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Chalcone based aryloxypropanolamines as potential antihyperglycemic agents☆

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Abstract—A series of chalcone based aryloxypropanolamines were synthesized and evaluated for their antihyperglycemic activity in SLM and STZ rat models. Most of the compounds exhibited moderate to good activity ranging from 6.5% to 31.1% in SLM and 8.3% to 22.6% in STZ models, respectively. The most potent compound **5g** exhibited glucose lowering of 26.7% in SLM and 22.6% in STZ models. A definite structure–activity relationship was observed while varying the nature as well as the position of the amine in ring B.

Diabetes of type-II (non-insulin dependent diabetes mellitus, NIDDM) is a chronic metabolic disease characterized by insulin resistance, hyperglycemia and hyperinsulinaemia. The disease is often associated with obesity, dyslipidemia and hypertension leading to cardiovascular risks.[1] In such cases, restoration of normal adipose tissue levels results in an alleviation of the insulin resistant state.[2] Given the link between obesity and type-II diabetes, reduction in body fat mass via diet and exercise is generally the first treatment for diabetes. The majority of previous and current anti-obesity drug based therapies are targeted at a reduction of energy intake or absorption (anorectic drugs) but pharmacological approaches to an increase in energy expenditure (thermogenic drugs) serve as an attractive alternative option for the treatment of obesity and hence, diabetes. There are approaches to induce thermogenesis either through stimulation of nuclear receptor of PPAR family[3] or adrenergic receptor (AR) in membrane of adipose tissue.[4]

An 'atypical' β_3-adrenergic receptor was discovered in early 1980s[4] on the cell surface of both white and brown adipose tissues. Agonists of the β_3-AR were observed to simultaneously increase lipolysis, fat oxidation, energy expenditure[5] and insulin action leading to the belief that, this receptor might serve as an attractive target for the treatment of diabetes and obesity.[6]

Arylethanolamines and aryloxypropanolamines were first reported as β_3-AR agonists in the mid 1980s.[7] CL-316,243 (I),[8] the most selective β_3-AR agonist tested in humans, led to concentration-dependent increase of lipolysis, fat oxidation and insulin activation.

Troglitazone is another antidiabetic drug of thiazolidinedione class. The unique structural feature of Troglitazone,[15] is the presence of the antioxidant moiety of vitamin E together with a PPAR-γ nuclear receptor stimulating pharmacophore in a single molecule. Troglitazone, however failed due to its toxic metabolites but provided a basis for further designing molecules for multi-factorial diseases. Thus molecules with multiple ligands are being designed for such diseases. Oxidative stress plays a crucial role in diabetic patients leading to macrovascular complications through Maillard reaction.[14] The chalcones are antioxidant molecules of plant origin which being consumed daily through fruits and vegetables have attracted our attention to explore hybrid structures with them for antidiabetic activity. Chalcones are also known to exhibit various biological activities including antioxidant,[9] antimalarial,[10] antileishmanial,[11] antiinflammatory[12] and antitumor.[13] The antioxidant property of chalcones may be one of the factors for various activities. In this ongoing programme,

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we have earlier synthesized hybrid chalcones with aryloxypropanol amine pharmacophore in ring A (Fig. 1) and few compounds of type-II in the series have exhibited potent antidiabetic activity in db/db mice with good bioavailability profile.[16] This led us to synthesize another structural motif III for structure–activity relationship study in order to optimize the activity in respect of ADME profile.

The general synthetic plan employed to prepare the different chalcones is by Claisen–Schmidt[17] condensation. Hydroxy chalcones **3** on reaction with epichlorohydrin in presence of sodium hydride yielded compound **4** which on reaction with appropriate amine provided the desired product **5** (Scheme 1).[18]

Antihyperglycemic activity: The compounds (**5a**–**n**) were evaluated for their anti-hyperglycemic activity in sucrose-loaded model (SLM) and in streptozotocin (STZ) induced β-cell damaged diabetic model of Sprague–Dawley strain male albino rats.

Sucrose-loaded rat model (SLM): compounds were tested for their effect on glucose tolerance curve in rats of average body weight 160 ± 20 g, an indirect effect of measuring anti-hyperglycemic activity. The blood glucose levels of all animals were checked after an overnight fasting (16 h) by Glucostrips (Boehringer–Mannheim). Animals showing blood glucose levels between 60 and 80 mg/dl (3.33–4.44 mM) were divided into groups of 5–6 animals in each. Animals of experimental group were administered the suspension of the synthetic compounds orally (in 1.0% gum acacia) at a dosage of 100 mg/kg-body weight. Animals of control group were given an equal amount of 1.0% gum acacia. A sucrose-load (10.0 g/kg) was given to each animal orally exactly after 30 min post administration of the test sample/vehicle. Blood glucose profile of each animal was determined at 30, 60, 90 and 120 min post administration of sucrose. Food but not water was removed from the cages during the course of experimentation. Quantitative glucose tolerance of each animal was calculated by area under curve (AUC) method. Comparing the AUC of experimental and control groups was calculated the percentage anti-hyperglycemic effect. Samples showing significant inhibition ($p < 0.05$) on postprandial hyperglycemia (AUC) were considered as active samples.

Streptozotocin-induced diabetic rat model (STZ): Sprague–Dawley strain male albino rats of average body weight 140 ± 20 g were selected having blood glucose profiles between 60 and 80 mg/dl. Streptozotocin (Sigma, USA) was dissolved in 100 mM citrate buffer (pH 4.5) and calculated amount of freshly prepared solution was injected to overnight fasted animals at a dose of 60 mg/kg-body weight intraperitoneally. Blood glucose profile was checked after 48 h using Glucostrips (Boehringer–Mannheim) and animals showing blood glucose profiles between 180–270 mg/dl were considered suitable for the experiment. These diabetic animals were again divided into groups and their blood glucose profiles were again checked on the day of experiment (day 3). Animals showing almost equal or similar blood glucose profiles were divided into groups consisting of 5–6 animals in each group. Animals of experimental group were administered the suspension of the test sample orally (in 1% gum acacia) at 100 mg/kg-body weight. Animals of control group were given an equal amount of 1% gum acacia. A sucrose-load (2.5 g/kg) was given to each animal orally exactly after 30 min post administration of the test sample/vehicle. Blood glucose profile of each animal was determined at 30, 60, 90, 120, 180, 240, 300 min and at 24 h post administration of sucrose. Food but not water was removed from the cages during the experimentation. The % fall in blood glucose by test sample was calculated according to the AUC method. The average fall in AUC in experimental group compared to control group provided % anti-hyperglycemic activity.

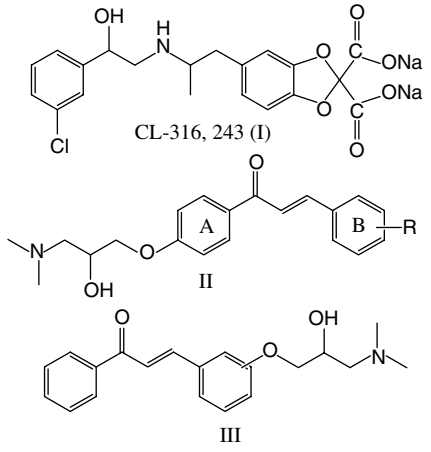
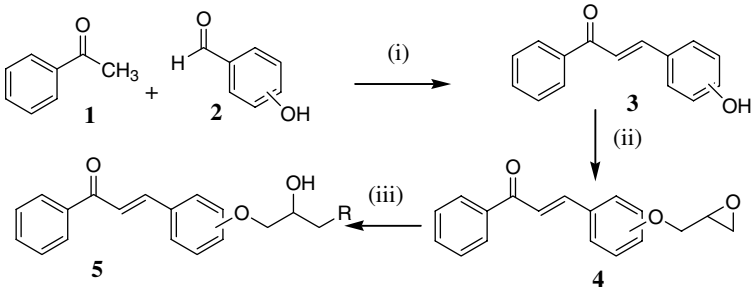
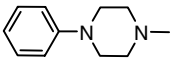
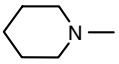
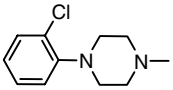
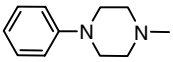
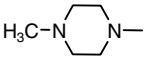
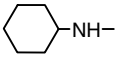


Figure 1.



Scheme 1. Reagents and conditions: (i) 50% aq NaOH, MeOH, rt; (ii) NaH, epichlorohydrin, DMF, rt; (iii) amine, MeOH, rt.

Table 1. In vivo anti-hyperglycemic activity in rat models

Compound	Position	R	% anti-hyperglycemic activity	
			SLM	STZ
5a	3	$(CH_3)_2$–CH_2NH–	14.5	NIL
5b	3	*t*-ButNH–	21.7	10.6
5c	3		22.9	10.4
5d	3		11.3	9.4
5e	3		19.0	8.3
5f	4		31.1	3.0
5g	3	$[(CH_3)_2$–$CH]_2N$–	26.7	22.6
5h	3		20.4	20.1
5i	4	*t*-ButNH–	29.0	10.3
5j	3	$Et_2N(CH_2)_3NH$–	20.8	8.3
5k	4	$[(CH_3)_2$–$CH]_2N$–	7.9	ND
5l	4		22.3	19.3
5m	3		Inactive	ND
5n	4	$(CH_3)_2CH_2NH$–	6.5	ND
Metformin			12.9	19.1
Glybenclamide			33.7	29.0

ND, not determined; NIL, insignificant activity.

The synthesized compounds were evaluated for their anti-hyperglycemic activity in above two models and compared with standard drugs Metformin and Glybenclamide. The most active compound **5g**, in the series having di-isopropyl amine in the chain, lowered blood glucose level up to 26.7% in SLM and 22.6% in STZ models. Besides, compounds **5h** and **5l** exhibited significant anti-hyperglycemic activity, 20.4% and 22.3% in SLM and 20.1% and 19.3% in STZ, models, respectively. On contrary to di-isopropylamine, the compounds **5i** and **5b** with *tert*-butylamine chain exhibited inferior activity whereas compounds **5a** and **5n** with isopropylamine chain have lost the activity. Compound **5l** with piperidine in the chain, a cyclic analogue is also exhibiting good activity. Compounds having aromatic residue at nitrogen atom as in phenylpiperazine exhibited insignificant activity in STZ model.

However, the substitution of propoxypropanol amine moiety at two different positions either at 3- or 4- did not exhibit much striking difference in activity profile. Compound **5i**, showed marked activity (29%) than the *meta* substituted **5b** (21.7%) in SLM model. Compound **5f** with phenylpiperazine in chain at *para* position exhibited better activity (31.1%) than its *meta* regiomer **5c** (22.9%) in SLM model. Similarly, piperidine compound **5l** showed a higher activity (22.3% and 19.3%) than its *meta* regiomer **5d** (11.3% and 9.4%) in SLM and STZ models, respectively Table 1.

Thus, the compounds with propoxypropanolamine pharmacophore at either 3- or 4-position in ring B of chalcone exhibit anti-hyperglycemic activity comparable to Metformin and Glybenclamide. The compounds with acyclic amine in the chain are specifically more active as compared to their cyclic congeners. Further work is in progress to improve the potency of these compounds.

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18. General procedure for the preparation of aryloxypropanolamines (Scheme 1): To a stirred solution of chalcone (8.9 mmol) in dry DMF (50 mL) was added NaH (22.3 mmol) at 0–5 °C followed by epichlorohydrin (30 mmol) and stirring was continued for another 10 h. The solvent removed under reduced pressure, and reaction mixture taken in water, extracted with chloroform. The organic layer dried (Na_2SO_4), filtered, solvent removed to yield crude product **4** which was purified on silica gel column. The compound **4** (5.20 mmol) was further treated with appropriate amine (6.5 mmol/excess) in methanol at room temperature for ~6 h. The solvent was removed and the product purified by column chromatography. Spectral data of the potent compounds: Compound **5g**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, J = 15.7 Hz, 1H, β-H), 8.03 (d, J = 7.0 Hz, 2H, 2′, 6′-H), 7.55-7.50 (m, 3H, 3′, 4′, 5′-H), 4.12-4.00 (m, 3H, –OCH_2–CHOH), 3.19 (d, J = 6.6 Hz, 2H, CH_2–N), 2.83–2.60 (m, 2H, CH), 1.12 (s, 12H, CH_3). Compound **5h**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (d, J = 15.7 Hz, 1H, β-H), 7.88 (d, J = 7.2 Hz, 2H, 2′, 6′-H), 7.40–7.34 (m, 3H, 3′, 4′, 5′-H), 6.80 (s, 1H, 2-H), 6.72 (d, J = 7.2 Hz, 1H, 4-H), 7.09 (d, J = 10.4 Hz, 1H, 5-H), 6.86 (d, J = 7.9 Hz, 1H, 6-H), 4.12–3.96 (m, 3H, –OCH_2–CHOH), 2.52 (d, J = 8.8 Hz, 2H, CH_2–N), 2.73 (m, 8H, 2″, 3″, 5″, 6″-H), 2.40 (s, 3H, N–CH_3). Compound **5l**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.78 (d, J = 15.8 Hz, 1H, β-H), 7.41 (d, J = 15.6 Hz, 1H, α-H), 8.01(d, J = 6.4 Hz, 2H, 2′, 6′-H), 7.62–7.53 (m, 3H, 3′, 4′, 5′-H), 6.97 (d, J = 8.6 Hz, 2H, 3, 5-H), 7.51 (d, J = 7.3 Hz, 2H, 2, 6-H), 4.14–4.02 (m, 3H, OCH_2–CHOH), 2.53 (d, J = 6.1 Hz, 2H, CH_2–N), 1.50 (m, 4H, 2″, 6″-H), 1.21 (m, 6H, 3″, 4″, 5″-H).