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Synthesis, Antibacterial and Anti-hyperglycemic Activity of Some 6-Substituted Quinoxaline-2,3-diones

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A new series of 6-substituted quinoxaline-2,3(1H,4H)-dione bearing sulphaneoamido, thiazolidinone and azomethine moiety were synthesized by treating quinoxaline-2,3(1H,4H)-dione-6-sulfonylhydrazide with substituted aromatic aldehydes to yield N^1-(substituted benzylideneamino)-6-(quinoxaline-2,3(1H,4H)-dione sulphanamide (**4a-f**) which on cyclization with thioglycolic acid in presence of anhydrous zinc chloride afforded 3-[6'-sulpaneoamidoquinoxaline-2',3'(1'H,4'H)-dione-2-(substituted-phenyl]-4-oxo-thiazolidine (**5a-f**). All the synthesized compounds were subjected to preliminary *in-vitro* evaluation for antibacterial activity against various Gram-positive bacterial strains *Staphylococcus aureus, Bacillus cereus* and Gram-negative strain *Pseudomonas aeruginosa* and moreover the componuds were also evaluated for their anti-hyperglycemic effect in alloxan induced diabetes in rats.

Key Words: Synthesis, Antibacterial, Anti-hyperglycemic activity, 6-Substituted quinoxaline-2,3-diones.

INTRODUCTION

It is well documented that quinoxaline and their heterocyclic derivatives possess antimicrobial[1], antifungal[2], tuberculostatic[3], antiviral[4], anticancer[5], antidiabetic[6], anti-inflammatory[7], antiallergic[8], AMPA receptor antagonists activity[9], anticonvulsant activity[10] and hypoxia-selective activity[11]. Literature reveals that azomethines and thiazolidinones have been claimed to possess higher degree of activities. The biological activity of azomethines were reported due to >C=N-R linkage and biological activity of thiazolidinones were due to -C-N-S- linkage. Azomethines possess antibacterial, antitubercular, antitumor, fungicidal and agrochemical activity. Thiazolidinones were also endowed with wide range of activities like antimicrobial, anticonvulsant, antitubercular, anti-HIV and anticancer[12-14].

Moreover sulphonamides represents an important class of biologically active compounds exhibiting a broad range of biological activities like antimicrobial, hyperglycemic, antianginal, antiarrhythmic, antihypertensive,

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cyclooxygenase-2-inhibitors, antiHIV, anticancer, antiplatelet agent, 5HT receptor antagonist, analgesic and anticonvulsant[15].

In the light of these findings we felt it is worth synthesizing a series of quinoxaline-2,3(1H,4H)-dione possessing the bioactive sulphonamido group, azomethine linkage and thiazolidinone moiety. In present work we report the synthesis of N^1-(substituted benzylideneamino)-6-[quinoxaline-2,3(1H,4H)-dione]sulphanamide and 3-[6'-sulpaneoamidoquinoxaline 2',3'(1'H,4'H)-dione-2-(substituted phenyl]-4-oxo-thiazolidine.

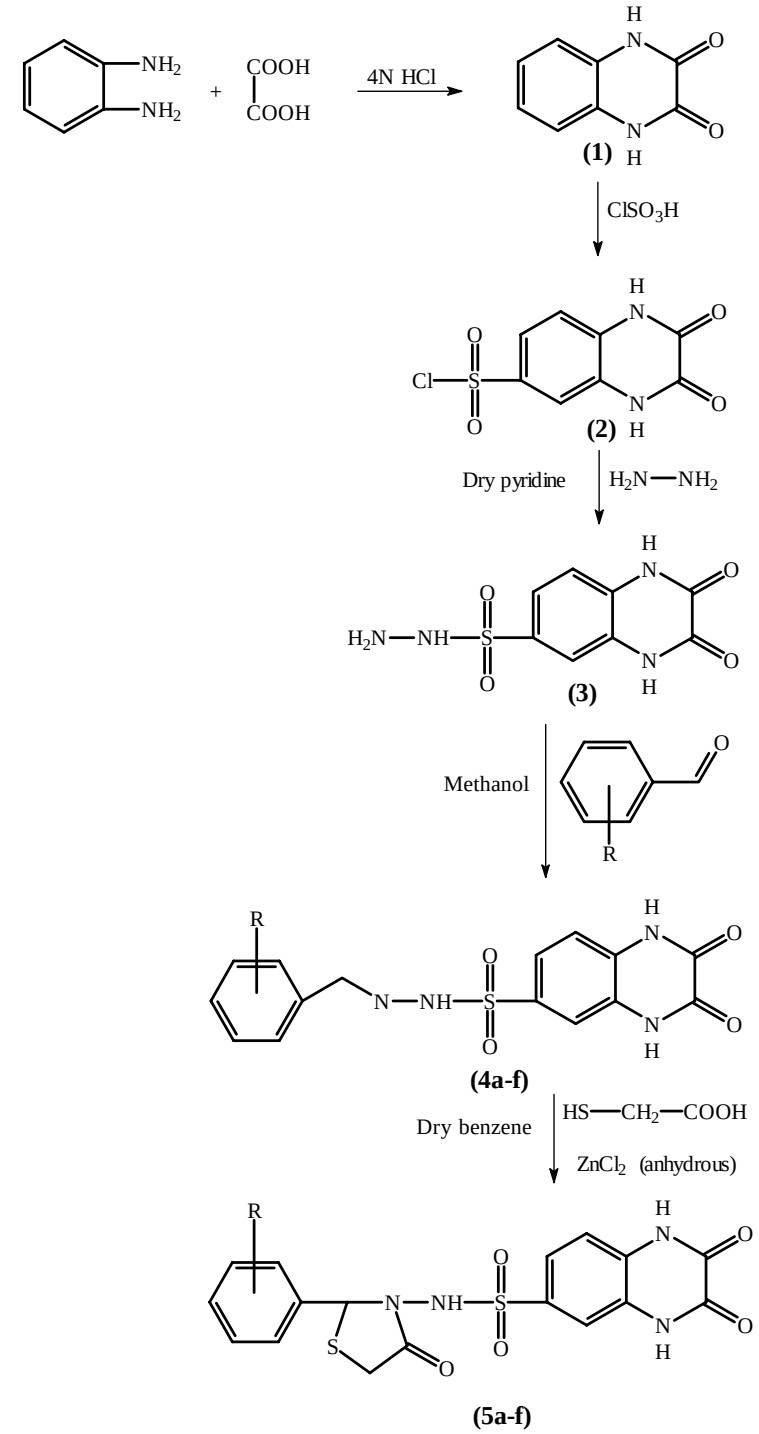
EXPERIMENTAL

All the melting points were recorded in open capillary tubes using liquid paraffin bath and are uncorrected. The IR spectra (cm^{-1}) were recorded on Perkin Elmer RXI-FTIR spectrophotometer using KBr pellet. The ^1H NMR spectra were recorded on Brucker AC 300F NMR spectrometer (300 MHz) using $CDCl_3$/DMSO as solvent and tetramethylsilane as internal standard (chemical shifts in δ ppm) and mass spectra were carried out on JEOL SX 102/DA-6000 mass spectrometer/data system using argon/xenon as the FAB gas. Elemental analysis was carried out with Elementar Vario EL III Carlo Erba 1108. All the compounds gave satisfactory elemental analysis within limits and the purity of the synthesized compounds was checked by thin layer chromatography using silica gel G. All the compounds were synthesized according to **Scheme-1**.

Synthesis of quinoxaline-2,3(1H,4H)-dione[16] compound 1: A solution of o-phenylene diamine (0.05 mol) and oxalic acid (0.05 mol) in 4N HCl (90 mL) was refluxed for 4 h. The reaction mixture was cooled in refrigerator overnight to give corresponding quinoxaline-2,3(1H,4H)-dione, the white solid obtained was filtered, washed with cold water and re-crystallized by using ethanol. Yield : 71 %, m.p. > 300ºC.

Synthesis of quinoxaline-2,3(1H,4H)-dione-6-sulfonyl chloride compound 2: To quinoxaline-2,3(1H,4H)-dione (0.01 mol) was added chlorosulfonic acid (0.015 mol) and the reaction mixture was refluxed for a period of 5 h. The mixture was poured slowly on ice-water mixture, white solid precipitated out was filtered, washed thoroughly with cold water to make it acid free and re-crystallized by using ethanol. Yield : 59 %, m.p.: 272ºC. IR (KBr) cm^{-1}: 2988 ν(NH, str.), 1705 ν(C=O, str.), 1511, 1488, 1410 ν(C=C, aromatic str.), 1374 ν(SO_2, symm), 1155 ν(SO_2, asymm.). ^1H NMR (DMSO) : δ 7.35 - 7.98 (m, 3H, Ar-H), 8.30 (s, 2H, -*NH*-CO-quinoxaline ring).

Synthesis of quinoxaline-2,3(1H,4H)-dione-6-sulfonyl hydrazide compound 3: Quinoxaline-2,3(1H,4H)-dione-6-sulfonyl chloride was dissolved in dry acetone (25 mL), cooled in ice-cold water and then 3 mL of dry pyridine was added. Hydrazine hydrate (0.015 mol) was added slowly with constant shaking. As reaction was exothermic, large amount of heat


NH2
NH2
+
COOH
COOH
4N HCl
(1)
ClSO3H
(2)
Dry pyridine
H2N—NH2
(3)
Methanol
R
(4a-f)
Dry benzene
HS—CH2—COOH
ZnCl2 (anhydrous)
(5a-f)

Scheme-1

was evolved, so cooled under ice-cold water. After complete addition of hydrazine hydrate the reaction mixture was refluxed for 4 h. The solvent was removed under reduced pressure, the residue was poured on crushed ice, yellow solid precipitated out. The solid was filtered washed with cold water and re-crystallized from acetic acid. Yield: 67 %, m.p.: 238ºC. IR (KBr, cm^{-1}): 3449 ν(NH, str.), 1694 ν(C=O, str.), 1590 ν(NH_2, deformation 1º-amine), 1411 ν(SO_2, symm.), 1210 ν(SO_2, asymm.). ^{1}H NMR (DMSO) : δ 3.34(s, 3H, -NH-NH_2), 7.23 -7.33 (m, 3H, Ar-H), 7.35 (s, 2H,-NH-CO-quinoxaline ring): MS m/z (%):269 (100), 307 (20), 289 (17), 255 (09), 240 (08).

Synthesis of N^1-(4-chlorobenzylideneamino)-6-(quinoxaline-2,3(1H,4H)-dione) sulphanamide (compound 4d): (0.01 mol) Quinoxaline-2,3(1H,4H)-dione-6-sulfonylhydrazide was dissolved in methanol and 4-chlorobenzaldehyde (0.011 mol) in methanol (40 mL) was added with shaking. The reaction mixture was refluxed for a period of 3 h, then concentrated under reduced pressure and was cooled in ice bath. The solid obtained was filtered, washed with cold water, dried and re-crystallized from methanol and acetic acid mixture to get pure **4d**. Similarly, the other compounds **4a-f** were synthesized.

(4d) IR (KBr, cm^{-1}): 3434 ν(NH, str.), 1704 ν(C=O, str.), 1400 ν(SO_2, symm.),1601 ν(-CH=N-, str.), 1164 ν(SO_2, asymm) 2945 ν(NH, Str.). ^{1}H NMR (DMSO): δ 2.95 (s, 1H, -NH-), 7.02-7.95 (m, 7H, Ar-H), 10.01 (s, 2H, -NH-CO-quinoxaline ring), 10.05 (s, 1H, -CH=N). MS m/z (%): 391 (100), 392 (34), 397 (20), 379 (27), 417 (27), 429 (14).

(4f) IR (KBr, cm^{-1}): 3431 ν(NH, str.), 1700 ν(C=O, str.), 1398 ν(SO_2, symm.), 1608 ν(-CH=N-, str.), 1172 ν(SO_2, asymm.), 2933 ν(NH, str.). ^{1}H NMR (DMSO): δ 2.70 (s, 1H, -NH-), 3.34 (s, 3H, OCH_3), 7.02-7.56 (m, 7H, Ar-H), 7.67 (s, 2H, -NH-CO-quinoxaline ring), 11.97 (s, 1H, -CH=N-). MS m/z (%): 391 (100), 392 (31), 389 (08), 368 (04).

Synthesis of 3-[(6´-sulphaneoamido-quinoxaline-2´,3´(1´H,4´H)-dione)-2-(4´-chloro-phenyl)]-4-oxo-thiazolidine (compound 5d): To a mixture of N^1-(4-chlorobenzylidene-amino)-6-(quinoxaline-2,3(1H,4H)-dione) sulphanamide (0.01 mol) in dry benzene (20 mL), thioglycolic acid (0.015 mol) and a catalytic amount of anhydrous zinc chloride was added and the reaction mixture was refluxed for 12 h. Solvent was evaporated under reduced pressure and separated residue was neutralized by saturated sodium bicarbonate solution. The precipitated solid was filtered, washed with cold water, dried and re-crystallized from acetic acid to get pure compound **5d**. Similarly, the other compounds **5a-f** were synthesized.

(5d) IR (KBr, cm^{-1}): 2933 ν(CH, str. aromatic), 3440 ν(NH, str.), 1700 ν(C=O, str.), 1597 ν(NH, str.), 1493 ν(NCO, str.), 1088-824 ν(C-C, str.). ^{1}H NMR (DMSO): δ 2.70 (s, 1H, -NH-), 2.99 (s, 2H, -S-CH_2 thiazolidinone

ring), 3.33 (s, 1H, -CH-thiazolidinone ring), 7.23 - 7.66 (m, 7H, Ar-H), 7.89 (s, 2H, -NH-CO-quinoxaline ring). MS m/z (%): 460 (100), 461 (50), 468 (34), 490 (34).

(5f) IR (KBr, cm^{-1}): 3423 ν(NH, str.), 2923 ν(CH, str. aromatic),1693 ν(C=O, str.), 1595 ν(NH, str.), 1466 ν(NCO, str.), 1025-814 ν(C-C, str.). ^{1}H NMR (DMSO): δ 2.70 (s, 1H, -NH-), 2.98 (s, 2H, -S-CH_2-thiazolidinone ring), 3.34 (s, 3H, -OCH_3), 4.01 (s, 1H, -CH-thiazolidinone ring), 6.75 - 7.34 (m, 7H, Ar-H), 11.71 (s, -NH-CO-quinoxaline ring). MS m/z (%): 460 (100), 461 (75), 462 (34), 449 (25).

Antibacterial activity: All the synthesized compounds **4a-f** and **5a-f** were evaluated *in vitro* for antibacterial activity against Gram-positive bacterial strains *Staphylococcus aureus*, *Bacillus cereus* and Gram-negative bacterial strain *Pseudomonas aeruginosa* at concentrations 20 to 80 μg/mL by well diffusion method using DMF as solvent control and nutrient agar was employed as culture media. After 24 h of incubation at 37ºC the zones of inhibition were measured in mm. The activity was compared with known antibiotic ciprofloxacin and the data is represented in Table-2. Moreover all the synthesized compounds has been reviewed, approved and accepted by *Tuberculosis Antimicrobial Acquisition and Coordinating Facility* (TAACF) U.S.A. for furthur anti-tuberculosis screening.

Antihyperglycemic activity: *Animals*: Male Wistar albino rats weighing 100-250 g were used for the study. The animals were housed in propylene cages under standard laboratory conditions, maintained on a natural light and dark cycle and had free access to food and water *ad libitum*. Animals were fed with standard rat pellet diet [Amrut, Laboratory Animal Feed, (Rat & Mice Feed) Pranav Agro Industries Ltd., Sangli, Maharashtra State]. The experimental protocols were approved by the institutional ethics committee and conducted according to the guidelines for the use and care of experimental animals.

Anti-hyperglycemic activity: Alloxan monohydrate 120 mg/kg, body weight was dissolved in normal saline and injected intraperitoneally after 12 h fasting to induce hyperglycemia. Alloxan is capable of producing fatal hyperglycemia as a result of massive pancreatic insulin release, therefore the rats were treated with a 20% glucose solution (15-20 mL) orally after 6 h[17] . After 1 h of alloxan administration the animals were fed on standard pellets and water. The blood glucose level (BGL) was monitored after alloxanization in blood samples collected by tail tipping method using a glucometer. It was confirmed after 48 h (on third day). Animals found hyperglycemic, having BGL above 150 mg/dL, of blood were selected for the study and were divided into different groups. Control group received only vehicle, standard group received glibenclamide (0.50 mg/kg;i.p.) and test groups were treated with a single dose of test compounds (5mg/kg;i.p).

The blood glucose level was monitored immediately before, and 1,2,3,5 and 24 h after administration of the test compounds.

Statistical analysis: Data obtained was subjected to statistical analysis to determine the statistical significance using student's 't' test, $P < 0.05$ was considered as significant.

RESULTS AND DISCUSSION

Table-1 shows the analytical data of compounds **4** and **5**.

TABLE-1
ANALYTICAL DATA OF COMPOUNDS **4** AND **5**

Compd.	R	m.f.	m.p. (ºC)	Yield (%)	Calcd. (Found) (%)	
					N	S
4a	H	$C_{15}H_{12}N_4O_4S$	254	40	16.27 (16.30)	9.31 (9.28)
4b	2-OH	$C_{15}H_{12}N_4O_5S$	291	45	15.55 (15.56)	8.90 (8.89)
4c	2-Cl	$C_{15}H_{11}N_4O_4SCl$	263	35	14.78 (14.82)	8.46 (8.49)
4d	4-Cl	$C_{15}H_{11}N_4O_4SCl$	254	60	14.78 (14.80)	8.46 (8.51)
4e	2-OCH_3	$C_{16}H_{14}N_4O_5S$	262	40	14.96 (14.99)	8.56 (8.61)
4f	4-OCH_3	$C_{16}H_{14}N_4O_5S$	296	55	14.96 (15.01)	8.56 (8.59)
5a	H	$C_{17}H_{14}N_4O_5S_2$	279	48	13.38 (13.42)	15.32 (15.35)
5b	2-OH	$C_{17}H_{14}N_4O_6S_2$	307	40	12.89 (12.92)	14.76 (14.79)
5c	2-Cl	$C_{17}H_{13}N_4O_5S_2Cl$	284	28	12.37 (12.41)	14.16 (14.20)
5d	4-Cl	$C_{17}H_{13}N_4O_5S_2Cl$	317	55	12.37 (12.39)	14.16 (14.21)
5e	2-OCH_3	$C_{18}H_{16}N_4O_6S_2$	277	50	12.49 (12.52)	14.30 (14.28)
5f	4-OCH_3	$C_{18}H_{16}N_4O_6S_2$	319	68	12.49 (12.50)	14.30 (14.32)

Table-2 shows the *in vitro* anti-bacterial activity data. All the compounds showed moderate to high activity against *Staphylococcus aureus* and *Bacillus cereus* while weak to moderate activity was observed against *Pseudomonas aureginosa*. The compounds **4b**, **5d** and **5e** were highly active against *Bacillus cereus*, compound **4d** was highly active whereas compounds **4a**, **4c**, **4e** and **5b** were moderately active against *Staphylococcus aureus*, compound **4b** was moderately active against *Pseudomonas aureginosa*. The rest of the compounds displayed weak activity against all organisms. However, the activities of the tested compounds are less than that of standard antibacterial agent used.

TABLE-2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **4a-f** AND **5a-f**, ZONE OF INHIBITION (mm)

Compd.	Concentration (μg/mL)	*S. aureus*	*B. cereus*	*P. aeruginosa*
4a	20	14	13	--
	40	14	14	--
	60	16	16	10
	80	17	17	12
4b	20	15	15	--
	40	15	14	--
	60	18	17	12
	80	18	18	16
4c	20	15	15	--
	40	16	15	--
	60	16	16	10
	80	17	17	12
4d	20	--	14	--
	40	13	15	--
	60	14	13	10
	80	19	14	12
4e	20	12	10	--
	40	15	12	--
	60	15	14	11
	80	18	16	14
4f	20	14	14	--
	40	14	14	--
	60	14	15	10
	80	16	17	14
5a	20	09	10	--
	40	10	11	--
	60	14	13	10
	80	15	14	11
5b	20	09	10	--
	40	10	11	--
	60	14	13	10
	80	15	14	11
5c	20	11	09	--
	40	13	10	--
	60	14	13	10
	80	14	14	12
5d	20	--	--	--
	40	--	13	--
	60	10	18	12
	80	12	20	14
5e	20	11	--	--
	40	12	13	--
	60	14	16	09
	80	15	19	11

Compd.	Concentration (μg/mL)	*S. aureus*	*B. cereus*	*P. aeruginosa*
5f	20	13	09	--
	40	12	13	--
	60	14	15	14
	80	13	18	15
Ciprofloxacin	20	21	23	20
	80	25	26	24
DMF (Control)		--	--	--

Table-3 shows the anti-hyperglycemic activity data of synthesized compounds. The control group developed significant ($P < 0.05$) hyperglycemia as compared to normal control. After treatment with test compounds, all the compounds were found to decrease blood glucose levels significantly ($P < 0.05$) when compared with normal and control groups. However the synthesized compounds showed a lesser activity than glibenclamide used as reference standard in the study and the order of anti-hyperglycemic activity for test compounds was found to be 4d > 4b > 4f > 5b > 5f > 5e > 5d > 4a > 5a > 5c > 5e > 4c.

TABLE-3
ANTI-HYPERGLYCEMIC ACTIVITY DATA OF SYNTHESIZED COMPOUNDS
[BLOOD GLUCOSE IN mg/dl]

Group	Treatment	0 h	1 h	2 h	3 h	5 h	24 h
I	**Normal**	78±3.84$^{\#}$	80±3.50$^{\#}$	82±2.40$^{\#}$	79±3.75$^{\#}$	85±2.61$^{\#}$	81±4.23$^{\#}$
II	**Control**	310±4.56*	319±5.37*	317±5.02*	323±6.86*	329±7.88*	331±7.16*
III	**Compd. 4a**	291±6.84$^{*\#}$	286±9.55$^{*\#}$	269±7.92$^{*\#}$	251±7.90$^{*\#}$	238±7.31$^{*\#}$	207±8.07$^{*\#}$
IV	**Compd. 4b**	248±8.33$^{*\#}$	238±8.49$^{*\#}$	213±7.32$^{*\#}$	191±7.64$^{*\#}$	166±7.47$^{*\#}$	137±5.95$^{*\#}$
V	**Compd. 4c**	284± 7.17$^{*\#}$	275±7.35$^{*\#}$	271±7.12$^{*\#}$	260±7.95$^{*\#}$	248±7.43$^{*\#}$	211±7.7$^{*\#}$
VI	**Compd. 4d**	219±8.25$^{*\#}$	190±8.72$^{*\#}$	186±7.72$^{*\#}$	127±8.60$^{*\#}$	120±10.53$^{*\#}$	107±10.12$^{*\#}$
VII	**Compd. 4e**	271±7.96$^{*\#}$	264±8.9$^{*\#}$	252±9.30$^{*\#}$	231±8.79$^{*\#}$	218±8.70$^{*\#}$	198±8.96$^{*\#}$
VIII	**Compd. 4f**	214±9.30$^{*\#}$	205±9.60$^{*\#}$	186±9.89$^{*\#}$	160±10.16$^{*\#}$	145±9.89$^{*\#}$	139±8.25$^{*\#}$
IX	**Compd. 5a**	302±4.78*	296±5.40$^{*\#}$	290±4.94$^{*\#}$	278±6.49$^{*\#}$	264±7.68$^{*\#}$	216±8.52$^{*\#}$
X	**Compd. 5b**	281± 8.13$^{*\#}$	253±10.45$^{*\#}$	245±11.73$^{*\#}$	242±12.60$^{*\#}$	207±7.92$^{*\#}$	184±7.31$^{*\#}$
XI	**Compd. 5c**	290±6.92$^{*\#}$	281±7.33$^{*\#}$	277±7.01$^{*\#}$	261±6.59$^{*\#}$	248±6.30$^{*\#}$	211±7.81$^{*\#}$
XII	**Compd. 5d**	261±9.80$^{*\#}$	258±8.12$^{*\#}$	255±6.88$^{*\#}$	221±10.18$^{*\#}$	208±10.23$^{*\#}$	185±12.13$^{*\#}$
XIII	**Compd. 5e**	288±6.79$^{*\#}$	285±7.05$^{*\#}$	271±6.84$^{*\#}$	264±6.96$^{*\#}$	248±7.73$^{*\#}$	201±6.51$^{*\#}$
XIV	**Compd. 5f**	274±9.69$^{*\#}$	265±9.30$^{*\#}$	260±7.97$^{*\#}$	243±8.24$^{*\#}$	230±8.26$^{*\#}$	183±8.30$^{*\#}$
XV	**Standard**	311±3.79*	224±11.90$^{*\#}$	203±12.88$^{*\#}$	178±10.96$^{*\#}$	132±5.37$^{*\#}$	85±4.22$^{*\#}$

All the values are expressed as mean ± SEM; n = 6
*P < 0.05 significant, compared to normal.
# P < 0.05 significant, compared to diabetic control.

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