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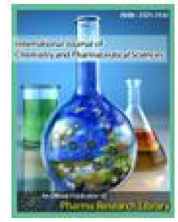

Research Article **Open Access**

Synthesis and Evaluation of Sulfonylureas for Anti Diabetic Activity

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A B S T R A C T

Drug ,synthesis and development multidisciplinary, creative, complex and highly regulated process New drug synthesis not only done loping new chemical entities but also important for therapeutic need Diabetes mellitus (DM) is one of the most daunting challenges posed by chronic diseases resulting from insulin deficiency or insulin resistance. Sulfonylureas have been used as hypoglycemic agents since the mid-1950s. Compounds in the first generation of this class such as chlorpropamide, tolbutamide etc. are still in use, but are less potent than the more recently introduced second generation drugs like glipizide, glibenclamide etc. The aim of our present study is to synthesize sulfonylureas derivatives with suitable substituents on Nitrogen and Sulfur and evaluate the antidiabetic activity of the synthesized compounds using albino wistar rats. Substituted sulfonylurea compounds were synthesized in three steps. In first step, oxidation of p-toluene sulfonamide **(19)** was carried out with KMnO4 to form p-Aminosulfonyl-benzoic Acid **(22)**. This was then, in second step, reacted with aniline in presence of EDCI, HOBt and triethylamine to form p-Aminosulfonyl-N-(phenyl) benzamide **(23)**. In third step, p-Aminosulfonyl-N-(phenyl)benzamide was reacted with triphosgene and various types of anilines **(24(a-j))** to form different substituted sulfonylurea derivatives **(25(a-j))**. The synthesized compounds were screened for antidiabetic activity by GOD/POD method and anti-oxidant activity by DPPH method. A total of 10 novel sulfonylureas were synthesized **(25(a-j))** which was characterized by m.p., TLC, elemental analysis, IR and 1H NMR. Data pertaining to the effect of compound on blood glucose levels for all 10 molecules was obtained. Anti-oxidant activity data for **25c, 25f** and **25g** was also obtained. Of the ten compounds **(25(a-j))** which were tested for blood glucose lowering effect, **25g** and **25i** were found to be very active. Other compounds were also showed good activity. The molecules that were tested for anti-oxidant activity were found to be very weak. Further work is proposed for blood glucose monitoring on diabetes induced rats.

Keywords: Diabetes mellitus, hypoglycemic agent, Sulfonylurea derivatives

A R T I C L E I N F O

CONTENTS

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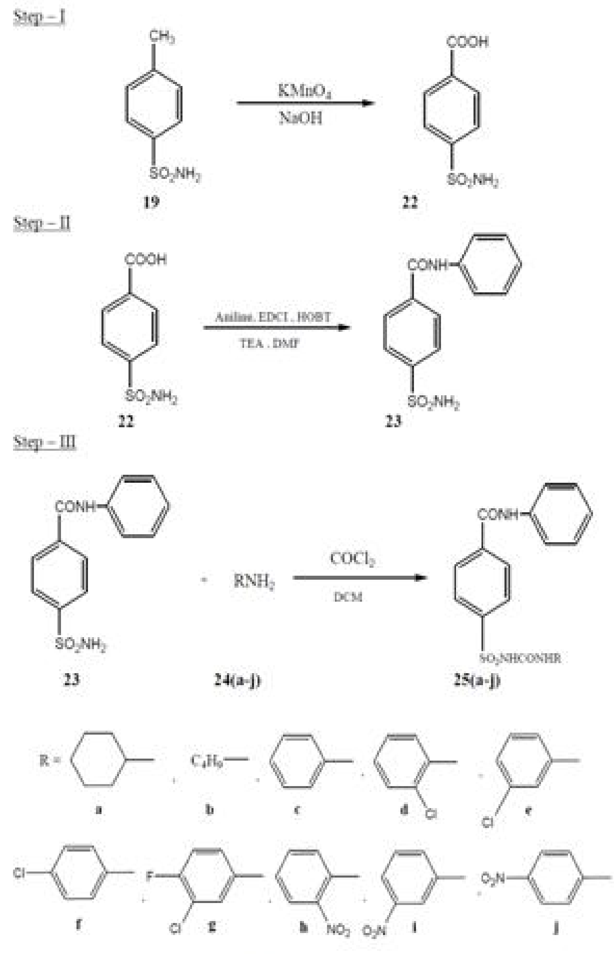
1. Introduction

Diabetes mellitus (DM) is one of the most daunting challenges posed by chronic diseases resulting from insulin deficiency or insulin resistance. Recent data show that approximately 135 million people suffer from diabetes mellitus worldwide, and that this number will rise to almost 300 million by the year 2025. While the rise will be of the order of 45% in developed countries, it will be almost 200% in developing countries. India has 35 million diabetics. As per WHO data the number would touch 50 million in 2020.1

Sulfonylureas have been used as hypoglycemic agents since the mid-1950s, and for many years this class of drugs has been one of the mainstays of oral antidiabetic therapy. Compounds in the first generation of this class such as acetohexamide, chlorpropamide, tolbutamide and tolazamide are still in use, but are less potent than the more recently introduced second-generation drugs like gliclazide, glimepiride, glipizide and glibenclamide. Glinides, e.g. nateglinide, and repaglinide represent newer group of hypoglycemic agents. Both groups of hypoglycemic agents (sulfonylureas and glinides) stimulate insulin secretion by closing ATP-sensitive potassium (KATP) channels in pancreatic beta cells, but have varying cross-reactivity with related channels in extrapancreatic tissues such as heart, vascular smooth and skeletal muscle. Sulfonylureas are commonly used in the treatment of type 2 diabetes mellitus because these drugs effectively reduce blood glucose levels in type 2 diabetes mellitus. Despite their beneficial effects, continuous use of sulfonylureas may cause β-cell dysfunction and apoptosis. Several reports have suggested that sustained enhancement of Ca2+ influx by sulfonylureas may be a causative mechanism for β-cell apoptotic cell death.4

Sulfonylureas stimulate insulin secretion from pancreatic β-cells. Their principal target is the ATP-sensitive potassium (KATP) channel, which plays a major role in the β-cell membrane potential. Inhibition of KATP channels by glucose or sulfonylureas causes depolarization of the β-cell membrane; in turn, this triggers the opening of voltage-gated Ca2+ channels, eliciting Ca2+ influx and a rise in intracellular Ca2+ which stimulates the exocytosis of insulin-containing secretory granules. KATP channels are also found at high density in a variety of other cell types, including cardiac, smooth, and skeletal muscle, and some brain neurons. In all these tissues, opening of KATP channels in response to metabolic stress leads to inhibition of electrical activity. Thus they are involved in the response to both cardiac and cerebral ischemia. They are also important in neuronal regulation of glucose homeostasis, seizure protection, and the control of vascular smooth muscle tone (and, thereby, blood pressure) Ca2+ion.

2. Materials and Methods



SCHEME - IV

1. Synthesis of p-Aminosulfonyl-benzoic Acid:
In a 100 ml RBF was placed a solution of 2.92 g (73.1 mmol) of sodium hydroxide in 50 ml water, 2.5 g (14.62 mmol) of p-toluene sulfonamide **(19)** was dissolved in the above. To this was added in portions, 3 g (19 mmol) of potassium permanganate with stirring and mixture heated to 70° C simultaneously. After addition, the reaction mixture was heated at 90 °C for 4 h. The mixture was then cooled, filtered and acidified with dil. HCl to yield a precipitate which was filtered, washed with water, dried in vacuum to give 2.55 g (87.3%) of the compound **(22)** as a white powder. The melting range recorded to be 290-292° C

2. Synthesis of p-Aminosulfonyl-N-(phenyl) benzamide:
In a 250 ml RBF were placed p-Aminosulfonyl-benzoic Acid **(22)** 3 g (14.925 mmol), EDCI 7.153 g (37.312 mmol), HOBt 5.042 g (37.312 mmol) and DMF 50 ml. The mixture was stirred at 0 °C and after 5 min of stirring 1.36 ml (14.925 mmol) of amine.

Methodology

Dept. of Pharmaceutical Chemistry, NCP, Bangalore 16 was added and stirred for further 5 min. To the above suspension, was added 6.22 ml (44.775 mmol) of triethylamine and continued stirring for 14 hrs at room temperature. The reaction mixture was washed with 100 ml of brine, acidified with 2N HCl and extracted with 3 successive portions of 25 ml ethyl acetate. The organic layer was washed with sodium bicarbonate solution to remove excess acid. Separated the organic layer, dried over sodium sulphate and removed solvent in vacuum to get 1.4 g of the compound (23), m.p. 170°C.

3. Synthesis of sulfonylurea derivatives:

23 24(a-j) 25(a-j)

In a 100 ml RBF were placed 150 mg (0.541 mmol, 1 eq.) of p-Aminosulfonyl-N-(phenyl)benzamide **(23)**, 0.23 ml (1.623 mmol, 3 eq) of triethylamine in 10 ml dichloromethane. The mixture was stirred at room temperature. After 15-20 min of stirring, 80 mg (0.27 mmol, 0.5 eq) of triphosgene was added and stirring was continued for further 15 mins. To this, 0.433 mmol (0.8 eq.) of amine in 1 ml DCM was added and continued stirring for 2 hrs. The reaction mixture was quenched using ammonia-methanol solution, washed with brine solution, acidified with 2N HCl and extracted with dichloromethane. The organic layer was dried over sodium sulphate and removed solvent to get the compound **25(a-j)**.

B) Biological Activity:

1. Antidiabetic Activity. Blood glucose lowering activity in rats:

a) Animal: Female Wistar rats (150-220 grams) were purchased from Biovivo services (kachohalli, Banglore, India). Institution Animals Ethics Committee has approved the experimental protocol (IAEC/NCP/18/09). Animals were housed in polypropylene cages. Paddy husk was provided as bedding material. Food and water was provided *ad libitum*. Rats were maintained on standard, pelleted rodent diet.

b) Sample Size Selection:

Sixty six female wistar rats were selected randomly and divided into 11 groups. Each group consists of 6 animals.

c) Dose Selection. Glibenclamide:

1 mg/kg body weight of the rats.17 **Test compounds:** Dose of test compounds was with reference to tolbutamide. Dose of tolbutamide in humans is 500 mg/day.18 This was extrapolated to rats and a dose of 45 mg/kg was fixed for rats.19

d) Procedure:

20 Animals are selected randomly and divided into 11 groups. Each group consist of 6 animals. Group 1: Received glibenclamide 1mg/kg body weight of rat. Group 2 to 11: Received the synthesized derivatives **25a, 25b, 25c, 25d, 25e, 25f, 25g, 25h, 25i, 25j** respectively at a dose of 45 mg/kg body weight of rat. Blood samples were collected before and after 4 hours of drug treatment by puncturing the retro orbital plexus under mild ether anesthesia. Blood glucose levels (GOD/POD) were estimated using commercial assay kit (Preicugent, Thane, India).

e) Biochemical Determinations:

Blood samples are collected in centrifuge tubes and kept aside for clotting. After clotting, the sample was centrifuged at 3000 rpm for 10 minutes and serum was separated and used for biochemical estimations. Blood glucose level (GOD/POD) was estimated by semi autoanalyser using the commercial assay kits (Preicugent, Thane, India).

2. Antioxidants Activity [21,22]

Antioxidants are any substance that when present in low concentration compared to those of an oxidisable substrate significantly delays or inhibits the oxidation of the substrate. These are the substance of synthetic or natural origin, which protects the Bio-membrane against reactive oxygen species (ROS) mediated tissue damage.

Types of antioxidants:

(A). Preventive anti-oxidants:

These mainly suppress the formation of free radicals since they act at very early stage of onset of free radicals. These are most valuable and safe. These are sub classified as:

a). Anti-oxidative enzymes:

These are super oxide dismutase, catalase, and glutathione reductase which convert ROS into non-reactive oxygen molecules.

b). Metal Chelating antioxidant:

Transition metals such as iron and copper play important roles in initiation and propagation steps of lipid oxidation. The presence of metal can accelerate the initiation step of lipid oxidation.

c). Singlet oxygen-quenching antioxidants

Singlet oxygen is highly reactive toward any molecules with electron or loan pairs of low ionization energy.

(B). Radical scavenging anti-oxidants

These can donate hydrogen atoms to free radicals, can scavenge free radicals and Prevent lipid oxidation. e.g. vitamin C, albumin (hydrophilic) and vitamin E.

(C). Repair and denova enzymes

These mainly act by repairing the damage and reconstituting the membranes. e.g. Lipase, Protease and DNA repair enzymes.

Free radical scavenging activity by DPPH method

Free radical scavenging potentials of the synthesized compounds were tested against a methanolic solution of α, α diphenyl-β-picryl hydrazyl (DPPH). Antioxidants reacts with DPPH and convert it to α, α diphenyl-β-picryl hydrazine. The degree of discoloration indicates the scavenging potentials of the antioxidant activity. The change in the absorbance produced at 517 nm has been used as a measure of antioxidant activity.

Reduction of DPPH free radical

Preparation of solutions:

DPPH stock solution (100 μM): 39.4 mg of DPPH was dissolved in one litre of methanol (AR). 10 mg of the synthesized compound was dissolved in 10 ml of methanol (AR). Ascorbic acid was taken as standard as 10 mg solution in 10 ml of methanol.

Procedure:

5 to 50 µl (5 to 50 µg) of ascorbic acid and synthesized compounds were taken in different test tubes. Then the volume was adjusted to 1000 µl with methanol. To this 4 ml of methanolic solution of DPPH was added, shaken well and the mixture was allowed to stand at room temperature

for 20 minutes. The control was prepared as above without sample. The readings were taken for blank (methanol), control and sample at 510 nm. Scavenging activity was expressed as the inhibition percentage calculated using the following formula, % Anti radical activity = Control Abs. – Sample Abs. × 100 Control Abs.

Note: Absorbance was measured at 510 nm in semi auto analyzer.

25a) 1-cyclohexyl-3-(4-(phenyl carbamoyl) phenyl sulfonyl) urea

C= 59.83, H= 5.77, N= 10.47, O= 15.94, S= 7.99 3332.5 (NH str.), 1649.19 (C=O str.), 1325, 1166 (S=O str.), 2932, 2855 (C-H str).

25b) 1-butyl-3-(4- (phenylcarbamoyl) phenyl sulfonyl) urea

C= 57.58, H= 5.64, N= 11.19, O= 17.05, S= 8.54, 3371.68, 3327.32 (NH str.), 1649.19, 1656.91 (C=O str), 1325.14, 1141.90 (S=O str.), 2950.04, 2926.11 (aliphatic C-H str.).

25c1-phenyl-3-(4- (phenyl carbamoyl) phenyl sulfonyl) urea

C= 60.75, H= 4.33, N= 10.63, O= 16.18, S= 8.113306.10, 3254.02 (NH str.), 1699.34, 1645.33 (C=O str), 1327.07, 1157.33 (S=O str.), 3132.5, 3101.64 (aromatic C-H str.), 1600.99 (N-H bend).

25d) Cl 1-(2-chlorophenyl)-3-(4-(phenylcarbamoyl) phenyl sulfonyl) urea

C= 55.88, H= 3.75, Cl= 8.25, N= 9.77, O= 14.89, S= 7.46 3286.81, 3252.09 (NH str.), 1699.34, 1645.33 (C=O str), 1327.07, 1168.09 (S=O str.), 756.12 (aromatic C-Cl str.).

25e) Cl 1-(3-chlorophenyl)-3-(4- (phenylcarbamoyl) phenyl sulfonyl) urea

C= 55.88, H= 3.75, Cl= 8.25, N= 9.77, O= 14.89, S= 7.46 3279.10, 3244.38 (NH str.), 1699.34, 1653.05 (C=O str), 1327.07, 1155.40 (S=O str.), 756.12 (aromatic C-Cl str.), 3134.43, 3090.07 (aromatic C-H str.).

25f) Cl 1-(4-chlorophenyl)-3-(4-(phenylcarbamoyl) phenyl sulfonyl) urea

C= 55.88, H= 3.75, Cl= 8.25, N= 9.77, O= 14.89, S= 7.46 3421.83, 3309.96 (NH str.), 1654.98, 1718.63 (C=O str), 1325.14, 1143.83 (S=O str.), 760 (aromatic C-Cl str.), 2924.18 (aromatic C-H str.).

25g) Cl1-(3-chloro-4-fluorophenyl)-3-(4-(phenyl carbamoyl) phenylsulfonyl)urea

C= 53.64, H= 3.38, Cl= 7.92, F= 4.24, N= 9.38, O= 14.29, S= 7.16 3317.67 (NH str.), 1653.05, 1680.05 (C=O str), 1325.14, 1143.83 (S=O str.), 759.98 (aromatic C-Cl str.), 3136.36 (aromatic C-H str.), 889.21 (aromatic C-Br str.).

25h) O_2N 1-(2-nitrophenyl)-3-(4- (phenyl carbamoyl) phenyl sulfonyl) urea

C= 54.54, H= 3.66, N= 12.72, O= 21.80, S= 7.28 3333.10, 3271.38 (NH str.), 1649.19 (C=O str), 1327.07, 1165.04 (S=O str.), 1570.11 (-NO2 str.), 2922.25 (C-H str.).

25i) NO_2 1-(3-nitrophenyl)-3-(4- (phenylcarbamoyl) phenylsulfonyl) urea

C= 54.54, H= 3.66, N= 12.72, O= 21.80, S= 7.28 3338.89, 3311.89, 3275.24 (NH str.), 1649.19, 1656.91 (C=O str), 1327.07, 1157.33 (S=O str.), 1572.04 (-NO2 str.), 3134.43, 3082.35 (C-H str.).

25j)$NO_2$1-(4-nitrophenyl)-3-(4(phenylcarbamoyl) phenyl sulfonyl) urea

C= 54.54, H= 3.66, N= 12.72, O= 21.80, S= 7.28 3344.68 (NH str.), 1653.05, 1683.91 (C=O str), 1327.07, 1165.04 (S=O str.), 1562.39 (-NO2 str.), 2924.18, 2854.74 (C-H str.).

NMR Spectral Data 1H NMR data for compound code 25c: (in DMSO-d6)

1H singlet at 10.443 δ (SO2NH proton), 2H doublet at 8.104-8.971 δ (CONH proton), 14H multiplet at 6.988 δ-8.126 δ (aromatic CH proton).

3. Result and Discussion

I had proposed synthesis of sulfonylureas for antidiabetic activity. The method adopted for the synthesis was using phosgene equivalent, namely triphosgene. Success was obtained in synthesizing ten molecules; **25(a-j)**, by this protocol. The characterization was done by TLC and in FTIR for all the compounds. NMR was also obtained for the molecule **25c** in DMSO. The NMR data proved the formation of sulfonylureas. The other compounds that were isolated was based on IR and TLC which showed the characteristic features. The IR spectra of compound **23** showed peaks at 3335.59 cm-1, 3313.52 cm-1 (NH str.), 1649.19 cm-1 (C=O str.), 1327.07 cm-1 and 1165.9 cm-1 (SO2 str.) indicated the formation of scaffold. Peaks observed at 2932 cm-1, 2855 cm-1 (aliphatic C-H str.) indicated the formation of compound **25a**. Similarly peaks observed at 2950.04 cm-1, 2926.11 cm-1 (aliphatic C-H str.) indicated the formation of compound **25b**.

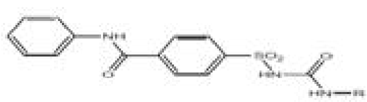
In the IR spectra of compound **25c**, absence of primary amine peak and presence of secondary amine peaks at 3306.10 cm-1, 3254.02 cm-1 indicated the formation of the product. Peaks observed at 756.12 cm-1 – 760 cm-1 (aromatic C-Cl str.) indicated the formation of compounds **25(d-f)**. Similarly peaks observed at 759.98 cm-1 (aromatic C-Cl str.) and 889.21 cm-1 (aromatic C-F str.) indicated the formation of compound **25g**. In the same way peaks observed at 1562.39 cm-1 – 1572.04 cm-1 (aromatic NO2 str.) indicated the formation of compound **25(h-j)**. Screening was undertaken for blood glucose lowering effect for all synthesized compound. Significant results were obtained for all the molecules synthesized.

The compounds **25g** and **25i** were found to be very active for percent blood glucose reduction. Compounds **25d, 25e** and **25h** were also showed good activity. However the compounds **25a, 25b, 25c** and **25f** were found to be less active. The presence of electron withdrawing groups (-Cl, -F, -NO2) at *ortho* or *meta* position of the phenyl ring as –R demonstrated better activity for blood glucose reduction **(25d, 25e, 25h** and **25i).** Presence of two electron withdrawing groups on phenyl ring further increased the activity **(25g)**. Bulky group (-NO2) on the phenyl ring at *ortho* or *meta* position has shown good reduction in blood glucose level **(25h** and **25i)** as compared to the small group (-Cl) **(25d** and **25e).** Some of the compounds **(25c, 25f** and **25g)** were also tested for anti-oxidant activity. All the tested compounds were found to possess very weak anti-oxidant activity.

Physical Properties of Synthesized compounds.

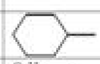
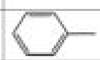
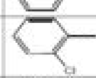
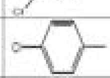
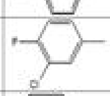
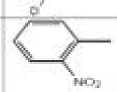
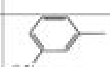
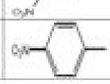
S.N.	Comp. Code	Molecular Formula	M.Wt.	% Yield	m.p. (˚C)	R_f Value
1.	**25a**	$C_{20}H_{21}N_3O_4S$	401	37 %	255	0.90
2.	**25b**	$C_{18}H_{21}N_3O_4S$	375	45 %	270	0.65
3.	**25c**	$C_{20}H_{17}N_3O_4S$	395	63 %	155	0.62
4.	**25d**	$C_{20}H_{16}N_3O_4SCl$	429	60 %	180	0.52
5.	**25e**	$C_{20}H_{16}N_3O_4SCl$	429	58 %	272	0.55
6.	**25f**	$C_{20}H_{16}N_3O_4SCl$	429	63 %	215	0.42
7.	**25g**	$C_{20}H_{15}N_3O_4SClF$	447	68 %	190	0.45
8.	**25h**	$C_{20}H_{16}N_4O_6S$	440	32 %	280	0.15
9.	**25i**	$C_{20}H_{16}N_4O_6S$	440	43 %	285	0.18
10.	**25j**	$C_{20}H_{16}N_4O_6S$	440	3 7%	275	0.20

mobile phase = n-Hexane : Ethyl Acetate : Methanol (4 : 5 : 1).



25(a-j)

Predicted biological activity of compounds by Chemexper and Molinspiration.

S.N.	R	cLogP	Drug Likeness	Drug Score	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand
1		3.36	1.72	0.59	0.13	-0.04	-0.26	-0.67
2	C_4H_9—	3.13	4.02	0.58	0.14	-0.02	-0.27	-0.79
3		3.35	5.34	0.65	-0.06	-0.17	-0.21	-0.64
4		3.96	5.85	0.41	-0.06	-0.19	-0.30	-0.81
5		3.96	5.62	0.52	-0.06	-0.16	-0.19	-0.82
6		3.96	6.3	0.52	-0.05	-0.15	-0.20	-0.68
7		4.02	1.85	0.44	0.02	-0.10	-0.06	-0.90
8		3.08	5.45	0.56	-0.16	-0.27	-0.33	-0.86
9		3.08	5.23	0.2	-0.18	-0.26	-0.32	-0.78
10		3.08	3.01	0.13	-0.17	-0.24	-0.31	-0.66

cLogP, Drug Likeness and Drug Score ⟶ +ve value favors the activity.
GPCR ligand, Ion channel modulator, Kinase inhibitor and Nuclear receptor ligand ⟶ -ve value favors the activity.

Animal Group	Compound	Dose (mg/kg) p.o.	Blood Glucose Level (mg/dl) Mean ± SEM, n = 6		% Blood Glucose Level Reduced
			Before drug treatment	4th hr. after drug treatment	
1	Glibenclamide	1	128.6 ± 2.63	63.9 ± 5.65***	50.31
2	**25a**	45	163.3 ± 7.07	140.0 ± 6.63***	14.26
3	**25b**	45	150.2 ± 3.60	125.0 ± 3.08**	16.77
4	**25c**	45	145.7 ± 6.95	117.2 ± 4.59***	19.56
5	**25d**	45	138.3 ± 4.28	103.8 ± 2.94***	24.94
6	**25e**	45	138.4 ± 5.11	106.3 ± 6.07***	23.2
7	**25f**	45	135.2 ± 4.88	108.8 ± 4.51***	19.52
8	**25g**	45	118.8 ± 1.93	67.4 ± 1.71***	43.26
9	**25h**	45	122.3 ± 2.32	91.20 ± 4.61***	25.34
10	**25i**	45	119.2 ± 2.47	72.32 ± 4.33***	39.32
11	**25j**	45	119.1 ± 3.72	97.0 ± 5.77**	18.55

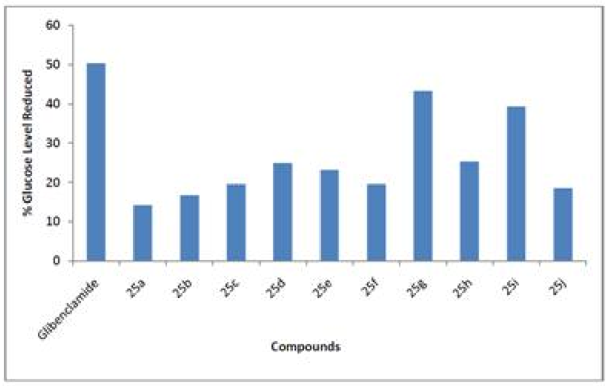


Figure 1 : Effect of Sulfonylurea compounds on blood glucose level in albino wistar rats.

4. Conclusion

The ten compounds **(25(a-j))** which were tested for blood glucose lowering effect, **25g** and **25i** were found to be very active. Other compounds also showed good activity. **25a** was found to be the least active. The molecules that were tested for anti-oxidant activity **(25c, 25f, 25g)** were found to be very weak active. Electron withdrawing groups at *ortho* or *meta* position of the phenyl ring as –R demonstrated better hypoglycemic activity. Presence of two electron withdrawing groups on phenyl ring further increased the activity **(25g)**. A wide range of electron withdrawing substituents at *ortho* and *meta* position needs to be studied to explore and optimize the hypoglycemic activity of this class of molecule.

5. References

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