OriginalArticle

In Vivo Evaluation Of The Antidiabetic Activity Of 2-Azetidinone Derivatives Induced By Streptozotocin In Rats

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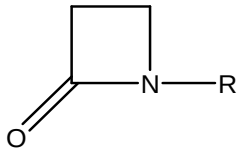
Abstract

This experimental study includes the synthesis of a novel N- Substituted-1, 3, 4-oxadiazol-2-yl)-3-chloro-4-phenylazetidin-2-one by refluxing substituted (styryl)-N-benzylidene-1, 3, 4-oxadiazol-2-amine in C_2H_5OH. The objective of this research was to evaluate the antidiabetic action of 2-azetidinonederivatives in STZ-induced diabetic rats. Azetidinone derivatives (AD1-AD5) were evaluated for antidiabetic action in STZ-induced diabetes in rats (50mg/kg, orally) was administered every day for twenty-one days in STZ induced diabetic rats. The result shows that compounds AD1 and AD5 are having significant antidiabetic activity, furthermore these compounds significantly lower Blood Sugar levels (BSL) and obesity in rats.

Keyword: Anti diabetic activity, 2-azetidinone derivatives, Blood glucose, Body weight, Glucometer, Streptozotocin (STZ)

INTRODUCTION

2-Azetidinone compounds are colourless or clear solid, highly sensitive and low melting point in case of solid and oils preparations.

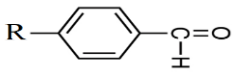


Medicinal chemistry, often commonly known as pharmaceutical chemistry, is a discipline of chemistry concerned with the production of therapeutic medications or biologically active (drugs) for the market [1].Azetidinone (AZD) comprises four rings of β-lactam (cyclic amide). Among organic and medicinal chemistry and it is acknowledging heterocyclic compound. AZD derivatives prepared from $R_2C=NR$which was condensation products of aldehyde and amino compounds. Due to their variety of biochemical implementations, they are generally considered valuable. They have been used in organic compounds as intermediates. Synthesis of heterocyclic compound has constantly drawn many years, chemists' attention was primarily due to their attention and significant biologic properties [15,16].The beta lactam ring, especially they have a special structure and a strong antibacterial structure and action. The typical ring system for 2-AZD (b-lactam) is a number of broad spectrum b-lactam antibiotics have structural features, Penicillins, cephalosporins, including Monobactams, sulbactams, clavulanic acid and tazobactams, they were commonly used as chemotherapeutic agents for the treatment of Infections and microbial diseases of bacteria Until the early 1990s, most of the studies centered on the synthesis of 2-AZD and their antibacterial property studies [12,13,14].Years of increased research have focused on the synthesis and remodeling of the b-lactam ring to develop a variety of molecules in recent years. Pharmacological actions include cholesterol absorption inhibition, antifungal, antidiabetic, anti-inflammatory, and anti-Parkinsonian action, and antifungal, antidiabetic, anti-inflammatory, anti-Human Immune deficiency virus activity. This ring's nitrogen is chemically reactive and also has anti-diabetic properties. [2, 3, 11].

Experimental procedure

Here in this section, we are reporting the chemical routes to synthesize the derivatives of 2-AZD as final product by taking derivatives of Benzaldehyde (see the flow of synthesis in Fig 1) in order to investigate the diabetic activity among the group of rats. Table 1 has listed the derivatives of Benzaldehyde[2,9]and IR, 1H NMR, Mass in m/z and Elementary Analysis were recorded and listed in Table 6. Characterization of data of Compound as listed in Table 7.

Table 1: List of Benzaldehyde derivatives

Benzaldehyde					
Alkyly group (R)	4-bromo (R_1)	2-Bromo-4-hydroxy (R_2)	2-chloro (R_3)	2-hydroxy-5-nitro (R_4)	2-Methoxy (R_5)
Benzaldehyde Derivatives (BD)	4-bromo Benzaldehyde (BD1)	2-Bromo-4-hydroxy Benzaldehyde (BD2)	2-chloro Benzaldehyde (BD3)	2-hydroxy-5-nitro Benzaldehyde (BD4)	2-Methoxy Benzaldehyde (BD5)

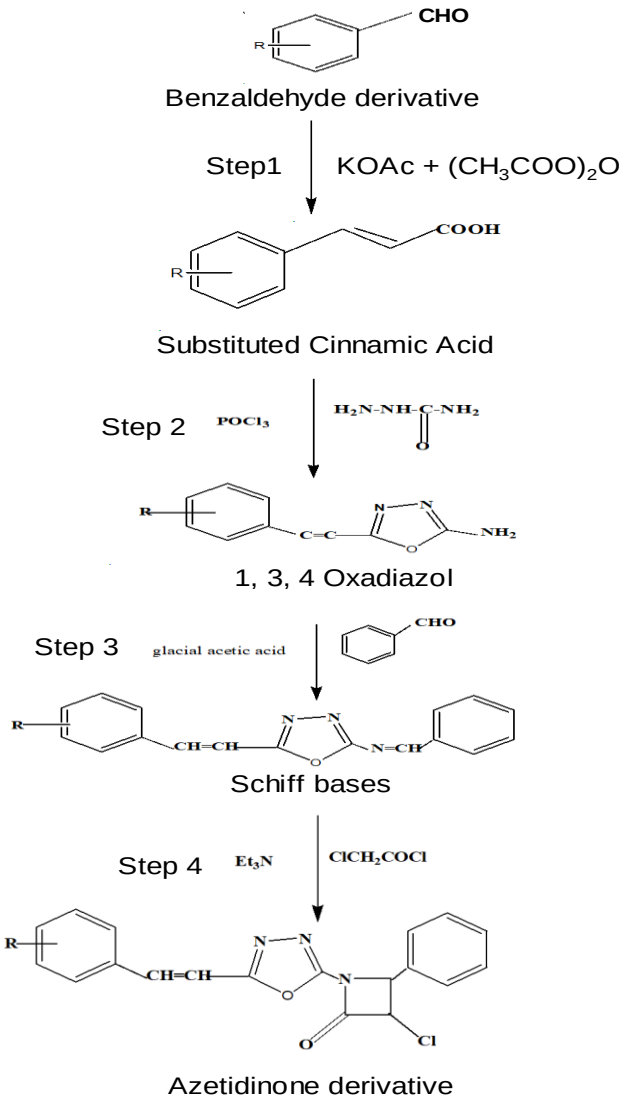
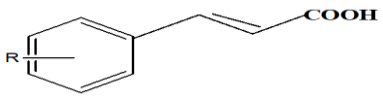


Figure1: Chemical routes to synthesize the derivatives of 2-Azetidinone as final product

Step1: Synthesis of Cinnamic acid derivatives

The five different samples of cinnamic acid derivatives are synthesised for every Benzaldehyde derivative listed in Table 1. A mixture of a Benzaldehyde derivatives-0.2 mole, acetic anhydride (0.29 mol) and fine powdered CH_3CO_2K-0.122 mole was poured in round bottom flask (RBF-1)of 250 ml which is mounted with the arrangement of connected condenser and $CaCl_2$ guard tube on the top of condenser mouth. After mixing the solution, sample was heated at 160^0C for 2-3 hrs by placing it on oil bath. The arrangement of TLC has been employed to observe the reaction end point.In an RBF-2, 100 ml of distilled H_2O was poured into the reaction Solution. Afterwards a saturated aqueous solution of Na_2CO_3 was poured into up to a drop of the liquid extracted from edge of a glass rod turned red litmus a sharp blue (basic pH). The steam distillation process was then continued until the unchanged benzaldehyde removed from the mixture. The final residue obtained then cooled and filtered out. The HCl was used to acidify the filtrate and vigorous stirring is applied until the CO_2 evolved out. Recrystallization of residue was achieved by using the mixture of 3 volume of H_2O and 1volume of 95.6 percent ethanol [17]. The final yield of dry cinnamic acid was obtained. This process was repeated with every Benzaldehyde derivative to achieve the derivates ofcinnamic acid (CAD1-CAD5) as given in Table 2.

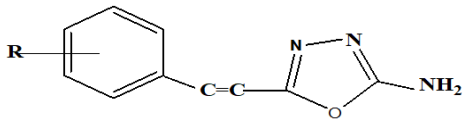
Table 2: List of synthesised Cinnamic acid derivatives from Benzaldehyde derivatives

Cinnamic acid					
Alkyly group (R)	R_1	R_2	R_3	R_4	R_5
Cinnamic acidDerivatives (CAD)	3-(4-Bromophenyl) acrylic acid (CAD1)	3-(2-bromo-4-hydroxyphenyl) acrylic acid) (CAD2)	3-(2-chlorophenyl) acrylic acid (CAD3)	3-(2-hydroxy-5-nitrophenyl) acrylic acid (CAD4)	3-(2-methoxyphenyl) acrylic acid (CAD5)

Step2. General procedure to synthesize 1, 3, 4 Oxadiazol

A mixture of Ethanol-25ml and semicarbazide Hydrochloride-0.2 mole was mixed in the solution of compound which was obtained from step-1. Afterward the mixture was set for refluxed process for 8 hrs in the presence of KOH. Excess amount of substance was concentratedby reducepressure, the solid mass was obtained, and then it transferred into chilled water, filtered and washed distilled water and recrystallized with absolute C_2H_5OH. The final yield obtained as 1, 3, 4 Oxadiazol*(Dubey et al2011)*. This process repeated for all cinnamic acid derivatives (CAD1-CAD2, see table 2) to achieve the derivate of 1, 3, 4 Oxadiazol (OD1-OD5) as given in Table 3.

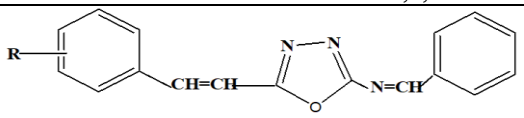
Table 3: List of Oxadiazol derivatives synthesized from Cinnamic acid

1, 3, 4 Oxadiazol					
Alkyly group (R)	R_1	R_2	R_3	R_4	R_5
1, 3, 4 OxadiazolDerivatives (OD)	5-(4-bromostyryl)-1, 3, 4 Oxadizol-2-amine (OD1)	(4-(2-(5-amino-1, 3, 4-oxadiazol-2-yl) vinyl)-3-bromophenol) (OD2)	(5-(2-chlorostyryl)-1, 3, 4-oxadiazol-2-amine) (OD3)	2-(2-(5-amino-1, 3, 4-oxadiazol-2-yl) vinyl)-4-nitrophenol (OD4)	(5-(2-methoxystyryl)-1, 3, 4-oxadiazol-2-amine) (OD5)

Step3. Following procedure for the synthesis of Schiff bases

Aromatic aldehyde derivatives- 0.005 mole and absolute ethanol-40ml was mixed with solution of compound which was obtained from step 2. Afterward dropwise of CH_3COOH were added, and then the solution mixture was set up refluxed process on copper water bath for 5to6 hrs. Distillation procedure was employed to take off all the excess amount of solvent, transferred onto ice cold water. The solid get separated by filtering and washing and then recrystallized from ethanol. The final yield obtained as Schiff bases [10]. This process repeated for all 1, 3, 4 Oxadiazol derivatives (OD1-OD2, see table 3) to achieve the derivatives of Schiff bases (SBD1-SBD5) as listed in Table 4.

Table 4: List of Synthesized Schiff bases derivatives from 1,2,3 oxadiazol

Schiff bases					
Alkyly group (R)	R_1	R_2	R_3	R_4	R_5
Schiffbases-Derivatives (SBD)	5-(4-bromostyryl)-N-benzylidene-1, 3, 4-oxadiazol-2-amine (SBD1)	4-(2-(5-(benzylideneamino)-1, 3, 4-oxadiazol-2-yl) vinyl)-3-bromophenol (SBD2)	5-(2-chlorostyryl)-N-benzylidene-1, 3, 4-oxadiazol-2-amine (SBD3)	2-(2-(5-(benzylideneamino)-1, 3, 4-oxadiazol-2-yl) vinyl)-4-nitrophenol (SBD4)	5-(2-methoxystyryl)-N-benzylidene-1, 3, 4-oxadiazol-2-amine (SBD5)

Step4. Following procedure for the synthesis of AZD derivatives

Triethylamine -0.02 ml was mixed in dioxane-25ml at 5-10ºC (mixture A) and$C_2H_2Cl_2O$-0.01 ml was gradually mixed one by one drop to Schiff's base which was obtained from (step3) (mixture B). The final mixture (mixture A + mixture B) was agitated for 20 hrs and left for three days at 25ºCtemperature. Afterward the reaction completed, the final mixture of the solution filtered, dried, and recrystallized from ethanol [19]. The final yield obtained as AZD derivatives. This process repeated for all Schiff bases (SBD1-SBD5, see table 4) to achieve the derivatives of Azetidinone (AD1-AD5) as listed in Table 5. Spectroscopy data analysis and characterization of compounds are mentioned in table 6 and 7 respectively.

Table 5: List of synthesized 2-AZD derivatives from Schiff bases

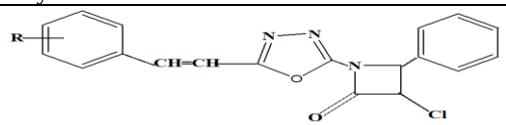
Azetidinone					
Alkyl group (R)	R_1	R_2	R_3	R_4	R_5
Azetidinone derivatives (AD)	(1-(5-(4-bromostyryl)-1, 3, 4-oxadiazol-2-yl)-3-chloro-4-phenylazetidin-2-one (AD1)	1-(5-(2-bromo-4-hydroxystyryl)-1, 3, 4-oxadiazol-2-yl)-3-chloro-4-phenylazetidin-2-one (AD2)	1-(5-(2-chlorostyryl)-1, 3, 4-oxadiazol-2-yl)-3-chloro-4-phenylazetidin-2-one (AD3)	1-(5-(2-hydroxy-5-nitrostyryl)-1, 3, 4-oxadiazol-2-yl)-3-chloro-4-phenylazetidin-2-one (AD4)	1-(5-(2-methoxystyryl)-1, 3, 4-oxadiazol-2-yl)-3-chloro-4-phenylazetidin-2-one (AD5)

Table 6: Spectroscopyanalysis and elementary analysis

Specto-Scopy	Compound	*(Ar-CH)*	*(N-N)*	*(C=N)*	*(C-Br)*	*(C=O) Azetidinonering)*	*(C=C) aliphatic & aromatic*	*(C-O-C)*	*(N=CH)*	*(C-Cl)*	*(C-H)*	*OH*	*(N=O)/(C=O)*
IR KBr cm^{-1}	AD1	3026	1865	1689	765	1776	1634&1639	1167	1756	623&65	2978	-	-
	AD2	3025	1768	1650	745	1715	1623&1698	1145	1567	780	2897	3605	-
	AD3	3070	1765	1689	-	1734	1668&1678	1123	1674	765	2890	-	-
	AD4	2908	1689	1646	-	1730	1689&1725	1240	1765	764	2983	3654	1534 (N=O)
	AD5	3098	1587	1678	-	1778	1623&1545	1123	1765	765	2987	-	1702 (C=O)

^1H NMR (δ) in ppm	Compound	*(1H, s, CH-Cl of Azetidinone ring)*	*(1H, s, Azetidinone proton)*	*(10H, m, Ar-H)*	*(HC=CH)*	*(NH)*	*(1H, s, CONH)*
	AD1	4.2	3.2	7.1 to 7.3	4.8	1.4	8.1
	AD2	3.9	3.1	7.3	4.8	1.3	8.4
	AD3	4.1	3.1	7.2 to 7.5	5.8	1.8	8.3
	AD4	4.2	3.2	7.1 to 7.3	4.8	1.4	8.1
	AD5	4.5	3.2	7.5	3.6	1.2	8.0

Massin m/z	428.45 (AD1)	440 (AD2)	374 (AD3)	378 (AD4)	379 (AD5)

Elementary analysis	Compound	C	H	Br	Cl	N	O
	AD1	52.99	3.04	18.55	8.23	9.76	7.4
	AD2	51.09	2.93	17.89	7.94	9.41	10.75
	AD3	59.08	3.39	-	18.36	10.88	8.28
	AD4	55.28	3.17	-	18.36	10.88	8.28
	AD5	62.91	4.22	-	9.29	11.01	12.57

Table 7: Characterization of compound

Compound	Mol.Formula	Melting Point(^{0}C)	Percentage	Recryt. Solvent	TLC	
					Solvent System	R_f
AD1	$C_{19}H_{13}BrClN_3O_2$	280-285^{0}C	80%	Ethanol	Chloroform: Benzene (7:3)	0.76
AD2	$C_{19}H_{13}BrClN_3O_3$	215-219^{0}C	76%	Ethanol	Chloroform: Benzene (7:3)	0.78
AD3	$C_{19}H_{13}Cl_2N_3O_2$	205-209^{0}C	55%	Ethanol	Chloroform: Benzene (7:3)	0.56
AD4	$C_{19}H_{13}ClN_4O_4$	198-204^{0}C	78%	Ethanol	Chloroform: Benzene (7:3)	0.70
AD5	$C_{20}H_{16}ClN_3O_3$	210-215^{0}C	45%	Ethanol	Chloroform: Benzene (7:3)	0.78

Anti-diabetic activity

Material and method

Wistar albino rats of either sex, weighing 280 to 300 gm, were used as experimental animals by using guidelines of IAEC (Regn.no.711/02/a CPCSEA). Before STZ was used to cause diabetes in rats, they were fasted for 20 hours. Over NAD (-) night fasting animals were given STZ (65mg/kg i.p.) for diabetic mellitus induction [3]. Before the research, the animals were given two weeks to acclimate. They were placed in polypropylene cabinets in a well-circulated room, with each cabinets containing not more than three rats. All laboratory conditions were maintained, including relative humidity-24-28ºC, temperature-60to70 percent, and a 12-hour day-night rotation. They were given a commercial pellet diet and free access to water. The rats' food should consist of a mixture of 71 percent carbohydrate, 18 percent protein, 7 percent fat, and 4 percent salt, as well as enough minerals and vitamins.[6,7].

2.3.5.2Estimation of serum glucose: The solution of streptozotocin was made in citric buffer (pH4.5) immediately before administrations. The diabetes induce by streptozotocin solution was injected intraperitoneally at s dose of the (65

mg/kg) [18]. Diabetes was induced by administration ofstreptozotocin (65kg/mg). Streptozotocin produced diabetes with extra lesion that mimic the pathological status found in human diabetic,BSL after the administration of streptozotocin [8].After 21days of induction, glucose level was estimated and animals having serum glucose level above 200±14.9 mg per dl were sort out for the research. The animals were allocated into eight groups, each with at least six rat repeats. The test drugs at a various concentration were administration to different groups of animals [6].

2.3.5.3Experimental Groups and Protocol:Male Wistar albino rats weighing 140-300gm were used. The animals were fasted for 12hrs before experimentation. In experiment, 30rats were used for performing the activity[20]. The rats were divided into 8 groups
Group1: Rats were normal saline (1mg/kg, i.p) (control)
Group2: STZ (65mg/kg i.p+ NAD) was administered in normal rats (D.Ctrol)
Group3: Glipizide (5mg/kg orally) was administered for 21 days daily in diabetic rats (standard drug)
Group 4: Test drug AD1 compound (50mg/kg, orally) was administered for 21days daily
Group 5: Test drug AD2 compound (50 mg/kg, orally) was administered for 21days daily
Group 6: Test drug AD3 compound (50mg/kg, orally) was administered for 21days daily
Group 7: Test drug AD4 compound (50mg/kg, orally) was administered for 21days daily
Group 8: Test drug AD5 compound (50mg/kg, orally) was administered for 21daysdaily. At the starting of experimental BSL and body weight were measured in overnight fasted animals. Test drugs given orally for Twenty-First days [7]. During experimental period animals were free to receive food and water. BSL was measured on day Zero-day, seventh day, fourteenth day and Twenty-First day with the help of oxidase peroxidase method and blood was taken from tip of the tail on overnight fasted animals. Body weight was also measured on day Zero, Seventh, Fourteenth, and Twenty-First on overnight fasted animals.Physical and biochemical parameters analysis: Physical parameters consist of body weight was estimated on day 0, 7, 14, 21days measured all the parameter in the morning between 9:00am –to10:00 am according to Indian standard time zone. Subsequently collected sample of blood from experimental group after specific intervals of time in heparinised tube. Separated out plasma from the blood by the centrifugation processed to find out the BSL by following standard protocols [11].
Principle of glucose oxidase-peroxidase (GOD-POD) method-
Beta-D glucose+oxgyen+water →Gluconic acid+H_2O_2
Hydrogen Peroxide+ 4-Aminoantipyrine + phenol → red dye + H_2O
The colour is measured at 505nm.

Statistical analysis

Theresult obtained was presented as mean±SEM. Statistical analysis was shown by Graph pad prism employing one-way Analysis of Variance. Statistical significance is expressed by $P < 0.05$*(Sunil et al 2010).*

Result and discussion

Physical parameter- It is shown in table including body weight (in gram) as mean±SEM of wistar albino rats at various day normal control group given carboxyl methyl cellulose (CMC) orally and diabetic group treated rats treated with 2-Azetidione derivatives. The interconnection of body weight with days, groups was not significant (P>0.05). Antidiabetic activity of synthesised compounds at the dose -50 mg per kg oral showing change in body weight at Zero-day, Seventh day, fourteenth day and Twenty-first day. All values express in Mean±SEM: *P≤0.05 Significant, ***P≤0.001 highly Significant from control. Results were analysed by employing one-way Analysis of variance (1-way ANOVA) followed by Dunnett's test. Biochemical parameters-In this study, result of biochemical parameter-such as glucose (mg/dL) after giving 2-Azetidione derivatives to wistar albino rats for 21 days are represented as mean±SEM in Fig 2 and Fig 3. It was found that 2-Azetidione derivatives as (D1, D4 and D9). Antidiabetic activity of synthesised compounds at the dose (50mg/kg, p.o) showing change in BSL(mg/dl) at Zero-day, seventh day, fourteenth day, and twenty-first dayas shown in table 8. For table 8 and table 9, all values express in Mean±SEM: *P≤0.05 less Significant, ** P≤0.01Significant, *** P≤0.001 highly significant from control. Results were analysed by employing 1-way ANOVA followed by Dunnett's test.Antidiabetic activity of synthesised compounds at the dose (50mg/kg, p.o) showing changein BSL(mg/dl) at Zero day, seventh day, fourteenth day, and 21stday (see table 8).

Table 8: Effect of substituted Azetidinone derivatives on BSL in STZ induced rats

Group	Treatment	BSL (mg/dl)			
		Zero day	Seventh day	Fourteenth day	Twenty-First day
1	Control	94.3±1.27	90.8±0.47	92.1±1.3	92.6±1.7
2	Diabetic Control(D.Ctrol)	381.66±2.53	389.33±2.17	391.33±2.66	395±1.96
3	Standard	360±4.00	345.16±4.26	260±3.87	110.16±2.04
4	AD1	379.16±2.91***	245.5±3.20***	221.5±2.20***	106.66±3.46***
5	AD2	386.1±3.1*	366.6±3.7***	260.8±2.5***	195.5±2.08***
6	AD3	379±2.51	370±2.05	365.5±1.5	368±1.9
7	AD4	372±2.26	370.8±2.5	368±3.4	362.5±2.1
8	AD5	374.1±3.84***	356.8±2.90***	254.1±3.49***	139.1±3.51***

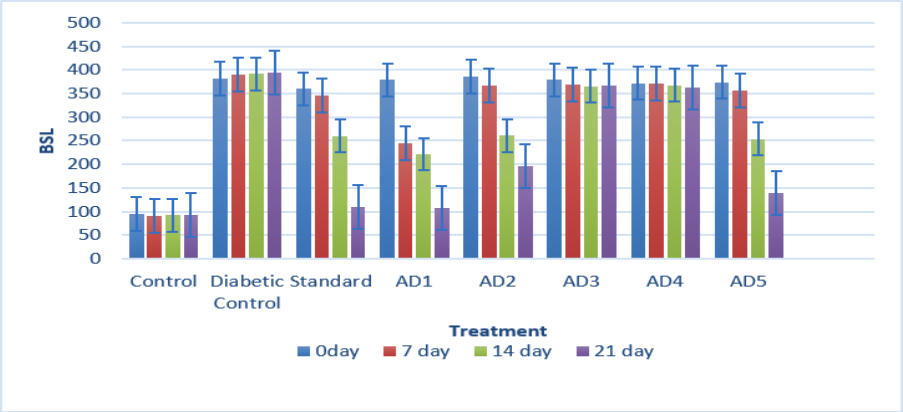


Fig: 2 Effect of substituted Azetidinone derivatives on BSL in STZ induced rats

Antidiabetic activity of synthesised compounds at the dose-50 mg per kg, oral, showing change in body weight at 0th day, seventh day, fourteenth day and Twenty-First day (see table 9).

Table 9: Effect of substituted Azetidinone derivatives on body weight in STZ induced rats

Group	Treatment	Body Weight(g)			
		Zero day	Seventh day	Fourteenth day	Twenty-First day
1	Control	280.6±2.4	285.3±2.1	290.3±3.3	289.0±2.4
2	D.Ctrol	280.8±2.9	249.6±3.5	235.5±2.3	210.8±2.1
3	Standard	275.0±2.9	259±3.9	266.5±2.2	273.8±3.3
4	AD1	274.0±5.6	102.1±5.4	261.0±5.6	253.0±5.3
5	AD2	255.0±3.0***	243.0±2.9***	240.6±2.5***	235.0±3.9***
6	AD3	265.2±0.7*	260.8±0.9***	259.0±0.8***	264.0±0.9***
7	AD4	273.0±0.9***	270.3±0.9***	269.0±0.8***	271.0±0.9***
8	AD5	276.0±0.9	254.1±0.8	241.0±0.6	226.0±0.7

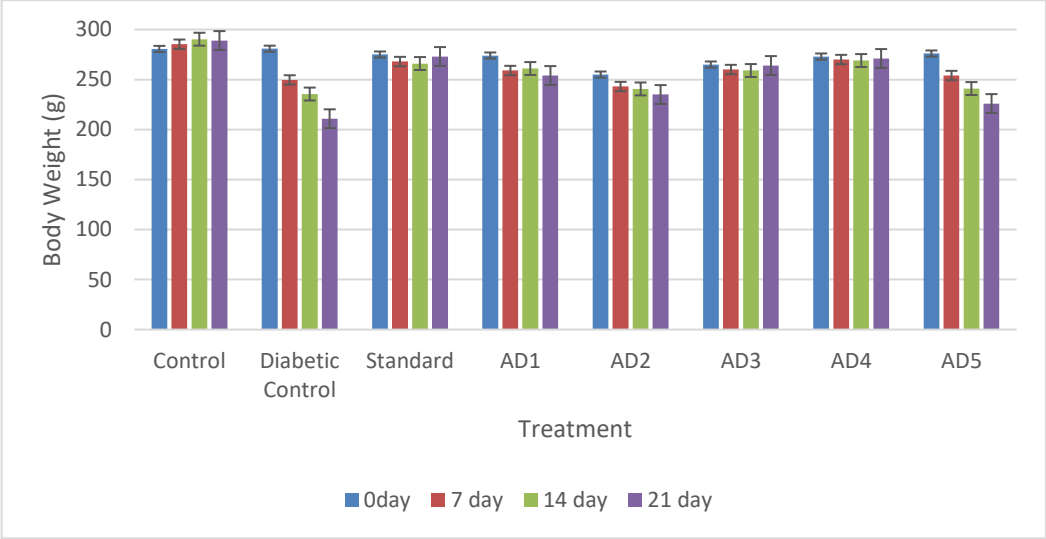


Fig: 3 Effect of substituted Azetidinone derivatives on body weight in STZ induce rats

The β-cell of islets of pancreas suffers with a selective destruction caused by STZ which results in BSLsincrement. The fasting means BSL values before and after treatment for three weeks in normal, D.Ctrol, and diabetic rats treated with test drugs are presents in Table 7.D.Ctrol rats were compared with diabetic rats that were treated with the test drug. In the case of diabetic treated rats with test drug, the fasting mean BSL showed a statistically significant reduces in BSL as estimate the D.Ctrol rats after one week during the experimental period. The fasting mean BSL of diabetic rats treated with Glipizide showed a reduction in BSL as compared with D.Ctro, (CMC) rats. The Compounds AD1 and AD5 were effective in the BSL in diabetic rats. The Compound AD2 was mild effective in the blood level in diabetic rats.Weight loss is a symptom of diabetes, and it was seen in this study. STZ treatment resulted in a significant reduction in body weight in rats.D.Ctrol rats showed a lower body weight than non-D.Ctrol rats. On the twenty-first day, the body weight of the normal control rat receiving Carboxyl methylcellulose(CMC) shows a considerable decline. A dose-dependent body weight improvementhas been observed from day 0 in diabetic rats treated with AD3 and AD4 Compounds.

Conclusion

Experimental results show that the synthesized AD1 and AD5 strongly reduces the BSL by 272.5 mg/dL and 235.0 mg/dL respectively among the rats in the study, whereas the compound AD2 shows mild effect and reduces the glucose level by 190.6 235.0 mg/dL. It can be also clearly depicted that the AD3 and AD4 results reverse impact with increasing the glucose level and reducing the body weight among the rats under the observation. Therefore, the benzaldehyde derivatives named as 2- chloro benzaldehyde (BD3) and 2- hydroxy 5- Nitro benzaldehyde (BD4) does not shows the effective substitution in this study.

Conflict of interest

No conflicts of interest among the authors in this research work.

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