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Synthesis and glycogen phosphorylase inhibitor activity of 2,3-dihydrobenzo[1,4]dioxin derivatives

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Abstract—Novel 5-benzyl and 5-benzylidene-thiazolidine-2,4-diones carrying 2,3-dihydrobenzo[1,4]dioxin pharmacophore were synthesized and their glycogen phosphorylase inhibitor activity was also studied.

1. Introduction

In the last decades the number of patients diagnosed with diabetes dramatically increased and approximately 6–10% of the adult population suffer from this disease in Western societies. Diabetes can be divided into two basic types depending on whether the patient secretes insulin or not: Type I or insulin dependent diabetes mellitus and Type II or non-insulin dependent diabetes mellitus (NIDDB). Ninety percent of the diabetics belong to NIDDB which can be controlled mainly by restriction of caloric intake and by use of hypoglycemic agents.[1] The most commonly used oral hypoglycemics are sulfonylurea drugs which increase insulin secretion but they can also induce serious hypoglycemia.[2,3] Recent developments of new hypoglycemic agents are focused on the synthesis of peroxisome proliferator-activated (PPAR) receptor agonists[4–8] and glycogen phosphorylase (GP) inhibitors.[9–13]

PPARs belong to the nuclear receptor superfamily[14] and they play important roles in regulation of proliferation and differentiation of several cell types. Its activation by thiazolidine-2,4-dione derivatives **1**–**5**[15–19] (called glitazones) (Fig. 1) results in insulin sensibilization and antidiabetic action.

Among related compounds Troglitazone (**2**) was put on the market in the USA and Japan in 1997. Although it was withdrawn in the early 2000s due to its hepatotoxicity, clinical development of other glitazones is still in progress.[20]

Glycogen phosphorylase (GP) is a key enzyme in the regulation of blood sugar level, and it catalyzes the

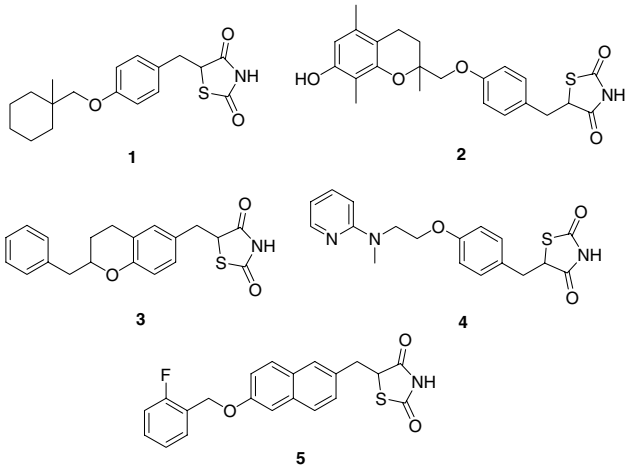

Figure 1. Structures of some glitazones.

Keywords: 2,3-Dihydrobenzo[1,4]dioxin; Glyogen phosphorylase; Diabetes; Glitazones.
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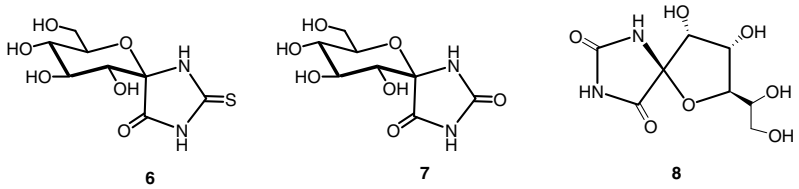


Figure 2. Structures of some glycogen phosphorylase inhibitors.

formation of glucose-1-phosphate from glycogen.[12] Because of the biological importance in the glycogen metabolism, GP has been exploited as a possible molecular target for potent inhibitors that may be relevant to the control of blood glucose concentrations in Type II diabetes.[21] Since several GP inhibitors **6**–**8** (Fig. 2) carry a hydantoin or thiohydantoin moiety,[22,23] we assumed that glitazone-type molecules may also have glycogen phosphorylase inhibitor activity.

Numerous pharmacologically active molecules **9**–**12** (Fig. 3) possess a 2,3-dihydrobenzo[1,4]dioxin moiety.[24–27] This type of molecules has been widely applied in the design of therapeutic agents with α-adrenergic blocking,[24] 5-HT_{1A} antagonist,[25,26] and antihepatotoxic[27] properties. Although several glitazones with dihydrobenzopyran or dihydrobenzofuran ring system were synthesized earlier and tested as hypoglycemic agents,[28] interestingly until now only a few 2,3-dihydrobenzo[1,4]-dioxin analogues of troglitazone were tested.[29]

In continuation of our study on the synthesis of biologically active *O*-heterocyclic compounds[30–32] several 5-benzyl- and 5-benzylidene-thiazolidine-2,4-diones carrying a 2,3-dihydrobenzo[1,4]dioxin moiety were synthesized and tested for GP inhibitor activity.

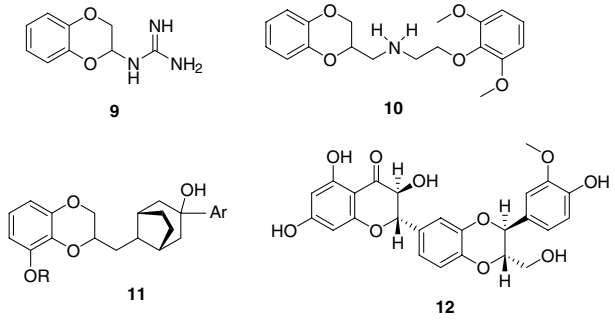


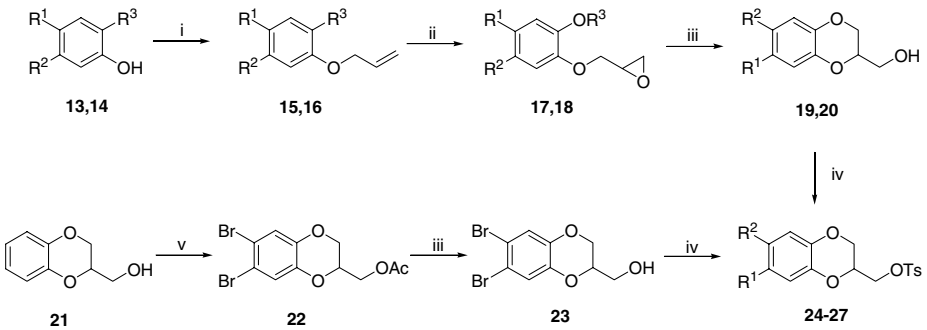
Figure 3. Structures of some biologically active 2,3-dihydribenzo[1,4]-dioxin derivatives.

2. Chemistry

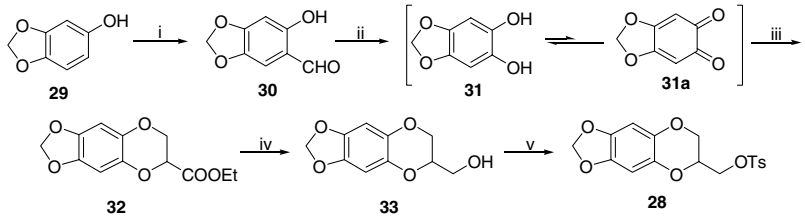
The synthesis of 2-hydroxymethyl-2,3-dihydrobenzo[1,4]- dioxins **19**–**21**, **23**, **33** is shown in Schemes 1 and 2 as well as in Table 1. Our synthetic approach—except for **21**, **23** and **33**—was based on the transformation of 1-(2-hydroxyphenyl)ethanones **13** and **14** into the corresponding 2-hydroxymethyl-2,3-dihydrobenzo[1,4]-dioxins **19** and **20**. In the first step 1-(2-allyloxyphenyl)ethanones **15** and **16** were obtained by simple alkylation of **13** and **14**, respectively, with allyl bromide in the presence of potassium carbonate in dry DMF at 80 °C. Bayer–Villiger oxidation[33] and epoxidation with mCPBA in $CHCl_3$ gave the epoxides **17** and **18** in good yields (80% and 71%) which were then reacted with NaOMe/MeOH to furnish the 2,3-dihydrobenzo[1,4]dioxins **19** and **20** in moderate yields (45% and 65%).

2-Hydroxymethyl-2,3-dihydrobenzo[1,4]dioxin (**21**)[34] served as a suitable starting material for the synthesis of **23**. Bromination of **21** with bromine in acetic acid in the presence of $AlCl_3$ afforded **22**, whose saponification with NaOMe/MeOH gave **23** in a moderate overall yield (45%). The synthesis of **33** was based on the Dakin oxidation of the aldehyde **30** (Scheme 2).[32]

Aldehyde **30** was prepared from sesamol **29** by a simple formylation using paraformaldehyde as the formylating agent in the presence of dry magnesium chloride and triethylamine in dry THF.[35] Oxidation of **30** did not serve the pirocatechin derivative **31** as a product under the well-known conditions of Dakin oxidation. However using triethylamine as the solvent oxidation of **30** at low



Scheme 1. Reagents and conditions: (i) allyl bromide/K_2CO_3/DMF, 80 °C; (ii) MCPBA/$CHCl_3$, reflux; (iii) NaOMe/MeOH, rt; (iv) TsCl/pyridine, rt; (v) Br_2; $AlCl_3$/AcOH.



Scheme 2. Reagents and conditions: (i) $(CHO)_n$, $MgCl_2/Et_3N$, THF, reflux; (ii) H_2O_2/Et_3N, 5 °C; (iii) ethyl dibromopropionate, K_2CO_3/acetone, reflux; (iv) $LiAlH_4$/dry ether; (v) TsCl/dry pyridine.

Table 1. List of the substituents of compounds **13**–**27** (Scheme 2)

Compound	R^1	R^2	R^3
13, **15**, **17**	Br	H	$COCH_3$
14, **16**, **18**	H	Br	$COCH_3$
19, **24**	Br	H	—
20, **25**	H	Br	—
26	Br	Br	—
27	H	H	—

temperature (5 °C) gave the desired product **31** which was transformed into the ester derivative **32** without purification in a moderate yield (58%). In the following step reduction of **32** with $LiAlH_4$ resulted in the 2-hydroxymethyl-2,3-dihydrobenzo[1,4]-dioxin **33** in 88% yield.

Treatment of the appropriate benzo[1,4]dioxins **19**, **20**, **23**, and **33** with 4-methylbenzenesulfonyl chloride (TsCl) in dry pyridine afforded the desired tosylates **24**–**28** with good yields (75–90%).

Using these tosylates **24**–**28** as starting materials, glitazones having a 2,3-dihydrobenzo[1,4]dioxin moiety were prepared in three steps (Scheme 3 and Table 2).

Reaction of the tosylates **24**–**28** with 4-hydroxybenzaldehyde or vanillin in the presence of potassium carbonate in DMF gave **34**–**43** in good to excellent yields (72–99%). Condensation of these compounds with thiazolidine-2,4-dione was carried out under solvent-free conditions by melting in the presence of sodium acetate. The desired products **44**–**53** could be isolated during a work up procedure by simple filtration in good yields (57–89%). It is known from the literature that 5-benzylidene-thiazolidine-2,4-diones can be transformed into the corresponding 5-benzyl derivatives by reduction with lithium borohydride in pyridine and tetrahydrofuran.[36] Surprisingly, under these circumstances no transformation of the benzylidene derivatives **44**–**53** could be detected. At the same time, catalytic hydrogenation of **46**, **48**, **51**, and **53** in acetic acid at high pressure (12 atm) resulted in the 5-benzyl-thiazolidine-2,4-diones **54**–**57** in good yields (65–86%).

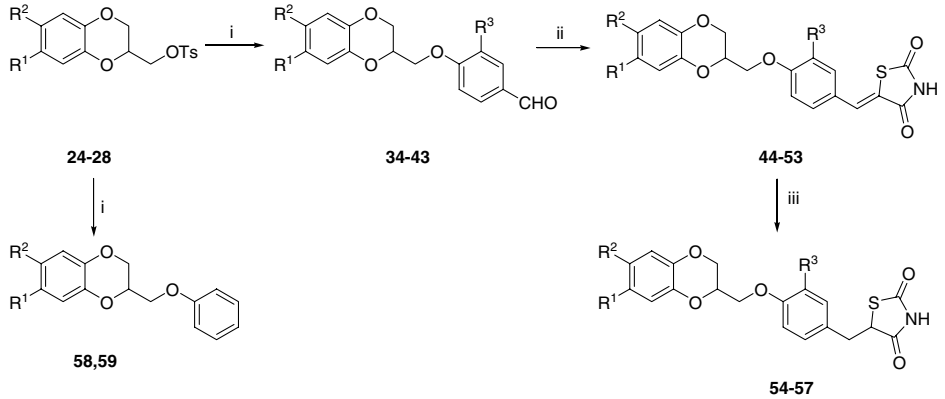
Table 2. List of the substituents of compounds **24**–**59** (Scheme 3)

Compound	R^1	R^2	R^3
24, **34**, **44**	Br	H	H
39, **49**	Br	H	OMe
25, **35**, **45**	H	Br	H
40, **50**	H	Br	OMe
26, **36**, **46**, **54**	O–CH_2–O		H
41, **51**, **56**	O–CH_2–O		OMe
27, **37**, **47**	Br	Br	H
42, **52**	Br	Br	OMe
28, **38**, **48**, **55**	H	H	H
43, **53**, **57**	H	H	OMe
58	H	H	—
59	Br	Br	—

3. Biology

3.1. Assays

Phosphorylase activities were assayed in the direction of the glycogen synthesis at 30 °C with 10 μg/ml enzyme, 1% glycogen in the absence of AMP (muscle or liver



Scheme 3. Reagents and conditions: (i) 4-hydroxybenzaldehyde or vanillin or phenol/K_2CO_3/DMF, 80 °C; (ii) thiazolidine-2,4-dione, NaOAc, 140 °C; (iii) H_2/Pd(C), AcOH, 12 atm.

phosphorylase a), or in the presence of AMP (1 mM AMP for muscle and 2 mM AMP for liver phosphorylase b), with or without the substrate in 50 mM triethanolamine/HCl (pH 6.8) buffer, 100 mM KCl, 1 mM dithiothreitol, and 1 mM EDTA. The kinetic studies were performed as described previously[37] except that higher D-glucose-1-phosphate concentrations were used for the assay of liver phosphorylases as suggested by Stalmanas and Hers.[38] The results are summarized in Table 3.

Due to the low solubility of the tested compounds the K_i value could be determined only in the case of **45**, **47**, and **52** (Table 3). These data clearly indicated that 2,3-dihydrobenzo[1,4]dioxin derivative **47** possesses a comparable GP inhibitor activity with that of **6** [K_i (GPb) = 5.1 μM] and **7** [K_i (GPb) = 4.2 μM] (all three compounds were tested in the same assay conditions).[22] Moreover as we assumed the glitazone-type molecules have glycogen phosphorylase inhibitor activity.

4. Experimental

Analytical TLC was performed on Kieselgel 60 plates F_{254} (Merck). The reagents were purchased from Sigma–Aldrich. For workup the solutions were dried ($MgSO_4$) and concentrated in vacuo. ^{1}H NMR spectra were recorded on a Bruker WP-200 spectrometer. The chemical shifts are given in δ (ppm) and the spin–spin coupling constants (J) in Hz. HRMS were recorded in FAB mode (glycerol) on a VG 70HS MS spectrometer.

4.1. General procedure for the preparation of 15 and 16

To the stirred solution of the substituted 1-(2-hydroxyphenyl)ethanones (42 mmol) in dry DMF (80 cm^3) 7.3 g K_2CO_3 and 4.4 cm^3 allyl bromide were added and stirring was continued for 24 h at 80 °C. The reaction mixture was then poured into 10washed with water, and dried.

Table 3. Study of GP inhibitor activities of 2.3-dihydrobenyo[1,4]dioxin derivatives **44**–**59**

Entry		K_i (GPa)	K_i (GPb)	IC_{50}
1	**44**[a]	—	—	—
2	**45**	—	80 μM	—
3	**46**[a]	—	—	—
4	**47**	10 μM	12 μM	—
5	**48**[b]	—	—	—
6	**49**	—	—	2 mM
7	**50**[a]	—	—	—
8	**51**[a]	—	—	—
9	**52**	9 μM	30 μM	—
10	**53**[a]	—	—	—
11	**54**	—	—	7 mM
12	**55**[b]	—	—	—
13	**56**[a]	—	—	—
14	**37**	—	—	550 μM
15	**38**	—	—	>5 mM
16	**58**	—	—	>5 mM
17	**59**	—	—	560 μM

[a] Insoluble.
[b] ~20% inhibition at 625 μM concentration.

4.1.1. 1-(2-Allyloxy-5-bromophenyl)ethanone (15). White crystals; yield: 87%; mp: 54–56 °C; ^{1}H NMR: δ (ppm): 2.62 (3H, s, CH_3), 4.62 (2H, dt, J = 1.33 and 5.24 Hz, OCH_2); 5.32 (1H, dq, J = 1.33 and 10.44; CH_{2A}); 5.42 (1H, dq, J = 1.33 and 17.23, CH_{2B}); 6.06 (1H, m, J = 5.24, 10.44 and 17.23, CH); 6.86 (1H, d, 8.86, H-3′); 7.52 (1H, dd, J = 2.65 and 8.86, H-4′); 7.83 (1H, d, J = 2.65, H-6′). HRMS m/z 253.9938 (calcd for $C_{11}H_{11}BrO_2$: 253.9942).

4.1.2. 1-(2-Allyloxy-4-bromophenyl)ethanone (16). White crystals; yield 90%; mp: 65–67 °C; ^{1}H NMR: δ (ppm): 2.6 (3H, s, CH_3), 4.61 (2H, dt, J = 1.20 and 5.38 Hz, OCH_2); 5.34 (1H, dq, J = 1.20 and 10.4, CH_{2A}); 5.42 (1H, dq, J = 1.20 and 17.3, CH_{2B}); 6.06 (1H, m, J = 5.38, 10.40 and 17.3, CH); 7.1 (1H, d, J = 1.7, H-3′); 7.15 (1H, dd, J = 1.7 and 8.59, H-5′); 7.61 (1H, d, J = 8.59, H-6′). HRMS m/z 253. 9940 (calcd for $C_{11}H_{11}BrO_2$: 253.9942).

4.2. General procedure for the preparation of 17 and 18

A solution of the allyl-ethers (**15**–**16**) (17 mmol) and MCPBA (77%, 2.5 equiv) in chloroform was boiled under reflux and the progress of the reaction was monitored by HPLC and ^{1}H NMR spectroscopy. After cooling, the reaction mixture was washed with saturated $NaHSO_3$ solution, saturated $NaHCO_3$ solution and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography on silica gel.

4.2.1. [5-Bromo-2-(2,3-epoxypropenyloxy)phenyl]-acetate (17). Mp: 44–47 °C ^{1}H NMR: δ (ppm): 2.3 (3H, s, CH_3), 2.70 (1H, dd, J = 2.63 and 4.87, CH_{2A}); 2.87 (1H, t, J = 4.87, CH_{2B}); 3.28 (1H, m, CH); 3.88 (1H, dd, J = 5.73 and 11.19, OCH_{2A}); 4.24 (1H, dd, J = 2.63 and 11.19, OCH_{2B}); 6.85 (1H, d, J = 8.74, H-6); 7.0–7.13 (2H, m, H-5, H-3). HRMS m/z 285.9843 (calcd for $C_{11}H_{11}BrO_4$: 285.9841).

4.2.2. [4-Bromo-2-(2,3-epoxypropenyloxily)phenyl]-acetate (18). Yield: 71%, yellow oil, ^{1}H NMR: δ (ppm): 2.3 (3H, s, CH_3), 2.68 (1H, dd, J = 2.63 and 4.86, CH_{2A}); 2.85 (1H, t, J = 4.61, CH_{2B}); 3.29 (1H, m, CH); 3.95 (1H, dd, J = 5.6 and 11.2, OCH_{2A}); 4.24 (1H, dd, J = 2.8 and 11.2, OCH_{2B}); 6.84 (1H, d, J = 8.74, H-3); 7.18 (1H, d, J = 2.34, H-6); 7.27 (1H, dd, J = 2.34 and 8.74, H-4). HRMS m/z 285.9839 (calcd for $C_{11}H_{11}BrO_4$: 285.9841).

4.3. General procedure for the preparation of 19 and 20

To the stirred solution of epoxyacetates (**17** and **18**) in dry methanol, 1 equiv of NaOMe was added. The progress of the reaction was monitored by TLC. The reaction mixture was acidified with aqueous HCl solution, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, and dried. Following evaporation, the residue was purified by column chromatography on silica gel.

4.3.1. 7-Bromo-2-hydroxymethyl-2,3-dihydrobenzo[1,4]-dioxin (19). Yield: 65%; mp: 54–57 °C, ^{1}H NMR: δ (ppm): 2.21 (1H, br s, OH); 3.7–4.4 (5H, m,); 6.27

(1H, d, J = 8.59, H-5); 6.95 (1H, dd, J = 2.3 and 8.59, H-6); 7.03 (1H, d, J = 2.3, H-8). HRMS m/z 243.9733 (calcd for $C_9H_9BrO_3$: 243,9735).

4.3.2. 6-Bromo-2-hydroxymethyl-2,3-dihydrobenzo[1,4]-dioxin (20). Yield: 45%; mp: 104–106 °C; ^{1}H NMR: δ (ppm): 1.94 (1H, s, OH); 3.7–4.4 (5H, m); 6.78 (1H, d, J = 8.56, H-8); 6.94 (1H, dd, J = 2.23 and 8.56, H-7); 7.03 (1H, d, J = 2.23, H-5). HRMS m/z 243.9732 (calcd for $C_9H_9BrO_3$: 243,9735).

4.3.3. 6,7-Dibromo-2-acetoxymethyl-2,3-dihydrobenzo-[1,4]dioxin (22). To a stirred solution of **21**[30] (3.2 g, 19.2 mmol) and $AlCl_3$ (200 mg) in acetic acid (50 cm^3), a solution of bromine (7.79 g, 48 mmol) in acetic acid (100 cm^3) was dropwise added at 0 °C and the mixture was stirred for eight hours. Then the reaction mixture was diluted with water and the precipitation filtered off. The product was washed with aqueous solutions of $NaHSO_3$ and $NaHCO_3$. Crystallization from methanol gave **22**, as white crystals (3.27 g, 53%, mp: 83–86 °C). ^{1}H NMR: δ (ppm): 2.1 (3H, s, CH_3CO); 4.02 (1H, dd, J = 6.78 and 11.54); 4.22–4.44 (4H, m); 7.15 (1H, s, H-5); 7.18 (1H, s, H-8). HRMS m/z 363.8948 (calcd for $C_{11}H_{10}Br_2O_4$: 363.8946).

4.3.4. 6,7-Dibromo-2-hydroxymethyl-2,3-dihydrobenzo-[1,4]dioxin (23). To a stirred solution of **22** (3.27g, 8.9 mmol) in dry methanol (120 cm^3), 1 ml of 1 M NaOMe was added at room temperature and stirred for 40 min. Subsequently the reaction mixture was acidified, diluted with water, extracted with ethyl acetate, and the organic layer was washed with saturated $NaHCO_3$ solution and dried. After evaporation of the solvent the residue was crystallized from hexane (2.48 g, 85%, mp: 88–90 °C). ^{1}H NMR: δ (ppm): 1.87 (1H, s, OH); 3.69–4.36 (5H, m); 7.15 (1H, s, H-5); 7.16 (1H, s, H-8). HRMS m/z 321.8837 (calcd for $C_9H_8Br_2O_3$: 321.8840).

4.3.5. 2-Hydroxy-4,5-methylenedioxybenzaldehyde (30). To a stirred solution of **29** (1.4 g, 10 mmol) in dry THF (50 cm^3), paraformaldehyde (2.1 g), dry magnesium chloride (1.4 g) and triethylamine (3.5 cm^3) were added. The reaction mixture was stirred at room temperature for 1 h and then boiled under reflux for two hours. The reaction mixture was poured onto water, acidified with 10% aqueous HCl solution. The organic layer was separated and the inorganic layer extracted with ethyl acetate (3 × 20 cm^3). The organic layer was washed with water and dried. Following evaporation the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 3:1) to give brown crystals (675 mg, 36%; mp: 125–127 °C). ^{1}H NMR: δ (ppm): 6.01 (2H, s, O–CH_2–O); 6.46 (1H, s, H-5); 6.86 (1H, s, H-8); 9.62 (1H, s, CHO); 11.79 (1H, s, OH). HRMS m/z 166.0264 (calcd for $C_8H_6O_4$: 166.0266).

4.3.6. Ethyl 6,7-methylenedioxy-2,3-dihydrobenzo[1,4]-dioxin-2-carboxylate (32). To a stirred suspension of **30** (11.5 g, 66 mmol) in dry triethylamine (100 cm^3), 18 cm^3, of 30% H_2O_2 was added dropwise during 1 h at 0 °C. The mixture was then concentrated and the residue (**31**) was dissolved in dry acetone (75 cm^3). Ethyl 1,2-dibromopropionate (20 g, 77 mmol) and K_2CO_3 were added and the reaction mixture was refluxed for 2 days. After filtration, acetone was evaporated and the residue was suspended with water. The suspension was extracted with the mixture of hexane and diethyl ether (ratio: 1:3; 5 × 25 cm^3) and dried. Evaporation of the solvent furnished a brown syrup which was purified by vacuum distillation (12.2 g; 58%; bp: 50–70 °C/0.5–1.5 Hgmm). ^{1}H NMR: δ (ppm): 1.25 (3H, t, J = 7.01, CH_3); 4.0–4.4 (4H, m, OCH_2 and 3-CH_2); 4.55 (1H, t, J = 3.5, H-2); 5.75 (2H, s, OCH_2O); 6.35 and 6.45 (2H, s, H-5 and H-8). HRMS m/z 252.0633 (calcd for $C_{12}H_{12}O_6$: 252.0634).

4.3.7. 6,7-Methylenedioxy-2-hydroxymethyl-2,3-dihydrobenzo[1,4]dioxin (33). To the stirred suspension of $LiAlH_4$ (0.9 g, 24 mmol) in dry ether (30 cm^3), a solution of **32** (5 g, 20 mmol) in dry ether (20 cm^3) was added dropwise during 30 min under nitrogen at room temperature. Then ethyl acetate and diluted H_2SO_4 were added to the reaction mixture (pH 4), the organic layer was separated, washed with water, and dried. After evaporation the residue was crystallized (3.7 g, 88%, 99–101 °C). ^{1}H NMR: δ (ppm): 1.20 ppm (1H, s, OH); 3.60–4.20 (5H, m; H-2, CH_2, O–CH_2–); 5.80 (2H, s, O–CH_2–O); 6.35 (2H, s, H-5 and H-8). HRMS m/z 210.0525 (calcd for $C_{10}H_{10}O_5$: 210.0528).

4.4. General procedure for the preparation of 24–28

To the stirred solution of the alcohols (7.36 mmol) in dry pyridine (25 cm^3) 1.6 g of 4-methylbenzenesulfonyl chloride (TsCl) was added and the mixture was stirred at room temperature for 12 h. Then the reaction mixture was poured into the mixture of crashed ice and diluted HCl. The precipitated product was filtered off, washed with water, and dried.

4.4.1. 7-Bromo-2-toluenesulfonyloxymethyl-2,3-dihydrobenzo[1,4]dioxin (24). Yield: 73%; mp: 78–83 °C; ^{1}H NMR: δ (ppm): 2.47 (3H, s, CH_3); 3.95–4.45 (5H, m, H-2, CH_2, O–CH_2–); 6.98 (1H, s, H-5); 7.09 (1H, s, H-8); 7.38 (2H, d, J = 8.15, H-tosyl); 7.65 (2H, d, J = 8.15, H-tosyl). HRMS m/z 397.9827 (calcd for $C_{16}H_{15}BrO_5S$: 397.9824).

4.4.2. 6-Bromo-2-toluenesulfonyloxymethyl-2,3-dihydrobenzo[1,4]dioxin (25). Yield: 85%; mp: 103–105 °C; ^{1}H NMR: δ (ppm): 2.43 (3H, s, CH_3); 3.91–4.4 (5H, m, H-2, CH_2, O–CH_2–); 6.64 (1H, d, J = 8.54, H-8); 6.89 (1H, dd, J = 2.27 and 8.54, H-7); 6.95 (1H, d, J = 2.27, H-5); 7.34 (2H, d, J = 8.33, H-tosyl); 7.74 (2H, d, J = 8.33, H-tosyl). HRMS m/z 397.9827 (calcd for $C_{16}H_{15}BrO_5S$: 397.9824).

4.4.3. 6,7-Dibromo-2-toluenesulfonyloxymethyl-2,3-dihydrobenzo[1,4]dioxin (26). Yield: 87%; mp: 94–97 °C; ^{1}H NMR: δ (ppm): 2.47 (3H, s, CH_3); 3.92–4.42 (5H, m, H-2, CH_2, O–CH_2–); 6.98 (1H, s, H-8); 7.09 (1H, H-5); 7.34 (2H, d, J = 8.34, H-tosyl); 7.76 (2H, d, J = 8.34, H-tosyl). HRMS m/z 475.8927 (calcd for $C_{16}H_{14}Br_2O_5S$: 475.8929).

4.4.4. 2-Toluenesulfonyloxymethyl-2,3-dihydrobenzo[1,4]-dioxin (27). Yield: 80%; mp: 71–73 °C; ^{1}H NMR: δ (ppm): 2.44 (3H, s, CH_3); 3.9–4.41 (5H, m, H-2, CH_2, O–CH_2–); 6.62–6.98 (5H, m, AR–H); 7.32 (2H, d, J = 8.28, H-tosyl); 7.76 (2H, d, J = 8.28, H-tosyl). HRMS m/z 320.0715 (calcd for $C_{16}H_{16}O_5S$: 320.0718).

4.4.5. 6,7-Methylenedioxy-2-toluenesulfonyloxymethyl-2,3-dihydrobenzo[1,4]dioxin (28). Yield: 92%; mp: 97–98 °C; ^{1}H NMR: δ (ppm): 2.45 (3H, s, CH_3); 3.90–4.40 (5H, m, H-2, CH_2, O–CH_2–); 5.80 (2H, s, O–CH_2–O); 6.28 and 6.34 (2H, s, H-5 and H-8); HRMS m/z 364.0619 (calcd for $C_{17}H_{16}O_7S$: 364.0617).

4.5. General procedure for the preparation of 34–43

The mixture of the tosylates **24**–**28** (6.25 mmol), 8.2 mmol of the hydroxyaldehyde, and 1,6 g K_2CO_3 in dry DMF (50 cm^3) was stirred at 80 °C. The progress of reaction was monitored by TLC (toluene/ethyl acetate = 4:1). Subsequently the reaction mixture was poured into cold water and extracted with ether. The organic phase was washed with aqueous $NaHCO_3$ solution and dried. After evaporation the residue was purified by column chromatography.

4.5.1. 4-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzaldehyde (34). Yield: 85.2%; mp: 86–88 °C; ^{1}H NMR: δ (ppm): 4.2–4.6 (5H, m); 6.77 (1H, d, J = 8.62, H-5); 6.96 (1H, dd, J = 2.22 and 8.62, H-6); 7.03 (2H, d, J = 8.7, H-3′, H-4′), 7.06 (1H, d, J = 2.2, H-8); 7.85 (2H, d, J = 8.7, H-2′, H-6′); 9.89 (1H, s, CHO). HRMS m/z 347.9999 (calcd for $C_{16}H_{13}BrO_4$: 347.9997).

4.5.2. 4-(6-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzaldehyde (35). Yield: 97%; mp: 126–129 °C; ^{1}H NMR: δ (ppm): 4.1–4.66 (5H, m); 6.77 (1H, d, J = 8.65, H-8); 6.96 (1H, dd, J = 2.4 and 8.65, H-7); 7.03 (2H, d, J = 8.46, H-3′, H-5′), 7.04 (1H, d, J = 2.4, H-8); 7.84 (2H, d, J = 8.46, H-2′, H-6′); 9.88 (1H, s, CHO). HRMS m/z 347.999 (calcd for $C_{16}H_{13}BrO_4$: 347.9997).

4.5.3. 4-(6,7-Methylenedioxy-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzaldehyde (36). Yield: 85%; mp: 160–161 °C; ^{1}H NMR: δ (ppm): 4.1–4.4 (4H, m); 4.5–4.65 (1H, m); 5.85 (2H, s, O–CH_2–O); 6.47 (1H, s, H-5); 6.48 (1H, s, H-8); 7.0 (2H, d, J = 8.73, H-3′, H-5′); 7.9 (2H, d, J = 8.73, H-2′, H-6′); 9.9 (1H, s, CHO). HRMS m/z 314.0791 (calcd for $C_{17}H_{14}O_6$: 314.0790).

4.5.4. 4-(6,7-Dibromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzaldehyde (37). Yield: 90%; mp: 117–120 °C; ^{1}H NMR: δ (ppm): 4.09–4.7 (5H, m); 7.02 (2H, d, J = 8.75; H-3′, H-5′); 7.17 (1H, s, H-5); 7.18 (1H, s, H-8); 7.85 (2H, d, J = 8.75, H-2′, H-6′); 9.9 (1H, s, CHO). HRMS m/z 425.9097 (calcd for $C_{16}H_{12}Br_2O_4$: 425.9102).

4.5.5. 4-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzaldehyde (38). Yield: 85%; mp: 60–62 °C; ^{1}H NMR: δ (ppm): 4.12–4.48 (4H, m); 4.49–4.65 (1H, m); 6.8–6.96 (4H, m, H-5′–H-8′); 7.0 ppm (2H, d, J = 8.75, H-3′, H-5′); 7.83 (2H, d, J = 8.75, H-2′, H-6′); 9.87 (1H, s, CHO). HRMS m/z 270.0887 (calcd for $C_{16}H_{14}O_4$: 270.0892).

4.5.6. 4-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxybenzaldehyde (39). Yield: 90.7%; mp: 88–90 °C; ^{1}H NMR: δ (ppm): 3.91 (3H, s, OCH_3), 4.24–4.64 (5H, m); 6.77 (1H, d, J = 8.62, H-5); 6.96 (1H, dd, J = 2.22 and 8.62, H-6); 7.01 (1H, d, J = 7.99, H-4′), 7.06 (1H, d, J = 2.2, H-8); 7.42–7.45 (2H, m, H-2′, H-6′); 9.86 (1H, s, CHO). HRMS m/z 378.0105 (calcd for $C_{17}H_{15}BrO_5$: 378.0103).

4.5.7. 4-(6-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxybenzaldehyde (40). Yield: 95%; mp: 129–129 °C; ^{1}H NMR: δ (ppm): 3.95 (3H, s, OCH_3), 4.16–4.46 (4H, m); 4.53–4.68 (1H, m); 6.77 (1H, d, J = 8.57), 6.91–7.06 (3H, m); 7.38–7.46 (2H, m); 9.9 (1H, s, CHO). HRMS m/z 378.0106 (calcd for $C_{17}H_{15}BrO_5$: 378.0103).

4.5.8. 4-(6,7-Methylenedioxy-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxybenzaldehyde (41). Yield: 99%; mp: 138–139 °C; ^{1}H NMR: δ (ppm): 3.91 (3H, s, CH_3O); 4.1–4.7 (5H, m); 5.85 (2H, s, O–CH_2–O); 6.43 (1H, s, H-5); 6.45 (1H, s, H-8); 6.99 (1H, d, J = 8.6, H-5′); 7.38–7.46 (2H, m, H-2′, H-6′); 9.85 (1H, s, CHO). HRMS m/z 344.0893 (calcd for $C_{18}H_{16}O_7$: 344.0896).

4.5.9. 4-(6,7-Dibromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxybenzaldehyde (42). Yield: 72.5%; mp: 127–129 °C; ^{1}H NMR: δ (ppm): 3.92 (3H, OCH_3); 4.19–4.48 (4H, m); 4.56–4.68 (1H, m); 7.00 (1H, d, J = 8.57, H-5′), 7.17 (1H, s, H-5) 7.18 (1H, s, H-8); 7.41–7.48 (2H, m; H-2′ and H-6′); 9.87 (1H, s, CHO). HRMS m/z 455.9206 (calcd for $C_{17}H_{14}Br_2O_5$: 455.9208).

4.5.10. 4-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxybenzaldehyde (43). Yield: 85%; mp: 73–75 °C; ^{1}H NMR: δ (ppm): 3.92 (3H, s, CH_3O); 4.16–4.73 (5H, m); 6.78–6.95 (4H, m, H-5, H-6, H-7,H-8); 7.02 (1H, d, J = 8.7, H-5′); 7.38–7.51 (2H, m, H-2′, H-6′); 9.86 (1H, s, CHO). HRMS m/z 300.0996 (calcd for $C_{17}H_{16}O_5$: 300.0998).

4.6. General procedure for the preparation of 44–53

A mixture of the aldehyde **34**–**43** (20 mmol) thiazolidine-2.4-dione (22 mmol), and sodium acetate was heated at 140 °C for 2 h without solvent. Then water was added to the reaction mixture, the solid product was filtered off, washed with chloroform for the removal of the excess of thiazolidine-2.4-dione, and dried.

4.6.1. 5-[4-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (44). Yield: 80%; mp: 208–211 °C; ^{1}H NMR (DMSO): δ (ppm): 4.06–4.73 (5H, m); 5.88 (1H, d, J = 8.57, H-5); 7.02 (1H, dd, J = 2.29 and 8.57, H-6); 7.13 (1H, d, J = 2.29, H-8); 7.14 (2H, d, J = 8.8, H-3′, H-5′); 7.59 (2H, d, J = 8.8, H-2′, H-6′); 7.76 (1H, s, CH). HRMS m/z 446.9778 (calcd for $C_{19}H_{14}BrNO_5S$: 446.9776).

4.6.2. 5-[4-(6-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (45). Yield: 80%; mp: 187–189 °C; ^{1}H NMR (DMSO): δ (ppm): 4.1–4.75 (5H, m); 6.92 (1H, d, J = 8.52, H-8), 7.06 (1H, dd, J = 2.12 and 8.52, H-7), 7.17 (1H, d, J = 2.12, H-5); 7.2 (2H, d, J = 8.64, H-3′, H-5′); 7.61 (2H, d, J = 8.64, H-2′, H-6′); 7.8 (1H, s, CH); 12.56 (1H, s, NH). HRMS *m/z* 446.9775 (calcd for $C_{19}H_{14}BrNO_5S$: 446.9776).

4.6.3. 5-[4-(6,7-Methylenedioxy-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (46). Yield: 63%; mp: >300 °C; ^{1}H NMR (DMSO): δ (ppm): 4.0–4.6 (5H, m); 5.93 (2H, s, O–CH_2–O); 6.61 (1H, s, H-5); 6.64 (1H, s, H-8); 6.63 (2H, d, J = 8.66, H-3′, H-5′); 7.49 (1H, s, CH); 7.91 (2H, d, J = 8.66, H-2′, H-6′). HRMS *m/z* (calcd for $C_{20}H_{15}NO_7S$: 413.0569).

4.6.4. 5-[4-(6,7-Dibromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (47). Yield: 60%; mp: >250 °C (decomposed); ^{1}H NMR (DMSO): δ (ppm): 4.2–4.8 (5H, m); 7.08 (2H, d, J = 8.65, H-3′, H-5′); 7.28 (1H, s, CH); 7.37 (1H, s, H-5); 7.40 (1H, s, H-8); 7.50 (2H, d, J = 8.65, H-2′, H-3′). HRMS *m/z* 542.8885 (calcd for $C_{19}H_{13}Br_2NO_5S$: 524.8881).

4.6.5. 5-[4-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (48). Yield: 57%; mp: 226–228 °C; ^{1}H NMR (DMSO): δ (ppm): 4.0–4.3 (5H, m); 6.72–6.96 (4H, m); 7.13 (2H, d, J = 8.72, H-3′, H-5′); 7.58 (2H, d, J = 8.72, H-2′, H-6′); 7.75 (1H, s, CH). HRMS *m/z* 369.0673 (calcd for $C_{19}H_{15}NO_5S$: 369.0671).

4.6.6. 5-[4-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxy-benzylidene]-thiazolidine-2,4-dione (49). Yield: 57%; mp: >230 °C (decomposed); ^{1}H NMR (DMSO): δ (ppm): 3.79 (3H, s, OCH_3), 4.08–4.8 (5H, m); 6.87 (1H, d, J = 8.64, H-5); 6.99 (1H, dd, J = 2.21 and 8.64, H-6); 7.01 (2H, m); 7.13 (1H, d, J = 2.21, H-8); 7.16 (1H, s); 7.25 (1H, s, CH). HRMS *m/z* 476.9884 (calcd for $C_{20}H_{16}BrNO_6S$: 476.9882).

4.6.7. 5-[4-(6-Bromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxy-benzylidene]-thiazolidine-2,4-dione (50). Yield: 89%; mp: 197–199 °C; ^{1}H NMR (DMSO): δ (ppm): 3.87 (3H, s, OCH_3); 4.1–4.7 (5H, m); 6.91 (1H, d, J = 8.62, H-8); 7.04 (1H, dd, J = 2.23 and 8.62, H-7); 7.12 (2H, s, H-2′, H-6′); 7.15 (1H, d, J = 2.23, H-5); 7.37 (1H, s, CH). HRMS *m/z* 476.9884 (calcd for $C_{20}H_{16}BrNO_6S$: 476.9882).

4.6.8. 5-[4-(6,7-Methylenedioxy-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxy-benzylidene]-thiazolidine-2,4-dione (51). Yield: 84%; mp: 174–176 °C; ^{1}H NMR (DMSO): δ (ppm): 3.83 (3H, s, OCH_3); 4.0–4.6 (5H, m); 5.93 (2H, s, O–CH_2–O); 6.61 (1H, s, H-5); 6.63 (1H, s, H-5); 7.1 (2H, s, H-2′, H-6′); 7.2 (1H, s, H-5′); 7.3 (1H, s, CH). HRMS *m/z* 443.0678 (calcd for $C_{21}H_{17}NO_8S$: 443.0675).

4.6.9. 5-[4-(6,7-Dibromo-2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxy-benzylidene]-thiazolidine-2,4-dione (52). Yield: 61%; mp: 170–172 °C; ^{1}H NMR (DMSO): δ (ppm): 3.74 (3H, s, OCH_3); 4.2–4.7 (5H, m); 7.14 (2H, s, H-2′, H-6′); 7.22 (1H, s, H-5′), 7.37 (1H, s, H-5′); 7.39 (1H, s, H-8′); 7.46 (1H, s, CH). HRMS *m/z* 554.8985 (calcd for $C_{20}H_{15}Br_2NO_6S$: 554.8987).

4.6.10. 5-[4-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxy-benzylidene]-thiazolidine-2,4-dione (53). Yield: 65%; mp: >230 °C (decomposed); ^{1}H NMR (DMSO): δ (ppm): 3.83 (3H, s, OCH_3); 4.1–4.7 (5H, m); 6.7–7.0 (4H, m, H-5–H-8); 7.1–7.2 (3H, 3, H-2′, H-5′, H-6′); 7.49 (1H, s, CH). HRMS *m/z* 399.0780 (calcd for $C_{20}H_{17}NO_6S$: 399.0777).

4.7. General procedure for the preparation of 54–57

Five hundred milligrams of the benzylidene derivatives **46**, **48**, **51**, and **53** hydrogenated in acetic acid (300 cm^3) in the presence of Pd(C) (300 mg) at 12 atm pressure until the level of the pressure was stabilized. Then the catalyst was filtered off and the pure product was isolated after evaporation of the solvent.

4.7.1. 5-[4-(6,7-Methylenedioxy-2,3-dihydrobenzo[1,4]-dioxin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione (54). Yield: 86%; mp: >300 °C; ^{1}H NMR (DMSO): δ (ppm): 2.62 (1H, dd, J = 10.36 and 13.84, CH_{2A}); 3.35 (1H, dd, J = 3.56 and 13.84, CH_{2B}); 4.1–4.7 (6H, m); 5.89 (2H, s, O–CH_2–O); 6.56 (1H, s, H-5′); 6.59 (1H, s, H-8′); 6.83 (2H, d, J = 8.57, H-3′, H-5′); 7.13 (2H, d, J = 8.57, H-2′, H-6′). HRMS *m/z* 415.0722 ($C_{20}H_{17}NO_7S$: 415.0726).

4.7.2. 5-[4-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione (55). Yield: 78%; mp: 154–156 °C; ^{1}H NMR (DMSO): δ (ppm): 3.05 (1H, dd, J = 8.87 and 14.01, CH_{2A}); 3.35 (1H, dd, J = 4.04 and 14.01, CH_{2B}); 4.05–4.62 (6H, m); 4.86 (1H, dd, J = 4.04 and 8.87, CH) 6.77–6.98 (6H, m); 7.17 (2H, d, J = 8.62; H-2′, H-6′). HRMS *m/z* 371.0824 (calcd for $C_{19}H_{17}NO_5S$: 371.0827).

4.7.3. 5-[4-(6,7-Methylenedioxy-2,3-dihydrobenzo[1,4]-dioxin-2-ylmethoxy)-3-methoxy-benzyl]-thiazolidine-2,4-dione (56). Yield: 65%; mp: 160–163 °C; ^{1}H NMR (DMSO): δ (ppm): 3.04 (1H, dd, J = 9.38 and 14.02, CH_{2A}); 3.33 (1H, dd, J = 4.28 and 14.02, CH_{2B}); 3.74 (3H, s, OCH_3); 3.96–4.51 (5H, m); 4.90 (1H, dd, J = 4.28 and 9.38, CH); 5.88 (2H, s, O–CH_2–O); 6.56 (1H, s, H-5); 6.59 (1H, s, H-8); 6.72 (1H, dd, J = 1.56 and 8.18; H-6′); 6.89 (1H, d, J = 1.56, H-2′); 6.93 (1H, d, J = 8.18, H-5′). HRMS *m/z* 445. 0829 (calcd for $C_{21}H_{19}NO_8S$: 445.0831).

4.7.4. 5-[4-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-3-methoxy-benzyl]-thiazolidine-2,4-dione (57). Yield: 65%; mp: 115–120 °C (decomposed); ^{1}H NMR (DMSO): δ (ppm): 3.1 (1H, dd, J = 9.7 and 14.4, CH_{2A}); 3.48 (1H, dd, J = 3.78 and 14.4, CH_{2B}); 3.85 (3H, s, OCH_3); 4.1–4.7 (6H, m); 6.7–7.3 (7H, m). HRMS *m/z* 401.0935 (calcd for $C_{20}H_{19}NO_6S$: 401.0933).

4.7.5. 2-Phenoxymethyl-2,3-dihydrobenzo[1,4]dioxin (58). The mixture of **27** (500 mg, 1.5 mmol), phenol (200 mg), and K_2CO_3 (300 mg) in dry DMF (20 cm^3) was stirred at 80 °C. The progress of reaction was monitored by TLC (toluene/ethyl acetate = 4:1). The reaction mixture was poured into cold water and extracted with ether, the organic phase was washed with aqueous $NaHCO_3$ solution and dried. Following evaporation of the solvent the residue was purified by column chromatography to obtain **58** as white crystals (124 mg, 35%, mp: 35–37 °C). ^1H NMR ($CDCl_3$): δ (ppm): 4.0–4.72 (5H, m); 6.66–7.08 (7H, m); 7.19–7.44 (2H, m). HRMS *m/z* 242.0945 ($C_{15}H_{14}O_3$: 242.0943).

4.7.6. 6,7-Dibromo-2-phenoxymethyl-2,3-dihydro-benzo-[1,4]dioxin (59). The mixture of **26** (200 mg, 0.42 mmol), phenol (60 mg, 0.63 mmol), and 710 mg of K_2CO_3 in dry DMF (10 cm^3) was stirred at 80 °C. The progress of reaction was monitored by TLC (toluene/ethyl acetate = 4:1). Subsequently the reaction mixture was poured into cold water and extracted with ether. The organic phase was washed with aqueous $NaHCO_3$ solution and dried. After evaporation, the residue was purified by column chromatography to yield **59** as white crystals (131.5 mg, 79%, mp: 78–84 °C). 1H NMR ($CDCl_3$): δ (ppm): 4.03–4.58 (5H, m); 6.8–7.0 (3H, m, Ar–H); 7.14 (1H, s, H-5); 7.15 (1H, s, H-8); 7.22–7.33 (2H, H, Ar–H). HRMS *m/z* (calcd for $C_{15}H_{12}Br_2O_3$: 397.9153).

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References and notes

1. Henges, E. J. Drugs Affecting Sugar Metabolism. In *Principles of Medicinal Chemistry*; Faye, W. O., Lembe, T. L., Williams, D. A., Eds.; Williams and Wilkins: Baltimore, 1995; p 581.
2. Goldman, J. M. *Drugs Today* **1989**, *25*, 689.
3. Ferner, R. E.; Neil, H. A. W. *Br. Med. J.* **1988**, *296*, 949.
4. Yamamoto, K.; Itoh, T.; Abe, D.; Shimizu, M.; Kanda, T.; Koyama, T.; Nishikawa, M.; Tamai, T.; Ooizumie, H.; Yamadaa, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 517.
5. Ushi, S.; Suzuki, T.; Hattori, Y.; Etoh, K.; Fujieda, H.; Nishizuka, M.; Imagawa, M.; Nakagawa, H.; Kohda, K.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1547.
6. John, J.; Acton, J. J.; Black, R. M.; Jones, A. B.; Moller, D. E.; Colwell, L.; Doebber, T. W.; MacNaul, K. L.; Berger, J.; Wood, H. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 357.
7. Kim, B. Y.; Ahn, J. B.; Lee, H. W.; Kang, S. K.; Lee, J. H.; Shin, J. S.; Ahn, S. K.; Hong, C. I.; Yoon, S. S. *Eur. J. Med. Chem.* **2004**, *39*, 433.
8. Kuhn, B.; Hilpert, H.; Benz, J.; Binggeli, A.; Grether, U.; Humm, R.; Märki, H. P.; Meyer, M.; Mohr, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4016.
9. Watson, K. A.; Chrysina, E. D.; Tsitsanou, K. E.; Zographos, S. E.; Archontis, G.; Fleet, G. W. J.; Oikonomakos, N. G. *Proteins Struct. Funct. Bioinformatics* **2005**, 966.
10. Somsák, L.; Nagy, V.; Docsa, T.; Tóth, B.; Gergely, P. *Tetrahedron Asymmetry* **2000**, *11*, 405.
11. Czifrák, K.; Kovács, L.; Kövér, E. K.; Somsák, L. *Carbohydr. Res.* **2005**, *340*, 2328.
12. Anagnostou, E.; Kosmopoulou, M. N.; Chrysina, E. D.; Leonidas, D. D.; Hadjiloi, T.; Tiraidis, C.; Zographos, S. E.; Györgydeák, Z.; Somsák, L.; Docsa, T.; Gergely, P.; Kolisis, F. N.; Oikonomakos, G. N. *Bioorg. Med. Chem.* **2006**, *14*, 181.
13. Archontis, G.; Watson, K. A.; Xie, Q.; Andreou, G.; Chrysina, E. D.; Zographos, S. E.; Oikonomakos, N. G.; Karplus, M. *Proteins Struct. Funct. Bioinformatics* **2005**, 984.
14. Olefsky, J. M. *J. Biol. Chem.* **2001**, *276*, 36863.
15. Fujiwara, T.; Yoshioka, S.; Yoshioka, T.; Ushiyama, I.; Horokoshi, H. *Diabetes* **1988**, *37*, 1549.
16. Stevenson, R. W.; Hutson, N. J.; Krupp, M. N.; Volkmann, R. A.; Holland, G. F.; Eggler, J. F.; Clark, D. A.; McPherson, R. K.; Hall, K. L.; Danbury, B. H. *Diabetes* **1990**, *39*, 1219.
17. Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, R. A.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurbly, P. L. *J. Med. Chem.* **1994**, *37*, 3977.
18. Liu, L. S.; Tanaka, H.; Ishii, S.; Eckel, J. *Endocrinology* **1998**, *139*, 4531.
19. Shoda, T.; Mizumo, K.; Imamiya, E.; Sugiyama, Y.; Fukits, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3580.
20. Parker, J. C. *Adv. Drug Deliv. Rev.* **2002**, *54*, 1173.
21. Treadway, J. L.; Mendys, P.; Hoover, D. J. *Expert Opin. Investig. Drugs* **2001**, *10*, 439.
22. Osz, E.; Somsák, L.; Szilágyi, L.; Kovács, L.; Docsa, T.; Tóth, B.; Gergely, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1385.
23. Agasimundin, Y. S.; Mumper, M. W.; Hasmane, R. S. *Bioorg. Med. Chem.* **1998**, *6*, 911.
24. Augstein, J.; Green, S. M.; Mouro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. *J. Med. Chem.* **1965**, *8*, 446.
25. Bolchi, C.; Catalano, P.; Fumagalli, L.; Gobbi, M.; Pallavicini, M.; Pedretti, A.; Villa, L.; Vistoli, G.; Valoti, E. *Bioorg. Med. Chem.* **2004**, *12*, 4937.
26. Gilbert, A. M.; Stack, G. P.; Nilakantan, R.; Kodah, J.; Tran, M.; Scerni, R.; Shi, X.; Smith, D. L.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 515.
27. Hörhammer, L.; Münster, R. *Naturwissenschaften* **1965**, *52*, 305.
28. Clark, D. A.; Goldstein, A. W.; Volkmann, R. A.; Eggler, J. F.; Holland, G. F.; Hulin, B.; Stevenson, R. W.; Kreutter, D. K.; Gibbs, E. M.; Krupp, M. N.; Merrigan, P.; Kelbaugh, P. L.; Andrews, E. G.; Tickner, D. L.; Suleske, R. T.; Lamphere, C. H.; Rajeckas, F. J.; Kappeler, W. H.; McDermott, R. E.; Hutson, N. J.; Johnson, M. R. *J. Med. Chem.* **1991**, *34*, 319.
29. De Nanteuil, G.; Herve, Y.; Duhault, J.; Espinal, J.; Boulanger, M.; Ravel, D. *Arzneim.-Forsch.* **1995**, *45*, 1176.
30. Antus, S.; Bauer, R.; Gottsegen, Á.; Seligmann, O.; Wagner, H. *Liebigs Ann. Chem.* **1987**, 357.
31. Juhász, L.; Kürti, L.; Antus, S. *J.A.C.S. J. Nat. Products* **2000**, *63*, 866.

32. Juhász, L.; Dinya, Z.; Gunda, T.; Antus, S. *Tetrahedron Lett.* **2000**, *41*, 2491.
33. Hudlick, M. *Oxidation Org. Synth. A.C.S.* **1990**, 186.
34. de Marohi, D. M. F.; Rosnati, V. *Gazz. Chim. Ital.* **1963**, *93*, 52.
35. Hofslokken, N. U.; Skattebol, L. *Acta Chem. Scand.* **1999**, *53*, 258.
36. Giles, R. G.; Lewis, N. J.; Quick, J. K.; Sasse, M. J.; Urquhart, M. W. J.; Youssef, L. *Tetrahedron* **2000**, *56*, 4531.
37. Osz, E.; Somsak, L.; Szilagy, L.; Kovacs, L.; Docsa, T.; Toth, B.; Gergely, P. *Bioorg. Med. Chem. Lett.* **1999**, *17*, 1385.
38. Stalmans, W.; Hers, H. G. *Eur. J. Biochem.* **1975**, *54*, 341.