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EVALUATION OF THE *IN VIVO* HYPOGLYCEMIC EFFECT OF SULFONYLUREA-CHALCONE HYBRID MOLECULES IN NORMOGLYCEMIC RABBITS

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ABSTRACT

Diabetes mellitus (DM), both insulin-dependent DM (IDDM) and non-insulin dependent DM (NIDDM) is a common and serious metabolic disorder throughout the world. The aim of the present study was to evaluate the hypoglycemic activity of a synthetic sulfonylurea-chalcones 1-3 which earlier reported from our research labs. The effect of oral administration of sulfonylurea-chalcones 1-3 on blood glucose levels was studied. The sulfonylurea-chalcones 1-3 (50 mg/kg, oral) reduced the normal blood glucose levels in normoglycemic rabbits.

Keywords: Sulfonylurea-chalcones 1-3, hypoglycemic activity.

INTRODUCTION

Diabetes mellitus is a common and very prevalent disease affecting the citizens of both developed and developing countries. It is estimated that 25% of the world population is affected by this disease. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin [1]. Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drugs continues because the existing synthetic drugs have several limitations. The herbal drugs with antidiabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine [2]. The plants provide a potential source of hypoglycemic drugs because many plants and plant derived compounds have been used in the treatment of diabetes. Many Indian plants have been investigated for their beneficial use in different types of diabetes and reports occur in numerous scientific journals. Ayurveda and other traditional medicinal system for the treatment of diabetes describe a number of plants used as herbal drugs.

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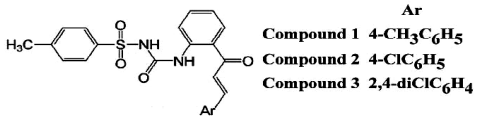
Hence, they play an important role as alternative medicine due to less side effects and low cost. The active principles present in medicinal plants have been reported to possess pancreatic beta cells re-generating, insulin releasing and fighting the problem of insulin resistance [3]. Hyperglycemia is involved in the etiology of development of diabetic complications. Hypoglycemic herbs increase insulin secretion, enhance glucose uptake by adipose or muscle tissues and inhibit glucose absorption from intestine and glucose production from liver [4]. Insulin and oral hypoglycemic agents like sulfonylureas and biguanides are still the major players in the management but there is quest for the development of more effective anti-diabetic agents. The present work aimed at evaluating the percentage blood glucose reducing capacity of a sulfonylurea-chalcones 1-3 derivative which earlier reported by one of the authors Vasudeva Rao Avupati et al [5].

MATERIALS AND METHODS

Chemical synthesis

The sulfonylurea-chalcone hybrid compounds 1-3 were procured from pharmaceutical chemistry research laboratories, as gift samples (Scheme 1).



Scheme 1

EXPERIMENTAL PROTOCOL

Acute Toxicity

As a general rule, the acute toxicological studies of test compounds 1-3 were performed as per OECD 425 guidelines in mice. These compounds were found to be safe up to dose (median lethal dose) 2000 mg/kg b.w. No changes in any of vital functions were observed throughout the study period.

In Vivo Hypoglycemic Activity

Approval of Animals Ethics Committee

The animal housing and handling were in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines and the experimental protocol has been approved by the Institutional Animal Ethics Committee (IAEC) (Proceedings No. 516/01/A/CPCSEA).

Animal model selected for the study

Healthy Albino rabbits of either sex weighing in between to 1-1.5 kg body weight.

Selected route of administration

Oral administration

Different groups of rabbits as considered as follows

Group I: Normal, receive normal fed and water, *ad libitum*

Group II: Control, receive sodium CMC, with normal fed and water, *ad libitum*

Group III: Standard, treated with Gliclazide (5mg/kg, oral suspension).

Group IV: Test, treated with the Test compound (5mg/kg, oral suspension)

Resting stage after dose given to rabbit

7-14 days.

Compound preparation:

Required amount of the test compound was weighed and suspended with Sodium CMC suspension in distilled water. Volume was made up with distilled water and administered through oral route.

Animal housing and maintenance:

Rabbits were procured from the Ghosh Enterprises, kolkata. Throughout the study protocol the animals were group-housed in polypropylene cages. Standard Laboratory Conditions with 10-15 air changes per hour, continuously monitored environment, room temperature of 24 ± 3 °C with a relative humidity of 30-70 % and 12/12 hours of day light / dark cycle were maintained.

Method

The standard (**Gliclazide 5 mg/kg bodyweight**) and test compounds (**Compound 1 to 3, 50 mg/kg bodyweight**) were administered with a single dose for 1 day. The rabbits were then subjected to blood sample collection from marginal ear vein using disposable insulin syringe for the time intervals of 0, 1, 2, 3, 4, 6, 8, 10, and 12 hrs respectively. The collected blood samples are further processed for the estimation of plasma blood glucose levels using Glucometer (ACCU CHEK ACTIVE).

Statistical analysis

The data obtained after completion of the study protocol was analyzed using statistical and graphical representations. All the data are expressed as Mean ± S.E.M given in the following **Tables 1-12**.

RESULTS AND DISCUSSION

The results of in vivo hypoglycemic activity studies are given in the following **Tables 1-12**.

Table 1: Blood glucose levels (mg/dL) with Gliclazide (5mg/kg) body weight in normal rabbits.

Gliclazide	Rabbit-1 (mg/dL)	Rabbit-2 (mg/dL)	Rabbit-3 (mg/dL)	Rabbit-4 (mg/dL)	Mean ±SEM
0	116	100	110	95	105.25±4.75
1	81	73	83	82	79.75±2.28
2	81	69	75	64	72.25±3.68
3	86	70	79	73	77±3.53
4	87	79	89	87	85.5±2.21
6	94	87	92	89	90.5±1.55
8	99	91	100	92	95.5±2.32
10	102	93	103	94	98±2.61
12	105	93	104	95	99.25±3.06

Table 2: Percentage blood glucose reduction values with Gliclazide (5mg/kg) body weight in normal rabbits.

Gliclazide	Rabbit-1 (%)	Rabbit-2 (%)	Rabbit-3 (%)	Rabbit-4 (%)	Mean ± SEM
1	30.17	27	24.5	13.68	23.83±3.57
2	30.17	31	31.8	32.63	31.4±0.52
3	25.86	30	28.1	32.6	29.14±1.43
4	25	21	19.09	8.42	18.37±3.54
6	18.96	13	16.36	6.31	13.65±2.73
8	14.6	9	10	2.10	8.92±2.58
10	12.06	7	6.36	1.05	6.61±2.25
12	9.48	7	5.45	0	5.48±2.00

Table 3: Blood glucose levels (mg/dL) with Sodium CMC (Vehicle) in normal rabbits.

Sodium CMC	Rabbit-1 (mg/dL)	Rabbit-2 (mg/dL)	Rabbit-3 (mg/dL)	Rabbit-4 (mg/dL)	Mean ±SEM
0	118	117	118	115	117±0.70
1	118	117	118	115	117±0.70
2	118	117	118	115	117±0.70
3	116	115	117	114	115.5±0.64
4	115	114	116	113	114.5±0.64
6	115	114	116	113	114.5±0.64
8	111	111	113	110	111.25±0.62
10	115	115	115	112	114.25±0.75
12	116	116	116	113	115.25±0.75

Table 4: Percentage blood glucose reduction values with Sodium CMC in normal rabbits

Sodium CMC	Rabbit-1 (%)	Rabbit-2 (%)	Rabbit-3 (%)	Rabbit-4 (%)	Mean ± SEM
1	0	0	0	0	0
2	0	0	0	0	0
3	1.69	0	0.84	0.86	0.84±0.34
4	2.54	0.84	1.69	1.79	1.71±0.34
6	3.89	0.84	1.69	1.79	2.05±0.64
8	5.93	5.12	4.23	4.34	4.90±0.39
10	3.89	3.41	2.54	2.60	3.11±0.32
12	1.69	0.84	1.69	1.79	1.50±0.22

Table 5: Blood glucose levels (mg/dL) in normal rabbit (Control)

Control	Rabbit-1 (mg/dL)	Rabbit-2 (mg/dL)	Rabbit-3 (mg/dL)	Rabbit-4 (mg/dL)	Mean ±SEM
0	115	115	115	115	115
1	115	115	115	115	115
2	115	115	115	115	115
3	114	114	114	114	114
4	113	113	113	113	113
6	111	111	111	111	111
8	109	109	109	109	109
10	109	109	109	109	109
12	106	106	106	106	106

Table 6: Percentage blood glucose reduction values in normal rabbit (Control)

Control	Rabbit-1 %)	Rabbit-2 (%)	Rabbit-3 (%)	Rabbit-4 (%)	Mean ± SEM
1	0	0	0	0	0
2	0	0	0	0	0
3	0.86	0.86	0.86	0.86	0.86
4	1.79	1.79	1.79	1.79	1.79
6	3.47	3.47	3.47	3.47	3.47
8	5.21	5.21	5.21	5.21	5.21
10	5.21	5.21	5.21	5.21	5.21
12	7.82	7.82	7.82	7.82	7.82

Table 7: Blood glucose levels (mg/dL) with Compound-1 (50 mg/kg) body weight in normal rabbits.

Cmpd-1	Rabbit-1 (mg/dL)	Rabbit-2 (mg/dL)	Rabbit-3 (mg/dL)	Rabbit-4 (mg/dL)	Mean ±SEM
0	117	114	118	112	115.25±1.37
1	112	109	113	107	110.25±1.37
2	109	106	110	104	107.25±1.37
3	101	98	102	96	99.25±1.37
4	86	83	87	81	84.25±1.37
6	89	86	90	84	87.25±1.37
8	94	91	95	89	92.25±1.37
10	100	97	101	95	98.25±1.37
12	107	104	108	102	105.25±1.37

Table 8: Percentage blood glucose reduction values with Compound-1 (50 mg/kg) body weight in normal rabbits.

Cmpd-1	Rabbit-1 (%)	Rabbit-2 (%)	Rabbit-3 (%)	Rabbit-4 (%)	Mean ± SEM
1	4.27	4.27	4.23	4.27	4.26±0.01
2	6.83	7.07	6..87	6.87	6.92±0.06
3	13.67	14.03	14.01	13.93	13.91±0.08
4	26.49	27.19	27.39	26.99	27.01±0.19
6	23.93	24.56	23.96	24.46	24.22±0.16
8	19.65	20.17	20.17	19.97	19.99±0.12
10	14.52	14.91	14.87	14.89	14.79±0.092
12	8.54	8.77	8.69	8.76	8.69±0.053

Graph 1. Plots of observed percentage blood glucose reduction values vs. Time (hrs) of compound 1

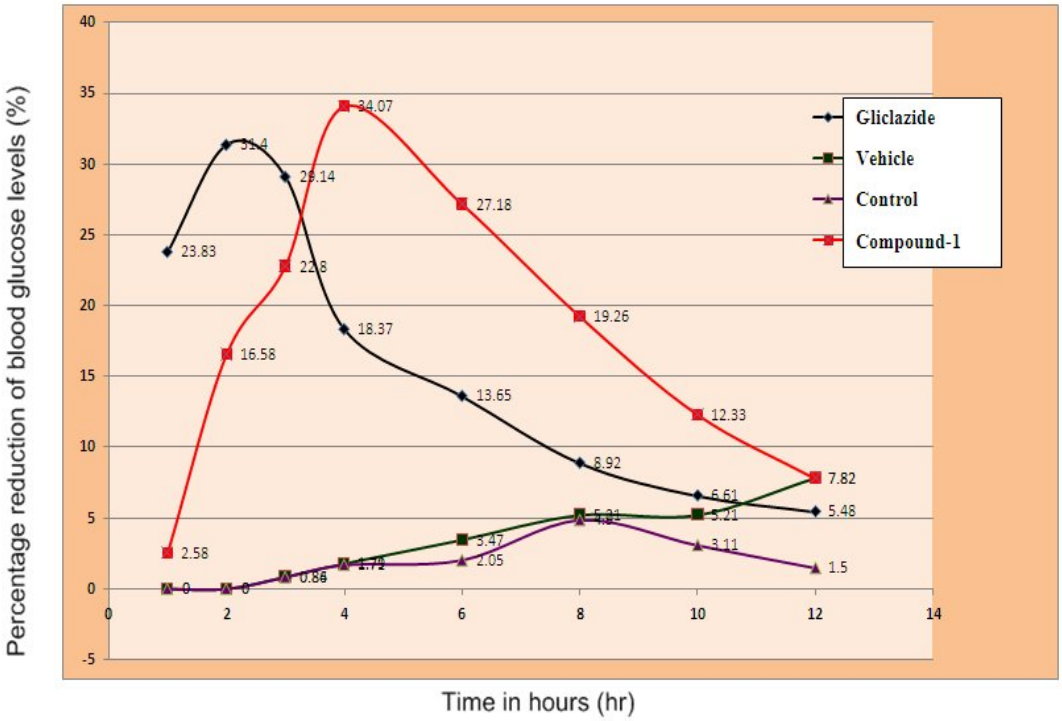


Table 9: Blood glucose levels (mg/dL) with Compound-2 (50 mg/kg) body weight in normal rabbits.

Cmpd-2	Rabbit-1 (mg/dL)	Rabbit-2 (mg/dL)	Rabbit-3 (mg/dL)	Rabbit-4 (mg/dL)	Mean ±SEM
0	118	116	113	114	115.25±1.10
1	108	106	103	104	105.25±1.10
2	102	100	97	98	99.25±1.10
3	95	93	90	91	92.25±1.10
4	80	78	75	76	77.25±1.10
6	88	86	83	84	85.25±1.10
8	99	97	94	95	96.25±1.10
10	104	102	99	100	101.25±1.10
12	112	110	107	108	109.25±1.10

Table 10: Percentage blood glucose reduction values with Compound-2 (50 mg/kg) body weight in normal rabbits.

Cmpd-2	Rabbit-1 (%)	Rabbit-2 (%)	Rabbit-3 (%)	Rabbit-4 (%)	Mean ± SEM
1	8.47	8.57	8.49	8.48	8.50±0.02
2	13.55	13.65	13.85	13.54	13.64±0.02
3	19.49	19.47	19.69	19.66	19.57±0.02
4	32.20	32.22	32.23	32.21	32.21±0.02
6	25.42	25.34	25.33	25.35	25.36±0.02
8	16.10	16.12	16.12	16.16	16.12±0.02
10	11.86	11.87	11.84	11.96	11.88±0.02
12	5.08	5.09	5.05	5.10	5.08±0.02

Graph 2. Plots of observed percentage blood glucose reduction values vs. Time (hrs) of compound 2

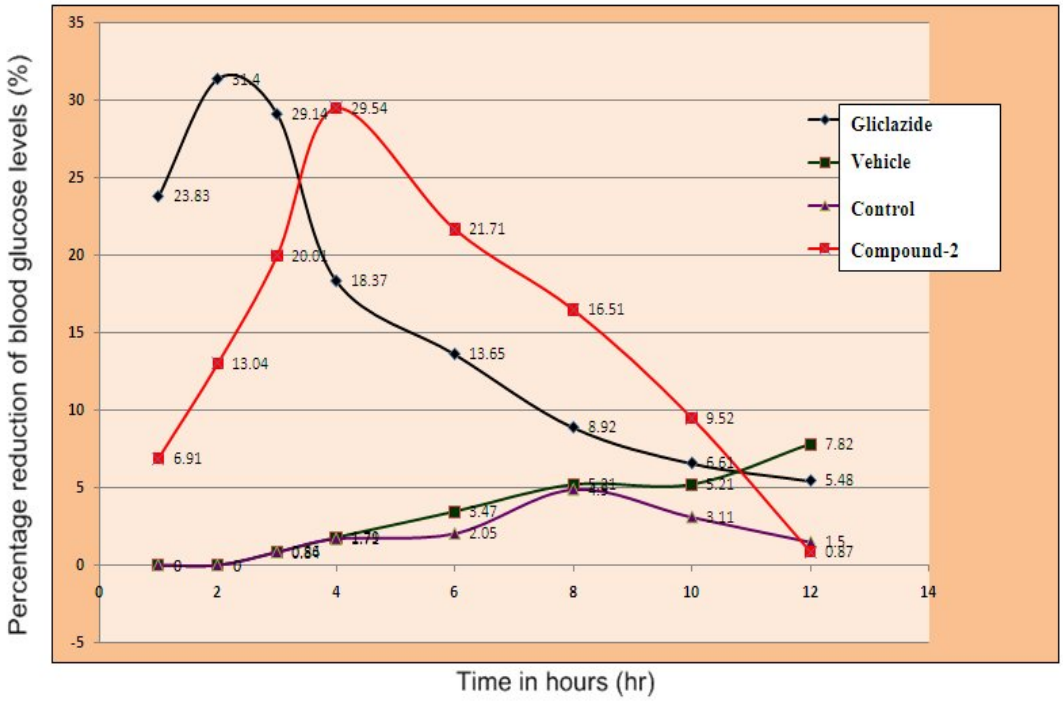


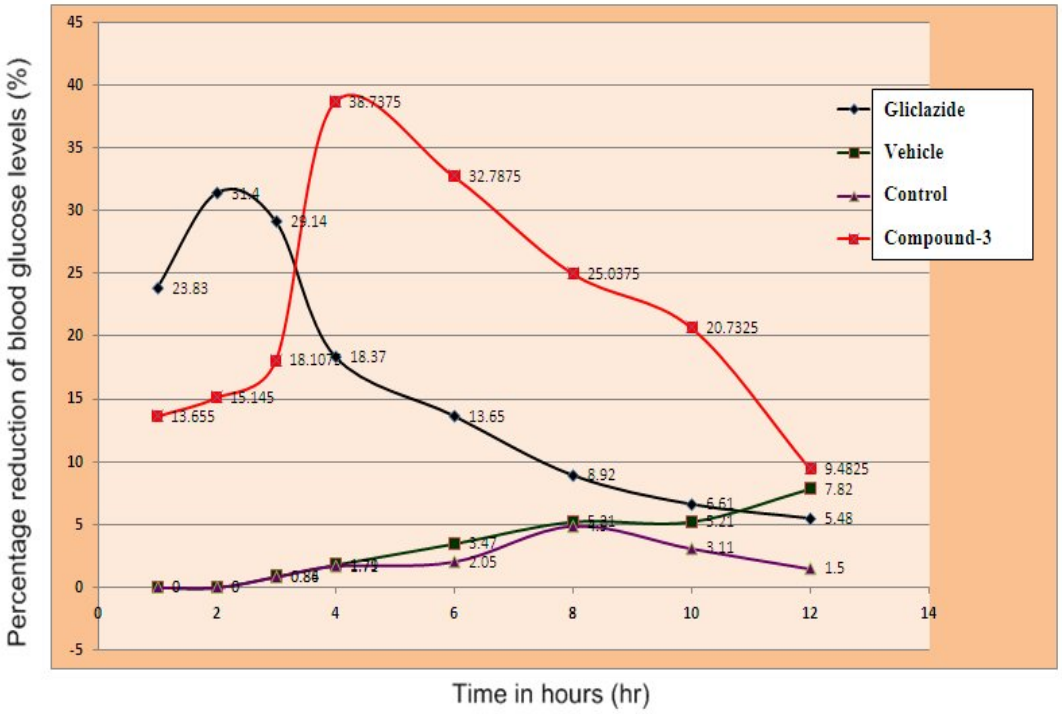
Table 11: Blood glucose levels (mg/dL) with Compound-3 (50 mg/kg) body weight in normal rabbits.

Cmpd-3	Rabbit-1 (mg/dL)	Rabbit-2 (mg/dL)	Rabbit-3 (mg/dL)	Rabbit-4 (mg/dL)	Mean ±SEM
0	116	119	114	117	116.5±1.04
1	100	103	98	101	100.5±1.04
2	98	101	96	99	98.5±1.04
3	95	99	93	96	95.75±1.25
4	71	75	69	72	71.75±1.25
6	78	82	76	79	78.75±1.25
8	87	89	85	88	87.25±0.85
10	92	94	100	93	94.75±1.79
12	105	107	113	106	107.75±1.79

Table 12: Percentage blood glucose reduction values with Compound-3 (50 mg/kg) body weight in normal rabbits.

Cmpd-3	Rabbit-1 (%)	Rabbit-2 (%)	Rabbit-3 (%)	Rabbit-4 (%)	Mean ± SEM
1	13.79	13.44	13.53	13.86	13.65±0.10
2	15.15	15.12	15.14	15.17	15.14±0.01
3	18.10	18.09	18.10	18.14	18.10±0.01
4	38.79	38.65	38.74	38.77	38.73±0.03
6	32.75	32.87	32.77	32.76	32.78±0.02
8	25	25	25.08	25.07	25.03±0.02
10	20.69	20.78	20.77	20.69	20.73±0.02
12	9.48	9.49	9.47	9.49	9.48±0.004

Graph 3. Plots of observed percentage blood glucose reduction values vs. Time (hrs) of compound 3



From the above results it is evident that all the sulfonylurea-chalcones 1-3 synthesized, showed hypoglycemic activity comparable with that of the standard drug Gliclazide. Among the compounds tested, **Compound-3** with dichlorophenyl moiety was found to be the most potent hypoglycemic agent with percentage blood glucose reduction (38.73) at 4 hr. Sulfonylurea-chalcones 1-3 with monochloro substitution **Compound-2** on the phenyl ring showed hypoglycemic levels of blood with percentage blood glucose reduction of (24.25). The **Compound-1** with *p*-methylphenyl also showed significant reduction of blood glucose levels with percentage reduction of 37.06%. The Structure-Activity Relationship study based on the above results clearly indicated that the compounds with more number of electron releasing or electron with drawing substituents on the aromatic ring at different positions can be synthesized to draw meaningful conclusions with respect to the influence of electronic effects on the hypoglycemic activity. All the compounds were displayed significant to moderate hypoglycemic activity and the results are comparable with that of the standard drug Gliclazide but not at the identical dose level.

CONCLUSION

The results obtained from the present study show that the sulfonylurea-chalcones 1-3 had beneficial effects on blood glucose levels in normoglycemic rabbits. This study confirms sulfonylurea-chalcones 1-3 as lead molecules for further studies, leading to possible drug development for diabetes.

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