

SACCHARIN DERIVATIVE PROTEOLYTIC ENZYME INHIBITORS

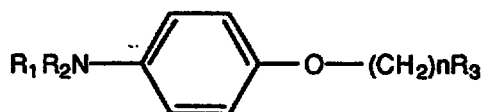
The invention relates to saccharin derivatives which inhibit the
5 enzymatic activity of proteolytic enzymes, to processes for preparation thereof, to
method of use thereof in treatment of degenerative diseases and to pharmaceutical
compositions thereof.

Inhibitors of proteolytic enzymes are useful in treatment of
degenerative disorders such as emphysema, rheumatoid arthritis and pancreatic in
10 which proteolysis is a substantive element. 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 a peptide bond in a
protein at a site at which the amino acid on the carbonyl side is Trp, Tyr, Phe, Met,
15 Leu or other amino acid which contains an aromatic or a large alkyl side chain.
Elastase and elastase-like enzymes normally cleave a peptide bond at a site at which
the amino acid residue on the carbonyl side of the bond is Ala, Val, Ser, Leu or
other small amino acid. Both chymotrypsin-like and elastase-like enzymes are
found in leukocytes, mast cells and pancreatic juice in higher organisms, and are
20 secreted by many types of bacteria, yeast and parasites.

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

Barber *et al.*, U.S. Patent 2,855,401 disclose compounds of the
formula:

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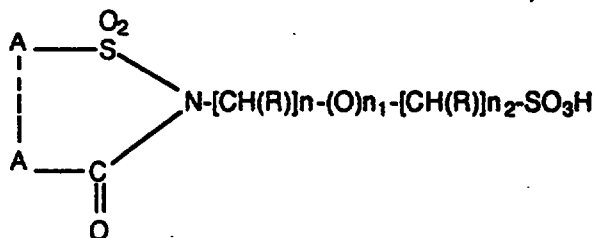


wherein R_1 and R_2 are each selected from hydrogen, lower-alkyl and lower
hydroxyalkyl, n is an integer from 5 to 9 and R_3 is a group selected from
30 methanesulphonamido, benzenesulphonamido and o-sulphonbenzimidido. The
compounds are said to be useful in the treatment of bilharziasis.

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Brown et al., U.S. Patent 3,220,940 disclose the use in acidic nickel baths of the compounds of the formula:



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or the Ni, Na, Co, K, Li, Mg, etc. sulfonate salts thereof, wherein A is selected from the group consisting of the benzene, biphenyl and naphthalene rings, R is selected from the group consisting of H, OH, Cl, Br, SO₃H and CH₃, n is an integer from 1 to 4 inclusive, n₁ is 0 or 1, n₂ is zero, 1 or 2, and when n₂ is zero then n₁ is zero.

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Sunket et al., European Patent Application 253092 disclose 2-saccharinyl-lower-alkyl-1,4-dihydropyridine-3-carboxylates having platelet aggregation inhibitory and antithrombotic activities. A substantially similar disclosure can be found in Sunket et al., J. Med. Chem. 31, 1886-1890 (1988).

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Mulvey et al., U.S. Patent 4,195,023 disclose R₁-2-R₂ CO-1,2-benzisothiazol-3-ones, where R₁ is halogen, alkoxy, alkylamino, dialkylamino, alkoxycarbonyl, amino, nitro or hydrogen in the benzenoid ring and R₂ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, halophenyl, heteroaryl or substituted heteroaryl R₁-2-A-CO saccharins, where R₁ 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. A similar disclosure is found in French Patent 2,321,288.

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Dunlap et al., European Patent Application 483928A1 disclose 4-R⁴-R⁵ 2-saccharinylmethyl aryl carboxylates and 4,5,6,7-tetrahydro-2-saccharinylmethyl aryl carboxylates which are said to have protease enzyme inhibitory activity and be useful in the treatment of degenerative diseases. A similar disclosure is found in Dunlap et al., U.S. Patent 5,128,339.

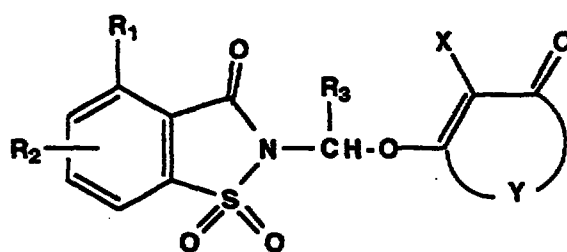
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Jones et al., U.S. Patent 4,276,298 disclose

2-R-1,2-benzisothiazolinone-1,1-dioxides, where R is phenyl substituted by
fluoro, dinitro, trifluoromethyl, cyano, alkoxycarbonyl, alkylcarbonyl, carboxyl,
carbamoyl, alkylacylamino, alkylsulfonyl, N,N-dialkylsulfamoyl, trifluoro-
methoxy, 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.

According to the present invention there is provided a compound
having the structural formula



Formula I

wherein

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

R₂ is from one to three substituents at any or all of the 5-, 6- and 7-positions and is selected from the group consisting of

B=N-(CH₂)_pC(O)O(CH₂)_{p'}-O-, -O-(CH₂)_p-(5-((CH₂)_{p'}-B=N-2-furanyl), and R-oxy-lower-alkoxy wherein p and p' are integers from 1 to 4, R is lower-alkyl, phenyl or phenyl-lower-alkyl, phenyl can have from one to three substituents selected from the group consisting of lower-alkyl, B=N-carbonyl, B=N, lower-alkoxy, B=N-lower-alkoxy and halo and B=N is amino, lower-alkylamino, di-lower-alkylamino, carboxy-lower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 1-azetidyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl or 1-imidazolyl;

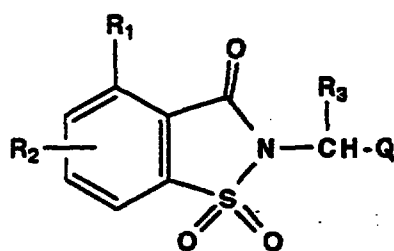
R₃ is hydrogen, lower-alkyl or phenyl;



X is hydrogen, nitro, halo, lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, phenyl, phenyl-lower-alkyl, phenylcarbonyl, pyridyl-lower-alkyl, formyl, lower-alkanoyl, carboxy, lower-alkoxycarbonyl, aminocarbonyl, lower-alkylaminocarbonyl, di-lower-alkylaminocarbonyl, cyano, B=N, B=N-lower-alkyl, B=N-lower-alkanoyl, B=N-lower-alkoxycarbonyl, hydroxy, lower-alkoxy, phenyloxy, B=N-lower-alkoxy, lower-alkylthio, phenylthio, lower-alkylsulfonyl, phenylsulfonyl or B=N-sulfonyl wherein phenyl is unsubstituted or has from one to three substituents selected from the group consisting of lower-alkyl, lower-alkoxy and halo and B=N is as defined above; and

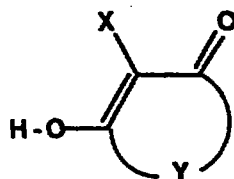
-Y- is the remaining atoms of a monocyclic or bicyclic, substituted or unsubstituted carbocyclic or heterocyclic ring system; or a pharmaceutically acceptable acid addition salt thereof if the compound has a basic functional group or a pharmaceutically acceptable base addition salt thereof if the compound has an acidic functional group.

The invention further provides a process for preparing a compound of Formula I which comprises condensing the corresponding compound having the structural formula



Formula II

wherein Q is chloro or bromo with the corresponding compound having the structural formula



Formula III

in the presence of a base or with a corresponding basic salt of the compound of Formula III.

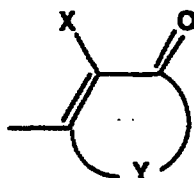


In another aspect there is provided a pharmaceutical composition for the treatment of degenerative disease which comprises a proteolytic enzyme inhibiting concentration of a compound of Formula I in a pharmaceutical carrier.

- 5 In yet another aspect the invention provides the use of a proteolytic enzyme inhibiting amount of a compound of Formula I for the preparation of a medicament for the treatment of a degenerative disease in a patient in need of such treatment.

The compounds of Formula I inhibit the enzymatic activity of proteolytic enzymes and are useful in treatment of degenerative diseases.

- 10 The part of the compound of Formula I having the structural formula



- 15 is also described below as having the formula -Z. The compound of Formula III is accordingly also described below as having the formula H-O-Z.

- Saccharin is 1,2-benzisothiazol-(1H)-3-one-1,1-dioxide and the compounds of Formula I, which are 2-[Z-O-CH(R₃)]-4-R₁-(5, 6 and/or 7)-R₂-1,2-benzisothiazol-(1H)-3-one-1,1-dioxides, are accordingly 2-[Z-O-CH(R₃)]-4-R₁-(5, 6 and/or 7)-R₂-saccharins.

In the compounds of Formulas I-III "corresponding" means that a defined variable in one formula has the same definition in another formula.

- The carbon chain part thereof has from one to ten carbon atoms, preferably from one to four carbon atoms, and is branched or unbranched in the following:- lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, lower-alkoxycarbonyl, lower-alkylamino, di-lower-alkylamino, lower-alkoxy, carboxy-lower-alkylamino, 4-lower-alkyl-1-piperazinyl, phenyl-lower-alkyl, pyridyl-lower-alkyl, lower-alkylaminocarbonyl, di-lower-alkylaminocarbonyl, lower-alkylthio and carboxy-lower-alkylamino.

- 30 In the following the carbon chain part thereof has from two to ten carbon atoms, preferably from two to four carbon atoms, and is branched or



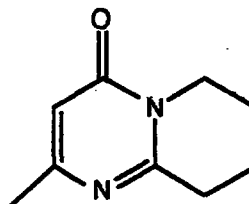
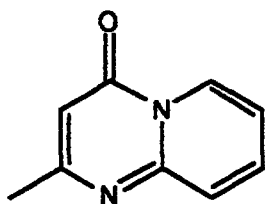
unbranched:- lower-alkenyl, lower-alkynyl, amino-lower-alkyl, the lower-alkoxy part of B=N-lower-alkoxy, lower-alkanoyl, B=N-lower-alkyl, B=N-lower-alkanoyl and B=N-lower-alkoxycarbonyl. Halo is fluoro, chloro, bromo or iodo.

- In the compounds of Formula I, R_1 is preferably primary or
- 5 secondary alkyl of two to four carbon atoms or lower-alkoxy and R_2 is preferably located at the 6-position and is most preferably $B=N-(CH_2)_pC(O)O(CH_2)_p'-O-$ or R-oxy-lower-alkoxy. Furthermore -Y- is preferably $-(CH_2)_m-$, $-C(=O)-$, $-(CH_2)_m-O-$, $-CHR-O-$, $-CR_2-O-$, $-C[(CH_2)_n]-O-$, $-C[CH_2CH_2N(R)CH_2CH_2]-O-$, $-(CH_2)_m-N(R')-$, $-CHR-N(R')-$, $-CR_2-N(R')-$,
- 10 $-C(R')=C(R')-O-$, $-C(R')=C(R')-N(R')-$, $-C(=O)-C(R'')=C(R'')-$, $-C(Z')=C(Z')-$, $-C(Z')=C(Z')-O-$, $-C(Z')=C(Z')-N(R')-$, $-N(Z'')-C(Z'')=N-$, $-N=C(Z'')-N(Z'')-$, $C(Z''')-C(Z''')-S-$, $N=C(R''')-N(R''')-$ or $-C(R''')=C(L)-N(L)-$ and wherein the Z'' groups taken together with the carbon atoms to which they are bonded are benzo; the
- 15 R''' groups taken together with the carbon or nitrogen atoms to which they are bonded are $-(CH_2)_n-$, $-(CH_2)_qN(R^*)$ $(CH_2)_q-$, or thiazolo; the L groups taken together with the carbon or nitrogen atoms to which they are bonded are pyrido;
- n' is an integer from 3 to 5;
- 20 R^* is hydrogen, phenyl, phenyl-lower-alkyl, or lower-alkyl;
- q is 1 or 2; q' is 1 or 2;
- R''' is hydrogen, cyano, CO_2L' , SO_2L'' or nitro;
- L' is hydrogen, lower-alkyl, or di-lower-alkylamino,
- L'' is hydroxy, lower-alkoxy, di-lower-alkylamino or trifluoromethyl;
- 25 m is 1, 2, 3, or 4; n is 3, 4, or 5,
- R is the same or different lower-alkyl, phenyl or phenyl-lower-alkyl,
- R' is H or R, R'' is H or R or the
- R'' groups taken together with the carbon atoms to which they are bonded are furano, the
- 30 Z' groups taken together with the carbon atoms to which they are bonded are benzo, furano, pyrido, pyrimidino or pyridazino, and the
- Z'' groups taken together with the carbon or nitrogen atoms to which they are bonded are pyrido, pyrimidino or pyridazino wherein phenyl, benzo, furano, pyrido, pyrimidino or pyridazino can have from one to three substituents selected



from the group consisting of lower-alkyl, B=N-carbonyl, B=N, lower-alkoxy, B=N-lower-alkoxy and halo wherein B=N is as defined above.

- Particularly preferred compounds are those wherein n' is 4, R^* is hydrogen; q is 1; q' is 2; R''' is hydrogen, cyano, CO_2L' or SO_2L'' ;
- 5 L' is lower-alkyl and L'' is di-lower-alkylamino, particularly when R_1 is lower-alkyl; R_2 is di-lower-alkylamino- $(CH_2)_pC(O)O(CH_2)_{p'}O-$ or phenyl-lower-alkyloxy-lower-alkoxy; R_3 is hydrogen and X is hydrogen, halo, lower-alkyl, phenyl, phenyl-lower-alkyl, phenylcarbonyl, B=N, B=N-lower-alkyl, phenyloxy, or lower-alkoxycarbonyl.
- 10 Most preferred compounds are those wherein R_1 is isopropyl; R_2 is 6-dimethylamino- $CH_2C(O)O(CH_2)_2O-$ or 6-benzyloxyethoxy and X is hydrogen, in particular when Z has one of the following structural formulae:



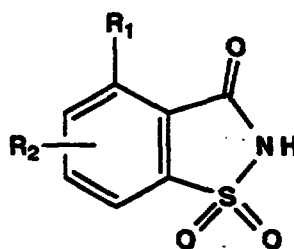
- 15 In carrying out the preparation of a compound of Formula I from a corresponding compound of Formula II and the corresponding compound of Formula III in the presence of a base, the base can be any base which is not itself a reactant under the reaction conditions and is preferably an alkali metal hydride, an
- 20 alkali metal carbonate, an alkali metal alkoxide, a tri-lower-alkylamine, a thallos lower-alkoxide, 1,8-diazabicyclo[5.4.0]undec-7-ene or 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. Under the reaction conditions the base may form the basic salt of the compound of Formula III, which then reacts with the compound of Formula II. The basic salt of the compound of Formula III can also be formed
- 25 separately and then condensed with the compound of Formula II and is preferably an alkali metal, especially cesium, or thallos salt thereof. The condensation is carried out in an organic solvent or mixture of organic solvents inert under the reaction conditions, for example acetone, methylethylketone, acetonitrile, tetrahydrofuran, diethylether, dimethylformamide, N-methylpyrrolidone, dichloromethane, xylene, toluene or a lower-alkanol or mixture thereof, at a temperature in
- 30



the range from ambient temperature to the boiling temperature of the solvent or solvent mixture.

The compounds of Formulae II and III are known or are made by known methods or by methods described below.

- 5 A compound of Formula II wherein R_3 is hydrogen can be prepared by diazotizing the corresponding lower-alkyl 2-amino-3, 4 or 5- R_2 -6- R_1 -benzoate ester, chlorosulfonylating the resulting lower-alkyl 3, 4 or 5- R_2 -6- R_1 -benzoate ester 2-diazonium salt with sulfur dioxide and cuprous chloride, and cyclizing the resulting lower-alkyl 2-chlorosulfonyl-10 3, 4 or 5- R_2 -6- R_1 -benzoate ester with ammonia to form the corresponding compound having the structural formula:



Formula IV,

- 15 hydroxymethylation of which with formaldehyde affords the corresponding 2-hydroxymethyl-4- R_1 -(5, 6 or 7)- R_2 -saccharin, displacement of whose hydroxyl with chloride or bromide using, for example thionyl chloride, thionyl bromide, phosphorus trichloride or phosphorus tribromide affords the corresponding
20 compound of Formula II.

A compound of Formula II wherein R_3 is hydrogen and Q is chloro can also be prepared in one step from the corresponding compound of Formula IV by chloromethylation with formaldehyde and chlorotrimethylsilane in the presence of a Lewis acid, for example stannic chloride.

- 25 A compound of Formula II wherein R_3 is lower-alkyl and Q is chloro can be prepared by vinylating the corresponding compound of Formula IV with the corresponding substituted or unsubstituted vinyl ester of a lower-alkanoic acid in the presence of disodium palladium tetrachloride, then treating the resulting



2-(substituted or unsubstituted vinyl)-4- R_1 -(5, 6 or 7)- R_2 -saccharin with hydrogen chloride. Use of unsubstituted vinyl acetate, for example, affords the corresponding compound of Formula II wherein R_3 is methyl.

5 A compound of Formula II wherein R_3 is hydrogen or phenyl can be prepared by phenylthio- R_3 -methylating the corresponding compound of Formula IV or basic salt thereof with the corresponding phenyl R_3 -chloromethyl sulfide to form the corresponding 2-(phenylthio- R_3 -methyl)-4- R_1 -(5, 6 or 7)- R_2 -saccharin and displacing phenylthio therefrom with chloro or bromo using, for example, sulfuryl chloride or sulfuryl bromide.

10 A compound of Formula IV can be prepared by lithiating the corresponding 2- R_1 -3, 4 or 5- R_2 -N,N-di-lower-alkylbenzamide with a lower-alkyl lithium, aminosulfonylating the resulting 2- R_1 -3, 4 or 5- R_2 -6-lithio-N,N-di-lower-alkylbenzamide with sulfur dioxide followed by hydroxylamine O-sulfonic acid or sulfuryl chloride followed by ammonia, and cyclizing the resulting
15 2- R_1 -3, 4 or 5- R_2 -6-aminosulfonyl-N,N-di-lower-alkylbenzamide in refluxing acetic acid.

A compound of Formula IV wherein R_1 is primary or secondary alkyl of two to four carbon atoms can be prepared by lithiating the corresponding compound of Formula IV wherein R_1 is methyl with two molar equivalents of a
20 lower-alkyl lithium in an inert solvent, for example tetrahydrofuran, and alkylating the resulting 4-lithiomethyl-5, 6 or 7- R_2 -saccharin with the appropriate alkyl halide. Both reactions are carried out at a temperature in the range from -80°C. to -50°C. The above-described 2- R_1 -3, 4 or 5- R_2 -N,N-di-lower-alkylbenzamide wherein R_1 is primary or secondary alkyl of two to four carbon atoms can be
25 prepared by a similar lithiation-alkylation sequence starting with the corresponding 2-methyl, ethyl or propyl-3, 4 or 5- R_2 -N,N-di-lower-alkylbenzamide.

A compound of Formula IV wherein R_1 is primary or secondary alkyl of two to four carbon atoms can also be prepared by introducing R_1 earlier in the synthesis. Conjugate addition of the appropriate R_1 -cuprate to 2-cyclo-
30 hexenone and methoxycarbonylation of the resulting copper enolate with methyl cyanoformate by the method of Winkler et al. (Tetrahedron Letters, p. 1051, 1987; Journal of Organic Chemistry, vol. 54, p. 4491, 1989) gives the corresponding 2-methoxycarbonyl-3- R_1 -cyclohexanone, enol etherification of which with benzylthiol and acidic clay gives a mixture of the corresponding 6- R_1 -2-benzyl-



thio-1-cyclohexenecarboxylic acid methyl ester and 6-R₁-2-benzylthio-3-cyclohexenecarboxylic acid methyl ester, aromatization of which with dichlorodicyanobenzoquinone gives the corresponding 2-R₁-6-benzylthiobenzoic acid methyl ester, oxidation-chlorination-debenzylation of which with chlorine in aqueous acetic acid gives 2-R₁-6-chlorosulfonylbenzoic acid methyl ester, cyclization of which with ammonia gives the corresponding 4-R₁-saccharin of Formula IV.

Preparation of certain compounds of Formula IV requires building up both rings thereof. For example, to prepare a compound of Formula IV wherein R₁ is lower-alkoxy and R₂ is hydroxy, 3,3-thiobispropionic acid is converted with thionyl chloride into the bis acid chloride, which is converted with benzylamine into the bis benzylamide, which on cyclization with sulfuryl chloride gives 5-chloro-2-benzyl-2H-isothiazol-3-one. Oxidation with one molar equivalent of a peracid gives 5-chloro-2-benzyl-2H-isothiazol-3-one-1-oxide, which on heating under pressure with a 2-lower-alkoxyfuran gives a 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzoisothiazol-2H-3-one-1-oxide and on oxidation with one molar equivalent of a peracid gives the corresponding 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzoisothiazol-2H-3-one-1,1-dioxide. Debenzylation by catalytic hydrogenation then gives the corresponding 4-lower-alkoxy-7-hydroxysaccharin of Formula IV.

Similarly alkylation of a thus prepared 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzoisothiazol-2H-3-one-1-oxide with a lower-alkyl halide or an appropriately substituted lower-alkyl halide followed by oxidation and debenzylation affords the corresponding 4-lower-alkoxy-7-R₂-saccharin of Formula IV wherein R₂ is lower-alkoxy, cycloalkoxy, B=N-lower-alkoxy, hydroxy-lower-alkoxy, polyhydroxy-lower-alkoxy or acetal or ketal thereof, lower-alkoxy-lower-alkoxy, poly-lower-alkoxy-lower-alkoxy, hydroxy-poly-lower-alkylenoxy or lower-alkoxy-poly-lower-alkylenoxy.

Simple chemical transformations which are conventional and well known to those skilled in the art of chemistry can be used for effecting changes in the functional groups of the compounds of the invention. For example, catalytic reduction of a heterocyclic ring system to produce the corresponding partially saturated heterocyclic ring system, catalytic debenzylation of benzyl ethers to produce the corresponding alcohols, coupling of alcohols with acids in the



presence of a coupling agent to produce the corresponding esters, or desilylation of silyl ethers to produce the corresponding alcohols.

5 The pharmaceutically acceptable acid or base addition salt can be any pharmaceutically acceptable acid or base addition salt but preferably has a common anion, for example the hydrochloride salt, or a common cation, for example the sodium or potassium salt, respectively. If the salt having a common anion or cation is unacceptable because it is not crystalline or insufficiently soluble or hygroscopic, a salt having a less common anion, for example the methane-sulfonate, or less common cation, for example the diethylammonium salt, can be
10 used respectively. In any event for use in a mammal the acid or base addition salt must be nontoxic and must not interfere with the elastase inhibitory effect of the free base or acid form of the compound of Formula I.

In the preparations and examples described below structures of products are inferred from known structures of starting materials and expected
15 courses of preparative reactions. Purification or purity and structural confirmation of starting materials and products were carried out or measured by melting temperature range (m.r.), optical rotation, elemental analysis, infrared spectral analysis, ultraviolet spectral analysis, mass spectral analysis, nuclear magnetic resonance spectral analysis, gas chromatography, column chromatography, high
20 pressure liquid chromatography, medium pressure liquid chromatography and/or thin layer chromatography.

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The invention will now be described with reference to the following examples which do not limit the invention in any way.

Example 1 Preparation of Starting Materials

5 a) Preparation of 2-Chloromethyl-4-isopropylsaccharin

(II; $R_1=i\text{-Pr}$, $R_2=H$, $R_3=H$, $Q=Cl$)

n-Butyllithium (2.5 M, 100 ml) was added with stirring under nitrogen at 0-5°C. during ten minutes to a solution of 2-isopropylbromobenzene in anhydrous ether (500 ml). The mixture was allowed to warm to room
10 temperature, stirred at room temperature for six hours, and cooled to -60°C. A solution of diethylcarbonyl chloride (34 g) in anhydrous ether (50 ml) was added during 20 minutes while maintaining the temperature below -50°C. The temperature was allowed to rise to room temperature during one hour. Water (100 ml) was added. The ether layer was washed with saturated aqueous
15 sodium chloride (200 ml), dried over magnesium sulfate and stripped of ether. Distillation of the residue (80-90°C./0.1 mm Hg) gave 2-isopropyl-N,N-diethylbenzamide (44 g, 80% yield).

To a solution of N,N,N',N'-tetramethylethylenediamine (25.5 g) in anhydrous ether (600 ml) was added s-butyllithium (1.3 M, 170 ml) and the
20 mixture was cooled to -70°C. under nitrogen. A solution of 2-isopropyl-N,N-diethylbenzamide (44 g) in anhydrous ether (300 ml) was added dropwise over 20 minutes. The temperature was maintained at or below -60°C. during the addition. After the addition the mixture was stirred at -70°C. for 30 minutes, allowed to warm to -50°C. during 30 minutes, held at -50°C. for 10 minutes, then
25 cooled back to -70°C. By cannulation tube a solution of sulfur dioxide (50 g) in anhydrous ether (50 ml) precooled to -60°C. was added under positive nitrogen pressure over a 10-minute period. The temperature of the reaction mixture during the addition was maintained below -50°C. A white powdery precipitate of aryllithium sulphinate separated out almost immediately. The temperature was
30 allowed to rise to room temperature during one hour. Sulfuryl chloride (54 g) was added dropwise with continued stirring during 15 minutes. After further stirring for 30 minutes at 0-5°C. a white precipitate was filtered off and washed with anhydrous ether (2 l). Removal of the solvent under vacuum gave a faint yellow oil, which was dissolved in tetrahydrofuran (150 ml). The solution was cooled to



0°C. and concentrated aqueous ammonia (28%, 60 ml) was added in portions over 15 minutes. The temperature was kept at 10°C. or below throughout the addition.

After stirring for 15 minutes at ambient temperature the tetrahydrofuran and excess ammonia were removed and the residue was acidified with

- 5 hydrochloric acid (2N) to pH 1. The resulting white solid was collected, washed with water (200 ml) and hexane (200 ml) and dried affording 2-aminosulfonyl-6-isopropyl-N,N-diethylbenzamide (54 g, 90% yield).

- A solution of 2-aminosulfonyl-6-isopropyl-N,N-diethylbenzamide (60 g) in acetic acid (400 ml) was refluxed for 24 hours, then cooled to
10 room temperature. The solvent was removed under vacuum. The oily residue was dissolved in water (500 ml) and the pH was adjusted to 1 with 2N hydrochloric acid. The crude product was collected by filtration, washed with water (300 ml), dried at 60°C. under vacuum for 18 hours and recrystallized from ether-hexane to give 4-isopropylsaccharin (40 g, 90% yield, m.p. 177°C.). (IV; R₁=iPr, R₂=H)

- 15 A mixture of 4-isopropylsaccharin (37.9 g), phenyl chloromethyl sulfide (33.3 g), tetrabutylammonium bromide (5.4 g) and toluene (200 ml) was heated under reflux for 24 hours, then stripped of volatiles. Column chromatography of the residue on silica gel (485 g) and elution first with hexane, then hexane-dichloromethane (1:1), then dichloromethane gave in the hexane-
20 dichloromethane eluate 2-phenylthiomethyl-4-isopropylsaccharin as a pale yellow oil (53.5 g, 92% yield).

- 2-Phenylthiomethyl-4-isopropylsaccharin (53.5 g), sulfuryl chloride (40 ml, 67.2 g) and dichloromethane (250 ml) were mixed with stirring at room temperature. The mixture underwent a slightly exothermic reaction and was
25 allowed to stand for 17 hours at room temperature, then stripped of volatiles. The residue crystallized with hexane in three crops (33.65 g, m.r. 101-102°C.; 3.45 g, m.r. 100-101°C.; 0.45 g, m.r. 99-100°C.; total, 38.55 g, 91% yield). The three crops were combined and recrystallized from isopropyl alcohol (30 ml)-cyclohexane (270 ml) affording 2-chloromethyl-4-isopropylsaccharin in two crops
30 (33.5 g, m.r. 101-102.5°C.; 2.65 g, m.r. 100-101°C.).

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(b) Preparation of 2-Chloromethyl-4-isopropyl-6-methoxysaccharin
(II; R₁=i-Pr, R₂=6-OMe, R₃=H, Q=Cl)

To a solution of N,N,N',N'-tetramethylethylenediamine (300 ml) in anhydrous ether (4 l) was added s-butyllithium (1.3 M, 4 l) and the mixture was cooled to -70°C. under nitrogen. A solution of 2-isopropyl-4-methoxy-N,N-diethylbenzamide (454.2 g) in anhydrous ether (300 ml) was added dropwise over 30 minutes. The temperature was maintained at or below -60°C. during the addition. After the addition the mixture was stirred at -70°C. for one hour, allowed to warm to -50°C., held at -50°C. for 30 minutes, then cooled back to -70°C. By cannulation tube a solution of sulfur dioxide (200 g) in anhydrous ether (200 ml) precooled to -40°C. was added 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 cooling bath was removed and the mixture was stirred at ambient temperature for two hours, then cooled to -5°C. With continued stirring sulfonyl chloride (190 ml) was added dropwise over a 15-minute period while maintaining the temperature below 10°C. After further stirring for 30 minutes at 0-5°C. a white precipitate was filtered off and washed with anhydrous ether (2 l). Removal of the solvent at atmospheric pressure gave a dark oil, which was dissolved in tetrahydrofuran (1.4 l). The solution was cooled to -10°C. and concentrated aqueous ammonia (28%, 540 ml) 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 tetrahydrofuran and excess ammonia were removed under vacuum to give a dark oil, which was diluted with water (6.0 l) and acidified with hydrochloric acid (3N) to pH 1. The resulting light yellow solid was collected by filtration, washed with water (800 ml), dried at 60°C. under vacuum for 18 hours and recrystallized from ethyl acetate-hexane (800 ml-3 l) to give 2-aminosulfonyl-6-isopropyl-4-methoxy-N,N-diethylbenzamide (429 g, 72% yield, m.r. 122-125°C.).

A solution of 2-aminosulfonyl-6-isopropyl-4-methoxy-N,N-diethylbenzamide (429.6 g) in acetic acid (1.5 l) was refluxed for 20 hours, then cooled to room temperature. The solvent was removed under vacuum. The oily residue was dissolved in water (6 l) and the pH was adjusted to 1 with



hydrochloric acid (6N). The crude product was collected by filtration, washed with water (2 l), dried at 60°C. under vacuum for 18 hours and recrystallized from ethyl acetate-hexane to give 4-isopropyl-6-methoxysaccharin (303 g, 91% yield, m.p. 188°C.) (IV; R₁=i-Pr, R₂=6-OMe).

5 To a suspension of paraformaldehyde (24 g) and chlorotrimethylsilane (86.4 g) in 1,2-dichloroethane (200 ml) was added dry tin(IV) chloride (0.8 ml) and the resulting solution was stirred on a steam bath for one hour. 4-Isopropyl-6-methoxysaccharin (51.4 g) was added to the clear solution and the mixture was refluxed for 18 hours, cooled to room temperature and poured
10 into water. The organic layer was separated, washed with aqueous sodium hydroxide solution (2N, 50 ml), dried over magnesium sulfate and concentrated under vacuum. The residue was crystallized from ethyl acetate-hexane to give 2-chloromethyl-4-isopropyl-6-methoxysaccharin (57 g, 87% yield, m.p. 151°C.).

(c.) Preparation of 2-Chloromethyl-4-isopropyl-6-[2-(benzyloxy)ethoxy]saccharin
15 (II; R₁=i-Pr, R₂=6-OCH₂CH₂OCH₂Ph, R₃=H, Q=Cl)

To a solution of 1.0 g (0.0039 mol) 4-isopropyl-6-methoxy-
saccharin in 15 ml MDC was added at ambient temperature 1.28 g (5.12 ml)
1 M solution boron tribromide in MDC. When addition was complete the reaction
mixture was heated under reflux for about five hours, cooled, taken to dryness
20 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 (IV; R₁=i-Pr,
25 R₂=6-OH) 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) of AlCl₃ in 500 ml chloroform at 0°C was added 43.9 g (0.7 mol) of ethanethiol. Within minutes a clear solution formed. To this a solution of 20.0 g (0.078 mol) 4-isopropyl-6-methoxysaccharin in
30 550 ml chloroform was added over a 30-min period. This solution was allowed to warm to RT and stirred for 3-4 hrs. at 60°C. 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.



6-hydroxy-4-isopropylsaccharin (30.0 g, 0.12 mol) in methanol was treated with Cs_2CO_3 (20.28 g, 0.062 mol). The mixture was stirred at ambient temperature for 3-4 hours, the excess methanol was removed under reduced pressure and the residue was dried under high vacuum. The residue was dissolved in DMF and chloromethylphenyl sulfide (21.72 g, 0.14 mol) was added. The mixture was heated at 70-80°C for 24 hours, cooled, treated with ice-water and extracted with ethyl acetate/ether. The organic layer was washed with water, then brine and was dried. The solvent was removed in *vacuo* and the residue was purified by column chromatography on silica eluting with ethyl acetate/hexane to afford 30.5 g (67%) of 4-isopropyl-6-hydroxy-2-phenylthiomethylsaccharin.

To a solution of 4-isopropyl-6-hydroxy-2-phenylthiomethylsaccharin (2.0 g, 5.5 mmol) in THF (40 ml) were added triphenylphosphine (1.46 g, 5.56 mmol), 2-benzyloxyethanol (0.87 g, 5.71 mmol) and diethylazodicarboxylate (0.99 g, 5.68 mmol). The mixture was stirred at room temperature for 16 hours, the solvent was removed in *vacuo* and the residue was purified by column chromatography on silica eluting with 20% EtOAc/hexane to afford 2.1 g (77%) of 4-isopropyl-6-[2-(benzyloxy)ethoxy]-2-phenylthiomethylsaccharin, m.p. 98-99°C.

Sulfuryl chloride (0.37 ml, 4.65 mmol) was added to a solution of the latter (2.1 g, 4.22 mmol) in CH_2Cl_2 at room temperature and the mixture was stirred for 3 hours. The solvent was removed in *vacuo*, the residue was triturated with hexane, and the solid thus formed was collected by filtration to afford 1.67 g (93%) of 2-chloromethyl-4-isopropyl-6-[2-(benzyloxy)ethoxy] saccharin, m.p. 101-102°C.

(d) Preparation of 2-chloromethyl-4-isopropyl-6-[2-(triisopropylsilyloxy)ethoxy] saccharin (II; $\text{R}_1=\text{i-Pr}$, $\text{R}_2=6\text{-OCH}_2\text{CH}_2\text{OSi}(\text{iPr})_3$, $\text{R}_3=\text{H}$, $\text{Q}=\text{Cl}$)

To a solution of 4-isopropyl-6-hydroxy-2-phenylthiomethylsaccharin (2.0 g, 5.509 mmol) in THF (35 ml) containing triphenylphosphine (1.59 g, 6.06 mmol) and 2-(triisopropylsilyloxy) ethanol (1.13 g, 6.0 mmol) at room temperature was added diethylazodicarboxylate (1.04 ml, 6.6 mmol). The mixture was stirred overnight (16 hours), the solvent was removed in *vacuo* and the residue was purified by column chromatography on silica eluting with 10% ethyl acetate/hexane to afford 2.66 g (86%) of 4-isopropyl-6-[2-(triisopropylsilyloxy)ethoxy]-2-phenylthiomethylsaccharin as an oil.



The latter (2.6 g, 4.62mmol) in CH_2Cl_2 (30 ml) was treated with sulfonyl chloride (0.65 g, 4.51mmol) and the mixture was stirred for 3 hours. The solvent was removed in *vacuo*, and the residue was triturated with hexane. The product was collected by filtration to afford 1.73 g (76%) of 2-chloromethyl-4-isopropyl-6-[2-(triisopropylsilyloxy) ethoxy] saccharin, m.p. 85-86°C.

(e) Preparation of 2-chloromethyl-4-isopropyl-6-(benzyloxycarbonylmethoxy) saccharin (II; $\text{R}_1=\text{i-Pr}$, $\text{R}_2=6\text{-OCH}_2(\text{CO})\text{OCH}_2\text{Ph}$, $\text{R}_3=\text{H}$, $\text{Q}=\text{Cl}$)

A mixture of 4-isopropyl-6-hydroxy-2-phenylthiomethylsaccharin (3.5 g, 9.63mmol), acetone (25 ml) and K_2CO_3 (2.66 g, 19.26mmol) was stirred under nitrogen for 2 minutes, then benzylbromoacetate (2.4 ml, 14.45mmol) was added. The mixture was stirred for 6 hours, filtered, and the filtrate was concentrated in *vacuo*. The residue was purified by medium pressure chromatography eluting with 20% ethyl acetate/hexane to afford 4.67 (100%) of 4-isopropyl-6-(benzyloxycarbonylmethoxy)-2-phenylthiomethylsaccharin.

To a solution of the latter (0.5 g 1.043mmol) in CH_2Cl_2 (5 ml) at room temperature was added sulfonyl chloride. The mixture was stirred for 4 hours, the solvent was removed in *vacuo* and the residue was purified by column chromatography on silica eluting with hexane (100%) to 20% ethyl acetate/hexane to afford 0.37 g (81%) of 2-chloromethyl-4-isopropyl-6-(benzyloxycarbonylmethoxy) saccharin.

(f) Preparation of 2-chloromethyl-4-isopropyl-6-hydroxysaccharin (II; $\text{R}_1=\text{i-Pr}$, $\text{R}_2=6\text{-OH}$, $\text{R}_3=\text{H}$, $\text{Q}=\text{Cl}$)

4-isopropyl-6-hydroxy-2-phenylthiomethylsaccharin (1.78 g) in methylene chloride was treated with sulfonyl chloride (0.43 mL, 0.73 g) to afford 1.2 g 84%) of 2-chloromethyl-4-isopropyl-6-hydroxysaccharin, m.p. 149-150°C.

(g) Preparation of 2-chloromethyl-4-sec-butyl-6-methoxysaccharin (II; $\text{R}_1=\text{sec-Bu}$, $\text{R}_2=6\text{-OMe}$, $\text{R}_3=\text{H}$, $\text{Q}=\text{Cl}$)

To a mixture of diethylamine (89.1 ml), triethylamine (120.2 ml) and CH_2Cl_2 (500 ml) cooled in an ice-bath was added dropwise p-anisoyl chloride (133.8 g) over 40 minutes. The reaction mixture was stirred at room temperature for 40 minutes, the mixture was filtered, washed with ether and the solvent was removed in *vacuo*. Ether was added, then water to the residue, then the organic layer was separate and washed with 5% NaOH , then in HCl , then brine and then



was dried over Na_2SO_4 . The solvent was removed in vacuo and the residue was purified by kugelrohr distillation at 140-180°C under high vacuum to afford 163.8 g of 4-methoxy-N,N-diethylbenzamide, m.p. 40-42°C.

To a solution of tetramethylethylenediamine (50.3 ml) in THF (800 ml) at -78°C was added sec-BuLi (308 ml, 1.08 M), followed by 4-methoxy-N,N-diethylbenzamide (62.2 g). The mixture was stirred at -78°C for 70 minutes, then ethyliodide (26.63 g, 333 mmol) was added over 35 minutes. The reaction mixture was warmed to room temperature and stirred for 1.5 hours. The reaction mixture was quenched with saturated NH_4Cl (100 ml). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by a kugelrohr distillation at 190-210°C under high vacuum to afford 58.1 g of 2-ethyl-4-methoxy-N,N-diethylbenzamide.

To a mixture of diisopropylamine (40.7 ml, 290 mmol) in THF (800 ml) at -78°C was added n-BuLi (100 ml, 255 mmol, 2.15M). The mixture was stirred for 1/4 hour, then 2-ethyl-4-methoxy-N,N-diethylbenzamide (235.3 g) in THF (300 ml) was added at -78°C. The mixture was stirred at -78°C for 2.5 hours, then at 0°C for 1 hour, and then ethyliodide (23.2 ml) in THF (150 ml) was added over 10 minutes at -78°C. The reaction mixture was stirred for about 1 hour, quenched with saturated NH_4Cl (100 ml) and the solvent was removed in vacuo. Ether (500 ml) was added to the residue, the ether layer was washed with saturated NaHCO_3 (50 ml), 1N HCl (50 ml), water, then brine, and then the ether layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by distillation under high vacuum (2 mm Hg) to afford 46.6 g (76%) of 2-sec-butyl-4-methoxy-N,N-diethylbenzamide.

To a solution of tetramethylethylenediamine (31 ml) in THF (500 ml) at -78°C was added sec-butyllithium (170 ml, 1.1M), followed by 2-sec-butyl-4-methoxy-N,N-diethylbenzamide (45 g) in THF (150 ml). The mixture was stirred at -78° for 15 minutes, then at 0°C for 30 minutes, then sulfur dioxide (50 ml) was condensed into the mixture at -78°C. The mixture was warmed to -10°C, sulfuryl chloride (17 ml) was added and then the mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was added to a solution of ammonium hydroxide (94 ml) in THF (200 ml), the mixture was filtered through a pad of silica/ Na_2SO_4 /sand to afford 51.8 g of 2-amino-sulfonyl-6-sec-butyl-4-methoxy-N,N-diethylbenzamide.



A mixture of acetic acid (200 ml) and 2-aminosulfonyl-6-sec-butyl-4-methoxy-N,N-diethylbenzamide (51.7 g) was refluxed overnight. The acetic acid was removed by distillation, the residue was poured into ice/2M NaOH (80 ml). The aqueous solution was washed with CH₂Cl₂, acidified with concentrated HCl and the precipitate which formed was collected by filtration to afford 4-sec-butyl-6-methoxysaccharin. (IV; R₁=secBu, R₂=OMe)

A mixture of 4-sec-butyl-6-methoxysaccharin (3 g), toluene, potassium t-butoxide (1.4 g), and tetrabutylammonium bromide (0.4 g) was brought to reflux and phenylchloromethyl sulfide (1.8 ml) was added. The reaction mixture was refluxed for about 27 hours, the solvent was removed *in vacuo*, the residue was extracted with ethyl acetate, washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica eluting with 10% ethyl acetate/hexane to afford 2.63 g (60%) of 2-phenylthiomethyl-4-sec-butyl-6-methoxysaccharin.

To a solution of 2-phenylthiomethyl-4-sec-butyl-6-methoxysaccharin (2.6 g) in CH₂Cl₂ (20 ml) was added sulfonyl chloride (0.7 ml). The mixture was stirred at ambient temperature overnight, and the solvent was removed *in vacuo*. The residue was treated with hexane and the mixture was sonicated for 6 hours. A precipitate formed with a collected by filtration to afford 1.33 g of 2-chloromethyl-4-sec-butyl-6-methoxysaccharin.

(h) Preparation of 2-chloromethyl-4-sec-butylsaccharin
(II; R₁=sec-Bu, R₂=H, R₃=H, Q=Cl)

To a solution of 4.74 ml (0.031 mol) tetramethylethylenediamine in 300 ml THF (passed through alumina prior to use) was added 5.8 g (0.03 mol) 2-ethyl-N,N-diethylbenzamide. The solution was cooled to -78°C and treated with 34.9 ml (0.031 mol) of a 0.9 M solution of butyl lithium in cyclohexane. When addition was completed, the mixture was stirred for twenty minutes and then treated with a solution of 3.2 ml (0.04 mol) ethyliodide while maintaining the temperature at -78°C. The temperature was then allowed to rise to ambient temperature and the mixture was 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.



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.

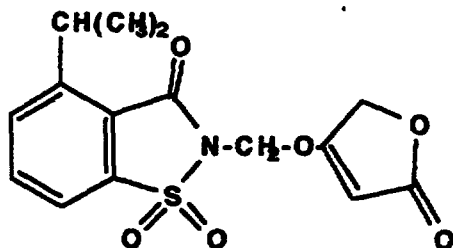
The latter (6.83 g, 0.22 mol) was dissolved in 100 ml glacial acetic acid and the solution heated under reflux for thirteen hours and then taken to dryness. The residue was triturated with diethylether and collected by filtration to give 5.7 g (83%) of the diethylammonium salt of 4-sec-butylsaccharin.

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-butylsaccharin.

Reaction of the latter (3.2 g, 0.00097 mol) with 2.3 ml (0.029 mol) sulfuryl chloride in 20 ml methylene chloride afforded 2.4 g (87%) of 2-chloromethyl-4-sec-butylsaccharin.

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Preparation of End-ProductsExample 1A2-[(2,5-dihydro-5-oxo-3-furanyl)oxymethyl]-4-isopropylsaccharin

5. A solution of tetronic acid (0.22 g) in dimethylformamide (5 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.10 g) in dimethylformamide (4 ml) under nitrogen with stirring and ice-bath cooling. The ice bath was removed, stirring was continued for 15 minutes, a solution of 2-chloromethyl-4-isopropylsaccharin (0.547 g) in dimethylformamide (10 ml) was added dropwise, stirring was continued for two and a half days, and the mixture was poured into water. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and stripped of ethyl acetate. Recrystallization of the resulting colorless solid (0.60 g) from ethyl acetate gave the title compound (0.34 g, 51% yield, m.r. 174-175°C.).

Examples 1B-1W

20 By methods similar to that of Example 1A above the compounds identified in Table I below were prepared from 2-chloromethyl-4-isopropylsaccharin or 2-chloromethyl-4-isopropyl-6-methoxysaccharin and the corresponding compound of Formula III (H-O-Z).

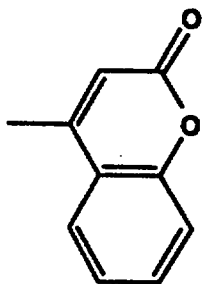
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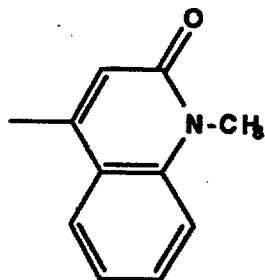
Table I



5				Yield (%)
				Melting Range (°C.)
				Recrystallization
	Example	R ₂	-Z	
	Solvent			
	1B	H		40
10				229-230
				Ethyl acetate



15	1C	H		51
				185-188
				Ethanol

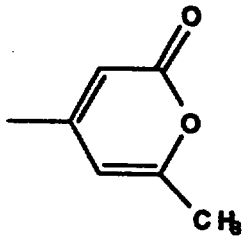
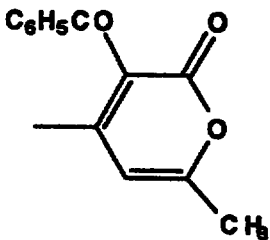
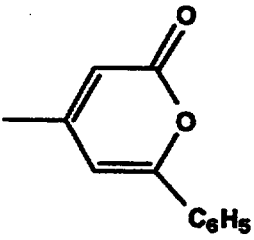


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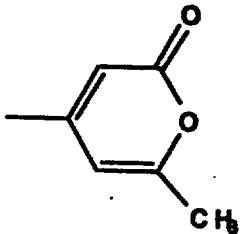
	Example	R ₂	-Z	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent					
10	1D	H		58	188-189.5	Ethanol-hexane
						
15	1E	H		13	204-207	Ethanol
						
20	1F	H		18	178-189.5	Isopropyl alcohol
						

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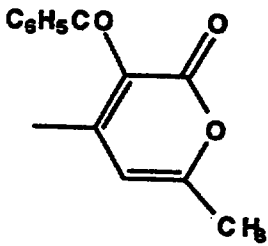
Table I (Continued)

5	Example Solvent	R ₂ — —Z—	Yield (%) Melting Range (°C.) Recrystallization
1G	CH ₃ O		50 172.5-174 Ethyl acetate



1H	CH ₃ O	
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24
175-177
Ethanol



1I	CH ₃ O	
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42
165.5-167.5
Ethyl acetate

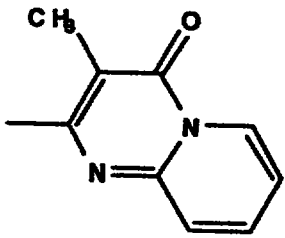
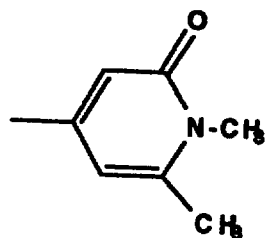


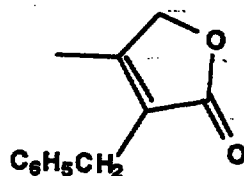
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5	Example Solvent	R_2 - Z	Yield (%) Melting Range (°C.) Recrystallization
1J	CH ₃ O		34 168-170 Ethyl acetate



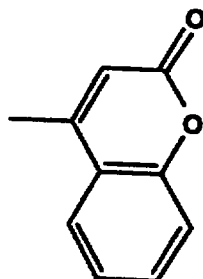
1K	CH ₃ O	
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47
126.5-128.5
Ethyl acetate



1L	CH ₃ O	
----	-------------------	--

39
261.5-263
Ethyl acetate



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Table I (continued)

5	Example Solvent 1M*	R_2 — $-Z$ _____	Yield (%) Melting Range (°C.) Recrystallization
10		CH_3O	6 129-131 Ethyl acetate- cyclohexane
15	1N	CH_3O	33 195-196.5 Ethyl acetate
20	10	CH_3O	48 136.5-137.5 Carbon tetrachloride

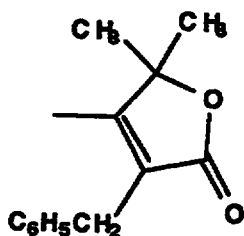
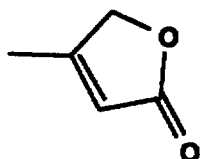
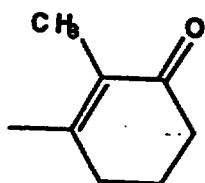


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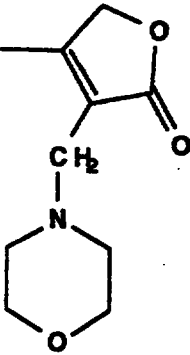
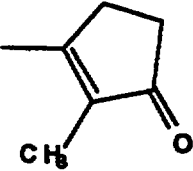
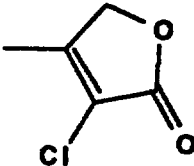
Example	R_2	$-Z-$	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent				
1P	CH_3O		8	145-147	Ethyl acetate- cyclohexane
10					
1Q	CH_3O		32	115-117	Carbon tetrachloride
15					
1R	CH_3O		29	149.5-150.5	Carbon tetrachloride
20					



Table I (continued)

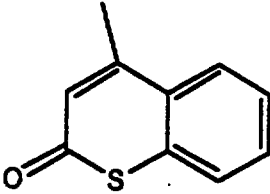
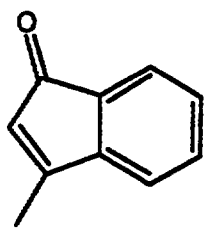
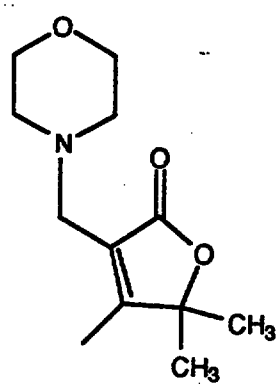
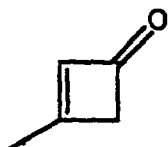
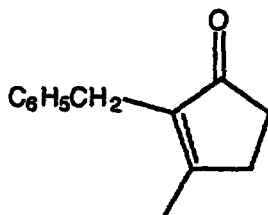
	Example	R ₂	-Z	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent					
	1S	CH ₃ O		29	227-228	Methanol
						
10	1T	CH ₃ O		7.7	193-203 (dec.)	Benzene/hexane(a)
						
15	1U	CH ₃ O		22.5	Foam	(b)
						
20						



Table I (continued)

	Example	R ₂	-Z	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent					
	1V	CH ₃ O		23	129-132 (dec.)	(c)
10						
	1W	CH ₃ O		36	122.5-124	Benzene/hexane ^(d)
15						

(a) Product was purified by column chromatography on silica eluting with CH₂Cl₂, followed by varying amounts of ethyl acetate/hexane prior to recrystallization.

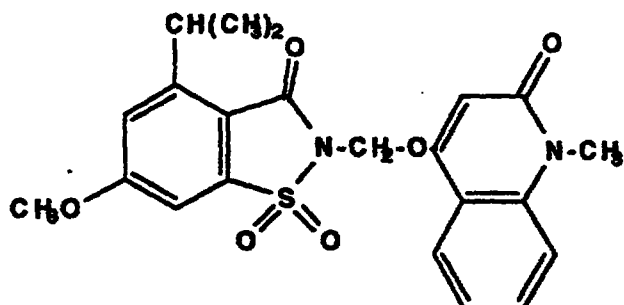
20 (b) Product was purified by column chromatography on silica eluting with CH₂Cl₂, followed by ethyl acetate/hexane in varying amounts.

(c) Product was purified by column chromatography (2x) on silica eluting with CH₂Cl₂, followed by varying amounts of ethyl acetate/hexane.

25 (d) Product was purified by column chromatography on silica eluting with ethyl acetate/hexane (1/3 to 1/2).

* In addition to the compound of Example 1M 2-(1-methyl-2,6-dioxo-cyclohexyl)methyl-4-isopropyl-6-methoxysaccharin (m.r. 159.5-161.5°C. from ethyl acetate) was isolated in 38% yield.

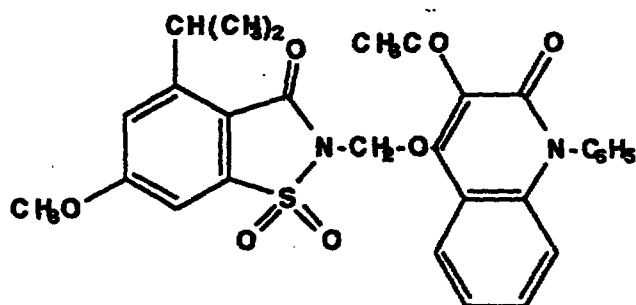


Example 2**2-(1-methylcarbostyryl-4-yl)oxymethyl-4-isopropyl-6-methoxysaccharin**

5

4-Hydroxy-1-methylcarbostyryl (1.44 g) was added with stirring to a suspension of sodium hydride (60% dispersion in mineral oil, 0.36 g) in dimethylformamide. The mixture was heated at 100°C. with continued stirring for three-quarters of an hour, then sonicated at room temperature for half an hour.

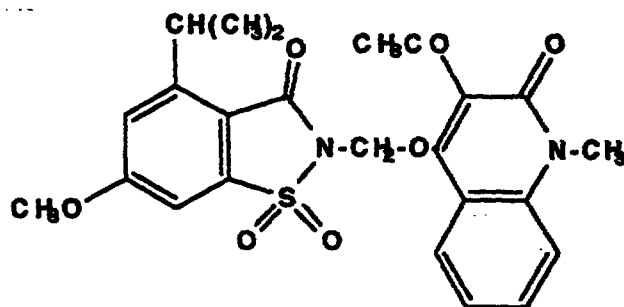
- 10 2-Chloromethyl-4-isopropyl-6-methoxysaccharin (1.83 g) was added. The resulting mixture was heated at 100°C. with continued stirring for two hours, then poured into water (300 ml). Hydrochloric acid (1N, 25 ml) was added, and the mixture was extracted with chloroform. The chloroform extract was dried over sodium sulfate and stripped of chloroform. Flash chromatography of the resulting
- 15 solid (3.3 g) on silica gel using ethyl acetate-hexane (1:1) as eluant and recrystallization of the resulting solid (0.7 g, 28% yield) from ethanol (90%) gave the title compound as a yellow solid (0.39 g, 15% yield, m.r. 198-200°C.).

Example 3A**2-(1-phenyl-3-acetylcarbostyryl-4-yl)oxymethyl-4-isopropyl-6-methoxysaccharin**

A mixture of 3-acetyl-4-hydroxy-1-phenylcarbostyryl (0.52 g), potassium carbonate (0.28 g) and dimethylformamide (7 ml) was stirred at room temperature for half an hour. 2-Chloromethyl-4-isopropyl-6-methoxysaccharin (0.71 g) was added and the mixture was sonicated for one hour at 40°C. and stirred at room temperature for 16 hours. Further sonication did not change the extent of reaction as shown by thin layer chromatography. The reaction mixture was poured into water and the mixture was extracted with ethyl acetate. The ethyl acetate extract was dried and stripped of ethyl acetate. Medium pressure liquid chromatography of the residue (0.5 g) on silica gel using ethyl acetate-hexane (3:7) as eluant and recrystallization of the product from methanol gave the title compound (0.24 g, 24% yield, m.r. 210-212°C.).

Example 3B

2-(1-methyl-3-acetylcarbostyryl-4-yl)oxymethyl-4-isopropyl-6-methoxysaccharin



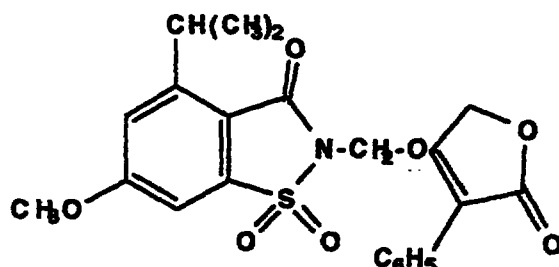
By a method similar to that of Example 3A above 3-acetyl-4-hydroxy-1-methylcarbostyryl (0.63 g) was condensed with 2-chloromethyl-4-isopropyl-6-methoxysaccharin (1.10 g) and the product was purified by crystallization from methanol-ether to give the title compound as an off-white powder (0.28 g, 20% yield, m.r. 194-196°C.).



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Example 4A

2-(2,5-dihydro-2-oxo-3-phenylfuran-4-yl)oxymethyl-4-isopropyl-6-methoxy-
saccharin



5

Cesium carbonate (0.82 g) was added to a solution of 3-phenyl-2(5H)-furanone (0.88 g) in methanol (15 ml) and the mixture was stirred at room temperature for one hour and stripped of methanol. 2-Chloromethyl-4-isopropyl-6-methoxysaccharin (1.52 g) was added to a solution of the residue in dimethylformamide (15 ml) and the mixture was stirred at room temperature for two days. Silica gel (4.4 g) was added, volatiles were removed under vacuum, and the solid was subjected to flash chromatography on silica gel using ethyl acetate-hexane (3:7) as eluant. Recrystallization of the product from ethanol-ether gave the title compound as a colorless solid (0.45 g, 20% yield, m.r. 180-182°C.).

15

Examples 4B-4I

By methods similar to that of Example 4A above the compounds identified in Table II below were prepared from 2-chloromethyl-4-isopropyl-6-methoxysaccharin and the corresponding compound of Formula III (H-O-Z).

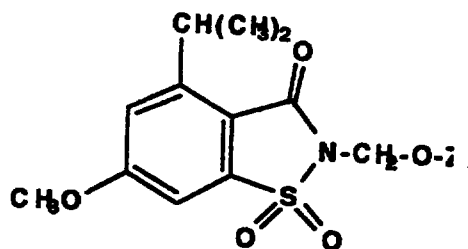
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Table II



Example -Z

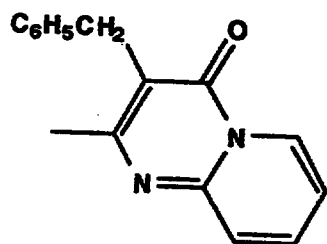
Solvent

4B

Yield (%)/
Melting Range (°C.)
Recrystallization

46/204-206

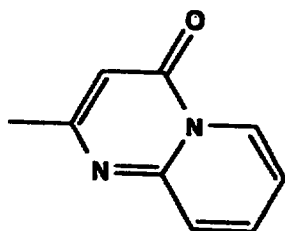
Dichloromethane-ether



4C

61/173-176

Methanol

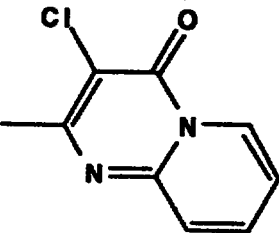
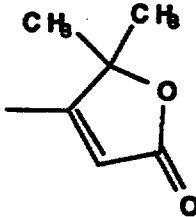
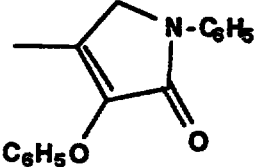


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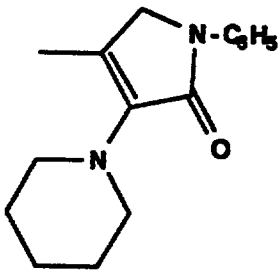
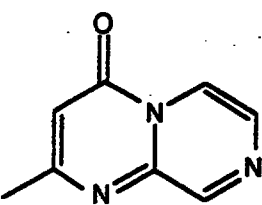
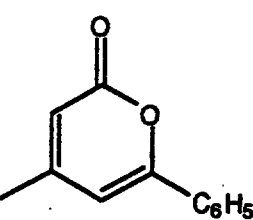
Table II (continued)

Example	-Z	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent			
	4D		9/225-227	Methanol-dichloromethane
				
10	4E		58/141-142.5	None
				
15	4F		51/85-87	None
				

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Table II (continued)

5	Example	-Z	Yield (%)
	Solvent		Melting Range (°C.)
	4G		Recrystallization
			19/83-88
			None
			
10			
	4H		20.5/133-135
			(as monohydrate)
			EtOH/Water ^(a)
			
15			
	4I		
			3.9/218-220 (as 1/4 hydrate)
			CH ₃ CN ^(b)
			

20

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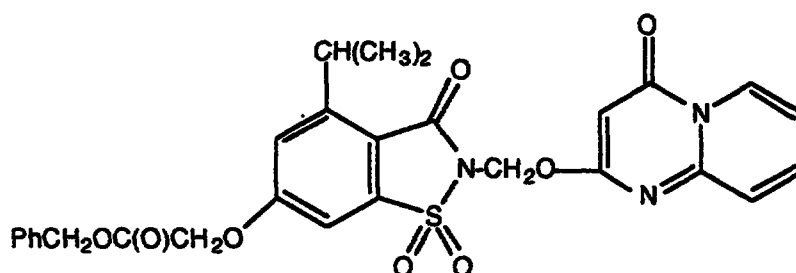


(a) The reaction mixture was worked-up by pouring it into ice/water, extracting with ethyl acetate, washing the organic layer with 5% NaOH, 1N HCl, water and then brine, and then removing the solvent in *vacuo*. The residue was then purified by column chromatography on silica eluting with 40% ethyl acetate/hexane prior to recrystallization.

(b) The reaction mixture was worked-up by pouring it into water, adding 5% NaOH, extracting with EtOAc/CH₂Cl₂, combining the organic layers, washing the organic layers with water then drying it over Na₂SO₄. The solvent was removed in *vacuo*, and the residue was purified by column chromatography on silica eluting with 25% EtOAc/hexane to EtOAc (100%) prior to recrystallization.

Example 4I

2-[4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl]oxymethyl-4-isopropyl-6-(benzyl-oxycarbonylmethoxy) saccharin



Following a procedure similar to that described in Example 4A, 0.71 g (62.8%) of the title compound was prepared, m.p. 69-71°C, from 2-chloromethyl-4-isopropyl-6-(benzyloxycarbonylmethoxy) saccharin (0.876 g), cesium carbonate (0.326 g), methanol, 2-hydroxypyrido-[1,2-a]pyrimidine-4-one (0.324 g), and DMF (5 ml). The reaction mixture was worked-up by pouring it into ice/water, extracting with ethyl acetate, separating out the organic layer and washing the organic layer with brine and then drying it over Na₂SO₄.

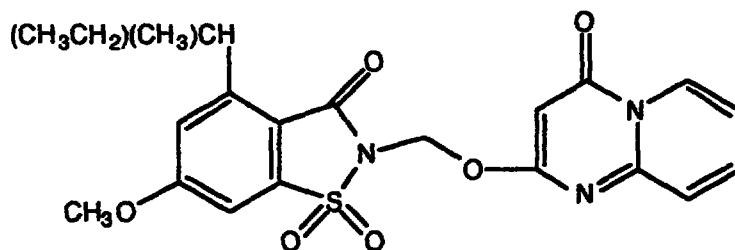
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Example 4K

2-[4-oxo-4H-pyrido[1,2-a]pyrimidine-2-yl]oxymethyl-4-sec-butyl-6-methoxysaccharin



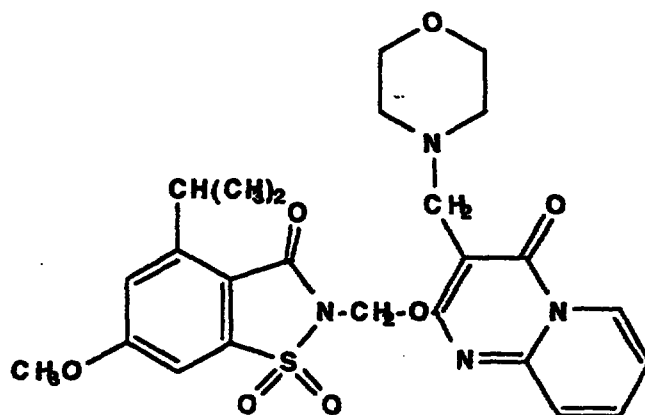
5

Following a procedure similar to that described in Example 4A, there was prepared 0.267 g (58%) of the title compound, m.p. 160-185°C, from 2-chloromethyl-4-sec-butyl-6-methoxysaccharin (0.318 g, 1.0 mmol), 2-hydroxy-
10 pyrido [1,2-a]pyrimidine-4-one (0.18 g, 1.11 mmol), cesium carbonate (0.18 g, 0.56 mmol), methanol (5 ml), and DMF. The reaction mixture was worked up by pouring it into saturated ammonium chloride, extracting with ethyl acetate, concentrating the organic layer *in vacuo* and purifying the residue by column chromatography on silica eluting with 50% ethyl acetate/hexane, followed by 5%
15 methanol/ethyl acetate.

Example 5

2-[3-(4-morpholinylmethyl)-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl]-oxymethyl-4-isopropyl-6-methoxysaccharin

20



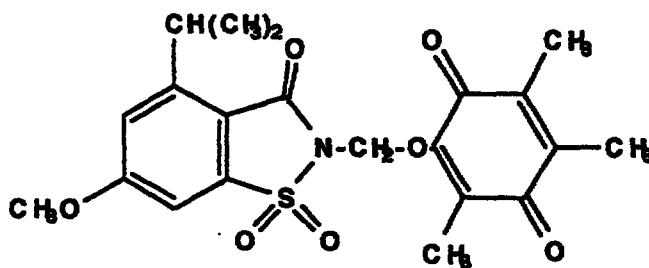
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A mixture of 3-(4-morpholinylmethyl)pyrido[1,2-a]pyrimidine-2,4-dione hydrochloride (0.6 g) and potassium t-butoxide (0.49 g) in dimethyl formamide (20 ml) was stirred at room temperature for five minutes. 2-Chloromethyl-4-isopropyl-6-methoxysaccharin (0.61 g) was added and stirring was continued at room temperature for one hour. The reaction mixture was diluted with water (50 ml) and extracted with dichloromethane (3 x 200 ml). The dichloromethane extract was dried over sodium sulfate and stripped of volatiles, finally under high vacuum. The crude product (780 mg) was combined with that (0.65 g) from another run at the same scale using sodium hydride (60% dispersion in mineral oil, 0.19 g) instead of potassium t-butoxide and purified by column chromatography on silica gel with dichloromethane-methanol (95:5) as eluant affording the title compound (500 mg, 23% yield), part of which was recrystallized from ethanol (m.r. 177-180°C.).

Example 6

2-(3,5,6-trimethyl-1,4-dioxo-2,5-cyclohexadien-2-yl)oxymethyl-4-isopropyl-6-methoxysaccharin

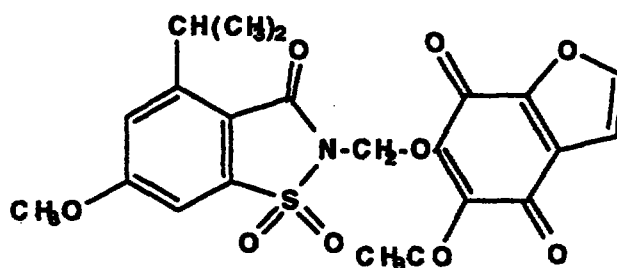


2-Chloromethyl-4-isopropyl-6-methoxysaccharin (0.34 g) was added with stirring at room temperature to a solution of 2-hydroxy-3,5,6-trimethyl-1,4-quinone (0.182 g) and methyltriazabicyclodecene (0.18 g) in acetonitrile (20 ml). Stirring at room temperature was continued for 24 hours and the dark colored solution was poured into ice-water containing a few drops of hydrochloric acid. The resulting tan solid was purified first by column chromatography on silica gel and then recrystallization from hot ethanol affording the title compound (60 mg, 12.7% yield, m.r. 164-166°C.)



Example 7

2-(5-acetyl-4,7-dihydro-4,7-dioxobenzofuran-6-yl)oxymethyl-4-isopropyl-6-methoxysaccharin



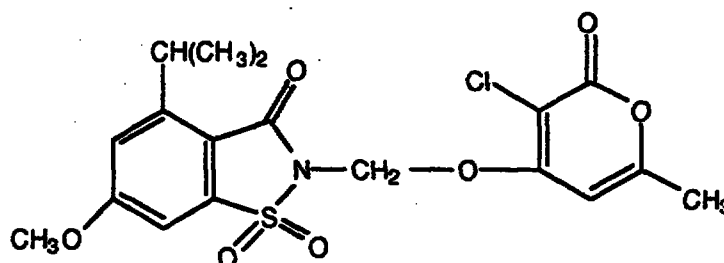
2-Chloromethyl-4-isopropyl-6-methoxysaccharin (0.5 g) was added with stirring at room temperature to a solution of 4,7-dimethoxy-5-acetyl-6-hydroxybenzofuran (0.39 g) and methyltriazabicyclodecene (0.28 g) in acetonitrile (20 ml). The mixture was stirred overnight at room temperature. Since thin layer chromatography showed unreacted 4,7-dimethoxy-5-acetyl-6-hydroxybenzofuran, more 2-chloromethyl-4-isopropyl-6-methoxysaccharin and a drop of base were added, stirring was continued for a total of 24 hours, and the reaction mixture was poured into ice-water containing hydrochloric acid. The resulting golden solid was partially purified using dichloromethane as eluant. The reaction was repeated with stirring overnight at 35-40°C. instead of room temperature. The product and the partially purified product of the first reaction were combined and purified by column chromatography on silica gel affording 2-(4,7-dimethoxy-5-acetylbenzofuran-6-yl)oxymethyl-4-isopropyl-6-methoxysaccharin (0.4 g, 24% yield).

A solution of triceric tetraammonium hexanitrate (0.98 g) in water (3 ml) was added dropwise to a solution of 2-(4,7-dimethoxy-5-acetylbenzofuran-6-yl)oxymethyl-4-isopropyl-6-methoxysaccharin (0.3 g) in acetonitrile (5 ml). The mixture was stirred at room temperature for 15 minutes and poured into ice-water. The resulting gold colored solid was purified by rapid chromatography on silica gel with dichloromethane-ether (95:5) as eluant and crystallization with sonication from ethanol affording the title compound (0.13 g, 46.6% yield, m.r. 193-195°C. with decomposition).



Example 8

2-(3-chloro-6-methyl-2-oxo-2H-pyran-4-yl)oxymethyl-4-isopropyl-6-methoxysaccharin,



A mixture of 3-chloro-4-hydroxy-6-methyl-2H-pyran-2-one (0.493 g, 3.07mmol), DMF and K₂CO₃ (0.467 g, 3.38mmol) was stirred at room temperature under N₂ for 0.5 hours then 2-chloromethyl-4-isopropyl-6-methoxy-saccharin (0.978 g, 3.22mmol) was added in one portion. The mixture was stirred at room temperature for 3 hours, and then at 75°C for 3 hours. The mixture was poured into water, extracted with ethyl acetate and the organic layer was washed with brine and dried. The solvent was removed in *vacuo* and the residue was purified by column chromatography on silica eluting with 30% ethyl acetate/hexane to afford 0.25 g (18.1%) of the title compound, m.p. 182.5-183.5°C after recrystallization from ether/hexane.

Examples 9A-9I

The compounds identified in Table III below were prepared by the following general procedure:

A mixture of the appropriate compound of Formula III (H-O-Z), about 1.0-1.5 equivalents of an appropriate base and an appropriate solvent was stirred at room temperature for about 0-60 minutes and then about 1.0-1.2 equivalents of an appropriate 2-chloromethyl-4-isopropyl-6-R₂-saccharin was added. The mixture was stirred at about room temperature to about 90°C for about 1-48 hours and was worked up as follows:

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Method 1: the reaction mixture was poured into ice/water and was either
(a) extracted with a suitable solvent (e.g. ethyl acetate, chloroform or methylene
chloride) and the organic layer was separated, dried over Na_2SO_4 , filtered and
concentrated, and the residue thus obtained was purified as shown in Table III; or

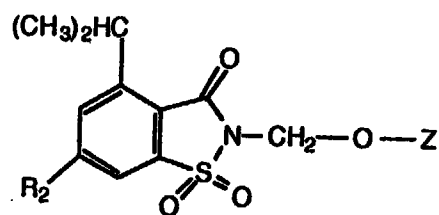
- 5 (b) the product precipitated from the ice/water and was collected by filtration and
was purified as shown in Table III; or

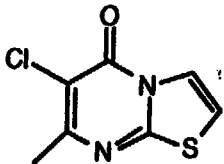
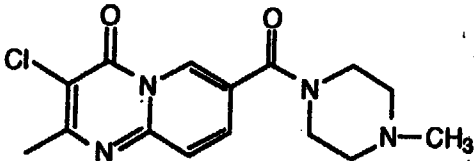
Method 2: the solvent was removed in vacuo and the residue was purified as
shown in Table III.

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TABLE III

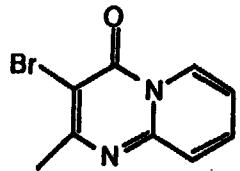
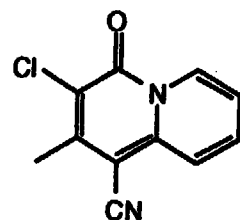
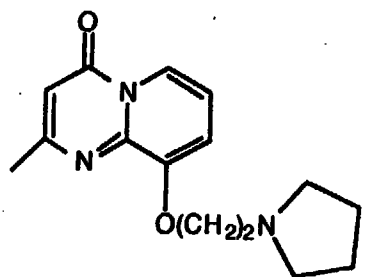


Example	Z	R ₂	Base/ Solvent	Work-Up Method	Melting Point (°C) /Yield (%)	Recrystal- lization Solvent
9A		CH ₃ O	K ₂ CO ₃ DMF	#1	211-213 9.3	Water
9B		CH ₃ O	K ₂ CO ₃ DMF	#1	197-200	Et ₂ O/ CH ₃ CN(a)

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TABLE III (continued)

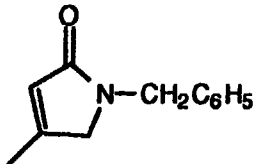
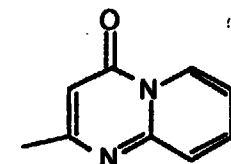
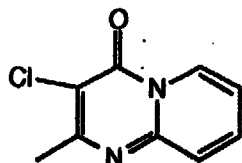
Example	Z	R ₂	Base/ Solvent	Work-Up Method	Melting Point (°C) /Yield (%)	Recrystal- lization Solvent
9C		CH ₃ O	K ₂ CO ₃ N-methyl- 2-pyrrolidinone	#1	217-218 26	EtOAc/ Et ₂ O/
9D		CH ₃ O	(iPr) ₂ NEt CH ₃ CN	#1	250-252 31.8	DMF/ Water ^(b)
9E		CH ₃ O	methyltriazabicy- clodecene/CH ₃ CN	#1	228-230(dec.) (HCl Salt) 43.5	(C)

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TABLE III (continued)

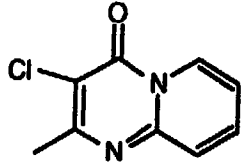
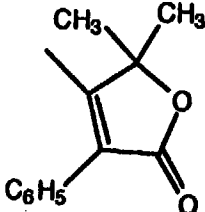
Example	Z	R ₂	Base/ Solvent	Work-Up Method	Melting Point (°C) /Yield (%)	Recrystal- lization Solvent
9F		CH ₃ O	methyltriazabicy- clodecene	#2	176.5-178 22.8	benzene/ hexane(d)
9G		PhCH ₂ O (CH ₂) ₂ O-	K ₂ CO ₃ DMF	#1	Foam 70	(e)
9H		(iPr) ₃ SiO (CH ₂) ₂ O	methyltriazabicy- clodecene/DMF	#1	Foam 31	(f)



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TABLE III (continued)

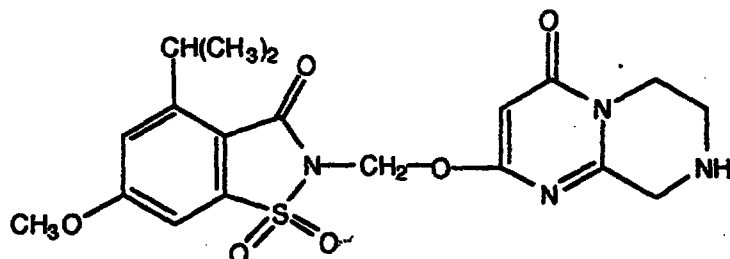
Example	Z	R ₂	Base/ Solvent	Work-Up Method	Melting Point (°C) /Yield (%)	Recrystal- lization Solvent
9I		H	(iPr) ₂ NEt DMF	#1	208.5-210 45.2	EtOAc
9J		CH ₃ O	Methyltriazabicy- clodecene/CH ₃ CN	#1	189-193 20.9	Benzene/ hexane(g)

- (a) Product was purified by column chromatography on silica eluting with 5% methanol/CHCl₃ prior to recrystallization.
 (b) Product was purified by recrystallization from CH₃CN and then by column chromatography on silica eluting with 5% ethyl acetate/CH₂Cl₂ prior to this recrystallization.
 (c) The free base of the product was purified by column chromatography on silica eluting with 65% ethyl acetate/30% methanol/5% triethylamine, prior to formation of the HCl salt by treatment with 4.6 N ethanolic HCl.
 (d) Product was purified by column chromatography on silica eluting with hexane/ethyl acetate (3/1 to 2/1) prior to recrystallization.
 (e) Product was purified by column chromatography on silica eluting with 60% ethyl acetate/hexane.
 (f) Product was purified by column chromatography on silica eluting with 40% ethyl acetate/hexane.
 (g) Product was purified by column chromatography on silica eluting with ethyl acetate/hexane (1/7) to (1/6) prior to recrystallization.

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Example 10

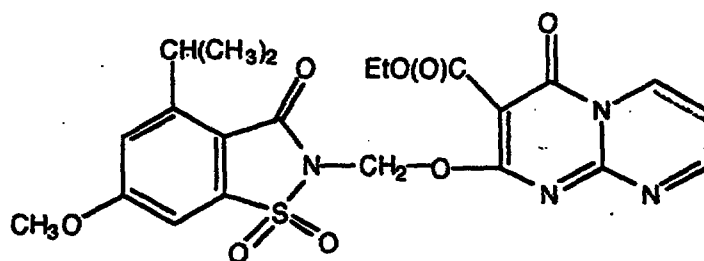
5

A mixture of the compound of Example 4H (0.359 g, 0.834mmol), ethyl acetate (35 ml), and palladium on carbon was hydrogenated at 50 psi on a Parr hydrogenator for 1 3/4 hours. Additional palladium on carbon (0.16 g) was added and the reaction was continued for an additional 2 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with EtOAc/MeOH/triethylamine (88.5/7.5/4) to afford 0.132 g (36.5%) of the desired product as the free base which was dissolved in ethanol, and treated with citric acid in ethanol to afford 0.142 g of the product as the citric acid salt, m.p. 198-200°C.

15

Example 11

2-[3-(ethoxycarbonyl)-4-oxo-4H-pyrimido[1,2-a] pyrimidin-2-yl]oxymethyl-4-isopropyl-6-methoxysaccharin



20

Ethyl 5-oxo-2-(pyrimidinyl-2-yl)-2,5-dihydro isoxaxole-4-carboxylate (0.70 g, 3.0mmol) was added to a mixture of potassium t-butoxide (0.37 g, 3.3mmol) in THF (20 ml) and the mixture was stirred at 40°C under nitrogen for 0.5 hours. The solvent was removed *in vacuo*, and the residue was

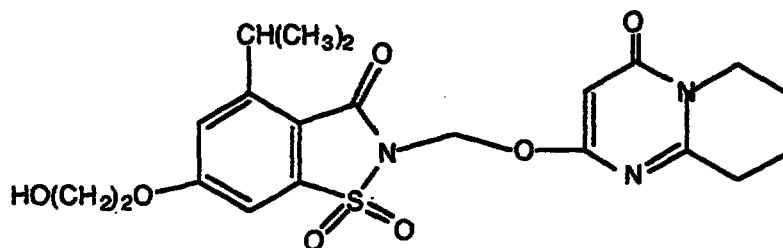
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dried under high vacuum. The residue was mixed with DMF (20 mL) and treated with 2-chloromethyl-4-isopropyl-6-methoxysaccharin (0.91 g, 3.0mmol) in DMF (5 ml). The mixture was stirred at room temperature for approximately 3 days, poured into ice/water and extracted with ethyl acetate. The organic layer was separated, dried over Na₂SO₄ and concentrated in *vacuo*. The residue was purified by column chromatography on silica eluting with 5% MeOH/EtOAc to afford 0.18 g (12%) of the title compound, m.p. 189-191°C after recrystallization from toluene/hexane.

10 Example 12

2-[4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-2-yl]oxymethyl-4-isopropyl-6-(2-hydroxyethoxy) saccharin



15

A mixture of the product of Example 9G (1.35 g) in ethyl acetate (200 ml)/methanol (5 ml) and 10% palladium on carbon (0.5 g) was hydrogenated at 50 psi on a Parr hydrogenator for 3 hours. Additional palladium on carbon (0.5 g) was added and the mixture was hydrogenated for 8-9 hours. The mixture was filtered, the filtrate was concentrated in *vacuo*, and the residue was purified by column chromatography on silica eluting with ethyl acetate to afford 0.89 g of the title compound as a white foam.

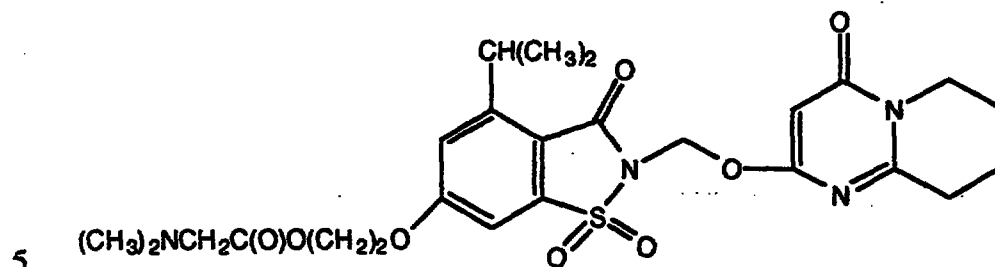
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Example 13

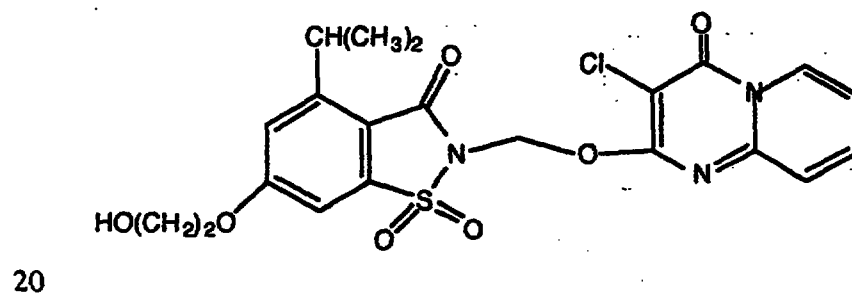
~~2-[4-oxo-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-2-yl]oxymethyl-4-isopropyl-6-[2-(dimethylaminomethylcarbonyloxy)ethoxy]saccharin~~



To a solution of the compound of Example 12 (0.8 g, 1.72mmol) in CH_2Cl_2 (25 ml) containing 1,3-dicyclohexylcarbodiimide (1.06 g, 5.14mmol) was added dimethyl glycine (0.19 g; 1.9mmol), followed by 4-dimethylamino-
 10 pyridine (0.21 g, 1.72mmol). The mixture was stirred at room temperature for 2 hours, the solvent was removed in *vacuo*, and the residue was purified by column chromatography on silica eluting with 10% methanol/ethyl acetate to afford 0.64 g (68%) of the title compound as a white foam.

Example 14

~~2-[3-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl]oxymethyl-4-isopropyl-6-[2-hydroxyethoxy]saccharin~~



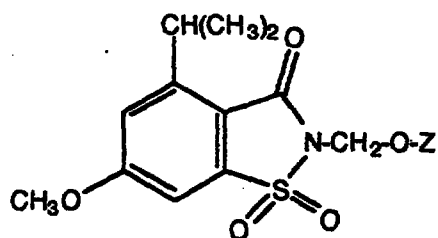
To a suspension of the compound of Example 9H (0.76 g) in methanol (30 ml), was added THF, followed by 2N HCl (20-30 ml). The mixture was stirred for 4-5 hours, additional 2N HCl was added and the mixture was stirred overnight. The solvent was removed in *vacuo*, the residue was diluted with
 25 THF and treated with concentrated HCl (2 ml). After stirring for 5-6 hours, the



solvent was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was washed with water, then brine and was dried. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica eluting with 80% ethyl acetate/hexane to afford 0.43 g of the title compound, m.p. 214.5-215.5 °C.

Examples 15A-15C

Following a procedure similar to that described in Example 9D, but substituting an appropriate compound of the Formula III (H-O-Z), it is contemplated that the following compounds can be prepared:

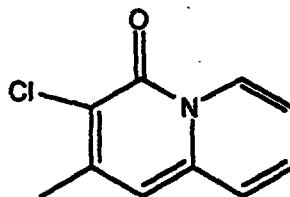


Example

Z

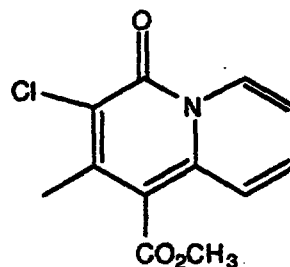
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15A



20

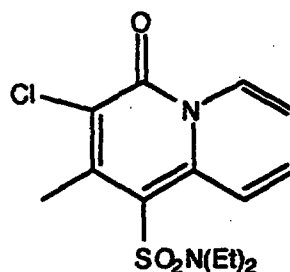
15B



Example

Z

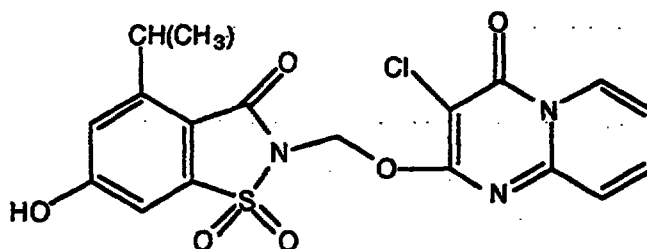
15C



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Example 16

(a) 2-[3-chloro-4-oxo-4H-pyrido-[1,2-a]pyrimidin-2-yl]oxymethyl-6-hydroxy-4-isopropylsaccharin

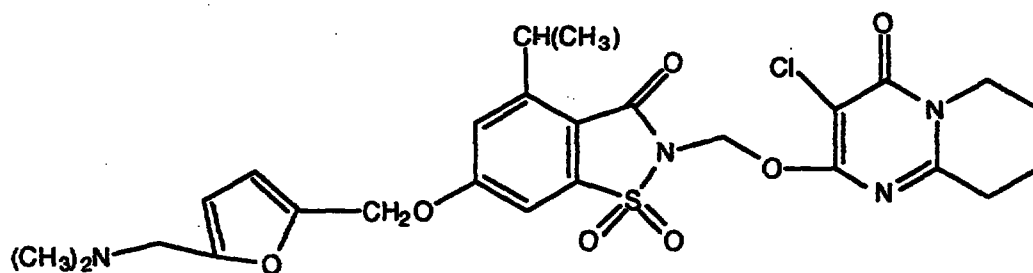


10

Following a procedure similar to that described in Example 6 it is contemplated that the title compound can be prepared from 3-chloro-pyrido-[1,2-a]pyrimidine-2,4-dione (2 equivalents), methyltriazabicyclodecene (2 equivalents), DMF and 2-chloromethyl-4-isopropyl-6-hydroxysaccharin.

15

(b) 2-[3-chloro-4-oxo-4H-pyrido-[1,2-a]pyrimidin-2-yl]oxymethyl-4-isopropyl-6-[1-(5-dimethylaminomethyl-2-furanyl)methoxy]saccharin



20

It is contemplated that the title compound can be prepared by treating a solution of 2-[3-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl]-

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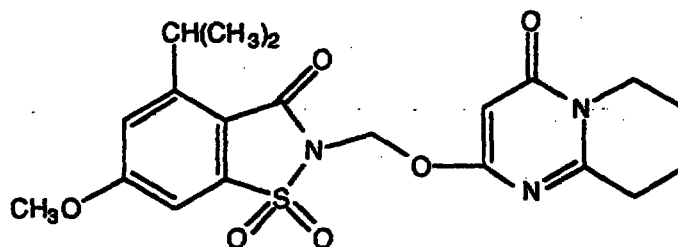


It is contemplated that the title compound can be prepared by treating a solution of 2-[3-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl]-oxymethyl-6-hydroxy-4-isopropyl-saccharin in DMF with triphenylphosphine, 5-dimethylaminomethyl-2-hydroxymethylfuran and diethylazodicarboxylate.

5

Example 17

2-[4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-2-yl]oxymethyl-4-isopropyl-6-methoxysaccharin



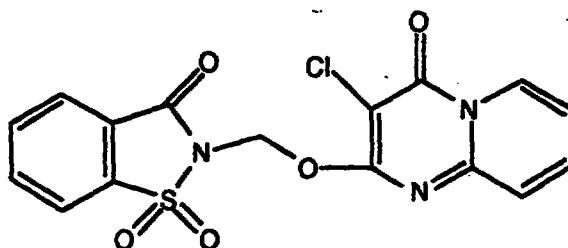
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A mixture of the compound of Example 4C (0.3 g, 0.708 mmol), ethyl acetate (14 ml) and 10% palladium on carbon (0.3 g) was hydrogenated on a Parr hydrogenator at 50 psi for 7 hours. The reaction mixture was filtered through celite, the filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica eluting with 50% ethyl acetate/hexane to 70% ethyl acetate/hexane to afford 0.165 g (54%) of the title compound, m.p. 183.5-185.5°C after recrystallization from ethyl acetate/hexane.

20

Example 18

2-[3-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-yl]oxymethylsaccharin



25

To a mixture of 2-hydroxy-3-chloropyrido[1,2-a]pyrimidine-4-one (0.324 g), and methyltriazabicyclodecene (0.24 ml) in DMF (15 ml) was added



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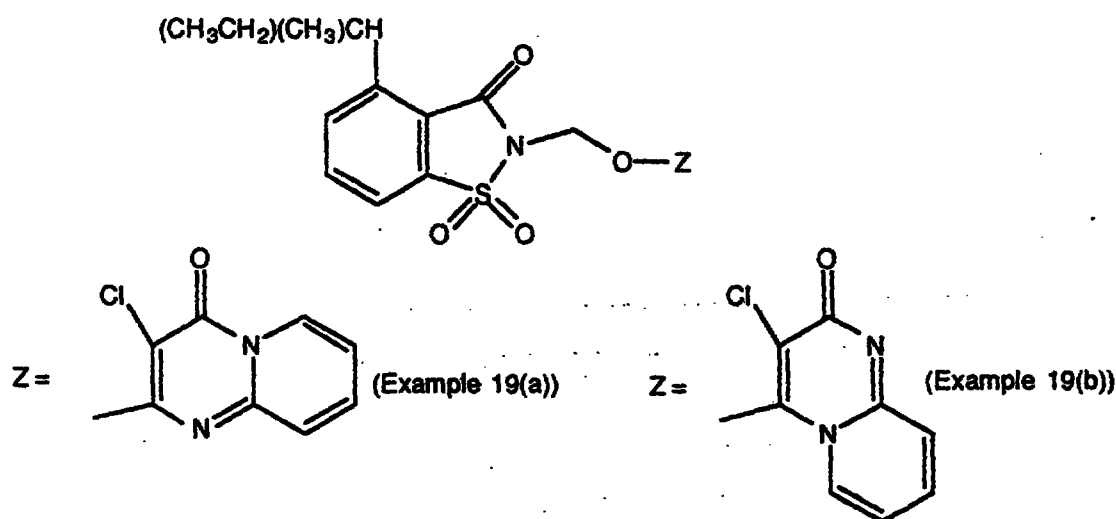
2-bromomethylsaccharin (0.414 g). The mixture was stirred overnight, poured into water and the precipitate which formed was collected by filtration and recrystallized from DMF to afford 0.371 g (65%) of the title compound.

5 Example 19(a)

2-[3-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-yl]oxymethyl-4-sec-butyl-
saccharin, and

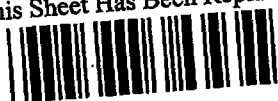
Example 19(b)

2-[3-chloro-2-oxo-2H-pyrido[1,2-a]pyrimidine-4-yl]oxymethyl-4-sec-butyl-
10 saccharin,



To a mixture of 2-hydroxy-3-chloropyrido[1,2-a]pyrimidine-4-one-
15 (6.29 g), and methyltriazabicyclodecene (0.22 ml) in DMF (12 ml) was added
2-chloromethyl-4-sec-butylsaccharin (0.39 g). The reaction mixture was stirred
for 8 hours, poured into water and the precipitate which formed was collected by
filtration. The solid residue was purified by column chromatography on silica
eluting with hexane/ethyl acetate (2/1) to ethyl acetate/hexane (1/1) to afford
20 0.284 g (46.7%) of the title compound of Example 19a, m.p. 211-212°C after
recrystallization from ethyl acetate; and 0.027 g of the title compound of
Example 19b, m.p. 268-271°C (dec.) after recrystallization from CH₂Cl₂.

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As stated above the compounds of Formula I inhibit the enzymatic activity of proteolytic enzymes and are useful in the treatment of degenerative diseases. More particularly they inhibit human leukocyte elastase and chymotrypsin-like enzymes and are useful in the treatment of emphysema, rheumatoid arthritis, pancreatitis, cystic fibrosis, chronic bronchitis, adult respiratory distress syndrome, inflammatory bowel disease, psoriasis, bullous pemphigoid and alpha-1-antitrypsin deficiency. This utility was demonstrated by an *in vitro* test of inhibition of compounds of Formula I against human leukocyte elastase.

Measurement of the inhibition constant (K_i) of a human leukocyte elastase inhibitor complex has been described (Cha, Biochemical Pharmacology, vol 24, pp. 2177-2185, 1975) for truly reversible inhibition constants usually concerning competitive inhibitors. The compounds of Formula I do not form truly reversible inhibitor complexes but rather are consumed by the enzyme to some extent. K_i^* , which is defined as the rate of reactivation of the enzyme divided by the rate of inactivation of the enzyme (k_{off}/k_{on}), was therefore determined instead. The values of k_{off} and k_{on} were measured and K_i^* was then calculated.

The value of k_{on} was determined by measuring the enzyme activity of an aliquot of the enzyme as a function of the time after addition of the test compound (inhibitor). By plotting the log of the enzyme activity against time an observed rate of inactivation (k_{obs}) was obtained by the equation $k_{obs} = \ln 2/t_{1/2}$ wherein $t_{1/2}$ is the time required for the enzyme activity to decrease by 50%. The value of k_{on} was then obtained by the equation $k_{on} = k_{obs}/[I]$ wherein $[I]$ is the concentration of the inhibitor. The value of k_{off} was similarly determined, and K_i^* was then obtained by the equation $K_i^* = k_{off}/k_{on}$.

The results shown in Table IV were obtained for compounds of Formula I of the examples.

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Table IV

Inhibition of Human Leukocyte Elastase

	<u>Compound of Example</u>	<u>K_i* (nM)</u>
5	1A	0.4
	1B	0.22
	1C	0.7
	1D	0.25
	1E	0.035
10	1F	0.22
	1G	0.05
	1H	0.027
	1I	0.25
	1J	0.85
15	1K	0.013
	1L	0.09
	1M	0.18
	1N	0.052
	1O	0.016
20	1P	0.041
	1Q	0.06
	1R	0.038
	2	0.5
	3A	0.43
25	3B	0.27
	4A	0.025
	4B	0.9
	4C	0.078
	4D	0.066
30	4E	0.093
	5	0.23
	6	0.92
	7	17

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The human-leukocyte elastase inhibitory activity of representative compounds of the invention was also demonstrated by the following procedure:

The test compound (inhibitor) is dissolved in DMSO in a vial to produce an inhibitor stock solution which has a concentration in the range of
5 200-1000 μ M. The inhibitor stock solution is diluted (1:4, 1:16 and 1:64) into assay vials (vials 1, 2 and 3 respectively) containing 2.4 ml buffer solution (50 mM N-[2-hydroxyethyl] piperazine-N'-[2-ethanesulfonic acid]/NaOH, 500 mM NaCl, pH 7.8 at 25°C) and DMSO is added so that the total volume in each vial is 3.2 ml. 70 μ l, 50 μ l 35 μ l and 25 μ l of inhibitor from assay vial 1 is
10 placed into the first four wells of a 96-well microtiter plate and each well is made up to 90 μ l total volume with the addition of a 25% DMSO/buffer solution. The inhibitor from assay vials 2 and 3 is processed in a similar manner and placed in wells 5-12 respectively to afford a total of 12 different inhibitor concentrations. Four wells (wells 13-16) containing 90 μ l of the 25% DMSO/buffer solution but
15 no inhibitor are also run simultaneously with the inhibited wells as a control. 150 μ l substrate solution (prepared by the addition of 500 μ l of the human leukocyte elastase (HLE) substrate MeOSuc-Ala-Ala-Pro-Val-pNA (18.7 mM in DMSO) to 19.5 ml buffer solution) was then added simultaneously into each of the 16 wells and the solution in each well was thoroughly mixed.

20 The 96-well microtiter plate was placed into a Microplate Reader #89815A spectrophotometer and 110 μ l of the enzyme solution (prepared as follows: a mixture of 20 ml of buffer solution and 20 mg of bovine serum albumen is gently vortexed in a scintillation vial) and 5 μ l HLE stock solution (1 mg/ml dissolved in deionized water) is added simultaneously to each of the 16 wells.
25 Each of the solutions in the wells is thoroughly mixed and then the time-dependent absorbance data is collected at an absorbance of 410 mM until the assay is complete. It should be noted that although this assay method can be done manually, it is preferred to perform the assay robotically using a Hewlett Packard MicroAssay System Robot.

30 A plot of the absorbance versus time data thus obtained affords progress curves the final slope of which is equal to the final steady-state velocities (V_F). Using the program ENZFITTER (Elsevier software), the progress curves for the four control assays ($[I]=0$) are fit by linear regression to yield the enzyme reaction velocity values in the absences of inhibitor (V_0) which are averaged to



produce a single fixed value. The inhibition constant K_i (nM) is then obtained from a plot of

5
$$\frac{[I]}{1-V_F/V_0} \text{ versus } V_0/V_F$$

which affords a linear plot wherein:

$$\text{slope} = K_i \left(1 + \frac{[S]}{K_m} \right)$$

and [S] is the concentration of the substrate and K_m is the Michaelis constant.

10 The following Table summarizes the results obtained from the testing of representative compounds of the invention utilizing this latter method.

Table V
Inhibition of Human Leukocyte Elastase

15

Compound of Example	K_i (nM)
1S	0.22
1T	0.083
1U	0.078
20 1V	0.033
1W	0.034
4F	0.08
4G	0.20
4H	0.066
25 4I	0.19
4J	0.120
4K	2.5
8	0.025
9A	0.044
30 9B	0.12
9C	0.058
9D	0.081
9E	0.035
9F	0.138



Table V (continued)
Inhibition of Human Leukocyte Elastase

	Compound of Example	K_i (nM)
5	9G	0.140
	9I	0.210
	9J	0.021
	10	0.120
	11	0.40
10	12	0.130
	13	0.063
	14	0.095
	17	0.110
	18	14.0
15	19a	0.72
	19b	4.7

The proteolytic enzyme inhibiting amount of the compound of Formula I can be estimated from the results of the test for human leukocyte elastase inhibition and can additionally be varied for a particular patient depending on the physical condition of the patient, the route of administration, the duration of treatment and the response of the patient. An effective dose of the compound of Formula I can thus only be determined by the clinician after consideration of all pertinent criteria and exercise of best judgment on behalf of the patient.

A compound of Formula I can be prepared for pharmaceutical use by incorporating it in a pharmaceutical composition for oral, parenteral or aerosol inhalation administration, which can be in solid or liquid dosage form including tablets, capsules, solutions, suspensions and emulsions and which can include one or more suitable adjuvants. Solid unit dosages in the form of tablets or capsules for oral administration are preferred. For this purpose the adjuvant can be for example one or more of calcium carbonate, starch, lactose, talc, magnesium stearate and gum acacia. The compositions are prepared by conventional pharmaceutical techniques.

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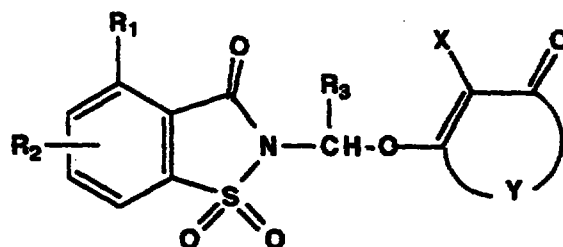




* C L M S *

CLAIMS

1. A compound having the structural formula:



Formula I

wherein

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

R₂ is from one to three substituents at any or all of the 5-, 6- and 7-positions and is selected from the group consisting of B=N-(CH₂)_pC(O)O(CH₂)_{p'}-O-, -O-(CH₂)_p-(5-((CH₂)_{p'}-B=N-2-furanyl), and R-oxy-lower-alkoxy wherein p and p' are integers from 1 to 4, R is lower-alkyl, phenyl or phenyl-lower-alkyl, phenyl can have from one to three substituents selected from the group consisting of lower-alkyl, B=N-carbonyl, B=N, lower-alkoxy, B=N-lower-alkoxy and halo and B=N is amino, lower-alkylamino, di-lower-alkylamino, carboxy-lower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 1-azetidyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl or 1-imidazolyl;

R₃ is hydrogen, lower-alkyl or phenyl;

X is hydrogen, nitro, halo, lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, phenyl, phenyl-lower-alkyl, phenylcarbonyl, pyridyl-lower-alkyl, formyl, lower-alkanoyl, carboxy, lower-alkoxycarbonyl, aminocarbonyl, lower-alkylaminocarbonyl, di-lower-alkylaminocarbonyl, cyano, B=N, B=N-lower-alkyl, B=N-lower-alkanoyl, B=N-lower-alkoxycarbonyl, hydroxy, lower-alkoxy, phenyloxy, B=N-lower-alkoxy, lower-alkylthio, phenylthio, lower-alkylsulfonyl, phenylsulfonyl or B=N-sulfonyl wherein phenyl is unsubstituted or has from one to three substituents selected from the group consisting of lower-alkyl, lower-





alkoxy and halo and B=N is amino, lower-alkylamino, di-lower-alkylamino, carboxy-lower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 1-azetidiny, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl or 1-imidazolyl; and

- 5 -Y- is the remaining atoms of a monocyclic or bicyclic, substituted or unsubstituted carbocyclic or heterocyclic ring system;
or a pharmaceutically acceptable acid addition salt thereof if the compound has a basic functional group or a pharmaceutically acceptable base addition salt thereof if the compound has an acidic functional group.
- 10 2. A compound according to claim 1 wherein R₂ is selected from the group consisting of B=N-(CH₂)_pC(O)O(CH₂)_{p'}-O- and R-oxy-lower-alkoxy.
3. A compound according to either of the preceding claims wherein
- Y- is -(CH₂)_m-, -C(=O)-, -(CH₂)_m-O-, -CHR-O-, -CR₂-O-, -C[(CH₂)_n]-O-,
 -C[CH₂CH₂N(R)CH₂CH₂]-O-, -(CH₂)_m-N(R')-, -CHR-N(R')-, -CR₂-N(R')-,
15 -C(R')=C(R')-O-, -C(R')=C(R')-N(R')-, -C(=O)-C(R'')=C(R'')-, -C(Z')=C(Z')-,
 -C(Z')=C(Z')-O-, -C(Z')=C(Z')-N(R')-, -N(Z'')-C(Z'')=N-, -N=C(Z'')-N(Z'')-,
 C(Z''')-C(Z''')-S-, N=C(R''')-N(R''')- or -C(R''')=C(L)-N(L)- and wherein the
 Z'' groups taken together with the carbon atoms to which they are bonded are benzo; the
- 20 R''' groups taken together with the carbon or nitrogen atoms to which they are bonded are -(CH₂)_{n'}-, -(CH₂)_qN(R*) (CH₂)_{q'}-, or thiazolo; the
 L groups taken together with the carbon or nitrogen atoms to which they are bonded are pyrido;
- n' is an integer from 3 to 5;
- 25 R* is hydrogen, phenyl, phenyl-lower-alkyl, or lower-alkyl;
 q is 1 or 2; q' is 1 or 2;
 R''' is hydrogen, cyano, CO₂L', SO₂L" or nitro;
 L' is hydrogen, lower-alkyl, or di-lower-alkylamino,
 L" is hydroxy, lower-alkoxy, di-lower-alkylamino or trifluoromethyl;
- 30 m is 1, 2, 3, or 4; n is 3, 4, or 5,
 R is the same or different lower-alkyl, phenyl or phenyl-lower-alkyl,
 R' is H or R, R" is H or R or the
 R" groups taken together with the carbon atoms to which they are bonded are furano, the





Z' groups taken together with the carbon atoms to which they are bonded are benzo, furano, pyrido, pyrimidino or pyridazino, and the

Z" groups taken together with the carbon or nitrogen atoms to which they are bonded are pyrido, pyrimidino or pyridazino wherein phenyl, benzo, furano,

- 5 pyrido, pyrimidino or pyridazino can have from one to three substituents selected from the group consisting of lower-alkyl, B=N-carbonyl, B=N, lower-alkoxy, B=N-lower-alkoxy and halo.

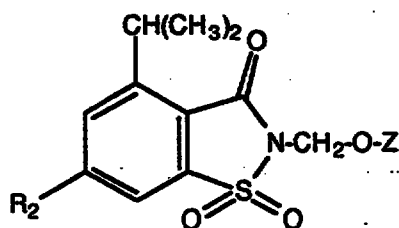
4. A compound according to claim 3 wherein n' is 4; R* is hydrogen; q is 1; q' is 2; R"" is hydrogen, cyano, CO₂L' or SO₂L"; L' is lower-alkyl and
10 L" is di-lower-alkylamino.

5. A compound according to any one of the preceding claims wherein R₁ is lower-alkyl; R₂ is di-lower-alkylamino-(CH₂)_pC(O)O(CH₂)_{p'}-O or phenyl-lower-alkyloxy-lower-alkoxy; R₃ is hydrogen; and X is hydrogen, halo, lower-alkyl, phenyl, phenyl-lower-alkyl, phenylcarbonyl, B=N, B=N-lower-alkyl, phenyloxy, or lower-alkoxycarbonyl.
15

6. A compound according to claim 5 wherein R₁ is isopropyl; R₂ is 6- dimethylamino-CH₂C(O)O(CH₂)₂-O- or 6- benzyloxyethoxy; and X is hydrogen.

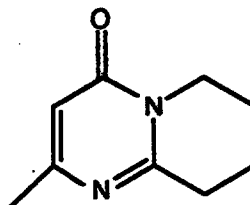
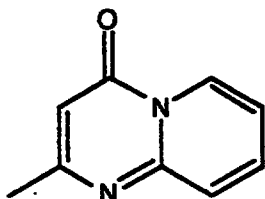
7. A compound according to claim 6 having the structural formula:

20



wherein R₂ is dimethylamino-CH₂C(O)O(CH₂)₂-O- or benzyloxyethoxy and Z has one of the following structural formulae:

25





* C L M S *

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8. A pharmaceutical composition for treatment of degenerative disease which comprises a proteolytic enzyme inhibiting concentration of a compound of Formula I according to any one of claims 1-7 in a pharmaceutically acceptable carrier.

5 9. The use of a compound according to any one of claims 1-7 for the preparation of a medicament for treating a patient having a degenerative disease.

10. The use of a composition according to claim 8 for the preparation of a medicament for treating a patient having a degenerative disease.

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