

**SACCHARIN DERIVATIVE PROTEOLYTIC ENZYME
INHIBITORS**

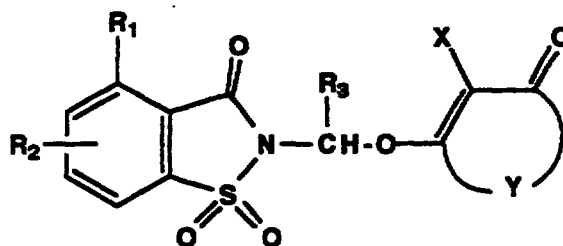
5 The invention relates to saccharin derivatives which inhibit the enzymatic activity of proteolytic enzymes, to processes for preparation thereof, to method of use thereof in the treatment of degenerative diseases and to pharmaceutical compositions thereof.

 Inhibitors of proteolytic enzymes are useful in treatment of which
10 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.

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

25



Formula I

wherein

30 R_1 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



R_2 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 hydrogen, lower-alkyl, cycloalkyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, 5 perfluoro-lower-alkyl, perchloro-lower-alkyl, formyl, cyano, carboxy, aminocarbonyl, R-oxycarbonyl, B=N, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, perfluoro-lower-alkylsulfonylamino, perchloro-lower-alkylsulfonylamino, nitro, hydroxy, R-carbonyloxy, lower-alkoxy, cycloalkoxy, B=N-lower-alkoxy, hydroxy-lower-alkoxy, poly-hydroxy-lower-alkoxy or acetal 10 or ketal thereof, lower-alkoxy-lower-alkoxy, poly-lower-alkoxy-lower-alkoxy, hydroxy-poly-lower-alkyleneoxy, lower-alkoxy-poly-lower-alkyleneoxy, B=N-carbonyloxy, carboxy-lower-alkoxy, R-oxycarbonyl-lower-alkoxy, methylenedioxy, di-lower-alkylphosphonyloxy, R-thio, R-sulfinyl, R-sulfonyl, perfluoro-lower-alkylsulfonyl, perchloro-lower-alkylsulfonyl, aminosulfonyl, 15 lower-alkylaminosulfonyl, di-lower-alkylaminosulfonyl and halo, wherein R is lower-alkyl, phenyl or phenyl-lower-alkyl, phenyl having 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.

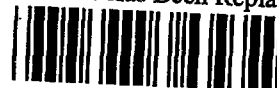
B=N is amino, lower-alkylamino, di-lower-alkylamino, carboxy-lower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 1-azetidyl, 4-morpholinyl, 20 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl or 1-imidazolyl;

R_3 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, 25 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 30 to three substituents selected from the group consisting of lower-alkyl, lower-alkoxy and halo, wherein B=N is as defined above,

-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 35 has a basic functional group or a pharmaceutically acceptable base addition salt thereof if the compound has an acidic functional group.



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

In a preferred aspect the invention provides a compound of Formula I wherein -Y- is $-(CH_2)_m-$, $-C(=O)-$, $-(CH_2)_m-O-$, $-CHR-O-$, $-CR_2-O-$,
 5 $-C[(CH_2)_n]-O-$, $-C[CH_2CH_2N(R)CH_2CH_2]-O-$, $-(CH_2)_m-N(R')-$, $-CHR-N(R')-$,
 $-CR_2-N(R')-$, $-C(R')=C(R')-O-$, $-C(R')=C(R')-N(R')-$, $-C(=O)-C(R'')=C(R'')-$,
 $-C(Z')=C(Z')-$, $-C(Z')=C(Z')-O-$, $-C(Z')=C(Z')-N(R')-$, $-N(Z'')-C(Z'')=N-$ or
 $-N=C(Z'')-N(Z'')-$

wherein m is 1, 2, 3, or 4,

10 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

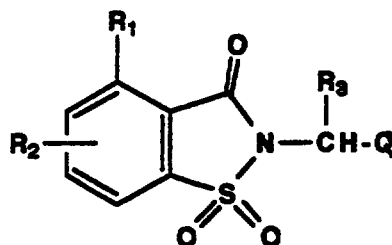
15 R'' groups taken together with the carbon atoms to which they are bonded
 are furano, the

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,

20 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.

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

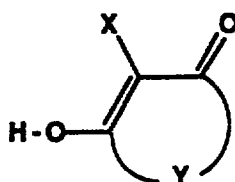


Formula II

wherein Q is chloro or bromo with the corresponding compound



having the structural formula



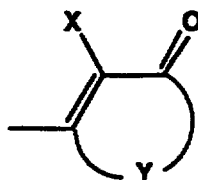
Formula III

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

In another aspect the invention provides the use of a compound of Formula I for preparation of a medicament for the treatment of a degenerative disease in a patient in need of such treatment

- 10 In yet 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.

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



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.

- 20 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.

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

- 30 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, the lower-alkylamino part of lower-alkylamino-lower-alkyl, the lower-alkylamino part of di-



lower-alkylamino-lower-alkyl, the lower-alkoxy part of lower-alkoxy-lower-alkyl, carboxy-lower-alkylamino, 4-lower-alkyl-1-piperazinyl, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, perfluoro-lower-alkylsulfonylamino, perchloro-lower-alkylsulfonylamino, the first lower-alkoxy part of lower-alkoxy-lower-alkoxy, the
5 first lower-alkoxy part of poly-lower-alkoxy-lower-alkoxy, the lower-alkoxy part of lower-alkoxy-poly-lower-alkyleneoxy, R-oxycarbonyl-lower-alkoxy, perfluoro-lower-alkylsulfonyl, perchloro-lower-alkylsulfonyl, lower-alkylaminosulfonyl, di-lower-alkylaminosulfonyl, 4-lower-alkyl-1-piperazinyl, phenyl-lower-alkyl, pyridyl-lower-alkyl, lower-alkylaminocarbonyl, di-lower-alkylaminocarbonyl,
10 lower-alkylthio and carboxy-lower-alkylamino.

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-alkyl part of lower-alkylamino-lower-alkyl, the lower-alkyl part of di-lower-alkylamino-
15 lower-alkyl, hydroxy-lower-alkyl, the lower-alkyl part of lower-alkoxy-lower-alkyl, the lower-alkoxy part of B=N-lower-alkoxy, hydroxy-lower-alkoxy, polyhydroxy-lower-alkoxy, the second lower-alkoxy part of lower-alkoxy-lower-alkoxy, the second lower-alkoxy part of poly-lower-alkoxy-lower-alkoxy, the alkyleneoxy part of hydroxy-poly-lower-alkyleneoxy, the alkyleneoxy part of
20 lower-alkoxy-poly-lower-alkyleneoxy, lower-alkanoyl, B=N-lower-alkyl, B=N-lower-alkanoyl and B=N-lower-alkoxycarbonyl. Alkylene is preferably 1,2-alkylene. Cycloalkyl and cycloalkoxy have from three to six ring carbon atoms and can be substituted by one or more lower-alkyl. Halo is fluoro, chloro, bromo or iodo.

25 R_1 is preferably primary or secondary alkyl of two to four carbon atoms or lower-alkoxy.

R_2 is preferably hydrogen, hydroxy, 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-alkyleneoxy, lower-alkoxy-poly-lower-alkyleneoxy, B=N-carbonyloxy, carboxy-lower-alkoxy, R-oxycarbonyl-lower-alkoxy, methylenedioxy or di-lower-alkylphosphonyloxy and, except methylenedioxy, is preferably located at the 6-position. Methylenedioxy can be located at the
30 5 and 6- or 6 and 7-positions.

35



THIS SHEET HAS BEEN
REPLACED

A compound of Formula I wherein R_1 is lower alkyl, R_2 is hydrogen or lower-alkoxy, R_3 is hydrogen and X is hydrogen, halo, lower-alkyl, phenyl, phenyl-lower-alkyl, phenylcarbonyl, lower-alkanoyl, $B=N$, $B=N$ -lower-alkyl or phenyloxy is particularly preferred.

- 5 Especially preferred is a compound of Formula I wherein R_1 is isopropyl, R_2 is hydrogen or 6-methoxy and X is hydrogen, chloro, methyl, phenyl, phenylmethyl, phenylcarbonyl, acetyl, 1-piperidinyl, 4-morpholinylmethyl or phenyloxy.

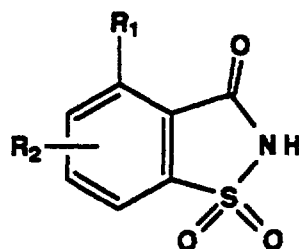
- 10 In carrying out the preparation of a compound of Formula I from a corresponding compound of Formula II and the corresponding compound of Formula III in the presence of a base, the base can be any base which is not itself a reactant under the reaction conditions and is preferably an alkali metal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

- 25 The compounds of Formulas II and III are known or are made by known methods or by methods described below.

- A compound of Formula II wherein R_3 is hydrogen can be prepared by diazotizing the corresponding lower-alkyl 2-amino-
- 30 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-3, 4 or 5- R_2 -6- R_1 -benzoate ester with ammonia to form the corresponding



compound having the structural formula:



Formula IV,

5

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

10 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 paraformaldehyde and chlorotrimethylsilane in the presence of a Lewis acid, for example stannic chloride.

15

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.

20

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, sulfur chloride or sulfur bromide.

25

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-

30



alkylbenzamide with sulfur dioxide followed by hydroxylamine O-sulfonic acid or sulfonyl chloride followed by ammonia, and cyclizing the resulting 2-R₁-3, 4 or 5-R₂-6-aminosulfonyl-N,N-di-lower-alkylbenzamide in refluxing acetic acid.

5 A compound of Formula IV wherein R₁ is primary or secondary alkyl of two to four carbon atoms can be prepared by lithiating the corresponding compound of Formula IV wherein R₁ is methyl with two molar equivalents of a lower-alkyl lithium in an inert solvent, for example tetrahydrofuran, and alkylating the resulting 4-lithiomethyl-5, 6 or 7-R₂-saccharin with the appropriate alkyl
10 halide. Both reactions are carried out at a temperature in the range from -80°C. to -50°C. The above-described 2-R₁-3, 4 or 5-R₂-N,N-di-lower-alkylbenzamide wherein R₁ is primary or secondary alkyl of two to four carbon atoms can be prepared by a similar lithiation-alkylation sequence starting with the corresponding 2-methyl, ethyl or propyl-3, 4 or 5-R₂-N,N-di-lower-alkylbenzamide.

15 A compound of Formula IV wherein R₁ is primary or secondary alkyl of two to four carbon atoms can also be prepared by introducing R₁ earlier in the synthesis. Conjugate addition of the appropriate R₁-cuprate to 2-cyclohexenone and methoxycarbonylation of the resulting copper enolate with methyl cyanoformate by the method of Winkler et al. (Tetrahedron Letters, p. 1051, 1987;
20 Journal of Organic Chemistry, vol. 54, p. 4491, 1989) gives the corresponding 2-methoxycarbonyl-3-R₁-cyclohexanone, enol etherification of which with benzylthiol and acidic clay gives a mixture of the corresponding 6-R₁-2-benzylthio-1-cyclohexenecarboxylic acid methyl ester and 6-R₁-2-benzylthio-3-cyclohexenecarboxylic acid methyl ester, aromatization of which with dichloro-
25 dicyanobenzoquinone 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.

30 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 sulfonyl chloride
35 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-benzisothiazol-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-benzisothiazol-2H-3-one-1,1-dioxide, followed
5 by debenzylation by catalytic hydrogenation to give the corresponding 4-lower-alkoxy-7-hydroxysaccharin of Formula IV.

Similarly alkylation of the 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzisothiazol-2H-3-one-1-oxide with a lower-alkyl halide or an appropriately substituted lower-alkyl halide followed by oxidation and
10 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-alkyleneoxy or lower-alkoxy-poly-lower-alkyleneoxy.

15 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 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
20 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 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 respectively of the compound of Formula I.

25 In the preparations and examples described below the structures of the products are inferred from known structures of starting materials and expected courses of preparative reactions. Purification or purity and structural confirmation of starting materials and products were carried out or measured by melting
30 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 pressure liquid chromatography, medium pressure liquid chromatography and/or thin layer chromatography.

35



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
35 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 hydrochloric acid (2N) to pH 1. The resulting white solid was collected, washed
5 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 room temperature. The solvent was removed under vacuum. The oily residue was
10 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)

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-dichloromethane eluate 2-phenylthiomethyl-4-isopropylsaccharin as a pale yellow
20 oil (53.5 g, 92% yield).

2-Phenylthiomethyl-4-isopropylsaccharin (53.5 g), sulfur 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 allowed to stand for 17 hours at room temperature, then stripped of volatiles. The
25 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 (33.5 g, m.r. 101-102.5°C.; 2.65 g, m.r. 100-101°C.).

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

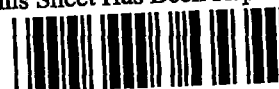
To a solution of N,N,N',N'-tetramethylethylenediamine (300 ml) in anhydrous ether (4 l) was added s-butyllithium (1.3 M, 4 l) and the mixture was cooled to -70°C. under nitrogen. A solution of 2-isopropyl-4-methoxy-
35 N,N-diethylbenzamide (454.2 g) in anhydrous ether (300 ml) was added dropwise over 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
5 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 sulfuryl chloride (190 ml) was
10 added dropwise over a 15-minute period while maintaining the temperature below 10°C . After further stirring for 30 minutes at $0-5^{\circ}\text{C}$. 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
15 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
20 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. $122-125^{\circ}\text{C}$.).

A solution of 2-aminosulfonyl-6-isopropyl-4-methoxy-
25 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
30 ethyl acetate-hexane to give 4-isopropyl-6-methoxysaccharin (IV; $\text{R}_1=\text{i-Pr}$, $\text{R}_2=6\text{-OMe}$) (303 g, 91% yield, m.p. 188°C .).

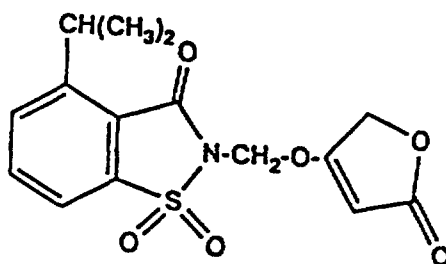
To a suspension of paraformaldehyde (24 g) and chlorotrimethylsilane (86.4 g) in 1,2-dichloroethane (200 ml) was added dry tin(IV) chloride (0.8 ml) and the resulting solution was stirred on a steam bath for one
35 hour. 4-Isopropyl-6-methoxysaccharin (51.4 g) was added to the clear solution and the mixture was refluxed for 18 hours, cooled to room temperature and poured



-13-

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.).

5

Preparation of Compounds of Formula IExample 1A2-[(2,5-dihydro-5-oxo-3-furanyl)oxymethyl]-4-isopropylsaccharin

15 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 dimethyl-
formamide (10 ml) was added dropwise, stirring was continued for two and one-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
20 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-1R

25

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).



-14-

Table I

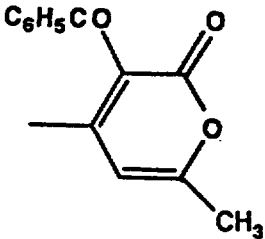
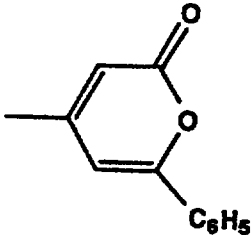
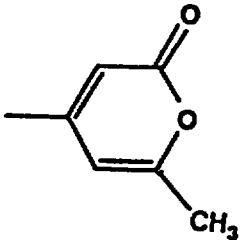
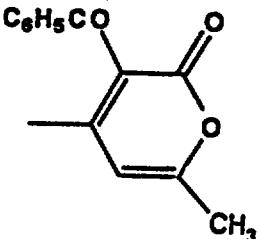


5				Yield (%)
	Example	R ₂	-Z	Melting Range (°C.)
	Solvent			Recrystallization
10	1B	H		40 229-230 Ethyl acetate
15	1C	H		51 185-188 Ethanol
20	1D	H		58 188-189.5 Ethanol-hexane

This Sheet Has Been Replaced



Table I (continued)

	Example	R_2	$-Z$	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent					
10	1E	H		13	204-207	Ethanol
						
15	1F	H		18	178-189.5	Isopropyl alcohol
						
20	1G	CH ₃ O		50	172.5-174	Ethyl acetate
						
25	1H	CH ₃ O		24	175-177	Ethanol
						

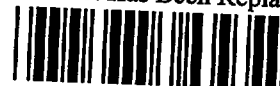
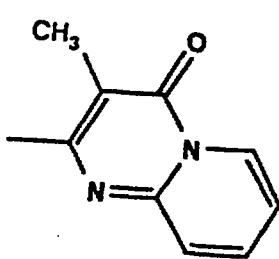
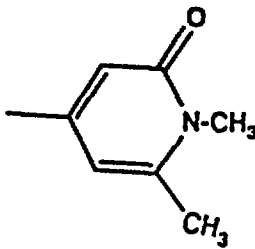
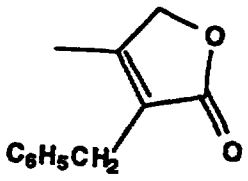
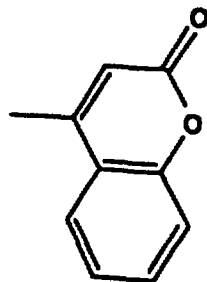


Table I (continued)

Example	Solvent	R ₂ —Z	Yield (%)	Melting Range (°C.)	Recrystallization
5	II	CH ₃ O	42	165.5-167.5	Ethyl acetate
10					
15	1J	CH ₃ O	34	168-170	Ethyl acetate
					
20	1K	CH ₃ O	47	126.5-128.5	Ethyl acetate
					
25	1L	CH ₃ O	39	261.5-263	Ethyl acetate
					



-17-

Table I (continued)

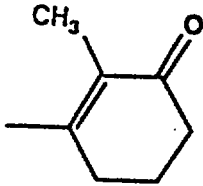
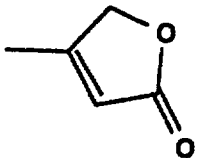
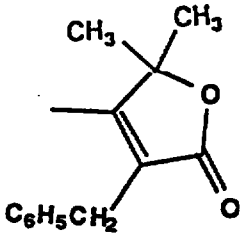
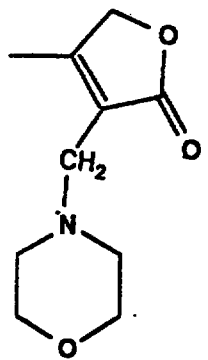
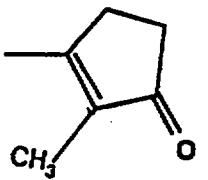
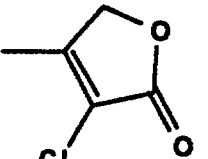
	Example	R_2 — $-Z$ —	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent				
10	1M*	CH ₃ O	6	129-131	Ethyl acetate- cyclohexane
					
15	1N	CH ₃ O	33	195-196.5	Ethyl acetate
					
20	1O	CH ₃ O	48	136.5-137.5	Carbon tetrachloride
					



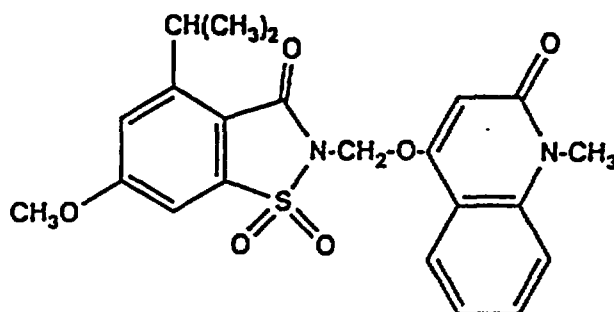
Table I (continued)

	Example	R ₂ — Z	Yield (%)	Melting Range (°C.)	Recrystallization
5	Solvent				
	1P	CH ₃ O	8	145-147	Ethyl acetate- cyclohexane
10					
15	1Q	CH ₃ O	32	115-117	Carbon tetrachloride
					
20	1R	CH ₃ O	29	149.5-150.5	Carbon tetrachloride
					

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



Example 2

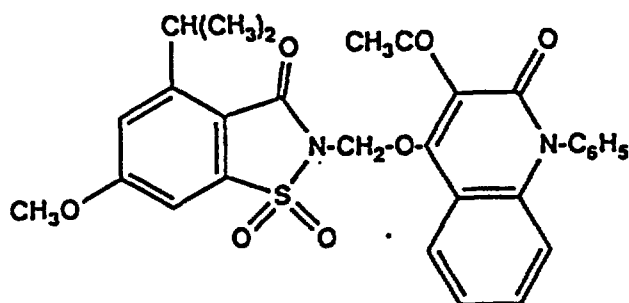
2-(1-methylcarbostyryl-4-yl)oxymethyl-4-isopropyl-6-methoxysaccharin

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

20 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

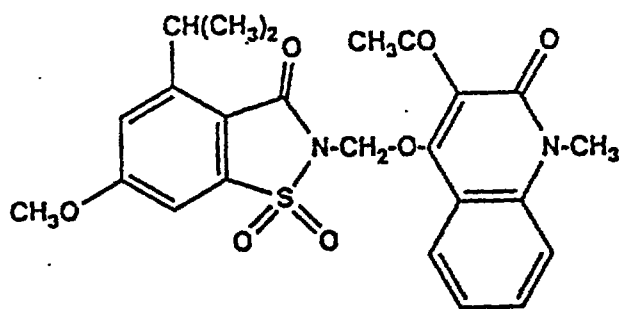


-20-

temperature for half an hour. 2-Chloromethyl-4-isopropyl-6-methoxy-saccharin (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

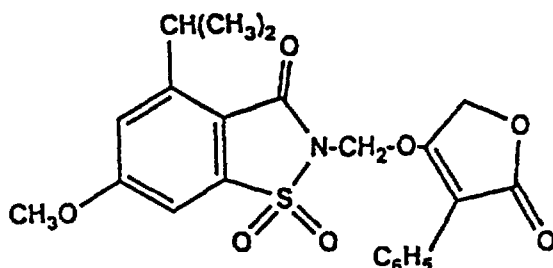


By a method similar to that of Example 3A above 3-acetyl-4-hydroxy-1-methylcarbostyryl (0.63 g) was condensed with 2-chloromethyl-4-isopropyl-6-methoxysaccharin (1.10 g) and the product was purified by crystallization from methanol-ether to give the title compound as an off-white powder (0.28 g, 20%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



Example 4A

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



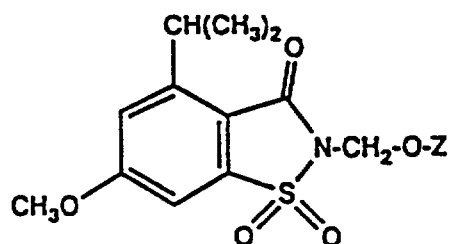
5
10
15
Cesium carbonate (0.82 g) was added to a solution of 3-phenyl-2(5H)-furanone (0.88 g) in methanol (15 ml) and the mixture was stirred at room temperature for one hour and stripped of methanol. 2-Chloromethyl-4-isopropyl-6-methoxysaccharin (1.52 g) was added to a solution of the residue in dimethylformamide (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.).

Examples 4B-4G

20 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).

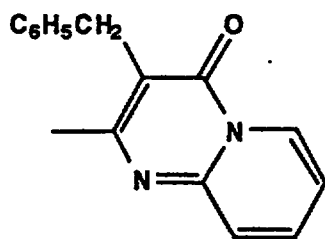


Table II

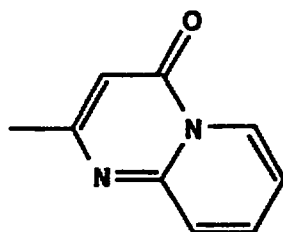


5	Yield (%) / Melting Range
(°C.)	
Example	- Z _____
Solvent	Recrystallization

10	4B	46/204-206 Dichloromethane-ether
----	----	-------------------------------------



15	4C	61/173-176 Methanol
----	----	------------------------



20	4D	9/225-227 Methanol-dichloromethane
----	----	---------------------------------------

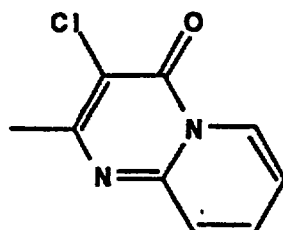
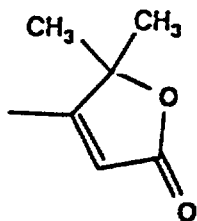


Table II(continued)

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

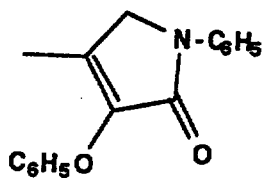
4E

58/141-142.5
None



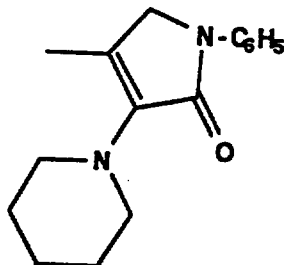
4F

51/85-87
None



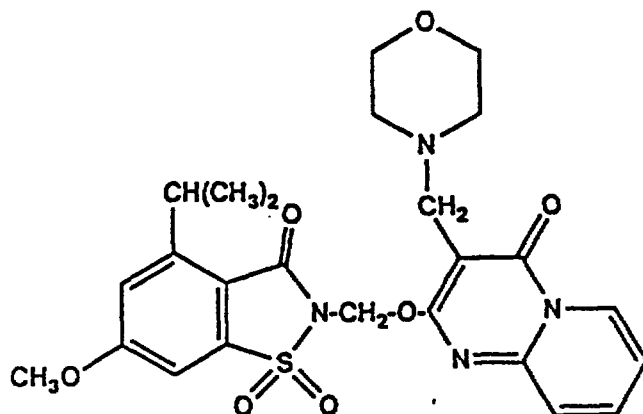
4G

19/83-88
None



Example 5

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



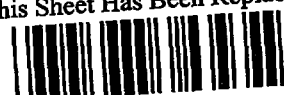
A mixture of 3-(4-morpholinylmethyl)pyrido[1,2-a]pyrimidine-2,4-dione hydrochloride (0.6 g) and potassium t-butoxide (0.49 g) in dimethylformamide (20 ml) was stirred at room temperature for five minutes. 2-Chloromethyl-4-isopropyl-6-methoxysaccharin (0.61 g) was added and stirring was continued at room 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.).



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-methoxy-saccharin (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 (0.13 g, 46.6% yield, m.r. 193-195°C. with decomposition).

Further examples of compounds of Formula I can be prepared wherein -Z is any of the moieties described above in Examples 1-7 and wherein R₁ is hydrogen, methyl, ethyl, n-propyl, 2-butyl, dimethylamino, methoxy, ethoxy, or isopropoxy and R₂ is hydrogen, 7-methyl, 6-(4-methyl-1-piperazinyl), 6-(1-methyl-2-pyrrolyl), 6-dimethylamino, 5-nitro, 6-nitro, 6-hydroxy, 7-hydroxy, 5-methoxy, 7-methoxy, 5,6-dimethoxy, 5,7-dimethoxy, 6,7-dimethoxy, 6-ethoxy, 6-isopropoxy, 6-cyclobutyloxy, 6-[2-(4-morpholinyl)-ethoxy], 6-[(2,3-dihydroxy)propoxy], 6-[(2,3-propylenedioxy)-propoxy], 6-[2,3-dimethoxypropoxy], 6-[2-(2-methoxyethoxy)ethoxy], 7-[2-(2-methoxyethoxy)ethoxy], 7-carboxymethoxy, 6-methoxycarbonylmethoxy, 6-(t-butoxycarbonyl)methoxy, 6-benzoyloxycarbonylmethoxy, 7-(t-butoxycarbonyl)methoxy, 7-dimethylaminocarbonyloxy, 6,7-methylenedioxy, 6-fluoro, 7-chloro, 6-(n-propyl)-7-methoxy, 6-methyl-5,7-dimethoxy, 5-hydroxy-6-methoxy or 6-dimethylamino-7-chloro.



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 the inhibition of the 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 III were obtained for compounds of Formula I of the examples.

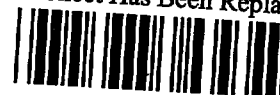


THIS SHEET HAS BEEN
REPLACED

Table III
Inhibition of Human Leukocyte Elastase
Compound of Formula I
of Example

	<u>K_i* (nM)</u>
1A	0.4
1B	0.22
1C	0.7
1D	0.25
1E	0.035
1F	0.22
1G	0.05
1H	0.027
1I	0.25
1J	0.85
1K	0.013
1L	0.10
	0.09
1M	0.18
1N	0.052
1O	0.016
1P	0.041
1Q	0.06
1R	0.038
2	0.5
3A	0.43
3B	0.27
4A	0.025
4B	0.9
4C	0.078
4D	0.066
4E	0.093
4F	0.06
4G	0.2
5	0.23
6	0.92
7	17

This Sheet Has Been Replaced



5
THIS SHEET HAS BEEN
REPLACED

5 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.

10 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
15 stearate and gum acacia. The compositions are prepared by conventional pharmaceutical techniques.

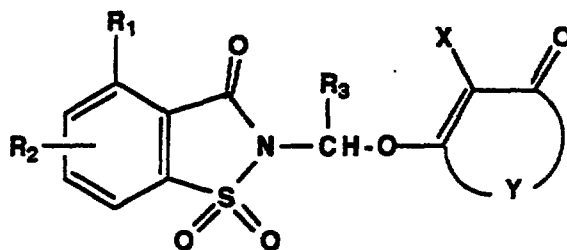
This Sheet Has Been Replaced





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 hydrogen, lower-alkyl, cycloalkyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, formyl, cyano, carboxy, aminocarbonyl, R-oxycarbonyl, B=N, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, perfluoro-lower-alkylsulfonylamino, perchloro-lower-alkylsulfonylamino, nitro, hydroxy, R-carbonyloxy, lower-alkoxy, cycloalkoxy, B=N-lower-alkoxy, hydroxy-lower-alkoxy, poly-hydroxy-lower-alkoxy or acetal or ketal thereof, lower-alkoxy-lower-alkoxy, poly-lower-alkoxy-lower-alkoxy, hydroxy-poly-lower-alkyleneoxy, lower-alkoxy-poly-lower-alkyleneoxy, B=N-carbonyloxy, carboxy-lower-alkoxy, R-oxycarbonyl-lower-alkoxy, methylenedioxy, di-lower-alkylphosphonyloxy, R-thio, R-sulfinyl, R-sulfonyl, perfluoro-lower-alkylsulfonyl, perchloro-lower-alkylsulfonyl, aminosulfonyl, lower-alkylaminosulfonyl, di-lower-alkylaminosulfonyl and halo, wherein R is lower-alkyl, phenyl or phenyl-lower-alkyl, phenyl having 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,

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, wherein B=N is as defined above,

-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.

2. A compound as claimed in claim 1

wherein -Y- is $-(CH_2)_m-$, $-C(=O)-$, $-(CH_2)_m-O-$, $-CHR-O-$, $-CR_2-O-$, $-C[(CH_2)_n]-O-$, $-C[CH_2CH_2N(R)CH_2CH_2]-O-$, $-(CH_2)_m-N(R')-$, $-CHR-N(R')-$, $-CR_2-N(R')-$, $-C(R')=C(R')-O-$, $-C(R')=C(R')-N(R')-$, $-C(=O)-C(R')=C(R')-$, $-C(Z')=C(Z')-$, $-C(Z')=C(Z')-O-$, $-C(Z')=C(Z')-N(R')-$, $-N(Z'')-C(Z'')=N-$ or $-N=C(Z'')-N(Z'')$

wherein 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, 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 in claim 1.

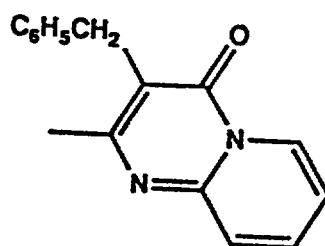
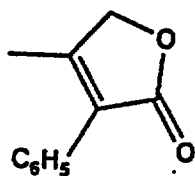
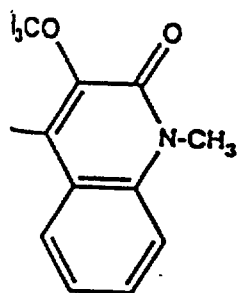
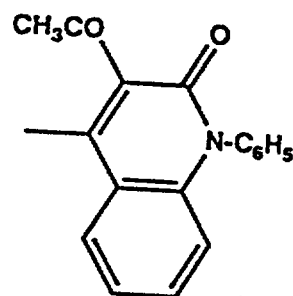
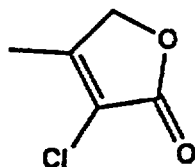
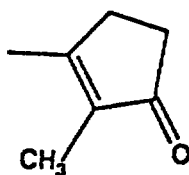
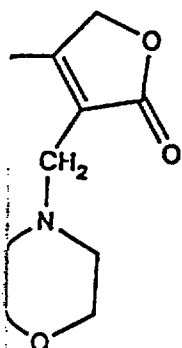
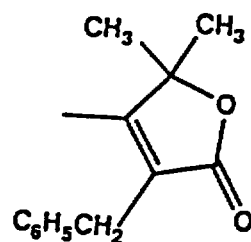
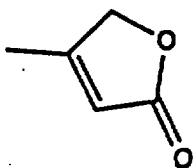
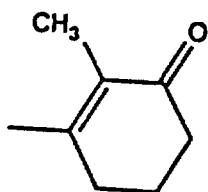
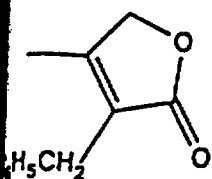




* C L M S *

-33-

THIS SHEET HAS BEEN
REPLACED



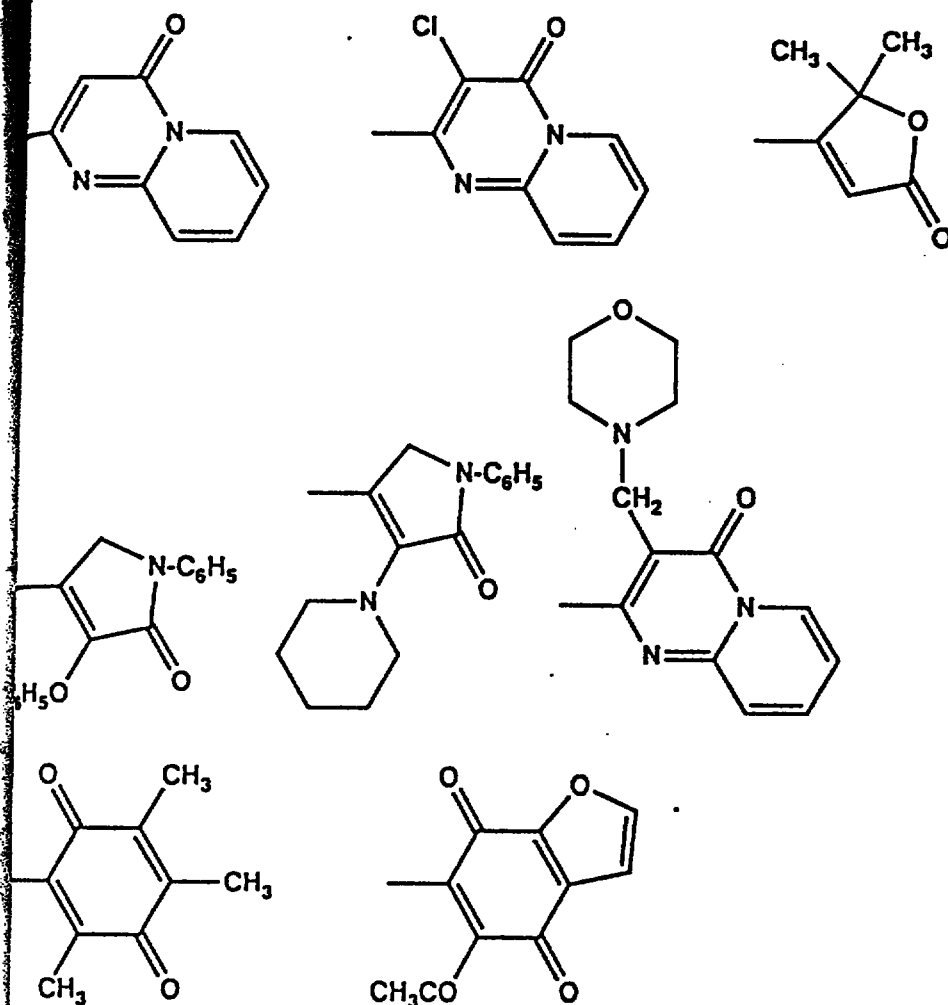
This Sheet Has Been Replaced





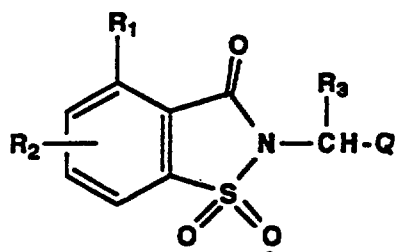
THIS SHEET HAS BEEN
REPLACED

-34-



6. A process for preparing a compound of Formula I as claimed in claim 1 which comprises condensing the corresponding compound having the structural formula

10



Formula II

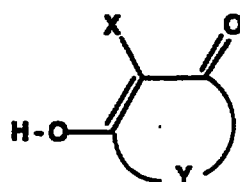
wherein Q is chloro or bromo with the corresponding compound having

This Sheet Has Been Replaced





the structural formula



Formula III

5

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

7. A process for preparing a compound of Formula I as claimed in claim 2 wherein -Y- is -C(=O)-C(Rⁿ)=C(Rⁿ)- and the Rⁿ groups taken together with the carbon atoms to which they are bonded are furano and X is lower-alkanoyl, which comprises oxidizing the corresponding 2-(4,7-dimethoxy-5-lower-alkanoyl-benzofuran-6-yl)oxy-R₃-methyl-4-R₁-5, 6 or 7-R₂-saccharin with a ceric salt.

8. A pharmaceutical composition comprising a proteolytic enzyme inhibiting concentration of a compound of Formula I as claimed in claim 1 and a pharmaceutical carrier.

9. A pharmaceutical composition comprising a proteolytic enzyme inhibiting concentration of a compound as claimed in any one of claims 2 to 5 and a pharmaceutical carrier.

10. The use of a compound of Formula I as claimed in claim 1 for preparation of a medicament for the treatment of a degenerative disease in a patient in need of such treatment.

11. The use of a compound as claimed in any one of claims 2 to 5 for preparation of a medicament for the treatment of a degenerative disease in a patient in need of such treatment.

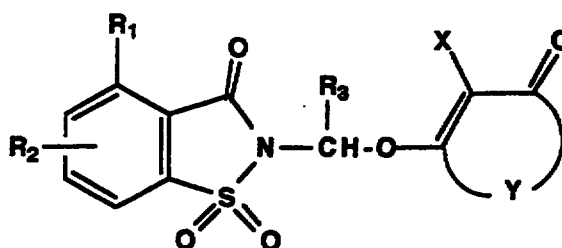


SACCHARIN DERIVATIVE PROTEOLYTIC ENZYME INHIBITORS

5

ABSTRACT

Compounds having the structural formula



10

Formula I,

which inhibit the enzymatic activity of proteolytic enzymes, and processes for preparation thereof, method of use thereof in treatment of degenerative diseases and pharmaceutical compositions thereof are disclosed.



SACCHARIN DERIVATIVE PROTEOLYTIC ENZYME REPLACEMENT SHEET
INHIBITORS

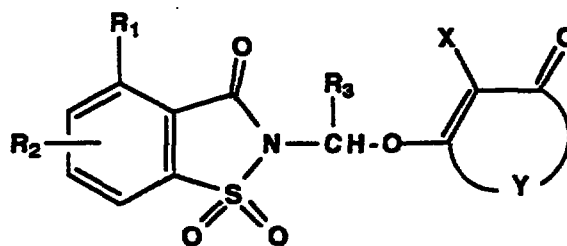
12 MAR 1997

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

Inhibitors of proteolytic enzymes are useful in treatment of 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, 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 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.

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

12 MAR 1997

-2-

R_2 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 hydrogen, lower-alkyl, cycloalkyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, formyl, cyano, carboxy, aminocarbonyl, R-oxycarbonyl, B=N, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, perfluoro-lower-alkylsulfonylamino, perchloro-lower-alkylsulfonylamino, nitro, hydroxy, R-carbonyloxy, lower-alkoxy, cycloalkoxy, B=N-lower-alkoxy, hydroxy-lower-alkoxy, poly-hydroxy-lower-alkoxy or acetal or ketal thereof, lower-alkoxy-lower-alkoxy, poly-lower-alkoxy-lower-alkoxy, hydroxy-poly-lower-alkyleneoxy, lower-alkoxy-poly-lower-alkyleneoxy, B=N-carbonyloxy, carboxy-lower-alkoxy, R-oxycarbonyl-lower-alkoxy, methylenedioxy, di-lower-alkylphosphonyloxy, R-thio, R-sulfinyl, R-sulfonyl, perfluoro-lower-alkylsulfonyl, perchloro-lower-alkylsulfonyl, aminosulfonyl, lower-alkylaminosulfonyl, di-lower-alkylaminosulfonyl and halo, wherein R is lower-alkyl, phenyl or phenyl-lower-alkyl, phenyl having 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,

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;

R_3 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, wherein B=N is as defined above,

-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.

12 MAR 1997

-3-

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

In a preferred aspect the invention provides a compound of Formula I wherein -Y- is $-(CH_2)_m-$, $-C(=O)-$, $-(CH_2)_m-O-$, $-CHR-O-$, $-CR_2-O-$, $-C[(CH_2)_n]-O-$, $-C[CH_2CH_2N(R)CH_2CH_2]-O-$, $-(CH_2)_m-N(R')-$, $-CHR-N(R')-$, $-CR_2-N(R')-$, $-C(R')=C(R')-O-$, $-C(R')=C(R')-N(R')-$, $-C(=O)-C(R'')=C(R'')$, $-C(Z')=C(Z')-$, $-C(Z')=C(Z')-O-$, $-C(Z')=C(Z')-N(R')-$, $-N(Z'')-C(Z'')=N-$ or $-N=C(Z'')-N(Z'')$ -

wherein 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

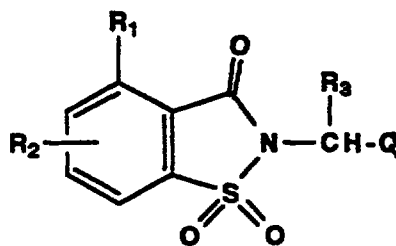
R'' groups taken together with the carbon atoms to which they are bonded are furano, the

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, 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.

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



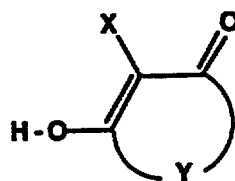
Formula II

wherein Q is chloro or bromo with the corresponding compound

12 MAR 1997

-4-

having the structural formula



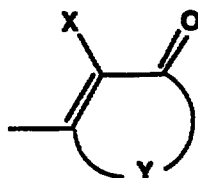
Formula III

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

In another aspect the invention provides the use of a compound of Formula I for preparation of a medicament for the treatment of a degenerative disease in a patient in need of such treatment

In yet 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.

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



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, the lower-alkylamino part of lower-alkylamino-lower-alkyl, the lower-alkylamino part of di-

12 MAR 1997

lower-alkylamino-lower-alkyl, the lower-alkoxy part of lower-alkoxy-lower-alkyl, carboxy-lower-alkylamino, 4-lower-alkyl-1-piperazinyl, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, perfluoro-lower-alkylsulfonylamino, perchloro-lower-alkylsulfonylamino, the first lower-alkoxy part of lower-alkoxy-lower-alkoxy, the first lower-alkoxy part of poly-lower-alkoxy-lower-alkoxy, the lower-alkoxy part of lower-alkoxy-poly-lower-alkyleneoxy, R-oxycarbonyl-lower-alkoxy, perfluoro-lower-alkylsulfonyl, perchloro-lower-alkylsulfonyl, lower-alkylaminosulfonyl, di-lower-alkylaminosulfonyl, 4-lower-alkyl-1-piperazinyl, phenyl-lower-alkyl, pyridyl-lower-alkyl, lower-alkylaminocarbonyl, di-lower-alkylaminocarbonyl, lower-alkylthio and carboxy-lower-alkylamino.

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-alkyl part of lower-alkylamino-lower-alkyl, the lower-alkyl part of di-lower-alkylamino-lower-alkyl, hydroxy-lower-alkyl, the lower-alkyl part of lower-alkoxy-lower-alkyl, the lower-alkoxy part of B=N-lower-alkoxy, hydroxy-lower-alkoxy, polyhydroxy-lower-alkoxy, the second lower-alkoxy part of lower-alkoxy-lower-alkoxy, the second lower-alkoxy part of poly-lower-alkoxy-lower-alkoxy, the alkyleneoxy part of hydroxy-poly-lower-alkyleneoxy, the alkyleneoxy part of lower-alkoxy-poly-lower-alkyleneoxy, lower-alkanoyl, B=N-lower-alkyl, B=N-lower-alkanoyl and B=N-lower-alkoxycarbonyl. Alkylene is preferably 1,2-alkylene. Cycloalkyl and cycloalkoxy have from three to six ring carbon atoms and can be substituted by one or more lower-alkyl. Halo is fluoro, chloro, bromo or iodo.

R₁ is preferably primary or secondary alkyl of two to four carbon atoms or lower-alkoxy.

R₂ is preferably hydrogen, hydroxy, 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-alkyleneoxy, lower-alkoxy-poly-lower-alkyleneoxy, B=N-carbonyloxy, carboxy-lower-alkoxy, R-oxycarbonyl-lower-alkoxy, methylenedioxy or di-lower-alkylphosphonyloxy and, except methylenedioxy, is preferably located at the 6-position. Methylenedioxy can be located at the 5 and 6- or 6 and 7-positions.

12 MAR 1997

A compound of Formula I wherein R_1 is lower alkyl, R_2 is hydrogen or lower-alkoxy, R_3 is hydrogen and X is hydrogen, halo, lower-alkyl, phenyl, phenyl-lower-alkyl, phenylcarbonyl, lower-alkanoyl, $B=N$, $B=N$ -lower-alkyl or phenyloxy is particularly preferred.

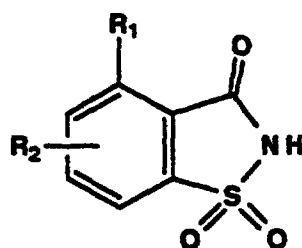
Especially preferred is a compound of Formula I wherein R_1 is isopropyl, R_2 is hydrogen or 6-methoxy and X is hydrogen, chloro, methyl, phenyl, phenylmethyl, phenylcarbonyl, acetyl, 1-piperidinyl, 4-morpholinylmethyl or phenyloxy.

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 carbonate, an alkali metal alkoxide, a tri-lower-alkylamine, a thalious 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 separately and then condensed with the compound of Formula II and is preferably an alkali metal, especially cesium, or thalious 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, diethyl ether, dimethylformamide, N-methylpyrrolidone, dichloromethane, xylene, toluene or a lower-alkanol or mixture thereof, at a temperature in the range from ambient temperature to the boiling temperature of the solvent or solvent mixture.

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

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-3, 4 or 5- R_2 -6- R_1 -benzoate ester with ammonia to form the corresponding

compound having the structural formula:



Formula IV,

hydroxymethylation of which with formaldehyde affords the corresponding 2-hydroxymethyl-4-R₁-(5, 6 or 7)-R₂-saccharin, displacement of whose hydroxyl with chloride or bromide using, for example thionyl chloride, thionyl bromide, phosphorus trichloride or phosphorus tribromide affords the corresponding compound of Formula II.

A compound of Formula II wherein R₃ is hydrogen and Q is chloro can also be prepared in one step from the corresponding compound of Formula IV by chloromethylation with paraformaldehyde and chlorotrimethylsilane in the presence of a Lewis acid, for example stannic chloride.

A compound of Formula II wherein R₃ 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-R₁-(5, 6 or 7)-R₂-saccharin with hydrogen chloride. Use of unsubstituted vinyl acetate, for example, affords the corresponding compound of Formula II wherein R₃ is methyl.

A compound of Formula II wherein R₃ is hydrogen or phenyl can be prepared by phenylthio-R₃-methylating the corresponding compound of Formula IV or basic salt thereof with the corresponding phenyl R₃-chloromethyl sulfide to form the corresponding 2-(phenylthio-R₃-methyl)-4-R₁-(5, 6 or 7)-R₂-saccharin and displacing phenylthio therefrom with chloro or bromo using, for example, sulfur chloride or sulfur bromide.

A compound of Formula IV can be prepared by lithiating the corresponding 2-R₁-3, 4 or 5-R₂-N,N-di-lower-alkylbenzamide with a lower-alkyl lithium, aminosulfonylating the resulting 2-R₁-3, 4 or 5-R₂-6-lithio-N,N-di-lower-

12 MAR 1997

-8-

alkylbenzamide with sulfur dioxide followed by hydroxylamine O-sulfonic acid or sulfuryl chloride followed by ammonia, and cyclizing the resulting 2-R₁-3, 4 or 5-R₂-6-aminosulfonyl-N,N-di-lower-alkylbenzamide in refluxing acetic acid.

A compound of Formula IV wherein R₁ is primary or secondary alkyl of two to four carbon atoms can be prepared by lithiating the corresponding compound of Formula IV wherein R₁ is methyl with two molar equivalents of a lower-alkyl lithium in an inert solvent, for example tetrahydrofuran, and alkylating the resulting 4-lithiomethyl-5, 6 or 7-R₂-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-R₁-3, 4 or 5-R₂-N,N-di-lower-alkylbenzamide wherein R₁ is primary or secondary alkyl of two to four carbon atoms can be prepared by a similar lithiation-alkylation sequence starting with the corresponding 2-methyl, ethyl or propyl-3, 4 or 5-R₂-N,N-di-lower-alkylbenzamide.

A compound of Formula IV wherein R₁ is primary or secondary alkyl of two to four carbon atoms can also be prepared by introducing R₁ earlier in the synthesis. Conjugate addition of the appropriate R₁-cuprate to 2-cyclohexenone and methoxycarbonylation of the resulting copper enolate with methyl cyanofornate 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-R₁-cyclohexanone, enol etherification of which with benzylthiol and acidic clay gives a mixture of the corresponding 6-R₁-2-benzylthio-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,

12 MAR 1997

-9-

which on heating under pressure with a 2-lower-alkoxyfuran gives a 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzisothiazol-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-benzisothiazol-2H-3-one-1,1-dioxide, followed by debenzylation by catalytic hydrogenation to give the corresponding 4-lower-alkoxy-7-hydroxysaccharin of Formula IV.

Similarly alkylation of the 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzisothiazol-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-alkyleneoxy or lower-alkoxy-poly-lower-alkyleneoxy.

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 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 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 respectively of the compound of Formula I.

In the preparations and examples described below the structures of the products are inferred from known structures of starting materials and expected 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 pressure liquid chromatography, medium pressure liquid chromatography and/or thin layer chromatography.

12 MAR 1997

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

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

(II; R₁=i-Pr, R₂=H, R₃=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 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 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 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 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 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

12 MAR 1997

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 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 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)

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-dichloromethane eluate 2-phenylthiomethyl-4-isopropylsaccharin as a pale yellow oil (53.5 g, 92% yield).

2-Phenylthiomethyl-4-isopropylsaccharin (53.5 g), sulfur 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 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 (33.5 g, m.r. 101-102.5°C.; 2.65 g, m.r. 100-101°C.).

(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

12 MAR 1997

-12-

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 $0-5^{\circ}\text{C}$. 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.p. $122-125^{\circ}\text{C}$.).

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 (IV; $\text{R}_1=\text{i-Pr}$, $\text{R}_2=6\text{-OMe}$) (303 g, 91% yield, m.p. 188°C .).

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

12 MAR 1997

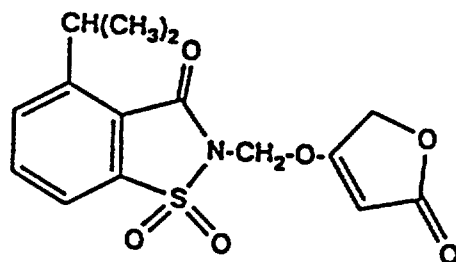
-13-

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.).

Preparation of Compounds of Formula I

Example 1A

2-[(2,5-dihydro-5-oxo-3-furanyl)oxymethyl]-4-isopropylsaccharin



A solution of tetrone 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 one-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.).

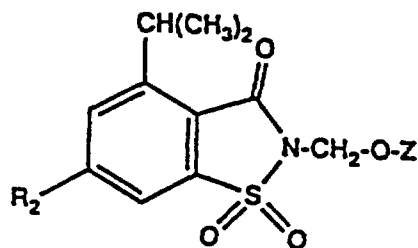
Examples 1B-1R

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).

1 2 MAR 1997

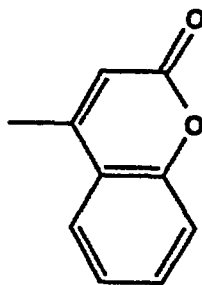
-14-

Table I

Example
SolventR₂ — —Z—Yield (%)
Melting Range (°C.)
Recrystallization

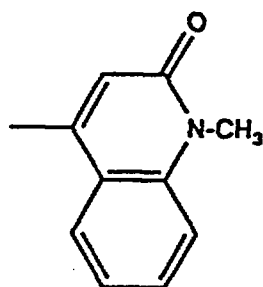
1B

H

40
229-230
Ethyl acetate

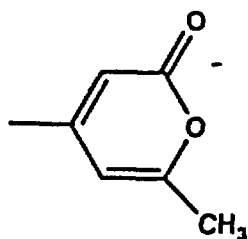
1C

H

51
185-188
Ethanol

1D

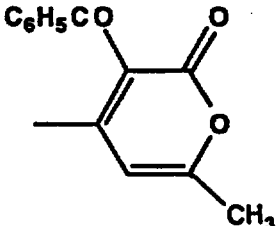
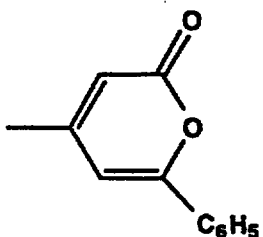
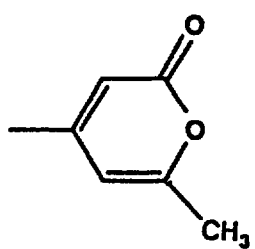
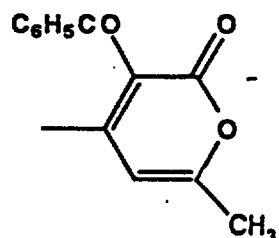
H

58
188-189.5
Ethanol-hexane

12 MAR 1997

-15-

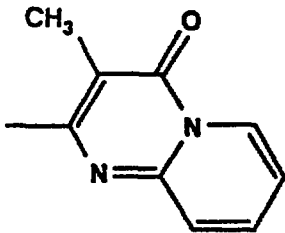
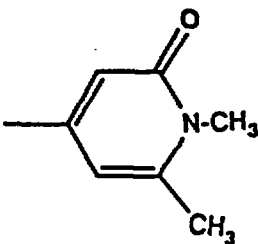
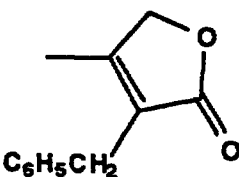
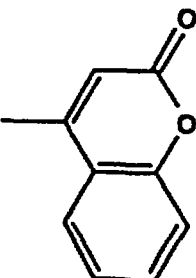
Table I (continued)

Example Solvent	R ₂ — — Z — — — — —	Yield (%) Melting Range (°C.) Recrystallization
1E	H	13 204-207 Ethanol
		
1F	H	18 178-189.5 Isopropyl alcohol
		
1G	CH ₃ O	50 172.5-174 Ethyl acetate
		
1H	CH ₃ O	24 175-177 Ethanol
		

12 MAR 1997

-16-

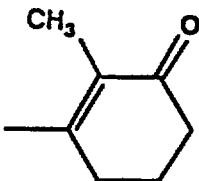
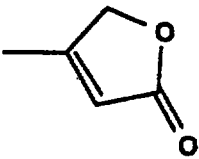
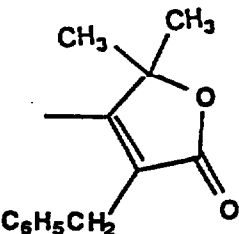
Table I (continued)

Example Solvent	R ₂ — —Z— —	Yield (%) Melting Range (°C.) Recrystallization
1I	CH ₃ O 	42 165.5-167.5 Ethyl acetate
1J	CH ₃ O 	34 168-170 Ethyl acetate
1K	CH ₃ O 	47 126.5-128.5 Ethyl acetate
1L	CH ₃ O 	39 261.5-263 Ethyl acetate

12 MAR 1997

-17-

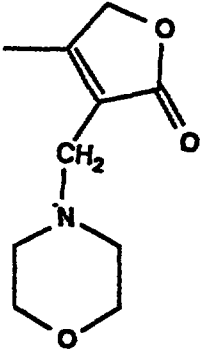
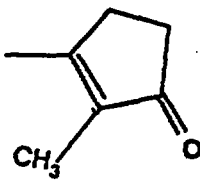
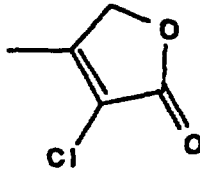
Table I (continued)

Example Solvent	R ₂ — —Z—	Yield (%) Melting Range (°C.) Recrystallization
1M*	CH ₃ O 	6 129-131 Ethyl acetate- cyclohexane
1N	CH ₃ O 	33 195-196.5 Ethyl acetate
1O	CH ₃ O 	48 136.5-137.5 Carbon tetrachloride

12 MAR 1997

-18-

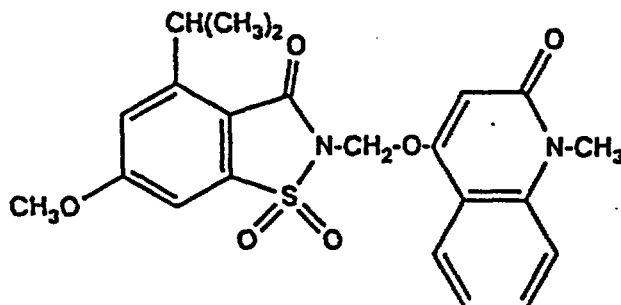
Table I (continued)

Example Solvent	R ₂ — —Z— —	Yield (%) Melting Range (°C.) Recrystallization
1P	CH ₃ O	8 145-147 Ethyl acetate- cyclohexane
		
1Q	CH ₃ O	32 115-117 Carbon tetrachloride
		
1R	CH ₃ O	29 149.5-150.5 Carbon tetrachloride
		

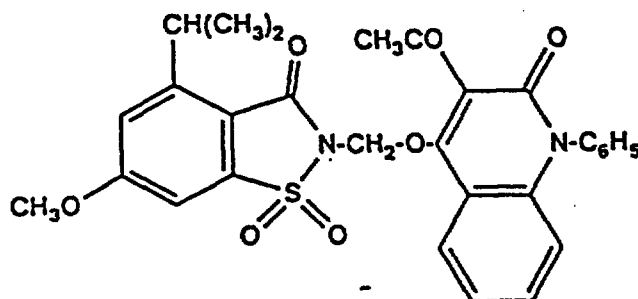
* In addition to the compound of Formula I of Example 1M 2-(1-methyl-2,6-dioxocyclohexyl)methyl-4-isopropyl-6-methoxysaccharin (m.r. 159.5-161.5°C. from ethyl acetate) was isolated in 38% yield.

12 MAR 1997

-19-

Example 22-(1-methylcarbostyryl-4-yl)oxymethyl-4-isopropyl-6-methoxysaccharin

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. 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 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 3A2-(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

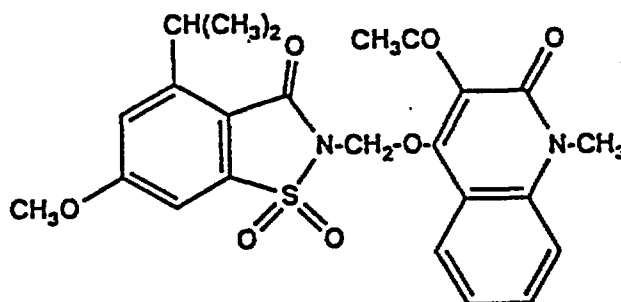
12 MAR 1997

-20-

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



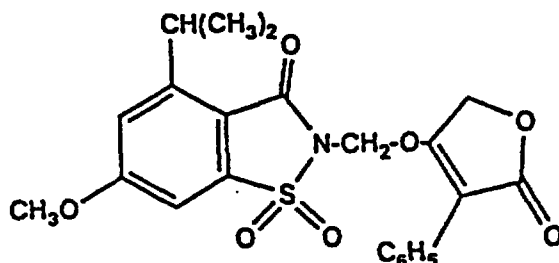
By a method similar to that of Example 3A above 3-acetyl-4-hydroxy-1-methylcarbostyryl (0.63 g) was condensed with 2-chloromethyl-4-isopropyl-6-methoxysaccharin (1.10 g) and the product was purified by crystallization from methanol-ether to give the title compound as an off-white powder (0.28 g, 20%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

12 MAR 1997

-21-

Example 4A

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



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.).

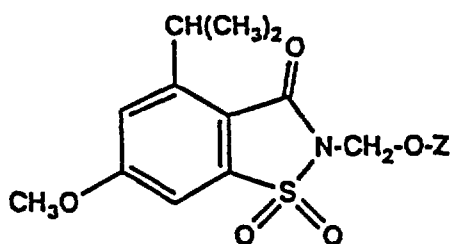
Examples 4B-4G

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).

12 MAR 1997

-22-

Table II



(°C.)

Example

Solvent

-Z

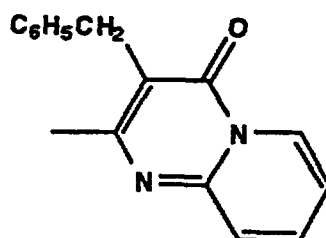
Yield (%) / Melting Range

Recrystallization

4B

46/204-206

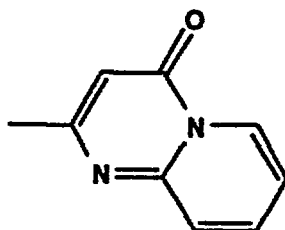
Dichloromethane-ether



4C

61/173-176

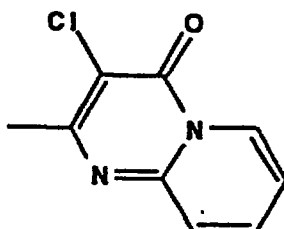
Methanol



4D

9/225-227

Methanol-dichloromethane



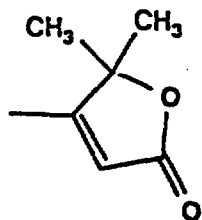
12 MAR 1997

-23-

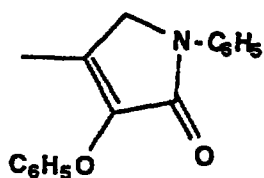
Table II(continued)

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

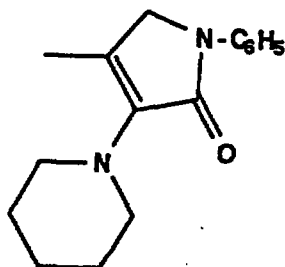
4E

58/141-142.5
None

4F

51/85-87
None

4G

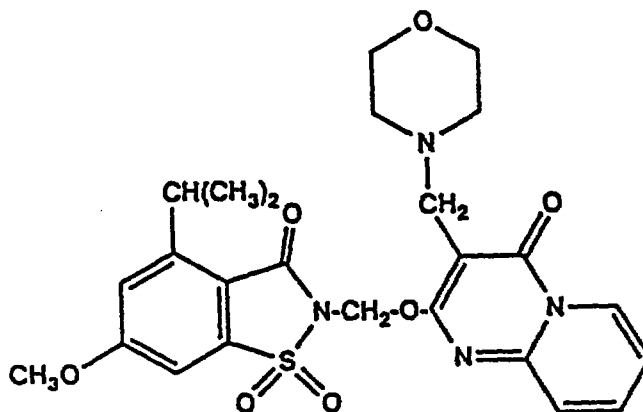
19/83-88
None

12 MAR 1997

-24-

Example 5

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



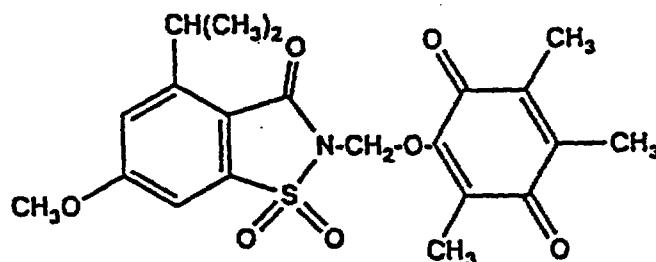
A mixture of 3-(4-morpholinylmethyl)pyrido[1,2-a]pyrimidine-2,4-dione hydrochloride (0.6 g) and potassium t-butoxide (0.49 g) in dimethylformamide (20 ml) was stirred at room temperature for five minutes. 2-Chloromethyl-4-isopropyl-6-methoxysaccharin (0.61 g) was added and stirring was continued at room 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.).

12 MAR 1997

-25-

Example 6

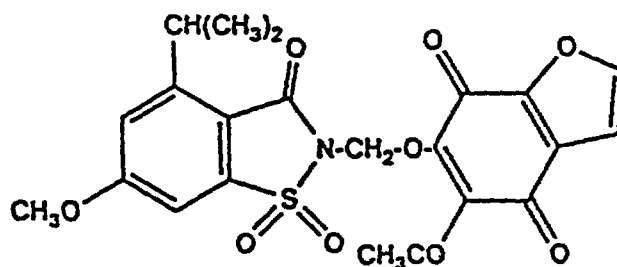
2-(3,5,6-trimethyl-1,4-dioxo-2,5-cyclohexadien-2-yl)oxymethyl-4-isopropyl-6-methoxysaccharin



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-

12 MAR 1997

-26-

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-methoxy-saccharin (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 (0.13 g, 46.6% yield, m.r. 193-195°C. with decomposition).

Further examples of compounds of Formula I can be prepared wherein -Z is any of the moieties described above in Examples 1-7 and wherein R₁ is hydrogen, methyl, ethyl, n-propyl, 2-butyl, dimethylamino, methoxy, ethoxy, or isopropoxy and R₂ is hydrogen, 7-methyl, 6-(4-methyl-1-piperaziny), 6-(1-methyl-2-pyrrolyl), 6-dimethylamino, 5-nitro, 6-nitro, 6-hydroxy, 7-hydroxy, 5-methoxy, 7-methoxy, 5,6-dimethoxy, 5,7-dimethoxy, 6,7-dimethoxy, 6-ethoxy, 6-isopropoxy, 6-cyclobutyloxy, 6-[2-(4-morpholinyl)-ethoxy], 6-[(2,3-dihydroxy)propoxy], 6-[(2,3-propylenedioxy)-propoxy], 6-[2,3-dimethoxypropoxy], 6-[2-(2-methoxyethoxy)ethoxy], 7-[2-(2-methoxyethoxy)ethoxy], 7-carboxymethoxy, 6-methoxycarbonylmethoxy, 6-(t-butoxycarbonyl)methoxy, 6-benzyloxycarbonylmethoxy, 7-(t-butoxycarbonyl)methoxy, 7-dimethylaminocarbonyloxy, 6,7-methylenedioxy, 6-fluoro, 7-chloro, 6-(n-propyl)-7-methoxy, 6-methyl-5,7-dimethoxy, 5-hydroxy-6-methoxy or 5-dimethylamino-7-chloro.

12 MAR 1997

-27-

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 the inhibition of the 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 III were obtained for compounds of Formula I of the examples.

12 MAR 1997

-28-

Table III
Inhibition of Human Leukocyte Elastase
Compound of Formula I
of Example

	<u>K_i* (nM)</u>
1A	0.4
1B	0.22
1C	0.7
1D	0.25
1E	0.035
1F	0.22
1G	0.05
1H	0.027
1I	0.25
1J	0.85
1K	0.013
1L	0.10
	0.09
1M	0.18
1N	0.052
1O	0.016
1P	0.041
1Q	0.06
1R	0.038
2	0.5
3A	0.43
3B	0.27
4A	0.025
4B	0.9
4C	0.078
4D	0.066
4E	0.093
4F	0.06
4G	0.2
5	0.23
6	0.92
7	17

12 MAR 1997

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.

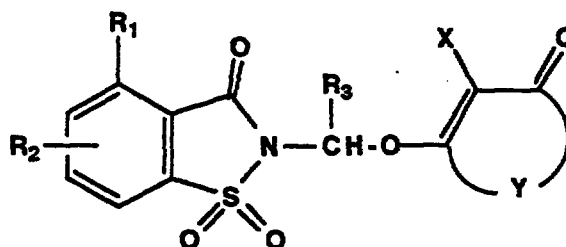
A compound of Formula I can be prepared for pharmaceutical use by incorporating it in a pharmaceutical composition for oral, parenteral or aerosol inhalation administration, which can be in solid or liquid dosage form including tablets, capsules, solutions, suspensions and emulsions and which can include 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.



12 MAR 1997

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 hydrogen, lower-alkyl, cycloalkyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, perfluoro-lower-alkyl, perchloro-lower-alkyl, formyl, cyano, carboxy, aminocarbonyl, R-oxycarbonyl, B=N, 1-lower-alkyl-2-pyrrolyl, lower-alkylsulfonylamino, perfluoro-lower-alkylsulfonylamino, perchloro-lower-alkylsulfonylamino, nitro, hydroxy, R-carbonyloxy, lower-alkoxy, cycloalkoxy, B=N-lower-alkoxy, hydroxy-lower-alkoxy, poly-hydroxy-lower-alkoxy or acetal or ketal thereof, lower-alkoxy-lower-alkoxy, poly-lower-alkoxy-lower-alkoxy, hydroxy-poly-lower-alkyleneoxy, lower-alkoxy-poly-lower-alkyleneoxy, B=N-carbonyloxy, carboxy-lower-alkoxy, R-oxycarbonyl-lower-alkoxy, methylenedioxy, di-lower-alkylphosphonyloxy, R-thio, R-sulfinyl, R-sulfonyl, perfluoro-lower-alkylsulfonyl, perchloro-lower-alkylsulfonyl, aminosulfonyl, lower-alkylaminosulfonyl, di-lower-alkylaminosulfonyl and halo, wherein R is lower-alkyl, phenyl or phenyl-lower-alkyl, phenyl having 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,

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;



12 MAR 1997

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, wherein B=N is as defined above,

-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.

2. A compound as claimed in claim 1

wherein -Y- is $-(CH_2)_m-$, $-C(=O)-$, $-(CH_2)_m-O-$, $-CHR-O-$, $-CR_2-O-$, $-C[(CH_2)_n]-O-$, $-C[CH_2CH_2N(R)CH_2CH_2]-O-$, $-(CH_2)_m-N(R')$, $-CHR-N(R')$, $-CR_2-N(R')$, $-C(R')=C(R')-O-$, $-C(R')=C(R')-N(R')$, $-C(=O)-C(R'')=C(R'')$, $-C(Z')=C(Z')$, $-C(Z')=C(Z')-O-$, $-C(Z')=C(Z')-N(R')$, $-N(Z'')-C(Z'')=N-$ or $-N=C(Z'')-N(Z'')$

wherein 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, 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 in claim 1.

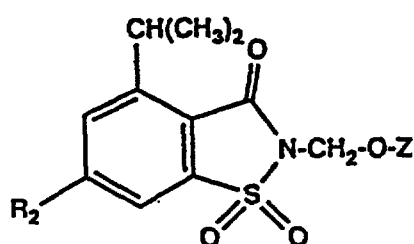


12 MAR 1997

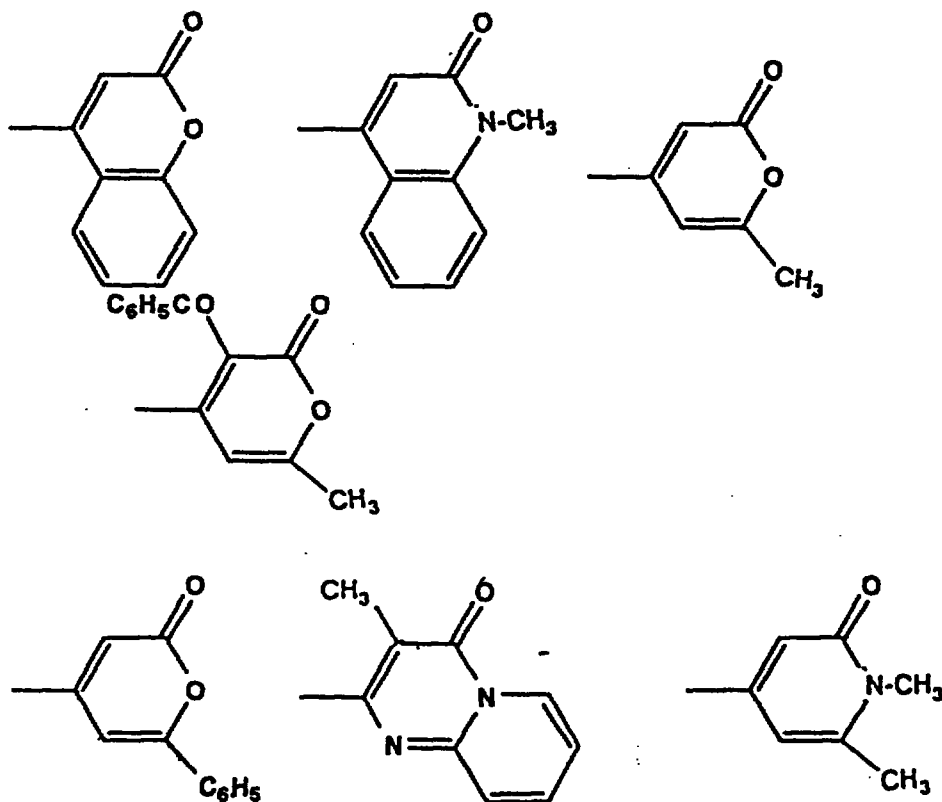
3. A compound as claimed in claim 2 wherein R_1 is lower-alkyl, R_2 is hydrogen or lower-alkoxy, R_3 is hydrogen and X is hydrogen, halo, lower-alkyl, phenyl, phenyl-lower-alkyl, phenylcarbonyl, lower-alkanoyl, $B=N$, $B=N$ -lower-alkyl or phenyloxy, wherein $B=N$ is as defined in claim 1.

4. A compound as claimed in claim 3 wherein R_1 is isopropyl, R_2 is hydrogen or 6-methoxy and X is hydrogen, chloro, methyl, phenyl, phenylmethyl, phenylcarbonyl, acetyl, 1-piperidinyl, 4-morpholinylmethyl or phenyloxy.

5. A compound as claimed in claim 4 having the structural formula



wherein R_2 is hydrogen or methoxy and -Z has one of the following structural formulas:

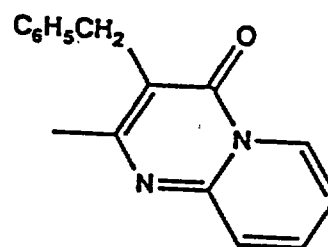
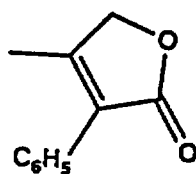
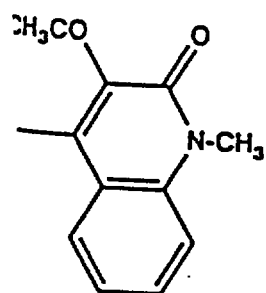
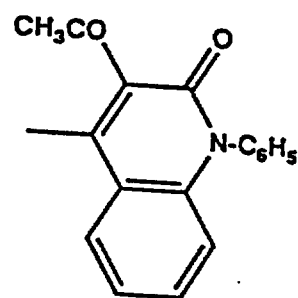
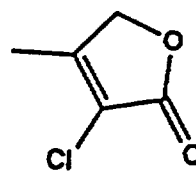
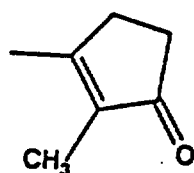
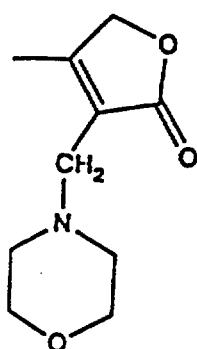
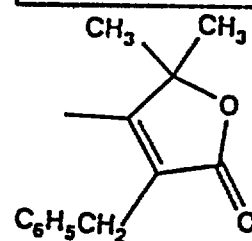
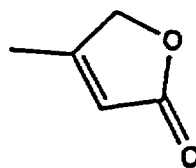
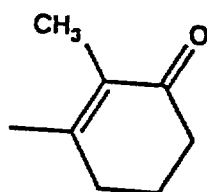
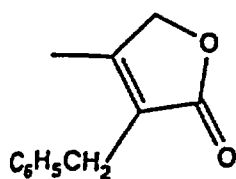




REPLACEMENT SHEET

12 MAR 1997

-33-

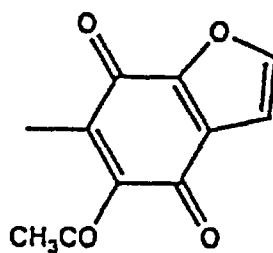
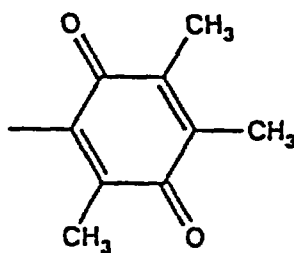
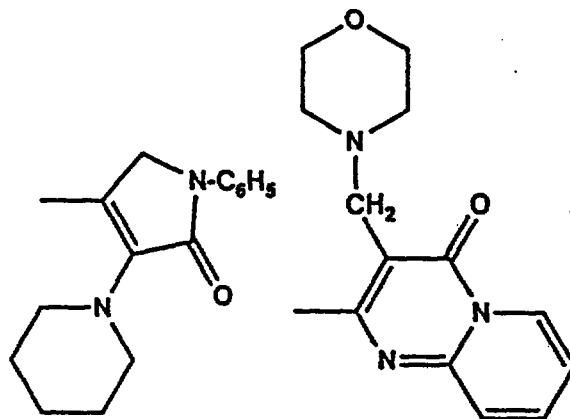
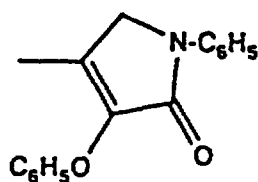
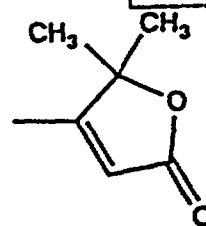
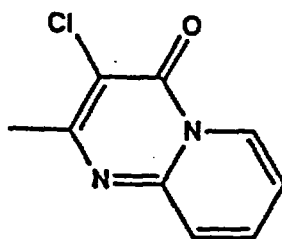
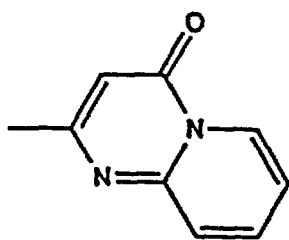




REPLACEMENT SHEET

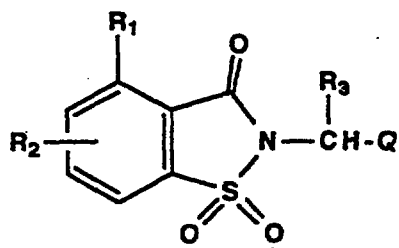
12 MAR 1997

-34-



6. A process for preparing a compound of Formula I as claimed in claim 1 which comprises condensing the corresponding compound having the structural formula

10



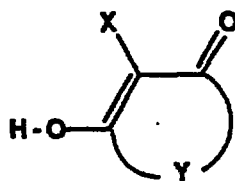
Formula II

wherein Q is chloro or bromo with the corresponding compound having



12 MAR 1997

the structural formula



Formula III

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

7. A process for preparing a compound of Formula I as claimed in claim 2 wherein -Y- is -C(=O)-C(R'')=C(R'')- and the R'' groups taken together with the carbon atoms to which they are bonded are furano and X is lower-alkanoyl, which comprises oxidizing the corresponding 2-(4,7-dimethoxy-5-lower-alkanoyl-benzofuran-6-yl)oxy-R₃-methyl-4-R₁-5, 6 or 7-R₂-saccharin with a ceric salt.

8. A pharmaceutical composition comprising a proteolytic enzyme inhibiting concentration of a compound of Formula I as claimed in claim 1 and a pharmaceutical carrier.

9. A pharmaceutical composition comprising a proteolytic enzyme inhibiting concentration of a compound as claimed in any one of claims 2 to 5 and a pharmaceutical carrier.

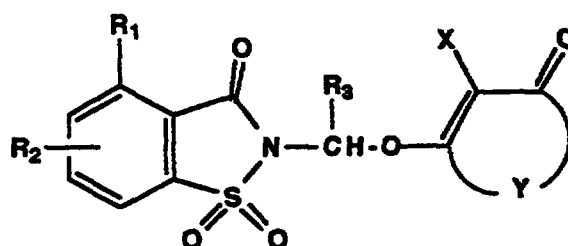
10. The use of a compound of Formula I as claimed in claim 1 for preparation of a medicament for the treatment of a degenerative disease in a patient in need of such treatment.

11. The use of a compound as claimed in any one of claims 2 to 5 for preparation of a medicament for the treatment of a degenerative disease in a patient in need of such treatment.

SACCHARIN DERIVATIVE PROTEOLYTIC ENZYME INHIBITORS

ABSTRACT

Compounds having the structural formula



Formula I,

which inhibit the enzymatic activity of proteolytic enzymes, and processes for preparation thereof, method of use thereof in treatment of degenerative diseases and pharmaceutical compositions thereof are disclosed.