Brief Articles

[1-(3,5-Difluoro-4-hydroxyphenyl)-1*H*-pyrrol-3-yl]phenylmethanone as a Bioisostere of a Carboxylic Acid Aldose Reductase Inhibitor

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[1-(3,5-Difluoro-4-hydroxyphenyl)-1*H*-pyrrol-3-yl]phenylmethanone (**6**) was synthesized as a putative bioisostere of the known aldose reductase (AR) inhibitor (3-benzoylpyrrol-1-yl)acetic acid (**I**). It was found that **6** is approximately 5 times more potent as an in vitro inhibitor of AR than **I**, with an IC_{50} value in the submicromolar range. Furthermore, **6** showed considerable activity in an in vitro experimental glycation model of diabetes mellitus. Our results support the notion that **6** might become a useful lead structure.

Introduction

Diabetes mellitus exacts a huge toll in money and human suffering. At its present rate of increase, within a few decades it will be one of the world's most common diseases and biggest public health problem, with an estimated minimum of half-a-billion cases.[1] The diabetic individual is prone to late onset complications that are largely responsible for the morbidity and mortality observed in patients. It has been demonstrated that the more severe and sustained the degree of hyperglycemia, the more likely it is that the chronic complications of diabetes will develop.[2] Pharmaceutical intervention of hyperglycemia-induced diabetic complications is actively pursued because it is very difficult to maintain normoglycemia by any means in patients with diabetes mellitus.[2,3] Aldose reductase enzyme (EC 1.1.1.21, AR) of the polyol metabolic pathway was first found to be implicated in the etiology of secondary complications of diabetes.[4] AR inhibitors (ARIs) have therefore been noted as possible pharmacotherapeutic agents. Although several ARIs have progressed to the clinical level, only one is currently on the market. However, the inhibition of the polyol pathway is considered to be a promising approach to control diabetes complications as well as a number of other pathological conditions such as ischemia, abnormal vascular smooth muscle cell proliferation, cancers, and mood disorders.[5] Thus, attention is currently targeted to discovering ARIs of distinct chemical structures, being derivatives of neither hydantoin nor carboxylic acid, which are known to cause toxicity or to possess a narrow spectrum of tissue activity.[6]

On the basis of the above, in the present study we replaced the acetic acid moiety of the known[7] ARI **I** (Figure 1) with a 2,6-difluorophenol ring. The latter has been proposed as a lipophilic isostere for molecules containing a carboxylic acid group.[8] Thus, the title compound **6** (Figure 1) was synthesized and its in vitro AR inhibitory activity was compared with that of **I**. Furthermore, for both **6** and **I** we evaluated their ability to interfere with the oxidative modification of serum albumin in an in vitro experimental glycation model of diabetes mellitus.[9] Advanced glycation end products (AGEs) are produced by nonenzymatic reaction between monosaccharides and proteins and have been implicated as a major pathogenesis process leading, for example, to diabetic complications, atherosclerosis, Alzheimer's disease, and Creutzfeldt−Jakob disease.[10]

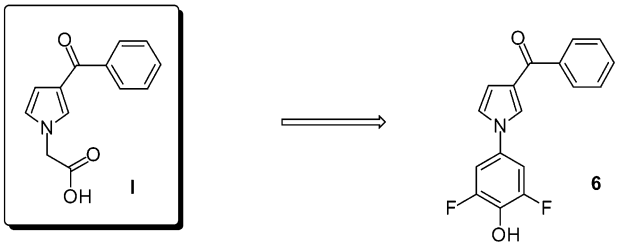

Figure 1. Synthesized target compound **6** based on the structure of **I**.

Chemistry

The synthesis of the target compound **6** is shown in Scheme 1. The reduction of the nitrophenol **1** has been previously reported under classical hydrogenation conditions.[8] Alternatively, we investigated the heterogeneous catalytic transfer hydrogenation[11a] in refluxing ethanol by using either 1,4-cyclohexadiene[11b] (65% yield) or cyclohexene[11c] (91% yield, which is comparable with that from using gaseous hydrogen[8]). The resulting amine was found to be unstable and could be isolated only as its hydrochloride salt. Thus, the formation of the pyrrole ring was attained with the use of 4-chloropyridine instead of the previously reported use of 4-chloropyridine hydrochloride.[12] The direct introduction of the benzoyl substituent on the pyrrole ring of **3** under

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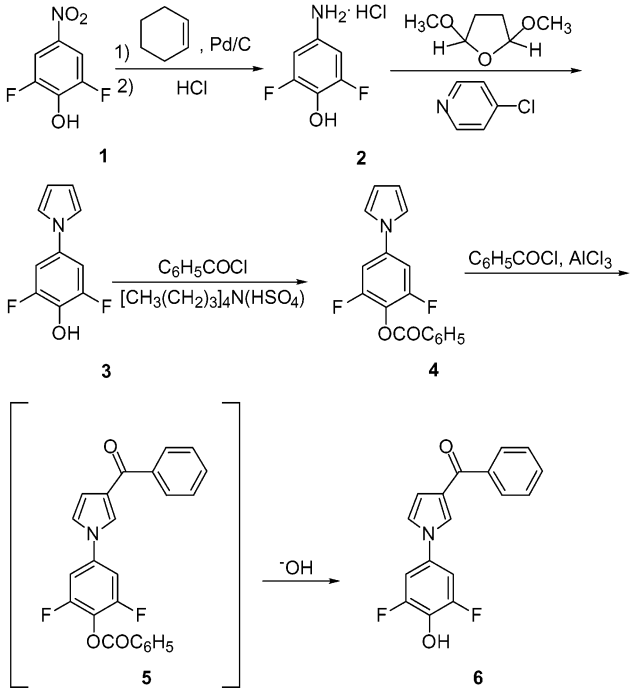
Table 1. Aldose Reductase Inhibitory Activity

	% inhibition (SEM)[a] at concn				
inhibitor	10^{-4} M	10^{-5} M	10^{-6} M	10^{-7} M	IC_{50},[b] M
3	77(0.0)	24(2.0)	13(1.5)		$234(4.9) \times 10^{-7}$
6		88(2.0)	68(0.5)	29(2.0)	$3.96(0.12) \times 10^{-7}$
I		78(2.5)	37(3.0)		$19.7(0.3) \times 10^{-7}$ [c]
sorbinil			49(0.9) at 2.5×10^{-7} M[d]		

[a] $n = 3$. [b] Mean (standard error from three determinations). [c] Reported IC_{50}: 25×10^{-7} M.[7] [d] Reported IC_{50}: 2.5×10^{-7} M.[7]

Scheme 1. Methodology Followed for the Synthesis of the Target Compound **6**



Friedel−Crafts conditions was hampered by the reactivity of the phenol group in this molecule. Thus, phenol **3** was first protected[13] in the form of its benzoate ester **4** and then benzoylated. The formed compound **5** was not isolated but directly hydrolyzed to **6**.

Results and Discussion

Compounds **3**, **6**, and **I** were tested in vitro for their ability to inhibit rat lens AR. It has been shown that there is an approximately 85% sequence similarity between rat lens and human AR, while the proposed active sites of both enzymes are identical.[14] The performed assay was based on the spectrophotometric monitoring of NADPH oxidation, which is proven to be a reliable method.[15]

It was found (Table 1) that the putative bioisostere of **I**, the difluorophenol derivative **6**, is approximately 5 times more potent than **I** in this in vitro assay. Its IC_{50} value is in the submicromolar range, which makes it an interesting lead for further optimization of activity.[6c,16] In this respect, it is also worth noting that 2,6-difluoro-4-pyrrol-1-ylphenol (**3**) shows a weak inhibitory activity (Table 1), while pyrrol-1-ylacetic acid is inactive at concentrations up to 100 μM.[7] Finally, inspection of low-energy conformations[17] reveals that the distances of the geometric (unweighted) centers of the aromatic areas of **6** and **I** (centroids) from the carboxylic or the phenolic oxygen are quite similar (7.1 and 7.2 Å, respectively).

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)	rel fluorescence (rel units)[a]	% inhib	carbonyl groups (nmol/mg BSA)[a]	% inhib
none		39.3 ± 3.0 (5)		5.78 ± 0.2 (5)	
6	5	10.4 ± 1.8 (4)[b]	74	2.27 ± 0.3 (4)[b]	61
6	2.5	12.6 ± 0.5 (4)[b]	68	2.58 ± 0.3 (5)[b]	55
6	1	14.2 ± 1.8 (4)[b]	64	3.01 ± 0.3 (4)[b]	48
I	5	7.3 ± 0.3 (4)[b]	81	1.91 ± 0.3 (4)[b]	67
I	2.5	12.8 ± 0.8 (5)[b]	67	2.82 ± 0.3 (5)[b]	51
I	1	20.5 ± 1.1 (4)[b]	48	4.19 ± 0.3 (4)[b]	28
trolox	1	16.2 ± 0.7 (5)[a]	59	3.72 ± 0.8 (5)[b]	36

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

Compounds **6** and **I** 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 it is known to be a more potent glycation agent.[18] This is derived from the fact that its acyclic (open chain) form, which is the reactive species, is approximately 10 times more potent than that of glucose. Fructose is also elevated in those tissues where the polyol pathway is active.[19]

It was found (Table 2) that the tested compounds showed considerable activity, comparable to that of the known[9] proteins' glycation inhibitor trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid). However, it should be noted that the latter is a weak ARI.[12b]

The above overall results support the notion that [1-(3,5-difluoro-4-hydroxyphenyl)-1*H*-pyrrol-3-yl]phenylmethanone (**6**) might become a useful lead structure because it has a biological profile that could target a number of pathological conditions, most notably the long-term complications of diabetes mellitus.

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 were obtained on a Perkin-Elmer 597 or on a Shimadzu FTIR-8101M spectrophotometer, and ^{1}H NMR spectra were obtained 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.

4-Amino-2,6-difluorophenol Hydrochloride (2). To a solution of 2,6-difluoro-4-nitrophenol (**1**) (5.39 g, 30.8 mmol) in EtOH (60 mL), cyclohexene (15.1 g, 184 mmol) and Pd/C (2.7 g) were added, and the mixture was refluxed under a nitrogen atmosphere for 3 h. The reaction mixture was cooled (ice bath), and then concentrated HCl (5.2 mL) was added. It was filtered through Celite, the Celite was washed with EtOH (3 × 20 mL), and the combined filtrates were evaporated under reduced pressure. The residue was recrystallized from EtOH/

Et_2O to provide the title compound (5.1 g, 91%), which was identical with an authentic sample.[8]

2,6-Difluoro-4-pyrrol-1-ylphenol (3). A mixture of 4-amino-2,6-difluorophenol hydrochloride (**2**) (1.11 g, 6.13 mmol), 2,5-dimethoxytetrahydrofuran (1.30 g, 9.85 mmol), and 4-chloropyridine (1.09 g, 9.6 mmol) in dioxane (120 mL) was refluxed under atmosphere and with vigorous stirring for 3 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Most of the residue was dissolved in CH_2Cl_2 by the gradual addition of several portions of this solvent, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was flash-chromatographed with petroleum ether/EtOAc (10:1) to provide the title compound (1.11 g, 86%). An analytical sample was prepared by recrystallization from petroleum ether: mp 53−55 °C; IR (Nujol) 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.25−6.45 (m, 3H, pyrrolyl-3,4*H* and phenyl-O*H*), 6.85−7.05 (m, 4H, pyrrolyl-2,5*H* and phenyl-*H*). Anal. ($C_{10}H_7F_2NO$) C, H, N.

Benzoic Acid 2,6-Difluoro-4-pyrrol-1-ylphenyl Ester (4). To a well stirred mixture of 2,6-difluoro-4-pyrrol-1-ylphenol (**3**) (0.98 g, 5 mmol), tetrabutylammonium hydrogen sulfate (0.1 g, 0.3 mmol), and pulverized NaOH (0.5 g) in dioxane (12.5 mL), benzoyl chloride (0.98 g, 7 mmol) in dioxane (5 mL) was added dropwise over a period of 0.5 h at room temperature and under a nitrogen atmosphere. The mixture was filtered and washed with dioxane (3 × 10 mL), and the combined filtrates were evaporated under reduced pressure. The solid residue was recrystallized from CH_2Cl_2/petroleum ether to provide the title compound (1.13 g, 75%): mp 124−125 °C; IR (Nujol) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.35−6.50 (m, 2H, pyrrolyl-3,4*H*), 6.95−7.30 (m, 5H, pyrrolyl-2,5*H* and phenyl-*H*), 7.50−7.75 (m, 2H, phenyl-*H*), 8.15−8.35 (m, 2H, phenyl-*H*). Anal. ($C_{17}H_{11}F_2NO_2$) C, H, N.

[1-(3,5-Difluoro-4-hydroxyphenyl)-1*H*-pyrrol-3-yl]phenylmethanone (6). To a stirred suspension of $AlCl_3$ (0.8 g, 6 mmol) in ethylene dichloride at room temperature and under a nitrogen atmosphere, benzoyl chloride (0.79 g, 5.6 mmol) was slowly added, and the resulting mixture was stirred for 10 min. A solution of benzoic acid 2,6-difluoro-4-pyrrol-1-ylphenyl ester (**4**) (1.5 g, 5 mmol) in 1,2-dichloroethane (5 mL) was then added, and the mixture was stirred for 90 min. The reaction mixture was poured onto stirred H_2O/ice (∼40 mL), the organic layer was collected, and the aqueous layer was extracted with $CHCl_3$ (2 × 20 mL). The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in dioxane (20 mL), to this a 5% solution of NaOH was added, and the reaction mixture was vigorously stirred at room temperature and under a nitrogen atmosphere for 24 h. The reaction mixture was concentrated under reduced pressure to half of its volume, H_2O (20 mL) was added, the mixture was cooled (ice bath) and acidified with concentrated HCl solution, and the product was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated under reduced pressure. H_2O (50 mL) was added to the residue, the mixture was basified with the dropwise addition of triethylamine under vigorous stirring, and the product was extracted with EtOAc (3 × 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 petroleum ether/EtOAc (5:1) to provide the title compound (0.82 g, 55%). An analytical sample was prepared by recrystallization fron toluene/petroleum ether: mp 186 °C; IR (Nujol) 3100, 1600 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 6.75−6.85 (m, 1H, pyrrolyl-4*H*), 6.90−7.10 (m, 3H, pyrrolyl-2,5*H* and phenyl-O*H*), 7.40−7.65 (m, 5H, phenyl-*H*), 7.75−7.95 (m, 2H, phenyl-*H*). Anal. ($C_{17}H_{11}F_2NO_2$) C, H, N.

In Vitro Aldose Reductase Enzyme Assay. The test compounds **3**, **6**, and **I** as well as sorbinil ($C_{11}H_9FN_2O_3$, 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.[12b,20] To generate IC_{50} values, **3**, **6**, and **I** were tested at five concentrations. The log(dose)−response curves were then constructed from the inhibitory data, and IC_{50} values were calculated by least-squares analysis of the linear portions of log(dose)−response curves ($0.880 < r^2 < 0.993$). All experiments were performed in triplicate. Results are shown in Table 1.

In Vitro Protein Glycation Assay. The assay was performed as previously described.[9,12b,21] It involved incubation of bovine serum albumin (BSA, fraction V, essentially fatty acid free) with fructose for 28 days. The test compounds **6** and **I** as well as trolox (reference) were dissolved in water in the form of their potassium salts. Results are shown in Table 2.

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