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Synthesis and Antihyperglycemic Activity of [2-(Substituted phenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}amino]-4-oxo-1,3-thiazolidin-5-yl] Acetic Acid

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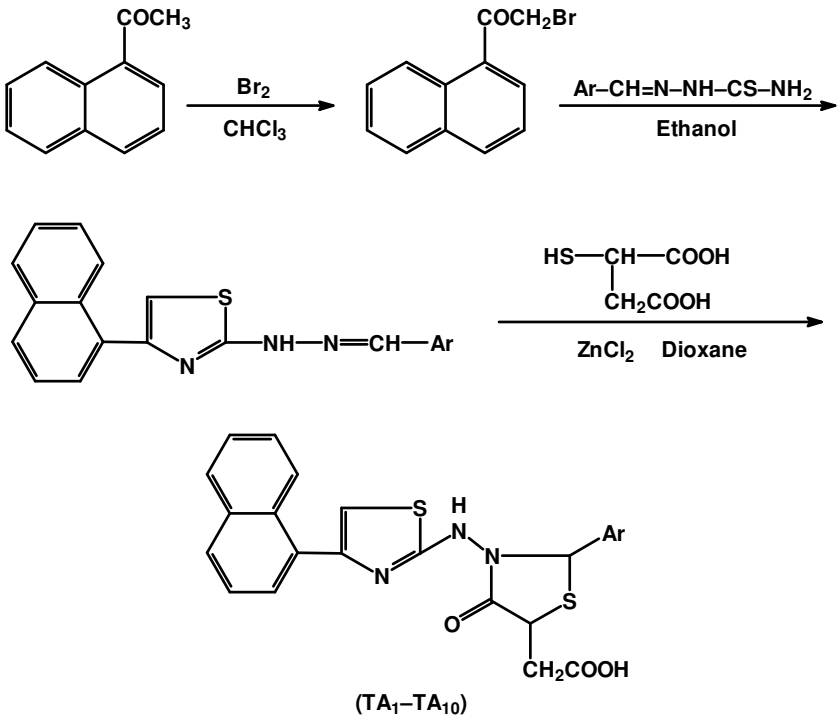
The title compounds were prepared by brominating 1-acetyl naphthalene in chloroform followed by condensation with substituted benzaldehyde thiosemicarbazones using ethanol to get 4-(1-naphthyl)-2-(substituted benzylidineamino)-1,3-thiazoles. These thiazole derivatives were then cyclized to title compounds by reacting with thiomalic acid in dioxane using $ZnCl_2$. All the synthesized compounds were characterized on the basis of their IR, ^1H NMR, mass and elemental analysis. The antihyperglycemic study was divided into two phases. Phase-I involved evaluation of blood glucose lowering ability of thiazolidinones in normal rats by sucrose loaded model (SLM). It was observed that compound with Ar = 4-nitrophenyl displayed highest antihyperglycemic activity in SLM. Phase-II study included the evaluation of blood sugar by alloxan model. It was observed that most of the compounds exhibited more antihyperglycemic activity than standard drug pioglitazone on 7th day of study. It was also observed that blood glucose lowering effects were more pronounced and stronger in alloxan model.

Key Words: Synthesis, Thiazolidinones, Antihyperglycemic activity.

INTRODUCTION

Diabetes mellitus is the root cause of several chronic and progressive diseases that adversely affect a number of organs including the nervous and vascular systems. Diabetes is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2000 of 150 million people, expected to rise to 220 million people by 2010[1]. The classes of drugs currently available include insulin and insulin analogues, sulfonyl ureas, glinides, biguanides, thiazolidinediones and α-glucosidase inhibitors. However most of the drugs can cause problems including compliance, hypoglycemia and obesity[2,3]. Thus, new antidiabetic drugs that have improved comliance and reduced side effects are still required. Thiazolidinone derivatives have been reported to possess antidiabetic activity[4-6].

Furthermore, thiazolidinone heterocyclic ring has structural similarity with clinically used thiazolidinedione derivatives[7]. With a view to study antihyperglycemic activity, some thiazolidinone derivatives are synthesized (**Scheme-I**) and screened for antihyperglycemic activity. All the synthesized compounds were characterized on the basis of their IR, ^{1}H NMR, mass and elemental analysis.



Scheme-I

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. The compounds were routinely chekced for their purity by TLC using silica gel-G. IR spectra were recorded in KBr on the Nicolet 5 PC FT-IR spectrophotometer. Proton magnetic resonance spectra (^{1}H NMR, PMR) were recorded on Bruker Model DRX-300 MHz NMR spectrophotometer in $CDCl_3$ and DMSO-d_6 using tetramethylsilane (TMS) as internal refernece. The FAB mass spectra were recorded on a Jeol SX 102/DA-6000 mass spectrometer. Elemental analysis was performed on Carlo Erba 1108 analyzer.

Synthesis of 1-bromoacetyl naphthalene: 1-Acetyl naphthalene (0.02 mol) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 mol) in chloroform was prepared. The bromic solution was added to flask containing 1-acetyl naphthalene soution drop wise with constant stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized from benzene. The purity of compound was established on the basis of TLC. Melting point 177-179 ºC, R_f value (T:E:F; 5:4:1): 0.73, yield (%): 85; IR (KBr, ν_{max}, cm^{-1}): 1702 (C=O), 1554 (C=C), 783 (C-Br); ^1H NMR ($CDCl_3$, DMSO-d_6) δ ppm: 4.74 (s, 2H, CH_2), 7.71 (m, 2H, Ar-H), 7.84 (t, *J* = 8 Hz, 1H, Ar-H), 8.00 (d, *J* = 10 Hz, 1H, Ar-H), 8.11 (d, *J* = 12 Hz, 1H, Ar-H), 8.39 (d, *J* = 12 Hz, 2H, Ar-H); Elemental analysis (%) ($C_{12}H_9OBr$), Found (Calcd.): C, 57.84 (57.86), H, 3.63 (3.64).

Synthesis of 4-(1-naphthyl)-2-(substituted benzylidine amino)-1,3-thiazoles: Equimolar quantities (0.01 mol) of 1-bromoacetyl naphthalene and substituted benzaldehyde thiosemicarbazones were dissolved in 50 mL of ethanol in a 100 mL round bottom flask. The reaction mixture was refluxed for 1-2 h. A solid was separated during refluxing which was hot filtered, dried and recrystallized from ethanol. The purity of compounds was established on the basis of TLC. Compound 4-(1-naphthyl)-2-(nitrobenzylidineamino)-1,3-thiazole: m.p. 188-190 ºC, R_f value (T:E:F; 5:4:1): 0.74, yield (%): 65; IR (KBr, ν_{max}, cm^{-1}): 3261 (N-H), 1627 (C=N), 1543 (C=C), 1515, 1453 and 1040 (characteristic of thiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6) δ ppm: 7.19 (s, 1H, Ar-H), 7.55 (m, 2H, Ar-H), 7.64 (t, *J* = 8 Hz, 2H, Ar-H), 7.83 (dd, 2H, Ar-H), 7.98 (d, *J* = 12 Hz, 1H, Ar-H), 8.10 (d, *J* = 12 Hz, 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 (Calcd.): C, 64.15 (64.16), H, 3.77 (3.77), N, 14.95 (14.96).

Synthesis of [2-(substituted phenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}amino]-4-oxo-1,3-thiazolidin-5-yl] acetic acid (TA_1-TA_{10}): A mixture of 4-(1-naphthyl)-2-(substituted benzylidineamino)-1,3-thiazoles (0.01 mol) and thiomalic acid (0.015 mol) in 25 mL of dioxane was taken in a 100 mL round bottom flask. To this solution a pinch of $ZnCl_2$ was added and the reaction mixture was refluxed for 6-10 h. The mixture was then poured on crushed ice and solid so obtained was filtered, washed with water, dried and recrystallized from dioxane. The purity of compounds was established on the basis of TLC. Compound [2-(4-nitrophenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}amino]-4-oxo-1,3-thiazolidin-5-yl] acetic acid: m.p. 187-189 ºC; R_f value (T:E:F; 5:4:1): 0.78, yield (%): 45; IR (KBr, ν_{max}, cm^{-1}): 3415 (O-H), 3247 (N-H), 1717 and 1693 (C=O), 1613 (C=N), 1542 (C=C), 1509, 1439 and 1040; ^1H NMR ($CDCl_3$, DMSO-d_6) δ ppm: 2.38 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.50 (t, *J* = 6 Hz, 1H, -CH-S-), 6.33 (s, 1H, -N-CH-), 7.56 (m,

9H, Ar-H), 7.92 (d, *J* = 12 Hz, 1H, Ar-H), 8.09 (d, *J* = 12 Hz, 1H, Ar-H), 8.24 (d, *J* = 12 Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 10.68 (s, 1H, OH); Elemental analysis (%) ($C_{24}H_{18}N_4O_5S_2$), Found (Calcd.): C, 56.89 (56.91), H, 3.56 (3.58), N, 11.04 (11.06). The physical data of title compounds is summarized in Table-1.

TABLE-1
PHYSICAL DATA OF 2-([2-(SUBSTITUTEDPHENYL)-3-[{4-(1-NAPHTHYL)-1,3-THIAZOL-2-YL}AMINO]-5-METHYL-1,3-THIAZOLIDIN-4-ONES

Compd. (m.f.)	Ar-	m.p. (± 2 ºC)	R_f value (Yield %)	N Found (Calcd.) %
TA_1 $C_{24}H_{18}N_4O_5S_2$	4-Nitrophenyl	188	0.78 (45)	11.04 (11.06)
TA_2 $C_{24}H_{18}N_3S_2O_3Cl$	3-Chlorophenyl	179	0.71 (55)	8.45 (8.47)
TA_3 $C_{24}H_{18}N_3S_2O_3Cl$	4-Chlorophenyl	187	0.74 (50)	8.45 (8.47)
TA_4 $C_{24}H_{17}N_3S_2O_3Cl_2$	2,4-Dichlorophenyl	197	0.70 (50)	7.90 (7.92)
TA_5 $C_{24}H_{17}N_3S_2O_3Cl_2$	2,6-Dichlorophenyl	210	0.72 (45)	7.90 (7.92)
TA_6 $C_{24}H_{18}N_3S_2O_3F$	3-Fluorophenyl	173	0.78 (50)	8.75 (8.76)
TA_7 $C_{24}H_{18}N_3S_2O_4Br$	2-Hydroxy-4-bromophenyl	194	0.68 (40)	7.54 (7.55)
TA_8 $C_{24}H_{18}N_3S_2O_4Cl$	2-Hydroxy-4-chlorophenyl	190	0.68 (45)	8.19 (8.21)
TA_9 $C_{26}H_{24}N_4O_3S_2$	4-Dimethylaminophenyl	176	0.69 (45)	11.08 (11.10)
TA_{10} $C_{25}H_{21}N_3O_4S_2$	4-Methoxyphenyl	170	0.73 (45)	8.54 (8.55)

All the compounds gave satisfactory elemental analysis with in ± 0.4 % of the theoretical values; R_f values were determined in toluene : ethyl acetate : formic acid (5:4:1).

Antihyperglycemic activity[8-10]: The experiment was divided into two phases to screen out compounds that have prominent antihyperglycemic activity. In phase-I, all the synthesized compounds were evaluated for their effect in sucrose loaded model (SLM). The test animals were kept fasted overnight and their blood glucose was recorded. Animals were administered with test compounds at a dose of 100 mg kg^{-1} body weight of each animal. After 0.5 h post test compounds treatment, the animals were fed with sucrose load of 1000 mg kg^{-1} body weight of each rat. The blood glucose was recorded after 1 and 4 h post sucrose load by microprocessor digital blood glucometer.

TABLE-2
ANTIHYPERGLYCEMIC ACTIVITY OF 2-([2-(SUBSTITUTEDPHENYL)-3[{4-(1-NAPHTHYL)-1,3-THIAZOL-2-YL}AMINO]-4-OXO-1,3-THIAZOLIDIN-5-YL]ACETIC ACID (TA_1-TA_{10})

Compound	%Blood sugar lowering activity ± SEM (SLM)		%Blood sugar lowering activity ± SEM (Alloxan model)			
	1 h	4 h	24 h	72 h	120 h	168 h
Pioglitazone	100.000 ± 8.810*	100.000 ± 4.920	100.000 ± 15.243	100.0000 ± 12.584	100.000 ± 16.093	100.000 ± 28.277
TA_1	87.150 ± 5.410†	93.750 ± 6.970‡	112.48 ± 19.146	114.0900 ± 5.123†	135.660 ± 2.738‡	139.370 ± 0.831‡
TA_2	64.770 ± 6.780	75.495 ± 5.360	30.982 ± 14.186	42.2850 ± 21.279	63.465 ± 15.093	71.692 ± 14.291
TA_3	69.040 ± 6.810*	73.905 ± 5.640	39.127 ± 17.642	47.0700 ± 21.367	66.472 ± 20.148	74.505 ± 17.923
TA_4	82.620 ± 7.560*	87.495 ± 6.840	79.890 ± 33.143	85.3650 ± 29.680	99.082 ± 12.744*	107.625 ± 31.390‡
TA_5	83.460 ± 5.410†	89.060 ± 6.220†	88.035 ± 12.361	91.2750 ± 5.250	115.605 ± 3.662†	123.405 ± 2.844‡
TA_6	81.217 ± 6.450*	85.147 ± 5.542†	90.060 ± 13.845	94.9350 ± 9.682*	117.307 ± 6.283*	127.117 ± 4.875‡
TA_7	66.510 ± 6.322*	71.250 ± 4.425*	37.095 ± 18.487	44.8420 ± 43.320	65.767 ± 20.587	74.182 ± 18.285
TA_8	84.890 ± 5.760†	88.275 ± 5.760†	100.000 ± 21.300	106.2667 ± 8.122*	127.830 ± 6.497‡	135.592 ± 2.017‡
TA_9	62.535 ± 6.094	69.127 ± 3.922	24.870 ± 13.710	40.5370 ± 21.247	63.220 ± 14.955	70.320 ± 12.945
TA_{10}	77.257 ± 6.982*	81.243 ± 5.527*	79.890 ± 16.252	82.9720 ± 14.385	98.962 ± 17.467*	107.902 ± 21.165*

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$; $n = 6$

The per cent fall in blood glucose level was calculated. In phase-II, diabetes was induced by injecting alloxan (50 mg dL^{-1} were selected as diabetic rats for the study. Blood glucose was again recorded 24, 72, 120 and 168 h post standard/test treatment.

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the basis of their IR, ^1H NMR and elemental analysis. The study was aimed at evaluating the antihyperglycemic effect of compounds on diabetic rats. The study was divided into two phases. Phase-I involved evaluation of blood glucose lowering ability of [2-(substitutedphenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}-amino]-4-oxo-1,3-thiazolidin-5-yl]acetic acid (**TA_1-TA_{10}**) in normal rats by sucrose loaded model. It was observed that compound **TA_1** (Ar = 4-nitrophenyl) displayed highest antihyperglycemic activity in SLM model (Table-2). This was followed by **TA_4** (Ar = 2,4-dichlorophenyl), **TA_5** (Ar = 2,6-dichlorophenyl), **TA_6** (Ar = 3-fluorophenyl), **TA_8** (Ar = 4-chloro-2-hydroxyphenyl) and **TA_{10}** (Ar = 4-methoxyphenyl) (Table-2). Phase-II included the evaluation of blood sugar by alloxan model (Table-2). It was observed that most of the compounds exhibited more antihyperglycemic activity than standard drug pioglitazone on 7th day of study (Table-2). These compounds included **TA_1** (Ar = 4-nitrophenyl), **TA_4** (Ar = 2,4-dichlorophenyl), **TA_5** (Ar = 2,6-dichlorophenyl), **TA_6** (Ar = 3-fluorophenyl), **TA_8** (Ar = 4-chloro-2-hydroxyphenyl) and **TA_{10}** (Ar = 4-methoxyphenyl). The compound **TA_1** exhibited highest activity followed by **TA_8**, **TA_6**, **TA_5**, **TA_4** and **TA_{10}** (Table-2). It was also observed that blood glucose lowering effects were more pronounced and stronger in alloxan model. From the above results, it has been concluded that [2-(substitutedphenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}amino]-4-oxo-1,3-thiazolidin-5-yl]acetic acid (**TA_1-TA_{10}**) may be used as lead compounds for antihyperglycemic activity and may further be evaluated for toxicological profile.

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REFERENCES

1. P.Z. Zimmet, K.G.M.M. Alberti and J. Shaw, *Nature*, **414**, 782 (2001).
2. H.S. Seltzer, *Endocrinol. Metab. Clin. North Am.*, **18**, 163 (1989).
3. T.M. O'Moore-Sullivam and J.B. Prins, *Med. J. Aust.*, **176**, 381 (2002).
4. N. Jacob and G.N. Kutty, *Indian Drugs*, **41**, 76 (2004).

5. J.M. Joy, N. Jacob and G.N. Kutty, *Indian Drugs*, **42**, 47 (2005).
6. N.J. Gaikwad and P. Gautam, *Indian J. Heterocycl. Chem.*, **12**, 181 (2002).
7. M. Diamant and R.J. Heine, *Drugs*, **63**, 1373 (2003).
8. A. Goel, N. Agarwal, F.V. Singh, A. Sharon, P. Tiwari, M. Dixit, R. Pratap, A.K. Srivastava, P.R. Maulik and V.J. Ram, *Bioorg. Med. Chem. Lett.*, **14**, 1089 (2004).
9. A.K. Wahi, *J. Nat. Rem.*, **2**, 80 (2002).
10. H.G. Vogel, Drug Discovery and Evaluation, Springer, edn. 2, p. 1017 (2002).

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