Substituted Pyrrol-1-ylacetic Acids That Combine Aldose Reductase Enzyme Inhibitory Activity and Ability To Prevent the Nonenzymatic Irreversible Modification of Proteins from Monosaccharides

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Starting from the known inhibitory activity of (3-benzoylpyrrol-1-yl)acetic acid (**I**) and (2-benzoylpyrrol-1-yl)acetic acid (**II**), a series of 3-aroyl and 2,4-bis-aroyl derivatives (**54**−**75**) were synthesized and tested for inhibition of aldose reductase, an enzyme involved in the appearance of diabetic complications. It was found that a number of the tested compounds exhibited considerable activity in the micromolar range. Important structural features for the potent compounds is the presence of substituents with relatively low Hammett σ values and/or moieties which increase their overall aromatic area. The most active derivative was the [2,4-bis(4-methoxybenzoyl)pyrrol-1-yl]acetic acid (**75**), with potency favorably compared to known ARIs such as tolrestat, epalrestat, zopolrestat, and fidarestat. Four selected derivatives were also evaluated for their ability to interfere with the oxidative modification of serum albumin in an in vitro experimental glycation model of diabetes mellitus. All of them showed considerable activity, comparable to the known inhibitor trolox. Our results, taken together, indicate that compound **75** combines favorably two biological activities directly connected to a number of pathological conditions related to the chronic diabetes mellitus.

Introduction

Diabetes mellitus is a universal health problem, and Type 2 diabetes is a disease fast approaching epidemic proportions throughout the world.[1] The clinical profile of diabetic subjects is often worsened by the presence of several serious long-term complications,[2] which mainly account for the economic burden in the treatment of the patients.[3] The Diabetes Control and Complications Trial,[4] as well as related trials,[5] demonstrated that the more severe and sustained the degree of hyperglycemia, the more likely it is that the chronic complications of diabetes will develop. Ideally, lowering glycated hemoglobin[6] by intensive glucose control will help to prevent the devastating complications of neuropathy, retinopathy, nephropathy, and vascular disease. For many people with diabetes, however, the achievement and maintenance of euglycemia is extremely difficult,[7] while a correlation between hyperinsulinemia and coronary artery disease is recognized.[8] Consequently, researchers have turned to pharmaceutical intervention as a way to prevent complications in a background of hyperglycemia.[7,9]

Hyperglycemia causes 'hyperglysolia',[10] within cells of vulnerable tissues. Although the molecular basis for the pathogenic effects of hyperglysolia remains to be proven, substantial evidence point to certain biochemical processes. Glucose can be reduced to sorbitol by aldose reductase (AR, EC 1.1.1.21), the first enzyme of the polyol pathway. Sorbitol's concentration is, thus, marked increased in some cells possessing insulin independent glucose transport. The increased accumulation of sorbitol has been linked to cellular damage (e.g., through hyperosmosis or depletion of NADPH, *myo*-inositol, and taurine).[11] In diabetic patients, fructose is also formed intracellularly from sorbitol by the action of sorbitol dehydrogenase (SDH, EC 1.1.1.14) and can reach the same concentrations of glucose in certain tissues.[12] Glucose and, especially, fructose can react with proteins to form alpha keto-amines via Amadori rearrangements. This can lead, through Maillard type reactions, to advanced glycation end products (AGE) and damage of proteins.[13] Glucose and fructose can undergo transition metal catalyzed oxidations, which contribute to acceleration of modifications in the tissues that are involved in late onset diabetic complications.[13a,b,14] Oxidative stress also induces the activity with changes in expression of the AR enzyme and transforms it to a state that is less sensitive to several of its inhibitors.[15] Furthermore, AGE induce increases in aldose reductase mRNA and protein.[16] Finally, oxidative stress and the resulting lipid peroxidation is implicated in the alternation of glucose transport in Type II diabetes.[17]

Although a considerable number of compounds have been synthesized and shown to be effective AR inhibitors (ARIs),[18] the only ARI available as a drug is Ono Pharmaceutical's epalrestat in Japan.[19] However, as the inhibition of the polyol pathway is considered to be a promising approach to control diabetes complications,[10,20] the already marketed epalrestat as well as new chemical entities are investigated in clinical trials for their efficacy.[21]

Various antioxidants,[22,23] as well as compounds not necessarily acting by an antioxidant mechanism,[24,25] have been found to inhibit AGE formation. In clinical trials,[26,27] a number of them exerted beneficial effects to diabetic patients.

Based on the above, in the present study we synthesized the compounds **54**−**75** shown in Figures 1 and

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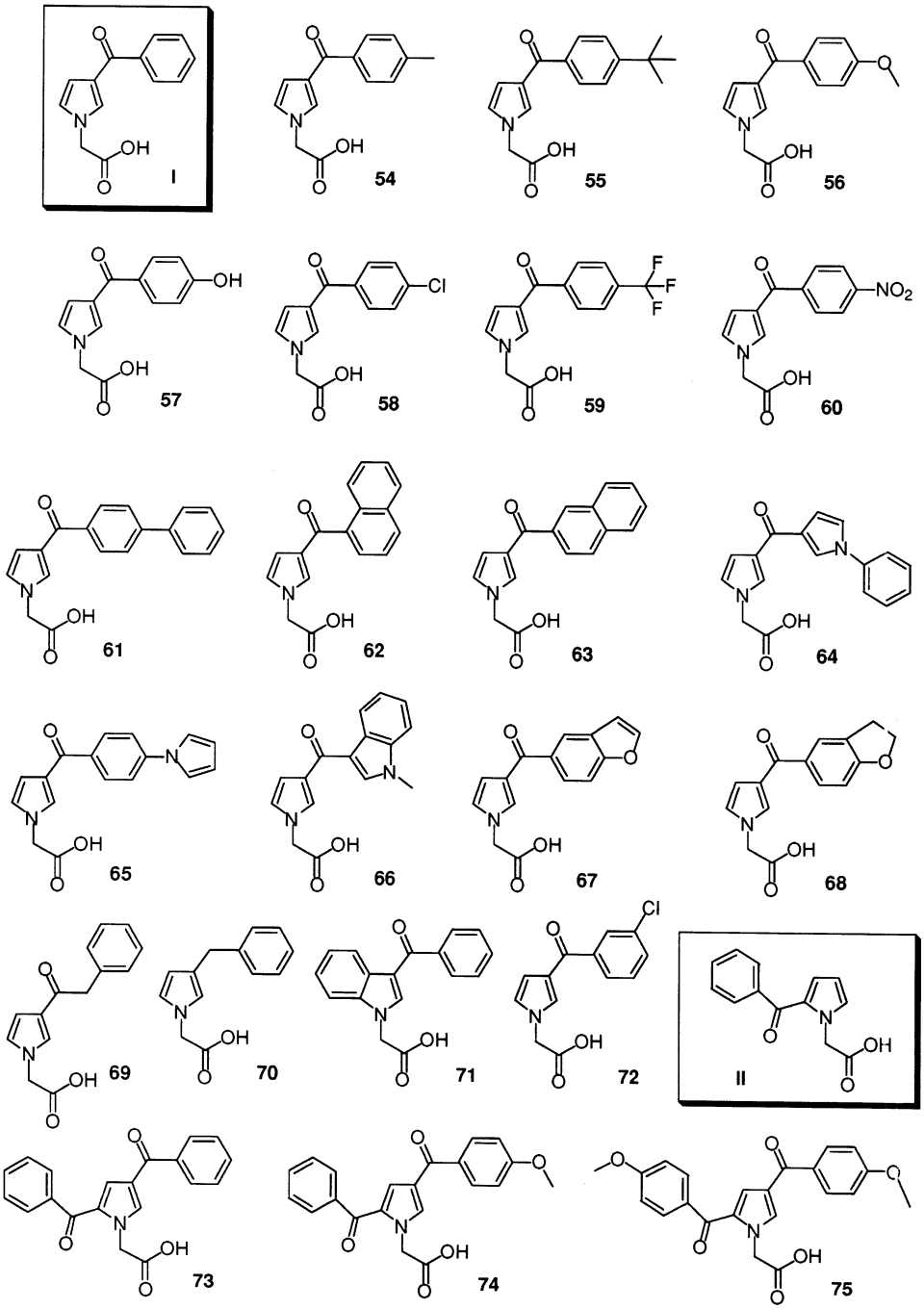


Figure 1. Synthesized target compounds **54**−**75** based on the structures of **I** and **II**.

tested them in vitro for their ability to inhibit AR. Furthermore, for selected more active ones we evaluated their ability to interfere with the oxidative modification of serum albumin in an in vitro experimental glycation model of diabetes mellitus.[22b]

The compounds **54**−**72** in Figure 1 are derivatives of (3-benzoylpyrrol-1-yl)acetic acid (**I**), which has been previously shown[28] that is an ARI. The changes, which were made in the structure of **I**, were generally selected as to confer variability to the physicochemical properties of the target compounds. The biphenyl, naphthyl, and benzofuran rings have also been identified to belong to the class of privileged substructures for protein binding.[29] In compounds **64**−**66** the additional pyrrole ring was introduced in the premise to increase their overall reductive ability.[30]

The compounds **73**−**75** (Figure 1) combine structural features of **I** and of (2-benzoylpyrrol-1-yl)acetic acid (**II**). The latter is also, although comparatively weaker, an ARI.[28] In compounds **73**−**75** there is a gradual addition of methoxy groups, aiming to an increase of the parts of the molecules, which could stabilize free radicals, based on the captodative principle.[31]

Chemistry. For the synthesis of the target pyrrole-1-ylacetic acid derivatives **54**−**75**, we followed the general methodology outlined in Scheme 1. Previously, it has been reported the synthesis of the starting aryl-(1*H*-pyrrol-3-yl)methanones **1**−**11** (Figure 2)[32a] as well as of the 2-phenyl-1-(1*H*-pyrrol-3-yl)ethanone (**12**)[32b] and of the (1*H*-indol-3-yl)phenylmethanone (**13**).[32c] Also, (3-chlorophenyl)(1*H*-pyrrol-3-yl)methanone (**14**) was syn-

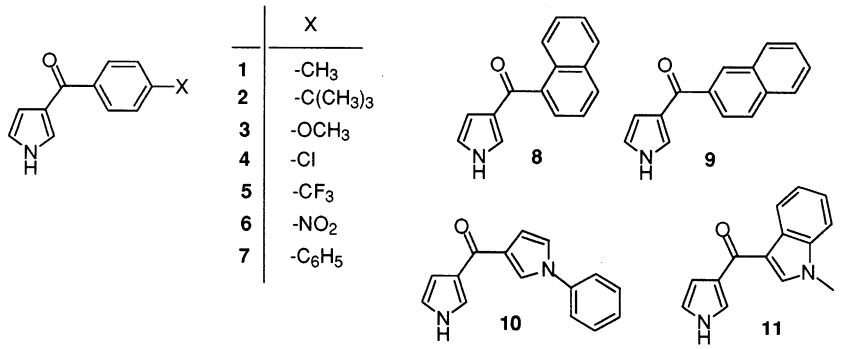
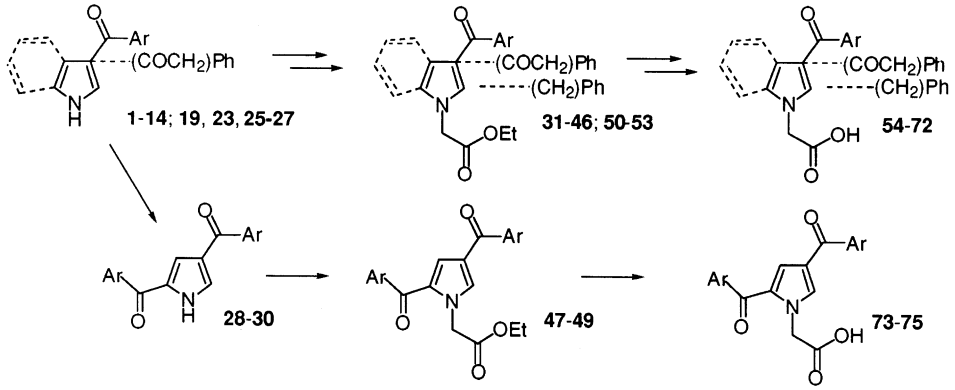
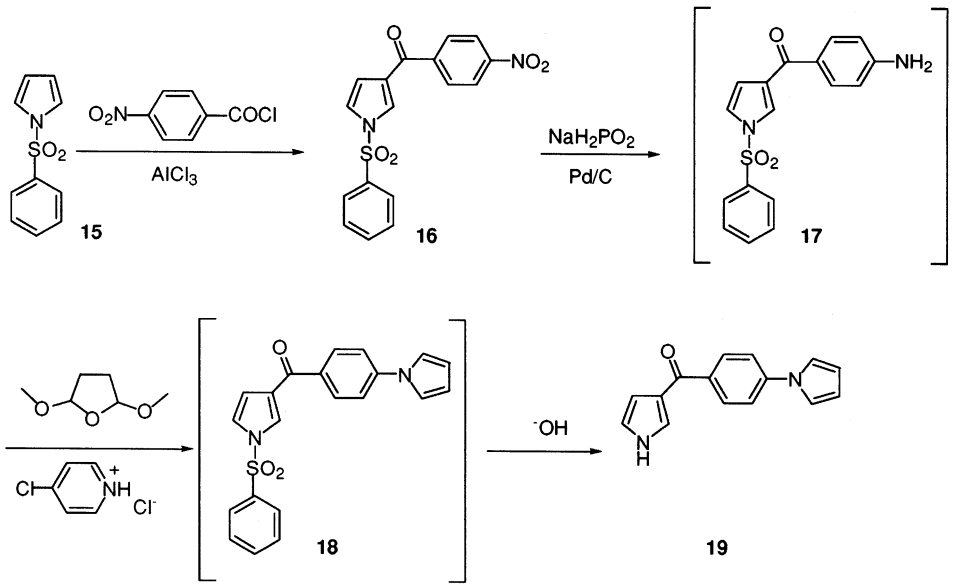


Figure 2. Structures of the previously reported[32a] starting pyrrolylmethanones **1**−**11**.

Scheme 1. General Methodology Followed for the Synthesis of the Target Compounds **54**−**75**



Scheme 2. Synthesis of the Pyrrolylmethanone **19**

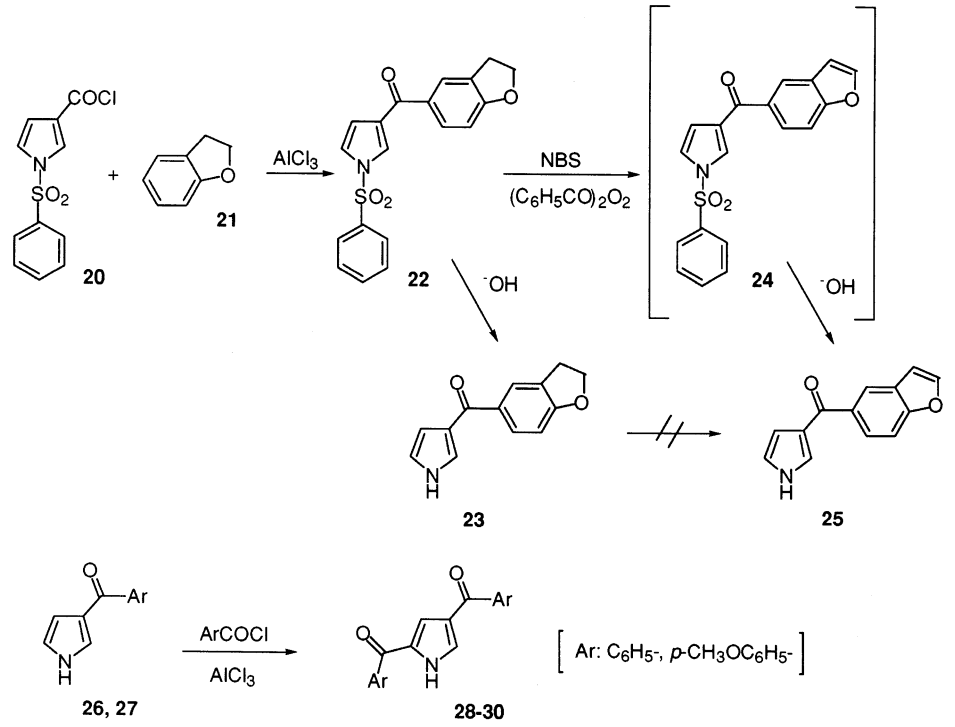


thesized in a similar way as the reported preparation of its *p*-chloro isomer **4**.[32a]

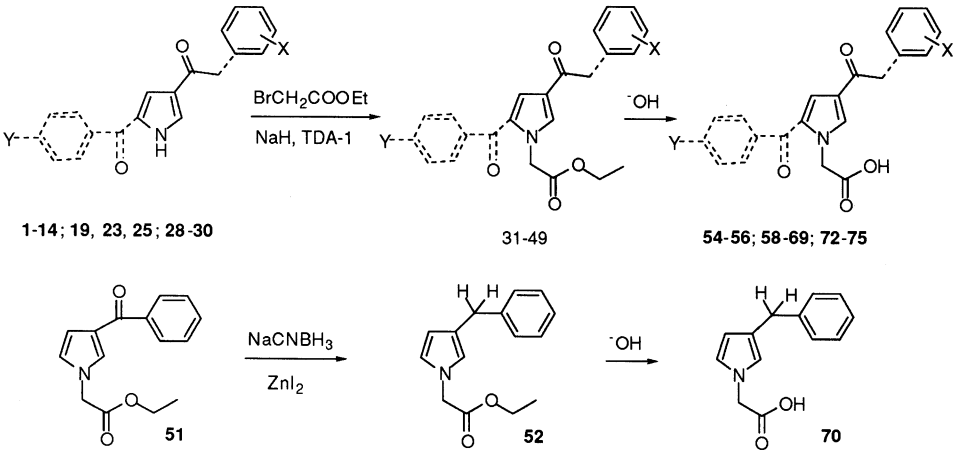
The sequence of reactions followed for the preparation of (1*H*-pyrrol-3-yl)(4-pyrrol-1-ylphenyl)methanone **19** is shown in Scheme 2. This involved the introduction[32a] of a nitrobenzoyl substituent in position-3 of 1-benzenesulfonyl-1*H*-pyrrole (**15**), reduction of the nitro group under hydrogen transfer hydrogenation conditions,[33] and formation of a pyrrole ring with Clauson−Kaas type methodologies. The experimental conditions studied for the Clauson−Kaas type reactions utilized either 1,4-dimethoxytetrahydrofurane and an acid catalyst (acetic acid,[34] phosphorus pentoxide,[35] and 4-cloropyridinium hydrochloride[36]) or 1,4-dichloro-1,4-dimethoxybutane and Amberlyst A-21.[37] The best results were obtained under acidic conditions with 4-cloropyridinium hydrochloride as the catalyst. The formed intermediates **17** and **18** were used in the next steps without further purification; the final ketone **19** was isolated after hydrolysis of the benzenesulfonyl group of **18**.

The sequence of reactions followed for the preparation of (1,2-dihydrobenzofuran-5-yl)(1*H*-pyrrol-3-yl)methanone **23** and (benzofuran-5-yl)(1*H*-pyrrol-3-yl)methanone **25** is shown in Scheme 3. The methodology was an adaptation of a previously reported preparation of a number of benzofuran derivatives which, however, did

Scheme 3. Synthesis of the Pyrrolylmethanones **23**, **25**, **28**−**30**



Scheme 4. Synthesis of Pyrrolylacetic Acids **54**−**56**, **58**−**70**, and **72**−**75**



not contain a pyrrole ring.[38a] It involved a Friedel−Crafts condensation of 1-benzenesulfonyl-1*H*-pyrrole-3-carbonyl chloride (**20**)[38b] with 2,3-dihydrobenzofuran (**21**) at a low temperature, followed by either hydrolysis to **23** or oxidation and then hydrolysis to **25**. Attempts to oxidize **23** to **25** resulted in a substantial bromination of the pyrrole ring.

The synthesis of (5-aroyl-1*H*-pyrrol-3-yl)arylmethanones (**28**−**30**, Scheme 3), from which **29** is a new one, was attained under Friedel−Crafts acylation conditions of aryl(1*H*-pyrrol-3-yl)methanones **26** and **27**.[39]

The general method for the formation of the aroyl heterocyclic ethyl *N*-acetate derivatives **31**−**49** involved nucleophilic substitution under the previously reported[28] phase transfer catalysis conditions (Scheme 4), while the reduction of ethyl (3-benzoylpyrrol-1-yl)acetic acid ethyl ester **51**[28] for the preparation of **52** was performed under mild reductive conditions[40] with the combination of sodium cyanoborohydride and zinc iodide (Scheme 4).

The formation of the final carboxylic acids **54**−**56**, **58**−**70**, and **72**−**75** was attained under basic hydrolytic conditions, with best results obtained in an equimolar mixture of 5% sodium hydroxide and dioxane (Scheme 4). The synthesis of (3-benzoylindol-1-yl)acetic acid (**71**) from **13**, via the intermediate (3-benzoylindol-1-yl)acetic acid ethyl ester (**50**), has been previously described.[41] The formation of the phenolic carboxylic acid **57** involved the effect of boron tribromide[42] on **33** followed by basic hydrolysis of the resulting mixture that contained the phenolic carboxylic ester and acid derivatives **53** and **57** (Scheme 5). Attempts to O-demethylate **33** with chlorothrimethylsilane/sodium iodide[43] was unsuccessful resulting in the isolation of only starting material.

Results and Discussion

The synthesized target compounds **54**−**75** were tested in vitro for their ability to inhibit rat lens AR. It has been shown that there is an approximately 85% se-

Scheme 5. Synthesis of Pyrrolylacetic Acid **57**

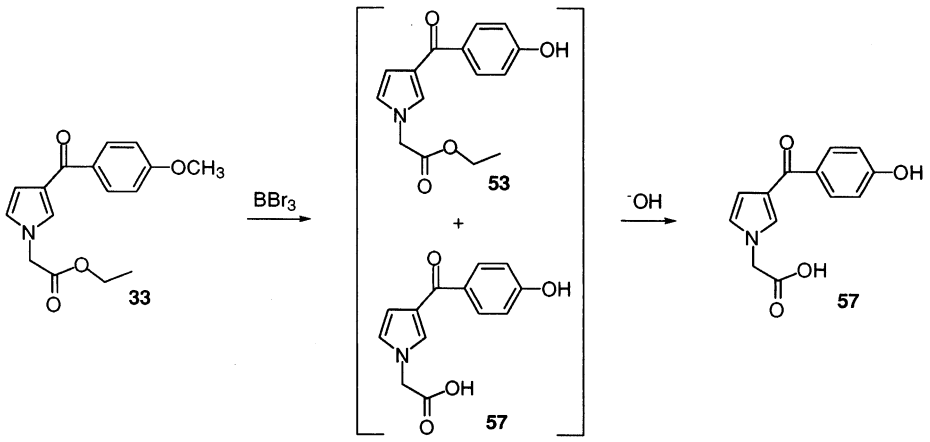


Table 1. Aldose Reductase Inhibitory Activity

	% inhibition (SEM)[a] at concn			
inhibitor	10^{-6} M	10^{-7} M	10^{-8} M	10^{-9} M
54	46 (2.5)			
55	41 (4.3)			
56	72 (6.5)	26 (1.0)		
57	45 (3.5)			
58	41 (3.5)			
59	47 (6.0)			
60	18 (5.6)			
61	76 (0.5)	37 (3.0)		
62	58 (2.5)	59 (3.2)	49 (4.5)	20 (5.9)
63	79 (5.5)	72 (1.0)	22 (2.0)	
64	67 (4.3)	39 (2.0)		
65	80 (1.0)	39 (1.5)		
66	38 (4.5)			
67	40 (4.0)			
68	42 (4.0)			
69	29 (3.8)			
70	9 (6.5)			
71	38 (3.8)			
72	44 (3.0)			
73	82 (1.5)	62 (2.0)	27 (1.5)	
74	93 (7.0)	51 (6.0)	13 (5.5)	
75	96 (0.5)	94 (2.5)	59 (3.9)	41 (4.2) $IC_{50} = 2.36$ (0.64)[b] nM
I[c]	27 (2.0)			
II[d]	36 (2.0) at 10^{-5} M			
trolox	12 (0.0) at 10^{-5} M			
sorbinil		48% (0.5) at 2.5×10^{-7} M[e]		

[a] $n = 3$. [b] Mean (standard error from three determinations). [c] (3-Benzoylpyrrol-1-yl)acetic acid. [d] (2-Benzoylpyrrol-1-yl)acetic acid. [e] Reported[28] IC_{50}: 0.25 μM.

quence similarity between rat lens and human AR, while the proposed active sites of both enzymes are identical.[45] The performed assay was based on the spectrophotometric monitoring of NADPH oxidation, which is proven to be a quite reliable method.[46]

It was found (Table 1) that a number of the tested compounds (**56**, **61**−**65**, and **73**−**75**) exhibited considerable activity in the micro molar range. The most active derivative was compound **75**, with potency favorably compared to known ARIs. This is supported from the indicative literature IC_{50} values, cited in parentheses, for some well studied active inhibitors such as tolrestat (35×10^{-9} M[47a]), epalrestat (10×10^{-9} M[47b]), zopolrestat (3.1×10^{-9} M[47c]), and fidarestat (35×10^{-9} M[47d]). Important structural features in the above-mentioned potent compounds is the presence of substituents with relatively low Hammett σ values and/or moieties which increase their overall aromatic area. These mentioned characteristics are not determinant for the biological profile of the compounds **57**, **66**−**68**, and **71**. An explanation could be phenomena like the decrease of lipophilicity (i.e. **56**: ClogP = 1.936 vs **57**: ClogP = 1.619),[48] possible steric hindrance during compound/enzyme interaction (i.e. **66** vs **62**, **68** vs **56** and **71** vs **I**) or the reduced aromatic character of the benzofuran ring[49] (i.e. **67** vs **63**). Compounds **69** and **70** exhibited weak inhibitory potency. Inspection of low energy conformations[50] of these compounds reveals that their two aromatic rings are almost perpendicular to each other, while in the cases of the active methanone derivatives these rings are almost in the same plane. This difference could be an explanation of their low activity in the particular in vitro experiment.

Compounds **64**, **65**, **74**, and **75** were also tested for their ability to inhibit in vitro the irreversible modification of the model protein albumin (the most abundant in the serum) in the presence of fructose (fructation) as the glycating monosaccharide. Fructose, instead of glucose (glucation), was chosen in the assay because is known to be a more potent glycation agent.[23] This derives from the fact that its acyclic (open chain) form, which is the reactive species, is approximately 10 times that of glucose. Fructose is also elevated in those tissues where the polyol pathway is active.[12] The selection of

Table 2. Glycation-Induced Fluorescence Changes of BSA and Formation of DNPH-Reactive Carbonyl Groups in BSA Exposed to Fructose. Effect of Inhibitors

compd	*C* (mM)	relative fluorescence (R.U.)[a]	% inhibn	carbonyl groups (nmol/mg BSA)	% inhibn
none	–	27.8 ± 2.5 (13)	–	5.03 ± 0.6 (14)	–
64	5	16.4 ± 0.9 (4)[b]	41	not detectable	100
64	2.5	21.0 ± 0.6(3)[b]	24	not detectable	100
64	1	21.0 ± 1.1 (3)[b]	24	1.55 ± 0.4[b]	69
65	5	4.7 ± 0.4 (6)[b]	83	not detectable	100
65	2.5	9.8 ± 0.2 (4)[b]	65	not detectable	100
65	1	17.4 ± 0.7 (4)[b]	37	not detectable	100
74	5	6.9 ± 0.3 (6)[b]	75	not detectable	100
74	2.5	11.5 ± 0.9 (5)[b]	41	1.7 ± 0.3 (6)[b]	66
74	1	23.1 ± 1.1 (3)[c]	17	4.38 ± 0.6 (5)[c]	20
75	5	3.3 ± 0.4 (3)[b]	89	not detectable	100
75	2.5	11.8 ± 0.9 (6)[b]	57	not detectable	100
75	1	17.3 ± 0.5 (3)[b]	38	2.52 ± 0.8 (4)[b]	50
trolox	1	12.8 ± 0.5 (5)[b]	54	3.44 ± 0.9 (5)[b]	32

[a] Results are means ± SD with number of samples in parentheses. [b] $P < 0.001$. [c] $P < 0.01$ vs control according to Student's *t* test.

the compounds to be tested was based on a suitable combination of three criteria: (a) AR inhibitory activity in the micromolar range, (b) absence of putative mutagenic moieties (e.g. biphenyl[51]), and (c) presence of chemical characteristics which could contribute to an increase of the antioxidant potential (e.g. an additional pyrrole ring[30] or substructures with captodative properties[31]).

It was found (Table 2) that the examined compounds were moderately less effective in inhibiting the glycation-iduced fluorescence changes of bovine serum albumin (BSA) than the known[22b] proteins' glycation inhibitor trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid). However, they were generally more effective than trolox to inhibit the formation of DNPH-reactive carbonyl groups in BSA. Furthermore, it should be mentioned that trolox is a weak AR inhibitor (Table 1).

The above results, taken together, indicate that [2,4-bis(4-methoxybenzoyl)pyrrol-1-yl]acetic acid (**75**) combines favorably two biological activities directly connected to a number of pathological conditions related to the chronic diabetes mellitus. Finally, a preliminary ($n = 6$) toxicity test showed that compound **75**, at a dose of 1 mmol (0.39 g)/kg ip did not produce any mortality to experimental rats after a 24 h period.

Experimental Section

General Notes. Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. UV spectra were recorded either on a Perkin-Elmer 554 or on a Hitachi U-2001 spectrophotometer, IR spectra on a Perkin-Elmer 597 spectrophotometer, and ^{1}H NMR spectra on a Bruker AW-80 spectrometer with internal TMS standard. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. Fluorescence was recorded on a Hitachi F-2000 spectrophotometer.

(3-Chlorophenyl)(1*H*-pyrrol-3-yl)methanone (14). This compound was synthesized in a similar way as the reported[32a] preparation of its *p*-chloro-isomer **4** in a 76% yield: mp 104–105 °C; IR (Nujol) 3200, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.65–6.80 (m, 2H, pyrrolyl-4,5*H*), 7.25–7.40 (m, 1H, pyrrolyl-2*H*), 7.40–7.85 (m, 4H, phenyl-*H*), 9.30 (br s, 1H, pyrrolyl-1*H*). Anal. ($C_{11}H_8NOCl$) C, H, N.

(1*H*-Pyrrol-3-yl)(4-pyrrol-1-ylphenyl)methanone (19). (1-Benzenesulfonyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanone (**16**)[32a] (1.63 g, 0.46 mmol) in tetrahydrofuran (20 mL) was stirred with Pd–C (10%) (0.16 g), and to this suspension was gradually added an aqueous solution of $NaH_2PO_2 \cdot H_2O$ (30%). Addition of the phosphinate solution was continued until no starting material remained. The mixture was filtered and the filtrate poured into water (20 mL) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and the solvents were evaporated under reduced pressure to give crude (1-benzenesulfonyl-1*H*-pyrrol-3-yl)(4-aminophenyl)methanone (**17**) (1.5 g) which was used directly in the next step.

A mixture of crude **17** (1.5 g), 4-chloropyridine hydrochloride (0.97 g, 6.47 mmol), and 2,5-dimethoxytetrahydrofuran (0.88 g, 5.8 mmol) in dioxane (30 mL) was refluxed for 3 h under a nitrogen atmosphere. The resulting solution was evaporated under reduced pressure, and the residue was dissolved in Et_2O, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in dioxane (50 mL), and to this a 5 N solution of NaOH (50 mL) was added. The reaction mixture was vigorously stirred at room temperature for 24 h. The organic layer was collected, and the aqueous was thoroughly extracted with EtOAc (2 × 50 mL). The combined organic layer and extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was flash chromatographed with EtOAc/petroleum ether (3:1) followed by recrystallization from toluene/petroleum ether to provide the title compound (0.26 g, 24%): mp 172–173 °C; IR (Nujol) 3200, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.20–6.50 (m, 2H, pyrrolyl$_{(phenyl)}$-3,4*H*), 6.60–6.90 (m, 2H, pyrrolyl-4,5*H*), 7.05–7.20 (m, 2H, pyrrolyl$_{(phenyl)}$-2,5*H*), 7.25–7.60 (m, 3H, pyrrolyl-2*H* and phenyl-3,5*H*), 7.90 (d, 2H, phenyl-2,6*H*, J = 8.3 Hz), 10.80 (br s, 1H, pyrrolyl-1*H*). Anal. ($C_{15}H_{12}N_2O$) C, H, N.

(1-Benzenesulfonyl-1*H*-pyrrol-3-yl)(2,3-dihydrobenzofuran-5-yl)methanone (22). To a solution of 2,3-dihydrobenzofuran (**21**) (0.52 g, 4.26 mmol) in CH_2Cl_2 (10 mL) at −10 °C under a N_2 atmosphere was added dropwise a solution of 1-benzenesulfonyl-1*H*-pyrrole-3-carbonyl chloride (**20**)[38b] (2 g, 7.42 mmol) in CH_2Cl_2 (10 mL) and then $AlCl_3$ (0.6 g, 4.5 mmol). After the addition was completed, the mixture was stirred for an additional 1 h at −5 to −10 °C. The reaction was quenched with ice and water and the product was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was flash chromatographed with EtOAc/petroleum ether (5:1) followed by recrystallization from toluene/petroleum ether to provide the title compound (1.19 g, 79%): mp 168–170 °C; IR (Nujol) 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.30 (t, 2H, dihydrobenzofuranyl-3*H*, J = 9.6 Hz), 4.65 (t, 2H, dihydrobenzofuranyl-2*H*, J = 9.6 Hz), 6.65–6.85 (m, 2H, pyrrolyl-4,5*H*), 7.10–7.30 (m, 1H, dihydrobenzofuranyl-7*H*), 7.45–8.00 (m, 8H, pyrrolyl-2*H*, dihydrobenzofuranyl-4,6*H* and $C_6H_5SO_2$). Anal. ($C_{19}H_{15}NO_4S \cdot 0.1H_2O$) C, H, N.

(2,3-Dihydrobenzofuran-5-yl)(1*H*-pyrrol-3-yl)methanone (23). Compound **22** (1 g, 2.83 mmol) was dissolved in dioxane (50 mL), and to this a 5 N solution of NaOH (50 mL) was added. The reaction mixture was vigorously stirred at room temperature for 24 h. The organic layer was collected, and the aqueous was thoroughly extracted with EtOAc (2 × 100 mL). The combined organic layer and extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was recrystallized from toluene/petroleum ether to provide the title compound (0.54 g, 90%): mp 111–112 °C; IR (Nujol) 3200, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.20 (t, 2H, dihydrobenzofuranyl-3*H*, J = 9.6 Hz), 4.60 (t, 2H, dihydrobenzofuranyl-2*H*, J = 9.6 Hz), 6.60–6.80 (m, 2H, pyrrolyl-4,5*H*), 7.15–7.40 (m, 2H, pyrrolyl-2*H* and dihydrobenzofuranyl-7*H*), 7.60–7.85 (m, 2H, dihydrobenzofuranyl-4,6*H*), 9.50 (br s, 1H, pyrrolyl-1*H*). Anal. ($C_{13}H_{11}NO_2$) C, H, N.

Benzofuran-5-yl-(1*H*-pyrrol-3-yl)methanone (25). Compound **22** (0.75 g, 2.12 mmol) was dissolved in CCl_4 (75 mL), and to the resulting solution was added *N*-bromosuccinimide (0.368, 2.07 mmol) and a catalytic amount of dibenzoyl peroxide. The mixture was refluxed under a N_2 atmosphere for 2 h, cooled to room temperature, filtered, and evaporated

under reduced pressure. The residue was dissolved in dioxane (50 mL), and to this a 5 N solution of NaOH (50 mL) was added. The reaction mixture was vigorously stirred at room temperature for 24 h. The organic layer was collected, and the aqueous was thoroughly extracted with EtOAc (2 × 100 mL). The combined organic layer and extracts were washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was flash chromatographed with EtOAc/petroleum ether (4:1) followed by recrystallization from toluene/petroleum ether to provide the title compound (0.25 g, 57%): mp 140−141 °C; IR (Nujol) 3200, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65−6.95 (m, 3H, pyrrolyl-4,5*H* and benzofuranyl-3*H*), 7.25−8.00 (m, 4H, pyrrolyl-2*H* and benzofuranyl-4,6,7*H*), 8.05−8.25 (m, 1H, benzofuranyl-2*H*), 10.70 (br s, 1H, pyrrolyl-1*H*). Anal. ($C_{13}H_9NO_2$) C, H, N.

[4-(4-Methoxybenzoyl)-1*H*-pyrrol-2-yl]phenylmethanone (29). A solution of benzoyl choride (1.94 g, 13.8 mmol) in CH_2Cl_2 (5 mL) was slowly added, at room temperature, to a stirred suspension of anhydrous $AlCl_3$ (3.98 g, 29.8 mmol) in CH_2Cl_2 (25 mL). After 10 min, a solution of (4-methoxyphenyl)(1*H*-pyrrol-3-yl)methanone (**3**) (2.5 g, 12.44 mmol) in CH_2Cl_2 (5 mL) was added dropwise at room temperature, and the resulting mixture was stirred for 30 min. The reaction was quenched with ice and water, and the product was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $NaSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed with EtOAc/petroleum ether (4:1) followed by recrystallization from toluene/petroleum ether to provide the title compound (2.28 g, 60%): mp 165−166 °C; IR (Nujol) 3250, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H, $_{(phenyl)}OCH_3$), 6.80−7.10 (m, 2H, pyrrolyl-3,5*H*), 7.20−8.10 (m, 9H, $_{(bis)}$phenyl-*H*), 10.70 (br s, 1H, pyrrolyl-1*H*). Anal. ($C_{19}H_{15}NO_3$) C, H, N.

General Procedure for the Preparation of the Ethyl Acetic Acid Ester Derivatives 31−49. To a cold (ice bath), stirred, and under a nitrogen atmosphere mixture of the corresponding either (aroyl-1*H*-pyrrol-3-yl)methanones (**1**−**11**;[32a] **14, 19, 23, 25**), or 2-phenyl-1-(*1H*-pyrrol-3-yl)ethanone (**12**),[32b] or (5-aroyl-1*H*-pyrrol-3-yl)arylmethanones (**28**,[39] **29**, **30**[39]) (15 mmol), ethyl bromoacetate (4.05 g, 24 mmol), and [tris[2-(methoxyethoxy)ethyl]amine [TDA-1] (0.75 mL, 2.4 mmol) in toluene (225 mL) was added NaH (50% dispersion in mineral oil) (1.05 g, 22.5 mmol). The resulting mixture was stirred at room temperature for 24−48 h. After this period, it was poured into a stirred, ice cold, mixture of Et_2O (150 mL) and 5% HCl (150 mL). The two phases were separated, and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with 10% $NaHCO_3$ (2 × 100 mL) and saturated NaCl solution and dried (K_2CO_3). The solvents were evaporated under reduced pressure, and the residue was flash chromatographed with a suitable mixture of EtOAc/petroleum ether followed (if solid material) by recrystallization from either Et_2O/petroleum ether or CH_2Cl_2/petroleum ether (**36**, **41**, **47**). The yields ranged between 40% to 80%.

[3-(4-Methylbenzoyl)pyrrol-1-yl]acetic acid ethyl ester (31): mp 74−75 °C; IR (Nujol) 1740, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_2CH_3, J = 4.8 Hz), 2.40 (s, 3H, $_{(phenyl)}CH_3$), 4.20 (q, 2H, CH_2CH_3, J = 4.8 Hz), 4.65 (s, 2H, CH_2CO_2), 6.65−6.80 (m, 2H, pyrrolyl-4,5*H*), 7.10−7.35 (m, 3H, pyrrolyl-2*H* and phenyl-3,5*H*), 7.70 (d, 2H, phenyl-2,6*H*, J = 6.7 Hz). Anal. ($C_{16}H_{17}NO_3$) C, H, N.

[3-(4-*tert*-Butylbenzoyl)pyrrol-1-yl]acetic acid ethyl ester (32): mp 89−90 °C; Anal. ($C_{19}H_{23}NO_3$) C, H, N.

[3-(4-Methoxybenzoyl)pyrrol-1-yl]acetic acid ethyl ester (33): mp 77−78 °C; Anal. ($C_{16}H_{17}NO_4$) C, H, N.

[3-(4-Chlorobenzoyl)pyrrol-1-yl]acetic acid ethyl ester (34): mp 89−90 °C; Anal. ($C_{15}H_{14}NO_3Cl$) C, H, N.

[3-(4-Trifluoromethylbenzoyl)pyrrol-1-yl]acetic acid ethyl ester (35): mp 118−119 °C; Anal. ($C_{16}H_{14}NO_3F_3$) C, H, N.

[3-(4-Nitrobenzoyl)pyrrol-1-yl]acetic acid ethyl ester (36): mp 126−127 °C; Anal. ($C_{15}H_{14}N_2O_5$) C, H, N.

[3-(Biphenyl-4-carbonyl)pyrrol-1-yl]acetic acid ethyl ester (37): mp 96−97 °C; Anal. ($C_{21}H_{19}NO_3$) C, H, N.

[3-(Naphthalene-1-carbonyl)pyrrol-1-yl]acetic acid ethyl ester (38): mp 74−75 °C; Anal. ($C_{19}H_{17}NO_3$) C, H, N.

[3-(Naphthalene-2-carbonyl)pyrrol-1-yl]acetic acid ethyl ester (39): mp 72−74 °C; Anal. ($C_{19}H_{17}NO_3$) C, H, N.

[3-(1-Phenyl-1*H*-pyrrol-3-carbonyl)pyrrol-1-yl]acetic acid ethyl ester (40): viscous oil; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, CH_2CH_3, J = 4.8 Hz), 4.25 (q, 2H, CH_2CH_3, J = 4.8 Hz), 4.65 (s, 2H, CH_2CO_2), 6.65−6.95 (m, 4H, pyrrolyl-4,5*H* and $_{(phenyl)}$pyrrolyl-4,5*H*), 7.05−7.15 (m, 1H, pyrrolyl-2*H*), 7.40 (s, 5H, phenyl-*H*), 7.65−7.80 (m, 1H, $_{(phenyl)}$pyrrolyl-2*H*).

[3-(4-Pyrrol-1-yl-benzoyl)pyrrol-1-yl]acetic acid ethyl ester (41): mp 81 °C; Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

[3-(1-Methyl-1*H*-indol-3-carbonyl)pyrrol-1-yl]acetic acid ethyl ester (42): viscous oil; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, CH_2CH_3, J = 4.8 Hz), 3.70 (s, 3H, $_{(indolyl)}CH_3$), 4.20 (q, 2H, CH_2CH_3, J = 4.8 Hz), 4.60 (s, 2H, CH_2CO_2), 6.50−6.70 (m, 2H, pyrrolyl-4,5*H*), 7.10−7.30 (m, 4H, pyrrolyl-2*H* and indolyl-5,6,7*H*), 7.60 (s, 1H, indolyl-2*H*), 8.15−8.40 (m, 1H, indolyl-4*H*).

[3-(Benzofuran-5-carbonyl)pyrrol-1-yl]acetic acid ethyl ester (43): mp 74−75 °C; Anal. ($C_{17}H_{15}NO_4$) C, H, N.

[3-(2,3-Dihydro-benzofuran-5-carbonyl)pyrrol-1-yl]acetic acid ethyl ester (44): mp 91−92 °C; Anal. ($C_{17}H_{17}NO_4$) C, H, N.

(3-Phenylacetylpyrrol-1-yl)acetic acid ethyl ester (45): mp 61−62 °C; Anal. ($C_{16}H_{17}NO_3$) C, H, N.

[3-(3-Chlorobenzoyl)pyrrol-1-yl]acetic acid ethyl ester (46): mp 59−60 °C; Anal. ($C_{15}H_{14}NO_3Cl$) C, H, N.

(2,4-Dibenzoylpyrrol-1-yl)acetic acid ethyl ester (47): mp 85−86 °C; Anal. ($C_{22}H_{19}NO_4$) C, H, N.

[2-Benzoyl-4-(4-methoxybenzoyl)pyrrol-1-yl]acetic acid ethyl ester (48): mp 105−106 °C; Anal. ($C_{23}H_{21}NO_5$) C, H, N: calcd, N 3.58; found 3.99.

[2,4-*bis*-(4-Methoxybenzoyl)pyrrol-1-yl]acetic acid ethyl ester (49): mp 112 °C; Anal. ($C_{24}H_{23}NO_6$) C, H, N.

(3-Benzylpyrrol-1-yl)acetic Acid Ethyl Ester (52). To a stirred, at room temperature, solution of (3-benzoylpyrrol-1-yl)acetic acid ethyl ester (**51**)[28] (2.87 g, 10 mmol) in 1,2-dichloroethane (50 mL) were added zinc iodide (4.79 g, 15 mmol) and sodium cyanoborohydride (4.7 g, 75 mmol). The reaction mixture was stirred at room temperature for 20 h. It was then filtered through Celite. The Celite was washed with dichloromethane (100 mL). The combined filtrates were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was flash chromatographed with petroleum ether/EtOAc (15:1) to provide the title compound (1.71 g, 63%) as a viscous oil: IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_2CH_3, J = 4.8 Hz), 3.80 (s, 2H, $_{(phenyl)}CH_2$), 4.20 (q, 2H, CH_2CH_3, J = 4.8 Hz), 4.55 (s, 2H, CH_2CO_2), 6.00−6.10 (m, 1H, pyrrolyl-4*H*), 6.25−6.40 (m, 1H, pyrrolyl-2*H*), 6.45−6.65 (m, 1H, pyrrolyl-5*H*), 7.25 (s, 5H, phenyl-*H*).

General Procedure for the Preparation of the Acetic Acid Derivatives 54−56, 58−70, and 72−75. A mixture of the previously described ethyl ester derivatives (6 mmol), dioxane (100 mL), and 5% NaOH solution (100 mL) was stirred at room temperature for 1 h. After this period, it was concentrated to half of its volume, H_2O (100 mL) was added, and the mixture was cooled (ice bath) and acidified with concentrated HCl. The formed precipitate was collected by filtration, and the filtrate was extracted with $CHCl_3$ (2 × 100 mL). The organic phase was washed with saturated NaCl solution and evaporated under reduced pressure. The residue was combined with the precipitate and recrystallized from toluene/petroleum ether, except for compound **70**. This acid was purified by flash chromatography EtOAc/EtOH (9:1) followed by recrystallization from toluene/petroleum ether. The yields of the target acids ranged from 68 to 97%.

[3-(4-Methylbenzoyl)pyrrol-1-yl]acetic acid (54): mp 159−160 °C; IR (Nujol) 3300−2500, 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6) δ 2.40 (s, 3H, $_{(phenyl)}CH_3$), 4.65 (s, 2H, CH_2CO_2), 6.40 (br s, 1H, CO_2H), 6.55−6.80 (m, 2H, pyrrolyl-4,5*H*),

7.10−7.35 (m, 3H, phenyl-3,5*H*, and pyrrolyl-2*H*), 7.70 (d, 2H, phenyl-2,6*H*, J = 7.0 Hz). Anal. ($C_{14}H_{13}NO_3$) C, H, N.

[3-(4-*tert*-Butylbenzoyl)pyrrol-1-yl]acetic acid (55): mp 155−156 °C; Anal. ($C_{17}H_{19}NO_3$) C, H, N.

[3-(4-Methoxybenzoyl)pyrrol-1-yl]acetic acid (56): mp 172−173 °C; Anal. ($C_{14}H_{13}NO_4$) C, H, N.

[3-(4-Chlorobenzoyl)pyrrol-1-yl]acetic acid (58): mp 175−176 °C; Anal. ($C_{13}H_{10}NO_3Cl$) C, H, N.

[3-(4-Trifluoromethylbenzoyl)pyrrol-1-yl]acetic acid (59): mp 169−170 °C; Anal. ($C_{14}H_{10}NO_3F_3$) C, H, N.

[3-(4-Nitrobenzoyl)pyrrol-1-yl]acetic acid (60): mp 185−186 °C; Anal. ($C_{13}H_{10}N_2O_5$) C, H, N.

[3-(Biphenyl-4-carbonyl)pyrrol-1-yl]acetic acid (61): mp 182−183 °C; Anal. ($C_{19}H_{15}NO_3$) C, H, N.

[3-(Naphthalene-1-carbonyl)pyrrol-1-yl]acetic acid (62): mp 178−180 °C; Anal. ($C_{17}H_{13}NO_3$) C, H, N.

[3-(Naphthalene-2-carbonyl)pyrrol-1-yl]acetic acid (63): mp 196−197 °C; Anal. ($C_{17}H_{13}NO_3$) C, H, N.

[3-(1-Phenyl-1*H*-pyrrol-3-carbonyl)pyrrol-1-yl]acetic acid (64): mp 168 °C; Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

[3-(4-Pyrrol-1-yl-benzoyl)pyrrol-1-yl]acetic acid (65): mp 217−218 °C; Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

[3-(1-Methyl-1*H*-indol-3-carbonyl)pyrrol-1-yl]acetic acid (66): mp 222−223 °C; Anal. ($C_{16}H_{14}N_2O_3 \cdot 0.48CHCl_3$) C, H, N.

[3-(Benzofuran-5-carbonyl)pyrrol-1-yl]acetic acid (67): mp 173−174 °C; Anal. ($C_{15}H_{11}NO_4$) C, H, N.

[3-(2,3-Dihydrobenzofuran-5-carbonyl)pyrrol-1-yl]acetic acid (68): mp 195−196 °C; Anal. ($C_{15}H_{13}NO_4$) C, H, N.

(3-Phenylacetylpyrrol-1-yl)acetic acid (69): mp 153−154 °C; Anal. ($C_{14}H_{13}NO_3 \cdot 0.1H_2O$) C, H, N.

(3-Benzylpyrrol-1-yl)acetic acid (70): mp 84−85 °C; Anal. ($C_{13}H_{13}NO_2$) C, H, N.

[3-(3-Chlorobenzoyl)pyrrol-1-yl]acetic acid (72): mp 151−152 °C; Anal. ($C_{13}H_{10}NO_3Cl$) C, H, N: calcd, C 59.22; found 58.78.

(2,4-Dibenzoylpyrrol-1-yl)acetic acid (73): mp 173−174 °C; Anal. ($C_{20}H_{15}NO_4$) C, H, N.

[2-Benzoyl-4-(4-methoxybenzoyl)pyrrol-1-yl]acetic acid (74): mp 158−160 °C; Anal. ($C_{21}H_{17}NO_5$) C, H, N.

[2,4-*bis*-(4-Methoxybenzoyl)pyrrol-1-yl]acetic acid (75): mp 200 °C; ^{1}H NMR ($CDCl_3$-DMSO-d_6) δ 3.90 (s, 6H, $_{(bis-phenyl)}OCH_3$), 5.10 (s, 2H, CH_2CO_2), 6.80−7.05 (m, 5H, pyrrolyl-3*H* and $_{(bis)}$phenyl-3,5*H*), 7.15 (s, 1H, pyrrolyl-5*H*), 7.60 (s, 1H, CO_2H) 7.80(d, 4H, $_{(bis)}$phenyl-2,6*H*, J = 7.1 Hz). Anal. ($C_{22}H_{19}NO_6$) C, H, N.

[3-(4-Hydroxybenzoyl)pyrrol-1-yl]acetic acid (57). To a solution of ester **33** (2.6 g, 9 mmol) in dry CH_2Cl_2 (35 mL) at −80 °C under a nitrogen atmosphere was added dropwise a solution of boron tribromide (7.5 g, 30 mmol) in dry CH_2Cl_2 (40 mL). When the addition was completed, the reaction mixture was stirred at room-temperature overnight. Then, it was quenched with a mixture of 10% HCl (50 mL) and EtOAc (50 mL), the two phases were separated, and the aqueous was extracted with EtOAc. The combined organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The hydrolysis, work up and purification was similar to that described above in the general procedure, to provide the title compound (1.33 g, 60%): mp 188 °C; IR (Nujol): 3420, 3300−2500, 1700, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$-DMSO-d_6): δ 4.75 (s, 2H, CH_2CO_2), 6.50−6.70 (m, 2H, pyrrolyl-4,5*H*), 6.85 (d, 2H, phenyl-3,5*H*, J = 6.7 Hz), 7.25−7.45 (m, 1H, pyrrolyl-2*H*), 7.60−7.85 (m, 4H, phenyl-2,6*H*, CO_2H, and $_{(phenyl)}OH$, after adition of D_2O changes to d, 2H, δ = 7.70, J = 6.7 Hz). Anal. ($C_{13}H_{11}NO_4$) C, H, N.

In Vitro Aldose Reductase Enzyme Assay. The test compounds **54**−**75**, (3-benzoylpyrrol-1-yl)acetic acid (**I**), (2-benzoylpyrrol-1-yl)acetic acid (**II**), trolox (6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid), and sorbinil (reference) were dissolved in 0.2 M $NaHCO_3$. Lenses were quickly removed from Fischer-344 rats of both sexes following euthanasia, and enzyme preparation and assay were performed as previously described.[38b] All experiments were performed in triplicate. Results are shown in Table 1.

In Vitro Protein Glycation Assay. The assay was performed as previously described.[22b,44] It involved incubation of bovine serum albumin (BSA, fraction V, essentially fatty acid free) with fructose for 28 days. The test compounds **64**, **65**, **74**, **75**, and trolox (reference) were dissolved in water in the form of their potassium salts. Results are shown in Table 2.

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References

(1) (a) King, H.; Aubert, R. E.; Herman, W. H. Global Burden of Diabetes, 1995−2025: Prevalence, Numeric Estimates, and Projections. *Diabetes Care* **1998**, *21*, 1414−1431. (b) Haigh, D.; Avandia-From Molecule to Market for Type 2 Diabetes. *Abstracts of Papers*; 223rd National Meeting of the American Chemical Society, Apr 7−11, 2002, Orlando, FL; American Chemical Society: Washington, DC, 2002; 132-MEDI.

(2) Costantino, L.; Rastelli, G.; Vianello, P.; Cignarella, G.; Barlocco, D. Diabetes Complications and their Potential Prevention: Aldose Reductase Inhibition and other Approaches. *Med. Res. Rev*. **1999**, *19*, 3−23.

(3) (a) Kangas, T.; Aro, S.; Koivisto, V. A.; Salinto, M.; Laakso, M.; Reunanen, A. Structure and Costs of Health Care of Diabetic Patients in Finland. *Diabetes Care* **1996**, *19*, 191−197. (b) Parving, H. H. Strategies to Reduce the Burden of Diabetic Complications. *Diabetologia* **1997**, *40*, B9−B10.

(4) The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N. Engl. J. Med*. **1993**, *329*, 977−986.

(5) (a) Okhubo, Y.; Kishikawa, H.; Araki, E.; Miyata, T.; Isami, S.; Motoyoshi, S.; Kojima, Y.; Furugoshi, N.; Shichiri, M. Intensive Insulin Therapy Prevents the Progression of Diabetic Microvascular Complications in Japanese Patients with Non-Insuline-Dependent Diabetes Mellitus: A Randomized Prospective 6-Year Study. *Diabetes Res. Clin. Pract*. **1995**, *28*, 103−117. (b) American Diabetes Association. Implications of the Diabetes Control and Complications Trial. *Diabetes Care* **1998**, *21*, S88−90.

(6) Barrett-Connor, E.; Wingard, D. L. "Normal" Blood Glucose and Coronary Risk. *Br. Med. J*. **2001**, *322*, 5−6.

(7) Carrington, A. L.; Litchfield, J. E. The Aldose Reductase Pathway and Nonenzymatic Glycation in the Pathogenesis of Diabetic Neuropathy: A Critical Review for the End of the 20th Century. *Diabetes Rev*. **1999**, *7*, 275−299.

(8) Stout, R. W. Insulin and Atheroma-An Update. *Lancet* **1987**, *1* (Iss. 8541), 1077−1079.

(9) Friedman, E. A. Advanced Glycosylated End Products and Hyperglycemia in the Pathogenesis of Diabetic Complications. *Diabetes Care*, **1999**, *22* (Suppl. 2), B65−71.

(10) Oates, P. J.; Mylari, B. L. Aldose Reductase Inhibitors: Therapeutic Implications for Diabetic Complications. *Expert Opin. Investig. Drugs* **1999**, *8*, 2095−2119.

(11) (a) Tomlinson, D. R.; Stevens, E. J.; Diemel, L. T. Aldose Reductase Inhibitors and their Potential for the Treatment of Diabetic Complications. *Trends Pharmacol. Sci*. **1994**, *15*, 293−297. (b) Nishimura, C. Aldose Reductase in Glucose Toxicity: A Potential Target for the Prevention of Diabetic Complications. *Pharmacol. Rev*. **1998**, *50*, 21−33. (c) Mistry, K. P.; Beyer-Mears, A.; Diecke, F. P. J. Mechanisms for D-Glucose Inhibition of *myo*-Inositol Influx into Rats Lens. *Diabetes* **1993**, *42*, 1737−1744. (d) Stevens, M. J.; Lattimer, S. A.; Kamijo, M.; Van Huysen, C.; Sima, A. A. F.; Greene, D. A. Osmotically-Induced Nerve Taurine Depletion and the Compatible Osmolyte Hypothesis in Experimental Diabetic Neuropathy in the Rat. *Diabetologia* **1993**, *36*, 608−614. (e) De Luca, G.; Calpona, P. R., Caponetti, A.; Romano, G.; Di Benedetto A.; Cucinotta, D.; Di Giorgio, R. M. Taurine and Osmoregulation: Platelet Taurine Content, Uptake, and Release in Type 2 Diabetic Patients. *Metab.-Clin. Exp*. **2001**, *50*, 60−64.

(12) Kawasaki, Y.; Fujii, J.; Miyazawa, N.; Hoshi, A.; Okado, A.; Tano, Y.; Taniguchi, N. Specific Detections of the Early Process of the Glycation Reactions By Fructose and Glucose in Diabetic Rat Lens. *FEBS Lett*. **1998**, *441*, 116−120.

(13) (a) Wolff, S. P.; Jiang, Z. Y.; Hunt, J. V. Protein Glycation and Oxidative Stress in Diabetes Mellitus and Aging. *Free Radic. Biol. Med*. **1991**, *10*, 339−352. (b) Takagi, Y.; Kashiwagi, A.; Tanaka, Y.; Asahina, T.; Kikkawa, R.; Shigeta, Y. Significance of Fructose-Induced Protein Oxidation and Formation of Advanced Glycation End Product. *J. Diabetes Complicat*. **1995**, *9*,

87−91. (c) Hayase, F.; Shibuya, T.; Sato, J.; Yamamoto, M. Effects of Oxygen and Transition Metals on the Advanced Maillard Reaction of Proteins with Glucose. *Biosci. Biotech. Biochem*. **1996**, *60*, 1820−1825.

(14) (a) Hunt, J. V.; Wolff, S. P. Oxidative Glycation and Free Radical Production: A Causal Mechanism of Diabetic Complications. *Free Rad. Res. Commun*. **1991**, *12*−*13*, 115−123.

(15) Constantino, L.; Rastelli, G.; Gamberini, M. C.; Vinson, J. A.; Bose, P.; Iannone, A.; Staffieri, M.; Antolini, L.; Del Corso, A.; Mura, U.; Albasini, A. 1-Benzopyran-4-one Antioxidants as Aldose Reductase Inhibitors. *J. Med. Chem*. **1999**, *42*, 1881−1893.

(16) Nakamura, N.; Obayashi, H.; Fujii, M.; Fukui, M.; Yoshimori, K.; Ogata, M.; Hasegawa, G.; Shigeta, H.; Kitagawa, Y.; Yoshikawa, T.; Kondo, M.; Ohta, M.; Nishimura, M.; Nishinaka, T.; Nishimura, C. Y. Induction of Aldose Reductase in Cultured Human Microvascular Endothelial Cells by Advanced Glycation End Products. *Free Radic. Biol. Med*. **2000**, *29*, 17−25.

(17) Oberley, L. W. Free Radicals and Diabetes. *Free Radic. Biol. Med*. **1988**, *5*, 113−124.

(18) Costantino, L.; Rastelli, G.; Gamberini, M. C.; Barlocco, D. Pharmacological Approaches to the Treatment of Diabetic Complications. *Expert Opin. Ther. Patents* **2000**, *10*, 1245−1262.

(19) Strupczewski, J. D.; Ellis, D. B. To Market, To Market-1992. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press Inc.: San Diego, 1993; vol. 28; p 330.

(20) (a) Banditelli, S.; Boldrini, E.; Vilardo, P. G.; Cecconi, I.; Cappiello, M.; dal Monte, M.; Marini I.; del Corso, A.; Mura, U. A New Approach Against Sugar Cataract Through Aldose Reductase Inhibitors. *Exp. Eye Res*. **1999**, *69*, 533−538. (b) Nakamura, J.; Kasuya, Y.; Hamad, Y.; Nakshima, E.; Naruse, K.; Yasuda, Y.; Kato, K.; Hotta, N. Glucose-Induced Hyperproliferation of Cultured Rat Aortic Smooth Muscle Cells through Polyol Pathway Hyperactivity. *Diabetologia* **2001**, *44*, 480−487. (c) Murata, M.; Ohta, N.; Sakurai, S.; Alam, S.; Tsai, J. Y.; Kador, P. F.; Sato, S. The Role of Aldose Reductase in Sugar Cataract Formation: Aldose Reductase Plays a Key Role in Lens Epithelial Cell Death (Apoptosis). *Chem.-Biol. Interact*. **2001**, *130* (1−3 Special Issue S1), 617−625.

(21) (a) Hamada, Y.; Nakamura, J.; Naruse, K.; Komori, T.; Kato, K.; Kasuya, Y.; Nagai, R.; Horiuchi, S.; Hotta, N. Epalrestat, an Aldose Reductase Inhibitor, Reduces the Levels of N-Epsilon-(Carboxymethyl)Lysine Protein Adducts and their Precursors in Erythrocytes from Diabetic Patients. *Diabetes Care* **2000**, *23*, 1539−1544. (b) Nakayama, M.; Nakamura, J.; Hamada, J.; Chaya, S.; Mizubayashi, R.; Yasuda, Y.; Kamiya, K.; Koh, N.; Hotta, N. Aldose Reductase Inhibition Ameliorates Pupillary Light Reflex and F-Wave Latency in Patients with Mild Diabetic Neuropathy. *Diabetes Care* **2001**, *24*, 1093−1098. (c) Johnson, B. F.; Law, G.; Nesto, R.; Pfeifer, M.; Slater, W.; Vinic, A.; Wackers, F.; Young, L. Aldose Reductase Inhibitor Zopolrestat Improves Systolic Function in Diabetics. *Diabetes*, **1999**, *48* (Iss. S1), 574. (d) Hotta, N.; Ishii, J.; Sakamoto, N. Effects of Fidarestat, an Aldose Reductase Inhibitor, on Diabetic Peripheral Neuropathy. A 52-Week Placebo-Controlled Double-Blind-Study. *Diabetes* **2000**, *49* (Iss. S1), 142.

(22) (a) Kawabata, T.; Packer, L. Alpha-Lipoate Can Protect Against Glycation of Serum Albumin, but not Low-Density Lipoprotein. *Biochem. Biophys. Res. Commun*. **1994**, *203*, 99−104. (b) Stefek, M.; Krizanova, L.; Trnkova, Z. Oxidative Modification of Serum Albumin in an Experimental Glycation Model of Diabetes Mellitus In Vitro: Effect of the Pyridoindole Antioxidant Stobadine. *Life Sci*. **1999**, *65*, 1995−1997.

(23) Vinson, J. A.; Howard, T. B., III. Inhibition of Protein Glycation and Advanced Glycation End Products by Ascorbic Acid and other Nutrients. *J. Nutr. Biochem*. **1996**, *7*, 659−663.

(24) Edelstein, D.; Brownlee, M. Mechanistic Studies of Advanced Glycation End Product Inhibition by Aminoguanidine. *Diabetes* **1992**, *41*, 26−29.

(25) Miyata, T.; Ueda, Y.; Asahi, K.; Izuhara, Y.; Inagi, R.; Saito, A.; Destrihou, C. V.; Kurokawa, K. Mechanism of the Inhibitory Effect of OPB-9195 [(±)-2-Isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide] on Advanced Glycation End-Product and Advanced Lipoxidation End-Product Formation. *J. Am. Soc. Nephrol*. **2000**, *11*, 1719−1725.

(26) (a) Cunningham, J. J. The Glucose/Insulin System and Vitamin C: Implications in Insulin-Dependent Diabetes Mellitus. *J. Am. Coll. Nutr*. **1998**, *17*, 105−108. (b) Tutuncu, N. B.; Bayraktar, M.; Varli, K. Reversal of Defective Nerve Conduction with Vitamin E Supplementation in Type 2 Diabetes-A Preliminary Study. *Diabetes Care* **1998**, *21*, 1915−1918.

(27) (a) Tsuchida, K.; Nakamura, S.; Fujii, W.; Atsumi, T.; Kawata, T.; Makita, Z.; Koike, T. Decrease of TGF−Beta and Type-IV Collagen Production in Diabetic Nephropathy by a Novel AGE Inhibitor OPB-9195. *Diabetes* **1998**, *47* (Iss. S1), 503. (b) Singh, R.; Barden, A.; Mori, T.; Beilin, L. Advanced Glycation End-Products: a Review. *Diabetologia* **2001**, *44*, 129−146.

(28) Demopoulos, V. J.; Rekka, E. Isomeric Benzoylpyrroleacetic Acids: Some Structural Aspects for Aldose Reductase Inhibitory and Antiinflammatory Activities. *J. Pharm. Sci*. **1995**, *84*, 79−82.

(29) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. Privileged Molecules for Protein Binding Identified from NMR−Based Screening. *J. Med. Chem*. **2000**, *43*, 3443−3447.

(30) Lehuédé, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J−M. Synthesis and Antioxidant Activity of new Tetraarylpyrroles. *Eur. J. Med. Chem*. **1999**, *34*, 991−996.

(31) Roberfroid, M. B.; Viehe, H. G.; Remacle, J. Free Radicals in Drug Research. In *Advances in Drug Research*; Testa, B., Ed.; Academic Press Limited: London, 1987; vol. 16; pp 15−19.

(32) (a) Nicolaou, I.; Demopoulos, V. J. A Study of the Friedel−Crafts Acylation of 1-Benzenesulfonyl-*1H*-pyrrole in the Preparation of 3-Aroylpyrroles. *J. Heterocycl. Chem*. **1998**, *35*, 1345−1348. (b) Greenhouse, R.; Ramrez, C.; Muchowski, J. M. Synthesis of Alkylpyrroles by the Sodium Borohydride Reduction of Acylpyrroles. *J. Org. Chem*. **1985**, 50, 2961−2965. (c) Ketcha, D. M.; Gribble, G. W. A Convenient Synthesis of 3-Acylindoles via Friedel−Crafts Acylation of 1-(Phenylsulfonyl)indole. A New Route to Pyridocarbazole-5,11-quinones and Ellipticine. *J. Org. Chem*. **1985**, *50*, 5451−5457.

(33) Entwistle, I. D.; Jackson, A. E.; Johnstone, A. W.; Telford, R. P. Reduction of Nitro-Compounds. *J. Chem. Soc., Perkins Trans. 1* **1977**, 443−447.

(34) Tembo, O. N.; Dallemagne, P.; Rault, S.; Robba, M. An Efficient Synthesis of New Phenylpyrrolizine and Phenylpyrrolopyrazine Derivatives. *Heterocycles* **1993**, *36*, 2129−2137.

(35) Leysen, F. Y.; Ottenheijm, H. C. J. A Facile Synthesis of N-Substituted Pyrroles. *Synth. Commun*. **1995**, *25*, 1857−1861.

(36) Cardinaud, I.; Gueiffier, A.; Debouzy, J−C.; Milhared, J−C.; Chapat, J−P. Synthesis of Pyrroloquinoline and Pyrrolonaphthiridine by an Intramolecular Cyclisation Reaction. *Heterocycles* **1993**, *36*, 2513−2522.

(37) Chan, T. H.; Lee, S. D. 1,4-Dichloro-1,4-dimethoxybutane as a Mild Reagent for the Conversion of Primary Amines to Pyrroles. Synthesis of a Pyrrole Compound from Tobacco. *J. Org. Chem*. **1983**, *48*, 3059−3061.

(38) (a) Dunn, J. P.; Ackerman, N. A.; Tomolonis, A. J. Analgetic and Antiinflammatory 7-Aroylbenzofuran-5-ylacetic Acids and 7-Aroylbenzothiophene-5-ylacetic Acids. *J. Med. Chem*. **1986**, *29*, 2326−2329. (b) Zaher, N; Nicolaou, I; Demopoulos, V. J. Pyrrolylbenzothiazole Derivatives as Aldose Reductase Inhibitors. *J. Enzyme Inhib. Med. Chem*. **2002**, *17*, 131−135.

(39) Cadamuro, S.; Degani, I.; Dagnera, S.; Fachi, R.; Gatti. A.; Piscopo. L. General Methods for Synthesizing 2,4-Diacylpyrroles and their Precursors Containing One or Two Masked Acyl Groups. *J. Chem. Soc., Perkin Trans. 1* **1993**, 273−283.

(40) Lau, C. K.; Dufrene, C.; Belanger, P. C.; Pietre, S.; Scheigetz J. Reductive Deoxygenation of Aryl Aldehydes and Ketones and Benzylic Allylic and Tertiary Alcohols by ZnI_2−$NaCNBH_3$. *J. Org. Chem*. **1986**, *51*, 3038−3043.

(41) Bell, Malcolm Rie (Sterling Drug Inc.) Ger. Offen. 1908541 (Cl. C 07d, A 61k), 18 Sep 1969, US Appl. Feb 1968; 1-(Carboxyalkyl)indoles. *Chem. Abstr*. 1**970**, *72*, 66807m.

(42) McOmie, J. F.; Watts, M. L.; West, D. E. Demethylation of Aryl Methyl Ethers by Boron Tribromide. *Tetrahedron* **1968**, *24*, 2289−2292.

(43) Olah, G. A.; Narany, S. C.; Gupta, B. J. B.; Mulhotra, R. Synthetic Methods and Reactions. Transformations with Chlorotrimethylsilane/Sodium Iodide, a Convenient in situ Iodotrimethylsilane Reagent. *J. Org. Chem*. **1979**, *44*, 1247−1251.

(44) Anagnostou, C.; Nicolaou, I.; Demopoulos, V. J. Synthesis of [5-(4-Pyrrol-1-yl-benzoyl)-1*H*-pyrrol-2-yl)]-acetic Acid and In Vitro Study of its Inhibitory Activity on Aldose Reductase Enzyme and on Protein Glycation. *Pharmazie* **2002**, *57*, 535−537.

(45) Gui, T.; Tanimoto, T.; Kokai, Y.; Nishimura, C. Presence of a Closely-Related Subgroup in the Aldo-Ketoreductase Family of the Mouse. *Eur. J. Biochem*. **1995**, *227*, 448−453.

(46) Del Corso, A.; Costantino, L; Rastelli, G.; Buono, F.; Mura, U. Aldose Reductase does Catalyse the Reduction of Glyceraldehyde through a Stoichiometric Oxidation of NADPH. *Exp. Eye Res*. **2000**, *71*, 515−521.

(47) (a) Sestanj, K.; Bellini, F.; Fung, S.; Abraham, N.; Treasurywala, A.; Humber, L.; Simard-Duquesne, N.; Dvornik, D. N-[[5-(Trifluoromethyl)−6-methoxy-1-naphthalenyl]-N-methylglycine (Tolrestat), a Potent, Orally Active Aldose Reductase Inhibitor. *J. Med. Chem*. **1984**, *27*, 255−256. (b) Terashima, H.; Hama, K.; Yamamoto, R.; Tsuboshima, M.; Kikkawa, R.; Hatanaka, I.; Shigeta, Y. Effects of a New Aldose Reductase Inhibitor on Various Tissues In Vitro. *J. Pharmacol. Exp. Ther*. **1984**, *229*, 226−230. (c) Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel. T. W.; Singleton. D. H. Novel Potent Aldose Reductase Inhibitors: 3,4-Dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]−1-phthalazineacetic Acid (Zopolrestat) and Congeners. *J. Med. Chem*. **1991**, *34*, 108−122. (d) Oka, M.; Matsumoto, Y.; Sug-

iyama, S.; Tsuruta. N.; Matsushima. M. A Potent Aldose Reductase Inhibitor, (2S,4S)−6-Fluoro-2′,5′-dioxospiro[chroman-4,4′-imidazolidine]−2-carboxamide (Fidarestat): Its Absolute Configuraton and Interactions with the Aldose Reductase by X-ray Crystallography. *J. Med. Chem*. **2000**, *43*, 2479−2483.
(48) ClogP Version 4.72, Daylight Chemical Information Systems Inc., (http://www.daylight.com/).
(49) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: Oxford, 1985; pp 76−79.
(50) SPARTAN SGI Version 5.1.3 OpenGL, Wavefunction, Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612.
(51) Llorens, O.; Perez, J. J. Toward the Design of Chemical Libraries for Mass Screening Biased against Mutagenic Compounds. *J. Med. Chem*. **2001**, *44*, 2793−2804.

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