether-hexane to provide 12.89 g (62%) of 2-aminosulfonyl-4,5-dimethoxy-6-isopropyl-N,N-diethylbenzamide, mp 138-140°C.

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Preparation 7

To a solution of 9.3 ml (0.058 mol) tetramethylethylenediamine in 340 ml THF at -78°C was added 52 ml of a 1.1 M solution (0.057 mol) of s-butyl lithium in cyclohexane. The solution was then treated with a solution of 11.37 g (0.052 mol) 2-propyl-N,N-diethylbenzamide in 75 ml THF at -78°C and the solution stirred for fifteen minutes and then treated with a solution of 8.3 ml (0.104 mol) ethyl iodide in THF. The solution was stirred for an hour and a half at -78°C and then quenched by the addition of saturated ammonium chloride added dropwise at -78°C. The mixture was then allowed to warm to ambient temperature, diluted with diethyl ether, washed first with dilute hydrochloric acid, then with water, then with saturated sodium bicarbonate, then with brine, dried and taken to dryness to give 12.91 g of crude product which was chromatographed on silica gel, eluting with 10% ethyl acetate/hexane to give 3.23 g (25%) of 2-(3-pentyl)-N,N-diethylbenzamide as a yellow oil.

Following a procedure similar to that described in Preparation 5 above, the latter (3.05 g, 0.0115 mol) in THF was reacted with 10.5 ml (0.126 mol) of a 1.2 M solution of s-butyl lithium in cyclohexane in the presence of 2.1 ml (0.014 mol) tetramethylenediamine. The resulting lithium salt was then reacted first with sulfur dioxide and then with sodium hydroxylamine-O-sulfonate to give 1.97 g (52%) of 2-aminosulfonyl-6-(3-pentyl)-N,N-diethylbenzamide as pale yellow crystals, mp 118-120°C (soft 102°), 1.84 g (0.0056 mol) of which was cyclized in 22 ml refluxing glacial acetic acid to give 1.28 g (70%) of the diethylammonium salt of 4-(3-pentyl)-saccharin, mp 107.5-109.5°C.

The latter (0.0037 mol), on reaction with 0.74 ml (0.0055 mol) chloromethyl phenyl sulfide in the presence of 116 mg (0.0004 mol) TBAB in 45 ml toluene, afforded 1.93 g of 2-phenylthiomethyl-4-(3-pentyl)saccharin as a pale yellow oil, 1.93 g (0.0037 mol) of which, on reaction

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with 0.59 ml (0.0073 mol) sulfuryl chloride in 37 ml MDC, afforded 1.2 g of 2-chloromethyl-4-(3-pentyl)saccharin as a pale yellow oil.

Preparation 8

A solution of 50.0 g (0.27 mol) 2,4-dimethoxy-benzoic acid in 60 ml (98.0 g, 0.82 mol) thionyl chloride was heated under reflux for three hours, then cooled, and the excess thionyl chloride distilled off. The resulting 2,4-dimethoxy-benzoyl chloride was dissolved in 150 ml MDC and the solution treated with a solution of 68 ml (48 g, 0.66 mol) diethylamine in 500 ml MDC, cooled to 0°C. When addition was complete the mixture was stirred for fifteen hours at ambient temperature, then washed with saturated sodium bicarbonate, water and brine and taken to dryness and the residue distilled in vacuo to give 44.78 g (69%) of 2,4-dimethoxy-N,N-diethylbenzamide, bp 155-163°C/0.4 mm.

Following a procedure similar to that described in Preparation 5 above, 10.0 g (0.042 mol) of the product in 250 ml THF was reacted with 40.57 ml of a 1.1 M solution (0.044 mol) of s-butyl lithium in cyclohexane and 6.35 ml (0.042 mol) tetramethylethylenediamine in THF. The resulting lithium salt was then reacted first with about 40 ml sulfur dioxide and then with an aqueous solution (0.13 mol) sodium hydroxylamine-O-sulfonate to give 8.26 g of 2-aminosulfonyl-4,6-dimethoxy-N,N-diethyl-benzamide, 7.0 g of which (0.022 mol) was cyclized in 80 ml refluxing glacial acetic acid to give 6.6 g (94%) of the diethylammonium salt of 4,6-dimethoxysaccharin which was used as such in the next step without further purification.

The latter (6.0 g, 0.019 mol), on reaction with 3.82 ml (0.028 mol) of chloromethyl phenyl sulfide in the presence of 0.611 g (0.0019 mol) TBAB in 200 ml toluene, afforded 6.2 g (89%) of 2-phenylthiomethyl-4,6-dimethoxy-saccharin, 5.82 g of which (0.016 mol), on reaction with

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3.23 g (0.0019 mol) sulfuryl chloride in 100 ml MDC, afforded 4.63 g (100%) of 2-chloromethyl-4,6-dimethoxysaccharin, mp 185-187°C.

Preparation 9A - 9G

Following a procedure similar to that described above in Preparation 5, substituting for the 2-methoxy-N,N-diethylbenzamide used therein an appropriate 2-R^4-R^5- substituted N,N-diethylbenzamide, the following 2-halomethyl-4-R^4-R^5-saccharinslisted in TABLE A were prepared via the corresponding 2-phenylthiomethylsaccharins. Wherever available, the melting point (°C), recrystallization solvent and yield are given for each of the 2-unsubstituted saccharins, the 2-phenylthiomethyl-saccharins and the 2-chloromethyl-saccharins in columns headed "mp/Solv." and "Yield". In all instances, the intermediate 2-phenylthiomethylsaccharins were used directly in the subsequent step without further characterization or purification.

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TABLE A

Prep	R^4/R^5	Sacc		2-$C_6H_5SCH_2$-Sacc		2-$ClCH_2$-Sacc	
		mp/Solv	Yield	mp/Solv	Yield	mp/Solv	Yield
9A	H 7-Cl	260-262	93	--	100	158.0-160.0 i-PrOH	51
9B	$CH(CH_3)_2$ H	177.0-178.0 MeOH	88	--	100	93.0-96.0 i-PrOH-Cyc hex	100
9C	CH_3O 5-CH_3O	(a)	64	--	100	190.0-192.0	76
9D	$COOCH_3$ H	(b) EtOAc-hex	76	--	65	186.0-187.0	
9E	C_2H_5O H	(a)	96	--	95	139.0-140.0	97
9F	$(CH_3)_2CHO$ H		87	--	75	142.5-143.5	94
9G	C_2H_5 5,7-$(CH_3O)_2$	i-PrOH	67	--	52	--	99

(a) Isolated and used in the next step as the diethylammonium salt.
(b) The 2-unsubstituted-saccharin was prepared by cyclization of dimethyl 3-aminosulfonylphthalate in methanol in the presence of a molar equivalent of sodium methoxide. The phthalate ester was prepared by diazotization of dimethyl 3-aminophthalate, decomposition of the diazonium salt with sulfur dioxide in the presence of cupric chloride and reaction of the resulting dimethyl 2-chlorosulfonylphthalate with ammonia. (84% yield overall).

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Preparation 10

Following a procedure similar to that described in Preparation 2, reaction of 18.3 g (0.1 mol) of saccharin with 70 ml 37% formalin in ethanol afforded 3.58 g (70%) of 2-hydroxymethylsaccharin. The latter (25 g, 0.117 mol) was reacted with 63.3 g (0.234 mol) phosphorus tribromide in diethylether to give 29.8 g (92%) of 2-bromomethylsaccharin, mp 155-157°C.

Preparation 11

To a solution of 4 g (0.0175 mol) 6-nitrosaccharin in 240 ml ethanol was added 4.4 g (0.0175 mol) thallium ethoxide, and the mixture was allowed to stand at room temperature for one hour, cooled for about 16 hours and the precipitated solid collected and dried to give 7.6 g (100%) of the thallium salt of 6-nitrosaccharin. The product was suspended in 50 ml DMF and the mixture treated with 3.07 g (0.0194 mol) chloromethyl phenyl sulfide, the mixture warmed at about 63°C for five hours, allowed to stand at ambient temperature for about 16 hours, and then poured into ice water. The crude product, obtained by filtration, was stirred in MDC and filtered to remove thallium salts. The filtrate was freed of solvent, and the resultant pale yellow solid was sonicated with warm ethanol and once again collected and dried to give 4.6 g (75%) of 6-nitro-2-phenyl-thiomethylsaccharin, mp 161-163°C. The latter, on reaction with sulfuryl chloride in MDC using the procedure described above in Preparation 4, afforded 3.7 g of 2-chloromethyl-6-nitrosaccharin.

Preparation 12

A solution of 49.8 g (0.199 mol) 2-hydroxy-5-(1,1,3,3-tetramethylbutyl)benzoic acid in 200 ml methanol was heated to 50°C and then treated dropwise with about 80 g sulfuric acid at a rate to maintain the reaction under reflux. The reaction mixture was heated under reflux for an additional 11 hours, then cooled and partitioned between water and ethyl acetate. The organic layer was washed with

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saturated sodium bicarbonate, then with brine, dried over sodium sulfate and taken to dryness to give 48.6 g (92%) methyl 2-hydroxy-5-(1,1,3,3-tetramethylbutyl)benzoate.

The latter dissolved in 250 ml DMF was treated first with 40.4 g (0.36 mol) 1,4-diazabicyclo[2.2.2]octane followed by 33.4 g (0.27 mol) N,N-dimethylchlorothio-carbamate and 100 ml DMF. The reaction mixture was heated at 45°C for about eight hours, cooled, poured into ice/water and concentrated hydrochloric acid and then extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid, then with sodium bicarbonate and then with brine, dried and taken to dryness to give 48.2 g (76%) of methyl 2-(N,N-dimethylthiocarbamyloxy)-5-(1,1,3,3-tetramethylbutyl)benzoate which was heated at 220°C for 15 hours, then cooled, dissolved in toluene and chromatographed on silica, eluting with 1:9 ethyl acetate:-toluene, to give 3.6 g (14%) of methyl 2-(N,N-dimethyl-carbamylthio)-5-(1,1,3,3-tetramethylbutyl)benzoate.

A solution of the latter (0.025 mol) in 40 ml MDC was treated, with stirring, with 80 ml glacial acetic acid, followed by 16 ml water. The reaction mixture was cooled to 0°C, and chlorine was bubbled through the reaction mixture for about five minutes while maintaining the temperature between 5 and 24°C. The reaction was stirred for an additional 30 minutes, concentrated in vacuo, and the remaining solution poured into ice water. Extraction of the mixture with ethyl acetate and isolation of the product from the combined organic extracts afforded 6.8 g (78%) of methyl 2-chlorosulfonyl-5-(1,1,3,3-tetramethylbutyl)benzoate.

The product (9.0 g, 0.026 mol) was dissolved in THF and added to 100 ml concentrated ammonium hydroxide with cooling in an ice bath. The resulting solution was stirred for about 16 hours, then concentrated in vacuo and the concentrated solution acidified to pH 3 with concentrated hydrochloric acid. The mixture was stirred for several hours,

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and the separated solid collected, washed with water and dried to give 9.0 g of 5-(1,1,3,3-tetramethylbutyl)saccharin, mp 213-215°C.

Following a procedure similar to that described in Preparation 11, 9.0 g (0.30 mol) of the product was reacted with thallium ethoxide in ethanol and the resulting thallium salt reacted with 3.33 g (0.021 mol) chloromethyl phenyl sulfide in DMF to give 5.76 g (66%) of 2-phenylthiomethyl-5-(1,1,3,3-tetramethylbutyl)saccharin, 3.3 g (0.007 mol) of which was treated with 0.944 g sulfuryl chloride in MDC to give 1 g (41%) of 2-chloromethyl-5-(1,1,3,3-tetramethyl)butyl saccharin.

Preparation 13

Following a procedure similar to that described in Preparation 12 above, 15.5 g (0.086 mol) ethyl 2-hydroxy-6-methylbenzoate was reacted with 15.9 g (0.129 mol) N,N-dimethylchlorothiocarbamate in the presence of 19.3 g (0.172 mol) of 1,4-diazabicyclo[2.2.2]octane in DMF to give 22.1 g (96%) of ethyl 2-(N,N-dimethylthiocarbamyloxy)-6-methyl-benzoate which was heated at 220°C for about 10 hours. The product was purified by chromatography on silica gel in MDC to give ethyl 2-(N,N-dimethylcarbamylthio)-6-methylbenzoate as a red-brown oil.

A solution of the latter (22.6 g, 0.0844 mol) in 170 ml MDC was treated with 340 ml glacial acetic acid and 68 ml water while cooling in an ice/acetone bath, and chlorine was bubbled through the reaction mixture for 10-15 minutes. The reaction vessel was evacuated to remove excess chlorine and MDC and the mixture poured into water and partitioned between MDC and water. The organic layer, on drying and evaporation to dryness, afforded 19 g of ethyl 2-chloro-sulfonyl-6-methylbenzoate, 5 g (0.019 mol) of which was reacted with concentrated ammonium hydroxide in THF to give 6.1 g (67%) of 4-methylsaccharin.

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Following a procedure similar to that described in Preparation 11 above, the product (10.1 g, 0.0512 mol) was converted to the thallium salt by reaction with 12.8 g (0.0512 mol) thallium ethoxide in ethanol and the thallium salt reacted with 6.7 g (0.0427 mol) chloromethyl phenyl sulfide in DMF to give 6.85 g (50%) of 2-phenylthio-methyl-4-methyl-saccharin.

Reaction of the latter (6.7 g, 0.021 mol) with sulfuryl chloride in MDC afforded 4.9 g (95%) of 2-chloro-methyl-4-methylsaccharin.

Preparation 14A

A mixture of 75 g (0.36 mol) 3,3-dithiobispropionic acid, 102 ml thionyl chloride and a catalytic amount of pyridine was stirred for about 24 hours and then evaporated to dryness in vacuo. The residue was treated with MDC and evaporated to dryness again to remove residual thionyl chloride and pyridine to give 87 g (98%) of the corresponding bis acid chloride, 44.8 g (0.18 mol) of which was dissolved in THF and added dropwise to a solution of 77.16 g (0.72 mol) benzyl-amine in THF. The mixture was stirred for two hours at 40-45°C, cooled and the precipitated solid collected, washed with water and dried to give 59 g (84%) of 3,3-dithiobis-propionic acid N,N'-dibenzyl-carboxamide, mp 162-165°C.

Reaction of 7.0 g (0.018 mol) of the latter with 10.25 g (0.076 mol) sulfuryl chloride in MDC gave a mixture of 2-benzyl-2H-isothiazol-3-one and 5-chloro-2-benzyl-2H-iso-thiazol-3-one which were largely separated from one another by sonication in MDC (which solubilized most of the former). The insoluble material was collected by filtration and chromatographed on silica gel with MDC. There was thus obtained 5-chloro-2-benzyl-2H-isothiazol-3-one, mp 58-68°C.

A solution of 10 g (0.044 mol) of the latter in MDC was cooled to 0°C and the solution treated with 7.6 g (0.044 mol) 3-chloroperbenzoic acid, the mixture stirred for 10 minutes and then treated with a second 7.6 g portion of the perbenzoic

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acid. The reaction mixture was filtered, the filter washed with MDC and the filtrate washed with saturated sodium bicarbonate, then with brine, dried over sodium sulfate and taken to dryness and the residue chromatographed in MDC on silica gel, the product being eluted with 50:50 hexane:MDC, to give 7.15 g (46%) of 5-chloro-2-benzyl-2H-isothiazol-3-one 1-oxide.

A solution of 1.1 g (0.0045 mol) of the latter in 8 ml benzene was treated with 0.55 g (0.0051 mol) 2-methoxyfuran and the solution heated in a pressure bottle at 70°C for 1-1/2 hours and then cooled and the solid collected, washed with benzene and dried to give 2-benzyl-7-hydroxy-4-methoxybenzisothiazol-3-one 1-oxide, mp 235-237°C.

A mixture of the product (1.85 g, 0.006 mol), 2.48 g (0.018 mol) potassium carbonate and 1.70 g (0.012 mol) methyl iodide in acetone was heated under reflux for 1-1/2 hours and then cooled and poured into water. The solid which separated was collected by filtration, washed with water and dried to give 1.70 g (89%) of 2-benzyl-4,7-dimethoxybenzisothiazol-3-one 1-oxide, 1.13 g (0.0035 mol) of which was oxidized with 1.20 g (0.007 mol) of 3-chloroperbenzoic acid in MDC using the procedure described above to give 1.03 g (88%) of 2-benzyl-4,7-dimethoxysaccharin.

A mixture of 2.07 g (0.0062 mol) of the product, 1.37 g (0.02 mol) ammonium formate and 1.5 g 10% palladium-on-charcoal catalyst in 80 ml methanol was heated under reflux for one hour, then cooled and filtered, and the filtrate taken to dryness to give 0.92 g (57%) of the ammonium salt of 4,7-dimethoxysaccharin.

A solution of 1.11 g (0.0042 mol) of the ammonium salt was dissolved in DMF, 0.67 g (0.0042 mol) chloromethyl phenylsulfide was added, and the solution heated under reflux for eight hours and then cooled and poured into ice water. The solid which separated was collected, washed with water and dried to give 0.50 g (33%) of 2-phenylthiomethyl-

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4,7-dimethoxysaccharin.

Reaction of the latter (0.5 g, 0.0013 mol) with sulfuryl chloride in MDC using the procedure described above in Preparation 4 afforded 0.22 g (58%) of 2-chloromethyl-4,7-dimethoxysaccharin.

Preparations 14B and 14C

Following a procedure similar to that described in Preparation 14A, other 2-chloromethylsaccharin derivatives were prepared as follows:

Preparation 14B

Reaction of 5.8 g (0.024 mol) 5-chloro-2-benzyl-2H-isothiazol-3-one-1-oxide with 3.76 g (0.0335 mol) 2-ethoxy-furan afforded 3.05 g (40%) of 2-benzyl-4-ethoxy-7-hydroxybenzisothiazol-3-one 1-oxide, 5.7 g of which was reacted with 3.6 g (0.0197 mol) of 2-(2-methoxyethoxy)ethyl bromide in the presence of 4.95 g (0.0358 mol) potassium carbonate in 125 ml methylethylketone and 25 ml DMF to give 7.0 g (93%) of 2-benzyl-4-ethoxy-7-[2-(2-methoxyethoxy)-ethoxy]benzisothiazol-3-one 1-oxide, which was oxidized as before with 3-chloroperbenzoic acid in MDC to give 2-benzyl-4-ethoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin. Debenzylation of 6.6 g (0.015 mol) of the latter with 3.34 g (0.053 mol) ammonium formate in the presence of 6.4 g 10% palladium-on-charcoal catalyst in methanol afforded the ammonium salt of 4-ethoxy-7-[2-(2-methoxyethoxy)-ethoxy]saccharin, which was reacted with 2.38 g (0.015 mol) of chloromethyl phenyl sulfide in 100 ml DMF to give 1.46 g (21%) 2-phenylthiomethyl-4-ethoxy-7-[2-(2-methoxy-ethoxy)-ethoxy]saccharin, mp 73-75°C (from isopropanol). Treatment of 1.4 g (0.0029 mol) of the product with 0.4 g (0.0029 mol) sulfuryl chloride in MDC afforded 1.16 g (100%) of 2-chloro-methyl-4-ethoxy-7-[2-(2-methoxy-ethoxy)ethoxy]saccharin.

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Preparation 14C

Reaction of 3.03 g (0.01 mol) 2-benzyl-7-hydroxy-4-methoxybenzisothiazol-3-one-1-oxide (Preparation 14A) with 2.01 g (0.011 mol) of 2-(2-methoxyethoxy)ethyl bromide in methylethylketone in the presence of 2 g (0.015 mol) potassium carbonate afforded 2.58 g (64%) of 2-benzyl-4-methoxy-7-[2-(2-methoxyethoxy)ethoxy]benzisothiazol-3-one-1-oxide, which, on oxidation with 1.1 g (0.0063 mol) 3-chloroperbenzoic acid in MDC, gave 2-benzyl-4-methoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin. Debenzylation of 0.25 g (0.0006 mol) of the product with 0.13 g (0.0021 mol) ammonium formate in methanol in the presence of 0.25 g, 10% palladium-on-charcoal gave 0.21 g (100%) of the ammonium salt of 4-methoxy-7-[2-(2-methoxyethoxy)-ethoxy]saccharin. Reaction of 1.4 g (0.004 mol) of the ammonium salt with 0.63 g (0.004 mol) chloromethylphenyl sulfide in DMF afforded 2-phenylthiomethyl-4-methoxy-7-[2-(2-methoxy-ethoxy)ethoxy]saccharin, which, on reaction with sulfuryl chloride in MDC, afforded 0.53 g (35%) of 2-chloromethyl-4-methoxy-7-[2-(2-methoxyethoxy)ethoxy]-saccharin.

Preparation 15

A solution of 1.89 g (0.011 mol) diethylamino sulfur trifluoride (DAST) in 20 ml MDC was added to a suspension of 2.13 g (0.01 mol) 2-hydroxymethylsaccharin in 25 ml MDC while maintaining the reaction mixture at -78°C.

The reaction mixture was stirred at -78°C for one hour, the temperature allowed to slowly rise to ambient temperature, the mixture stirred for 16 hours and then poured into ice-water. The organic layer was separated and washed with water, dried over magnesium sulfate and taken to dryness to give 2.2 g of product which was recrystallized from ethyl acetate to give 1.6 g (74%) of 2-fluoromethylsaccharin, mp 96-98°C.

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Preparation 16A

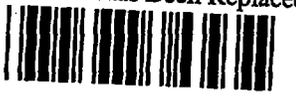
To a solution of 0.5 g (0.0025 mol) 4-methyl-saccharin in THF cooled to -78°C by a dry ice/acetone bath was added, dropwise with stirring, a solution of 5.2 ml of a 1.3 M solution of s-butyl lithium in cyclohexane. The mixture was stirred an additional hour at -78°C and then treated with 0.16 ml (0.025 mol) methyl iodide over a 1-1/2 hour period. The mixture was stirred for an hour and 45 minutes, quenched in 25 ml 1N hydrochloric acid, the reaction mixture rendered basic, the aqueous mixture extracted with chloroform and then acidified and extracted with ethyl acetate. The combined organic extracts were washed with 10% sodium thiosulfate, then with brine, dried over sodium sulfate and taken to dryness to give a product, whose PMR spectrum indicated a mixture consisting of 74% 4-ethylsaccharin and 21% 4,7-dimethylsaccharin.

Following a procedure similar to that described in Preparation 4 above, the crude material (0.47 g, 0.0022 mol) was reacted with 0.24 ml (0.0028 mol) chloromethyl phenyl sulfide in toluene in the presence of tetrabutylammonium bromide, and the product chromatographed on silica gel, eluting with MDC, 5 ml fractions being collected. The first 420 ml of eluate were discarded. The next 20 fractions, on evaporation, afforded 0.07 g of material, predominantly 2-phenylthiomethyl-4,7-dimethylsaccharin, which was set aside. The next 25 fractions afforded 0.37 g of 2-phenylthiomethyl-4-ethylsaccharin, which was reacted with sulfuryl chloride in MDC to give 0.19 g (66%) of 2-chloromethyl-4-ethylsaccharin.

Preparation 16B

Following a procedure similar to that described in Preparation 16A, 10 g (0.051 mol) 4-methylsaccharin in THF was reacted with 86 ml (0.10 mol) of a 1.18 M solution of s-butyl lithium in cyclohexane and the resulting solution treated with 4.5 ml (0.050 mol) ethyl iodide to give

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10.15 g (89%) of 4-propylsaccharin, which, on reaction with 5.32 ml (0.056 mol) chloromethyl phenyl sulfide in toluene in the presence of tetrabutylammonium bromide, afforded a crude mixture from which was isolated by flash chromatography on silica gel 2-phenylthiomethyl-4-propyl-saccharin as an oil, 1.8 g (0.0052 mol) of which, on reaction with 1.25 ml (0.016 mol) sulfuryl chloride in MDC, afforded 0.94 g (66%) of 2-chloromethyl-4-propylsaccharin.

Preparation 16C

A preferred alternative to Preparation 16A is as follows:

To a solution of 5.13 g (25 mmol) N,N,2-triethyl-benzamide in THF (50 ml) at -78°C was added a solution of LDA (Aldrich 2.0M, 15.63 ml, 31.25 mmol). The solution was warmed to -10°C with ice water over 1 hr, then cooled to -78°C with dry ice-acetone. TMSCl (6.34 ml, 50 mmol) was added neat at -78°C and then reaction brought to room temperature after 1 hr. The reaction was quenched with saturated NH_4Cl and extracted with ether (2 x 100 ml), dried over $MgSO_4$, stripped and the residue distilled in a Kugelrohr (130-140°C, 0.65 mm) to obtain 6.51 g (94%) of N,N-diethyl-2-[1-(trimethylsilyl)ethyl]benzamide.

To a solution of sec BuLi (0.97M, 5.10 ml, 4.96 mmol), TMEDA (0.75 ml, 4.96 mmol) in THF at -78°C was added the amide (1.25 g, 4.50 mmol) in THF. Excess SO_2 in THF was added quickly at -78°C then warmed to room temperature. The THF was removed in vacuo then reacted at 0°C with two equivalents of a 1:1 solution of sodium hydroxide (0.36 g, 9.0 mmol) and hydroxylamine-O-sulfonic acid (1.0 g, 9.0 mmol) in H_2O. The reaction was stirred at room temperature for 4 hrs, extracted with EtOAc and flash chromatographed on silica gel with 20% ethyl acetate/hexane to give 0.62 g (47%) of 2-aminosulfonyl-N,N-diethyl-6-[1-(trimethylsilyl)ethyl]benzamide. The benzamide (0.95 g, 2.66 mol) was refluxed in glacial acetic acid (20 ml) for 18 hr, stripped to dryness, triturated with hot cyclohexane (30 ml)

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and a trace of EtOAc (3 ml), cooled with scratching and filtered. There was obtained 0.81 g (85%) of 4-[1-(trimethylsilyl)ethyl]-saccharin, mp 123-125°C.

To the trimethylsilylethylsaccharin (0.25 g, 0.70 mmol) in DMF (9 ml) at room temperature was added H_2O (1 ml) and cesium fluoride (0.75 g, 4.94 mmol, 7 equivalents). After 7 hr the reaction was poured into 5% NaOH and extracted with EtOAc. The aqueous layer was acidified with 12N HCl and extracted with Et_2O-EtOAc (1:1), dried over Na_2SO_4, filtered and stripped to give a colorless solid in quantitative yield. It was recrystallized from 5% Et_2O-hexanes to give 0.091 g (64%) of 4-ethylsaccharin, mp 183-185°C.

Preparation 17

The 0.07 g sample of material obtained in the early fractions from the chromatographic separation described above in Preparation 16A consisting predominantly of 2-phenylthiomethyl-4,7-dimethylsaccharin was reacted with 0.05 ml sulfuryl chloride in MDC and the product recrystallized from cyclohexane-ethyl acetate to give 20 mg (51%) of 2-chloromethyl-4,7-dimethylsaccharin, mp 107-108°C.

Preparation 18A

To a solution of 40.0 g (0.174 mol) 2-isopropyl-4-methoxybromobenzene in 600 ml diethylether at 0°C was added 103.68 ml (0.175 mol) of a 1.69 M solution of butyl lithium in diethylether. When the addition was complete the solution was cooled to 0°C for one hour and stirred for an additional five hours at ambient temperature, then recooled to -78°C and treated with a solution of 23.68 g (0.175 mol) N,N-diethylcarbamyl chloride in 80 ml diethylether. The resulting solution was stirred for about 12 hours while the reaction temperature was allowed to rise and then quenched with saturated ammonium chloride solution. The aqueous and organic layers were separated, the aqueous layer back-extracted with ethyl acetate and the combined organic extracts

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washed once with brine, then dried and the solution taken to dryness to give a crude product which was flashed chromatographed on silica gel, eluting with 30% ethyl acetate/hexane to give 34.4 g (79%) of 2-isopropyl-4-methoxy-N,N-diethylbenzamide as an oil which was used as such in the next step without further purification. The oil can be distilled, if desired, and boils at 123-129°C/0.2-0.3 mm.

Following a procedure similar to that described in Preparation 5 above, the latter (15.0 g, 0.060 mol) in 100 ml diethylether was reacted with 77.8 ml (0.784 mol) of a 1.2 M solution of s-butyl lithium in cyclohexane in the presence of 6.98 g (0.06 mol) tetramethylethylenediamine. The resulting lithium salt was then reacted first with 50 ml sulfur dioxide and then with 0.181 mol sodium hydroxylamine-O-sulfonate to give 11.6 g (59%) of 2-amino-sulfonyl-6-isopropyl-4-methoxy-N,N-diethylbenzamide, mp 103-105°C (from ethyl acetate/hexane), 11.0 g (0.034 mol) of which was cyclized in 200 ml refluxing glacial acetic acid to give 10.3 g of the diethylammonium salt of 4-isopropyl-6-methoxysaccharin, mp 132-135°C.

The latter (0.030 mol), on reaction with 6.14 ml (7.25 g, 0.046 mol) of chloromethylphenylsulfide in the presence of 0.98 g (0.003 mol) TBAB in 250 ml toluene, afforded 10.1 g (88%) of 2-phenylthiomethyl-4-isopropyl-6-methoxysaccharin as an oil, 9.7 g (0.026 mol) of which, on reaction with 3.1 ml (5.21 g, 0.039 mol) sulfuryl chloride in MDC, afforded 6.9 g (88%) of 2-chloromethyl-4-isopropyl-6-methoxy-saccharin, mp 151-152°C.

Preparation 18B

An alternative procedure was also followed:

To a solution of 300 ml N,N,N',N'-tetramethyl-ethylenediamine (TMEDA) (1.99 moles) in 4 l anhydrous ether was added 1550 ml of sec-BuLi (1.3 M) and the system was cooled to -70°C under a nitrogen atmosphere. A solution of 454.2 g 2-isopropyl-4-methoxy N,N-diethylbenzamide

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(1.82 moles) in 300 ml anhydrous ether was added dropwise over 30 minutes (the temperature was maintained at or below -60°C during the addition). After the addition was complete, the reaction was stirred at -70°C for one hour and allowed to warm to -50°C. After holding the temperature at -50°C for 30 minutes, the mixture was cooled back to -70°C. To this stirred solution was added via cannulating tube a solution of 200 g SO_2 in 200 ml dry ether precooled to -40°C under positive nitrogen pressure over a 20-minute period. The temperature of the reaction mixture during the addition was maintained below -40°C. (A white powdery precipitate of aryllithium sulphinate separated out almost immediately). After the addition, the ice-bath was removed and the reaction was allowed to stir at ambient temperature for two hours. It was cooled to -5°C and to this stirred solution was added 190 ml sulfuryl chloride (2.36 moles) dropwise over a 15-minute period maintaining the temperature below 10°C during the addition. After further stirring for 30 minutes at 0-5°C, a white insoluble precipitate was filtered off and washed with 2 l of anhydrous ether. Removal of the solvent at atmospheric pressure afforded the sulfonyl chloride as a crude dark oil. This crude sulfonyl chloride was dissolved in 1.4 l THF, cooled to -10°C, and 540 ml concentrated NH_4OH (28%) was added in portions over 15 minutes (the temperature was kept at 15°C or below throughout the addition). After stirring for 15 minutes at ambient temperature, the THF and excess ammonia were removed under vacuum to give a dark oil, which was diluted with 6.0 l of water and acidified with 3N HCl to pH 1. The light yellow solid was collected by filtration and washed with 800 ml water. The solid was dried at 60°C under vacuum for 18 hours and recrystallized from a mixture of 800 ml ethyl acetate and 3 l hexane to give 429 g (72%) of 2-aminosulfonyl-6-isopropyl-4-methoxy-N,N-diethylbenzamide, mp 122-125°C.

A solution of 429.6 g of the diethylbenzamide

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(1.31 mole) in 1.5 l acetic acid was refluxed for 20 hours. It was cooled to room temperature and the solvent removed under vacuum. The oily residue was dissolved in 6 l water and adjusted to pH 1 with 6N HCl. The crude product was collected by filtration and washed with 2 l water. The solid was dried at 60°C under vacuum for 18 hours and recrystallized from ethyl acetate/hexane to give 303 g (91%) 4-isopropyl-6-methoxysaccharin, mp 188°C.

To a suspension of 24 g paraformaldehyde (0.8 mole) and 86.4 g chlorotrimethylsilane (1.6 moles) in 200 ml 1,2-dichloroethane was added 0.8 ml anhydrous tin(IV) chloride and the resulting solution stirred on a steam bath for one hour. At the end of this period, 51 g 4-isopropyl-6-methoxysaccharin (0.2 mole) was added to the clear solution and the reaction mixture was further refluxed for 18 hours. It was cooled to room temperature, poured into water, the organic layer separated and washed with 50 ml 2N sodium hydroxide solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated under vacuum to give crude product. It was purified by crystallization from ethyl acetate/hexane to give 57 g (87%) of 2-chloromethyl-4-isopropyl-6-methoxysaccharin, mp 151°C.

Preparation 18C

Following the procedure of preparation 18A, 5 g 2-bromo-N,N-dimethylaniline was converted to 3.5 g N,N-diethyl-2-dimethyl-aminobenzamide. The amide was reacted by the method of preparation 18B to provide 65 mg of 4-dimethylaminosaccharin, which can be converted into 2-chloromethyl-4-dimethylaminosaccharin as shown in preparation 23V.

Preparation 19

To a solution of 1.0 g (0.0039 mol) 4-isopropyl-6-methoxysaccharin in 15 ml MDC was added at ambient temperature 1.28 g (5.12 ml) M solution boron tribromide in MDC. When addition was complete the reaction mixture was

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heated under reflux for about five hours, cooled, taken to dryness in vacuo and the residue treated with ice and saturated sodium bicarbonate. The aqueous solution was extracted once with ethyl acetate and then acidified to pH 1 with concentrated hydrochloric acid. Extraction of the mixture with ethyl acetate/diethyl ether (8:2), drying the organic extracts and removal of the solvent in vacuo afforded 0.9 g (96%) of 6-hydroxy-4-isopropylsaccharin as a white crystalline solid which was used as such in the next step.

An alternative procedure was also used. To a stirred suspension of 62.74 g (0.47 mol) $AlCl_3$ in 500 ml chloroform at 0° was added 43.9 g (0.7 mol) ethanethiol. Within minutes a clear solution formed. To this a solution of 20.0 g (0.078 mol) 4-isopropyl-6-methoxysaccharin in 550 ml chloroform was added over a 30-min period. This solution was allowed to warm to RT and stirred for 3-4 hr at 60°. After cooling, the mixture was poured into ice-water and acidified with dilute HCl. The solid which separated was collected by filtration, washed with water and dried to give 18.4 g (97%) of 6-hydroxy-4-isopropylsaccharin.

Following a procedure similar to that described in Preparation 4 above, the latter (0.004 mol) was reacted with 0.61 ml (0.0046 mol) chloromethyl phenyl sulfide in toluene in the presence of 0.133 g (0.004 mol) TBAB to give 0.32 g (21%) of 4-isopropyl-6-hydroxy-2-phenylthio-methylsaccharin, m.p. 127-129.5, 1.78 g of which was treated with 0.43 ml (0.73 g) of sulfuryl chloride in MDC to give 1.2 g (84%) of 2-chloromethyl-4-isopropyl-6-hydroxy-saccharin, m.p. 149-150°C.

Preparation 19A

Following a procedure substantially similar to that described in preparation 19 but substituting 4-methoxy-saccharin for 4-isopropyl-6-methoxysaccharin it is contemplated that 2-chloromethyl-4-hydroxysaccharin can be prepared.

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Preparation 20

5g (0.0207 mol) 6-hydroxy-4-isopropyl-saccharin was dissolved in 150 ml methanol and 3.4 g (0.0104 mol) Cs_2CO_3 was added. The mixture was stirred for 3-4 hr at RT. The excess methanol was removed under reduced pressure and the residue was dried for 2 hr under high vacuum. The residue was then dissolved in 110 ml DMF and 0.32 g (0.0209 mol) chloromethyl phenyl sulfide was added. The stirred mixture was heated at 70-75°C for 12 hr, cooled, treated with ice water and extracted with 600 ml 4:1 ethyl acetate:ether. The organic layer was washed with water and saturated NaCl and dried. The solvent was removed under reduced pressure. The residue was purified by flash chromatography with 20% ethyl acetate in MDC. There was obtained 4.5 g (60%) of 6-hydroxy-4-isopropyl-2-phenyl-thiomethylsaccharin, mp 150-151.5°C which, on reaction with sulfuryl chloride as described in Preparation 19, yielded 2-chloromethyl-6-hydroxy-4-isopropylsaccharin as before.

Preparation 21

To a solution of 5-chloro-2-benzyl-4-isothiazolin-3-one (J. Het. Chem. 8, 571, 1971) (9.4 g, 0.04 mol) in MDC (100 ml) was added in one portion 80-85% 3-chloroperoxy-benzoic acid (10.8 g, 0.06 mol) and the resulting mixture stirred at room temperature overnight under nitrogen. The precipitated solids were filtered off and washed with MDC (50 ml). The combined filtrate was evaporated to near dryness and the residue partitioned between ethyl acetate (300 ml) and saturated $NaHCO_3$ (100 ml). The layers were separated and the organic phase washed with saturated $NaHCO_3$ (2 x 100 ml), brine (1 x 100 ml) and dried. Removal of the solvent in vacuo afforded 10.0 g (99%) of 5-chloro-2-benzyl-4-isothiazolin-3(2H)-one 1-oxide as a pale yellow oil.

The 1-oxide (10.0 g, 0.04 mol) in glacial acetic acid (200 ml) was treated with 30% H_2O_2 (100 ml, 0.88 mol) and heated on a steam bath for 2 hr during which time an

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additional 30 ml (0.26 mol) 30% H_2O_2 was added. After heating on a steam bath for an additional hour, the reaction mixture was cooled to room temperature and poured into ice cold water (1 l) and stirred. The precipitated solids were collected by filtration, washed with water (2 x 100 ml), hexanes and air-dried to give 4.8 g (45%) of 5-chloro-2-benzyl-4-isothiazolin-3(2H)-one 1,1-dioxide as a colorless solid.

The dioxide (1.2 g, 4.7 mmol) was mixed with 2.02 g (11 mmol) of 2-trimethylsiloxy-5-methylhexa-1,3-diene (prepared from 5-methylhex-3-ene according to the method of E.J. Corey et al., Tet. Lett. 495, 1984) in toluene (50 ml) and refluxed for a period of 20 hr under nitrogen. The resulting mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in THF (25 ml) and treated with 2N HCl (10 ml). After stirring under nitrogen at room temperature for 10 min, ether (100 ml) was added and the layers separated. The organic phase was washed with water, brine, dried and evaporated to dryness to give a pale yellow foam. The foam was dissolved in toluene (30 ml), DBN (1.5 ml) was added and stirred at room temperature for 2 hr. MDC (100 ml) and 2N HCl (50 ml) were added and stirring continued for 5 min. The layers were separated and the organic phase washed with water, brine and dried. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (5:4:1, hexanes:MDC:ether) gave 0.6 g (39%) of 2-benzyl-4-isopropyl-6-oxo-tetrahydrosaccharin as a pale yellow foam.

The tetrahydrosaccharin (0.59 g, 1.7 mmol) was dissolved in toluene (50 ml), dimethylamine hydrochloride (1.5 g, 18.0 mmol) and 4 A sieves (2.0 g) were added. The resulting mixture was refluxed with azeotropic removal of water for 96 hr. It was necessary to add additional dimethyl-amine hydrochloride (0.8 g, 10.0 mmol) and 4 A sieves every 12 hr during this 96 hr period at the end of which time, the

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reaction mixture was cooled to room temperature and filtered. The filter cake was washed with diethylether (100 ml) and the combined filtrates were concentrated in vacuo to give 0.63 g (99%) of 2-benzyl-4-isopropyl-6-dimethylamino-(4,5)-dihydrosaccharin as a pale yellow solid.

To a solution of the dihydrosaccharin (0.63 g, 1.7 mmol) in refluxing chloroform (50 ml) was added activated manganese dioxide (4.3 g, 49.5 mmol) in portions over a period of 4 hr. After the addition of the last portion of manganese dioxide, the reaction was refluxed for an additional hour, cooled to room temperature and filtered through a pad of Super-Cel, eluting with ethyl acetate. The combined eluates were concentrated in vacuo and the residue purified by flash chromatography on silica gel (5:4:1, hexanes:MDC:ether) to give 0.32 g (50%) of 2-benzyl-4-isopropyl-6-dimethylamino-saccharin as a colorless solid.

The 2-benzylsaccharin (0.32 g, 0.9 mmol) in methanol (20 ml) was treated with ammonium formate (0.24 g, 3.8 mmol) and 10% Pd on Carbon (0.25 g) and refluxed for 1 hr, cooled to room temperature and filtered through a pad of Super-Cel, eluting with methanol (100 ml). The combined eluates were concentrated in vacuo. The residue was dissolved in MDC (10 ml), glacial acetic acid (0.25 ml) was added, stirred for 5 min and evaporated to dryness in vacuo to give 0.25 g (100%) of 4-isopropyl-6-dimethylaminosaccharin as a colorless foam.

Following a procedure similar to that described in Preparation 1, a mixture of 4-isopropyl-6-dimethylamino-saccharin (0.27 g, 1.0 mmol), chloromethyl phenylsulfide (0.32 g, 2.0 mmol) and tetrabutylammonium bromide (0.1 g, 0.2 mmol) in toluene was converted to 0.22 g (56%) 2-phenylthiomethyl-4-isopropyl-6-dimethylaminosaccharin which was treated with sulfuryl chloride (1.86 ml 0.31 M solution, 0.6 mmol) to give 0.15 g of a yellow gum that contained 25% (by NMR) of 2-chloromethyl-4-isopropyl-

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6-dimethylamino-7-chlorosaccharin.

Preparation 22A

Thirty-one grams 4-isopropyl-1,2-dimethoxybenzene was treated with N-bromosuccinimide followed by butyllithium and diethyl carbamyl chloride as in preparation 6B to yield 15.2 g of 2-isopropyl-4,5-dimethoxy-N,N-diethylbenzamide as a viscous oil. The benzamide was treated according to preparation 18B with butyllithium and sulfur dioxide followed by sulfuryl chloride then ammonia to provide 4.5 g of the sulfonamide, mp 181-182°C from ether. This was cyclized in acetic acid as in preparation 18B to obtain 2.86 g of 6,7-dimethoxy-4-isopropylsaccharin, mp 210-212°C from ethyl acetate-hexane.

To a solution of 0.5 g 4-isopropyl-6,7-dimethoxysaccharin in 3 ml DMF was added 0.5 ml diisopropylethylamine at room temperature. After 15 min, 0.35 g chloromethyl phenyl sulfide was added and the mixture heated at 80°C for 16 hrs. The reaction mixture was poured into EtOAc and washed with aqueous Na_2CO_3 solution, aqueous 2N HCl solution, saturated aqueous NaCl solution. The organic layer was dried over Na_2SO_4 and the solvents removed. Chromatography with MDC gave 0.35 g of desired product, which was used immediately. Treatment of the 0.35 g sample of phenylthiomethyl saccharin in 3 ml MDC with 0.1 ml sulfuryl chloride for 30 min at 20° followed by removal of solvents and trituration with hexane gave 0.3 g of 2-chloromethyl-6,7-dimethoxy-4-isopropylsaccharin.

Preparation 22B

To a solution of 5.7 g of methyl piperonylate in 20 ml dry ether was added 30 ml 3.0 methyl magnesium bromide in ether at 0°C over 20 min. The mixture was stirred for 20 hrs then diluted with 200 ml ether and washed with water. The organic layer was dried with Na_2SO_4 and the solvents removed to yield 5.6 g crude 3,4-dimethoxy-

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(1'-hydroxy-1'-methylethyl)benzene. This material was immediately treated in 50 ml acetic acid with 1 g 0% Pd/C under 50 psi of hydrogen for 20 hrs. Filtration to remove catalyst and removal of solvent yielded 4.5 g of 5-isopropyl-1,3-benzodioxole. The isopropyldioxole was brominated, amidated, sulfonated and cyclized as in 22A to yield 700 mg 4-isopropyl-6,7-methylenedioxysaccharin, mp 226-228° from ethyl acetate/hexane. 500 mg saccharin was chloromethylated as in 22A to provide 300 mg of 2-chloromethyl-4-isopropyl-6,7-methylenedioxysaccharin, mp 174-176°.

Other 4-R_1-R_2-R_3-saccharins of formula II useful as intermediates for the preparation of compounds of formula I can be prepared as follows.

Reaction of 2-trifluoromethylbenzoic acid with thionyl chloride affords 2-trifluoromethylbenzoyl chloride, which, on reaction with diethylamine, affords 2-trifluoro-methyl-N,N-diethylbenzamide. Following a procedure similar to that described in Freparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-trifluoromethyl-6-aminosulfonyl-N,N-diethyl benzamide, which, on heating in glacial acetic acid, affords 4-trifluoromethylsaccharin.

Similarly, reaction of 2-trichloromethylbenzoic acid with thionyl chloride affords 2-trichloromethylbenzoyl chloride, which, on reaction with diethylamine, affords 2-trichloro-methyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-trichloromethyl-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-trichloromethylsaccharin.

Reaction of 4-cyclohexylbenzoic acid with thionyl chloride affords 4-cyclohexylbenzoyl chloride, which, on

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reaction with diethylamine, affords 4-cyclohexyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 4-cyclohexyl-2-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 6-cyclohexylsaccharin.

Benzylation of 6-nitrosaccharin affords 2-benzyl-6-nitrosaccharin which on reduction with stannous chloride and aqueous hydrogen chloride affords 2-benzyl-6-aminosaccharin. Reaction of the latter with methanesulfonyl chloride, trifluoromethylsulfonyl chloride or trichloromethylsulfonyl chloride in MDC in the presence of pyridine followed by transfer hydrogenolysis of the 2-benzyl protecting group affords, respectively, 6-methylsulfonylaminosaccharin, 6-trifluoromethylsulfonylaminosaccharin or 6-trichloromethylsulfonylaminosaccharin.

Diazotization of 6-aminosaccharin with nitrous acid in an acid medium and decomposition of the resulting diazonium salt in the presence of cupric cyanide or cupric chloride and sulfur dioxide, or cupric chloride and an alkali metal salt of methyl mercaptan or trifluoromethyl mercaptan affords, respectively, 6-cyanosaccharin, 6-chlorosulfonyl-saccharin, 6-methylthiosaccharin or 6-trifluoromethylthio-saccharin. Reaction of the 6-chlorosulfonylsaccharin in situ with ammonia or methanesulfonylamide affords, respectively, 6-aminosulfonylsaccharin and 6-methanesulfonylaminosulfonylsaccharin. Oxidation of 6-methylthiosaccharin and 6-trifluoromethylthiosaccharin with two molar equivalents of 3-chloroperbenzoic acid affords 6-methylsulfonylsaccharin and 6-trifluoromethylsulfonylsaccharin, respectively.

Hydrolysis of 6-cyanosaccharin by heating with aqueous sodium hydroxide affords saccharin-6-carboxylic acid. N-Benzylation of 6-cyanosaccharin affords 2-benzyl-6-cyanosaccharin. The latter on alkaline hydrolysis affords

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2-benzylsaccharin-6-carboxylic acid which on conversion to 2-benzylsaccharin-6-carboxylic acid chloride by reaction with thionyl chloride followed by exhaustive hydrogenation over palladium-carbon affords 6-hydroxymethylsaccharin. Oxidation of the latter with pyridine:chromium trioxide (2:1) complex (Collins reagent) in MDC affords 6-formylsaccharin, which on reductive amination with ammonia affords 6-aminomethylsaccharin.

Reaction of 4-trifluoromethylbenzoic acid with thionyl chloride affords 4-trifluoromethylbenzoyl chloride, which on reaction with diethylamine, affords 4-trifluoro-methyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 4-trifluoromethyl-2-aminosulfonyl-N,N-diethylbenzamide, which on heating in glacial acetic acid, affords 6-trifluoromethylsaccharin.

Reaction of 4-trichloromethylbenzoic acid with thionyl chloride affords 4-trichloromethylbenzoyl chloride, which, on reaction with diethylamine, affords 4-trichloro-methyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 4-trichloromethyl-2-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 6-trichloromethylsaccharin.

Reaction of 2-ethenylbenzoic acid with thionyl chloride affords 2-ethenylbenzoyl chloride, which on reaction with diethylamine, affords 2-ethenyl-N,N-diethylbenzamide. Reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-ethenyl-6-amino-

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sulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-ethenylsaccharin.

Reaction of 2-ethenyl-6-aminosulfonyl-N,N-diethylbenzamide with bromine affords 2-(1,2-dibromo-ethyl)-6-aminosulfonyl-N,N-diethylbenzamide which, on reaction with sodium amide in ammonia affords 2-ethynyl-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-ethynylsaccharin.

Reaction of ethyl 2-aminobenzoate with two molar equivalents of benzyl chloride in acetone in the presence of potassium carbonate affords ethyl 2-(N,N-dibenzylamino)-benzoate which, on saponification in aqueous ethanolic potassium hydroxide and isolation of the product from a neutral medium, affords 2-(N,N-dibenzylamino)benzoic acid. Reaction of the latter with thionyl chloride affords 2-(N,N-dibenzylamino)benzoyl chloride, which, on reaction with diethylamine, affords 2-(N,N-dibenzylamino)-N,N-diethylbenzamide. Reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-(N,N-dibenzyl)-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-(N,N-dibenzylamino)saccharin which, on catalytic debenzylation with hydrogen over palladium-on-charcoal, affords 4-aminosaccharin. Reductive alkylation of the latter with one molar equivalent of formaldehyde in formic acid affords 4-methylaminosaccharin. Diazotization of 4-aminosaccharin with nitrous acid in an acid medium and decomposition of the resulting diazonium salt in the presence of cupric cyanide affords 4-cyanosaccharin.

Selective N-benzylation of the cesium salt of 6-hydroxy-4-isopropylsaccharin (Preparation 19) with benzyl bromide and reaction of the 2-benzyl-6-hydroxy-4-isopropylsaccharin with N,N-diethylthiocarbamyl chloride in DMF using the procedure described above in Preparation 12 affords

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2-benzyl-4-isopropyl-6-(N,N-diethylthiocarbamyloxy)-saccharin which, on heating, rearranges to 2-benzyl-4-isopropyl-6-(N,N-diethylcarbamylthio)saccharin. The latter, on hydrolysis with alkali, affords 2-benzyl-4-isopropyl-6-mercaptosaccharin which on reaction with methyl iodide, and transfer hydrogenolysis affords 4-isopropyl-6-methylthiosaccharin. Oxidation of the latter with one or two molar equivalents of 3-chloroperbenzoic acid affords 4-isopropyl-6-methylsulfinylsaccharin and 4-isopropyl-6-methylsulfonylsaccharin.

Reaction of 2-isopropyl-4-fluorobenzoic acid with thionyl chloride affords 2-isopropyl-4-fluorobenzoyl chloride, which, on reaction with diethylamine, affords 2-isopropyl-4-fluoro-N,N-diethylbenzamide. Reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-isopropyl-4-fluoro-2-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-isopropyl-6-fluorosaccharin.

Reaction of the latter with thiophenol, 4-methylphenylthiophenol, 4-methoxyphenylthiophenol, 4-chlorophenylthiophenol, 1-mercapto-4-methylnaphthalene or 1-mercaptonaphthalene by heating the reactants in DMF affords, respectively, 4-isopropyl-6-phenylthiosaccharin, 4-isopropyl-6-(4-methylphenylthio)saccharin, 4-isopropyl-6-(4-methoxy-phenylthio)saccharin, 4-isopropyl-6-(4-chlorophenylthio)saccharin, 4-isopropyl-6-(4-methyl-1-naphthylthio)saccharin and 4-isopropyl-6-(1-naphthylthio)saccharin, oxidation of which in each case with one or two molar equivalents of 3-chloroperbenzoic acid affords 4-isopropyl-6-phenylsulfinyl-saccharin, 4-isopropyl-6-phenylsulfonylsaccharin, 4-isopropyl-6-(4-methylphenylsulfinyl)-saccharin, 4-isopropyl-6-(4-methylphenylsulfonyl)saccharin, 4-isopropyl-6-(4-methoxy-phenylsulfinyl)saccharin, 4-isopropyl-6-(4-methoxyphenyl-sulfonyl)saccharin, 4-isopropyl-

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6-(4-chlorophenylsulfinyl)-saccharin, 4-isopropyl-6-(4-chlorophenylsulfonyl)saccharin, 4-isopropyl-6-(4-methyl-1-naphthylsulfinyl)saccharin, 4-isopropyl-6-(4-methyl-1-naphthylsulfonyl)saccharin, 4-isopropyl-6-(1-naphthylsulfinyl)saccharin and 4-isopropyl-6-(1-naphthylsulfonyl)-saccharin.

Reaction of 2-benzyl-6-hydroxy-4-isopropyl-saccharin with one molar equivalent of acetic anhydride, benzoyl chloride or 1-naphthylcarboxylic acid chloride followed in each case by transfer hydrogenolysis affords, respectively, 4-isopropyl-6-acetoxysaccharin, 4-isopropyl-6-benzoyloxy-saccharin and 4-isopropyl-6-(1-naphthyl-carbonyloxy)-saccharin.

Heating 4-isopropyl-6-fluorosaccharin in DMF with azetidine, pyrrolidine, piperidine, morpholine, 1-benzyl piperazine, 1-methylpiperazine, imidazole, t-butyl alpha-aminoacetate or ammonia affords, respectively, 4-isopropyl-6-(1-azetidinyl)saccharin, 4-isopropyl-6-(1-pyrrolidinyl)-saccharin, 4-isopropyl-6-(1-piperidinyl)saccharin, 4-isopropyl-6-(4-morpholinyl)saccharin, 4-isopropyl-6-(4-benzyl-1-piperazinyl)saccharin, 4-isopropyl-6-(4-methyl-1-piperazinyl)saccharin, 4-isopropyl-6-(1-1H-imidazolyl)-saccharin, 4-isopropyl-6-(t-butoxycarbonylmethylamino)-saccharin and 4-isopropyl-6-aminosaccharin.

Catalytic debenzylation of 4-isopropyl-6-(4-benzyl-1-piperazinyl)saccharin with hydrogen over palladium-on-charcoal affords 4-isopropyl-6-(1-piperazinyl)-saccharin.

Hydrolysis of 4-isopropyl-6-(t-butoxycarbonyl-methylamino)saccharin with dilute hydrochloric acid and isolation of the product from a neutral medium affords 4-isopropyl-6-carboxymethylaminosaccharin.

Reaction of 4-isopropyl-6-aminosaccharin with one molar equivalent of acetyl chloride affords 4-isopropyl-6-acetylaminosaccharin.

Saponification of 4-methoxycarbonylsaccharin

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(Preparation 9D) to the corresponding saccharin-4-carboxylic acid by alkaline hydrolysis, conversion of the acid to the corresponding acid chloride by reaction of the acid with thionyl chloride and reaction of the acid chloride with ammonia affords saccharin-4-carboxamide.

Reaction of each of the 4-R^4-R^5-saccharins so-prepared with paraformaldehyde and chlorotrimethylsilane in the presence of stannic chloride in ethylene dichloride affords the 4-R^4-R^5-2-chloro-methylsaccharins of formula IV listed in TABLE B where, in each instance, X is Cl.

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TABLE B

Preparation	R^4	R^5
23A	CF_3	H
23B	CCl_3	H
23C	H	6-cyclohexyl
23D	H	6-CH_3SO_2NH
23E	H	6-CF_3SO_2NH
23F	H	6-CCl_3SO_2NH
23G	H	6-CN
23H	H	6-NH_2SO_2
23I	H	6-$CH_3SO_2NHSO_2$
23J	H	6-CH_3SO_2
23K	H	6-CF_3SO_2
23L	H	6-HOOC
23M	H	6-$HOCH_2$
23N	H	6-OHC
23O	H	6-NH_2CH_2
23P	H	6-CF_3
23Q	H	6-CCl_3
23R	$CH=CH_2$	H
23S	C≡CH	H
23T	NH_2	H
23U	CH_3NH	H
23V	$(CH_3)_2N$	H
23W	$CH(CH_3)_2$	6-CH_3S
23X	$CH(CH_3)_2$	6-CH_3SO
23Y	$CH(CH_3)_2$	6-CH_3SO_2
23Z	$CH(CH_3)_2$	6-F
23AA	$CH(CH_3)_2$	6-C_6H_5S
23AB	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4S$)
23AC	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4S$)
23AD	$CH(CH_3)_2$	6-(4-ClC_6H_4S)
23AE	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-S)

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TABLE B (cont'd)

Preparation	R^4	R^5
23AF	$CH(CH_3)_2$	6-(1-naphthyl-S)
23AG	$CH(CH_3)_2$	6-C_6H_5SO
23AH	$CH(CH_3)_2$	6-$C_6H_5SO_2$
23AI	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4SO$)
23AJ	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4SO_2$)
23AK	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4SO$)
23AL	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4SO_2$)
23AM	$CH(CH_3)_2$	6-(4-ClC_6H_4SO)
23AN	$CH(CH_3)_2$	6-(4-$ClC_6H_4SO_2$)
23AO	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-SO)
23AP	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-SO_2)
23AQ	$CH(CH_3)_2$	6-(1-naphthyl-SO)
23AR	$CH(CH_3)_2$	6-(1-naphthyl-SO_2)
23AS	$CH(CH_3)_2$	6-CH_3COO
23AT	$CH(CH_3)_2$	6-C_6H_5COO
23AU	$CH(CH_3)_2$	6-(1-naphthyl-COO)
23AV	$CH(CH_3)_2$	6-(1-azetidinyl)
23AW	$CH(CH_3)_2$	6-(1-pyrrolidinyl)
23AX	$CH(CH_3)_2$	6-(1-piperidinyl)
23AY	$CH(CH_3)_2$	6-(4-morpholinyl)
23AZ	$CH(CH_3)_2$	6-(4-benzyl-1-piperazinyl)
23BA	$CH(CH_3)_2$	6-(4-methyl-1-piperazinyl)
23BB	$CH(CH_3)_2$	6-(1-1H-imidazolyl)
23BC	$CH(CH_3)_2$	6-($NHCH_2COOC_4H_9$-t)
23BD	$CH(CH_3)_2$	6-NH_2
23BE	$CH(CH_3)_2$	6-(1-piperazinyl)
23BF	$CH(CH_3)_2$	6-($NHCH_2COOH$)
23BG	$CH(CH_3)_2$	6-(CH_3CONH)
23BH	$CONH_2$	H
23BI	H	$CONH_2$
23BJ	CN	H

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Preparation 23BK

Reaction of isothiazole-5-carboxaldehyde with lithium 3-(triphenylphosphoranylidene)propanoate under standard Wittig conditions provides 4-(5-isothiazolyl)-3-butenoic acid which is reduced and cyclized with aluminum chloride to provide 4-oxo-4,5,6,7-tetrahydrobenzisothiazole. The 4-oxo compound is reacted with methylenetriphenyl phosphorane under standard Wittig conditions and a methylene is inserted into the resulting 4-methylene compound via a Simmons Smith reaction to provide 6,7-dihydrospiro[benzisothiazol-4(5H),1'-cyclopropane] which is oxidized with hydrogen peroxide in acetic acid to give 6,7-dihydrospiro[3-oxo-benzisothiazol-4(5H),1'-cyclopropane 1,1-dioxide (4-spirocyclopropyl tetrahydrosaccharin). This is chloromethylated according to the procedure of Preparation 1A to give 2-chloromethyl-4-spirocyclopropyl-4,5,6,7-tetrahydrosaccharin.

Preparation 23BL

2-Benzyl-4-isopropyl-6-oxo-tetrahydrosaccharin of preparation 21 is reduced with sodium borohydride and methylated with methyl iodide in the presence of sodium hydride to provide 2-benzyl-4-isopropyl-6-methoxytetrahydrosaccharin. This is debenzylated and chloromethylated as in preparation 21 to provide 2-chloromethyl-4-isopropyl-6-methoxy-4,5,6,7-tetrahydrosaccharin.

Preparation 24

Following a procedure substantially similar to that described by Cale et al. (J. Med. Chem. 1989, 32, 2178) there was prepared: 3,5-dichloro-4-pyridinecarboxylic acid, white crystals, m.p. 231-235°C (dec.).

Preparation 25

97% sodium hydride (2.72 g. 0.11 mol) was suspended in THF (100 ml) under nitrogen and a solution of N-(2-hydroxyethyl)morpholine (14.4 g, 0.11 mol) in THF

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(15 ml) was added in portions. When hydrogen evolution had ceased, a solution of 2,3,5-trichloropyridine (18.2 g, 0.10 mol) in THF (25 ml) was added at such a rate as to maintain a gentle reflux. The reaction mixture was refluxed for 2 hours and the solvent was subsequently removed in vacuo. The residue was taken up in water/CH_2Cl_2, the organic layer was separated and the solvent was removed in vacuo to afford 26.3 g. (94.9%) of 3,5-dichloro-2-[2-(4-morpholinyl)ethoxy]-pyridine as a crystalline solid.

A solution of lithium diisopropylamide (6.4 g, 0.06 mol) in THF (100 ml) under nitrogen was cooled to -70°C and a solution of 3,5-dichloro-2-[2-(4-morpholinyl)-ethoxy]pyridine (13.0 g, 0.047 mol) in THF (10 ml) was added via syringe. The yellow/red solution was stirred for 30 minutes at -70°C and then was slowly warmed to room temperature. The mixture was poured onto crushed dry ice/THF and upon evaporation of the dry ice the solvent was removed in vacuo. The residue was taken up in dilute ammonium hydroxide and extracted with chloroform (2X). The organic layer was separated and concentrated in vacuo to afford 6.0 g of recovered starting material. The aqueous layer was concentrated in vacuo and 3N HCl was added to the residue. The solution was cooled and a solid was obtained which was collected by filtration. The solid was recrystallized from water to afford 3,5-dichloro-2-[2-(4-morpholinyl)-ethoxy]pyridine-4-carboxylic acid hydrochloride as a white solid in 71% yield (based on recovered starting material), m.p. 230-231°C (dec.).

By a substantially similar process it is contemplated that 3,5-dichloro-2-[2-(pyrrolidinyl)ethoxy]-pyridine, 3,5-dichloro-2-[2-(pyrrolidinyl)ethoxy]pyridine-4-carboxylic acid hydrochloride, 3,5-dichloro-2-[2-(piperidinyl)ethoxy]pyridine, 3,5-dichloro-2-[2-(piperidinyl)-ethoxy]pyridine-4-carboxylic acid hydrochloride, 3,5-dichloro-2-[2-(piperazinyl)ethoxy]pyridine, 3,5-dichloro-2-[2-

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(piperazinyl)ethoxy]pyridine-4-carboxylic acid hydrochloride, 3,5-dichloro-2-[2-(4-methylpiperazinyl)ethoxy]pyridine and 3,5-dichloro-2-[2-(4-methylpiperazinyl)ethoxy]pyridine-4-carboxylic acid hydrochloride can be prepared from 2,3,5-trichloropyridine and the appropriate N-(2-hydroxyethyl)amine derivative.

Preparation 26

Following a procedure substantially similar to that described in preparation 25 there was prepared: 3,5-dichloro-2-[2-dimethylamino)ethoxy]pyridine, in a 36% yield and 3,5-dichloro-2-[2-(dimethylamino)ethoxy]pyridine-4-carboxylic acid hydrochloride in 1.3% yield, m.p. 184-186°C (dec.) when recrystallized from water.

Preparation 27

Concentrated HCl (450 ml) was added to ethyl 2,4-dioxovalerate (177.8 g, 1.1 mol) followed by hydroxylamine hydrochloride (103.7 g, 1.68 mol). The reaction mixture was stirred for 7 hours, then allowed to stand for 60 hours. The solvent was removed in vacuo and the residue was chilled on ice. A solid formed which was collected by filtration and washed with cold water. The solid was dissolved in THF (1 l), the solution was filtered and the solvent was removed in vacuo. The residue was slurried with ethyl acetate (200 ml) and the solid collected by filtration. Concentration of filtrate to approximately 30 ml afforded a second crop of the product. The two crops were combined and recrystallized from methanol to afford 82.1 g (58%) of 3-methylisoxazole-5-carboxylic acid, m.p. 209-211°C

.Preparation of The Final Products

Example 1

A mixture of isonicotinic acid (0.98 g, 0.008 mol), 2-bromomethylsaccharin (2.11 g, 0.008 mol), triethylamine (0.81 g, 0.008 mol) and xylene (25 ml) were refluxed for 1 hour. The solvent was removed in vacuo and the residue was partitioned between water and methylene dichloride. The

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organic layer was separated and the solvent removed in vacuo. The solid residue was recrystallized from CH_3CN to afford 0.9 g (37%) of 2-saccharinylmethyl pyridine-4-carboxylate as a yellow solid, m.p. 145-146°C.

Example 2

Following a procedure which was substantially similar to that described in Example 1 but substituting 3,5-dichloro-4-pyridinecarboxylic acid for isonicotinic acid there was obtained 2-saccharinylmethyl 3,5-dichloro-pyridine-4-carboxylate in a 29% yield, m.p. 159-160°C.

Example 3

A solution of the free base of 3,5-dichloro-2-[2-(4-morpholinyl)ethoxy)pyridine-4-carboxylic acid hydrochloride (3.6 g, 0.01 mol) and cesium carbonate (4.85 g, 0.015 mol) in methanol (50 ml) was stirred for 30 minutes. The methanol was removed in vacuo and the residue was dissolved in DMF (50 ml). 2-Chloromethyl-4-(isopropyl)-saccharin (3.0 g, 0.01 mol) was then added and the reaction mixture was heated at 80°C for 3 hours. The DMF was removed in vacuo, the residue was taken up in methylene dichloride and was filtered through charcoal. The solvent was removed in vacuo, the residue was taken up in t-butylmethyl-ether and the solution was filtered. The solvent was removed in vacuo and the residue was treated with ethereal HCl. A gum was obtained which was triturated with CH_3CN to afford 0.5 g (9%) of 4-(isopropyl)-2-saccharinylmethyl 3,5-dichloro-2-[2-(4-morpholinyl)ethoxy]pyridine-4-carboxylate hydrochloride as a white solid, m.p. 120-140°C.

Example 4

A mixture of 3,5-dichloro-4-pyridinecarboxylic acid (0.42 g, 0.002 mol), cesium carbonate (0.36 g, 0.001 mol) and methanol (10 ml) was stirred for 30 minutes. The solvent was removed in vacuo and 2-chloromethyl-4-isopropyl-saccharin (0.55 g, 0.002 mol) and DMF (10 ml) were added to the residue. The mixture was heated to 75°C and stirred for

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hours. The solvent was removed in vacuo and the residue was partitioned between water/methylene dichloride. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was treated with ethereal HCl to afford a white gum which was triturated with Et_2O (2X), then acetone. A white solid was obtained which was collected by filtration and dried in high vacuum to afford 0.14 g (15%) of 4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate hydrochloride, m.p. 93-95°C.

Example 5

A mixture of 3,5-dichloro-2-[2-(dimethylamino)-ethoxy]pyridine-4-carboxylic acid hydrochloride (2.65 g, 0.0084 mol), cesium carbonate (4.1 g, 0.013 mol), tetrabutyl-ammonium bromide (1.0 g, 0.003 mol) and DMF (25 ml) was stirred for 10 minutes, then 2-chloromethyl-4-isopropyl-6-methoxysaccharin (2.4 g, 0.0084 mol) was added. The mixture was heated to 80°C. and stirred for 1 hour. The solvent was removed in vacuo and the residue was partitioned between water/methylene dichloride. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was dissolved in ethyl acetate and filtered through a plug of silica. Ethereal HCl was added to the filtrate and the solvent was removed in vacuo. The residue was washed with ether (50 ml), treated with saturated $NaHCO_3$ and extracted with methylene dichloride. The solvent was removed in vacuo, the residue was triturated with methanol and an off-white solid was collected by filtration. The product was dried in high vacuum to afford 0.096 g (2.1%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl 3,5-dichloro-2-[2-(dimethylamino)ethoxy] pyridine-4-carboxylate, m.p. 155-160°C.(dec).

By a substantially similar process it is contemplated that 4-isopropyl-6-methoxy-2-saccharinyl-methyl 3,5-dichloro-2[2-(pyrrolidinyl)ethoxy]pyridine-

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4-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl 3,5-dichloro-2-[2-(piperidinyl)ethoxy]pyridine-4-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl 3,5-dichloro-2-[2-(piperazinyl)ethoxy]pyridine-4-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl 3,5-di-chloro-2-[2-(4-methylpiperazinyl)ethoxy]pyridine-4-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl 2-trifluoro-methylpyridine-4-carboxylate and 4-isopropyl-6-methoxy-2-saccharinylmethyl 2-methoxypyridine-4-carboxylate can be prepared from 2-chloromethyl-4-isopropyl-6-methoxy-saccharin and the appropriate carboxylic acid derivative.

Example 6

A mixture of 3-thiophene carboxylic acid (0.26 g, 2.0 mmol), K_2CO_3 (0.28 g, 2.0 mmol) and DMF (4 ml) was stirred for 1 hour. 2-Chloromethyl-4-isopropyl-6-methoxy-saccharin (0.61 g, 2.0 mmol) was then added and the mixture was stirred for 24 hours. Water (20 ml) was added to the reaction mixture and the solution was extracted with ether (2 x 40 ml). The organic layer was separated, washed with water, then brine and was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the solid residue was recrystallized from toluene/hexane to afford 0.5 g (65%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl thiophene-3-carboxylate as a white powder, m.p. 125-127°C.

By a substantially similar process it is contemplated that 4-isopropyl-6-methoxy-2-saccharinyl-methyl 4-methoxy-thiophene-3-carboxylate can be prepared from 2-chloromethyl-4-isopropyl-6-methoxysaccharin and 4-methoxy-3-thiophene carboxylic acid.

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Example 7

Following a procedure substantially similar to that described in Example 6 but substituting 3-methyl-2-thiophene carboxylic acid for 3-thiophene carboxylic acid there was obtained 4-isopropyl-6-methoxy-2-saccharinylmethyl 3-methylthiophene-2-carboxylate as a white powder in 78% yield, m.p. 132-134°C.

Example 8

Following a procedure substantially similar to that described in Example 6 but substituting 2-thiophene carboxylic acid for 3-thiophene carboxylic acid there was obtained 4-isopropyl-6-methoxy-2-saccharinylmethyl thiophene-2-carboxylate as white crystals in 62% yield, m.p. 139-141°C.

Example 9

Following a procedure substantially similar to that described in Example 6 but substituting 3-chloro-2-thiophene carboxylic acid for 3-thiophene carboxylic acid there was obtained 4-isopropyl-6-methoxy-2-saccharinylmethyl 3-chlorothiophene-2-carboxylate as an off-white powder in 65% yield, m.p. 138-140°C.

Example 10

A mixture of 3-methylisoxazole-5-carboxylic acid (0.63 g, 5.0 mmol), cesium carbonate (0.8 g, 2.45 mmol) and methanol was stirred for 30 minutes. The solvent was removed in vacuo and the residue was dried in high vacuum for 1 hour. The residue was suspended in DMF (30 ml) and 2-chloromethyl-4-isopropyl-6-methoxysaccharin (1.0 g, 3.3 mmol) was added. The mixture was stirred at room temperature for 19 hours and was poured into water. The mixture was extracted with ethyl acetate/ether (4/1, 300 ml) and the organic layer was separated and washed with water, then brine. The solvent was removed in vacuo and the residue was purified by flash chromatography (30% ethyl acetate/-hexanes) to afford 1.1 g (85%) of 4-isopropyl-6-methoxy-

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2-saccharinylmethyl 3-methylisoxazole-5-carboxylate as a white powder, m.p. 157-158°C.

Example 11

A mixture of 2-pyrrolidone-5-carboxylic acid (0.85 g, 6.6 mmol), cesium carbonate (1.07 g, 3.3 mmol) and methanol was stirred for 30 minutes. The solvent was removed in vacuo and the residue was dried in high vacuum for 1 hour. The residue was suspended in DMF (30 ml) and 2-chloromethyl-4-isopropyl-6-methoxysaccharin (1.0 g, 3.3 mmol) was added. The mixture was stirred at room temperature for 24 hours and was poured into water. The mixture was extracted with ethyl acetate/ether (4/1) and the organic layer was separated and washed with water, then brine. The solvent was removed in vacuo and the residue was purified by flash chromatography (CH_2Cl_2 followed by 2% methanol/CH_2Cl_2) to afford 0.56 g (53%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl 2-oxopyrrolidine-5-carboxylate, m.p. 159-160°C.

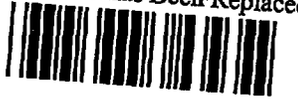
Example 12

Acetonitrile (3 ml), followed by N,N-diisopropylethylamine (0.26 ml, 1.5 mmol) were added to 3,5-dimethylisoxazole-4-carboxylic acid (0.21 g, 1.5 mmol). The mixture was stirred for 5 minutes, then 2-chloromethyl-4-isopropyl-6-methoxysaccharin (0.30 g, 1 mmol) was added. The reaction mixture was stirred at room temperature for 18 hours, diluted with ethyl acetate (75 ml) and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by preparative layer chromatography eluting with CH_2Cl_2 (100%) to afford 0.041 g (10%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl 3,5-dimethylisoxazole-4-carboxylate as a white solid, m.p. 136.8-139.1°C.

Example 13

Acetonitrile (3 ml), followed by N,N-diisopropylethylamine (0.26 ml, 1.5 mmol) were added to 3,5-dimethyl-

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1-phenylpyrazole-4-carboxylic acid (0.44 g, 2.0 mmol). The mixture was stirred for 5 minutes then 2-chloromethyl-4-isopropyl-6-methoxysaccharin (0.30 g, 1 mmol) was added. The reaction mixture was stirred at room temperature for 35 hours, then at 80°C for 1 hour. The mixture was diluted with ethyl acetate (75 ml), washed with saturated $NaHCO_3$, and the organic layer was dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized from ethanol to afford 0.31 g (64%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl 3,5-dimethyl-1-phenylpyrazole-4-carboxylate as a yellow solid, m.p. 167.3-169.4°C.

Example 14

Acetonitrile (20 ml), followed by N,N-diisopropylethylamine (5.8 ml, 33 mmol) were added to 2,4-dimethyl-3-pyridinecarboxylic acid (5.1 g, 33 mmol). The mixture was stirred for 5 minutes, then 2-chloromethyl-4-isopropyl-6-methoxysaccharin (4.3 g, 14 mmol) was added. The reaction mixture was stirred at room temperature for 47 hours, then at 80°C for 1 hour. The mixture was diluted with ethyl acetate (100 ml), washed with saturated $NaHCO_3$, and the organic layer was dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized from ether to afford 3.4 g (57%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,4-dimethylpyridine-3 carboxylate, m.p. 132.1-133.5°C.

Example 15

Following a procedure substantially similar to that described in Example 11 but substituting 1,3-dimethyl-5-chloroindole 2-carboxylic acid (prepared via a standard Fischer indole synthesis using 4-chlorophenylhydrazine hydrochloride and alpha-ketobutyric acid, followed by N-methylation of the resulting ethyl 3-methyl-5-chloroindole-2-carboxylate and saponification of the ester) for 2-pyrrolidone-5-carboxylic acid there was obtained 4-isopropyl-6-methoxy-2-saccharinylmethyl 1,3-dimethyl-

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5-chloroindole-2-carboxylate as white crystals in 38% yield, m.p. 183-184°C when recrystallized from ethyl acetate/-hexanes.

Example 16

Following a procedure substantially similar to that described in Example 11 but substituting furan-3-carboxylic acid, pyrrole-2-carboxylic acid, 1-methylpyrrole-2-carboxylic acid, pyrazole-4-carboxylic acid, pyrrolidine-2-carboxylic acid, isoxazole-5-carboxylic acid, or imidazole-2-carboxylic acid for 2-pyrrolidone-5-carboxylic acid it is contemplated that the following can be prepared: 4-isopropyl-6-methoxy-2-saccharinylmethyl furan-3-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl pyrrole-2-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl 1-methylpyrrole-2-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl pyrazole-4-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl pyrrolidine-2-carboxylate, 4-isopropyl-6-methoxy-2-saccharinylmethyl isoxazole-5-carboxylate and 4-isopropyl-6-methoxy-2-saccharinylmethyl imidazole-2-carboxylate.

Example 17

By reaction of an appropriate 4-R^4-R^5-2-halomethylsaccharin of formula IV with an appropriate heterocyclylcarboxylic acid using procedures substantially similar to those described above in Examples 1, 3 and 5, it is contemplated that the compounds of formula I listed in TABLE 1 can be prepared.

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TABLE 1

Example	R^4	R^5	Het
17A	Br	H	4-pyridinyl
17B	Cl	H	3-thienyl
17C	CH_3O	H	3,5-Cl_2-4-pyridinyl
17D	$CH(C_2H_5)_2$	H	3,5-Cl_2-4-pyridinyl
17E	CH_3O	6-CH_3O	3,5-Cl_2-4-pyridinyl
17F	H	7-Cl	3,5-Cl_2-4-pyridinyl
17G	CH_3O	5-CH_3O	3-CH_3-5-isoxazolyl
17H	$COOCH_3$	H	3,5-Cl_2-4-pyridinyl
17I	C_2H_5O	H	3-quinolinyl
17J	$(CH_3)_2CHO$	H	3,5-Cl_2-4-pyridinyl
17L	H	6-NO_2	3,5-Cl_2-4-pyridinyl
17M	H	5-$(CH_3)_3CCH_2C(CH_3)_2$	3,5-Cl_2-4-pyridinyl
17N	H	4,7-$(CH_3O)_2$	3,5-Cl_2-4-pyridinyl
17-O	C_2H_5O	7-$CH_3(OCH_2CH_2)_2O$	3-quinolinyl
17P	CH_3O	7-$CH_3(OCH_2CH_2)_2O$	3,5-Cl_2-4-pyridinyl
17Q	n-C_3H_7	H	3,5-Cl_2-4-pyridinyl
17R	CH_3	7-CH_3	2-oxo-5-pyrrolidinyl
17T	CF_3	H	3,5-$(CH_3)_2$-4-isoxazolyl

TABLE 1 (cont'd)

Example	R^4	R^5	Het
17U	CCl_3	H	3,5-Cl_2-4-pyridinyl
17V	H	6-cyclohexyl	3,5-Cl_2-4-pyridinyl
17W	H	6-CH_3SO_2NH	3,5-Cl_2-4-pyridinyl
17X	H	6-CF_3SO_2NH	3-isoquinolinyl
17Y	H	6-CCl_3SO_2NH	3,5-Cl_2-4-pyridinyl
17Z	H	6-CN	3,5-Cl_2-4-pyridinyl
17AA	H	6-NH_2SO_2	3,5-Cl_2-4-pyridinyl
17AB	H	6-$CH_3SO_2NHSO_2$	3,5-Cl_2-4-pyridinyl
17AC	H	6-CH_3SO_2	3-isoquinolinyl
17AD	H	6-CF_3SO_2	3,5-Cl_2-4-pyridinyl
17AE	H	6-HOOC	3,5-Cl_2-4-pyridinyl
17AF	H	6-$HOCH_2$	3,5-Cl_2-4-pyridinyl
17AG	H	6-OHC	3,5-Cl_2-4-pyridinyl
17AH	H	6-NH_2CH_2	3,5-Cl_2-4-pyridinyl
17AI	H	6-CF_3	3,5-$(CH_3)_2$-1-C_6H_5-4-pyrazolyl
17AJ	H	6-CCl_3	3,5-Cl_2-4-pyridinyl
17AK	$CH=CH_2$	H	3,5-Cl_2-4-pyridinyl
17AL	C≡CH	H	3,5-Cl_2-4-pyridinyl

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TABLE 1 (cont'd)

Example	R^4	R^5	Het
17AM	NH_2	H	3,5-Cl_2-4-pyridinyl
17AN	CH_3NH	H	1,3-$(CH_3)_2$-5-Cl-2-indolyl
17AO	$(CH_3)_2N$	H	3,5-Cl_2-4-pyridinyl
17AP	$CH(CH_3)_2$	6-CH_3S	3,5-Cl_2-4-pyridinyl
17AQ	$CH(CH_3)_2$	6-CH_3SO	3,5-Cl_2-4-pyridinyl
17AR	$CH(CH_3)_2$	6-CH_3SO_2	3,5-Cl_2-4-pyridinyl
17AS	$CH(CH_3)_2$	6-F	3-CH_3-2-thienyl
17AT	$CH(CH_3)_2$	6-C_6H_5S	3,5-Cl_2-4-pyridinyl
17AU	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4S$)	3,5-Cl_2-4-pyridinyl
17AV	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4S$)	3,5-Cl_2-4-pyridinyl
17AW	$CH(CH_3)_2$	6-(4-ClC_6H_4S)	3,5-Cl_2-4-pyridinyl
17AX	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-S)	5-benzimidazolyl
17AY	$CH(CH_3)_2$	6-(1-naphthyl-S)	3,5-Cl_2-4-pyridinyl
17AZ	$CH(CH_3)_2$	6-C_6H_5SO	3,5-Cl_2-4-pyridinyl
17BA	$CH(CH_3)_2$	6-$C_6H_5SO_2$	3,5-Cl_2-4-pyridinyl
17BB	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4SO$)	3,5-Cl_2-4-pyridinyl
17BC	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4SO_2$)	2-benzofuranyl
17BD	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4SO$)	3,5-Cl_2-4-pyridinyl
17BE	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4SO_2$)	3,5-Cl_2-4-pyridinyl
17BF	$CH(CH_3)_2$	6-(4-ClC_6H_4SO)	3,5-Cl_2-4-pyridinyl

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TABLE 1 (cont'd)

Example	R^4	R^5	Het
17BG	$CH(CH_3)_2$	6-(4-$ClC_6H_4SO_2$)	2-quinoxalinyl
17BH	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-SO)	3,5-Cl_2-4-pyridinyl
17BI	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-SO_2)	3,5-Cl_2-4-pyridinyl
17BJ	$CH(CH_3)_2$	6-(1-naphthyl-SO)	3,5-Cl_2-4-pyridinyl
17BK	$CH(CH_3)_2$	6-(1-naphthyl-SO_2)	3,5-Cl_2-4-pyridinyl
17BL	$CH(CH_3)_2$	6-CH_3COO	3,5-Cl_2-4-pyridinyl
17BM	$CH(CH_3)_2$	6-C_6H_5COO	2-quinoxalinyl
17BN	$CH(CH_3)_2$	6-(1-naphthyl-COO)	3,5-Cl_2-4-pyridinyl
17BO	$CH(CH_3)_2$	6-(1-azetidinyl)	3,5-Cl_2-4-pyridinyl
17BP	$CH(CH_3)_2$	6-(1-pyrrolidinyl)	3,5-Cl_2-4-pyridinyl
17BQ	$CH(CH_3)_2$	6-(1-piperidinyl)	3,5-Cl_2-4-pyridinyl
17BR	$CH(CH_3)_2$	6-(4-morpholinyl)	2-thianapthenyl
17BS	$CH(CH_3)_2$	6-(4-benzyl-1-piperazinyl)	3,5-Cl_2-4-pyridinyl
17BT	$CH(CH_3)_2$	6-(4-methyl-1-piperazinyl)	3,5-Cl_2-4-pyridinyl
17BU	$CH(CH_3)_2$	6-(1-1H-imidazolyl)	3,5-Cl_2-4-pyridinyl
17BV	$CH(CH_3)_2$	6-($NHCH_2COOC_4H_9$-t)	3,5-Cl_2-4-pyridinyl
17BW	$CH(CH_3)_2$	6-NH_2	2-benzothiazolyl
17BX	$CH(CH_3)_2$	6-(1-piperazinyl)	3,5-Cl_2-4-pyridinyl
17BY	$CH(CH_3)_2$	6-($NHCH_2COOH$)	3,5-Cl_2-4-pyridinyl
17BZ	$CH(CH_3)_2$	6-(CH_3CONH)	3,5-Cl_2-4-pyridinyl
17CA	$CONH_2$	H	3,5-Cl_2-4-pyridinyl

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TABLE_1 (cont'd)

Example	R^4	R^5	Het
17CB	CH_3	H	2-benzisothiazolyl
17CC	Ph	H	3,5-Cl_2-4-pyridinyl
17CD	$(CH_3)_3C$	H	3,5-Cl_2-4-pyridinyl
17CE	$C_2H_5CHCH_3$	H	3,5-Cl_2-4-pyridinyl
17CF	n-C_3H_7	5,6-$(CH_3O)_2$	5-benzimidazolyl
17CG	CH(CH3)2	5,6-$(CH_3O)_2$	3,5-Cl_2-4-pyridinyl
17CH	CH_3O	5-CH_3O	3,5-Cl_2-4-pyridinyl
17CI	C_2H_5	5,7-$(CH_3O)_2$	3,5-Cl_2-4-pyridinyl
17CJ	CH_3	H	3,5-Cl_2-4-pyridinyl
17CK	CH_3O	7-CH_3O	3-(1,8-naphthyridinyl)
17CL	C_2H_5	H	3,5-Cl_2-4-pyridinyl
17CM	$CH(CH_3)_2$	6-OH	3,5-Cl_2-4-pyridinyl
17CN	$CH(CH_3)_2$	6-$N(CH_3)_2$-7-Cl	3,5-Cl_2-4-pyridinyl
17CO	$CH(CH_3)_2$	6,7-CH_3O	3,5-Cl_2-4-pyridinyl
17CP	$CH(CH_3)_2$	6,7-methylenedioxy	3,5-Cl_2-4-pyridinyl
17CQ	OH	H	3,5-Cl_2-4-pyridinyl

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Example 17CQ

It is contemplated that following the procedure of Example 17, 2-chloromethyl-4-spirocyclopropyl-4,5,6,7-tetrahydrosaccharin of preparation 23BI can be coupled with 2,4-dimethyl-3-pyridinecarboxylic acid to provide 4-spirocyclopropyl-4,5,6,7-tetrahydro-2-saccharinylmethyl 2,4-dimethylpyridine-3-carboxylate.

Example 17CR

It is contemplated that following the procedure of Example 17, 2-chloromethyl-4-isopropyl-6-methoxy-4,5,6,7-tetrahydrosaccharin of preparation 23BJ can be coupled with 2,4-dimethyl-3-pyridinecarboxylic acid to provide 4-isopropyl-6-methoxy-4,5,6,7-tetrahydro-2-saccharinylmethyl 2,4-dimethylpyridine-3-carboxylate.

Example 18A

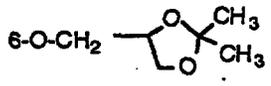
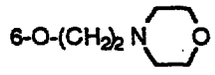
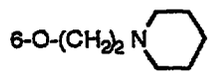
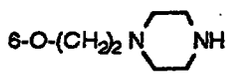
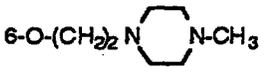
It is contemplated that 6-ethoxy-4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate can be prepared by treatment of 6-hydroxy-4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate with triphenylphosphine and diethyl azodicarboxylate in the presence of ethanol.

Following a procedure substantially similar to that of Example 18A it is contemplated that the compounds of Table 2 can be prepared from 6-hydroxy-4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate and the appropriate alcohol.

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Table 2

Example	R^5
18B	6-$OCH(CH_3)_2$
18C	
18D	6-$(OCH_2CH_2)_2OCH_3$
18E	6-OCH_2COOCH_3
18F	6-$OCH_2CH(OCH_3)$-CH_2OCH_3
18G	6-O-cyclobutyl
18H	6-O-$PO(OC_2H_5)_2$
18I	
18J	
18K	
18L	6-$O(CH_2)_2N(CH_3)_2$
18M	
18N	

The glycerol which can be used in the synthesis of Example 18F was obtained as follows:

A solution of 10.0 g (0.055 mol) of DL-alpha-O-benzylglycerol in a little THF was added to a suspension of 15.38 g (0.137 mol) of potassium tert-butoxide in 300 ml THF. The mixture was stirred for 1 hr at RT and 18.72 (0.132 mol) of iodomethane was added. A white solid immediately separated. The reaction was stirred for 10 hr at RT, cooled, carefully diluted with sodium chloride solution and extracted with ether. The organic layer was washed with water, 5% HCl, water and saturated NaCl and dried. The solvent was removed

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and the residue was purified by flash chromatography to give 1-benzyloxy-2,3-dimethoxypropane, 9.16 g (79%), as an oil.

A solution of 8.8 g (0.042 mol) of this material in 200 ml of MeOH was hydrogenated using 1.1 g 10% Pd/C at 50 psi. The catalyst was removed by filtration and the solvent under reduced pressure to give 4.4 g (87%) of 2,3-dimethoxy-1-propanol.

Example 18O

6-Ethoxy-4-isopropyl-2-phenylthiomethyl-saccharin was prepared from the 6-hydroxy analog (Preparation 19) by the procedure of Example 18A in 85% yield as a solid, mp 111.5-112.5°C, which was converted to 2-chloromethyl-6-ethoxy-4-isopropylsaccharin in 91% yield, mp 127-128°C, following the procedure of Preparation 18A.

Example 18P

Following a procedure substantially similar to that described in Example 18A it is contemplated that 4-benzyl-oxy-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate can be prepared from benzyl alcohol and 4-hydroxy-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate.

Example 19

It is contemplated that 6-hydroxy-4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate can be treated with trifluoromethanesulfonic anhydride in the presence of triethylamine to afford 4-isopropyl-6-trifluoro methanesulfonyloxysaccharinylmethyl 3,5-dichloropyridine-4-carboxylate.

The trifluoromethanesulfonate can then be heated with 1-methyl-2-trimethylstannyl-pyrrole, tetrakis (triphenylphosphine) palladium (O), lithium chloride and 2,6-di-t-butyl-4-methylphenol and p-dioxane to produce 4-isopropyl-6-[2-[1-methyl]pyrrolyl]saccharinylmethyl 3,5-dichloropyridine-4-carboxylate.

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Example 20

It is contemplated that treatment of the trifluoromethanesulfonate of Example 19 with dimethylamine will produce 4-isopropyl-6-dimethylaminosaccharinylmethyl 3,5-dichloropyridine-4-carboxylate.

Example 21

It is contemplated that heating a mixture of 4-isopropyl-6-hydroxy-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate and di-(sec-butoxymethyl)methylamine in toluene will produce 2-(3,5-dichloro-4-pyridylcarboxymethyl)-4-isopropyl-8-methyl-2,3,7,8-tetrahydro-9H-[1,3]oxazino[6,5-g]benzisothiazol-3-one 1,1-dioxide.

Example 22

It is contemplated that treatment of the isopropylidene of Example 18C, Table 2, with p-toluenesulfonic acid monohydrate in methanol-chloroform will afford 6-(2,3-dihydroxypropoxy)-4-isopropylsaccharinylmethyl 3,5-dichloropyridine-4-carboxylate.

Example 23

It is contemplated that treatment of 6-hydroxy-4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate with t-butyl bromoacetate and K_2CO_3 in acetone will afford 6-(2-t-butoxy-2-oxoethoxy)-4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate.

In a similar manner 6-(2-benzyloxy-2-oxoethoxy)-4-isopropyl-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate can be prepared using benzyl bromoacetate.

Example 24A

To freshly distilled cyclopentadiene (25 ml) at 0°C was added 4-bromo-2-(t-butyl)isothiaziol-3(2H)-one 1,1-dioxide (Helv. Chim. Acta., 72, 1416, 1989) (7.9 g, 0.03 mol). After stirring at 0°C under nitrogen for 16 hr, the reaction mixture was concentrated in vacuo. The residue was purified by filtering through silica gel, eluting

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with hexanes (500 ml) followed by 20% ethyl acetate in hexanes (500 ml). The latter eluents were concentrated in vacuo to give 9.8 g (100% of the norbornene adduct, 3a-bromo-2-t-butyl-3a,4,7,7a-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, as a white solid.

The adduct (0.4 g, 1.2 mmol) in 25 ml ethyl acetate containing 5% Pd on $CaCO_3$ (0.2 g) was stirred under one atmosphere of hydrogen for 4 hr, and the reaction mixture was filtered through a pad of silica gel, eluting with ethyl acetate (100 ml). The eluents were concentrated in vacuo and the residue crystallized from hexanes to give 0.4 g (100%) of the bromo norbornane as a white crystalline solid.

To a solution of the bromo norbornane (3.7 g, 0.011 mol) in toluene (25 ml) at 0°C was added diazabicyclononene (1.37 g, 0.011 mol) in toluene (10 ml). After stirring at 0°C for 20 min, silica gel (25 g) was added to the reaction mixture. The resulting slurry was loaded on top of a 15 cm pad of silica gel and eluted with 20% ethyl acetate in hexanes (800 ml). The eluents were concentrated in vacuo to give 2.8 g (100%) of the dehydrobrominated compound as a white solid.

The 2-t-butyl-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)one 1,1-dioxide (2.8 g, 0.011 mol) in trifluoroacetic acid (30 ml) was heated at reflux for 48 hr and let stand at room temperature for 4 days. The resulting mixture was concentrated in vacuo, treated with methanol (20 ml) and evaporated to dryness. The residue was taken up in ether (100 ml) and washed with saturated $NaHCO_3$ (1 x 50 ml). The layers were separated, the aqueous phase acidified to pH 1 with 2N HCl and extracted with MDC (2 x 100 ml). The combined organic extracts were dried and concentrated in vacuo to give 0.9 g (42%) of the bicyclo (2.2.1) saccharin derivative as a white solid.

A mixture of the bicyclo (2,2,1) saccharin derivative (0.9 g, 5 mmol), chloromethyl phenylsulfide

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(0.07 g, 7 mmol) and tetrabutylammonium bromide (0.36 g, 0.16 mmol) in toluene (50 ml) was refluxed under nitrogen for 16 hr, cooled to room temperature and evaporated to dryness under vacuum. The residue was purified by flash chromatography on silica gel (100 g) using 100% MDC as the eluent to give 1.05 (72%) of the sulfide as a viscous oil.

The sulfide (1.05 g, 3 mmol) in dichloromethane (100 ml) was treated with sulfuryl chloride (0.66 g, 5 mmol) and stirred for 2 hr. The resulting yellow solution was diluted with MDC (100 ml), washed with saturated $NaHCO_3$ solution, dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (33% MDC in hexanes) to give 0.66 g (81%) of 2-chloromethyl-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide.

It is contemplated that treatment of the 2-chloromethyl compound with 3,5-dichloro-4-pyridine carboxylic acid, 3-methyl-2-thiophene carboxylic acid, furan-3-carboxylic acid, 2-trifluoromethyl-4-pyridine carboxylic acid, 2-methoxy-4-pyridine carboxylic acid or 3,5-dichloro-2-[2-(4-morpholinyl)ethoxy]pyridine-4-carboxylic acid, respectively, using procedures similar to those described in Example 17 will produce 2-(3,5-dichloro-4-pyridinylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-methano-1,2-benziso-thiazol-3(2H)-one 1,1-dioxide, 2-(3-methyl-2-thienylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-methano-1,2-benziso-thiazol-3(2H)-one 1,1-dioxide, 2-(3-furanylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, 2-(2-trifluoromethyl-4-pyridinylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, 2-(2-methoxy-4-pyridinylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide or 2-(3,5-dichloro-2-[2-(4-morpholinyl)ethoxy]-4-pyridinylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-methano-

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1,2-benzisothiazol-3(2H)-one 1,1-dioxide.

Examples 24B and 24C

By a process analagous to that of Example 24A, it is contemplated that cyclohexadiene and 1,1-dimethylcyclopentadiene may be converted respectively to 2-chloromethyl-4,5,6,7-tetrahydro-4,7-ethano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide and 2-chloromethyl-8,8-dimethyl-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, which in turn can be treated with an appropriate heterocyclic carboxylic acid using procedures similar to those described in Example 17 to afford 2-(3-methylisoxazolylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-ethano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, 2-(1,3-dimethyl-5-chloro-2-indolylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-ethano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, 2-(2-imidazolylcarbonyloxymethyl)-4,5,6,7-tetrahydro-4,7-ethano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, 2-(2-oxo-5-pyrrolidinylcarbonyloxymethyl)-8,8-dimethyl-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1,-dioxide, 2-(3,5-dimethyl-1-phenyl-4-pyrazolylcarbonyloxymethyl)-8,8-dimethyl-4,5,6,7-tetrahydro-4,7-methano-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, or 2-(1-methyl-2-pyrrolylcarbonyloxymethyl)-8,8-dimethyl-4,5,6,7-tetrahydro-4,7-methano-1,2-benziso-hiazol-3(2H)-one 1,1-dioxide.

Examples 25A-25I

General procedure for the preparation of methyl-2-alkyl-cyclohexan-6-one carboxylate: To a suspension of anhydrous CuI (10 mmol) in anhydrous THF (100 ml) was added Me_2S (100 mmol) and the resulting solution was cooled to -78°C. The appropriate alkyl lithium reagent (20 mmol) was added over a period of 15 min. After being stirred at -78°C for an hour, a solution of cyclohexenone (10 mmol) in THF was added and stirring continued for another 15 min. To the resulting mixture was added HMPA (5 ml) and, after 15 min, methyl cyanoformate (30 mmol) in THF (20 ml) and the reaction

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warmed to room temperature and stirred overnight. The reaction mixture was quenched with 2N HCl (50 ml). The layers were separated and the aqueous phase extracted with Et_2O (1 x 100 ml). The combined organic extracts were washed with saturated NH_4Cl solution (3 x 50 ml), water (2 x 50 ml), brine (1 x 50 ml) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification by either Kugelrohr distillation or flash chromatography afforded the desired methyl 2-alkylcyclohexan-6-one carboxylate (Table C).

Table C

Intermediate	Alkyl	Yield	b.p.
B	Me	82	--
C	Et	70	100-110°C (0.2 mm)
D	iPr	74	106-109°C (0.5 mm)

General procedure for the preparation of methyl 2-benzylthio-6-alkylcyclohex-2-ene carboxylate and 2-benzylthio-6-alkyl-cyclohex-1-ene carboxylate: A mixture of methyl-2-alkyl-cyclohexan-6-one carboxylate (1 eq), benzylmercaptan (1.1 eq) and the acidic clay montmorillonite, KSF (1.5 times the weight of methyl-2-alkylcyclohexan-6-one carboxylate) in anhydrous toluene (50-100 ml) was refluxed under nitrogen with azeotropic removal of water for 12-14 hr and cooled to room temperature. The solids were filtered off and washed with ether. The combined filtrate was washed with 10% Na_2C0_3, water, brine and dried. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (10% ether in hexanes) gave a mixture of methyl 2-benzylthio-6-alkylcyclohex-2-ene carboxylate and methyl 2-benzylthio-6-alkylcyclohex-1-ene carboxylate (Table D) which was used in the next step as a mixture.

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Table D

Intermediate	Alkyl	Combined Yield of Mixture
A	H	40
B	Me	44
C	Et	50
D	iPr	52

General procedure for the preparation of 4-alkyl-tetrahydro saccharins: A solution of methyl 2-benzylthio-6-alkylcyclohex-2-ene-carboxylate and methyl 2-benzylthio-6-alkylcyclohex-1-ene carboxylate (1-10 mmol of the mixture) in 10 ml MDC was diluted with 20-50 ml glacial acetic acid and 1-5 ml water, the mixture cooled to -10°C, and chlorine gas was bubbled through the mixture until the exothermic reaction subsided. The mixture was then stirred for 10 minutes and taken to dryness to give a mixture of methyl 2-chlorosulfonyl-6-alkylcyclohex-2-ene carboxylate and 2-chlorosulfonyl-6-alkylcyclohex-1-ene carboxylate, which was dissolved in 10 ml THF and added to 25 ml of a solution of concentrated ammonium hydroxide while cooling in an ice/acetone bath. After stirring for 2 hr, the reaction mixture was concentrated in vacuo, the residue taken up in water, acidified to pH 1 with 2N HCl, and extracted with MDC. The organic phase was dried and concentrated in vacuo to give a mixture of methyl 2-aminosulfonyl-6-alkylcyclohex-2-ene carboxylate and 2-aminosulfonyl-6-alkylcyclohex-1-ene carboxylate. The mixture was dissolved in methanol and added to a freshly prepared solution of sodium methoxide (10-50 mmol) and stirred at ambient temperature for 12 hr. The reaction mixture was concentrated in vacuo, diluted with water and extracted with ether. The organic phase was discarded, and the aqueous phase was acidified to pH 1 with concentrated HCl and extracted with MDC. The organic extracts, on washing with brine, drying and evaporation to dryness, afforded

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4-alkyl-4,5,6,7-tetrahydrobenzisothiazol-3-one 1,1-dioxide or 4-alkyl-tetrahydrosaccharins (Table E).

Table E

Intermediates	Alkyl	Yield
A	H	50
B	Me	85
C	Et	80
D	iPr	74

A mixture of 4-alkyl-4,5,6,7-tetrahydrobenzisothiazol-3-one 1,1-dioxide (4-alkyltetrahydro saccharin) (1.0 eq), chloromethyl phenyl sulfide (1.5 eq) and tetrabutylammonium bromide (0.2 eq) in toluene (25 ml/g saccharin) was refluxed under nitrogen for 16-24 hr and then cooled to room temperature. The resulting mixture was evaporated to dryness and the residue chromatographed on silica gel eluting with hexanes/MDC (1:1 to 1:3) to give the corresponding 2-phenylthiomethyl-4-alkyl-4,5,6,7-tetrahydrobenziso-thiazole-3-one 1,1 dioxide or 2-phenylthiomethyl-4-alkyl-tetrahydrosaccharin (Table F).

Table F

Example	Alkyl	Yield
A	H	40
B	Me	55
C	Et	40
D	iPr	53

A solution of 2-phenylthiomethyl-4-alkyl-tetrahydro saccharin (1.0 eq) was treated with sulfuryl chloride (1.5 eq) and stirred for 2 hr. The resulting yellow solution was taken to dryness to give 2-chloromethyl-4-alkyltetrahydrosaccharin. It is contemplated that this derivative can be heated with an appropriate heterocyclic carboxylic acid, anhydrous potassium

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carbonate and tetrabutylammonium bromide in DMF to give the corresponding 4-alkyl-4,5,6,7-tetrahydro-2-saccharinyl-methyl heterocyclic carboxylate (Table G).

Table G

Example	Alkyl	Het
25A	H	3,5-Cl_2-4-pyridinyl
25B	Me	3-CH_3-2-thienyl
25C	Et	3-CH_3-5-isoxozolyl
25D	iPr	2-oxo-5-pyrrolidinyl
25E	H	3,5-$(CH_3)_2$-1-phenyl-4-pyrazolyl
25F	Me	1,3-$(CH_3)_2$-5-Cl-2-indolyl
25G	Et	3-furanyl
25H	iPr	1-CH_3-2-pyrrolyl
25I	iPr	2-imidazolyl
25J	iPr	2-CF_3-4-pyridinyl
25K	iPr	2-CH_3O-4-pyridinyl
25L	iPr	3,5-Cl_2-2-[2-(4-morpholinyl)ethoxy]-4-pyridinyl

Example 26

Methyl 2,2-dimethylcyclohexan-6-one carboxylate: To a suspension of anhydrous CuI (70.0 g, 0.37 mol) in anhydrous ether (500 ml) at 0°C was added halide-free methyl lithium (520 ml of 1.4 M solution in ether, 0.73 mol). After being stirred at 0°C for 15 minutes, a solution of 3-methyl-2-cyclohexenone (20.0 g, 0.18 mol) in ether (50 ml) was added and stirring continued for another 1 hr. To the resulting mixture was aded THF (50 ml) and HMPA (25 ml) and after 15 min methyl cyanoformate (45.0 g, 0.53 mol) in THF (20 ml) and the reaction warmed to room temperature and stirred for 3 hr. The reaction mixture was quenched with 2N HCl (50 ml). The layers were separated and the aqueous phase extracted with Et_2O (1 x 500 ml). The combined organic extracts were washed with saturated NH_4Cl solution (3 x 50 ml), water

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(2 x 50 ml), brine (1 x 50 ml) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification by Kugelrohr distillation afforded 34.0 g (99%) of methyl 2,2-dimethyl cyclohexane-6-one carboxylate, bp 80-84°C/0.6 mm.

The cyclohexanone can be converted to 4,4-dimethyl-4,5,6,7-tetrahydro-2-saccharinylmethyl 3,5-dichloropyridine-4-carboxylate following the procedure described above for Examples 25A-25L.

It should be appreciated that the methods described above would be equally applicable to the preparation of various other specific 4-R^4-R^5-2-saccharinylmethyl or 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylate derivatives. For example, treatment of an appropriate 4-R^4-R^5-2-halomethylsaccharin or 4,5,6,7-tetrahydro-2-halomethylsaccharin derivative with an appropriate heterocyclic carboxylic acid derivative will produce the desired 4-R^4-R^5-2-saccharinylmethyl or 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylate derivative, which in turn can undergo functional group transformations such as those described in Examples 18A-18P to produce other 4-R^4-R^5-saccharinylmethyl or 4,5,6,7-tetrahydro-2-saccharinylmethyl heterocyclic carboxylates.

Measurement of the inhibition constant, K_i, of a 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 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 K_i^* is then calculated.

The rate of inactivation, k_{on}, of enzymatic activity was determined for the compounds tested by measuring the

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enzyme activity of an aliquot of the respective enzyme as a function of time after addition of the test compound. By plotting the log of the enzyme activity against time, an observed rate of inactivation, k_{obs}, is obtained which can be represented as $k_{obs} = 1n2/t_{1/2}$ where $t_{1/2}$ is the 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.

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

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

The values obtained for k_{on} and K_i^* for specific substituted saccharin derivatives are shown in TABLE 3, the compounds being identified by the Example numbers above where their preparations are described.

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TABLE 3

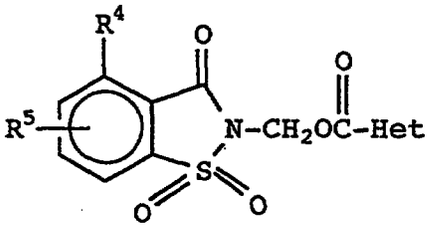
Example	K_{on} X 10^{-3} M^{-1} Sec^{-1}	K*i (nM)
1	1.2	40
2	11	10
3	1500	0.015
4	2300	0.01
5	455	0.022
6	47.6	0.21
7	625	0.016
8	100	0.10
9	131	0.076
10	63	0.16
11	50	0.20
12	28	0.36
13	9	1.1
14	500	0.02
15	6	1.5

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CLAIMS

1. A compound having the formula:



wherein:

Het is a 5- or 6-membered monocyclic heterocycle or a 9- or 10-membered bicyclic heterocycle containing from 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur or said heterocycles substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, oxo, phenyl, halogen, and -O-(C_2-C_{10} alkylene)-N=B where N=B is dilower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, or 4-lower-alkyl-1-piperazinyl;

R^4 is hydrogen, halogen, lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, lower-alkenyl, lower-alkynyl, cyano, carboxamido, amino, lower-alkylamino, dilower-alkylamino, lower-alkoxy, benzyloxy, lower-alkoxycarbonyl, hydroxy or phenyl; and

R^5 is hydrogen or from one to two substituents in any of the 5-, 6- or 7-positions selected from halogen, cyano, nitro, N=B', lower-alkyl-2-pyrrolyl, lower-alkylsulfonyl-amino, polyfluorolower-alkylsulfonylamino, polychlorolower-alkylsulfonyl-amino, aminosulfonyl, lower-alkyl, polyfluoro-lower-alkyl, polychlorolower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxylower-alkyl, methylenedioxy, cycloalkyloxy, formyl, aminomethyl, polyfluorolower-alkylsulfonyl, poly-

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chlorolower-alkylsulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxycarbonyl-lower-alkylamino, lower-alkylcarbonyl-amino, di(lower-alkyl)phosphonoxy, lower-alkoxy-poly-lower-alkyleneoxy, hydroxy-lower-alkoxy, polyhydroxy-alkoxy, or acetal or ketal thereof, polyalkoxy-alkoxy, -SR, -SOR, $-SO_2R$, -OCOR, -O-(C_1-C_{10} alkylene)-COOR, -O-(C_2-C_{10} alkylene)-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 and where N=B' is amino, lower-alkylamino, dilower-alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl or (carboxy-lower-alkyl)amino; or R^5 is a 5- or 6-membered saturated ring fused to the saccharin ring at the 5,6 or 6,7 positions, said ring containing two heteroatoms chosen from the group consisting of nitrogen, oxygen and sulfur or a methylated derivative of said ring;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof, with the proviso that, when R^4 and R^5 are both hydrogen, Het cannot be a dihydropyridine.

2. A compound as claimed in claim 1 wherein R^4 is hydrogen, halogen, lower-alkyl or lower-alkoxy and R^5 is hydrogen, lower-alkoxy, methylenedioxy, cycloalkyloxy, hydroxylower-alkoxy, polyhydroxy-alkoxy or acetal or ketal thereof, polyalkoxy-alkoxy, -O-(C_1-C_{10} alkylene)-COOR, or -O-(C_2-C_{10} alkylene)-N=B'.

3. A compound as claimed in claim 1 wherein Het is a 5- or 6-membered monocyclic heterocycle.

4. A compound as claimed in claim 3 wherein Het is pyridinyl or a substituted pyridinyl, R^4 is hydrogen, halogen, lower-alkyl or lower-alkoxy and R^5 is hydrogen, lower-alkoxy, methylenedioxy, cycloalkyloxy, hydroxylower-alkoxy,

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polyhydroxy-alkoxy or acetal or ketal thereof, polyalkoxy-alkoxy, -O-(C_1-C_{10} alkylene)-COOR, or -O-(C_2-C_{10} alkylene)-N=B'.

5. A compound as claimed in claim 4 wherein Het is 4-pyridinyl, 3,5-dichloro-4-pyridinyl, 2,4-dimethyl-3-pyridinyl, or 3,5-dichloro-2-[O-(C_2-C_{10} alkylene)-N=B]-4-pyridinyl; R^4 is hydrogen or lower-alkyl and R^5 is hydrogen, lower-alkoxy, or polyalkoxyalkoxy.

6. A compound as claimed in claim 5 wherein Het is 4-pyridinyl, 3,5-dichloro-4-pyridinyl, 2,4-dimethyl-3-pyridinyl, 3,5-dichloro-2-[2-(4-morpholinyl)ethoxy]-4-pyridinyl, or 3,5-dichloro-2-[2-(dimethylamino)ethoxy]-4-pyridinyl, R^4 is hydrogen or isopropyl, and R^5 is hydrogen or methoxy.

7. A compound as claimed in claim 3 wherein Het is thienyl or thienyl substituted by one or two, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy and halogen.

8. A compound as claimed in claim 7 wherein Het is thienyl, lower-alkylthienyl, lower-alkoxythienyl or halothienyl, R^4 is hydrogen, halogen, lower-alkyl or lower-alkoxy and R^5 is hydrogen, lower-alkoxy, methylenedioxy, cycloalkyloxy, hydroxylower-alkoxy, polyhydroxy-alkoxy or acetal or ketal thereof, polyalkoxy-alkoxy, -O-(C_1-C_{10} alkylene)-COOR, or -O-(C_2-C_{10} alkylene)-N=B' .

9. A compound as claimed in claim 8 wherein R^4 is lower-alkyl and R^5 is lower-alkoxy or polyalkoxyalkoxy.

10. A compound as claimed in claim 9 wherein Het is thienyl, methylthienyl, or chlorothienyl, R^4 is isopropyl and R^5 is methoxy.

11. A compound as claimed in claim 3 wherein Het is isoxazolyl or isoxazolyl substituted by one or two, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy and halogen.

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12. A compound as claimed in claim 11 wherein Het is isoxazolyl or (lower-alkyl)substituted isoxazolyl, R^4 is hydrogen, halogen, lower-alkyl or lower-alkoxy and R^5 is hydrogen, lower-alkoxy, methylenedioxy, cycloalkyloxy, hydroxylower-alkoxy, polyhydroxy-alkoxy or acetal or ketal thereof, polyalkoxy-alkoxy, -O-(C_1-C_{10} alkylene)-COOR, or -O-(C_2-C_{10} alkylene)-N=B'.

13. A compound as claimed in claim 12 wherein R^4 is lower-alkyl and R^5 is lower-alkoxy or polyalkoxyalkoxy.

14. A compound as claimed in claim 13 wherein Het is 3-methyl-5-isoxazolyl or 3,5-dimethyl-4-isoxazolyl, R^4 is isopropyl and R^5 is methoxy.

15. A compound as claimed in claim 3 wherein Het is pyrrolyl or pyrrolidinyl, or pyrrolyl or pyrrolidinyl substituted by one or two, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, oxo and halogen.

16. A compound as claimed in claim 3 wherein Het is pyrazolyl, imidazolyl or said heterocycle substituted by one or two, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, phenyl, and halogen.

17. A compound as claimed in claim 1 wherein Het is a 9- or 10-membered bicyclic heterocycle.

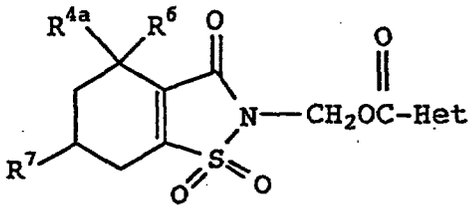
18. A compound as claimed in claim 17 wherein Het is indolyl or indolyl substituted by one or two, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy and halogen.

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19. A compound having the formula



wherein:

R^{4a} is hydrogen, lower-alkyl or phenyl;

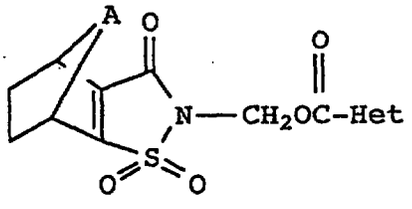
R^6 is hydrogen or primary lower-alkyl;

R^{4a} and R^6 together form a spirocyclopropyl ring;

R^7 is hydrogen or lower-alkoxy; and

Het is a 5- or 6-membered monocyclic heterocycle or a 9- or 10-membered bicyclic heterocycle containing from 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur or said heterocycles substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, oxo, phenyl, halogen, and -O-(C_2-C_{10} alkylene)-N=B where N=B is dilower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, or 4-lower-alkyl-1-piperazinyl;

20. A compound of formula



wherein:

A is methylene, ethylene or dimethylmethylene; and

Het is a 5- or 6-membered monocyclic heterocycle or a 9- or 10-membered bicyclic heterocycle containing from

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1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur or said heterocycles substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, oxo, phenyl, halogen, and -O-(C_2-C_{10} alkylene)-N=B where N=B is dilower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, or 4-lower-alkyl-1-piperazinyl;

21. A composition for the treatment of degenerative diseases which comprises a pharmaceutical carrier and an effective proteolytic enzyme-inhibiting amount of a compound as claimed in claim 1.

22. A composition for the treatment of degenerative diseases which comprises a pharmaceutical carrier and an effective proteolytic enzyme-inhibiting amount of a compound as claimed in any one of claims 2-18.

22. A composition for the treatment of degenerative diseases which comprises a pharmaceutical carrier and an effective proteolytic enzyme-inhibiting amount of a compound as claimed in claim 19.

23. A composition for the treatment of degenerative diseases which comprises a pharmaceutical carrier and an effective proteolytic enzyme-inhibiting amount of a compound as claimed in claim 20.

24. The use of a compound as claimed in claim 1 for the preparation of a medicament for the treatment of degenerative diseases in a patient in need of such treatment.

25. The use of a compound as claimed in any one of claims 2-18 for the preparation of a medicament for the treatment of degenerative diseases in a patient in need of such treatment..

26. The use of a compound as claimed in claim 19 for the preparation of a medicament for the treatment of degenerative diseases in a patient in need of such treatment.

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27. The use of a compound as claimed in claim 20 for the preparation of a medicament for the treatment of degenerative diseases in a patient in need of such treatment.

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