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Synthesis and antihyperglycemic activity of novel *N*-acyl-2-arylethylamines and *N*-acyl-3-coumarylamines☆

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Abstract—A series of novel *N*-acyl-2-arylethylamines and *N*-acyl-3-coumarylamines were synthesized and evaluated for their antihyperglycemic activity. Compounds **3g** and **6d** exhibited lowering of postprandial plasma glucose by 30.7%, 23.3% in SLM and 25.6%, 25.4% in STZ models respectively which is significant compared to metformin and glybenclamide. Other compounds exhibited moderate to good activity ranging from 19.5% to 32.8% in SLM and 3.26% to 25.4% in STZ models.

Diabetes mellitus (type-II diabetes, T2D) is an acquired syndrome of elevated blood glucose and develops due to the effect of sedentary lifestyle, dietary changes and genetic factors. T2D is closely associated with obesity and other metabolic syndromes, and is characterized by initial phase progressive insulin resistance and subsequent phase exhaustion of β cells in the pancreas. It is estimated that over 330 million people worldwide would be affected by T2D by 2030.[1] The current treatment of T2D includes efficient oral antidiabetic agents such as Metformin, sulfonyl ureas, glinides, and glitazones. Metformin though safe and well tolerated poses a risk of inducing lactic acidolysis and is contraindicated in the setting of renal failure. Both sulfonyl ureas and glinides induce weight gain and have adverse effect in obese patients. The glitazones pose a risk of oedema, weight gain, and is contraindicated in the setting of congestive heart failure. A number of candidates based upon action on different molecular targets such as DPP4 inhibitors, GLP1 analogues, SGL2 inhibitors are at various stages of clinical trials and soon may replace existing drugs.[2] Despite the remarkable progress in the management of diabetes mellitus there has been a resurgence of phytotherapeutical approach for the generation of new leads from active principle of medicinal plants traditionally used worldwide for the treatment of T2D and related metabolic disorders.[3] The active compounds isolated from some of the plants such as Scoparone from *Artemesia Capillaris*,[4] 3-hydroxyumbelliferone derivatives from *Bahia ambrosioides*,[5] Glycyrin from *Glycyrrhiza uralensis*[6] and Marmesin and Umbelliferone ether isolated from *Aegle marmelos*[7] used traditionally for the management of diabetes and related metabolic disorders contain 7-hydoxycoumarin motif. An alkaloid, Aegeline (*N*-cinnamoyl-4-methoxyphenylethanolamine) isolated from the same plant *Aegle marmelos* reported to exhibit both antihyperglycemic and antidyslipidemic activities.[8] The active constituent isolated from the plants *Actaea dahurica*, *Cinnamomum aromaticum* Nees, *Ipomoea batatas*, *Scrophularia buergeriana* are derivative of either mono or polyhydroxylated cinnamic acids.[3] Based upon these phytochemical leads it was envisaged that a library of *N*-acyl 2-arylethylamines and *N*-acyl-3-coumarylamines of type **A** (Chart 1) should possess antihyperglycemic activity. The synthesis and our preliminary study on antihyperglycemic activity of *N*-acyl-2-arylethylamines and *N*-acyl-3-coumarylamines are presented in this letter.

N-Cinnamoyl-3,4-dimethoxyphenylethylamines **3** were synthesized by the acylation of **2** with substituted cinnamic acid **1** (Scheme 1). Thus, the acid chloride obtained on treatment of cinnamic acid **1** with either

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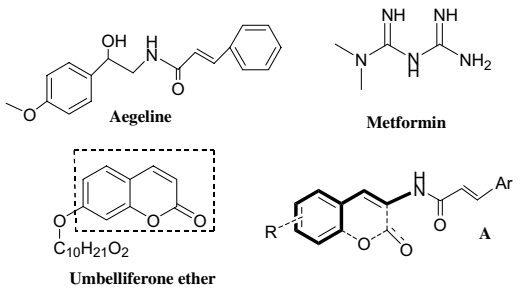
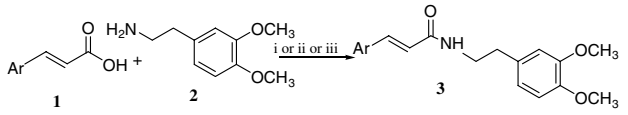


Chart 1.



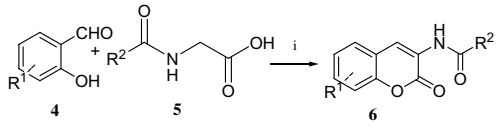
Scheme 1. Reagents and conditions: (i) **1** + $SOCl_2$ (excess), reflux, evaporation; the addition of **2**, Et_3N, DCM, 0 °C, rt, 2 h. (ii) **1** + oxalyl chloride in DCM, stirring at rt evaporate; the addition of **2**, Et_3N, dichloromethane, 0 °C, rt, 2 h. (iii) EDC·HCl, Et_3N, 0 °C, rt.

oxalyl chloride or thionyl chloride was reacted with **2** in the presence of triethylamine at low temperature to furnish **3**[9] (Scheme 1).

Alternatively condensation of **1** with **2** mediated by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC. HCl) at 0 °C afforded **3g**.[10]

The *N*-acyl-3-coumaryl amines **6** were synthesized[11] in moderate to good yield by modified Pechmann condensation of *N*-acylglycine **5** with substituted salicyladehyde **4** in the presence of acetic anhydride and sodium acetate as shown in Scheme 2.

All the compounds were tested for their effect on glucose tolerance curve in mice of average body weight 160 ± 20 g, an indirect effect of measuring antihyperglycemic 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. By comparing the AUC of experimental and control groups the percentage of antihyperglycemic effect was calculated. Samples showing significant inhibition ($p < 0.05$) on postprandial hyperglycemia (AUC) were considered as active samples. Streptozotocin-induced diabetic mice 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 a 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 and 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 % antihyperglycemic activity.

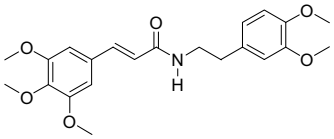
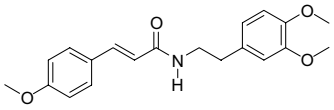
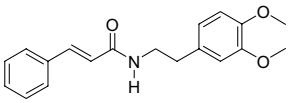
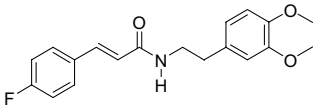
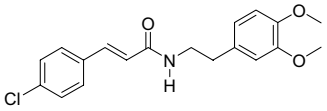
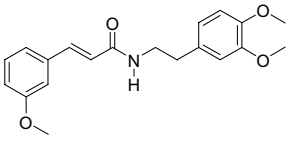
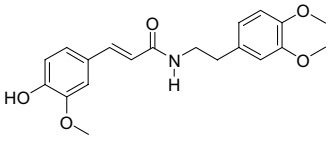
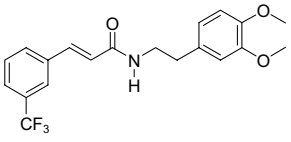
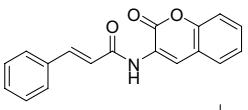
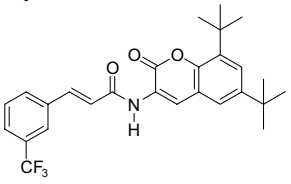
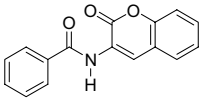
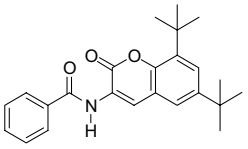


Scheme 2. Reagents and condition: (i) Acetic anhydride, sodium acetate, reflux.

The antihyperglycemic activity evaluated in the above two models were compared with standard drugs metformin and glybenclamide (Table 1). The most active compound **3g** (*N*-feruloyl-3,4-dimethoxy phenethyl amine), lowered blood glucose level up to 30.7% in SLM and 25.6% (5 h) in STZ models. *N*-feruloyl-4-hydroxyphenylethyl amine, an analog of **3g**, isolated from *Tinospora tuberculata* was reported to exhibit antibacterial activity.[12] Ferulic acid amides were reported[13] to exhibit their stimulatory abilities on insulin secretion in rat pancreatic RIN-5F cells. Compounds **3f**, **3g** and **3h** having both electron donating or withdrawing substitution at meta position of the cinnamoyl component showed an appreciable increase in activity, whereas groups (electron donating or electron withdrawing) at para position as in **3b**, **3d**, **3e** sustain the activity in SLM model but were found inferior in STZ models. Surprisingly, 3,4,5-trimethoxycinnamic acid amide **3a** has low antihyperglycemic activity.

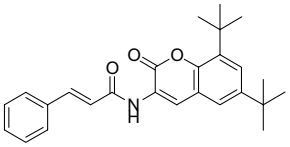
In general, as compared to the compounds **3a**–**h**, 3-coumaryl amides **6a**–**c** have uniformly higher effect in the reduction of plasma glucose both in sucrose loaded

Table 1. In-vivo antihyperglycemic evaluation of *N*-acyl-2-arylethyl-amines and *N*-acyl-3-coumarylamines in SLM and STZ-s model

Compound	Structure	% Antihyperglycemic activity		
		SLM	STZ/5 h	STZ/24 h
3a		2.41	ND	ND
3b		19.5	7.17	4.44
3c		20.1	6.7	3.26
3d		23.4	8.56	4.19
3e		21.5	8.94	3.17
3f		25.2	13.4	9.21
3g		30.7	25.6	23.8
3h		32.8	21.5	19.8
6a		22.3	19.8	23.0
6b		21.1	21.1	19.8
6c		10.7	ND	ND
6d		23.3	23.0	25.4

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	% Antihyperglycemic activity		
		SLM	STZ/5 h	STZ/24 h
6e		8.89	ND	ND
Standard	Metformin	12.9	19.1	20.5
Standard	Glybenclamide	33.7	29.0	25.5

ND, not done.

and streptozotocin induced models. Amongst the series, **6d** 6,8-bis *tert*-butylcoumarin derivative lowered post-pand- ial plasma glucose by 23.0 and 25.4% at 5 and 24 h, respectively, in steptozotocin induced mice. In contrast, **6e** corresponding *N*-cinnamoyl analog has lower effect in the reduction of plasma glucose. The reverse trend was observed in series **6a**–**c**. The benzamide **6c** had low antihyperglycemic activity compared to cinnamic acid amides **6a** and **6b**. The variation of blood glucose at different interval of time after the administration of most active compounds **3g**, **3h** and **6d** has been shown in Figure 1.

In conclusion, the *N*-acyl-2-arylethylamines **3** and *N*-acyl-3-coumarylamines **6** exhibited moderate to excellent in vivo antihyperglycemic activity ranging from 19.5% to 32.8% in SLM and 3.26% to 25.4% in STZ models respectively. Compounds **3g** and **6d** were lowered of postprandial plasma glucose at 30.7%, 23.3% in SLM and 23.8%, 25.4% after 24 h in STZ models, respectively, which is significant compared to metformin and glybenclamide. The activity of **3g** was found to be statistically overlapping with that of **3h** and **6d** in the range of animals in both SLM and STZ models. Further study on lead optimization and mechanism of action is in progress.

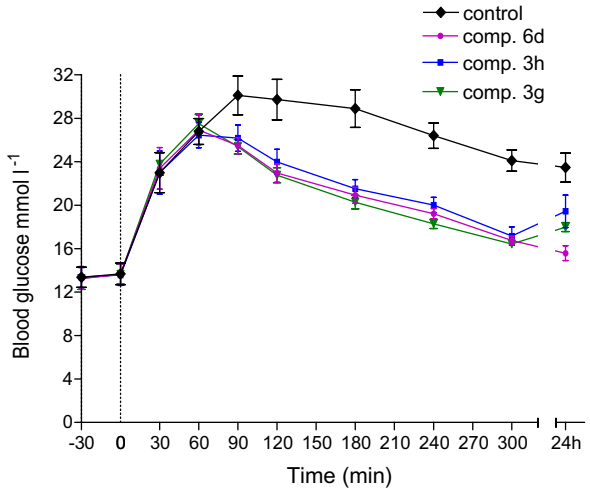


Figure 1. Blood glucose levels in sucrose challenged streptozotocin-induced diabetic rats before, and up to 24 h after administration of vehicle and test samples.

Acknowledgments

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Supplementary data

The physical and spectral data of all synthesized compounds are presented as pdf file. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.03.003.

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9. *Typical procedure.* To a stirred solution of 3-trifluoromethylcinnamic acid (10 mmol) in DCM (20 mL), oxalyl chloride (12 mmol) was added at rt. After stirring for 2 h, the solvent was stripped off. The residual liquid was

dissolved in DCM (20 mL) and to the resulting solution was added dropwise a mixture of triethyl amine (12 mmol) and 2-(3,4-dimethoxy-phenyl)-ethylamine (11 mmol) at 0 °C with stirring, and the stirring was continued for next 2 h at rt. After the completion of the reaction saturated solution of sodium bicarbonate (10 mL) was added to the reaction mixture and the organic layer was separated, washed successively with 3% aqueous hydrochloric acid solution (10 mL), 5% $NaHCO_3$ solution. It was dried over sodium sulfate and evoporated to furnish the desired product, *N*-[2-(3,4-dimethoxyphenyl)ethyl]-3-(3-trifluoro-methyl-phenyl) acrylamide (**3h**).

10. *Typical procedure.* A mixture of 3-(4-hydroxy-3-methoxy-phenyl)-acrylic acid (10 mmol), 2-(3,4-dimethoxy-phenyl)-ethylamine (11 mmol), EDC·HCl (12 mmol) triethylamine (12 mmol) in DCM (15 mL) was stirred at 0 °C for 1 h and then at rt for 5 h. Aqueous workup followed by silica gel chromatography afforded *N*-[2(3,4-dimethoxyphenyl) ethyl]-3-(4-hydroxy-3-met-hoxyphenyl) acrylamide (**3g**).
11. *Typical procedure.* The mixture of salicylaldehyde (10 mmol), hippuric acid (11 mmol), acetic anhydride (20 mmol) sodium acetate (12 mmol) was allowed to reflux with continous stirring for 2–4 h. The reaction mixture was brought to rt and cooled at 0 °C. The solid obtained was crystallized with alcohol and was filtered, dried in air to get the pure *N*-(2-oxo-2H-chromen-3-yl)-3-phenyl-acrylamide (**6a**).
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