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Synthesis and Aldose Reductase–Inhibitory Activity of Benzo[*b*]furan Derivatives Possessing a Carboxymethylsulfamoyl Group

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Various benzo[*b*]furan derivatives with a carboxymethylsulfamoyl group were prepared and evaluated for aldose reductase–inhibitory potency. Most of the compounds displayed significant inhibitory activities (IC_{50}, 10^{-8}—10^{-7} M). Among the test compounds, the compounds having a carboxymethylsulfamoyl group at the 3- or 4-position exhibited the greatest inhibitory potency. Structure–activity trends of the tested compounds are discussed.

Keywords carboxymethylsulfamoyl group; benzo[*b*]furan; aldose reductase; enzyme inhibition; structure–activity trend

Many studies on compounds with hypoglycemic activity as potential antidiabetic agents have been reported, yielding several clinically useful agents. However, no effective drug is known for diabetic complications, such as neuropathy, retinopathy, cataracts and nephropathy. In 1973, Dvornik *et al.* proposed that inhibition of aldose reductase might be a reasonable approach to prevent the diabetic complications.[1] Since this proposal, many compounds have been examined for aldose reductase inhibition, and some of them have been found to be effective in preventing the complications.[2] We have also prepared several types of compounds with a carboxy group[3] derived from amino acids (mainly glycine)[4] in order to find effective aldose reductase inhibitors. We found that the carboxymethylsulfamoyl group is an effective functional group to inhibit aldose reductase, and benzo[*b*]furan derivatives with the carboxymethylsulfamoyl group were the most effective among the derivatives which were prepared at the time. A part of this work was preliminarily revealed in our patents.[5] DeRuiter and Mayfield reported on the activity of compounds with a carboxymethylsulfamoyl group subsequently.[6]

In this paper, we present the synthesis of benzo[*b*]furan derivatives with a carboxymethylsulfamoyl group, the results of a screening test for inhibitory activity of the derivatives toward rat lens aldose reductase and several structure–activity trends.[7]

Chemistry 2-Acetyl-7-hydroxybenzo[*b*]furan (**1**)[8] was alkylated with various alkyl halides in the presence of K_2CO_3 to give the corresponding 2-acetyl-7-alkyloxybenzo[*b*]furans (**2a**—**j**). Solutions of these alkyloxy compounds (**2a**—**j**) in dichloroethane were treated with chlorosulfonic acid to give the 4-chlorosulfonyl compounds (**3a**—**j**).[9] When the chlorosulfonylation reactions were carried out at -20—$-15\,^{\circ}C$ with about eight equivalents of chlorosulfonic acid and the same volume of dichloroethane with respect to the reagent, the chlorosulfonyl compounds were obtained in 75—95% yields. When less than eight equivalents of the reagent and a large amount of the solvent were used, the yields of the desired product were low because of the formation of a phenolic product and a product with a sulfonic acid group. Subsequently, the 4-chlorosulfonyl compounds (**3a**—**j**) without purification were reacted with glycine ethyl ester hydrochloride in the presence of triethylamine in CH_2Cl_2 to afford 2-acetyl-4-ethoxycarbonylmethylsulfamoyl-7-alkyloxybenzo[*b*]furans (**4a**—**j**). The esters (**4a**—**j**) were hydrolyzed with 2 N aque-

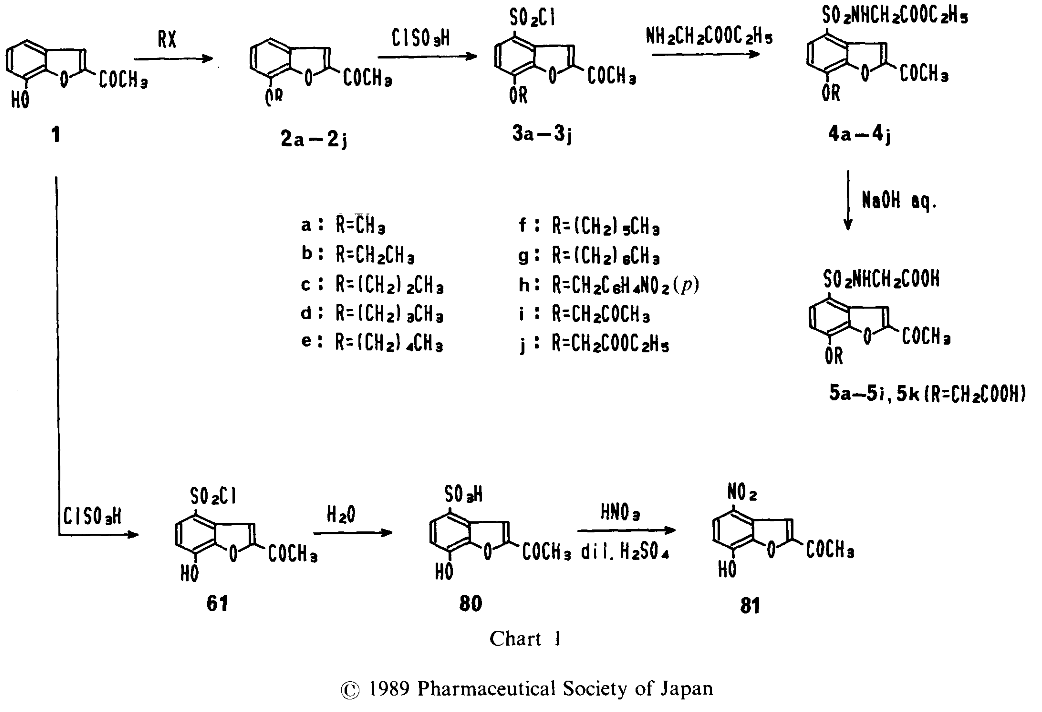


Chart 1

ous NaOH solution followed by neutralization with 1 N HCl to give the corresponding carboxylic acid (**5a**—**i**,**k**) (Chart 1).

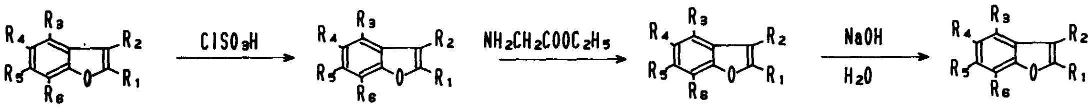
Nitration of 2-acetyl-7-methoxybenzo[*b*]furan gives a mixture of two regioisomers with predominant formation of the 4-nitro isomer.[10] But the chlorosulfonation of the 7-alkyloxy compounds (**2a**—**j**) always gave a single product under the reaction conditions used. The position of the introduced chlorosulfonyl group was confirmed as follows. Chlorosulfonation of **1** with chlorosulfonic acid in the absence of any solvent also afforded a single chlorosulfonated product (**61**). Its nuclear magnetic resonance (NMR) spectrum resembled that of 2-acetyl-7-hydroxy-4-nitrobenzo[*b*]furan.[10] The compound (**61**) was heated at 70 °C in water to give the sulfonic acid (**80**).[11] Nitration of **80** with HNO_3 ($d=1.42$) in 5 N H_2SO_4 afforded 2-acetyl-7-hydroxy-4-nitrobenzo[*b*]furan (**81**).[10,12] This revealed that **61** was 2-acetyl-4-chlorosulfonyl-7-hydroxybenzo[*b*]furan (Chart 1). The 4-chlorosulfonyl compound (**61**) was reacted with glycine ethyl ester hydrochloride to give 2-acetyl-4-ethoxycarbonylmethylsulfamoyl-7-hydroxybenzo[*b*]furan (**62**), which was treated with aqueous NaOH solution to afford the corresponding carboxylic acid (**63**). On the other hand, 2-acetyl-4-ethoxycarbonylmethylsulfamoyl-7-methoxybenzo[*b*]furan (**4a**) was treated with $AlCl_3$ in chlorobenzene at 110 °C to produce the demethylated carboxylic acid (**63**). This carboxylic acid was identical to the carboxylic acid (**63**) obtained from **61**, based on a comparison of their physical data, and infrared (IR) and NMR spectra (Chart 4). The structures of **5a**—**j**,**k** were confirmed on the basis of these experiments.

Furthermore, several kinds of compounds with a carboxymethylsulfamoyl group were prepared by similar reactions to those described above. 7-Methyl-(**10a**) and 7-*sec*-butyl-2-acetyl-4-carboxymethylsulfamoylbenzo[*b*]furan (**10b**), 2-acetyl-4-carboxymethylsulfamoyl-5,6-methylenedioxybenzo[*b*]furan (**16**), and 2-acetyl-7-carboxymethylsulfamoyl-4-methoxybenzo[*b*]furan (**20**) were obtained from 2-acetylbenzo[*b*]furan derivatives (**7a**,**b**,**13**,**17**, respectively). The structure of **16** was confirmed by the proton nuclear magnetic resonance (^{1}H-NMR) spectrum on the basis of $J_{3H-7H}=0.5$ Hz.[13] 7-Methoxy-(**25**) and 7-carboxymethyloxy-2-carboxy-4-carboxymethylsulfamoylbenzo[*b*]furan (**30**) were obtained from the benzo[*b*]furans (**22**, **27**, respectively) with an ester group at the 2-position. 2-Ethyl-7-methoxybenzo[*b*]furan (**37**)[14] gave 4,6-bis(carboxymethylsulfamoyl)-2-ethyl-7-methoxybenzo[*b*]furan (**40**) having two carboxymethylsulfamoyl groups. To prepare the benzo[*b*]furan derivatives bearing a carboxymethylsulfamoyl group at the 3-position (**44**, **48**), 2-ethyl-5-nitrobenzo[*b*]furan (**41**)[10] and 2-ethyl-5-acetylaminobenzo[*b*]furan (**45**) were employed, respectively (Chart 2).

An attempt to obtain the derivative with a nitrile group at the 2-position was made using 2-carboxycarbonyl-7-ethoxybenzo[*b*]furan (**31**) as a starting material. The keto acid (**31**) was converted into 2-cyano-7-ethoxybenzo[*b*]furan (**33**) through the oxime (**32**). The nitrile (**33**) was converted to 2-cyano-4-ethoxycarbonylmethylsulfamoyl-7-ethoxybenzo[*b*]furan (**35**) in a similar manner. But, the cyano group of **35** was easily hydrolyzed in the last reaction of the process to give the 2-carboxylic acid (**36**) (Chart 3).

A series of investigations on hydantoin derivatives (2,4-imidazolidinedione) have been carried out in order to find more effective aldose reductase inhibitors.[15] Thus, we prepared benzo[*b*]furan derivatives possessing both a carboxymethylsulfamoyl group and a hydantoin group. 2-Acetyl-7-methoxybenzo[*b*]furan (**2a**) was treated with $(NH_4)_2CO_3$ and NaCN to afford 7-methoxy-2-(5-methyl-2,4-dioxoimidazolidin-5-yl)benzo[*b*]furan (**49**).[16] Chlorosulfonation of **49** always gave the 4,6-dichlorosulfonyl compound (**50**) alone, similarly to that of 2-ethyl-7-methoxybenzo[*b*]furan (**37**). The di-*tert*-butyl ester (**51**) obtained from the reaction of **50** with glycine *tert*-butyl ester hydrochloride was treated with trifluoroacetic acid (TFA) to give 4,6-bis(carboxymethylsulfamoyl)-7-methoxy-2-(5-methyl-2,4-dioxoimidazolidin-5-yl)benzo[*b*]furan (**52**) in a reasonable yield. The hydantoin compound (**55**) with a carboxymethylsulfamoyl group was prepared as follows. Treatment of **3a** with glycine *tert*-butyl ester hydrochloride gave 2-acetyl-4-*tert*-butyloxycarbonylmethylsulfamoyl-7-methoxybenzo[*b*]furan (**53**). The acetyl compound (**53**) was treated with $(NH_4)_2CO_3$ to give **54**. Subsequently, **54** was treated with TFA to give 4-carboxymethylsulfamoyl-7-methoxy-2-(5-methyl-2,4-dioxoimidazolidin-5-yl)benzo[*b*]furan (**55**) (Chart 3).

When the chlorosulfonyl compound (**3d**) was treated with *N*-methylglycine ester hydrochloride (**56a**), L-alanine ethyl ester hydrochloride (**56b**) and *N*-methyl-L-alanine



7a: R_1=Ac, R_6=CH$_3$	**8a**: R_1=Ac, R_3=SO$_2$Cl, R_6=CH$_3$	**9a**: R_1=Ac, R_3=A, R_6=CH$_3$	**10a**: R_1=Ac, R_3=B, R_6=CH$_3$
7b: R_1=Ac, R_6=*sec*-Bu	**8b**: R_1=Ac, R_3=SO$_2$Cl, R_6=*sec*-Bu	**9b**: R_1=Ac, R_3=A, R_6=*sec*-Bu	**10b**: R_1=Ac, R_3=B, R_6=*sec*-Bu
13: R_1=Ac, R_4=OCH$_2$O=R_5	**14**: R_1=Ac, R_3=SO$_2$Cl, R_4=OCH$_2$O=R_5	**15**: R_1=Ac, R_3=A, R_4=OCH$_2$O=R_5	**16**: R_1=Ac, R_3=B, R_4=OCH$_2$O=R_5
17: R_1=Ac, R_3=OCH$_3$	**18**: R_1=Ac, R_3=OCH$_3$, R_6=SO$_2$Cl	**19**: R_1=Ac, R_3=OCH$_3$, R_6=A	**20**: R_1=Ac, R_3=OCH$_3$, R_6=B
22: R_1=COOCH$_3$, R_6=OCH$_3$	**23**: R_1=COOCH$_3$, R_3=SO$_2$Cl, R_6=OCH$_3$	**24**: R_1=COOCH$_3$, R_3=A, R_6=OCH$_3$	**25**: R_1=COOH, R_3=B, R_6=OCH$_3$
27: R_1=COOCH$_2$COOC$_2$H$_5$, R_6=OCH$_2$COOC$_2$H$_5$	**28**: R_1=COOCH$_2$COOC$_2$H$_5$, R_3=SO$_2$Cl, R_6=OCH$_2$COOC$_2$H$_5$	**29**: R_1=COOCH$_2$COOC$_2$H$_5$, R_3=A, R_6=OCH$_2$COOC$_2$H$_5$	**30**: R_1=COOH R_3=B, R_6=OCH$_2$COOH
37: R_1=C$_2$H$_5$, R_6=OCH$_3$	**38**: R_1=C$_2$H$_5$, R_3=R_5=SO$_2$Cl, R_6=OCH$_3$	**39**: R_1=C$_2$H$_5$, R_3=R_5=A, R_6=OCH$_3$	**40**: R_1=C$_2$H$_5$, R_3=R_5=B, R_6=OCH$_3$
41: R_1=C$_2$H$_5$, R_4=NO$_2$	**42**: R_1=C$_2$H$_5$, R_2=SO$_2$Cl, R_4=NO$_2$	**43**: R_1=C$_2$H$_5$, R_2=A, R_4=NO$_2$	**44**: R_1=C$_2$H$_5$, R_2=B, R_4=NO$_2$
45: R_1=C$_2$H$_5$, R_4=CH$_3$CONH	**46**: R_1=C$_2$H$_5$, R_2=SO$_2$Cl, R_4=CH$_3$CONH	**47**: R_1=C$_2$H$_5$, R_2=A, R_4=CH$_3$CONH	**48**: R_1=C$_2$H$_5$, R_2=B, R_4=CH$_3$CONH

A=$SO_2NHCH_2COOC_2H_5$, B=SO_2NHCH_2COOH, substituent groups(R) without any descriptions exhibit H

Chart 2

TABLE I. Physical Data for the Benzo[*b*]furan Derivatives

Compd.	mp (°C)	^{1}H-NMR (ppm)	Analysis (%) Calcd (Found)		MS (*m*/*z*)
			C	H	
5a	223—225	2.48 (3H, s, $COCH_3$), 3.45 (2H, br d, $NHC\underline{H}_2$), 3.52 (1H, br s, COOH), 3.90 (3H, s, OCH_3), 7.03 (1H, d, 6-H), 7.58 (1H, d, 5-H), 7.70 (1H, br s, NH), 7.02 (1H, s, 3-H)$^{a)}$	47.70 (47.48	4.00 3.98)	372 (M^+), 282, 253, 189
5b	143—145	1.35 (3H, t, $CH_2C\underline{H}_3$), 2.43 (3H, s, $COCH_3$), 3.35 (1H, br s, COOH), 3.38 (2H, br d, $NHC\underline{H}_2$), 4.08 (2H, q, $C\underline{H}_2CH_3$), 6.93 (1H, d, 6-H), 7.42 (1H, d, 5-H), 7.78 (1H, s, 3-H), 7.90 (1H, br s, NH)$^{a)}$	49.26 (49.38	4.43 4.41)	n.d.
5c	202—205	0.99 (3H, t, $CH_2C\underline{H}_3$), 1.66 (2H, m, $C\underline{H}_2CH_3$), 2.47 (3H, s, $COCH_3$), 3.43 (2H, br d, $NHC\underline{H}_2$), 3.58 (1H, br s, COOH), 4.04 (2H, t, CH_2O), 6.98 (1H, d, 6-H), 7.46 (1H, d, 5-H), 7.83 (1H, s, 3-H), 7.94 (1H, br s, NH)$^{a)}$	50.70 (51.09	4.82 4.76)	355 (M^+), 313, 267, 239
5d	163—164	0.95 (3H, t, $CH_2C\underline{H}_3$), 1.40—1.73 (4H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_3$), 2.47 (3H, s, $COCH_3$), 3.44 (2H, br d, $NHC\underline{H}_2$), 3.55 (1H, br s, COOH), 4.07 (2H, t, CH_2O), 6.90 (1H, d, 6-H), 7.36 (1H, d, 5-H), 7.72 (1H, s, 3-H), 7.80 (1H, br s, NH)$^{a)}$	52.03 (52.19	5.18 5.11)	369 (M^+), 313, 239
5e	172—174	0.83 (3H, t, $CH_2C\underline{H}_3$), 1.20—1.40 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.60—1.80 (2H, m, $OCH_2\underline{H}_2$), 2.45 (3H, s, $COCH_3$), 3.41 (2H, br d, $NHCH_2$), 3.52 (1H, br s, COOH), 4.06 (2H, t, CH_2O), 6.97 (1H, d, 6-H), 7.45 (1H, d, 5-H), 7.83 (1H, s, 3-H), 7.90 (1H, br s, NH)$^{a)}$	53.25 (53.41	5.52 5.39)	383 (M^+), 313, 268, 239
5f	204—207	0.89 (3H, t, $CH_2C\underline{H}_3$), 1.05—1.80 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 2.40 (3H, s, $COCH_3$), 3.30 (1H, br s, COOH), 3.35 (2H, br d, $NHC\underline{H}_2$), 4.24 (2H, t, OCH_2), 6.68 (1H, d, 6-H), 7.31 (1H, d, 5-H), 7.72 (1H, s, 3-H), 7.82 (1H, br s, NH)$^{a)}$	54.40 (54.11	5.83 5.72)	397 (M^+), 313, 268, 239
5g	165—166	0.80 (3H, t, $CH_2C\underline{H}_3$), 1.42 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.72 (2H, m, $OCH_2C\underline{H}_2$), 2.44 (3H, s, $COCH_3$), 3.40 (2H, br d, $NHCH_2$), 4.06 (2H, t, OCH_2), 5.39 (1H, br s, COOH), 7.00 (1H, d, 6-H), 7.46 (1H, d, 5-H), 7.80 (1H, br s, NH), 7.82 (1H, s, 3-H)$^{a)}$	55.46 (55.39	6.12 6.10)	411 (M^+), 313, 239
5h	157—159	2.45 (3H, s, CH_3), 3.40 (2H, d, $NHC\underline{H}_2$), 5.33 (2H, s, OCH_2), 7.01 (1H, d, 6-H), 7.42 (1H, d, 5-H), 7.48 (2H, d, 2′ and 6′-H), 7.78 (1H, s, 3-H), 7.92 (1H, t, NH), 7.96 (2H, d, 3′ and 5′-H)$^{a)}$	50.89 (51.01	3.60 3.32)	448 (M^+), 402, 389, 373, 310
5i	97—99	2.06 (3H, s, $OCH_2COC\underline{H}_3$), 2.43 (3H, s, $COCH_3$), 3.37 (2H, d, $NHC\underline{H}_2$), 3.51 (1H, br s, COOH), 4.92 (2H, s, $OC\underline{H}_2COCH_3$), 6.70 (1H, d, 6-H), 7.33 (1H, d, 5-H), 7.73 (1H, d, 3-H), 7.88 (1H, t, NH)$^{a)}$	48.78 (48.61	4.09 4.25)	369 (M^+), 326, 310
5j	232—235	2.51 (3H, s, $COCH_3$), 3.20 (2H, br s, COOH × 2), 3.47 (2H, s, $NHC\underline{H}_2$), 4.92 (2H, s, OCH_2), 7.07 (1H, s, 6-H), 7.59 (1H, d, 5-H), 7.98 (1H, s, 3-H), 8.14 (1H, br s, NH)$^{a)}$	45.29 (45.10	3.53 3.59)	371 (M^+), 326, 312, 297
10a	193—196	2.38 (3H, s, 7-CH_3), 2.43 (3H, s, $COCH_3$), 3.38 (2H, br d, $NHC\underline{H}_2$), 3.65 (1H, br s, COOH), 7.15 (1H, d, 6-H), 7.35 (1H, d, 5-H), 7.74 (1H, s, 3-H), 7.95 (1H, br s, NH)$^{a)}$	50.17 (50.02	4.21 4.29)	311 (M^+), 266, 266, 237, 173
10b	172—174	0.76 (3H, t, $CH_2C\underline{H}_3$), 1.27 (3H, d, $CHC\underline{H}_3$), 1.66 (2H, m, CH_2), 2.47 (3H, s, $COCH_3$), 3.08 (1H, m, CH), 3.46 (2H, br s, $NHC\underline{H}_2$), 3.70 (1H, br s, COOH), 7.36 (1H, d, 6-H), 7.52 (1H, d, 5-H), 7.85 (1H, s, 3-H), 8.08 (1H, br s, NH)$^{a)}$	54.38 (54.22	5.42 5.31)	353 (M^+), 324, 279
16	240—244	2.33 (3H, s, $COCH_3$), 3.55 (2H, br s, $NHC\underline{H}_2$), 3.62 (1H, br s, COOH), 5.92 (2H, s, OCH_2O), 7.08 (1H, br d, 7-H), 7.53 (1H, br d, 3-H), 7.70 (1H, br s, NH)$^{b)}$	45.75 (46.01	3.25 3.30)	341 (M^+), 326, 266, 203, 189
20	186—188	2.46 (3H, s, OCH_3), 3.66 (2H, br d, $NHC\underline{H}_2$), 3.75 (1H, br s, COOH), 3.85 (3H, s, $COCH_3$), 5.79 (1H, d, 5-H), 7.65 (1H, d, 6-H), 7.74 (1H, s, 3-H), 7.90 (1H, br s, NH)$^{a)}$	47.70 (47.61	4.00 4.09)	327 (M^+), 282, 253, 189
25	264—267	3.20 (2H, br s, COOH × 2), 3.37 (2H, br d, $NHC\underline{H}_2$), 3.39 (3H, s, OCH_3), 6.96 (1H, d, 6-H), 7.58 (1H, d, 5-H), 7.60 (1H, s, 3-H), 7.82 (1H, br s, NH)$^{a)}$	43.77 (43.51	3.37 3.39)	329 (M^+), 284, 255, 191
30	266—269	3.32 (2H, br d, $NHC\underline{H}_2$), 3.70 (3H, br s, COOH × 2), 4.70 (2H, s, OCH_2), 6.80 (1H, d, 6-H), 7.33 (1H, s, 5-H), 7.53 (1H, s, 3-H), 7.88 (1H, br s, NH)$^{a)}$	41.83 (41.70	2.87 2.99)	n.d.
36	221—224	1.34 (3H, t, CH_3), 3.35 (2H, br d, $NHC\underline{H}_2$), 3.73 (2H, br s, COOH × 2), 4.07 (2H, q, $C\underline{H}_2$-CH_3), 6.88 (1H, d, 6-H), 7.39 (1H, d, 5-H), 7.59 (1H, s, 3-H), 7.92 (1H, br t, NH)$^{a)}$	45.48 (45.70	3.82 3.80)	343 (M^+), 298, 269, 241
40	158—160	1.26 (3H, s, $CH_2C\underline{H}_3$), 2.78 (2H, q, $C\underline{H}_2CH_3$), 3.40 (4H, br s, $NHC\underline{H}_2COO$ × 2), 4.15 (3H, s, OCH_3), 4.40 (1H, br s, COOH), 6.65 (1H, s, 3-H), 7.55 (1H, s, 5-H), 7.60 (1H, t, NH), 8.00 (1H, t, NH)$^{a)}$	40.00 (39.79	4.03 3.92)	n.d.
44	137—139	1.25 (3H, t, CH_3), 3.05 (2H, q, $C\underline{H}_2CH_3$), 3.35 (1H, br s, COOH), 3.63 (2H, br d, $NHC\underline{H}_2$), 7.78 (1H, d, 7-H), 8.18 (1H, d, 6-H), 8.45 (1H, br s, NH), 8.60 (1H, s, 4-H)$^{a)}$	43.90 (43.59	3.68 3.70)	328 (M^+), 283, 254, 189, 143
48	254—256	1.21 (3H, t, $CH_2C\underline{H}_3$), 1.94 (3H, s, $COCH_3$), 2.90 (2H, q, $C\underline{H}_2CH_3$), 3.40 (1H, br s, COOH), 3.48 (2H, d, $NHC\underline{H}_2$), 7.26 (1H, d, 7-H), 7.40 (1H, d, 6-H), 7.74 (1H, s, 4-H), 8.00 (1H, t, $N\underline{H}CH_2$), 9.82 (1H, s, CONH)$^{a)}$	49.41 (49.58	4.74 4.69)	340 (M^+), 298, 267, 204, 160
52	198—200	1.70 (3H, s, CH_3), 3.38 (2H, br d, CH_2), 3.52 (2H, br d, CH_2), 4.16 (3H, s, OCH_3), 5.60 (2H, br s, COOH × 2), 7.12 (1H, s, 3-H), 5.24 (1H, s, 5-H), 8.10 (2H, br d, NH × 2), 8.56 (1H, s, ring NH), 11.00 (1H, br s, ring NH)$^{a)}$	38.20 (38.01	3.39 3.47)	n.d.
55	256—258	1.69 (3H, s, CCH_3), 3.38 (2H, br d, COOH), 3.83 (3H, s, OCH_3), 6.92 (1H, d, 6-H), 7.00 (1H, br s, COOH), 7.10 (1H, s, 3-H), 7.47 (1H, d, 4-H), 7.96 (1H, br s, $N\underline{H}CH_2$), 8.51 (1H, br s, ring NH), 10.88 (1H, br s, ring NH)$^{a)}$	45.34 (45.60	3.81 3.72)	n.d.
58	101—103	0.87 (3H, t, $CH_2C\underline{H}_3$), 1.10—1.80 (4H, m, $CH_2C\underline{H}_2C\underline{H}_3$), 2.45 (3H, s, $COCH_3$), 2.64 (3H, s, NCH_3), 3.55 (1H, br s, COOH), 3.74 (2H, s, NCH_2), 4.09 (2H, t, OCH_2), 7.01 (1H, d, 6-H), 7.46 (1H, d, 5-H), 7.66 (1H, s, 3-H)$^{a)}$	53.25 (53.10	5.52 5.57)	383 (M^+), 338, 295, 281, 239
59	181—183	0.86 (3H, t, $CH_2C\underline{H}_3$), 1.04 (3H, d, $CHC\underline{H}_3$), 2.40 (3H, s, $COCH_3$), 3.30 (1H, br s, COOH), 3.50 (1H, m, $C\underline{H}CH_3$), 3.98 (2H, t, OCH_2), 6.86 (1H, d, 6-H), 7.32 (1H, d, 5-H), 7.70 (1H, s, 3-H), 7.88 (1H, br d, NH)$^{a)}$	53.25 (53.49	5.52 5.50)	383 (M^+), 338, 295, 239
60	148—150	0.90 (3H, t, $CH_2C\underline{H}_3$), 1.09 (3H, d, $CHC\underline{H}_3$), 1.25—1.88 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 2.44 (3H, s, $COCH_3$), 2.58 (3H, s, NCH_3), 3.75 (1H, br s, COOH), 4.05 (2H, t, OCH_2), 4.48 (1H, q, CH_3), 7.00 (1H, d, 6-H), 7.48 (1H, d, 5-H), 7.68 (1H, s, 3-H)$^{a)}$	54.40 (54.63	5.83 5.72)	397 (M^+), 353, 296, 239
63	>280	2.40 (3H, s, $COCH_3$), 3.38 (2H, d, $NHC\underline{H}_2$), 3.50 (1H, br s, COOH), 6.80 (1H, d, 6-H), 7.40 (1H, d, 5-H), 7.60 (1H, br s, NH), 7.80 (1H, s, 3-H)$^{a)}$	46.01 (46.26	3.54 3.66)	n.d.

Table I. (continued)

Compd.	mp (°C)	^{1}H-NMR (ppm)	Analysis (%) Calcd (Found)		MS (m/z)
			C	H	
70	178—180	2.41 (3H, s, CH_3), 3.40 (2H, d, $NHC\underline{H}_2$), 5.27 (2H, s, OCH_2), 6.98 (1H, d, 6-H), 7.42 (1H, d, 5-H), 7.29 (2H, d, 2′ and 6′-H), 7.67 (2H, d, 3′ and 5′-H), 7.77 (1H, s, 3-H), 7.93 (1H, t, NH)$^{a)}$	55.42 (55.33	4.42 4.28)	n.d.
71	271—274	2.45 (3H, s, $COCH_3$), 3.39 (1H, br s, COOH), 3.54 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.85 (2H, s, $NC\underline{H}_2COOH$), 4.62 (2H, s, $NC\underline{H}_2C_6H_4$), 5.16 (2H, s, $OC\underline{H}_2C_6H_4$), 6.57—7.03 (8H, m, phenyl H), 7.18 (1H, d, 5-H), 7.65 (1H, d, 6-H), 7.76 (1H, s, 3-H)$^{a)}$	60.75 (60.39	4.92 4.71)	553 (M^+), 494
72	135—137	2.50 (3H, s, $COCH_3$), 3.40 (2H, d, $NHC\underline{H}_2$), 3.55 (1H, br s, COOH), 5.10 (2H, s, $OC\underline{H}_2C_6H_5$), 6.70—7.35 (7H, m, 5 and 6-H and 2′, 3′, 4′, 5′ and 6′-H), 7.63 (1H, s, 3-H), 7.80 (1H, t, NH)$^{a)}$	56.57 (56.37	4.25 4.14)	403 (M^+), 358, 326
73	144—146	2.43 (3H, s, $COCH_3$), 3.50 (1H, br s, COOH), 3.70 (2H, s, $NC\underline{H}_2COOH$), 4.20 (2H, s, $NC\underline{H}_2$-C_6H_5), 5.20 (2H, s, $OC\underline{H}_2C_6H_5$), 6.80—7.50 (12H, m, 5 and 6-H and phenyl H), 7.60 (1H, s, 3-H)$^{a)}$	63.28 (63.22	4.70 4.66)	493 (M^+), 434
74	178—180	2.60 (3H, s, $COCH_3$), 3.42 (2H, d, $NC\underline{H}_2COOH$), 3.50 (1H, br s, COOH), 5.12 (2H, s, $OC\underline{H}_2$-C_6H_4), 6.90 (1H, d, 6-H), 7.00—7.25 (4H, m, 2′, 3′, 5′ and 6′-H), 7.30 (1H, s, 5-H), 7.63 (1H, s, 3-H), 7.80 (1H, t, NH)$^{a)}$	52.12 (52.30	3.68 3.76)	437 (M^+), 326
75	168—170	2.40 (3H, s, $COCH_3$), 3.45 (1H, br s, COOH), 3.78 (2H, s, $NC\underline{H}_2COOH$), 4.25 (2H, s, $NC\underline{H}_2$-C_6H_4), 5.18 (2H, s, $OC\underline{H}_2C_6H_4$), 6.85—7.55 (10H, m, 5 and 6-H and phenyl H), 7.60 (1H, s, 3-H)$^{a)}$	55.53 (55.39	3.76 3.92)	561 (M^+), 516
78	169—171	2.20—2.63 (2H, m, $OCH_2C\underline{H}_2$), 2.50 (3H, s, $COCH_3$), 3.45 (2H, d, $NC\underline{H}_2COOH$), 3.50 (1H, br s, COOH), 4.15 (2H, t, OCH_2), 4.78—5.08 (2H, m, $CH=C\underline{H}_2$), 5.20—5.80 (1H, m, $C\underline{H}=CH_2$), 6.85 (1H, d, 6-H), 7.32 (1H, d, 5-H), 7.63 (1H, s, 3-H), 7.75 (1H, t, NH)$^{a)}$	52.31 (52.03	4.66 4.50)	367 (M^+), 313, 239
79	190—192	2.55 (3H, s, $COCH_3$), 3.45 (2H, d, $NC\underline{H}_2COOH$), 3.55 (1H, br s, COOH), 4.63 (2H, d, OCH_2), 5.05—5.35 (2H, dd, $CH=C\underline{H}_2$), 5.60—6.03 (1H, m, $C\underline{H}=CH_2$), 6.50 (1H, d, 6-H), 7.35 (1H, d, 5-H), 7.65 (1H, s, 3-H), 7.83 (1H, t, NH)$^{a)}$	50.99 (51.12	4.28 4.31)	352 (M^+), 278

n.d., not detected. *a*) In DMSO-d_6. *b*) In acetone-d_6.

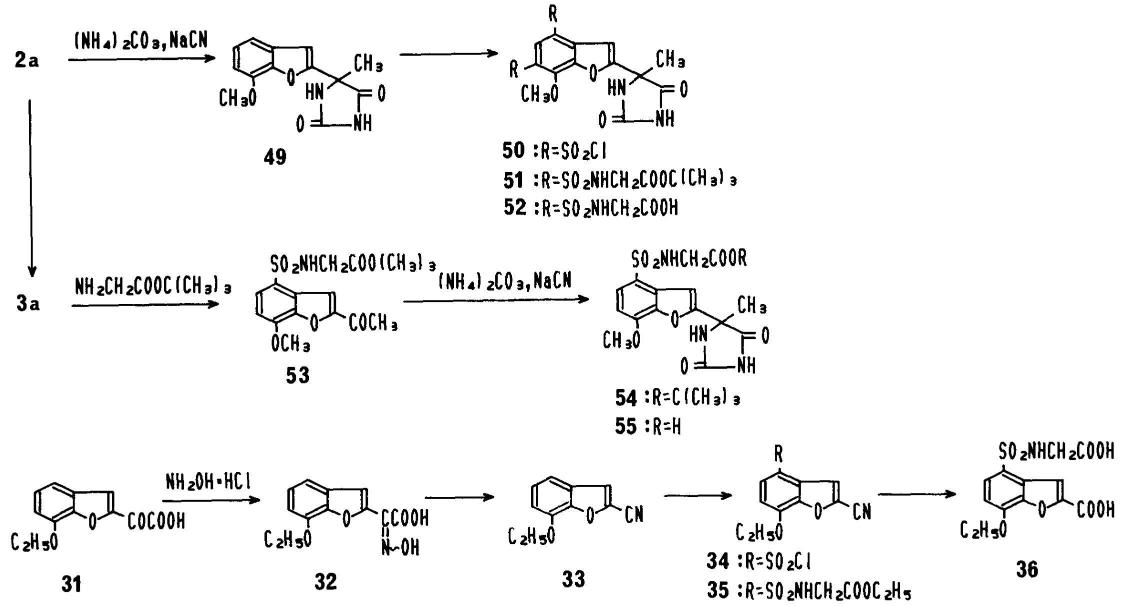


Chart 3

methyl ester hydrochloride (**56c**),[17] the corresponding products (**57a**, **b**, **c**, respectively) were obtained. However, the reaction of **3d** with L-tyrosine ethyl ester hydrochloride having a bulkyl group at the α-position resulted in the formation of an inseparable complex mixture. The esters (**57a**, **b**, **c**) were treated with aqueous NaOH solution to afford **58**, **59** and **60**, respectively (Chart 4). Furthermore, alkylations of the phenolic hydroxy group and the sulfonamide NH group in 2-acetyl-4-carboxymethylsulfamoyl-7-hydroxybenzo[*b*]furan (**63**) were carried out in order to obtain more lipophilic compounds. Treatments of **63** with several benzyl bromides afforded two series of products, O- and N-substituted esters (**65**, **67**, **69**) and O-substituted esters (**64**, **66**, **68**). Both series of the esters were hydrolyzed to give six carboxylic acids (**70**—**75**). Treatment of **63** with olefinic bromides gave only O-substituted compounds (**76**, **77**). These were also hydrolyzed to give carboxy compounds (**78**, **79**) (Chart 4).

Results and Discussion

All of the benzo[*b*]furan derivatives were tested for their ability to inhibit aldose reductase obtained from rat lens. The inhibitor IC_{50} values are shown in Table II, in which the benzo[*b*]furans are classified into seven series according to their structural types.

In series 1, benzo[*b*]furans have an acetyl group at the 2-

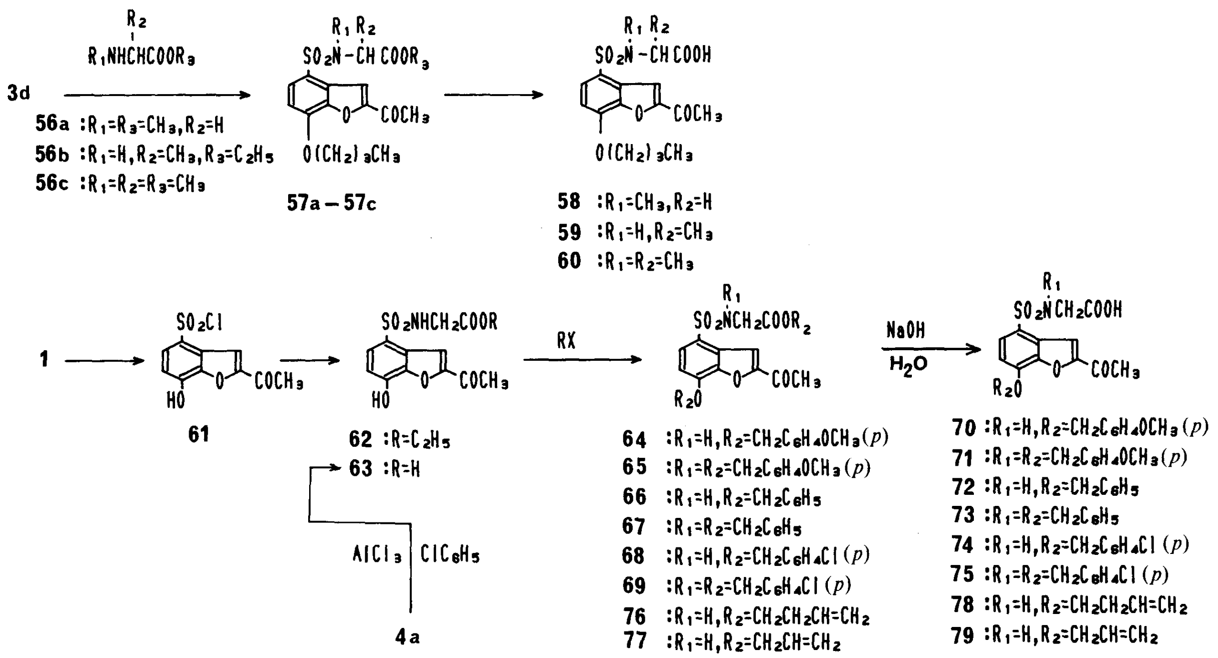


Chart 4

TABLE II. Aldose Reductase-Inhibitory Activity

Series	Compd.	IC_{50} ($\times 10^{-7}$ M)	Series	Compd.	IC_{50} ($\times 10^{-7}$ M)
1	**5a**	2	2	**10a**	4
	5b	1		**10b**	5
	5c	0.6	3	**20**	50
	5d	0.4	4	**52**	3
	5e	0.5		**55**	20
	5f	0.5	5	**25**	1
	5g	0.3		**30**	2
	5h	0.5		**36**	0.7
	5i	2	6	**40**	5
	5k	2		**44**	0.5
	16	20		**48**	0.5
	63	0.8	7	**58**	10
	70	0.3		**59**	50
	72	0.5		**60**	70
	74	0.4		**71**	8
	78	0.3		**73**	7
	79	0.5		**75**	8
				Sorbinil	2

position, a carboxymethylsulfamoyl group at the 4-position, and various alkyloxy groups at the 7-position except for **16** and **63**. This type includes several of the most effective inhibitors (**5d**, **e**, **f**, **g**, **h**, **70**, **72**, **74**, **78**, **79**), with an IC_{50} of about 10^{-8} M. Among the compounds with a saturated alkyloxy group, the derivatives with a longer-chain alkyloxy group are obviously more active. For example, the 7-heptyloxy compound (**5g**) is about seven times more potent than the methoxy compound (**5a**). The similar trend can be observed in the unsaturated alkyloxy compounds (**78**, **79**). All the compounds (**5h**, **70**, **72**, **74**) with a benzyloxy group also display potent inhibitory activity comparable to that of the compounds (**5d**—**g**) with a long-chain alkyloxy group. Varying the electronic nature of the substituent on the benzyl ring slightly affects the activity of the benzyloxy compounds. It appears that the benzyloxy group is functionally distinct from the carboxymethylsulfamoyl group. Polar compounds (**5k**, **63**) are also as active as the short alkyloxy group compounds (**5a**, **b**) having moderate activity. On the other hand, the 5,6- methylenedioxy analogue (**16**), bearing an electron-donating moiety at the 5- and 6-positions, has only weak inhibitory activity. These data show that compounds with a more lipophilic alkyloxy group at the 7-position exhibit excellent inhibitory activity in series 1.

In series 2, the benzo[*b*]furans have an alkyl group at the 7-position, an acetyl group at the 2-position and a carboxymethylsulfamoyl group at the 4-position. Replacement of the alkyloxy group in series 1 by an alkyl group considerably decreases the activity. For example, **10b** displays only 1/10 of the inhibitory activity of the corresponding alkyloxy compound (**5d**).

In series 3, the carboxymethylsulfamoyl group is present at the 7-position, but **20**, with an IC_{50} of 5×10^{-6} M, displays only 1/25 of the inhibitory activity of the corresponding 4-carboxymethylsulfamoyl derivative (**5a**).

In series 4, the compounds contain a hydantoin moiety, but **55** is ten times less active than **5a**. Compound **52**, bearing two carboxymethylsulfamoyl groups, is as active as the 2-ethyl compound (**40**). These data suggest that the introduction of the hydantoin moiety into the benzo[*b*]furans with a carboxymethylsulfamoyl group is not a useful approach to enhance the activity.

In series, 5, the compounds have a carboxy group in place of the acetyl group of the compounds in series 1. The compounds (**25**, **30**, **36**) have similar activity to the corresponding acetyl analogues (**5a**, **k**, **b**). Thus, the attempt to enhance the inhibitory activity by using a carboxy group was unsuccessful.

In series 6, the compounds have an ethyl group at the 2-position. Two compounds (**44**, **48**) with a carboxymethylsulfamoyl group at the 3-position display inhibitory potency comparable to that of the most active compounds in series 1. The potent inhibitory activity of the two compounds (**44**, **48**) is presumably a result of the presence of the carboxymethylsulfamoyl group at the 3-position, because the electronic characters of the substituent at the 5-position of the two compounds (**44**, **48**) are opposite, and the compound (**40**) without the carboxymethylsulfamoyl group displays only moderate activity.

In series 7, the influence of an alkyl substituent on the carboxymethylsulfamoyl group on the activity was investigated. The *N*-methyl-(**58**), α-methyl-(**59**) and *N*-methyl and α-methyl analogue (**60**) were prepared on the basis of the potent derivative (**5d**) as the parent compound. These methylated compounds were 25—175 times less active than the parent compound (**5d**). Several *N*-benzyl compounds (**71**, **73**, **75**) were also 14—27 less potent than the corresponding parent compounds (**70**, **72**, **74**).

The position of the carboxymethylsulfamoyl group and variation of the substituent group on the benzo[*b*]furan ring both significantly affect the inhibitory potency.

In this study, the compounds with the carboxymethylsulfamoyl group at the 3- or 4-position were found to be considerably more active than those with the group at some other position. Among the 4-carboxymethylsulfamoyl derivatives, more lipophilic 7-alkyloxy groups increase the potency significantly. They may enhance the activity through an interaction with a secondary hydrophobic site present on the enzyme.[6a] A more electron-donating nature of the 7-substituent group would presumably also be important for high activity because 7-alkyl derivatives display only moderate activity. In the case of the 3-carboxymethylsulfamoyl compounds (**44**, **48**), we may speculate that the benzene moiety of the benzo[*b*]furan ring plays a role in the interaction with a secondary hydrophobic site of the enzyme.

Compounds **16** and **20** characteristically contain a ring ether moiety adjacent to the carboxymethylsulfamoyl group. Both compounds (**16**, **20**) display very low activity.

The 2-carboxy compounds (**25**, **30**, **36**) are as active as the corresponding 2-acetyl compounds (**5a**, **k**, **b**), which display moderate activity. The 2-ethyl compounds (**40**, **44**, **48**) also exhibit high activity. These data suggest that the nature of the substituent group at the 2-position has little effect on the activity.

Alkyl substitution of the α carbon and/or sulfamoyl moiety of the carboxymethylsulfamoyl group decreases the potency significantly. The result is consistent with reported structure–activity data.[6a,18] The binding mechanism of the benzo[*b*]furan derivatives toward the enzyme could be similar that proposed by DeRuiter and Mayfield.[6a]

We prepared several kinds of compounds which had a carboxymethylsulfamoyl group on benzene, naphthalene, indene, tetrahydronaphthalene, benzophenone, thiazole and benzothiazole and evaluated their inhibitory activity. It was found that the benzo[*b*]furans with the carboxymethylsulfamoyl group exhibited the highest inhibitory potency among all of the compounds. Thus, the benzo[*b*]furan ring seems to be a suitable parent skeleton for further attempts to enhance the inhibitory potent of carboxymethylsulfamoyl-substituted compounds.

Experimental

All melting points were measured with a Thomas Hoover capillary melting point apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded with a JEOL PS-100 spectrometer. Chemical shifts are given in δ values with tetramethylsilane (TMS) as an internal standard and the following abbreviations are used: s, singlet; d, doublet; dd, double doublet; br s, broad singlet; br d, broad doublet. Low-resolution mass spectra (MS) were obtained with a Hitachi M-52 instrument. IR spectra were recorded with a Shimadzu IR-17G spectrometer.

2-Acetyl-4-carboxymethylsulfamoyl-7-heptyloxybenzo[*b*]furan (5e) General Procedure for **5a**—**h**: 2-Acetyl-7-heptyloxybenzo[*b*]furan (**2e**) was obtained by usual alkylation from **1**. A solution of **2e** (5.0 g, 0.020 mol) in dichloroethane (10 ml) was added to $ClSO_3H$ (17.5 g, 0.15 mol) at −20 °C. The mixture was stirred for 2 h at −15 °C, poured into ice-water, and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and concentrated to yield crude **3e** (5.8 g, 83%). ^{1}H-NMR (DMSO-d_6) δ: 0.87 (3H, t, CH_3), 1.10—1.90 (6H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.47 (3H, s, $COCH_3$), 4.04 (2H, t, CH_2O), 6.85 (1H, d, 6-H), 7.29 (1H, d, 5-H), 7.71 (1H, s, 3-H). MS *m/z*: 344 (M^+), 309, 274, 239. Triethylamine (3.8 g, 0.037 mol) was added to a mixture of the crude **3e** (5.8 g, 0.017 mol), glycine ethyl ester–HCl (2.8 g, 0.020 mol) and dichloromethane (60 ml) at 23 °C and the mixture was stirred for 1 h at 27 °C. Ethyl acetate (300 ml) was then added and the extract layer was washed with 1 N HCl (200 ml) and brine, and dried over Na_2SO_4. The product, obtained by removal of the solvent under reduced pressure, was recrystallized from ethyl acetate to furnish **4e** (5.2 g, 75%). ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, $C\underline{H}_3CH_2CH_2$), 0.96 (3H, t, $C\underline{H}_3CH_2O$), 1.10—1.90 (6H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.51 (3H, s, $COCH_3$), 3.57 (2H, br s, $NHC\underline{H}_2$), 3.72 (2H, t, $CH_3C\underline{H}_2O$), 4.12 (2H, t, CH_2O), 7.04 (1H, d, 6-H), 7.50 (1H, d, 5-H), 7.85 (1H, s, 3-H), 8.08 (1H, br s, NH). MS *m/z*: 411 (M^+), 341, 239. A solution of **4e** (5.2 g, 0.013 mol) in methanol (55 ml) was treated with 1 N aqueous NaOH solution (29 ml) for 1.5 h at 25 °C and then acidified with 1 N HCl at 0 °C. The acidic solution was extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried (Na_2SO_4), and concentrated to yield a pale yellow powder, which was recrystallized from acetonitrile to give **5e** (5.6 g, 86%). Physical data, see Table I.

2-Acetyl-7-acetylmethoxy-4-carboxymethylsulfamoylbenzo[*b*]furan (5i) A mixture of **1** (7 g, 0.040 mol), K_2CO_3 (8.3 g, 0.060 mol), chloroacetone (4.8 g, 0.052) and dimethylformamide (DMF) (150 ml) was stirred for 3 h at 27 °C. After usual work-up, the product was recrystallized from ethanol to give colorless prisms (**2i**, 6.3 g, 89%). Subsequently **2i** (2.1 g, 0.009 mol) was converted to **5i** (1.0 g, 31%) under conditions similar to those used for **2e**. Physical data, see Table I.

2-Acetyl-7-carboxymethyloxy-4-carboxymethylsulfamoylbenzo[*b*]furan (5k) A mixture of **1** (3.0 g, 0.017 mol), K_2CO_3 (3.5 g, 0.026 mol), ethyl bromoacetate (3.7 g, 0.022 mol), and tetrahydrofuran (100 ml) was stirred for 20 h at 25 °C. After usual work-up, the product was recrystallized from ethyl acetate to give colorless prisms (**2j**, 3.4 g, 76%). Subsequently **2j** (1 g, 0.004 mol) was converted to **5k** (0.9 g, 57%) under conditions similar to those used for **2e**. Physical data, see Table I.

2-Acetyl-4-chlorosulfonyl-7-hydroxybenzo[*b*]furan (61) The hydroxy compound (**1**, 10.0 g, 0.057 mol) was added to chlorosulfonic acid (30 ml) in portions at 25 °C. The mixture was stirred for 1.5 h at 25 °C and poured into ice-water. Extraction with ethyl acetate was washed with brine and dried over Na_2SO_4. Removal of the ethyl acetate under reduced pressure gave a pale yellow powder (crude **61**, 11.6 g, 74%). ^{1}H-NMR (acetone-d_6) δ: 2.71 (3H, s, CH_3), 7.24 (1H, d, 6-H), 7.91 (1H, s, 3-H), 8.01 (1H, d, 5-H). MS *m/z*: 274 (M^+), 259, 239, 175.

4-(2-Acetyl-7-hydroxybenzo[*b*]furanyl)sulfonic Acid (80) A mixture of crude **61** (0.7 g, 0.003 mol) and water (50 ml) was stirred for 1 h at 70 °C. The solution was filtered and the filtrate was evaporated off under reduced pressure to give a colorless powder (crude **80**, 0.6 g, 92%). ^{1}H-NMR (DMSO-d_6) δ: 2.56 (3H, s, $COCH_3$), 6.97 (1H, d, 5-H), 7.51 (1H, d, 6-H), 7.92 (1H, s, 3-H). IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1683 (C=O), 1175 ($\nu_{as}$ SO_2), 1041 ($\nu_s SO_2$), 696 (νSO). MS: not detectable.

2-Acetyl-7-hydroxy-4-nitrobenzo[*b*]furan (81) Nitric acid (2 ml, *d*=1.42) was added to a mixture of **80** (0.6 g, 0.002 mol) and 5 N H_2SO_4 (11 ml) at 12 °C. The mixture was stirred for 10 min at 50 °C and extracted with ethyl acetate. Removal of the solvent gave a yellow powder which was recrystallized from dimethyl sulfoxide to afford pale yellow prisms (**81**, 0.37 g, 71%). The ^{1}H-NMR spectrum of the prisms was identical with that of an authentic sample.[10]

2-Acetyl-4-carboxylmethylsulfamoyl-7-hydroxybenzo[*b*]furan (63) Compound **61** (3.0 g, 0.011 mol) was converted to **63** (2.0 g, 57%) under conditions similar to those used for **3e**. Physical data, see Table I.

2-Acetyl-4-carboxymethylsulfamoyl-7-methylbenzo[*b*]furan (10a) A mixture of 3-methylsalicylaldehyde (3.1 g, 0.023 mol), chloroacetone (2.7 g, 0.030 mol), K_2CO_3 (6.3 g, 0.046 mol) and acetone (35 ml) was refluxed for 5 h. After usual work up, the product was purified by distillation under reduced pressure to give 2-acetyl-7-methylbenzo[*b*]furan (**7a**, 3.3 g, 83%), $bp_{0.7}$ 147—150 °C. ^1H-NMR (CCl_4) δ: 2.45 (3H, s, CH_3 or $COCH_3$). 2.48 (3H, s, $COCH_3$ or CH_3), 6.85—7.27 (3H, m, 4-, 5-, 6-H), 7.13 (1H, m, 3-H). MS *m/z*: 174 (M^+), 159, 131. Subsequently **7a** (2.7 g, 0.016 mol) was converted to **10a** (2.2 g, 41%) under conditions similar to those used for **2e**. Physical data, see Table I.

2-Acetyl-7-*sec*-butyl-4-carboxymethylsulfamoylbenzo[*b*]furan (10b) 2-*sec*-Butylphenol was treated with chloromethyl methyl ether to give the corresponding methoxymethyl ether. The ether was reacted with *N,N,N′,N′*-tetramethylethylenediamine to afford the formyl compound. The formyl compound was treated with *p*-toluenesulfonic acid to give 3-*sec*-butylsalicylaldehyde (**6b**) (bp_{20} 128—131 °C, 43% overall yield). A mixture of **6b** (5.2 g, 0.029 mol), chloroacetone (3.5 g, 0.038 mol), K_2CO_3 (6.0 g, 0.044 mol) and acetone (50 ml) was refluxed for 5 h. After usual work up, the product was purified by column chromatography (SiO_2, hexane) to give **7b**. ^1H-NMR (CCl_4) δ: 0.80 (3H, t, $CH_2C\underline{H}_3$), 1.36 (3H, d, $CHC\underline{H}_3$), 1.70 (2H, m, CH_2). 2.41 (3H, s, $COCH_3$), 3.07 (1H, m, CH), 6.84—7.33 (4H, m, 3-, 4-, 5-, 6-H). MS *m/z*: 216 (M^+), 187. Subsequently **7b** (3 g, 0.014 mol) was converted to **10b** (1.8 g, 37%) under conditions similar to those used for **2e**. Physical data, see Table I.

2-Acetyl-4-carboxymethylsulfamoyl-5,6-methylenedioxybenzo[*b*]furan (16) 4,5-Methylenedioxysalicylaldehyde (**12**) was obtained from 3,4-methylenedioxyphenol (**11**) by means of the Vilsmeier reaction. A mixture of **12** (0.83 g, 0.005 mol), chloroacetone (0.6 g, 0.007 mol), K_2CO_3 (0.8 g, 0.006 mol), acetone (20 ml), and DMF (2 ml) was refluxed for 3 h. After usual work-up, the product was recrystallized from isopropyl alcohol to give prisms (**13**, 0.85 g, 83%). mp 156—157.5 °C. ^1H-NMR (DMSO-d_6) δ: 2.40 (3H, s, CH_3), 5.90 (2H, s, CH_2), 6.94 (1H, s, 4-H), 7.04 (1H, s, 7-H), 7.43 (1H, s, 3-H). Subsequently **13** (0.85 g, 0.004 mol) was converted to **16** (0.45 g, 32%) under conditions similar to those used for **2e**. Physical data, see Table I. A long-range coupling between 3-H and 7-H, with $J = 0.5$ Hz, was confirmed in the ^1H-NMR spectrum of **16**.

2-Acetyl-7-carboxymethylsulfamoyl-4-methoxybenzo[*b*]furan (20) 2-Acetyl-4-methoxybenzo[*b*]furan (**17**)[19] (2.7 g, 0.014 mol) was converted to **20** (1.2 g, 25%) under conditions similar to those used for **2e**. Physical data, see Table I.

2-Carboxy-4-carboxymethylsulfamoyl-7-methoxybenzo[*b*]furan (25) A mixture of 2-carboxy-7-methoxybenzo[*b*]furan (**21**)[20] and 10% HCl–methanol was stirred for 70 h at 25 °C. After usual work-up, 2-carbomethoxy-7-methoxybenzo[*b*]furan (**22**) (yellow needles) was obtained. ^1H-NMR ($CDCl_3$) δ: 3.84 (3H, s, $COOCH_3$ or OCH_3), 3.90 (3H, s, OCH_3 or $COOCH_3$), 6.70—7.30 (4H, m, 3-, 4-, 5-, 6-H). Subsequently **22** (6.3 g, 0.031 mol) was converted to **25** (2.3 g, 23%) under conditions similar to those used for **2e**. Physical data, see Table I.

2-Carboxy-7-carboxymethoxy-4-carboxymethylsulfamoylbenzo[*b*]furan (30) A mixture of 2-carboxy-7-hydroxybenzo[*b*]furan (**26**),[20] ethyl bromoacetate, K_2CO_3 and DMF was stirred for 40 h at 28 °C. After usual work-up, 2-ethoxycarbonylmethoxycarbonyl-7-ethoxycarbonylmethoxybenzo[*b*]furan (**27**) was obtained. ^1H-NMR ($CDCl_3$) δ: 1.16 (3H, t, CH_3), 1.19 (3H, t, CH_3), 4.10 (4H, q, $C\underline{H}_2CH_3 \times 2$), 4.69 (2H, s, OCH_2), 4.72 (2H, s, OCH_2), 6.68—7.25 (4H, m, 3-, 4-, 5-, 6-H). Subsequently **27** (8 g, 0.023 mol) was converted to **30** (1.8 g, 21%) under conditions similar to those used for **2e**. Physical data, see Table I.

2-Carboxy-4-carboxymethylsulfamoyl-7-ethoxybenzo[*b*]furan (36) A mixture of 2-acetyl-7-ethoxybenzo[*b*]furan (**2b**), SeO_2 and pyridine was stirred for 2 h. After usual work-up, 2-carboxycarbonyl-7-ethoxybenzo[*b*]furan (**31**) was obtained. This compound (**31**) was treated with NH_2OH–HCl to give the oxime (**32**). A solution of **32** in acetic anhydride was heated at 60 °C for 0.5 h. Removal of acetic anhydride gave 2-cyano-7-ethoxybenzo[*b*]furan (**33**). ^1H-NMR ($CDCl_3$) δ: 1.46 (3H, t, CH_2), 4.13 (2H, q, CH_2), 7.05—7.15 (3H, m, 4-, 5-, 6-H), 7.29 (1H, s, 3-H). IR ν_{max}^{KBr} cm^{-1}: 2240 (CN). The nitrile (**33**) (1 g, 0.005 mol) was treated with chlorosulfonic acid followed by treatment with glycine ethyl ester–HCl under conditions similar to those used for **2e** to give 2-cyano-4-ethoxycarbonylmethylsulfamoyl-7-ethoxybenzo[*b*]furan (**35**) (0.6 g, 36%). ^1H-NMR (DMSO-d_6) δ: 0.94 (3H, t, $COOCH_2C\underline{H}_3$), 1.34 (3H, t, $OCH_2C\underline{H}_3$), 2.54 (2H, brs, $NHC\underline{H}_2$), 3.71 (2H, q, $COOC\underline{H}_2CH_3$), 4.16 (2H, q, $OC\underline{H}_2CH_3$), 7.08 (1H, d, 6-H), 7.56 (1H, d, 5-H), 8.04 (1H, s, 3-H), 8.15 (1H, brs, NH). MS *m/z*: 352 (M^+), 279, 250, 222. mp 139—141 °C. A suspension of **35** (1.4 g, 0.024 mol) in 2 N aqueous NaOH solution was stirred at 27 °C for 1.5 h. After neutralization with 1 N HCl, the mixture was extracted with ethyl acetate. Removal of ethyl acetate gave a yellow powder, which was recrystallized from ethyl acetate to give pale yellow prisms (**36**) (0.85 g, 62%) Physical data, see Table I.

4,6-Bis(carboxymethylsulfamoyl)-2-ethyl-7-methoxybenzo[*b*]furan (40) Preparation of **40** was carried out by same procedure as used for **2e**. Treatment of **37**(3.7 g, 0.021 mol) with chlorosulfonic acid (19.0 g, 0.163 mol) gave **38** (6.1 g, 78%). The dichlorosulfonyl compound (**38**) (6.1 g, 0.016 mol) was treated with glycine ethyl ester–HCl (5.0 g, 0.036 mol) to give **39** (6.5 g, 80%). The diester (**39**) (6.5 g, 0.013 mol) was treated with 1 N aqueous NaOH solution (35 ml) to afford **40** (4.5 g, 78%). Physical data, see Table I.

3-Carboxymethylsulfamoyl-2-ethyl-5-nitrobenzo[*b*]furan (44) Compound **41** (1.8 g, 0.009 mol) was converted to **44** (1.5 g, 47%) under conditions similar to those used for **2e**. Physical data, see Table I.

5-Acetylamino-3-carboxymethysulfamoyl-2-ethylbenzo[*b*]furan (48) Catalytic reduction of **41** in acetic anhydride afforded acetylamino compound (**45**). Subsequently **45** (2.3 g, 0.011 mol) was converted to **48** (1.9 g, 51%) under conditions similar to those used for **2e**. Physical data, see Table I.

4,6-Bis(carboxymethylsulfamoyl)-7-methoxy-2-(5-methyl-2,4-dioxoimidazolidin-5-yl)benzo[*b*]furan (52) A mixture of **2a** (10.5 g, 0.055 mol), NH_4CO_3 (20 g, 0.256 mol), NaCN (3.2 g, 0.065 mol), and 60% EtOH (100 ml) was stirred for 2 h at 60 °C. Cooling of the mixture gave a yellow powder, which was recrystallized from ethyl acetate to give **49** (6.4 g, 45%). ^1H-NMR (DMSO-d_6) δ: 1.65 (3H, s, CH_3), 3.69 (3H, s, OCH_3), 6.50—6.85 (4H, m, 3-, 4-, 5-, 6-H), 8.20 (2H, brs, NH × 2). MS *m/z*: 260 (M^+), 245, 189, 174. mp 202—204 °C. Compound **49** (3.0 g, 0.012 mol) was added to chlorosulfonic acid at −5 °C and the mixture was stirred for 5 h at 5 °C, then poured into ice-water and extracted with ethyl acetate. Removal of ethyl acetate gave crude **50** (4.4 g, 83%). ^1H-NMR (DMSO-d_6) δ: 1.12 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 6.78 (1H, s, 3-H), 7.73 (1H, s, 5-H), 8.46 (2H, brs, NH × 2). MS *m/z*: 456 (M^+), 421, 385, 350. Triethylamine (13.4 g, 0.133 mol) was added to a mixture of **50** (8.5 g, 0.019 mol), glycine *tert*-butyl ester-HCl (9.3 g, 0.057 mol) and CH_2Cl_2 (350 ml) at 25 °C and the mixture was stirred for 5 h at 27 °C. After usual work-up, a colorless powder was obtained. The powder was recrystallized from ethanol to give the diester (**51**) (9.6 g, 78%). ^1H-NMR (acetone-d_6) δ: 1.23 (18H, s, $C(CH_3)_3 \times 2$), 1.83 (3H, s, CH_3), 3.55 (4H, d, $NHCH_2 \times 2$), 4.27 (3H, s, OCH_3), 7.07 (1H, s, 3-H), 7.75 (1H, s, 5-H). A mixture of **51** (6.8 g, 0.011 mol) and TFA (30 ml) was stirred for 1.5 h at 20 °C. After concentration under reduced pressure, the product was extracted with ether. Removal of the solvent gave a colorless powder, which was recrystallized from ethanol to give colorless prisms (**52**) (3.9 g, 70%). Physical data, see Table I.

4-Carboxymethylsulfamoyl-7-methoxy-2-(5-methyl-2,4-dioxoimidazolidin-5-yl)benzo[*b*]furan (55) Triethylamine (1.6 g, 0.016 mol) was added to a mixture of 2-acetyl-4-chlorosulfonyl-7-methoxybenzo[*b*]furan (**3a**) (1.7 g, 0.006 mol), glycine *tert*-butyl ester–HCl (1.8 g, 0.009 mol) and CH_2Cl_2 (75 ml) at 27 °C. The mixture was stirred for 7 h at 27 °C. After usual work-up, the product was recrystallized from ethanol to give colorless needles (**53**) (1.7 g, 75%). ^1H-NMR (DMSO-d_6) δ: 1.17 (9H, s, $CH_3 \times 3$), 2.53 (3H, s, $COCH_3$), 3.57 (2H, brs, CH_2), 3.94 (3H, s, OCH_3), 6.65 (1H, brs, NH), 6.94 (1H, d, 6-H), 7.48 (1H, d, 5-H), 7.66 (1H, s, 3-H). MS *m/z*: 383 (M^+), 282, 253. A mixture of **53** (1.0 g, 0.003 mol), NH_4CO_3 (2.7 g, 0.035 mol), NaCN (2.6 g, 0.053 mol) and 60% EtOH (18 ml) was stirred for 5 h at 65 °C. After neutralization, the mixture was extracted with ethyl acetate. Removal of the ethyl acetate gave crude **54** (yellow powder, 0.9 g, 75%). MS *m/z*: 367 (M^+). A mixture of **54** (0.9 g, 0.002 mol) and TFA (25 ml) was stirred for 2 h at 20 °C, then evaporated. The product was recrystallized from ethyl acetate–petroleum benzine (3 : 2) to give pale yellow plates (**55**) (0.34 g, 43%). Physical data, see Table I.

2-Acetyl-4-(*N*-carboxymethyl-*N*-methylaminosulfonyl)-7-butyloxybenzo[*b*]furan (58) *N*-methylglycine (20 g, 0.224 mol) was added to a mixture of methanol (100 ml) and thionyl chloride (68 ml, 0.246 mol) at −16 °C. The solution was stirred for 2 h at 55 °C and evaporated under reduced pressure to give *N*-methylglycine methyl ester–HCl (28.8 g, 92%, colorless powder). MS *m/z*: 103 (M^+), 44. Triethylamine (2 g, 0.020 mol) was added to a mixture of **3d** (2.7 g, 0.008 mol), *N*-methylglycine methyl ester–HCl (1.9 g, 0.014 mol) and CH_2Cl_2 (50 ml) at 26 °C and the mixture was stirred for 4 h at 35 °C. After usual work-up, the product was recrystallized from cyclohexane–ethyl acetate (4 : 1) to give plates (**57a**) (1.4 g, 43.1%). ^1H-NMR (DMSO-d_6) δ: 0.96 (3H, t, $C\underline{H}_3CH_2CH_2CH_2$), 1.15—1.95 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 2.55 (3H, s, $COCH_3$), 2.75 (3H, s, NCH_3), 3.43 (3H, s, $COOCH_3$), 3.97 (2H, s, NCH_2), 4.17 (2H, t, OCH_2), 7.07 (1H, d, 6-H), 7.52 (1H, d, 5-H), 7.70 (1H, s, 3-H). MS *m/z*: 397 (M^+), 338, 295. A mixture of **57a** (0.8 g, 0.002 mol) and 2 N aqueous NaOH solution (8.5 ml) was stirred for 1 h at 23 °C. After work-up, the product was recrystallized from ethanol to give pale yellow prisms (**58**) (0.5 g, 65%). Physical data, see Table I.

2-Acetyl-7-butyloxy-4-(1-carboxyethylaminosulfonyl)benzo[*b*]furan (59) The chlorosulfonyl compound (**3d**) was treated with L-alanine ethyl ester–HCl under the conditions similar to those used for preparation of **58** to give **57b**. MS *m*/*z*: 411 (M^+), 338, 295. The ester (**57b**) was treated with aqueous 2 N NaOH solution to give the acid (**59**). Physical data, see Table I.

2-Acetyl-7-butyloxy-4-[*N*-(1-carboxyethyl)-*N*-methylaminosulfonyl]-benzo[*b*]furan (60) The chlorosulfonyl compound (**3d**) was treated with *N*-methyl-L-alanine methyl ester–HCl under conditions similar to those used for preparation of **58** to give **57c**. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, $C\underline{H}_3CH_2CH_2CH_2$), 1.31 (3H, d, CH_3CH), 1.33—1.90 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 2.56 (3H, s, $COCH_3$), 2.73 (3H, s, NCH_3), 3.36 (3H, s, $COOCH_3$), 4.14 (2H, t, OCH_2), 4.65 (1H, q, CH), 6.73 (1H, d, 6-H), 7.47 (1H, d, 5-H), 7.60 (1H, s, 3-H). MS *m*/*z*: 411 (M^+), 352, 295. The ester (**57c**) was treated with 2 N aqueous NaOH solution to give the acid (**60**). Physical data, see Table I.

Enzyme Inhibitory Activity Aldose reductase activity was measured by the method of Hoyman and Kinoshita.[21] Assays were performed at 30 °C in 0.1 M sodium phosphate buffer (pH 6.2) containing 1.5 mM DL-glyceraldehyde, 0.25 mM reduced nicotinamide adenine diphosphate (NADPH) and an appropriate amount of enzyme (supernatant of homogenates of rat lens) in a total volume of 1.5 ml. The effect of an inhibitor on the enzyme activity was determined by adding 15 μl of dimethylsulfoxide solution of a test compound to the reaction mixture. The concentration of the inhibitor giving 50% inhibition of enzyme activity (IC_{50}) was estimated from the least-squares regression line in the plot of the logarithm of inhibition concentration versus remaining activity.

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