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Synthesis and Oral Hypoglycemic Activity of 3-[5'-Methyl-2'-aryl-3'-(thiazol-2''-yl amino) thiazolidin-4'-one]coumarin Derivatives

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Abstract: Number of heterocyclic compounds has been exploited to develop pharmaceutically important molecules, out of which biheterocyclic coumarins are clinically used potential drug candidates showing oral hypoglycemic and antidiabetic activities. A new series of 3-[5'-methyl-2'-aryl-3'-(thiazol-2''-yl amino)thiazolidin-4'-one]coumarin derivatives were designed and synthesized. The title compounds were synthesized from starting material 3- acetyl coumarin. All the synthesized compounds were characterized and screened for hypoglycemic activity. Some of the compounds exhibited promising activity.

Keywords: Oral hypoglycemic, Coumarins, Thiazilidinones.

Introduction

Diabetes mellitus is one of life threatening disorder found in most of the countries in the world which is due to impaired carbohydrate, fat and protein metabolism[1]. A defective or deficient insulin secretion, which translates into impaired carbohydrate (glucose) use, is a characteristic feature of diabetes mellitus results in hyperglycemia in the blood[2]. Recent survey showed that it is fourth leading cause of death in developed countries and worry more than 5% of world's population; suffer from diabetes. There are more than 125 million persons with diabetes in the world today and by 2010, this number is expected to approach 220 million[3]. A standard treatment regimen has considered the use of Insulin and number of other chemical classes of drugs which may increase the production of Insulin. The chemical compounds like sulphonyl ureas, biguanides, thiazolidinediones that reduce the hyperglycemia by inducing the $\tilde{\beta}$cells to release more insulin[3]. However, prolonged use of sulphonylureas cause undesirable effects which include hypoglycemic episodes, ultimate

exertion of β cell as well as long term angiogenic side effects that are results of chronic day long exposure to increased insulin level[4]. From literature survey, it was found that thiazolidine derivatives exhibited 10 fold more potent antidiabetic activity (ED25=0.05 mg/kg/d) than pioglitazone (ED25=0.05 mg/kg/d) in Wistar fatty rats[4]. Even it was found that 3,5-dimethyl pyrazoles possess hypoglycemic activity as greater as 100 times that of tolbutamide in glucose prime in rats[5].

Coumarins are very important oxygen containing heterocycles having diverse biological activities of natural and synthetic origin as anticoagulants and antithrombotics[6]. Some of the coumarin derivatives are found to possess antimicrobial[7,] antitumour[8], antiviral[9] and other activities[10]. Due to these importance of thiazolidinones and coumarin derivatives we have planed to synthesize new series of 3-[5'-methyl-2'-aryl-3'-(thiazol-2''-yl amino)thiazolidin-4'-one] coumarin derivatives and test for oral hypoglycemic activity.

Experimental

The synthetic pathway for the coumarins derivatives presented here is shown in Scheme 1. In the first step the 3-bromoacetyl derivatives were prepared by bromination of 3-acetyl coumarin (**1**) in acetic acid afforded 3-(2'-bromoacetyl)coumarins (**2**). The 3-[2'-(2''-arylidenehydrazinyl) thiazolyl]coumarins (**3**) was prepared by the reaction of 3- bromoacetyl coumarin with benzaldehyde thiosemicarbazones in ethanol under refluxing conditions. The reaction undergone smoothly in ethanol as solvent. Further the reaction of 3 with thiolactic acid in the presence of zinc chloride in dioxane under refluxing condition to afford 5-methyl-3-(4'-(2''-methyl-3-(4'-(2''-oxo-2*H*-chromen-3'-yl)thiazol-2'-ylamino)-2-phenylthiazolidin-4-one (**4a-4j**) in moderate yields (Scheme 1). All the synthesized compounds were characterized by spectroscopic and elemental analysis. The physical data of title compounds is summarized in Table 1.

Table 1. Physical data of the compounds **4a-j**

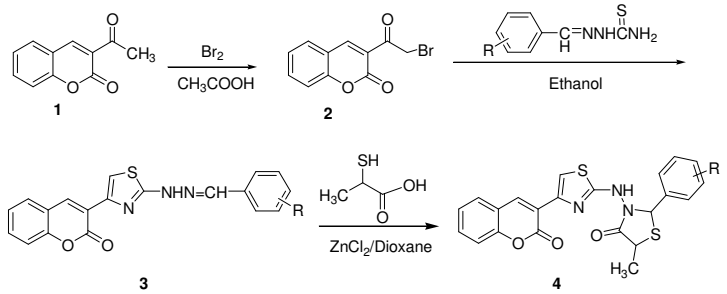
Compound code	R	MP ^{O}C	% Yield	R_f
4a	H	133-135	69	0.5
4b	4-CH_3	223-228	68.6	0.6
4c	4-Cl	255-260	63.21	0.6
4d	4-OH	202-207	60.46	0.6
4e	5,6-benzo	220-230	56	0.6
4f	4-F	220-225	56	0.6
4g	4-NO_2	178-180	60	0.5
4h	2-Cl	156-158	62	0.5
4i	2-Br	187-189	63	0.5
4j	4-Br	224-226	58	0.5

Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and were uncorrected. IR spectra were recorded on the Nicolet FT-IR spectrophotmeter using KBr pressed pellet technique. ^{1}H NMR were recorded on Bruker Model DRX-300 MHz NMR spectrophotometer in $CDCl_3$ and DMSO-d_6 using Tetramethylsilane (TMS) as internal reference. MS spectra were obtained on Jeol SX 102/DA-6000 mass spectrometer. Elemental analysis was performed on Carlo Erba 1108 analyzer.

Results and Discussion

As outlined in Scheme 1, 3-(2-bromoacetyl)coumarins **2** were prepared by bromination of 3-acetyl coumarins **1** in chloroform at room temperature. 3-bromoacetyl)coumarin **2** were

allowed to react with substituted benzaldehyde thiosemicarbazones under reflux in ethanol for 8 h to afford 3-[2'-(2''-arylidenehydrazinyl)thiazolyl]coumarin **3** derivatives in good yields. The structures of compounds **3** were substantiated from analytical and spectral data. Thus, the IR spectral data showed the presence NH, C=O and C=N stretching vibrations. In addition the ^{1}H NMR spectra showed signals corresponding to hydrazinyl, aromatic and NH protons. Further the formation of the compound **3** is also confirmed by mass spectral data. The compound **3** was treated with thiolactic acid in the presence of $ZnCl_2$ under refluxing conditions in dioxane gave 3-[5'-methyl-2'-aryl-3'-(thiazol-2''-ylamino)thiazolidin-4'-one]coumarins **4** in moderate to good yields. We have tried with many reaction conditions for the preparation of the titled compounds such as DMF and dichloro methane. The dioxane with zinc chloride under reflux was found to undergo the reaction smoothly. The structure of the titled compound was assigned by IR, ^{1}H NMR and Mass spectra accordance with the structure.



Scheme 1.

*Synthesis of 3-[2'-(2''-arylidenehydrazinyl) thiazolyl] coumarin (**3**)*

Equal molar (0.01 mole) of **2** and substituted benzaldehyde thiosemicarbazones were dissolved in 25 mL of ethanol in a 100 mL round bottom flask. The reaction mixture was refluxed for 8 h. After completion of the reaction, monitored by TLC the reaction mixture was cooled to room temperature. The solvent was removed by rotary evaporator and the solid was washed with water, dried and recrystallized from ethanol. M.P.: 155-160 ^oC; R_f Value (T:E:F; 5:4:1): 0.74; % Yield : 65; IR (KBr) cm^{-1}: 3264 (N-H), 1622 (C=N), 1543 (C=C), 1515, 1455 and 1040 (characteristic of thiazole nucleus); ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ ppm: 7.19 (s, 1H, Ar-H), 7.55 (m, 2H, Ar-H), 7.64 (t, J=8Hz, 2H, Ar-H), 7.83 (dd, 2H, Ar-H), 7.98 (d, J=12Hz, 1H, Ar-H), 8.10 (d, J=12Hz, 1H, Ar-H), 8.24 (m, 4H, Ar-H, -N=CH), 11.78 (s, 1H, NH); Elemental Analysis ($C_{20}H_{14}N_4O_2S$), Found % (Calculated %): C, 64.15 (64.16); H, 3.77 (3.77); N, 14.95 (14.96).

*Synthesis of 3-[5-methyl-2-aryl-3-(thiazol-2-ylamino)thiazolidin-4-one]coumarin (**4**) -General Procedure (c.f. Table 1)*

To the solution of compound **3** (0.01 moles) and thiolactic acid (0.015 mol) in dioxane, a pinch of $ZnCl_2$ was added at room temperature. The reaction mixture was heated under reflux for 8-10 h. After the completion of the reaction, which is monitored by TLC, the reaction mixture was concentrated. It was then poured on crushed ice and solid so obtained was filtered, washed with water, dried and recrystallized from dioxane.

*3-[5-Methyl-2-(4-nitrophenyl)-3 (thiazol-2-ylamino)thiazolidin-4-one]coumarin (**4a**)*

M.P.:133-135 ^oC; R_f Value (T:E:F; 5:4:1): 0.79; % Yield : 55: IR (KBr) cm^{-1}: 3241 (N-H), 1687 (C=O), 1614 (C=N), 1543 (C=C), 1512, 1444 and 1046 (characteristic of thiazole nucleus); ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ ppm: 1.34 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-

S-), 6.45 (s, 1H, -N-CH-), 7.35 (s, 1H, Ar-H), 7.42 (d, J=12Hz, 2H, Ar-H), 7.56 (m, 2H, Ar-H), 7.67 (m, 4H, Ar-H), 7.97 (d, J=12Hz, 1H, Ar-H), 8.07 (d, J=12Hz, 1H, Ar-H), 8.21 (d, J=12Hz, 1H, Ar-H), 8.92 (s, 1H, NH); Elemental Analysis ($C_{23}H_{18}N_4O_3S_2$), Found % (Calculated %): C, 59.69 (59.72); H, 3.90 (3.92); N, 12.09 (12.11); Mass(*m/z*): 474 (M^+, $C_{24}H_{18}N_4O_3S_2$), 181 (100%, $C_7H_5N_2O_2S$), 154 ($C_{11}H_8N$), 70(C_3H_4NO), 57 (C_3H_5O).

Pharmacological activity (Oral hypoglycemic activity)

Three months old Wistar strain *Albino* rats of either sex, weighing 200-250 g were used. The animals were allowed food and water *ad libitum.* They were housed in room temperature at 25±2° for 24 h. The animals were randomly allocated into 12 groups, each group contained 6 animals. The blood glucose level was induced by Streptozocin Model 16. All the test compounds and standard drug were suspended in Tween- 80 and were administered orally. This study was carried out in twelve different groups. The standard used is rosiglutazone.

Determination of LD50

There was no mortality in control group of rats up to a dose of 5000 mg/kg body weight; all the coumarino thaizolo thiazolidinones derivatives up to a dose of 1000 mcg/kg body weight did not produce mortality. Hence 1/5th dose of LD50 *i.e.* 200 mcg/kg body weight of the title compounds were used for screening oral hypoglycemic activity1[11]. The results are shown in the Table 2.

Table 2. Hypoglycemic activity of the test compounds (**4a-j**) were compared with respect to control

S. No	Compound No.	Mean glucose concentration mg/d ± SEM	Mean % change in hypoglycemic activity ± SEM
1	Control	103.55 ±2.23	-
2	Standard	68.51±1.331**	44.089±1.233
3	**4a**	74.33±1.156**	23.845±2.134
4	**4b**	82.53±1.019**	20.764±2.592
5	**4c**	99.18±1.575ns	4.880±2.653
6	**4d**	87.88±2.462**	15.569±3.919
7	**4e**	83.53±1.493**	19.885±1.862
8	**4f**	95.55±1.455*	6.88±1.598
9	**4g**	75.58±1.375**	27.567±1.708
10	**4h**	75.63±1.197**	27.394±2.564
11	**4i**	99.18±1.575ns	4.880±2.653
12	**4j**	105.8±1.535ns	-1.495±3.021

*Data were analyzed by one way ANOVA followed by Tukey-Kramer's Multiple Comparisons Test n = 6, ** P<0.001, * P<0.01, ns P>0.05*

Hypoglycemic activity

The test group of animal were treated with different derivatives of coumarino thaizolo thaizolidinones (**4a-4j**) with defined dose (200 mcg/kg) orally. Control and standard groups of animals were treated with normal saline and rosiglitazone (200 mcg/kg) respectively. After 2 h blood samples were collected via retro orbital plexus. Estimated the blood glucose level by Semi-auto analyzer (Qualigens AR 601, GSK), using commercially available glucose estimation kit (Span diagnostics), as per manufacturers brochure. The statistical analysis of data was carried out by one way ANOVA followed by Tukey-Kramer's Multiple Comparisons Test[12-14]. All the values are expressed as mean blood glucose level (mg/dl) ±S.E.M, (n=6).

Conclusion

Several Coumarino Thaizolo thaizolidinones were synthesized from 3-acetyl coumarin as starting material. Among the synthesized compounds **4a, 4b, 4d, 4e, 4f, 4g** and **4h** were significantly active, where as others were inactive derivatives. The lipophilicity of the side chains and their electronegativity seemed to be responsible for variation of the hypoglycemic activity.

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