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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-YLACETIC ACID DERIVATIVES

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Abstract: The title compounds were prepared by brominating 1-acetylnaphthalene in chloroform followed by condensation with substituted benzaldehyde thiosemicarbazones using ethanol to get 4-naphthalen-1-yl-2-{2-[(substituted phenyl)methylidene]hydrazino}-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, ^{1}H NMR, 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). Phase-II study included the evaluation of blood sugar by alloxan model.

Keywords: thiazolidinones, antihyperglycemic activity

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, sulfonylureas, 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 compliance and reduced side effects are still required. Thiazolidinone derivatives have been reported to possess antidiabetic activity (4-6). Furthermore, thiazolidinones have structural similarity with clinically used thiazolidinediones (7). With a view to study antihyperglycemic activity, we have prepared some thiazolidinone derivatives (Scheme 1) and screened them for antihyperglycemic activity.

1-Acetylnaphthalene on bromination in chloroform afforded 1-ω-bromoacetylnaphthalene (**1**) that on subsequent treatment with benzaldehyde thiosemicarbazones resulted in the formation of 4-naphthalen-1-yl-2-{2-[(substituted phenyl)methylidene]hydrazino}-1,3-thiazoles (**2**) which on reaction with thiomalic acid in dioxane using $ZnCl_2$ as cyclizing agent resulted in the formation of title compounds (**TA_1-TA_{10}**). All the synthesized compounds were characterized on the basis of their IR, ^{1}H NMR, MS spectra and elemental analysis.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. The compounds were routinely checked for their purity by TLC using silica gel G (Merck) and visualization with iodine vapors. The R_f values were determined in mobile phase toluene: ethyl acetate: formic acid (5 : 4 : 1, v/v/v). The IR spectra were recorded in KBr on the Nicolet 5 PC FT-IR spectrophotometer. The 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 reference. The FAB mass spectra were recorded on a Jeol SX 102/DA-6000 mass spectrometer/Data system using Argon/Xenon (6 kV, 10 mA) as FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature using *m*-nitrobenzyl alcohol (NBA)

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matrix. Elemental analysis was performed on Carlo Erba 1108 analyzer.

General Method

Synthesis of 1-bromoacetylnaphthalene (1) (8)

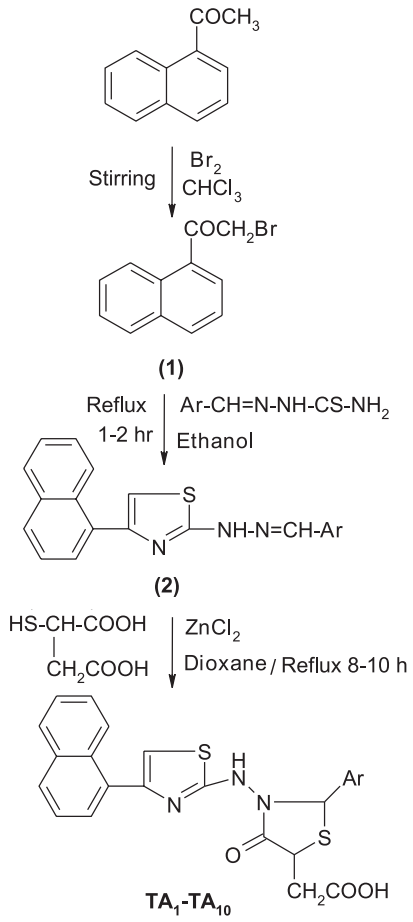
1-Acetylnaphthalene (0.02 moles) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 moles) in chloroform was prepared. The bromine solution was added to flask containing 1-acetylnaphthalene solution, dropwise with stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized from benzene yielding **1**. M. p.: 177-179°C; R_f value = 0.73; % yield = 85, IR (KBr, cm^{-1}): 1702.12 (C=O), 1554.16 (C=C), 783.36 (C-Br); ^{1}H NMR (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: for $C_{12}H_9OBr$, found % (calculated %): C, 57.84 (57.86); H, 3.63 (3.64).

Synthesis of 4-naphthalen-1-yl-2-{2-[(substituted phenyl)methylidene]hydrazino}-1,3-thiazole (2) (9, 10)

Equimolar quantities (0.01 mole) of 1-bromoacetylnaphthalene 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 yielding **2.** For 4-naphthalen-1-yl-2-{2-[(4-nitrophenyl)methylidene]hydrazino}-1,3-thiazole: m. p.: 188-190°C; R_f value = 0.74; % yield = 65; IR (KBr, cm^{-1}): 3261.18 (N-H), 1627.64 (C=N), 1543.42 (C=C), 1515.17, 1453.73 and 1040.10 (characteristic of thiazole nucleus); ^{1}H NMR (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: for $C_{20}H_{14}N_4O_2S$, found % (calculated %): C, 64.15 (64.16); H, 3.77 (3.77); N, 14.95 (14.96).

General method for synthesis of [2-(substituted phenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl] amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acids (TA_1-TA_{10})

A mixture of respective thiazole derivative (**2**) (0.01 mole) and thiomalic acid (0.015 mole) in 25 mL of dioxane was taken in a 100 mL round bottom flask. To this solution 25 mg 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 physical data of the compounds are summarized in Table 1.



Scheme 1

[2-(4-Nitrophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_1)

IR (KBr, cm^{-1}): 3415.18 (O-H), 3247.32 (N-H), 1717.06 and 1693.88 (C=O), 1613.71 (C=N), 1542.12 (C=C), 1509.66, 1439.98 and 1040.10; ^{1}H NMR (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: for $C_{24}H_{18}N_4O_5S_2$, found % (calculated %): C, 56.89 (56.91); H, 3.56 (3.58); N, 11.04 (11.06).

[2-(3-Chlorophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_2)

IR (KBr, cm^{-1}): 3416.42 (O-H), 3247.50 (N-H), 1713.08 and 1694.84 (C=O), 1611.16 (C=N), 1543.24 (C=C), 1515.15, 1452.66 and 1039.98; ^1H NMR (DMSO-d_6, δ ppm): 2.39 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.48 (t, *J* = 6 Hz, 1H, -CH-S-), 6.58 (s, 1H, -N-CH-), 7.14 (m, 3H, Ar-H), 7.35 (s, 1H, Ar-H), 7.59 (m, 5H, Ar-H), 7.94 (d, *J* = 12 Hz, 1H, Ar-H), 8.09 (d, *J* = 12 Hz, 1H, Ar-H), 8.22 (d, *J* = 12 Hz, 1H, Ar-H), 8.96 (s, 1H, NH), 10.66 (s, 1H, OH). Elemental analysis: for $C_{24}H_{18}N_3S_2O_3Cl$, found % (calculated %): C, 58.10 (58.12); H, 3.65 (3.66); N, 8.45 (8.47).

[2-(4-Chlorophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_3)

IR (KBr, cm^{-1}): 3414.68 (O-H), 3247.55 (N-H), 1712.88 and 1697.42 (C=O), 1614.20 (C=N), 1551.18 (C=C), 1510.02, 1449.74 and 1040.10; ^1H NMR (DMSO-d_6, δ ppm): 2.41 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.48 (t, *J* = 6 Hz, 1H, -CH-S-), 6.33 (s, 1H, -N-CH-), 7.17 (d, *J* = 12 Hz, 2H, Ar-H), 7.33 (m, 3H, Ar-H), 7.56 (m, 4H, Ar-H), 7.92 (d, *J* = 12 Hz, 1H, Ar-H), 8.10 (d, *J* = 12 Hz, 1H, Ar-H), 8.25 (d, *J* = 12 Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 10.68 (s, 1H, OH). Elemental analysis: for $C_{24}H_{18}N_3S_2O_3Cl$, found % (calculated %): C, 58.10 (58.12); H, 3.65 (3.66); N, 8.45 (8.47).

[2-(2,4-Dichlorophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl] acetic acid (TA_4)

IR (KBr, cm^{-1}): 3415.16 (O-H), 3246.55 (N-H), 1716.04 and 1693.72 (C=O), 1613.44 (C=N), 1548.10 (C=C), 1510.16, 1445.66 and 1042.44; ^1H NMR (DMSO-d_6, δ ppm): 2.40 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.52 (t, *J* = 6 Hz, 1H, -CH-S-), 6.75 (s, 1H, -N-CH-), 7.10 (d, *J* = 12 Hz, 2H, Ar-H), 7.33 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 7.62 (m, 4H, Ar-H), 7.95 (d, J=12Hz, 1H, Ar-H), 8.11 (d, *J* = 12 Hz, 1H, Ar-H), 8.25 (d, *J* = 12 Hz, 1H, Ar-H), 8.96 (s, 1H, NH), 10.65 (s, 1H, OH). Elemental analysis: for $C_{24}H_{17}N_3S_2O_3Cl_2$, found % (calculated %): C, 54.32 (54.34); H, 3.22 (3.23); N, 7.90 (7.92).

[2-(2,6-Dichlorophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl] acetic acid (TA_5)

IR (KBr, cm^{-1}): 3417.04 (O-H), 3244.64 (N-H), 1712.08 and 1691.98 (C=O), 1609.50 (C=N), 1551.28 (C=C), 1510.10, 1448.62 and 1050.66; ^1H NMR (DMSO-d_6, δ ppm): 2.41 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.50 (t, *J* = 6 Hz, 1H, -CH-S-), 6.85 (s, 1H, -N-CH-), 7.33 (s, 1H, Ar-H), 7.53 (m, 7H, Ar-H), 7.96 (d, *J* = 12 Hz, 1H, Ar-H), 8.13 (d, *J* = 12 Hz, 1H, Ar-H), 8.26 (d, *J* = 12 Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 10.66 (s, 1H, OH). Elemental analysis ($C_{24}H_{17}N_3S_2O_3Cl_2$), Found % (Calculated %): C, 54.33 (54.34); H, 3.22 (3.23); N, 7.90 (7.92).

[2-(3-Fluorophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_6)

IR (KBr, cm^{-1}): 3417.44 (O-H), 3243.88 (N-H), 1713.98 and 1695.15 (C=O), 1610.10 (C=N), 1548.42 (C=C), 1510.04, 1447.90 and 1045.44; ^1H NMR (DMSO-d_6, δ ppm): 2.38 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.48 (t, *J* = 6 Hz, 1H, -CH-S-), 6.52 (s, 1H, -N-CH-), 6.90 (m, 1H, Ar-H), 7.16 (m, 2H, Ar-H), 7.33 (s, 1H, Ar-H), 7.58 (m, 5H, Ar-H), 7.94 (d, *J* = 12 Hz, 1H, Ar-H), 8.10 (d, *J* = 12 Hz, 1H, Ar-H), 8.23 (d, *J* = 12 Hz, 1H, Ar-H), 8.94 (s, 1H, NH), 10.64 (s, 1H, OH). Elemental analysis: for $C_{24}H_{18}N_3S_2O_3F$, found % (calculated %): C, 60.09 (60.11); H, 3.77 (3.78); N, 8.75 (8.76).

[2-(2-Hydroxy-4-bromophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_7)

IR (KBr, cm^{-1}): 3442.96 and 3417.84 (O-H), 3248.50 (N-H), 1715.16 and 1692.38 (C=O), 1609.65 (C=N), 1540.10 (C=C), 1510.18, 1445.08 and 1040.12; ^1H NMR (DMSO-d_6, δ ppm): 2.41 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.50 (t, *J* = 6 Hz, 1H, -CH-S-), 6.52 (s, 1H, -N-CH-), 7.02 (m, 3H, Ar-H), 7.33 (s, 1H, Ar-H), 7.58 (m, 4H, Ar-H), 7.98 (d, *J* = 12 Hz, 1H, Ar-H), 8.10 (d, *J* = 12 Hz, 1H, Ar-H), 8.26 (d, *J* = 12 Hz, 1H, Ar-H), 8.89 (s, 1H, NH), 10.55 (s, 1H, OH), 10.95 (s, 1H, OH). Elemental analysis: for $C_{24}H_{18}N_3S_2O_4Br$, found % (calculated %): C, 51.78 (51.80); H, 3.25 (3.26); N, 7.54 (7.55).

[2-(2-Hydroxy-4-chlorophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_8)

IR (KBr, cm^{-1}): 3438.98 and 3414.62 (O-H), 3247.55 (N-H), 1713.22 and 1695.15 (C=O), 1611.84 (C=N), 1547.50 (C=C), 1510.10, 1446.38 and 1041.02; ^1H NMR (DMSO-d_6, δ ppm): 2.41 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 4.50 (t, *J* = 6 Hz, 1H, -CH-S-), 6.52 (s, 1H, -N-CH-), 6.98 (m, 3H, Ar-H), 7.33 (s, 1H, Ar-H), 7.58 (m, 4H, Ar-H), 7.92 (d, *J* = 12 Hz, 1H, Ar-H), 8.10 (d, *J* = 12 Hz, 1H, Ar-H), 8.26 (d, *J* = 12 Hz, 1H, Ar-H), 8.92 (s, 1H, NH), 10.57 (s, 1H, OH), 10.90 (s, 1H, OH). Elemental

Table 1. Physical data for [2-(substituted phenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acids (**TA_1-TA_{10}**).

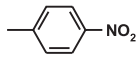
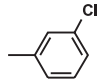
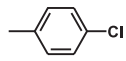
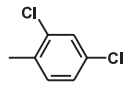
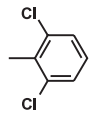
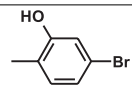
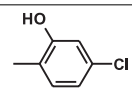
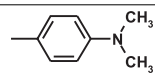
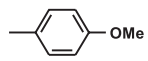
Compd. No.	Ar-	m.p. (± 2°C)	R_f value	% yield	Molecular formula	% N found (calcd.)
TA_1		188	0.78	45	$C_{24}H_{18}N_4O_5S_2$	11.04 (11.06)
TA_2		179	0.71	55	$C_{24}H_{18}N_3S_2O_3Cl$	8.45 (8.47)
TA_3		184	0.74	50	$C_{24}H_{18}N_3S_2O_3Cl$	8.45 (8.47)
TA_4		197	0.70	50	$C_{24}H_{17}N_3S_2O_3Cl_2$	7.90 (7.92)
TA_5		210	0.72	45	$C_{24}H_{17}N_3S_2O_3Cl_2$	7.90 (7.92)
TA_6		173	0.78	50	$C_{24}H_{18}N_3S_2O_3F$	8.75 8.76)
TA_7		194	0.68	40	$C_{24}H_{18}N_3S_2O_4Br$	7.54 (7.55)
TA_8		190	0.68	45	$C_{24}H_{18}N_3S_2O_4Cl$	8.19 (8.21)
TA_9		176	0.69	45	$C_{26}H_{24}N_4O_3S_2$	11.08 (11.10)
TA_{10}		170	0.73	45	$C_{25}H_{21}N_3O_4S_2$	8.54 (8.55)

Table 2. Antihyperglycemic activity of [2-(substituted phenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acids (TA_1-TA_{10}) in SLM model

Compound	%age of blood sugar lowering activity ± SEM by SLM model (100 mg kg^{-1})	
	1 h	4 h
Pioglitazone	100.00 ± 8.81*	100.00 ± 4.92
TA_1	87.15 ± 5.41**	93.75 ± 6.97***
TA_2	64.77 ± 6.78	72.49 ± 5.36
TA_3	69.04 ± 6.81*	73.90 ± 5.64
TA_4	82.62 ± 7.56*	87.49 ± 6.84
TA_5	83.46 ± 5.41**	89.06 ± 6.22**
TA_6	81.21 ± 6.45*	85.14 ± 5.542**
TA_7	66.51 ± 6.322*	71.25 ± 4.425*
TA_8	84.89 ± 5.76**	88.27 ± 5.76**
TA_9	62.53 ± 6.094	69.12 ± 3.922
TA_{10}	77.25 ± 6.982*	81.24 ± 5.527*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Antihyperglycemic activity of [2-(substituted phenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acids (TA_1-TA_{10}) in alloxan model

Compound	%age of blood sugar lowering activity ± SEM by alloxan model (100 mg kg^{-1})			
	24 h	72 h	120 h	168 h
Pioglitazone	100.00 ± 15.24	100.00 ± 12.58	100.00 ± 16.09	100.00 ± 28.27
TA_1	112.48 ± 19.14	114.09 ± 5.12**	135.66 ± 2.73***	139.37 ± 0.83***
TA_2	30.98 ± 14.18	42.28 ± 21.27	63.46 ± 15.09	71.69 ± 14.29
TA_3	39.12 ± 17.64	47.07 ± 21.36	66. 47 ± 20.14	74.50 ± 17.92
TA_4	79.89 ± 33.14	85.36 ± 29.68	99.08 ± 12.74*	107.62 ± 31.39***
TA_5	88.03 ± 12.36	91.27 ± 5.25	115.60 ± 3.66**	123.40 ± 2.84***
TA_6	90.06 ± 13.84	94.93 ± 9.68*	117.30 ± 6.28*	127.11 ± 4.87***
TA_7	37.09 ± 18.48	44.84 ± 43.32	65.76 ± 20.58	74.18 ± 18.28
TA_8	100.00 ± 21.30	106.266 ± 8.12*	127.83 ± 6.49***	135.59 ± 2.01***
TA_9	24.87 ± 13.71	40.537 ± 21.24	63.22 ± 14.95	70.32 ± 12.94
TA_{10}	79.89 ± 16.25	82.97 ± 14.38	98.96 ± 17.46*	107.90 ± 21.16*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

analysis: for $C_{24}H_{18}N_3S_2O_4Cl$, found % (calculated %): C, 56.28 (56.30); H, 3.53 (3.54); N, 8.19 (8.21).

[2-(4-Dimethylaminophenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_9)

IR (KBr, cm^{-1}): 3416.02 (O-H), 3239.92 (N-H), 1713.44 and 1697.60 (C=O), 1608.98 (C=N), 1544.10 (C=C), 1510.18, 1445.48 and 1040.08; ^{1}H NMR (DMSO-d_6, δ ppm): 2.38 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 3.01 (s, 6H, CH_3), 4.50 (t, *J* = 6 Hz, 1H, -CH-S-), 6.56 (m, 3H, Ar-H, -N-CH-), 7.10 (d, *J* = 12 Hz, 2H, Ar-H), 7.32 (s, 1H, Ar-H), 7.56 (m, 4H, Ar-H), 7.95 (d, *J* = 12 Hz, 1H, Ar-H), 8.11 (d, *J* = 12 Hz, 1H, Ar-H), 8.24 (d, *J* = 12 Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 10.67 (s, 1H, OH). Elemental analysis: for $C_{26}H_{24}N_4O_3S_2$, found % (calculated %): C, 61.85 (61.88); H, 4.77 (4.79); N, 11.08 (11.10).

[2-(4-Methoxyphenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl]acetic acid (TA_{10})

IR (KBr, cm^{-1}): 3417.76 (O-H), 3245.10 (N-H), 1714.86 and 1693.08 (C=O), 1609.46 (C=N), 1545.55 (C=C), 1510.10, 1443.72 and 1045.15; ^{1}H NMR (DMSO-d_6, δ ppm): 2.38 (d, *J* = 12 Hz, 2H, -CH_2-CO-), 3.75 (s, 3H, OCH_3), 4.50 (t, *J* = 6 Hz, 1H, -CH-S-), 6.53 (s, 1H, -N-CH-), 7.22 (m, 5H, Ar-H), 7.59 (m, 4H, Ar-H), 7.98 (d, *J* = 12 Hz, 1H, Ar-H), 8.13 (d, *J* = 12 Hz, 1H, Ar-H), 8.26 (d, *J* = 12 Hz, 1H, Ar-H), 8.95 (s, 1H, NH), 10.66 (s, 1H, OH). Elemental analysis: for $C_{25}H_{21}N_3O_4S_2$, found % (calculated %): C, 61.06 (61.08); H, 4.30 (4.31); N, 8.54 (8.55).

Antihyperglycemic activity (11-13)

The synthesized compounds (TA_1-TA_{10}) were evaluated for antihyperglycemic activity. The animals were procured from "Central Animal House Facility", Jamia Hamdard (Hamdard University), New Delhi (India) and were maintained in colony cages at 25 ± 2°C, relative humidity of 45-55%, maintained under 12 h light and dark cycle and were fed with standard animal feed. All the animals were acclimatized for a week before use. Animals had free access to food and water. The test compounds and the standard drugs were administered in the form of a suspension (carboxymethylcellulose as a vehicle) by the same route of administration. Male Wistar albino rats weighing between 200-250 g, 6 per group, were used for study. All the drugs, including the standard drug, pioglitazone, were administered *i.p*. at 100 mg kg^{-1} doses.. Guidelines issued by Institutional ethics committee (Jamia Hamdard, Hamdard University, New Delhi-110062, India) for the care and uses of laboratory animals were followed.

The whole 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 antihyperglycemic effect by 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 half hour post test compounds treatment the animals were fed with sucrose load of 100 mg kg^{-1} body weight of each rat. The blood glucose was recorded after 1 h and 4 h post sucrose load by microprocessor digital blood glucometer. The percent fall in blood glucose level was calculated (Table 2). In phase-II, diabetes was induced by injecting alloxan (50 mg kg^{-1}) *i.p.* in distilled water and animals with fasting glucose levels of > 250 mg dL^{-1} of blood were selected as diabetic rats for the study. Blood glucose level was recorded 24 h, 72 h, 120 h and 168 h post test compound treatment (Table 3).

Statistical analysis

The mean ± SEM was calculated. The data were analyzed using Kruskal Wallis analysis of variance (ANOVA) followed by Dunnett's multiple comparison test, wherever applicable p values < 0.05 were considered significant.

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the basis of their IR, ^{1}H NMR, spectra 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-(substituted phenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}amino]-4-oxo-1,3-thiazolidin-5-yl]acetic acid derivatives (**TA_1-TA_{10}**) in normal rats by sucrose loaded model. It was observed that compound **TA_1** (Ar = 4-nitrophenyl) displayed the highest antihyperglycemic activity in SLM model. This was followed by **TA_5** (Ar = 2,6-dichlorophenyl), **TA_8** (Ar = 4-chloro-2-hydroxyphenyl), **TA_4** (Ar = 2,4-dichlorophenyl), **TA_6** (Ar = 3-fluorophenyl), and **TA_{10}** (Ar = 4-methoxyphenyl). Phase-II included the evaluation of blood sugar by alloxan model. It was observed that a majority of the compounds exhibited more antihyperglycemic activity than standard drug pioglitazone on the 7th day of study. The compound **TA_1** exhibited the highest activity followed by **TA_8**, **TA_6**, **TA_5**, **TA_4** and **TA_{10}**. It was also observed that blood glucose lowering effects were more pronounced and stronger in alloxan model.

CONCLUSION

From the above results it has been concluded that [2-(substituted phenyl)-3-{[4-(1-naphthyl)-1,3-thiazol-2-yl]amino}-4-oxo-1,3-thiazolidin-5-yl] acetic acids (**TA_1-TA_{10}**) further should be evaluated for toxicological profile to confirm their potential as antihyperglycemic agents.

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