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Research article

In vivo biological evaluation of some benzamide derivatives as potential antidiabetic agents in streptozotocin induced diabetic model

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ABSTRACT

Diabetes Mellitus (DM) is a chronic health illness that is caused by a number of geanetic and/or environmental factors. Type 2 diabetes mellitus (T2DM) accounts for more than 95 percent of all instances of diabetes in adults. According to the World Health Organization, India is one of the epicenters of the global diabetes epidemic, and it has the second highest number of diabetics in the world, with a population of over 900 million people (about 69 million people as of 2015).In present study, *in vivo* antidiabetic activity of some benzamide derivatives have been performed in STZ-nicotinamide-induced diabetic model in rats. The antidiabetic potential has been determined by estimating different serum biochemical and antioxidant parameters. Amongst all the tested molecules, compound 5h demonstrated significant antidiabetic and antioxidant potential when compared to metformin treated group. Compound 5h possess cloprothiazole substitution with benzamide nucleus. It was concluded that compound 5h can treated as lead molecule for the design and development of novel antidiabetic agents.

Keywords: T2DM, Streptozotocin, Benzamide, Diabetes, Rats.

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INTRODUCTION

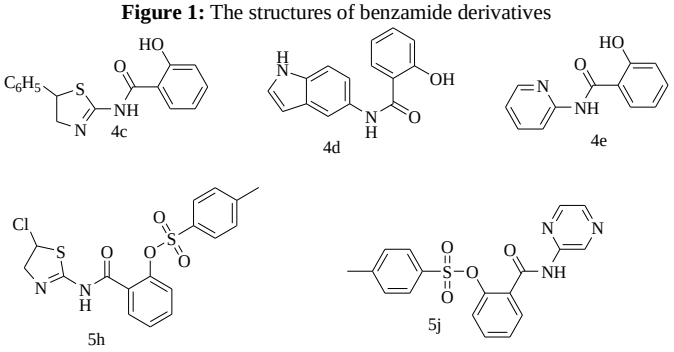
Diabetes Mellitus (DM) is a chronic health illness that is caused by a number of genetic and/or environmental factors. DM is a multi-factorial disease that affects both children and adults. According to the National Diabetes Education and Prevention Program, the prevalence of diabetes varies among different ethnic groups, such as black and Hispanic people, and some minorities, such as American Indians and Natives of Alaska, are more likely to have diabetes than others because they have a specific genetic profile, which makes them more susceptible to the disease. [1]. The number of individuals living with diabetes has more than doubled since 1980, according to the World Health Organization's (WHO) Global Report on Diabetes. The number of people living with diabetes is expected to reach 693 million by 2045, according to projections. [2]. Diabetes is characterized by elevated blood sugar levels, which are caused by a decrease in insulin concentration and/or activity, the pancreatic hormone responsible for regulating blood sugar levels [3]. To keep blood glucose levels as close to normal as possible while also delaying or maybe avoiding the development of diabetes-related health issues in the future, pharmacological treatment and/or insulin may be necessary. The American Diabetes Association (ADA) proposed classification of diabetes into three groups based on the etiology and clinical presentation of the disease: type 1 diabetes (T1DM), type 2 (T2DM), and gestational diabetes (GDM). Diabetic complications resulting from monogenic diabetes and secondary diabetes are two kinds of diabetes that are less common than other types. [4]. T2DM accounts for more than 95 percent of all instances of diabetes in adults. According to the World Health Organization, India is one of the epicenters of the global diabetes epidemic, and it has the second highest number of diabetics in the world, with a population of over 900 million people (about 69 million people as of 2015). [1]. From the literature it has been observed that, benzamide nucleus plays an important role for the development of potential antidiabetic agents. [5-8]. We have designed and synthesized some benzamide derivatives and in vivo biological evaluation was performed. All the designed derivatives have been screened through molecular docking studies and the molecules with best binding mode were subjected for wet lab synthesis followed by in vivo biological evaluation. The synthetic part with molecular docking studies have been communicated to the Current Enzyme Inhibition and the manuscript is under review now. In this paper we are reporting *in vivo* antidiabetic activity of the synthesized molecules.

MATERIAL AND METHODS

Drugs and Chemicals

50 mM sodium citrate buffer, pH 4.5: prepared just before use. 1.5-ml microcentrifuge tubes, aluminum foil, 1mL syringes, 23-G needles, one touch basic glucose monitoring system (Life scan), Metformin, streptozotocin (STZ), and other required chemicals were purchased and procured from Lab Trading Laboratory, Aurangabad, Maharashtra. The structures of benzamide derivatives used for the animal activity are illustrated in Figure 1.

Figure 1: The structures of benzamide derivatives



Ethical approval and animal used

In this investigation, healthy Wistar rats of either sex weighing 180 to 250 g were employed. They were kept in regular settings, with a temperature of 25^{0}C and a relative humidity of 45 to 55 percent. They were given a conventional pellet feed and free access to water *ad libitum*. All of the animals were properly monitored and cared for in accordance with the standards for the control and supervision of experimental animals established by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The animals were kept in polypropylene cages, and all procedures on them were carried out in an aseptic environment. The protocols for the study were approved with Institutional Animal Ethics committee (IAEC) approval number CPCSEA/IAEC/JLS/16/07/21/10.

Acute toxicity studies and dose selection

The acute toxicity studies have been performed as per the OECD test guideline 423. Separately, the animals were divided into six groups, each of which received oral administration of a different synthetic drug at dosages ranging from 50, 300, 500, 1000, and 2000 mg/kg body weight (b.w). The animals were monitored continuously for 1 hour, then continuously for the first 4 hours and sporadically for the next 6 hours, then again at 24 hours and 48 hours after drug administration, and then on a regular basis for the next 14 days. [9-10]. No deaths were observed any of the groups and hence 100 mg/kg dose was selected for all the compounds for the study of antidiabetic activity because therapeutic dose of metformin is also 100 mg.

Grouping and induction of diabetes

STZ-nicotinamide causes damage to pancreatic cells, which results in hyperinsulinemia and hyperglycemia. A diabetic condition may be induced by STZ in one of two ways, depending on the dosage. When STZ binds to the GLUT2 glucose transporter receptor, it accumulates in cells more readily than in other cells. This is due to the chemical's structural resemblance with glucose, which enables STZ to attach to the receptor. The most convincing demonstration of the method of action has come from mice research. Therefore STZ-nicotinamide-induced diabetes model has been used in the present study. On the first day of the experiment, all of the rats were fasted for 6 to 8 hours prior to receiving the STZ-nicotinamide injection. Water was delivered in the usual manner. Each rat received one 1.5 ml microcentrifuge tube containing 32.5 mg of STZ, which was sealed tightly with aluminum foil. One tube was used for each rat. It was necessary to make a citrate buffer with a pH of 4. A concentration of 32.5 mg/ml of STZ-nicotinamide was prepared prior to the injection by dissolving the compound in 50 mM sodium citrate buffer pH 4.5. For the study groups, STZ-nicotinamide solution was administered intraperitoneally (i.p.) at 65 mg/kg (2.0 ml/kg) using a 1mL syringe with a 23-G needle; for the control group, an identical amount of citrate buffer was injected intraperitoneally (i.p.). The rats were returned to their cages and given their usual diet as well as 10 percent sucrose water to keep them healthy. On the second day of the experiment, the 10 percent sucrose water was replaced with ordinary water. [11-12].

The rats were divided into 8 groups as follows, Group I served as normal control which received vehicle, Group II served as diabetic control, Group III, IV, V, VI, and VII served as tests group, receive 100 mg/kg b.w. of compounds 4c, 4d, 4e, 5h, and 5j respectively whereas Group VIII served as standard which received Metformin (100 mg/kg b.w.). The administration was performed on a daily basis for 21 days, and blood was drawn from the tail for the purpose of determining blood glucose levels.

Estimation of biochemical parameters in animal groups

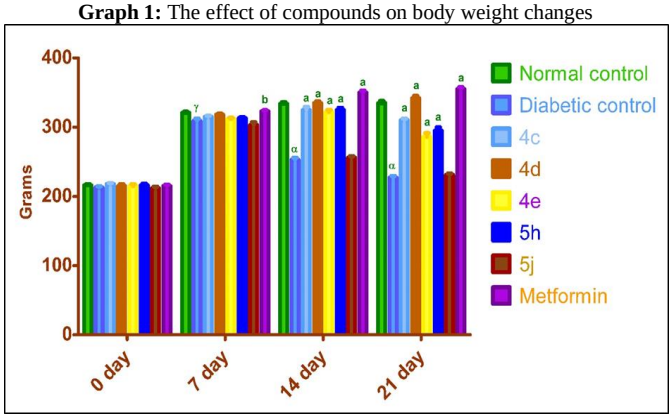
Different biochemical parameters have been estimated to determine the antidiabetic potential of the molecules. The parameters such as body weight (g), serum glucose level (mg/dl), serum total cholesterol (TC) (mg/dl), serum HDL-cholesterol levels (HDL-c) (mg/dl), serum LDL-cholesterol level (LDL-c) (mg/dl), serum VLDL-cholesterol level (VLDL-c) (mg/dl), serum triglyceride (TG) level (mg/dl),serum glutamic-oxaloacetic transaminase (SGOT, AST) (U/L), and serum glutamic pyruvic transaminase (SGPT, ALT) (U/L). As antioxidants helps to prevent the generation of free radicals which ultimately prevent biological damage of the cells and tissues. We have determined different antioxidant parameters such as superoxide dismutase's (SOD) (U/mL), catalase (CAT) (kU), malondialdehyde (MDA) (μM), and reduced glutathione (GSH) (mg/dl). [13-14].

RESULTS AND DISCUSSION

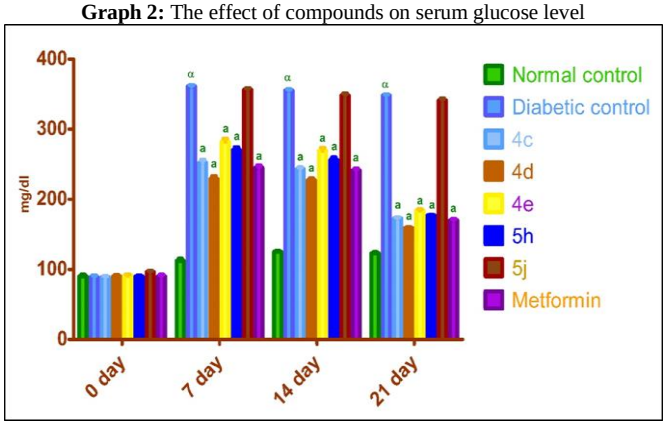
Effect on body weight and serum glucose level

Insulin deficiency in diabetes patients hinders the body from delivering glucose from the bloodstream to the cells of the body for use as energy. It is at this point that the body begins to burn fat and muscle for energy, which results in a decrease in total body weight. The basal body weight of animals of all the groups was found to be statistically equivalent. Diabetes induction caused significant decrease in the body weight during the experimental period when compared to normal control group. The mean body weights of normal control group, at the end of the treatment period was found to be 335±2.9 grams, this was significantly ($p<0.001$) decreased to 227±2.7 grams in diabetic control group. The decreased body weight was significantly ($p<0.001$) improved in 4c, 4d, 4e, 5h, and metformin groups, however administration of compound 5j did not show any significant increase in body weight (Graph 1 and Table 1).

Graph 1: The effect of compounds on body weight changes



Graph 2: The effect of compounds on serum glucose level



Data were expressed as mean±SEM, n=6, and analyzed by ANOVA followed by Tukey's post hoc test. $^{\alpha}p<0.001$, $^{\gamma}p<0.05$, when compared to the normal control group; $^{a}p<0.001$, $^{b}p<0.01$, when compared to diabetic control group.

The basal serum glucose level of animals of all groups was found to be statistically equivalent. Over the course of the trial, the diabetic control group had a considerable rise in blood glucose levels, indicating that they were diabetic. When comparing the diabetes control group to the normal control group, the blood glucose levels of the diabetic control group were considerably ($p<0.001$) higher (from 123±1.6 to 348±1.6mg/dl) at the conclusion of the research. The increased serum glucose level was significantly decreased with treatment with the compounds 4c, 4d, 4e, 5h, and metformin ($p<0.001$), however treatment with compound 5j has failed to show any significant decrease (Graph 2 and Table 1).

Table 1: The effect of compounds of body weight changes and serum glucose level

Day	Normal control group	Diabetic control group	4c group	4d group	4e group	5h group	5j group	Metformin group
Body weight (g)								
0	216±1.8	213±1.9	218±1.4	215±2.6	215±2.7	216±2.5	212±2.3	215±2.1
7	321±1.5	309±3.7$^{\gamma}$	315±1.6	318±1.7	312±1.6	313±1.6	303±4.3	323±1.8^{b}
14	334±2.4	253±2.9$^{\alpha}$	325±4.7^{a}	335±2.3^{a}	322±3.2^{a}	325±3.2^{a}	256±2.1	350±2.9^{a}
21	335±2.9	227±2.7$^{\alpha}$	310±2.7^{a}	342±3.3^{a}	286±5.7^{a}	295±4.8^{a}	231±2.1	355±2.9^{a}
Serum glucose (mg/dl)								
0	90.0±2.4	89±2.3	89±1.4	90±2.1	91±1.9	90±1.4	96±1.9	90±2.5
7	112±3.3	361±1.9$^{\alpha}$	252±4.2^{a}	229±4.0^{a}	282±4.6^{a}	270±4.1^{a}	356±2.6	245±3.1^{a}
14	125±1.5	355±2.2$^{\alpha}$	243±2.7^{a}	227±2.7^{a}	269±4.3^{a}	256±3.8^{a}	348±2.7	241±2.8^{a}
21	123±1.6	348±1.6$^{\alpha}$	173±1.2^{a}	159±1.3^{a}	184±1.9^{a}	177±0.87^{a}	341±2.8^{a}	170±1.8^{a}

Effect of compounds on lipid profile

Effect on TC levels

Normal control group serum total cholesterol levels were 92±1.8 mg/dl, whereas diabetes control group serum total cholesterol levels were considerably ($p<0.001$) higher at 157±2.6 mg/dl. Treatment with compounds 4c, 4d, 5h, and metformin ($p<0.001$), 4e ($p<0.01$), and 5j ($p<0.05$) considerably reduced these elevated levels (Graph 3A and Table 2).

Effect on serum HDL-c level

When compared to the normal control group, diabetes induction resulted in a substantial ($p<0.001$) reduction in blood HDL cholesterol levels from 41±1.4 to 20±1.1 mg/dl. Treatment with compounds 4c, 4d, 5h, and metformin ($p<0.001$), 4e ($p<0.05$), caused significant increase in serum HDL-c levels. However, treatment with compound 5j have not shown any significant change in HDL-c levels (Graph 3B and Table 2).

Effect on serum LDL-c level

Normal control control group serum LDL-c levels was 31±1.6mg/dl, whereas diabetes control group serum LDL-c levels was considerably ($p<0.001$) higher at 102±1.6mg/dl. Treatment with the compounds 4c, 4d, 5h, and metformin ($p<0.001$), as well as 4e ($p<0.05$), substantially reduced the elevated blood LDL-c level. However, as compared to diabetes control, there were no significant differences in the 5j group. (Graph 3C and Table 2).

Effect on serum VLDL-c level

When compared to the normal control group, diabetes

induction produced a substantial ($p<0.001$) rise in serum VLDL-c levels from 20±1.2mg/dl to 40±1.2mg/dl. Treatment with compounds 4d and metformin ($p<0.001$), as well as 4c ($p<0.05$), effectively reduced the elevated serum VLDL-c level. When compared to the diabetic control group, therapy with 4e, 5h, and 5j did not reveal any significant change in VLDL-c levels (Graph 3D and Table 2).

Effect on serum TG level

The normal control group had a mean serum triglyceride level of 100±1.4mg/dl, which increased considerably ($p<0.001$) to 189±1.4mg/dl in the diabetes control group. Treatment with the compounds 4c, 4d, 5h, and metformin, 4e, substantially reduced the elevated blood TG level ($p<0.05$). When compared to the diabetic control group, no significant alterations were detected with compound 5j administration (Graph 3E and Table 2).

Graph 3: The effect of compounds on lipid profile A) Serum TC level, B) Serum HDL-c level, C) Serum LDL-c level, D) Serum VLDL-c level, E) Serum TG level

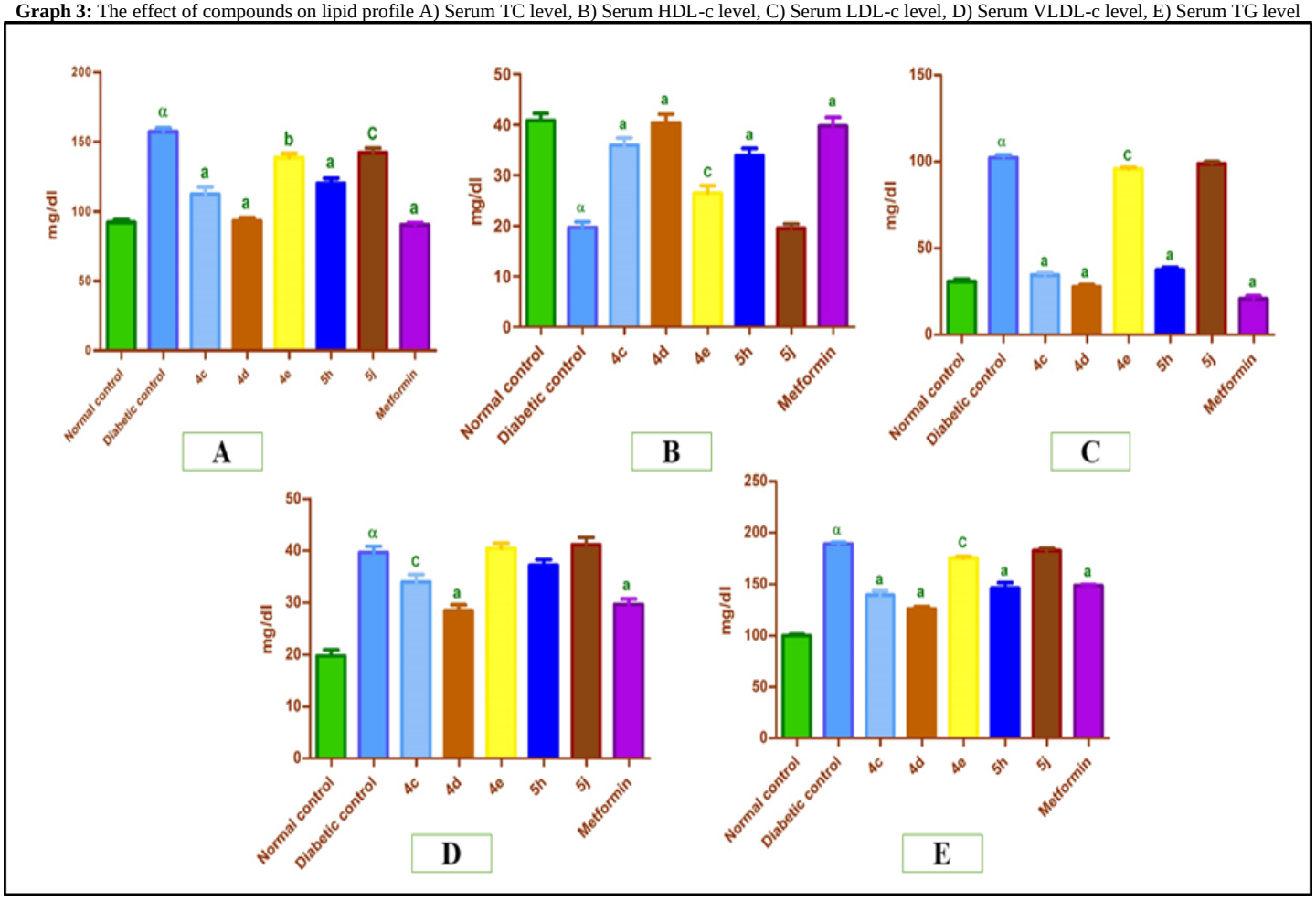


Table 2: The effect of compounds on lipid profile

Parameters	Normal control group	Diabetic control group	4c group	4d group	4e group	5h group	5j group	Metformin group
TC (mg/dl)	92±1.8	157±2.6$^{\alpha}$	112±5.0^{a}	93±2.1^{a}	139±3.0^{b}	120±3.7^{a}	142±3.4^{c}	90±1.6^{a}
HDLc (mg/dl)	41±1.4	20±1.1$^{\alpha}$	36±1.4^{a}	40±1.7^{a}	26±1.5^{c}	34±1.4^{a}	20±0.89	40±1.7^{a}
LDLc (mg/dl)	31±1.6	102±1.6$^{\alpha}$	34±1.5^{a}	28±1.2^{a}	96±0.92^{c}	37±1.7^{a}	99±1.3	21±1.6^{a}
VLDLc (mg/dl)	20±1.2	40±1.2$^{\alpha}$	34±1.4^{c}	28±1.1^{a}	40±0.98	37±1.1	41±1.4	30±1.1^{a}
TG (mg/dl)	100±1.4	189±1.4$^{\alpha}$	139±4.1^{a}	126±2.3^{a}	176±1.5^{c}	146±5.3^{a}	183±2.4	149±0.91^{a}

Data were expressed as mean±SEM, n=6, and analyzed by ANOVA followed by Tukey's post hoc test. $^{\alpha}p<0.001$, when compared to the normal control group; $^{a}p<0.001$, $^{b}p<0.01$, $^{c}p<0.01$, when compared to Diabetic control group.

Effect of compounds on serum SGOT and SGPT

The mean serum SGOT level of normal control group was 41±1.8U/L, which significantly ($p<0.001$) increased to 73±1.8U/L in diabetic control group, the increased levels were significantly decreased in 4c, 4d, 5h, and metformin group ($p<0.001$), 4e group ($p<0.05$), when compared to diabetic control group. However, significant changes were not observed in 5j treated group (Graph 4A and Table 3).

Diabetes induction caused significant increase ($p<0.001$) in SGPT levels from 39±1.5U/L to 90±1.9U/L, when compared to the normal control group. The increased SGPT levels were significantly decreased in 4c, 4d, 5h, and metformin group ($p<0.001$), 4e group ($p<0.01$), when compared to diabetic control group. However, no significant change was observed in 5j treated group (Graph 4B and Table 3).

Graph 4.: The effect of compounds on Serum A) SGOT and B) SGPT

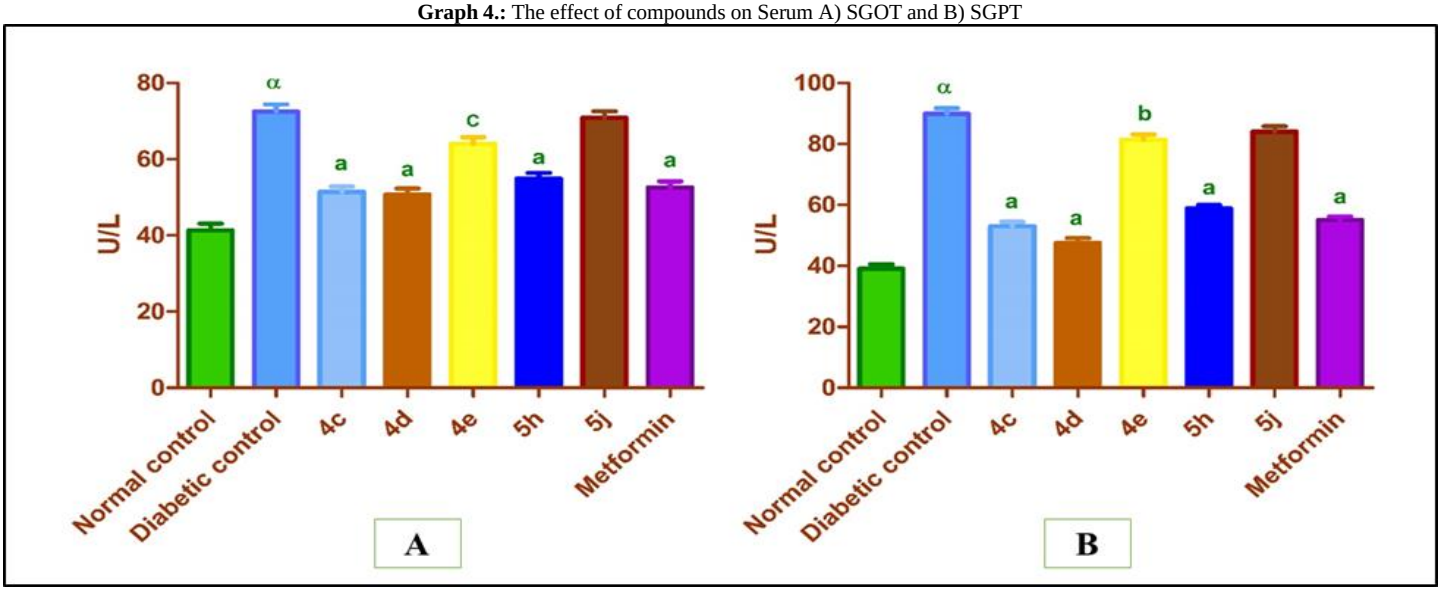


Table 3: The effect of compounds on serum SGOT and SGPT

Parameters	Normal control group	Diabetic control group	4c group	4d group	4e group	5h group	5j group	Metformin group
SGOT (U/L)	41±1.8	73±1.8$^{\alpha}$	51±1.4^{a}	51±1.6^{a}	64±1.8^{c}	55±1.5^{a}	71±1.7	53±1.6^{a}
SGPT (U/L)	39±1.5	90±1.9$^{\alpha}$	53±1.4^{a}	48±1.6^{a}	81±1.7^{b}	59±1.0^{a}	84±1.7	55±1.2^{a}

Data were expressed as mean±SEM, n=6, and analyzed by ANOVA followed by Tukey's post hoc test. $^{\alpha}p<0.001$, when compared to the normal control group; $^{a}p<0.001$, $^{b}p<0.01$, $^{c}p<0.01$, when compared to Diabetic control group.

Effect of compounds on serum antioxidant parameters

Effect on SOD level

The induction of diabetes caused significant decrease ($p<0.001$) in SOD level in diabetes control group from 4.5±0.12U/ml to 1.5±0.056U/ml when compared to normal control group. The decreased SOD level was significantly increased in 4c, 4d, 5h, and metformin ($p<0.001$), 4e ($p<0.05$). However, no significant changes were observed in 5j treated group (Graph 5A and Table 4).

Effect on CAT level

The mean serum CAT level of normal control group was 8.8±0.54kU, which was significantly decreased in diabetic control group to 2.6±0.28kU. The decreased CAT levels were significantly increased in 4c, 4d, 5h and metformin group ($p<0.001$), 4e group ($p<0.05$) when compared to normal control group. However, no significant changes were observed in 5j treated group (Graph 5B and Table 4).

Effect on MDA level

Induction of diabetes caused significant increase ($p<0.001$) in MDA level in diabetic control group from 4.0±0.23µM to 8.9±0.30µM. The increased level of MDA was significantly decreased in 4c, 4d, 5h, and metformin group, and 4e group ($p<0.05$). However, no significant change was observed in 5j group (Graph 5C and Table 4).

Effect on GSH level

The mean serum GSH level of normal control group was 2.1±0.23mg/dl which was significantly decreased in diabetic control group to 0.35±0.059mg/dl. The decreased level of GSH was significantly increased in 4c, 4d, 5h and metformin group ($p<0.001$), and 4e treated group ($p<0.05$). However, no significant change was observed in 5j treated group (Graph 5D and Table 4).

Graph 5: The effect of compounds on serum antioxidant parameters, A) SOD, B) CAT, C) MDA, and D) GSH level

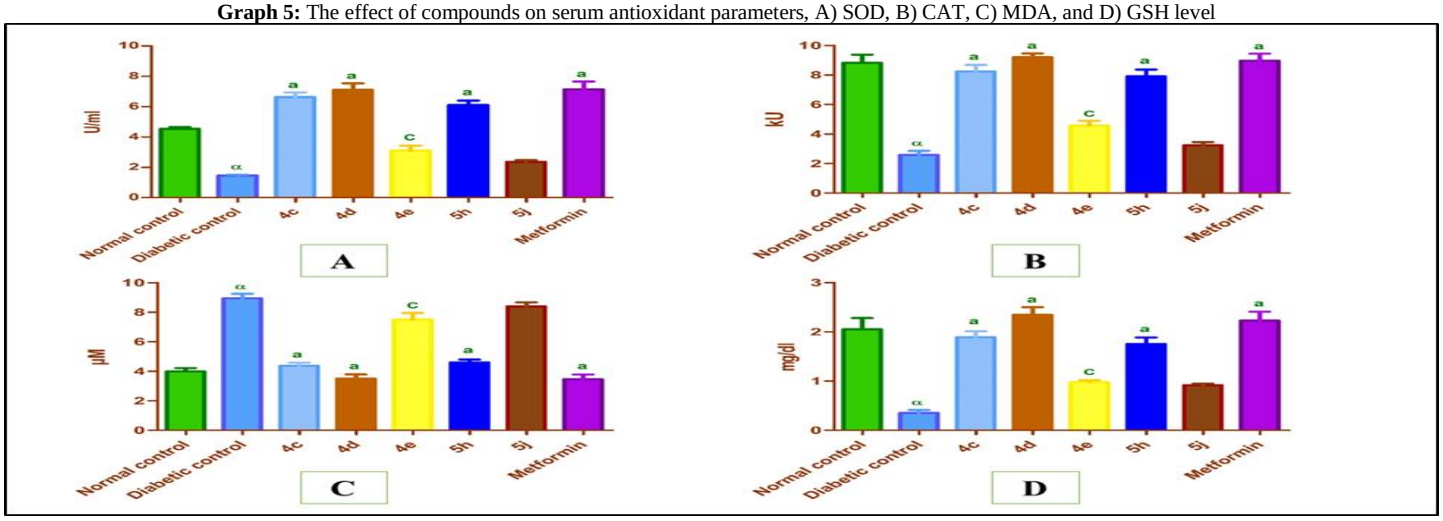


Table 4: The effect of compounds on serum antioxidant parameters

Parameters	Normal control group	Diabetic control group	4c group	4d group	4e group	5h group	5j group	Metformin group
SOD(U/ml)	4.5±0.12	1.5±0.056$^{\alpha}$	6.6±0.31^{a}	7.1±0.44^{a}	3.1±0.33^{c}	6.1±0.29^{a}	2.4±0.12	7.1±0.52^{a}
Catalase(kU)	8.8±0.54	2.6±0.28$^{\alpha}$	8.2±0.44^{a}	9.2±0.25^{a}	4.6±0.32^{c}	7.9±0.46^{a}	3.2±0.22	9.0±0.48^{a}
MDA(μM)	4.0±0.23	8.9±0.30$^{\alpha}$	4.4±0.20^{a}	3.5±0.28^{a}	7.5±0.46^{c}	4.6±0.19^{a}	8.4±0.27	3.5±0.31^{a}
GSH (mg/dl)	2.1±0.23	0.35±0.059$^{\alpha}$	1.9±0.12^{a}	2.3±0.15^{a}	0.98±0.043^{c}	1.8±0.13^{a}	0.92±0.034	2.2±0.18^{a}

Data were expressed as mean±SEM, 6 rats in each group, and analyzed by ANOVA followed by Tukey's post hoc test. $^{\alpha}p<0.001$, when compared to the normal control group; $^{a}p<0.001$, $^{c}p<0.01$, when compared to diabetic control group.

CONCLUSION

In present study, in vivo antidiabetic activity of some benzamide derivatives have been performed in STZ-nicotinamide-induced diabetic model in rats. The antidiabetic potential has been determined by estimating different biochemical parameters such as body weight (g), serum glucose level (mg/dl), serum total cholesterol (TC) (mg/dl), serum HDL-cholesterol levels (HDL-c) (mg/dl), serum LDL-cholesterol level (LDL-c) (mg/dl), serum VLDL-cholesterol level (VLDL-c) (mg/dl), serum triglyceride (TG) level (mg/dl),serum glutamic-oxaloacetic transaminase (SGOT, AST) (U/L), and serum glutamic pyruvic transaminase (SGPT, ALT) (U/L). As antioxidants helps to prevent the generation of free radicals which ultimately prevent biological damage of the cells and tissues. We have determined different antioxidant parameters such as superoxide dismutases (SOD) (U/mL), catalase (CAT) (kU), malondialdehyde (MDA) (μM), and reduced glutathione (GSH) (mg/dl). Amongst all the tested molecules, compound 5h demonstrated significant antidiabetic and antioxidant potential when compared to metformin treated group. Compound 5h possess cloprothiazoles substitution with benzamide nucleus. It was concluded that compound 5h can be treated as lead molecule for the design and development of novel antidiabetic agents.

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CONFLICT OF INTEREST: Declared none

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