Synthesis and Antihyperglycemic Activity of Erythrose, Ribose and Substituted Pyrrolidine Containing Thiazolidinedione Derivatives

Bok Young KIM, Joong Bok AHN, Hong Woo LEE,* Kyoung Sik MOON, Tae Bo SIM, Jae Soo SHIN, Soon Kil AHN, and Chung Il HONG

New Drug Research Laboratories, Chong Kun Dang Research Institute; Cheonan P.O. Box 74, Cheonan, 330–831, South Korea. Received October 21, 2002; accepted December 19, 2002

A series of erythrose, ribose, and substituted pyrrolidine containing 2,4-thiazolidinediones were synthesized. Among them, thirteen unsaturated thiazolidinediones, six saturated thiazolidinediones and two unsaturated malonates were evaluated for their ability to enhance glucose utilization in cultured L6 myocytes. On the basis of the *in vitro* activity, 5-{4-[2-(1-benzyl-3,4-*bis*-benzyloxypyrrolidin-2-yl)ethoxy]benzylidene}thiazolidine-2,4-dione 24b was selected as the candidate for further pharmacological studies.

Key words erythrose; ribose; substituted pyrrolidine; thiazolidinedione; glucose utilization; insulin sensitizing agent

Resistance to the metabolic actions of insulin is one of the salient features of impaired glucose tolerance and Type 2 diabetes mellitus (Type 2 DM). A number of prospective studies have shown that the development of insulin resistance is an early event in the natural progression of the disease.[1,2] Thus, drugs that reverse the onset of insulin resistance fulfill a major medical need for the treatment of Type 2 DM.[3] Insulin resistance is characterized by the impaired uptake and utilization of glucose in insulin-sensitive target organs such as adipocytes and skeletal muscle and by the impaired inhibition of hepatic glucose output.[4—6] Thiazolidinediones are a class of oral insulin-sensitizing agents that improve glucose utilization without stimulating insulin release. They significantly reduce glucose, lipid, and insulin levels in rodent models of Type 2 DM and obesity,[7—9] and recent clinical data support their efficacy in obese diabetic patients.[10] The discovery of compounds which improve insulin resistance enables the continued treatment of Type 2 DM patients without inducing hypoglycemia. Clofibrate is the first such compound found to improve insulin resistance.[11,12] It was followed by the discovery of thiazolidinedione compounds, typically represented by ciglitazone.[13—15]

Of the thiazolidinedione compounds, ciglitazone (**A**), troglitazone (**B**),[16—18] englitazone (**C**),[19] pioglitazone (**D**),[20] and rosiglitazone (**E**)[21] are potential antidiabetic compounds that have been clinically examined.

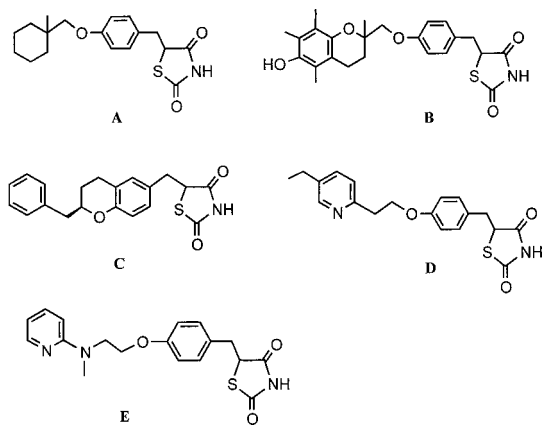


Chart 1

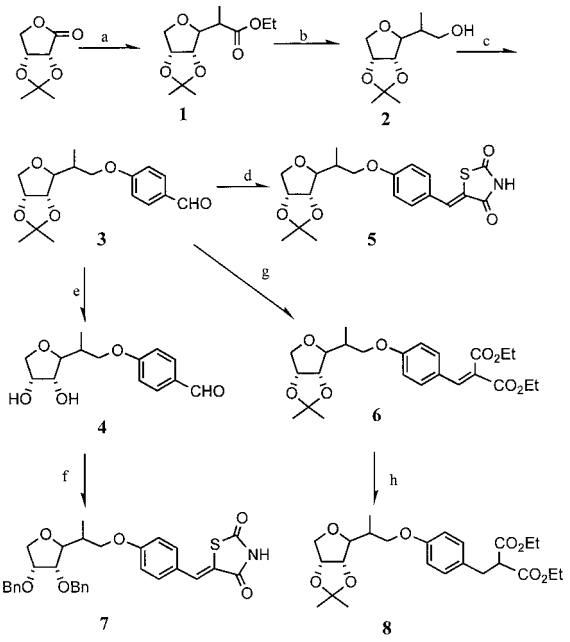
Scientists at Glaxo identified rosiglitazone as the first high-affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ), a receptor subtype selectively expressed in adipocytes and shown to induce adipocyte differentiation.[22—24] These studies are predicting the thiazolidinedione compounds to be promising compounds, capable of ameliorating Type 2 DM by improving insulin resistance without inducing hypoglycemia. Troglitazone is the first of a novel class of compounds, the thiazolidinedione derivatives, to reach clinical practice. Troglitazone induces preadipocyte differentiation, probably *via* PPAR$_\gamma$ receptors.[25] While it is not clear whether the antihyperglycemic mechanism requires preadipocyte differentiation, the maximum glucose-lowering effect (about 40 mg/dl) of troglitazone is similar to that seen with metformin. Thiazolidinediones have been shown to improve insulin sensitivity/glucose utilization in animal model and to enhance insulin sensitivity in human.[26—29] But, it was assumed that troglitazone has the hepatotoxicity[30—32] due to the enterohepatic circulation of the metabolites, that is quinone moiety.

In order to prevent this and to discover novel compounds which have the ability to increase glucose utilization, we focused our attention on the modification of chroman moiety to erythrose, ribose and substituted pyrrolidine group. As a result of our efforts, in this paper, we describe the synthesis and the *in vitro* glucose utilization activity. Since we found that the compounds **24a** and **24b**, having a *O*-protected *N*-benzyl pyrrolidine group involving thiazolidinedione moiety, showed an excellent glucose utilization activity in L6 myocytes (Table 1), our subsequent research will be focused on the antihyperglycemic activity of these compounds *in vivo*.

Chemistry

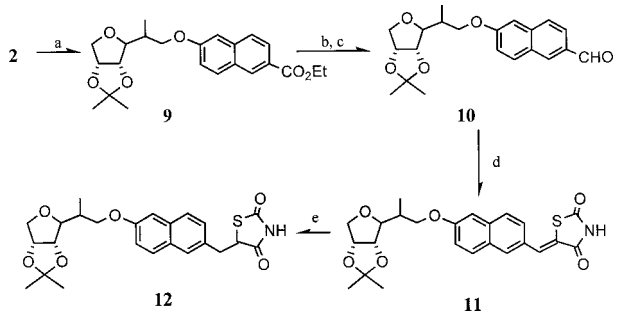
Several erythrose, ribose and substituted pyrrolidine-containing thiazolidinediones were prepared. A general synthetic route is shown in Chart 1. First, synthesis of the protected erythrose-containing thiazolidinedione compound **5** was carried out by the Knoevenagel's condensation[33] of a key intermediate aldehyde **3** with 2,4-thiazolidinedione and desired compound **7** also was obtained from **3** by deprotection, benzylation of erythrose group and condensation procedure as shown in Chart 1 respectively.

* To whom correspondence should be addressed. e-mail: hwlee@ckdpharm.com



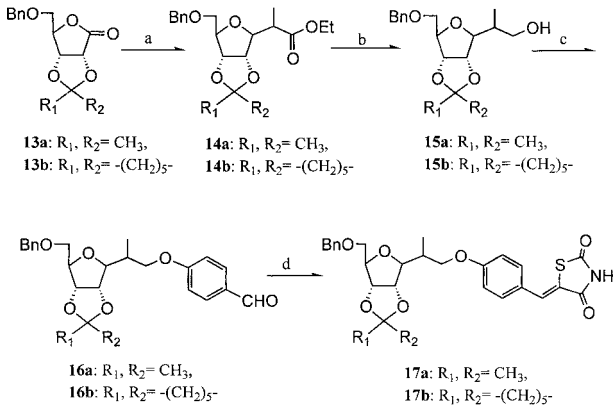
a) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; $Ph_3P{=}C(CH_3)CO_2Et$, CH_3CN, reflux to rt, *t*-BuOK, 3 h, b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, c) 4-hydroxybenzaldehyde, Ph_3P, DEAD, THF, 1 d, d) 2,4-thiazolidinedione (TZD), piperidine, EtOH, reflux, 1 d, e) TFA-H_2O, rt, 1 d, f) BnBr, NaH, DMF, rt, 1 d, then, TZD, piperidine, EtOH, reflux, 1 d, g) diethyl malonate, piperidine, EtOH, reflux, 1 d, h) 20% $Pd(OH)_2$, H_2, MeOH, rt, 1 d.

Chart 2



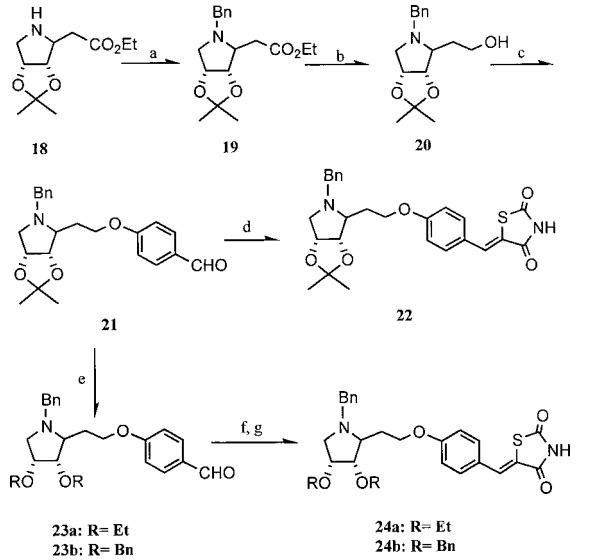
a) 6-hydroxy-2-naphthoic acid ethyl ester, Ph_3P, DEAD, THF, rt, 1 d, b) DIBAL-H, CH_2Cl_2, −78 °C to 0 °C, 1 h, c) CH_2Cl_2, Dess–Martin periodinane, rt, 1 h, d) TZD, piperidine, EtOH, reflux, 2 d, e) 20% $Pd(OH)_2$, H_2, EtOAc/MeOH, 1 d.

Chart 3



a) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; $Ph_3P{=}C(CH_3)CO_2Et$, CH_3CN, reflux, 15 h, b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, c) 4-hydroxybenzaldehyde, Ph_3P, DEAD, THF, 2 d, d) 2,4-thiazolidinedione, piperidine, EtOH, reflux, 1 d.

Chart 4



a) benzaldehyde, $NaBH_3CN$, AcOH, MeOH, rt, 1 d, b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, c) 4-hydroxybenzaldehyde, Ph_3P, DEAD, THF, 1 d, d) 2,4-thiazolidinedione, piperidine, EtOH, reflux, 1 d, e) TFA-H_2O, rt, f) NaH, DMF, R-I, rt, 1 d, g) TZD, piperidine, EtOH, 1 d.

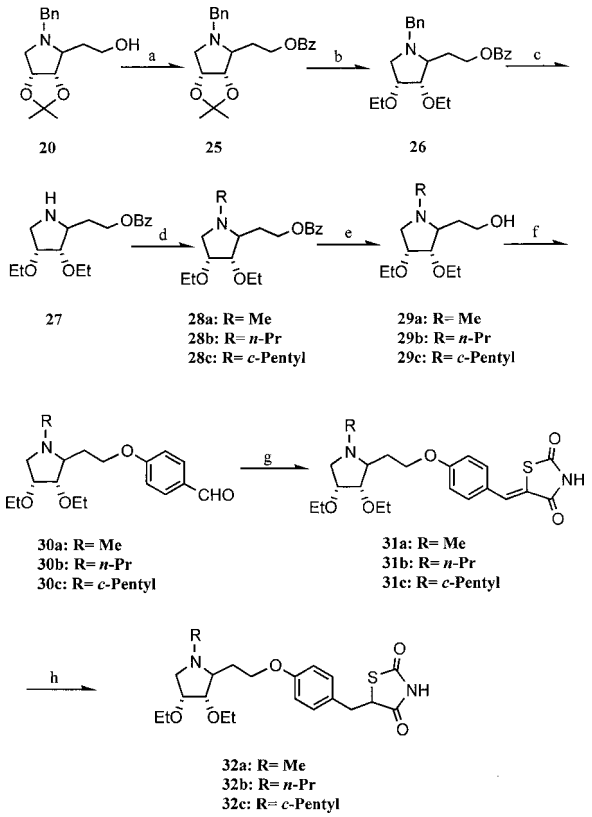
Chart 5

Desired compounds **8** and **6** were prepared by condensation and reduction with 20% $Pd(OH)_2$ under hydrogen atmosphere. Treatment of the D-erythrono-*r*-lactol under the Wittig's condition with phosphonium ylide generated the erythrose ethyl ester **1** which were reduced into the erythrose alcohol compound **2** by reduction. Synthesis of the key intermediate aldehyde **3** was carried out by the Mitsunobu's condition[34,35] as shown in Chart 2. The erythrose naphthylmethylene thiazolidinedione **12** was synthesized as shown in Chart 3. Mitsunobu's condition of the alcohol **2** with 6-hydroxy-2-naphtoic acid ethyl ester gave naphthyl ethyl ester compound **9**, which were transformed into the desired erythrose naphthylmethylene thiazolidinedione **12** *via* catalytic hydrogenation with 20% $Pd(OH)_2$ of the unsaturated naphthylmethylene thiazolidinedione **11** by the same procedure above described for the Knoevenagel's condition (Chart 3).

Synthesis of *O*-protected ribose benzylidene thiazolidinediones **17a**, **b** (Chart 4) were carried out *via* the Wittig reaction, reduction, Mitsunobu reaction, and condensation from the starting materials **13a**, **b** through the same procedure as describe in Chart 2.

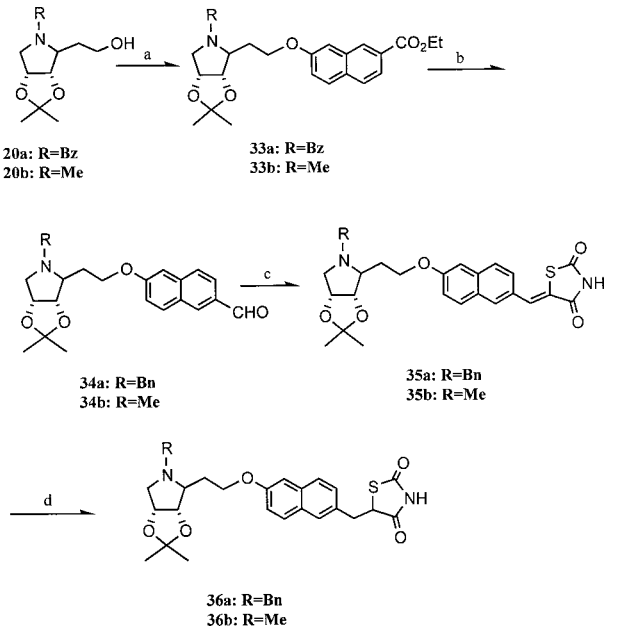
Unsaturated *O*-protected *N*-benzyl pyrrolidine derivatives **22** and **24a**, **b** (Chart 5) were derived from the benzylation of the *O*-protected pyrrolidine ethyl ester (**18**) by using the general procedures described in Charts 2—4.

N-Alkyl pyrrolidine benzylidene analogues **31a**—**c** (Chart 6) were synthesized by the similar procedure described in Chart 5. Benzoylation of **20**, followed by deprotection, *O*-alkylation and removal of the *N*-benzyl group by treatment with 20% $Pd(OH)_2$ at hydrogen atmosphere produced compound **27**. The aldehyde compounds **30a**—**c** were prepared by Mitsunobu reaction *via* reductive alkylation of **27** with *para*-formaldehyde, propionaldehyde or cyclopentanone in the presence of sodium cyanoborohydride which was con-



a) Bz_2O, Pyr, DMAP, rt, 2 h, b) TFA–H_2O, rt, 1 d; EtI, NaH, TBAI, DMF, 0 °C, 2 h, c) 20% $Pd(OH)_2$, H_2, MeOH, 1 d, d) *para*-formaldehyde, propionaldehyde, or cyclo-pentanone, $NaBH_3CN$, AcOH, MeOH, rt, 1 d, e) NaOMe, MeOH, rt, 2 h, f) 4-hydroxybenzaldehyde, Ph_3P, DEAD, THF, 1 d, g) TZD, piperidine, EtOH, reflux, 1 d, h) 20% $Pd(OH)_2$, H_2, MeOH, 1 d.

Chart 6



a) 6-hydroxy-2-naphthoic acid ethyl ester, Ph_3P, DEAD, THF, rt, 1 d, b) DIBAL-H, CH_2Cl_2, −78 °C to 0 °C, 1 h; Dess–Martin periodinane, CH_2Cl_2, rt, c) TZD, piperidine, EtOH, reflux, 2 d, d) 20% $Pd(OH)_2$, H_2, EtOAc/MeOH, 1 d.

Chart 7

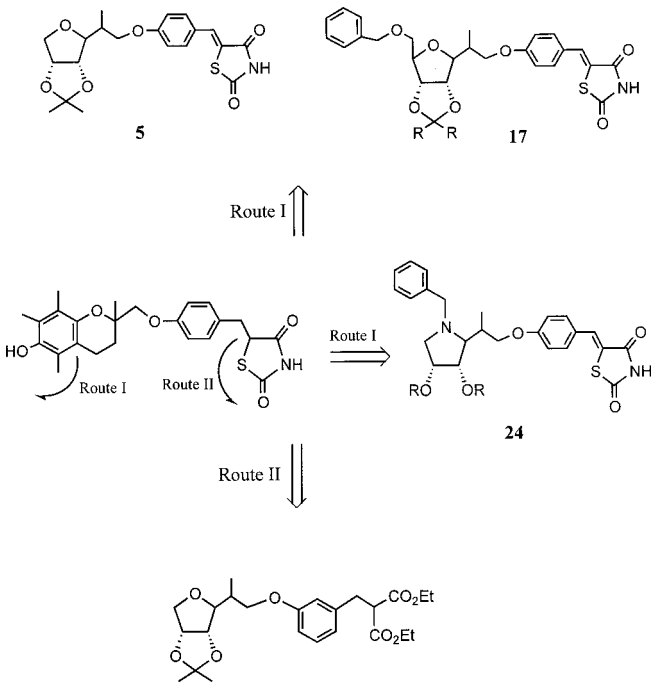


Chart 8

verted into the benzylidene thiazolidinediones **31a**—**c** by the Knoevenagel condition. *N*-alkyl pyrrolidine benzyl derivatives **32a**—**c** were prepared by catalytic hydrogenation of **31a**—**c** in Chart 6.

N-Protected naphthalene-containing pyrrolidine derivatives (**36a**, **b**) (Chart 7) were prepared by using the general procedures described in Chart 7.

Results and Discussion

Several thiazolidinedione derivatives, represented by compounds **A**—**E** (Chart 1) described above, have been reported to possess very good antihyperglycemic activity. Of these compounds, troglitazone was found to prevent the inhibitory effect of inflammatory cytokines such as TNF-α, which induce peripheral insulin resistance in glucose uptake in insulin-induced adipocyte differentiation of 3T3-L1 cells.[36] Troglitazone (**B**) is reported to have the potent agonism to PPARγ and a good antihyperglycemic effect in genetically diabetic ob/ob mice.[37] Considering the structure of troglitazone (**B**), we designed and synthesized erythrose, ribose, and substituted pyrrolidine thiazolidinedione derivatives with a nitrogen or oxygen containing 5-membered ring system at the lipophilic moiety as shown in Chart 8.

Erythrose, ribose and substituted pyrrolidine thiazolidinediones **5**, **8**, **17**, and **24** designed by troglitazone structure having a fused chromane ring open *via* routes I, and II, respectively, were synthesized and evaluated for their glucose utilization in L6 myocytes assay *in vitro*. First of all, in order to examine the effect of pharmacophore head site, two different type erythrose-containing compounds **5** and **8** were synthesized, that is, the thiazolidinedione or malonate group and evaluated their activity. Almost erythrose compounds having a thiazolidinedione moiety **5**, **7**, **11**, and **12**, except for malonate-containing erythrose compounds **6**, and **8**, showed better glucose utilization in L6 myocytes assay than rosiglitazone (Table 1). These data suggest that a pharmacophore of a

Table 1. Glucose Utilization Activity, Cytotoxicity and Safety Index for the Erythrose, Ribose, and Substituted Pyrrolidine Derivatives

Compound	Glucose utilization activity in L6 cell (EC_{40}, μM)[a]	Cytotoxicity (TC_{25}, μM)[b]	Safety index (toxicity/activity)
5	12.3	111.3	9.0
6	>100	ND	ND[c]
7	11.8	107.5	9.1
8	>100	ND	ND
11	7.6	33.6	4.4
12	15.9	159.5	10
17a	2.6	16.9	6.5
17b	54.8	>100	>1.8
22	5.6	32.7	5.8
24a	3.2	30.4	9.5
24b	3.8	45.7	12
31a	>100	ND	ND
31b	>100	ND	ND
31c	24.7	58.9	2.4
32a	>100	ND	ND
32b	>100	ND	ND
32c	20.8	ND	ND
35a	>100	160	1.6
35b	80.0	>100	1.3
36a	2.9	20	6.9
36b	30.4	88.9	2.9
Rosiglitazone	39.3	116	2.9
Troglitazone	7.9	21.8	2.8

a) Effective concentration (EC_{40}) means increase of glucose utilization in L6 cells. *b*) Toxic concentration (TC_{25}) means increase of neutral red uptake in cultured hepatocytes. *c*) Not determined.

erythrose ring with a thiazolidinedione group is required for *in vitro* activity.

Considering these results, the ribose derivatives **17a**, **b** containing the bulky aromatic group were synthesized and examined their activity in L6 myocytes. The results revealed that the ribose derivative containing benzylidene compound **17a** showed an excellent glucose utilization activity than rosiglitazone and troglitazone as shown in Table 1, but tricyclic ribose having a spiro-cyclohexylidene dioxol compound **17b** exhibited a reduced activity than reference compounds in L6 myocytes. To explore the effect of the orientation and proximity of the substituent, the oxygen atom of the erythrose or ribose group replaced by the nitrogen atom. As a consequence, several substituted pyrrolidine containing benzylidene or benzyl thiazolidinedione derivatives **24a**, **b**, **31a**—**c**, **32a**—**c**, **35a**, **b** and **36a**, **b** were prepared and the results are shown in Table 1. The substituent on the nitrogen at the 1-position of the pyrrolidine ring was varied. Among these synthesized compounds, benzyl substituted pyrrolidine derivatives **24a**, **b**, and **36a** showed the excellent glucose utilization than reference compounds in L6 myocytes cell assay. But the *N*-methyl, *N*-propyl or *N*-benzyl substituted pyrrolidine derivatives **31a**, **b**, **32a**, **b**, **35a**, **b** and **36b** exhibited reduced glucose utilization activity. Compared with phenyl-tethered thiazolidinediones **24a**, **b** and naphthylmethylene-tethered thiazolidinediones **35a**, **b**, naphthylmethylene-tethered thiazolidinedione **35a**, **b** showed reduced glucose utilization activity. Reduction of unsaturated thaizolidinediones **35a**, **b** to saturated thiazolidinediones **36a**, **b** results in dramatic increase of glucose utilization activity as shown in Table 1. As a result of these studies, the substituted pyrrolidine derivatives **24a**, **b**, and **36a** exhibited not only the better activity in enhancing glucose utilization activity in L6 myocytes but also had better safety index than rosiglitazone and troglitazone.

In conclusion, on the basis of both *in vitro* glucose utilization activity and preliminary toxicity evaluation, 5-{4-[2-(1-benzyl-3,4-*bis*-benzyloxypyrrolidin-2-yl)ethoxy]benzylidene}thiazolidine-2,4-dione (**24b**) was selected for further evaluation and is presently under pharmacological studies.

Experimental

All reactions were conducted under anhydrous condition in solvents dried over molecular sieves type 4 Å under nitrogen atmosphere and performed using oven dried glassware. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400 MHz for proton and 100 MHz for carbon NMR and were performed in DMSO-d_6 solutions using tetramethylsilane as the internal reference except where indicated otherwise. The coupling constants (J) are reported in Hz. Mass spectra were recorded on a HP 5989B instrument. Flash chromatography was performed using Merck silica gel 60 (230—400 mesh) according to the published procedure.[38]

2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic Acid Ethyl Ester 1 To a solution of 2,3-isopropylidene-D-erythrono-γ-lactone (5 g, 31.61 mmol) in dry dichloromethane (100 ml) at −78 °C was added DIBAL-H (1.0 M in CH_2Cl_2, 40 ml, 40 mmol) by syringe pump under N_2 atmosphere at the same temperature. After stirring for 1 h, the reaction mixture was quenched with methanol (10 ml), and stirred at room temperature for 1 h. Rochelle's solution (100 ml) was added gradually to the vigorously stirred the reaction mixture and stirred overnight. The organic layer was separated and washed with water, brine, respectively, and dried ($MgSO_4$), and the filtrate was concentrated by evaporation under reduced pressure. The obtained residue and ethoxycarbonyl ethylidene triphenylphosphorane (17 g, 46.95 mmol) was dissolved in toluene (150 ml), and the resulting mixture was stirred at 110 °C for 24 h. The reaction mixture was cooled at room temperature, and was cyclized by the addition of potassium *tert*-butoxide (3.5 g, 31.61 mmol) and was stirred for 3 h, and quenched with saturated NH_4OH, and washed water, dried ($MgSO_4$), and concentrated *in vacuo* to leave an oil residue which was purified by column chromatography on SiO_2 with *n*-hexane–EtOAc (5 : 1, v/v) as elution solvent to give the title compound **1** as a yellowish oil (2.50 g, 34.1% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2980, 2937, 1724, 1457. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 478 (m, 1H), 4.64 (m, 1H), 4.09 (m, 1H), 3.92 (s, 1H), 3.78 (m, 1H), 3,67 (s, 3H), 2,29 (m, 1H), 1.48 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 9.8, 29.1, 34.8, 50.7, 67.3, 75.4, 76.8, 78.1, 101.6, 174.5. High resolution (HR)-MS, *m*/*z*: Calcd for $C_{11}H_{18}O_5$, 230.2569. Found: 230.2578. *Anal.* Calcd for $C_{11}H_{18}O_5$: C, 57.37; H, 7.87. Found: C, 57.42; H, 7.88.

2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propion-1-ol (2) DIBAL-H (1.0 M in CH_2Cl_2 3.37 ml, 3.37 mmol) was added dropwise to a stirred solution of 2-(2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic acid ethyl ester (**1**) (590 mg, 2.41 mmol) in CH_2Cl_2 at −78 °C. After stirring at −78 °C for 2 h, the reaction mixture was quenched 2 N HCl and extracted with EtOAc. The extracted was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 with *n*-hexane–EtOAc (3 : 1, v/v) to give the title compound **2** (525 mg, 98% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3442, 2979, 2937, 2879, 1459. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.37 (s, 3H), 1.53 (s, 3H) 1.88 (m, 1H), 2.01 (br s, 1H), 3.66 (br s, 1H), 3.67—3.89 (m, 2H), 4.03 (m, 1H), 4.63 (m, 1H), 4.83 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.5, 28.6, 31.8, 64.5, 66.0, 76.1, 77.1, 78.7, 101.6. HR-MS, *m*/*z*: Calcd for $C_{11}H_{18}O_4$, 202.2468. Found: 202.2478. *Anal.* Calcd for $C_{11}H_{18}O_4$: C, 59.38; H, 9.87. Found: C, 59.39; H, 9.99.

4-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]benzaldehyde (3) An ice-cooled solution of diethyl azodicarboxylate (DEAD, 0.5 ml, 3.11 mmol) in tetrahydrofuran (THF, 30 ml) was treated with the title alcohol compound **2** (525 mg, 2.59 mmol) for 15 min, and then 4-hydroxybenzaldehyde (412 mg, 3.37 mmol), and triphenyl phosphine (Ph_3P, 817 mg, 3.11 mmol) were added to the mixture. The resultant was stirred at ice-cooled temperature for 30 min, and then allowed to warm to room temperature overnight. The mixture was quenched with saturated NH_4OH (20 ml) and extracted with EtOAc. The organic layer was washed with water, dried

($MgSO_4$), and concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 with *n*-hexane–EtOAc (4 : 1, v/v) to give the title compound **3** (773 mg, 97.2% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1689, 1601. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 3H), 1.35 (s, 3H), 1.54 (s, 3H), 2.18 (m, 1H), 3.96 (m, 3H), 4.06 (m, 2H), 4.72 (m, 1H), 4.48 (m, 1H), 7.01 (m, 2H), 7.87 (m, 1H), 9.9 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.8, 28.6, 29.2, 66.0, 73.6, 76.5, 77.1, 78.7, 101.6, 114.7, 128.3, 130.3, 164.6, 190.9. HR-MS *m/z*: Calcd for $C_{17}H_{22}O_5$, 306.3527. Found: 306.3531. *Anal.* Calcd for $C_{17}H_{22}O_5$: C, 66.64; H, 7.23. Found: C, 66.67; H, 7.25.

4-[2-(3,4-Dihydroxytetrahydrofuran-2-yl)propoxy]benzaldehyde (4) A mixture of 4-[2-(2-,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-propoxy]benzaldehyde (**3**) (2.33 g, 7.6 mmol) in trifluoroacetic acid–H_2O (4 : 1, v/v) was stirred at room temperature for 24 h. The reaction mixture was poured into water (60 ml) and extracted with EtOAc (3×100 ml). The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 with *n*-hexane–EtOAc (4 : 1, v/v) to give the title compound **4** as an oil (723 mg, 35.7% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1685, 1601. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.1 (s, 3H), 2.15 (m, 1H), 3.65 (m, 2H), 3.95 (m, 4H), 4.75 (m, 1H), 7.01 (m, 2H), 7.45 (m, 2H), 9.91 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.8, 28.9, 67.9, 73.6, 74.7, 76.3, 78.3, 114.7, 128.3, 130.5, 164.9, 190.0. HR-MS *m/z*: Calcd for $C_{14}H_{18}O_5$, 266.2897. Found: 266.2899. *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63,14; H, 6.81. Found: C, 63.16 ; H, 6.91.

5-{4-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]-benzaldehyde}thiazolidine-2,4-dione (5) A mixture of 4-[2-(2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]benzaldehyde (**3**) (100 g, 0.32 mmol), 2.4-thiazolidinedione (60 mg, 0.48 mmol), catalytic amount of piperidinum acetate was stirred at reflux for 24 h. The reaction mixture was cooled at room temperature and concentrated *in vacuo*. To leave an oil which was purified by column chromatography on SiO_2 with *n*-hexane–EtOAc (5 : 1, v/v) to give the title compound **5** as an oil (45 mg, 23% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3164, 3058, 2984, 2935, 1739, 1701, 1596, 1511. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 3H), 1.38 (s, 3H), 1.55 (s, 3H), 2.15 (m, 1H), 3.95 (m, 3H), 4.06 (m, 2H), 4.75 (m, 1H), 4.85 (m, 1H), 7.00 (m, 2H), 7.43 (m, 2H), 7.78 (s, 1H), 8.44 (br s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.5, 28.8, 29.5, 66.0, 73.6, 76.5, 77.1, 78.7, 101.6, 114.5, 120, 126.1, 126.9, 142.1, 158.1, 166.3, 167.1. HR-MS *m/z*: Calcd for $C_{20}H_{23}NO_6S$, 405.4648. Found: 405.4654. *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59,24; H, 5.71; N, 3.45. Found: C, 59.21; H, 5.74; N, 3.42.

2-{4-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]-benzaldehyde}malonic Acid Diethyl Ester (6) A mixture of a aldehyde compound **4** (300 mg, 1.02 mmol), diethylmalonate (0.18 ml, 1.23 mmol), piperidine (0.12 ml, 1.23 mmol), and EtOAc (30 ml) was heated at reflux temperature through Dean-stark trap for overnight. After being cooled to room temperature, the mixture was concentrated reduced pressure. The residue was purified by column chromatography using *n*-hexane–EtOAc (3 : 1, v/v) to give the title compound **6** as an oil (250 mg, 54% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2983, 1726, 1602. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 3H), 1.34 (m, 6H), 1.53 (s, 3H), 2.14 (m, 1H), 3.89—4.02 (m, 5H), 4.31 (m, 4H), 4.76 (m, 1H), 4.80 (m, 1H), 6.89 (m, 2H), 7.42 (m, 2H), 7.88 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.5, 13.7, 28.5, 29.5, 59.6, 66.0, 73.5, 76.4, 77.1, 78.7, 101.6, 115.9, 122.9, 126.5, 126.9, 149.9, 158.0, 165.1. HR-MS *m/z*: Calcd for $C_{24}H_{32}NO_8S$, 448.5048. Found. 448.5051. *Anal.* Calcd for $C_{24}H_{32}NO_8$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.23.

5-{4-[2-(3-Benzyloxy-4-methyltetrahydrofuran-2-yl)propoxy]benzylidene}thiazolidine-2,4-dione (7) To a suspension of sodium hydride (60% in mineral oil, previously washed with *n*-hexane, 162 mg, 4.05 mmol) in dimethylformamide (DMF) (15 ml) was added 4-[2-(3,4-dihydroxytetrahydrofuro-2-yl)propoxy]benzaldehyde (**4**) (360 mg, 1.35 mmol), and benzyl bromide (0.58 ml, 4.86 mmol) over N_2 atmosphere at 0 °C. After stirring at room temperature for 24 h, the reaction mixture was poured into ice-water and acidified with 1 N HCl to give the product and extracted with EtOAc (100 ml). The extract was washed with water, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in EtOH (30 ml) and added 2,4-thiazolidivedione (158 mg, 1.35 mmol), and piperidime (0.13 ml, 1.35 mmol), respectively. The reaction mixture was refluxed in a Dean-stark trap for 24 h. After cooling to room temperature, the solution was concentrated *in vacuo*. The residue was chromatography on SiO_2 eluted with *n*-hexane–EtOAc (4 : 1, v/v) to give the title compound **7** as an oil (290 mg, 42% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3446, 1751, 1700. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 3H), 2.23 (m, 1H), 3.86—4.15 (m, 7H), 4.47 (m, 1H), 4.57 (m, 1H), 4.73 (m, 2H), 6.94 (s, 2H), 7.28—7.44 (m, 14H), 7.80 (s, 1H), 8.58 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.5, 29.1, 127.6, 128.4, 137.2, 158.3, 78.9, 114.1, 120.1, 126.6, 127.6, 128.4, 137.2, 158.3, 166.3, 167.2. HR-MS *m/z*: Calcd for $C_{31}H_{31}NO_6S$, 504.6457. Found: 545.6468. *Anal.* Calcd for $C_{31}H_{31}NO_6S$: C, 68.23; H, 5.72; N, 2.56. Found: C, 68.12; H, 5.81; N, 2.61.

2-{4-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]-benzaldehyde}malonic Acid Diethyl Ester (8) A solution of 2-{4-[2-(2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]benzaldehyde}malonic acid diethyl ester (**6**) (70 mg, 0.15 mmol) in a mixture of methanol (10 ml) and dioxane (10 ml) was stirred in the presence of 20% palladium hydroxide on charcoal (35 mg, 50% w/w) under an atmosphere of hydrogen at room temperature until hydrogen uptake ceased. The reaction mixture was filtered through celite, and the filtrated was evaporated under a vacuum. The crude product was chromatography on SiO_2 eluted with CH_2Cl_2–MeOH (2 : 1, v/v) to give the title compound **8** as an oil (54 mg, 80% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2983, 1726, 1602. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.08 (m, 3H), 1.21 (m, 6H), 1.35 (s, 3H), 1.52 (s, 3H), 2.09 (m, 1H), 3.16 (m, 2H), 3.60 (m 1H), 3.84—4.00 (m, 5H), 4.15 (m, 4H), 4.73—4.79 (m, 2H), 6.80 (m, 2H), 7.11 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.1, 13.6, 28.6, 29.2, 30.7, 51.6, 59.5, 66.0, 73.6, 76.4, 77.1, 78.7, 101.6, 114.1, 128.5, 131.8, 156.1, 172.0. HR-MS *m/z*: Calcd for $C_{24}H_{34}NO_8S$, 450.5206. Found: 450.5218. *Anal.* Calcd for $C_{24}H_{34}NO_8S$: C, 63.98; H, 7.60. Found: C, 63.95; H, 7.64.

6-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]-naphthalene-2-carboxylic Acid Ethyl Ester (9) The title compound **9** (590 mg, 95% yield) was prepared as a thick oil from 2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propan-1-ol (**2**) (300 mg, 1.48 mmol), 6-hydroxy-2-naphtoic acid ethyl ester (416 mg, 1.93 mmol), triphenyl phosphine (506 mg, 1.93 mmol), DEAD (0.31 ml, 1.93 mmol) by a procedure similar to that described for the preparation of the title compound **3**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2938, 1711, 1626, 1626, 1199. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.19—1.58 (m, 12H), 2.11 (m, 1H), 3.48 (m, 3H), 3.97 (m, 3H), 4.20 (m, 1H), 4.43 (m, 2H), 4.70 (m, 1H), 4.84 (m, 1H), 7.20 (m, 2H), 7.73 (m, 1H), 7.85 (m, 1H), 8.04 (m, 1H), 8.53 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.8, 13.6, 28.6, 29.2, 59.1, 66.1, 73.5, 76.4, 77.1, 78.7, 101.6, 105.8, 119.7, 125.5, 125.9, 127.3, 128.3, 130.9, 136.5, 160.1, 167.0. HR-MS *m/z*: Calcd for $C_{23}H_{28}NO_6S$, 400.4637. Found: 400.4641. *Anal.* Calcd for $C_{31}H_{31}NO_6S$: C, 68.98; H, 7.04. Found: C, 68.96, H, 7.09.

6-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]-naphthalene-2-carbaldehyde (10) DIBAL-H (1.0 M in CH_2Cl_2, 2.4 ml, 2.4 mmol) was added dropwise to a stirred solution of 6-[2-(2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]naphthalene-2-carboxylic acid ethyl ester (**9**) (650 mg, 1.62 mmol) in CH_2Cl_2 at −78 °C. After stirring at the same temperature for 1 h, the reaction mixture was quenched with 1 N HCl and extracted with CH_2Cl_2. The extracted was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* the residue was dissolved in dry CH_2Cl_2 (20 ml) and added Dess–Martin periodate (815 mg, 1.92 mmol). The reaction mixture was stirred at room temperature for 1 h, and quenched with saturated $Na_2S_2O_3$ and washed water, dried ($MgSO_4$), and concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 with *n*-hexane–EtOAc (5 : 1, v/v) to give the title compound **10** as an oil (419 mg, 72.5% yield for 2 steps from **9**). IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1691, 1622. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.17 (s, 3H), 1.39 (s, 3H), 1.54 (s, 3H), 2.20 (m, 1H), 3.95—4.22 (m, 5H), 4.77 (m, 1H), 4.84 (m, 1H), 7.24 (m, 2H), 7.79—7.95 (m, 3H), 8.27 (s, 1H). ^{13}C-NMR (100 MHZ, $CDCl_3$) δ: 10.8, 28.6, 29.3, 66.5, 73.5, 76.4, 77.1, 78.7, 101.5, 105.6, 119.8, 122.7, 127.6, 131.3, 131.6, 131.7, 133.2, 160.6, 190. HR-MS *m/z*: Calcd for $C_{21}H_{24}O_5$, 356.4113. Found: 356.4125. *Anal.* Calcd for $C_{21}H_{24}O_5$: C, 70.76; H, 6.78. Found: C, 70.79; H, 6.81.

5-{6-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]-naphthalene-2-ylmethylene}thiazolidine-2,4-dione (11) The title compound **11** (200 mg, 37% yield) was prepared as an yellowish oil from 6-[2-(2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]naphthalene-2-carboaldehyde (**10**) (419 mg, 1.17 mmol), TZD (180 mg, 1.53 mmol), and catalytic amount of piperidium acetate by a similar to that described for the preparation of the title compound **5**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2986, 1738, 1700. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.16 (s, 3H), 1.42 (s, 3H), 1.59 (s, 3H), 2.22 (m, 1H), 3.93—4.20 (m, 5H), 5.32 (m, 2H), 7.11—7.37 (m, 3H), 7.65—7.86 (m, 4H), 9.06 (br s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.1, 28.5, 29.3, 66.5, 73.6, 76.4, 77.1, 78.7, 101.6, 105.4, 119.0, 120.1, 123.5, 126.5, 129.1, 129.5, 132.6, 134.7, 142.4, 157.5, 166.3, 167.1. HR-MS *m/z*: Calcd for $C_{24}H_{25}NO_6S$, 455.5234. Found: 455.5248. *Anal.* Calcd for $C_{24}H_{25}NO_6S$: C, 63.28; H, 5.53; N, 3.07. Found: C, 63.31; H, 5.53; N, 3.09.

5-{6-[2-(2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]-naphthalene-2-ylmethylene}thiazolidine-2,4-dione (12) The title com-

pound **12** (104 mg, 67% yield) was prepared as an yellowish oil from 5-{6-[2-(2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]naphthalene-2-ylmethylene}thiazolidine-2,4-dione (**10**) (154 mg, 0.33 mmol) and 20% $Pd(OH)_2$ (70 mg, 50% w/w) by a similar to that described for the preparation of the title compound **8**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2934, 1739, 1700, 1595, 1159. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.15 (m, 3H), 1.38 (s, 3H), 1.55 (s, 3H), 2.19 (m, 1H), 3.17 (m, 1H), 3.66 (m, 1H), 3.93—4.17 (m, 5H), 4.47 (m, 1H), 4.83 (m, 1H), 7.13—7.72 (m, 6H), 8.95 (br s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.8, 28.9, 29.3, 35.6, 56.6, 66.2, 73.6, 76.4, 77.1, 78.7, 101.9, 105.6, 118.6, 126.4, 128.4, 132.6, 133.0, 157.1, 167.1, 175.5. HR-MS *m/z*: Calcd for $C_{24}H_{27}NO_6S$, 457.5392. Found: 457.5401. *Anal.* Calcd for $C_{24}H_{27}NO_6S$: C, 63.00; H, 5.94; N, 3.06. Found: C, 63.05; H, 5.99; N, 3.09.

2-(6-Benzyloxymethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic Acid Ethyl Ester (14a) The title compound **14a** (1.38 g, 81% yield for 2 steps) was prepared as an yellowish oil from 6-benzyloxymethyl-2,2-dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4-one (**13a**) (1.3 mg, 4.67 mmol), ethoxycarbonylethylidene triphenylphosphorane (3.5 g, 9.06 mmol), and DIBAL-H (1.0 M in CH_2Cl_2 6.07 ml, 6.07 mmol) by a similar to that described for the preparation of the title compound **1**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1735, 1100. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25—1.77 (m, 13H), 2.67 (m, 2H), 3.59 (m, 2H), 4.15—4.58 (m, 7H), 4.66 (m, 1H), 7.33 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 9.6, 13.8, 28.9, 36.5, 59.8, 69.3, 73.1, 74.2, 75.3, 75.9, 101.7, 127.6, 128.9, 137.2, 174.5. HR-MS *m/z*: Calcd for $C_{20}H_{28}O_6$, 364.4316. Found: 364.4329. *Anal.* Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.89; H, 7.81.

2-(6-Benzyloxymethyl-2,2-cyclohexyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic Acid Ethyl Ester (14b) The title compound **14b** (1.29 mg, 62.8% yield for 2 steps) was prepared as an colorless oil form from 6-benzyloxymethyl-2,2-cyclohexyldihydrofuro[3,4-*d*]dioxol-4-one **13b** (1.62 g, 5.09 mmol), ethoxycarbonylethylidene triphenylphosphorane (1.95 g, 5.37 mmol) and DIBAL-H (1.0 M in CH_2Cl_2 7.6 ml, 7.6 mmol) by a similar to that described for the title compound **1**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2937, 1732, 1099. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.22—1.77 (m, 16H), 2.68 (m, 1H), 3.58 (m, 2H), 4.06—4.18 (m, 4H), 4.62—4.76 (m, 4H), 7.35 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 9.6, 13.6, 15.3, 27.7, 36.2, 36.9, 59.8, 69.3, 73.1, 75.2, 75.9, 76.0, 76.5, 106.1, 127.6, 128.5, 137.2, 174.5. HR-MS *m/z*: Calcd for $C_{23}H_{32}O_6$, 404.4953. Found: 404.4965. *Anal.* Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.31; H, 7.99.

2-(6-Benzyloxymethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic-1-ol (15a) The title compound **15a** (400 mg, 32.7% yield) was prepared as an yellowish oil from 2-(6-benzyloxymethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic acid ethyl ester (**14a**) (1.38 g, 30.78 mmol), and DIBAL-H (1.0 M in CH_2Cl_2 15.1 ml, 15.1 mmol) by a similar to that described for the title compound **9**. IR ($CHCl_3$) ν_{max} cm^{-1}: 3425, 2936, 1721, 1101. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 3H), 1.30 (s, 3H), 1.48 (s, 3H), 2.10 (br s, 1H), 2.59 (m, 1H), 3.61 (m, 2H), 3.83 (m, 1H), 4.06 (m, 1H), 4.14 (m, 1H), 4.42 (m, 1H), 4.60 (m, 3H), 7.36 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.5, 28.9, 32.1, 64.3, 73.9, 74.5, 75.6, 76.0, 76.5, 101.9, 127.6, 128.4, 137.2, HR-MS *m/z*: Calcd for $C_{18}H_{26}O_5$, 322.3964. Found: 322.3975. *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.05; H, 8.12. Found: C, 67.08; H, 8.14.

2-(6-Benzyloxymethyl-2,2-cyclohexyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic-1-ol (15b) The title compound **15b** (219 mg, 56% yield) was prepared as an oil from 2-(6-benzyloxymethyl-2,2-cyclohexyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propionic acid ethyl ester (**14b**) (137 mg, 1.08 mmol) and DIBAL-H (1.0 M in CH_2Cl_2, 3.24 ml, 3.24 mmol) by a similar to that described for the preparation of the title compound **9**. IR ($CHCl_3$) ν_{max} cm^{-1}: 3421, 2935, 2801, 1721.92, 1100. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40—2.10 (m, 13H), 1.48 (s, 3H), 3.56 (m, 2H), 3.83 (m, 2H), 4.42 (m, 1H), 4.53 (m, 2H), 4.70 (m, 1H), 4.80 (m, 1H), 7.35 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.7, 15.3, 27.7, 32.1, 36.9, 64.3, 69.3, 73.9, 74.5, 76.0, 76.2, 77.1, 106.3, 127.6, 128.4, 137.2. HR-MS *m/z*: Calcd for $C_{21}H_{30}O_5$, 362.2085. Found: 362.2094. *Anal.* Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.53; H, 8.43.

4-[2-(6-Benzyloxymethyl-2,2-dimetgthyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-yl)propoxy]benzaldehyde (16a) The title compound **16a** (270 mg, 51% yield) was prepared as an oil from 2-(6-benzyloxymethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propan-1-ol (**15a**) (400 mg, 1.24 mmol), 4-hydroxybenzaldehyde (200 mg, 1.61 mmol), Ph_3P (390 mg, 1.48 mmol) and DEAD (0.24 ml, 1.48 mmol) by a similar to that described for the preparation of the title compound **3**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2975, 2925, 1685, 1685, 1600. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (s, 3H), 1.30 (s, 3H), 1.48 (s, 3H), 2.18 (m, 1H), 3.58—4.20 (m, 6H), 4.45—4.54 (m, 4H), 7.05 (m, 2H), 7.31 (m, 5H), 7.85 (m, 2H), 9.91 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.0, 15.6, 27.5, 29.4, 35.8, 69.5, 73.9, 74.2, 76.1, 77.6, 106.9, 115.1, 127.6, 128.5, 130.4, 137.6, 164.6, 190.1. HR-MS *m/z*: Calcd for $C_{25}H_{30}O_6$, 426.2034. Found: 426.2041. *Anal.* Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.44; H, 7.13.

4-[2-(6-Benzyloxymethyl-2,2-cyclohexyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-yl)propoxy]benzaldehyde (16b) The title compound **16b** (200 mg, 72% yield) was prepared as an oil from 2-(6-benzyloxymethyl-2,2-cyclohexyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propan-1-ol (**15b**) (219 mg, 0.6 mmol), 4-hydroxybenzaldehyde (96 mg, 0.78 mmol), Ph_3P (190 mg, 0.73 mmol) and DEAD (0.11 ml, 0.73 mmol) by a similar to that described for the preparation of the title compound **3**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2972, 2925, 1686, 1600. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.13—1.70 (m, 13H), 2.18 (m, 1H), 3.58—4.20 (m, 6H), 4.50—4.60 (m, 4H), 7.00 (m, 2H), 7.31 (m, 5H), 7.83 (m, 2H), 9.90 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.8, 15.3, 27.8, 29.5, 36.9, 69.3, 73.6, 74.2, 76.0, 76.2, 77.1, 106.1, 114.7, 127.6, 128.3, 130.3, 137.2, 190.9. HR-MS *m/z*: Calcd for $C_{28}H_{34}O_6$, 466.2346. Found: 466.2352. *Anal.* Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35. Found: C, 72.11; H, 7.38.

5-{4-[2-(6-Benzyloxymethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-yl)propoxy]benzylidene}thiazolidine-2,4-dione (17a) The title compound **17a** (103 mg, 30.1% yield) was prepared as an oil from 4-[2-(6-benzyloxymethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]benzaldehyde (**16a**) (270 mg, 0.63 mmol), TZD (90 mg, 0.75 mmol), piperidine (0.1 mg, 0.94 mmol) by a similar to that described for the preparation of the title compound **5**. IR ($CHCl_3$) ν_{max} cm^{-1}: 3445, 2928, 1751, 1700, 1514. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 3H), 1.45 (s, 3H), 1.84 (s, 3H), 3.59 (m, 1H), 3.75 (m, 1H), 4.12 (m, 1H), 4.24 (m, 1H), 4.50 (s, 2H), 4.61 (s, 2H), 5.06 (m, 1H), 5.76 (m, 1H), 7.00 (m, 2H), 7.41 (m, 7H), 7.73 (s, 1H), 8.57 (br s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.9, 28.6, 29.5, 69.3, 73.6, 74.3, 75.6, 76.0, 76.5, 101.9, 114.1, 120, 126.8, 127.6, 128.4, 137.2, 158.1, 166.3, 167.1. HR-MS *m/z*: Calcd for $C_{28}H_{41}NO_7S$, 535.2593. Found: 535.2598. *Anal.* Calcd for $C_{28}H_{41}NO_7S$: C, 62.77; H, 7.71; N, 2.61. Found: C, 62.81; H, 7.75; N, 2.64.

5-{4-[2-(6-Benzyloxymethyl-2,2-cyclohexyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-yl)propoxy]benzylidene}thiazolidine-2,4-dione (17b) The title compound **17b** (154 mg, 63% yield) was prepared as an oil from 4-[2-(6-benzyloxymethyl-2,2-cyclohexyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propoxy]benzaldehyde (**16b**) (200 mg, 0.42 mmol), TZD (83 mg, 0.64 mmol), piperidine (0.05 ml, 0.55 mmol) by a similar to that described for the preparation of the title compound **3**. IR ($CHCl_3$) ν_{max} cm^{-1}: 3444, 2935, 1750, 1700, 1513. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12—1.78 (m, 12H), 2.30 (m, 1H), 3.59—4.12 (m, 6H), 4.55 (m, 4H), 6.96—7.43 (m, 9H), 7.72 (s, 1H), 8.69 (bs, NH). ^{13}C-NMR (100 MHZ, $CDCl_3$) δ: 10.8, 15.3, 27.7, 29.5, 36.9, 69.3, 73.6, 74.2, 74.5, 76.2, 77.1, 106.4, 114.1, 120.1, 126.5, 126.8, 127.6, 128.4, 137.2, 142, 158.2, 166.1, 167.1. HR-MS *m/z*: Calcd for $C_{31}H_{45}NO_7S$, 575.2905. Found: 575.2911. *Anal.* Calcd for $C_{31}H_{45}NO_7S$: C, 64.66; H, 7.87; N, 0.69. Found: C, 64.71; H, 7.91; N, 0.71.

(5-Benzyloxymethyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)acetic Acid Ethyl Ester (19) A mixture of (2,2-dimethyltetrahydro-[1,3]dioxol[4,5-*c*]pyrrol-4-yl)acetic acid ethyl ester (3.0 g, 13.08 mmol), and benzaldehyde (3.99 ml, 39.2 mmol) in methanol (30 ml) was adjusted pH 3 by acetic acid (12 ml), at 0 °C, and gradually added sodium cyanoborohydride (1.23 g, 19.62 mmol), the resulting mixture was stirred at room temperature overnight, and quenched with 2 N NaOH and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 with *n*-hexane–EtOAc (1 : 1, v/v) to give the title compound **19** as an oil (1.75 g, 73% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2982, 2935, 1733, 1378, 1209, 1179. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (m, 3H), 1.37 (s, 3H), 1.55 (s, 3H), 2.08 (m, 1H), 2.66 (m, 1H), 2.85 (m, 3H), 3.04 (m, 1H), 3.17 (m, 1H), 3.95 (m, 1H), 4.76 (m, 1H), 7.28 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.6, 28.6, 31.8, 48.4, 51.3, 57.2, 59.5, 73.5, 77.6, 101.3, 127.0, 128.2, 129.0, 136.3, 172.0. HR-MS *m/z*: Calcd for $C_{18}H_{25}NO_4$, 319.1777. Found: 319.1754. *Anal.* Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.80; H, 7.95; N; 4.50.

2-(5-Benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-ethanol (20) The title compound **20** (10.6 g, 86% yield) was prepared as an oil from (5-benzyl-2,2-dimethyltetrahydro[1,3]dioxol[4,5-*c*]pyrrol-4-yl)acetic acid ethyl ester (**19**) (14.22 g, 44.5 mmol), DIBAL-H (1.0 M in CH_2Cl_2, 134 ml, 133.5 mmol) by a procedure analogous to that described for the preparation of compound **15**. IR ($CHCl_3$) ν_{max} cm^{-1}: 3384, 2932, 1454, 1378, 1207. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 1.57 (s, 3H), 2.00 (m, 2H), 2.11 (m, 1H), 2.31 (m, 1H), 3.07 (m, 2H), 3.87 (m, 2H), 4.11 (m,

1H), 4.66 (m, 2H), 7.28 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.6, 31.4, 48.7, 52.2, 57.5, 58.8, 73.8, 78.2, 101.3, 127.0, 128.2, 129.0, 136.3. HR-MS *m/z*: Calcd for $C_{16}H_{23}NO_3$, 277.1672. Found: 277.1702. *Anal.* Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.05; H, 8.25; N, 4.95.

4-[2-(5-Benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-ethoxy]benzaldehyde (21) The title compound **21** (1.77 g, 76% yield) was prepared as an oil from 2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxol[4,5-*c*]pyrrol-4-yl)ethanol (**20**) (1.69 g, 6.09 mmol), 4-hydroxybenzaldehyde (967 mg, 7.92 mmol), Ph_3P (2.4 g, 9.14 mmol) and DEAD (1.44 ml, 9.14 mmol) by a procedure analogous to that described for the preparation of compound **16**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2972, 1687, 1600, 1256, 1159. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 1.58 (s, 3H), 2.05 (m, 1H), 2.26 (m, 2H), 2.43 (m, 1H), 7.04 (m, 2H), 7.27 (m, 5H), 7.86 (m, 2H), 9.91 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.8, 48.7, 52.0, 57.6, 68.5, 73.8, 78.5, 101.5, 114.5, 127.0, 128.2, 128.3, 129.0, 130.5, 136.5, 164.5, 190.1. HR-MS *m/z*: Calcd for $C_{23}H_{27}NO_4$, 381.1933. Found: 381.1945. *Anal.* Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.09; H, 7.30; N, 3.59.

5-{4-[2-(5-Benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)ethoxy]benzylidene}thiazolidine-2-one (22) The title compound **22** (600 mg, 95% yield) was prepared as yellow solid from 4-[2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxol[4,5-*c*]pyrrol-4-yl)ethoxy]benzaldehyde (**21**) (500 mg, 1.31 mmol), TZD (230 mg, 1.97 mmol), and with catalytic amount of piperidium acetate by a similar to that described for the preparation of compound **5**. IR (KBr) ν_{max} cm^{-1}: 2936, 1697, 1597, 1510, 1254. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H), 1.58 (s, 3H), 2.10 (m, 1H), 2.27 (m, 2H), 2.45 (m, 1H), 3.10 (m, 1H), 3.25 (m, 1H), 4.10 (m, 1H), 4.27 (m, 2H), 4.64 (m, 2H), 7.47—7.02 (m, 9H), 7.80 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.5, 28.8, 48.5, 52.5, 57.5, 68.5, 73.8, 78.2, 101.5, 114.5, 120.6, 126.8, 127.0, 128.2, 136.3, 142.5, 158.0, 167.0, 167.5. HR-MS *m/z*: Calcd for $C_{26}H_{28}N_2O_5S$, 480.1712. Found: 480.1795. *Anal.* Calcd for $C_{26}H_{28}N_2O_5S$: C, 64.98; H, 5.87; N, 5.83. Found: C, 65.01; H, 5.95; N, 5.75.

4-[2-(1-Benzyl-3,4-diethoxypyrrolidin-2-yl)ethoxy]benzaldehyde (23a) The title compound **23a** (300 mg, 58% yield) was prepared as an oil from 5-{4-[2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxol[4,5-*c*]pyrrol-4-yl)ethoxy]benzaldehyde (**21**) (500 mg, 1.31 mmol), TFA–H_2O (10 ml, 4/1 v/v), sodium hydride (60% in mineral oil, 79 mg, 1.97 mmol), and ethyl iodide (0.42 mg, 5.24 mmol) by a similar to that described for the preparation of compounds **4** and **7**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2934, 2796, 1688, 1600, 1255, 1212. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23 (m, 6H), 2.00—2.30 (m, 2H), 2.91 (m, 1H), 3.07 (m, 2H), 3.52 (m, 4H), 3.75 (m, 1H), 3.91 (m, 3H), 4.26 (m, 2H), 7.01 (d, J=8.7 Hz, 2H), 7.25 (m, 5H), 7.83 (d, J=8.7 Hz, 2H), 9.89 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5, 28.8, 48.7, 52.5, 57.5, 60.8, 61.6, 68.5, 74.1, 78.5, 114.7, 127.0, 128.2, 128.3, 129.0, 130.3, 136.5, 164.6, 190.0. HR-MS *m/z*: Calcd for $C_{24}H_{31}NO_4$, 397.2245. Found: 397.2210. *Anal.* Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.61; H, 7.70; N, 3.65.

4-[2-(1-Benzyl-3,4-*bis*-benzyloxypyrrolidin-2-yl)ethoxy]benzaldehyde (23b) The deprotection and *O*-benzylation of the title compound 4-[2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxol[4,5-*c*]pyrrol-4-yl)ethoxy]benzaldehyde **21** (200 mg, 70 mmol) was conducted in a similar procedure as employed in the synthesis of the title compounds **4** and **7**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2920, 1685, 1600, 1256, 1158. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.05—2.35 (m, 2H), 2.53 (m, 1H), 3.15 (m, 2H), 3.50 (d, J=13.5 Hz, 1H), 4.00 (d, J=13.5 Hz, 1H), 4.05—4.20 (m, 15H), 7.74 (d, J=8.7 Hz, 2H), 9.89 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.5, 48.7, 52.5, 57.5, 68.1, 73.5, 73.8, 74.0, 78.4. HR-MS *m/z*: Calcd for $C_{34}H_{35}NO_4$, 521.2557. Found: 521.2580. *Anal.* Calcd for $C_{34}H_{35}NO_4$: C, 78.28; H, 6.76; N, 2.69. Found: C, 78.50; H, 6.90; N, 2.55.

5-{4-[2-(1-Benzyl-3,4-diethoxypyrrolidin-2-yl)ethoxy]benzylidene}thiazolidine-2,4-dione (24a) The title compound **24a** (30 mg, 36% yield) was prepared as an oil from 4-[2-(1-benzyl-3,4-dimethypyrrolidin-2-yl)-ethoxy]benzaldehyde (**23a**) (69 mg, 0.17 mmol), TZD (40 mg, 0.35 mmol) and with catalytic amount of piperidinium acetate by a similar to that described for the preparation of compound **5**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2975, 1697, 1595, 1510, 1252, 1177. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23 (m, 6H), 2.20 (m, 2H), 2.70 (m, 1H), 3.05 (m, 1H), 3.30 (m, 1H), 3.52 (m, 3H), 3.63—4.02 (m, 5H), 4.19 (m, 2H), 6.93—7.42 (m, 9H), 7.69 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.0, 28.5, 48.6, 52.5, 57.9, 60.5, 61.5, 68.5, 74.1, 78.5, 114.5, 120.5, 126.5, 126.8, 127.5, 128.2, 129.0, 136.3, 142.5, 158.5, 166.5, 167.1. HR-MS *m/z*: Calcd for $C_{27}H_{32}N_2O_5S$, 496.2024. Found: 496.2094. *Anal.* Calcd for $C_{27}H_{32}N_2O_5S$: C, 65.30; H, 6.49; N, 5.64. Found: C, 65.50; H, 6.57; N, 5.95.

5-{4-[2-(1-Benzyl-3,4-*bis*-benzyloxypyrrolidin-2-yl)ethoxy]benzylidene}thiazolidine-2,4-dione (24b) The title compound **24b** (200 mg, 84% yield) was prepared as an oil from 4-[2-(1-benzyl-3,4-*bis*-benzyloxypyrrolidin-2-yl)ethoxy]benzaldehyde (**23b**) (200 mg, 0.384 mmol) TZD (90.0 mg, 0.768 mmol) and with catalytic amount of piperidinium acetate by a similar to that described for the preparation of compound **5**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2930, 1698, 1604, 1377, 1266. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.07—2.27 (m, 2H), 2.56 (m, 1H), 3.18 (m, 2H), 3.55 (m, 1H), 3.97—4.19 (m, 4H), 4.54—4.83 (m, 4H), 6.85 (m, 2H), 7.32 (m, 17H), 7.92 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.5, 48.5, 52.5, 57.5, 68.1, 73.5, 74.0, 78.4, 114.1, 120.5, 126.5, 126.8, 127.0, 127.6, 128.2, 128.4, 129.0, 136.3, 137.2, 142.5, 158.0, 167.5, 166.0. HR-MS *m/z*: Calcd for $C_{37}H_{36}N_2O_5S$, 620.2336. Found: 620.2350. *Anal.* Calcd for $C_{37}H_{36}N_2O_5S$: C, 71.59; H, 5.85; H, 4.51. Found: C, 71.70; H, 5.90; N, 4.45.

Benzoic Acid-2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]-pyrrol-4-yl)ethyl Ester (25) The title compound **25** (13.6 g, 93% yield) was prepared as an oil from 2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)ethanol (**20**) (10.6 g, 38.36 mmol) benzoic anhydride (13 g, 57.5 mmol) and with catalytic amount of DMAP by a similar to that described for the preparation of compound **7**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2934, 2791, 1717, 1452, 1378, 1275, 1112, 712. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 1.57 (s, 3H), 2.06 (dd, J=11.2, 4.6 Hz, 1H), 2.29—2.35 (m, 3H), 3.07 (d, J=11.2 Hz, 1H), 3.24 (d, J=13.6 Hz, 1H), 4.10 (d, J=13.6 Hz, 1H), 4.51—4.69 (m, 4H), 7.24—7.59 (m, 8H), 8.10 (d, J=6.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.5, 48.7, 52.5, 57.5, 62.1, 73.8, 78.0, 100.5, 127.0, 128.2, 128.4, 129.4, 129.0, 129.5, 132.8, 136.3, 167.5. HR-MS *m/z*: Calcd for $C_{23}H_{27}NO_4$, 381.1933. Found: 981.1940. *Anal.* Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.50; H, 7.50; N, 3.90.

Benzoic Acid-2-(1-benzyl-3,4-diethoxypyrrolidin-2-yl)ethyl Ester (26) The title compound **26** (2.18 g, 52% yield) was prepared as an oil from benzoic acid 2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)ethyl ester (4.0 g, 10.48 mmol) TFA–H_2O, ethyl iodide, NaH, and catalytic amount of TBAI by a similar to that described for the preparation of compound **23**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2974, 1717, 1376, 1275, 1113. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23 (q, J=5.5 Hz, 6H), 2.00 (m, 1H), 2.20 (m, 1H), 2.53 (m, 1H), 2.80 (m, 1H), 3.15 (m, 2H), 3.48—3.95 (m, 7H), 4.43 (t, J=6.5 Hz, 2H), 7.28—7.60 (m, 8H), 8.07 (d, J=6.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.0, 28.9, 49.0, 53.0, 57.5, 60.0, 61.1, 62.5, 75.5, 79.2, 127.0, 128.2, 128.4, 129.0, 129.7, 136.0, 137.5, 167.5. HR-MS *m/z*: Calcd for $C_{24}H_{31}NO_4$, 397.2245. Found: 397.2290. *Anal.* Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.59; H, 7.99; N, 3.60.

Benzoic Acid-2-(3,4-diethoxypyrrolidin-2-yl)ethyl Ester (27a) The title compound **27a** (15 g, 76% yield) was prepared as an oil from benzoic acid-2-(1-benzyl-3,4-diethoxypyrrolidin-2-yl)ethyl ester (**26**) (2.55 g, 6.42 mmol) 20% $Pd(OH)_2$ (1.1 g) under H_2 atmosphere by a similar to that described for the preparation of compound **19**. IR ($CHCl_3$) ν_{max} cm^{-1}: 3419, 2983, 1732, 1379, 1210. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23 (m, 6H), 1.99—2.16 (m, 2H), 2.55 (br s, 1H), 3.04 (m, 2H), 3.20 (m, 1H), 3.55 (m, 3H), 3.78 (m, 2H), 3.95 (m, 1H), 4.45 (t, J=6.5 Hz, 2H), 7.41—7.58 (m, 3H), 8.05 (d, J=6.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5, 30.0, 45.0, 50.5, 60.5, 61.1, 61.8, 76.3, 80.5, 128.5, 129.7, 130.5, 132.8, 167.0. HR-MS *m/z*: Calcd for $C_{17}H_{25}NO_4$, 307.1777. Found: 307.1790. *Anal.* Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.50; H, 8.55; N, 4.85.

2-(2-Benzyloxyethyl)3,4-diethoxy-*N*-methylpyrrolidine (28a) The title compound **28a** (318 mg, 61% yield) was prepared from benzoic acid-(3,4-diethoxypyrrolidin-2-yl)ethyl ester (**27**) (500 mg, 1.62 mmol), *para*-formaldehyde (488 mg, 16.3 mmol), sodium cyanoborohydride (153 mg, 2.43 mmol), and acetic acid by a similar to that described for the preparation of compound **19**. The following compound **28b**, **c** were prepared by a similar to the procedure above. IR ($CHCl_3$) ν_{max} cm^{-1}: 2794, 1717, 1275, 1113, 715. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.90—2.55 (m, 7H), 3.18 (m, 1H), 3.46—3.94 (m, 6H), 4.44 (m, 2H), 7.46 (m, 2H), 7.58 (m, 1H), 8.07 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5, 27.5, 37.6, 51.5, 55.0, 61.1, 62.1, 62.5, 73.8, 77.9, 128.4, 129.7, 130.5, 132.5, 132.9, 167.7. HR-MS *m/z*: Calcd for $C_{18}H_{27}NO_4$, 321.1930. Found: 321.1955. *Anal.* Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.35; H, 8.60; N, 4.55.

2-(2-Benzoyloxyethyl)3,4-diethoxy-*N*-propylpyrrolidine (28b) Yield: 280 mg, 58%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2973, 1734, 1623, 1509, 1252, 1176. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88—1.28 (m, 9H), 1.90 (m, 2H), 2.20 (m, 1H), 2.55 (m, 1H), 2.65 (m, 1H), 2.80 (m, 1H), 3.17 (m, 1H), 3.53 (m, 3H), 3.79—3.99 (m, 3H), 4.56 (m, 2H), 7.47 (m, 2H), 7.57 (m, 1H), 8.05 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.5, 15.5, 23.1, 28.1, 49.5, 52.9, 54.5, 60.9, 61.5, 62.3, 74.1, 78.5, 128.5, 129.9, 130.5, 167.0. HR-MS *m/z*: Calcd for $C_{20}H_{31}NO_4$, 349.2245. Found: 349.2279. *Anal.* Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.90; H, 8.79; N, 4.20.

2-(2-Benzyloxyethyl)3,4-diethoxy-*N*-cyclopentylpyrrolidine (28c) Yield: 328 mg. 67%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2972, 1730, 1509, 1254, 1177, 687. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12—2.30 (m, 16H), 2.80 (m, 1H), 3.05 (m, 3H), 3.49—3.98 (m, 6H), 7.44 (m, 2H), 7.57 (m, 1H), 8.06 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5, 21.5, 28.4, 30.5, 46.9, 50.6, 55.7, 61.5, 62.0, 62.5, 75.0, 79.5, 128.5, 129.8, 130.6, 134.5, 167.9. HR-MS *m/z*: Calcd for $C_{22}H_{33}NO_4$, 375.2401. Found: 375.2386. *Anal.* Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.55; H, 8.99; N, 3.84.

2-(3,4-Diethoxy-1-methylpyrrolidin-2-yl)ethanol (29a) Sodium methoxide (25% wt in MeOH, 0.68 ml, 2.97 mmol) was added dropwise to a stirred solution of 2-(2-benzyloxyethyl-3,4-diethoxy-1-methyl)pyrrolidine (318 mg, 0.99 mmol) in methanol at 0 °C. The resulting mixture was stirred at room temperature for 2 h, then evaporated under reduce pressure. The crude product was chromatography over silica gel using CH_2Cl_2–MeOH (3 : 1, v/v) to afford of the title compound **29a** as an oil (83% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3385, 2975, 2931, 1648, 1455, 1377, 1116, 1063. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.78 (m, 6H), 1.84 (m, 2H), 2.38 (s, 3H), 2.50 (m, 1H), 2.78 (m, 1H), 3.12 (m, 1H), 3.51 (m, 3H), 3.68 (m, 2H), 3.79 (m, 1H), 3.91 (m, 2H), 4.52 (br s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5, 32.5, 37.0, 51.5, 55.0, 58.2, 61.0, 61.5, 74.5, 18.0. HR-MS *m/z*: Calcd for $C_{11}H_{23}NO_3$, 217.1671. Found: 217.1711. *Anal.* Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.45. Found: C, 60.89; H, 11.01; N, 6.80.

The following compound **29b, c** were synthesized by a similar procedure to that described for the preparation of **29a**.

2-(3,4-Diethoxy-1-propylpyrrolidin-2-yl)ethanol (29b) Yield: 290 mg, 74%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3424, 2974, 1600, 1509, 1176, 688. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 0.96 (t, J=7.2 Hz, 3H), 1.25—1.55 (m, 2H), 1.74 (m, 1H), 2.05 (m, 1H), 2.33 (m, 1H), 2.60—2.91 (m, 3H), 3.11 (m, 1H), 3.51—4.05 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.0, 15.0, 23.5, 32.1, 49.1, 52.5, 54.0, 58.5, 61.0, 61.5, 74.5, 78.0. HR-MS *m/z*: Calcd for $C_{13}H_{27}NO_3$, 245.1984. Found: 245.1999. *Anal.* Calcd for $C_{13}H_{27}NO_3$: C, 63.64; H, 11.09; N, 5.71. Found: C, 63.80; H, 11.22; N, 5.91.

2-(3,4-Diethoxy-1-cyclopentylpyrrolidin-2-yl)ethanol (29c) Yield: 476 mg, 87%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3430, 2972, 1596, 1509, 1255. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.16—1.25 (m, 9H), 1.60—1.95 (m, 7H), 2.49 (m, 1H), 2.78 (m, 1H), 3.05 (dd, J=11.2, 2.8 Hz, 1H), 3.30 (m, 1H), 3.48—3.90 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.0, 21.5, 30.5, 31.5, 47.0, 51.5, 55.1, 58.0, 61.5, 63.0, 75.5, 78.7. HR-MS *m/z*: Calcd for $C_{15}H_{29}NO_3$, 217.2140. Found: 217.2154. *Anal.* Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found C, 66.50; H, 10.98; N, 5.35.

3-[2-(3,4-Diethoxy-1-methylpyrrolidin-2-yl)ethoxy]benzaldehyde (30a) The title compound **30a** (100 mg, 75% yield) was prepared as an oil from 2-(3,4-diethoxy-1-methylpyrrolidin-2-yl)ethanol (**29**) (90 mg, 0.414 mmol) 4-hydroxybenzaldehyde (101 mg, 0.828 mmol), Ph_3P (217 mg, 0.828 mmol) and DEAD, (0.13 ml, 0.828 mmol) by a similar to procedure that described for the preparation of the title compound **3**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1685, 1601, 1437, 1160, 1119, 721. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.26 (t, J=6.8 Hz, 6H), 2.19 (m, 4H), 2.30 (s, 3H), 3.29 (m, 1H), 3.98—4.26 (m, 6H), 4.79 (m, 2H), 7.02 (d, J=4.4 Hz, 2H), 7.86 (d, J=4.4 Hz, 2H), 9.91 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.0, 28.5, 36.0, 51.5, 53.1, 61.5, 62.0, 68.5, 73.1, 78.5, 115.1, 128.6, 130.5, 160.9, 190.7. HR-MS *m/z*: Calcd for $C_{18}H_{27}NO_4$, 321.1933. Found: 321.1950. *Anal.* Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.50; H, 8.50; N, 4.55.

3-[2-(3,4-Diethoxy-1-propylpyrrolidin-2-yl)ethoxy]benzaldehyde (30b) Yield: 120 mg, 83%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2974, 1680, 1600, 1509, 1252. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 0.88 (m, 3H), 1.20—1.60 (m, 10H), 2.01—2.25 (m, 2H), 2.51 (m, 1H), 2.90—3.21 (m, 3H), 3.40—3.60 (m, 4H), 3.80—4.35 (m, 5H), 6.83 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 9.90 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.5, 15.7, 23.0, 24.5, 44.5, 53.0, 55.5, 61.5, 62.0, 64.5, 73.0, 78.5, 115.7, 129.1, 13.5, 167.5, 190.7. HR-MS *m/z*: Calcd for $C_{20}H_{31}NO_4$, 349.2245. Found: 349.2245. *Anal.* Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.91; H, 9.01; N, 4.24.

3-[2-(3,4-Diethoxy-1-cyclopentylpyrrolidin-2-yl)ethoxy]benzaldehyde (30c) Yield: 335 mg, 73%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2972, 1697, 1509, 1176, 687. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.22 (m, 9H), 1.60 (m, 1H), 1.77—1.91 (m, 7H), 2.46 (m, 1H), 2.80 (m, 1H), 3.09 (m, 1H), 3.31 (m, 1H), 3.50—3.91 (m, 9H), 6.86 (d, J=8.8 Hz, 2H), 7.28 (d, J=8.8 Hz, 2H), 9.91 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5, 21.5, 29.0, 30.5, 67.1, 51.0, 55.7, 60.5, 62.0, 64.5, 73.5, 79.0, 115.0, 129.1, 130.5, 167.0, 191.5. HR-MS *m/z*: Calcd for $C_{22}H_{33}NO_4$, 375.2401. Found: 375.2455. *Anal.* Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.50; H, 8.90; N, 3.95.

5-{3-[2-(3,4-Diethoxy-1-methylpyrrolidin-2-yl)ethoxy]benzaldehyde}-thiazolidine-2,4-dione (31a) The title compound **31a** (90 mg, 69% yield) was prepared as an oil from 3-[2-(3,4-diethoxy-1-methylpyrrolidin-2-yl)-ethoxy]benzaldehyde (**30a**) (100 mg, 0.311 mmol), TZD (55 mg, 0.467 mmol), and using catalytic amount of piperidium acetate by a similar to that described for the preparation of the title compound **5**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2974, 1698, 1601, 1509, 1251, 1177. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.26 (m, 6H), 2.01 (m, 1H), 2.20 (m, 1H), 2.36 (s, 3H), 2.43 (m, 1H), 2.65 (m, 1H), 3.17 (m, 1H), 3.45—4.15 (m, 8H), 6.99 (d, J=8.8 Hz, 2H), 7.39 (d, J=8.8 Hz, 2H), 7.73 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.6, 28.5, 37.5, 51.5, 54.5, 60.1, 61.5, 68.7, 73.0, 78.9, 114.5, 119.5, 127.1, 128.0, 141.7, 458.1, 165.1, 167.0. HR-MS *m/z*: Calcd for $C_{21}H_{28}N_2O_5S$, 420.1712. Found: 420.1754. *Anal.* Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 60.01; H, 6.90; N, 6.81.

5-{3-[2-(3,4-Diethoxy-1-propylpyrrolidin-2-yl)ethoxy]benzaldehyde}-thiazolidine-2,4-dione (31b) Yield: 120 mg, 86%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2974, 1696, 1624, 1601, 1509, 1252, 1176. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 0.93 (m, 3H), 1.25 (m, 6H), 1.38 (m, 2H), 1.55 (m, 1H), 1.80 (m, 1H), 2.85 (m, 2H), 3.05 (m, 3H), 3.35 (m, 1H), 3.61 (m, 4H), 3.93 (m, 2H), 4.15 (m, 3H), 6.88 (m, 2H), 7.29 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.0, 15.5, 23.5, 28.0, 49.0, 53.5, 54.0, 60.5, 61.6, 68.5, 73.5, 78.5, 113.5, 118.5, 127.5, 128.0, 142.5, 158.5, 166.7, 169.1. HR-MS *m/z*: Calcd for $C_{23}H_{32}N_2O_5S$, 448.2024. Found: 448.2029. *Anal.* Calcd for $C_{23}H_{32}N_2O_5S$: C, 61.58; H, 7.19; N, 6.24. Found: C, 61.69; H, 7.35; N, 6.25.

5-{3-[2-(3,4-Diethoxy-1-cyclopentylpyrrolidin-2-yl)ethoxy]benzaldehyde}thiazolidine-2,4-dione (31c) Yield: 91%. IR (KBr) ν_{max} cm^{-1}: 2973, 1733, 1697, 1596, 1509, 1254, 1176. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.21—2.20 (m, 14H), 2.30 (m, 2H), 2.89 (m, 1H), 3.10 (m, 2H), 3.25 (m, 1H), 3.59 (m, 3H), 3.75—3.96 (m, 3H), 4.14—4.22 (m, 2H), 6.96 (m, 2H), 7.42 (m, 2H), 7.76 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.6, 22.0, 29.5, 31.0, 67.5, 51.6, 55.9, 60.1, 61.5, 68.5, 73.9, 79.5, 114.9, 119.8, 128.5, 128.9, 141.5, 158.5, 163.0, 164.1. HR-MS *m/z*: Calcd for $C_{25}H_{34}N_2O_5S$, 474.2180. Found: 474.2184. *Anal.* Calcd for $C_{25}H_{34}N_2O_5S$: C, 63.27; H, 7.22; N, 5.90. Found: C, 63.50; H, 7.54; N, 5.76.

5-{3-[2-(3,4-Diethoxy-1-methylpyrrolidin-2-yl)ethoxy]benzaldehyde}-thiazolidine-2,4-dione (32a) The title compound **32a** (47 mg, 64% yield) was prepared as yellow foam 5-{3-[2-(3,4-diethoxy-1-methylpyrrolidin-2-yl)ethanol]benzyl}thiazolidine-2,4-dione **31a** (73 mg, 0.174 mmol), and 20% $Pd(OH)_2$ under H_2 atmosphere by a similar to that described for the preparation of the title compound **12**. IR (KBr) ν_{max} cm^{-1}: 2794, 1698, 1605, 1508, 1254, 1178, 829. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.26 (m, 6H), 2.05—2.31 (m, 3H), 2.37 (s, 3H), 3.00 (m, 1H), 3.20 (m, 1H), 3.40—3.60 (m, 4H), 3.70—4.01 (m, 5H), 6.85 (m, 2H), 7.12 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5, 28.5, 35.4, 37.6, 51.0, 55.4, 57.0, 61.0, 62.5, 68.9, 72.5, 78.0, 114.5, 127.9, 132.0, 155.9, 164.6, 175.5. HR-MS *m/z*: Calcd for $C_{21}H_{30}N_2O_5S$, 422.1868. Found: 422.1890. *Anal.* Calcd for $C_{21}H_{30}N_2O_5S$: C, 59.69; H, 7.16; N, 6.63. Found: C, 59.80; H, 7.35; N, 6.54.

5-{3-[2-(3,4-Diethoxy-1-propylpyrrolidin-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione (32b) Yield: 95 mg, 80%. IR (KBr) ν_{max} cm^{-1}: 2795, 1734, 1696, 1623, 1601, 1509, 1289, 1252, 1176. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 0.88—1.60 (m, 13H), 2.00—2.30 (m, 3H), 2.60 (m, 1H), 2.75 (m, 1H), 3.00 (m, 1H), 3.20 (m, 1H), 3.39—3.60 (m, 4H), 3.72—4.06 (m, 5H), 6.84 (m, 2H), 7.13 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.0, 15.6, 22.4, 29.1, 35.0, 48.9, 51.5, 55.0, 58.9, 60.5, 62.0, 68.5, 75.0, 78.5, 113.5, 128.5, 130.9, 155.4, 167.6, 175.0. HR-MS *m/z*: Calcd for $C_{23}H_{34}N_2O_5S$, 450.2180. Found: 450.2194. *Anal.* Calcd for $C_{23}H_{34}N_2O_5S$: C, 61.31; H, 7.61; N, 6.22. Found: C, 61.45; H, 7.82; N, 6.44.

5-{3-[2-(3,4-Diethoxy-1-cyclopentylpyrrolidin-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione (32c) Yield: 350 mg, 77%. IR (KBr) ν_{max} cm^{-1}: 2972, 1748, 1698, 1582, 1511, 1245, 1177, 1112. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 2.05—1.12 (m, 13H), 2.40 (m, 4H), 2.80—3.10 (m, 3H), 3.40—4.15 (m, 9H), 4.50 (m, 1H), 6.87 (m, 2H), 7.15 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.6, 21.0, 29.5, 30.5, 35.1, 47.2, 51.0, 55.5, 57.0, 60.5, 61.9, 68.5, 74.1, 79.1, 116.0, 124.9, 133.5, 156.1, 164.1, 175.0. HR-MS *m/z*: Calcd for $C_{25}H_{36}N_2O_5S$, 476.2336. Found: 476.2354. *Anal.* Calcd for $C_{25}H_{36}N_2O_5S$: C, 63.00; H, 7.61; N, 5.88. Found: C, 63.15; H, 7.85; N, 6.01.

6-[2-(5-Benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-propoxy]naphthalene-2-carboxylic Acid Ethyl Ester (33a) The title compound **33a** (470 mg, 74% yield) was prepared as an oil from 2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propan-1-ol (370 mg, 1.34 mmol), 6-hydroxy-2-naphthoic acid ethyl ester (376 mg, 1.74 mmol), Ph_3P (527 mg, 2.01 mmol), and DEAD by a similar to that described for the preparation of the title compound **9**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2938, 1711, 1626, 1437, 1276, 1199. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.36 (s, 3H), 1.46 (m, 3H), 1.56 (s, 3H), 2.14 (m, 4H), 4.44 (m, 2H), 4.64 (m, 2H), 7.20—8.03 (m, 5H), 8.54 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 28.0, 29.5, 48.5, 52.3, 58.0, 59.1, 68.5, 73.5, 78.0, 102.5, 105.6, 120.1,

125.5, 126.0, 127.0, 128.1, 129.5, 130.5, 131.0, 136.5, 137.0, 160.1, 167.0. HR-MS *m/z*: Calcd for $C_{29}H_{33}NO_5$, 475.2350. Found: 475.2394. *Anal.* Calcd for $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99; N, 2.95. Found: C, 73.25; H, 7.05; N, 3.06.

6-[2-(2,2,5-Trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-propoxy]naphthalene-2-carboxylic Acid Ethyl Ester (33b) The title compound **33b** (300 mg, 56% yield) was prepared as an oil from 2-(2,2,5-trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propan-1-ol (**20b**) (273 mg, 1.35 mmol), 6-hydroxy-2-naphtonic acid ethyl ester (381 mg, 1.76 mmol), and DEAD by a similar to that described for the preparation of the title compound **9**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2939, 2779, 1711, 1627, 1473, 1438, 1278, 1200, 1096. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.35 (s, 3H), 1.46 (t, J=7.2 Hz, 3H), 1.56 (s, 3H), 2.11—2.22 (m, 4H), 2.33 (s, 3H), 3.24 (d, J=11.2 Hz, 1H), 4.29 (m, 2H), 4.45 (t, J=7.2 Hz, 2H), 4.65 (s, 2H), 7.21 (m, 2H), 7.74 (m, 1H), 7.85 (m, 1H), 8.05 (m, 1H), 8.54 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 28.6, 38.5, 51.9, 54.5, 59.0, 64.1, 72.5, 78.0, 101.5, 105.6, 120.1, 125.0, 125.5, 126.0, 128.0, 130.5, 131.0, 135.6, 160.5, 167.0. HR-MS *m/z*: Calcd for $C_{23}H_{29}NO_5S$, 399.2038. Found: 399.2058. *Anal.* Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.34; H, 7.50; N, 3.55.

6-[2-(5-Benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-propoxy]naphthalene-2-carbaldehyde (34a) The title compound **34a** (158 mg, 37% yield) was prepared as an oil from 6-[2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-carboxylic acid ethyl ester **33a** (470 mg, 0.99 mmol), DIBAL-H (1.0 M in CH_2Cl_2, 2.96 ml, 2.96 mmol), and Dess–Martin reagent by a similar to that for the preparation of the title compound **10**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1691, 1622, 1471, 1335, 1268, 1178. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.37 (s, 3H), 1.60 (s, 3H), 2.08 (m, 1H), 2.33 (m, 1H), 2.48 (m, 1H), 3.10 (m, 1H), 3.23 (m, 1H), 4.13 (m, 3H), 4.36 (m, 2H), 4.66 (m, 2H), 7.25—7.95 (m, 10H), 8.28 (s, 1H), 10.12 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.0, 29.5, 48.1, 52.3, 58.6, 68.5, 73.1, 79.1, 101.9, 105.6, 120.1, 122.4, 122.9, 124.0, 125.5, 129.0, 131.0, 132.5, 133.6, 135.1, 137.4, 138.0, 161.4, 190.5. HR-MS *m/z*: Calcd for $C_{27}H_{29}NO_4$, 431.2089. Found: 431.2099. *Anal.* Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.30; H, 6.90; N, 3.30.

6-[2-(2,2,5-Trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-propoxy]naphthalene-2-carbaldehyde (34b) The title compound **34b** (185 mg, 69% yield) was prepared as an oil from 6-[2-(2,2,5-trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-carboxylic acid ethyl ester (**33b**) (300 mg, 0.751 mmol), DIBAL-H (1.0 N in CH_2Cl_2, 2.3 ml, 2.25 mmol), and Dess–Martin reagent by a similar to that for the preparation of the title compound **10**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2936, 2792, 1692, 1623, 1472, 1333, 1268, 1180, 1021. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.36 (s, 3H), 1.56 (s, 3H), 2.19 (m, 3H), 2.33 (s, 3H), 3.24 (m, 1H), 4.31 (m, 2H), 4.64 (m, 2H), 7.24—7.94 (m, 5H), 8.27 (s, 1H), 10.11 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.9, 38.0, 51.9, 55.0, 67.1, 72.5, 78.5, 101.5, 105.0, 119.5, 122.0, 127.0, 131.5, 132.0, 133.0, 133.5, 161.0, 190.5. HR-MS *m/z*: Calcd for $C_{21}H_{25}NO_4$, 355.1777. Found: 355.1809. *Anal.* Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.05; H, 7.11; N, 4.01.

5-{6-[2-(5-Benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-yl-methylene}thiazolidine-2,4-dione (35a) The title compound **35a** (170 mg, 97% yield) was prepared as a yellow solid 6-[2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-carbaldehyde (**34a**) (158 mg, 0.366 mmol), TZD (64 mg, 0.549 mmol) and piperidinum acetate by a similar to that described for the preparation of the title compound **11**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1739, 1700, 1594, 1272. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.38 (s, 3H), 1.61 (s, 3H), 2.13 (m, 1H), 2.35 (m, 2H), 2.54 (m, 1H), 3.11 (m, 1H), 3.29 (m, 1H), 4.13 (m, 1H), 4.37 (m, 2H), 4.70 (m, 2H), 7.20—7.91 (m, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.5, 48.0, 52.5, 57.5, 68.0, 74.1, 78.2, 101.5, 405.0, 119.0, 119.5, 123.0, 123.5, 125.0, 125.7, 128.0, 129.5, 132.5, 133.0, 137.0, 142.5, 158.7, 166.5, 168.0. HR-MS *m/z*: Calcd for $C_{30}H_{30}N_2O_5S$, 530.1868. Found: 530.1887. *Anal.* Calcd for $C_{30}H_{30}N_2O_5S$: C, 67.90; H, 5.70; N, 5.28. Found: C, 68.02; H, 5.89; N, 5.34.

5-{6-[2-(2,2,5-Trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-yl-methylene}thiazolidine-2,4-dione (35b) The title compound **35b** (130 mg, 55% yield) was prepared as a yellow solid 6-[2-(2,2,2-trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-carbaldehyde (**34b**) (185 mg, 0.52 mmol), TZD (91 mg, 0.78 mmol) and piperidinum acetate by a similar to that described for the preparation of the title compound **11**. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1733, 1698, 1595, 1558, 1271, 1184. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.35 (s, 3H), 1.58 (s, 3H), 2.46—2.19 (m, 7H), 3.25 (m, 1H), 4.27 (m, 2H), 4.70 (m, 2H), 4.78—7.01 (m, 7H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.5, 36.5, 52.1, 55.0, 68.5, 73.0, 77.5, 102.0, 105.5, 118.5, 119.5, 123.0, 125.0, 126.9, 128.0, 129.0, 132.4, 134.0, 142.0, 157.5, 166.5, 167.0. HR-MS *m/z*: Calcd for $C_{24}H_{26}N_2O_5S$, 454.1556. Found: 454.1570. *Anal.* Calcd for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.50; H, 5.90; N, 6.34.

5-{6-[2-(5-Benzyl-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-yl-methyl}thiazolidine-2,4-dione (36a) The title compound **36a** (50 mg, 33% yield) was prepared as yellow solid oil from 5-{6-[2-(5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-yl-methylene}thiazolidine-2,4-dione (**35a**) (150 mg, 0.283 mmol), and 20% $Pd(OH)_2$ (120 mg) under H_2 atmosphere by a similar to that described for the preparation of the title compound **12**. IR (KBr) ν_{max} cm^{-1}: 2936, 1739, 1701, 1594, 1472, 1394, 1272. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.36 (s, 3H), 1.59 (s, 3H), 2.06 (m, 1H), 2.31 (m, 2H), 2.48 (m, 1H), 3.08—3.31 (m, 3H), 3.70 (m, 1H), 4.13 (m, 1H), 4.30 (m, 2H), 4.64 (m, 3H), 7.18—7.74 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.5, 36.6, 48.5, 52.4, 56.7, 57.5, 68.0, 73.5, 78.0, 102.5, 105.7, 118.1, 125.0, 125.5, 126.0, 127.5, 128.4, 129.6, 129.9, 133.0, 133.5, 136.0, 155.5, 166.7, 175.0. HR-MS *m/z*: Calcd for $C_{30}H_{32}N_2O_5S$, 532.2024. Found: 532.2071. *Anal.* Calcd for $C_{30}H_{32}N_2O_5S$: C, 67.65; H, 6.06; N, 5.26. Found: C, 67.80; H, 6.20; N, 5.30.

5-{6-[2-(2,2,5-Trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-propoxy]naphthalene-2-yl-methyl}thiazolidine-2,4-dione (36b) The title compound **36b** (71 mg, 62% yield) was prepared as an yellow solid 5-{6-[2-(2,2,5-trimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)propoxy]naphthalene-2-yl-methylene}thiazolidine-2,4-dione (**35b**) (114 mg, 0.251 mmol), 20% $Pd(OH)_2$ (160 mg) under H_2 atmosphere by a similar to that described for the preparation of the title compound **12**. IR (KBr) ν_{max} cm^{-1}: 2936, 1734, 1696, 1596, 1558, 1472, 1384, 1184. ^{1}H-NMR (400 MHz, MeOH-d_4) δ: 1.34 (s, 3H), 1.53 (s, 3H), 2.23 (m, 4H), 2.33 (s, 3H), 3.24 (m, 2H), 3.65 (m, 1H), 4.25 (m, 2H), 4.55 (m, 1H), 4.64 (m, 2H), 7.17—7.72 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.9, 36.0, 37.5, 51.5, 55.0, 57.0, 67.5, 73.4, 78.0, 102.5, 104.6, 118.9, 125.0, 125.5, 128.5, 128.9, 129.4, 134.0, 135.1, 156.4, 166.9, 175.0. HR-MS *m/z*: Calcd for $C_{24}H_{28}N_2O_5S$, 456.1712. Found: 456.1754. *Anal.* Calcd for $C_{24}H_{28}N_2O_5S$: C, 63.14; H, 6.18; N, 6.14. Found: C, 63.24; H, 6.26; N, 6.15.

Biological Procedures *in Vitro* Stimulation of Glucose Utilization in L6 Myocytes Rat L6 myoblasts (American Type Culture Collection) were maintained in Dulbecco's modified Eagle's medium (DMEM, containing 5 mM glucose and 10% heat-inactivated fetal bovine serum, 100 u/ml penicillin, 100 μg/ml streptomycin) and were plated in 96-well microtiter plates at a density of 3000 cells/well. After confluence, differentiation of the cells into myotubes was induced by changing the supplementation of the medium from 10% to 2% fetal bovine serum (FBS). Cells were used in experiments once they had differentiated, on the 13th—15th day following plating. L6 cells were treated with the test compound and serum-free DMEM containing 5 mM glucose for 48 h. The test compound was dissolved in DMSO (the final concentration of DMSO in the serum-free testing media (1%) had no effects on glucose utilization). The compound was tested in quadruplicate in each experiment at a final concentration of 0.3, 1, 3, 10, 30, and 100 μM. Glucose utilization was assessed by measurement of glucose remaining in the media using a glucose oxidase assay (Glucose-E kit, Young Dong Diagnostics, Seoul, Korea). Effective concentration (EC_{40}) for 40% increase of glucose utilization was calculated. The maximum enhancement of glucose utilization was approximately 85% over control.

***In Vitro* Cytotoxicity in Cultured Ret Hepatocytes** Primary cultures of hepatocytes isolated by collagenase perfusion of adult rat were used as an *in vitro* system for assessing cytotoxicity of the compounds. Hepatocytes were isolated from male Sprague–Dawly rats weighing about 200 g by the collagenase perfusion method of Seglen.[21] Cells with >85% viability (confirmed by trypan blue exelusion) were distributed onto collagen type I-coated 24 well plates at a subconfluent density (10^5 cells/cm^2), and cultured in DMEM containing 5 mM glucose, 10% heat-inactivated FBS, 10^{-7} M human insulin, 10^{-6} M dexamethasone. After incubation for 24 h, the medium was collected and the cells were washed twice with phosphate-buffered saline. Then, hepatocytes were cultured in serum-free DMEM as described above. This medium was supplemented with either 12.5, 25, 50, 100 or 200 μM compounds or with the solvent (1% DMSO) only. Cells were exposed to the compounds and/or solvent for 24 h. All cultures were performed at 37 °C in an atmosphere of 5% CO_2 and 95% air with a relative humidity of 100%. Cytotoxicity of the compounds tested was determined by means of the Neutral Red uptake assay.[40,41]

Acknowledgements The authors like to thanks for the Research Grant

(HMP-00-B-21500-014) from Ministry of Health and Welfare, Korea for financial support.

References and Notes

1) Warram J. H., Martin B. C., Krolewski A. S., Soeldner J. S., Kahn C. R., *Ann. Intern. Med.*, **113**, 909—915 (1990).
2) Lillioja S., Mott K. M., Spraul M., Ferraro R., Foley J. E., Ravussin E., Knowler W. C., Bennett P. H. N., *Engl. J. Med.*, **329**, 1988—1992 (1993).
3) Colca J. R., Tanis S. P., "Annual Reports in Medicinal Chemistry," Vol. 27, ed. by Bristol J. A., Academic Press Inc., San Diego, 1992, pp. 219—226.
4) Reaven G. M., *Diabetes*, **37**, 1595—1607 (1988).
5) Kahn C. R., *Diabetes*, **43**, 1066—1084 (1994).
6) Reaven G. M., *Physiol. Rev.*, **75**, 473—486 (1995).
7) Fujita T., Sugiyama Y., Taketomi S., Sohda T., Kawamatsu Y., Iwatsuka H., Suzuoka Z., *Diabetes*, **32**, 804—810 (1983).
8) Chang A. Y., Wyse B. M., Gilchrist B. J., Peterson T., Diani A. R., *Diabetes*, **32**, 830—838 (1983).
9) Sugiyama Y., Taketomi S., Shimura Y., Ikeda H., Fujita T., *Arzneim. Forsch./Drug Res.*, **40**, 263—267 (1990).
10) Nolan J. J., Ludvik B., Beerdsen P., Joyce M., Olefsky J., *N. Engl. J. Med.*, **331**, 1188—1193 (1994).
11) Ferrarl C., Testorl G. P., Betazzonl A., Romussl M., Caldara R., Frezzati S., *Horm. Metab. Res.*, **10**, 4—6 (1978).
12) Barnett K., Cralg J. G., Robinson D. S., Rogers M., *Br. J. CLIN. Pharmacol.*, **4**, 455—458 (1977).
13) Sohda T., Mizuno K., Imamiya E., Sugiyama Y., Fujita T., Kawamatsu Y., *Chem. Pharm. Bull.*, **30**, 3580—3600 (1982).
14) Fujita T., Sugiyama Y., Taketomi S., Sohda T., Kawamatsu Y., Iwatsuka H., Suzuoki Z., *Diabetes*, **32**, 804—810 (1983).
15) Chang A. Y., Wyse B. M., Gilchrist B. J., Peterson T., Dianl A. R., *Diabetes*, **32**, 830—838 (1983).
16) Yoshloka T., Fujita T., Kanai T., Alzawa Y., Kurumada T., Hasegawa K., Horikoshi H., *J. Med. Chem.*, **32**, 421—428 (1989).
17) Fujiwara T., Yoshioka S., Yoshioka T., Ushiyama I., Horikoshi H., *Diabetes*, **37**, 1549—1558 (1988).
18) Suter S. L., Nolan J. J., Wallace P., Gumbine J. M., Olefsky J. M., *Diabetes Care*, **15**, 193—203 (1992).
19) Clark D. A., Goldsteln S. 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., *J. Med. Chem.*, **34**, 319—325 (1991).
20) Momose Y., Meguro K., Ikeda H., Hatanaka C., Oi S., Sohda T., *Chem. Pharm. Bull.*, **39**, 1440—1445 (1991).
21) Cantello B. C. C., Cawthorne M. A., Haigh D., Hindley R. M., Smith S. A., Thurlby P. L., *Biomed. Chem. Lett.*, **4**, 1181—1184 (1994).
22) Lehmann J. M., Moore L. B., Smith-Oliver T. A., Wilkison W. O., Willson T. M., Kliewer S. A., *Biol. Chem.*, **270**, 12953—12956 (1995).
23) Saltiel A. R., Olefsky J. M., *Diabetes*, **45**, 1661—1669 (1996).
24) Pearson S. L., Cawthorn M. A., Clapham J. C., Dunmore S. L., Holmes S. D., Moore G. B. T., Smith S. A., Tadayyon M., *Biochem. Biophys. Res. Commun.*, **229**, 752—757 (1996).
25) Willson T. M., Cobb J. E., Cowan D. J., Wiethe R. W., Correa I. D., Prakash S. R., Beck K. D., Moore L. B., Kliewer S. A., Lehmann J. M., *J. Med. Chem.*, **39**, 665—668 (1996).
26) Fujiwara T., Yoshioka S., Yoshioka T., Ushiyama I., Horikoshi H., *Diabetes*, **37**, 1549—1558 (1988).
27) Chang A. Y., Wyse B. M., Gilchrist B. J., Peterson T., Diani A. R., *Diabetes*, **32**, 830—838 (1983).
28) Iwamoto Y., Kuzuya T., Matsuda A., Awata T., Kumakura S., Inooka G., Shiraishi I., *Diabetes Care.*, **14**, 1083—1086 (1991).
29) Henry R. R., *Endocrinol. Metab. Clin. N. Am.*, **26**, 553—573 (1997).
30) Anji Reddy A. K., Lohray B. B., Bhushan V., Sekar Reddy A., Rao Mamidi N. V. S., Papi Reddy P., Saibaba V., Jaipal Deddy N., Suryaprakash A., Parimal M., Vikramadithyan R. K., Rajagopalon R., *J. Med. Chem.*, **42**, 3265—3278 (1999).
31) Yamazaki H., Shibata A., Suzuki M., Nakajima M., Shimada N., Guengerich F. P., Yokoi T., *Drug Metabolism and Disposition*, **27**, 1260—1266 (1999).
32) Kawai K., Kawasaki-Toku Y., Odaku T., Tsuruta F., Kazui M., Iwabuchi H., Nakamina T., Kinoshita T., Ikeda T., Yoshioka T., Komai T., Nakamura T., *Arzneim-Forsch*, **47**, 356—368 (1997).
33) Johnson J. R., *Org. React.*, **1**, 210 (1942).
34) Mitsunobu O., *Synthesis*, **1981**, 1—28 (1981).
35) Tsunoda T., Yamamiya Y., Ito S., *Tetrahedron Lett.*, **34**, 1639—1642 (1993).
36) Ohsumi J., Sakakibara S., Yamahuchi J., Miyadai K., Yoshioka S., Fujiwara T., Horikoshi H., Serizawa N., *Endocrinology*, **135**, 2279—2282 (1994).
37) Cantello B. C. C., Cawthorne M. A., Haigh D., Hindley R. M., Smith S. A., Thrulby P. L., *Biomed. Chem. Lett.*, **4**, 1181—1184 (1994).
38) Still W. C., Kahn M., Mitra A., *J. Org. Chem.*, **43**, 2923—2925 (1978).
39) Seglen P. O., *Methods in Cell Biol.*, **13**, 29—83 (1976).
40) Fautz R., Husein B., Hechenberger C., *Mutation Res.*, **253**, 173—179 (1991).
41) Borenfreund E., Puerner J. A., *J. Tissue Culture Methods*, **9**, 7—9 (1984).