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BIOLOGICAL EVALUATION OF GLYCOGEN SYNTHASE KINASE-3 B INHIBITORS AS ANTIDIABETIC AGENT

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Abstract:
A series of phenylmethylenehydantoin and phenylmethylenerhodanine derivatives (Der 1 to Der 8) were synthesized. These newly synthesized derivatives have been characterized by elemental analysis molecular weight measurements as well as spectral (IR, 1H NMR 13CNMR) studies. All the compounds show significant increase in liver glycogen level at 25 mg/kg dose levels, in- vivo & these compounds were also screened for anti diabetic activity on albino rats. Most of these compounds have shown significant antidiabetic activity at 25 mg/kg dose levels.

Keywords: *Phenylmethylenehydantoin; Phenylmethylenerhodanine; Antidiabetic; GSK-3β.*

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1. Introduction

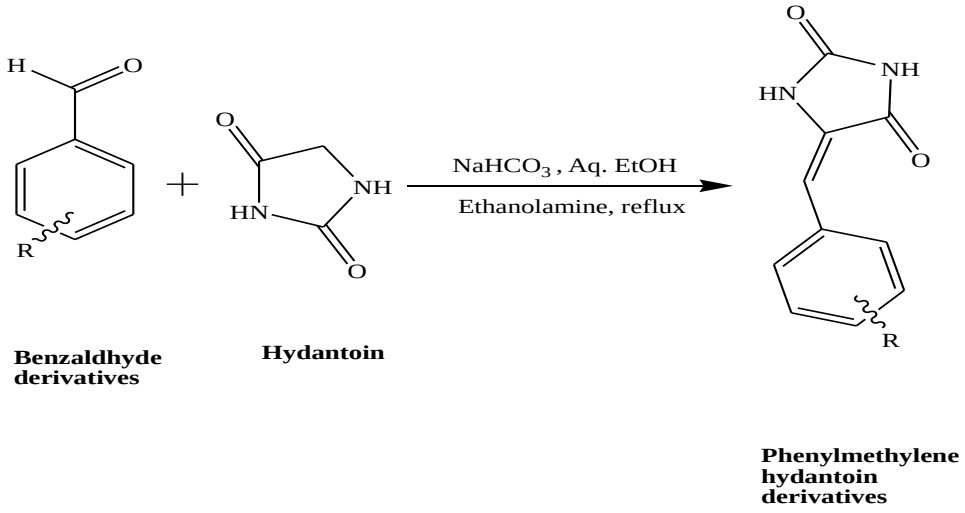


Figure 1: Graphical Abstract

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. GSK3 was discovered over 20 years ago as one of several protein kinases that phosphorylated and inactivated glycogen synthase, the final enzyme in glycogen biosynthesis. Three isoforms of GSK-3 have been identified in mammalian cells, GSK-3α, GSK-3β, and GSK 3β2 (a splicing variant of GSK-3β). The β isoforms show a substantial deviation in protein sequence, mostly outside the kinase core (308 residues), but the core has 97% sequence similarity and overall 91% identity. Glycogen synthase kinase (GSK-3β) is a serine/threonine kinase that phosphorylates glycogen synthase and inhibits its activity. Thus, inhibition of GSK-3β is expected to activate glycogen synthase and promote glucose uptake into muscle in that way it decreases the blood glucose level.[1]

This interest has been heightened by the report that the level and activity of GSK-3β is moderately elevated in diabetic and obese strains of mice. Investigators at GlaxoSmithKline have recently developed a class of maleimides that are potent and relatively selective inhibitors of GSK-3β. In liver cells, these compounds mimic insulin signaling, as expected by promoting the dephosphorylation and activation of glycogen synthase, thereby facilitating the conversion of extracellular glucose into glycogen. However, interestingly, they also mimic a further action of insulin, namely its ability to repress the expression of the genes encoding glucose-6phosphatase and phosphoenol pyruvate carboxykinase, the enzymes that control hepatic gluconeogenesis. These recent observations are exciting, since they imply that GSK3 inhibitors may suppress hepatic glucose output, as well as aiding glucose disposal by the tissues. Such drugs may therefore have greater therapeutic potential for the treatment of type II diabetes than recognized previously 2-5.

Glycogen synthase kinase-3β (GSK-3β) is a unique multifunctional serine/threonine kinase that is inactivated by phosphorylation in response to insulin binding; PKB/AKT phosphorylates GSK-3β on serine9, which prevents the enzyme from phosphorylating glycogen synthase. Unphosphorylated glycogen synthase is active & able to synthesize glycogen. Tyrosine phosphorylation (pY) of IRS-1 is a positive trigger of insulin action, which initiates numerous signaling components. Yet its serine/threonine phosphorylation (pS) results in the opposite effect, presumably by direct interaction of IRS-1 with the insulin receptor. These studies implicated serine/threonine protein kinases as important regulators in insulin resistance. Phosphorylation of IRS-1 on multiple serine residues by GSK-3 impaired insulin receptor tyrosine kinase activity and insulin action in intact cells. This notion fits well with the fact that GSK-3 is constitutively active and phosphorylates IRS-1 in the absence of stimulus. Thus, GSK-3 serves as a 'gatekeeper' to limit activation of insulin receptor signaling. In the absence of insulin, GSK-3 maintains the phosphorylation state of the multiple serine residues on IRS-1, thereby limiting insulin receptor signaling. In the presence of insulin, GSK-3 is inhibited, and tyrosine phosphorylation of IRS-1 mediates the downstream insulin signaling pathway. Thus it is clear that GSK-3 inhibits insulin receptor coupled protein IRS-1, which in turn inhibits glycogen synthesis and glucose uptake.[2-5]

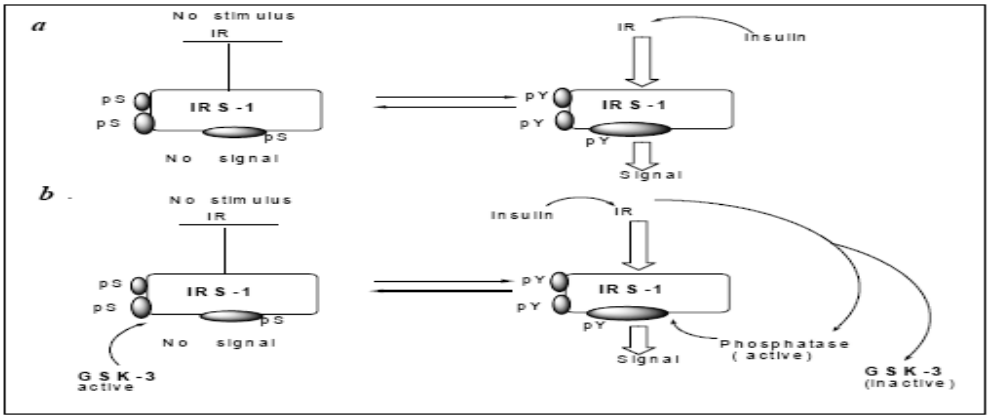


Figure 2: Effect of GSK-3 on Insulin Signaling

Phenylmethylene hydantoins (PMHs) forms strong interactions with the hinge region of GSK-3β; carbonyl oxygen at position 2 form a H-bonding with backbone nitrogen of Val135 and the NH at position 3 to the carbonyl oxygen of Asp133. The hydantoin ring was sandwiched between Ala83, on top, and Leu188, on the bottom. The aromatic ring is rotated out of plane from the hydantoin plane, allowing extensive interactions with the nucleotide-binding loop. Furthermore, the substituted benzylidene ring system builds an H-bonding interaction with the guanidine moiety of Arg141. Targeting Arg141 is important to improve the activity in the process of designing new derivatives because it is considered the selectivity residue for GSK-3β.[2]

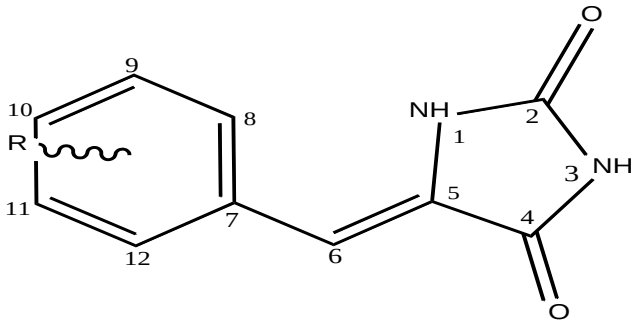


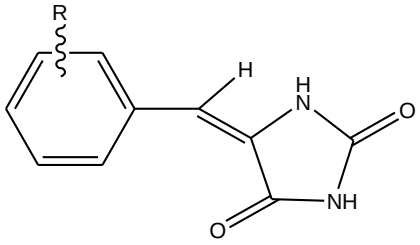
Figure 3: Phenylmethylenehydantoin

Design of potent and selective GSK-3β inhibitors should consider the following important hot spots[2-5]-

- H-bonding interaction with the hinge region of Asp133 and Val135.
- Targeting Arg141 and Gln185 amino acids.
- Filling the Val70, Lys85 and Cys99 hydrophobic pocket. For example, keeping the hydantoin ring and chemical moiety at benzylidene ring system can afford potent and selective GSK-3β inhibitor.

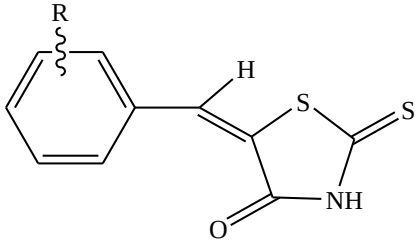
The wide chemical diversity of possible inhibitors and the existence of multiple sites for potential inhibition encourage researcher to pursue the development of GSK-3β inhibitors as potential drugs. Therefore it is worthwhile to develop bioisoesteric substituted GSK-3β inhibitors as antidiabetic agents. The proposed work is intended for the design and synthesis of some

glycogen synthase kinase inhibitors. Such attempt is likely to help in the management of diabetes with minimum side effects.



(Der 01-Der 05)

Figure 4: Hydantoin Derivatives



(Der 06-Der 08)

Figure 5: Rhodanine Derivatives

2. Materials and Methods

All chemicals used in the synthesis are of synthetic grade and they were procured from Loba, Highmedia and E. Merck. The melting points were determined in open capillaries and are uncorrected. IR spectra (FTIR in cm^{-1}) were recorded on ABB FTLA 2000 series, ^{1}H NMR were recorded on Brucker 200 MHz NMR spectrophotometer using DMSO as solvent. The mass spectra were recorded on shimadzu LCMS 2010 EB. Thin layer chromatographic method was used for monitoring of the reaction progress and product formation. The purification of compounds was carried out through column chromatography.

2.1. Synthesis of Drugs

Two synthetic schemes were used for synthesizing the proposed compounds viz. scheme A & B.

Scheme A:

Synthesis of phenylmethylenehydantoin derivatives [Der 01- Der 05]:

Hydantoin (9.9 mM) was dissolved in 10 mL water at 70°C on oil bath with continuous stirring. After complete dissolution the pH was adjusted to 7.0 using saturated sodium bicarbonate solution. The temperature was then raised to 90°C after the addition of 0.9 mL ethanolamine. Equimolar quantity of the different benzaldehyde derivatives solution in 4 mL ethyl alcohol was then added drop wise with continuous stirring.The reaction was kept under reflux for approximately 8h. The reaction was monitored by TLC. After complete depletion of the starting aldehyde, the mixture was cooled and the precipitate was filtered and washed with ethanol/water (1:5). Compound was purified through column chromatography.

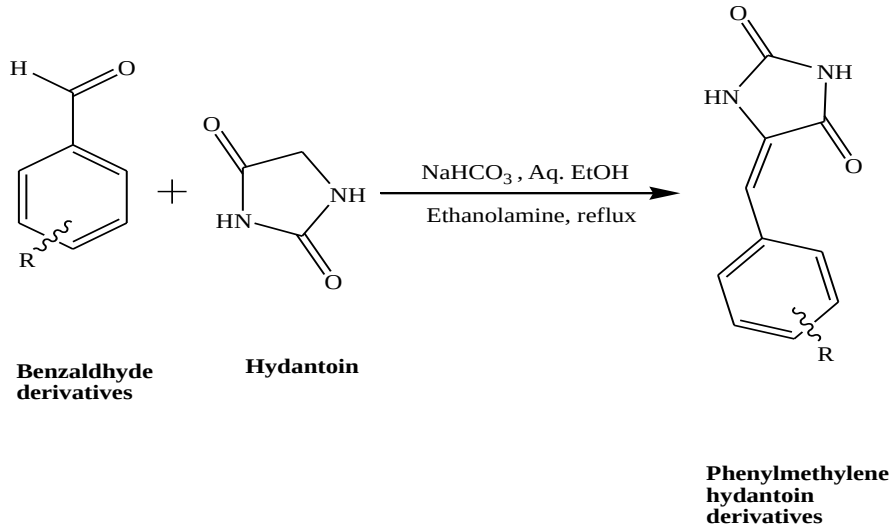


Figure 6: Synthetic schemes for Hydantoin Derivatives (Der 01-Der 05)

Scheme B:

Synthesis of Phenylmethylenerhodanine Derivatives [Der 06-Der 08]:

Rhodanine (7.4 mM) was dissolved in 10 mL water at 70°C on oil bath with continuous stirring. After complete dissolution the pH was adjusted to 7.0 using saturated sodium bicarbonate solution. The temperature was then raised to 90°C after the addition of 0.9 mL ethanolamine. Equimolar quantity of the different benzaldehyde derivatives solution in 5 mL ethyl alcohol was then added drop wise with continuous stirring. The reaction was kept under reflux for approximately 8h. The reaction was monitored by TLC. After complete depletion of the starting aldehyde, the mixture was cooled and the precipitate was filtered and washed with ethanol/water (1:5). Compound was purified through column chromatography.

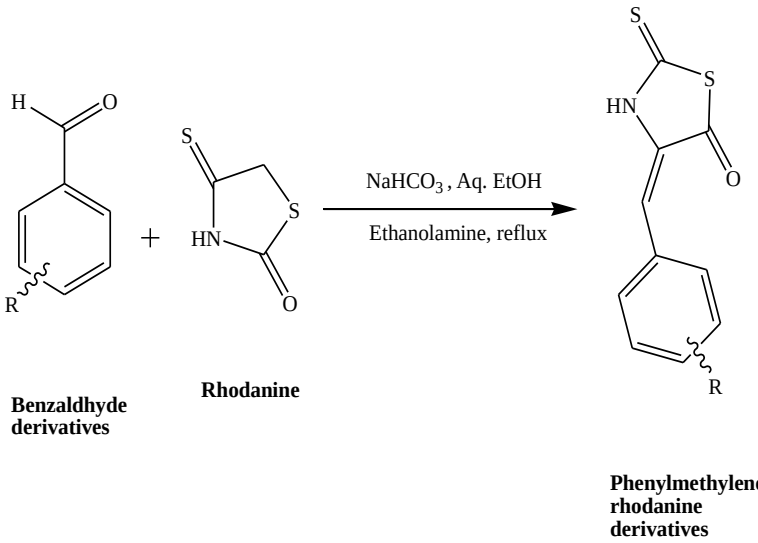


Figure 7: Synthesis of phenylmethylenerhodanine derivatives [Der 06-Der 08]:

Table 1: Synthetic, and physical data for (Der 01-Der 05) and of [Der 06-Der 08]:

Sr. No.	Compound Code	Substitution on Benzene (R)	IUPAC Name	M.Wt.	% Yield	M.P. (°C)
1	($C_{11}H_{10}N_2O_3$)	4-methoxy	5-(4-(Methoxy)benzylidene) hydantoin	218	65.59%	254°C
2	($C_{12}H_{13}N_3O_2$)	4-dimethylamino	5-(4-(dimethyl amino)benzylidene) hydantoin	231	63.87%	262°C
3	($C_{10}H_7N_3O_4$)	4-nitro	5-(4-(nitro)benzylidene) hydantoin	233	68%	261°C
4	($C_{13}H_{14}N_2O_5$)	3,4,5-trimethoxy	5-(3,4,5-(trimethoxy)benzylidene)hydantoin	278	60.43%	263°C
5	($C_{11}H_{10}N_2O_4$)	(3-methoxy,4-hydroxy)	5-(3-methoxy,4-hydroxy)benzylidene) hydantoin	234	62.82%	256°C
6	($C_{10}H_6ClNOS_2$)	4-chloro	5-(4-(chloro)benzylidene)rhodanine	254	69%	220°C
7	($C_{11}H_9NO_2S_2$)	4-methoxy	5-(4-(Methoxy)benzylidene) rhodanine	251	70.56%	246°C
8	($C_{10}H_6N_2O_3S_2$	4-nitro	5-(4-(nitro)benzylidene) rhodanine	265	78%	238°C

Derivatives (Abbreviation Dr Means = Compounds 1 to 8)

2.2. Spectral Data Analysis

The analytical data of synthesized compounds are as follows:

Der 01 ($C_{11}H_{10}N_2O_3$): Practical yield and M.P. of the compound was found to be 65.59% and 252-254°C respectively. The λ_{max} of the compound was determined in methanol and it was found to be 332.6 nm. Der 01 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.87 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1751 (C=O ketone), 1652 (C=C alkene), 1599 (C=C benzene), 1097 (C-O ether).

Der 02 ($C_{12}H_{13}N_3O_2$): Practical yield and M.P. of the compound was found to be 63.87% and 260-262°C respectively.

The λ_{max} of the compound was determined in methanol and it was found to be 385 nm. Der 02 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.78 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1738 (C=O ketone), 1675 (C=C alkene), 1594 (C=C benzene).

Der 03 ($C_{10}H_7N_3O_4$): Practical yield and M.P. of the compound was found to be 68% and 258-261°C respectively.

The λ_{max} of the compound was determined in methanol and it was found to be 350 nm. Der 03 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.94 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1730 (C=O ketone), 1668 (C=C alkene), 1521 (C=C benzene), 1340 (NO_2 nitro).

Der 04 ($C_{13}H_{14}N_2O_5$): Practical yield and M.P. of the compound was found to be 60.43% and 258-263°C respectively. The λ_{max} of the compound was determined in methanol and it was found to be 331 nm. Der 04 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.86 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1763 (C=O ketone), 1653 (C=C alkene), 1590 (C=C benzene), 1000 (C-O ether); MS, m/z: 277.1[M-H]$^-$;

^{1}H NMR (DMSO): 6.37 δ (s, 1H, -CH-), 6.84 δ (s, 2H, Ar-H), 3.35-3.83 δ (m, 9H, -OCH_3).

Der 05 ($C_{11}H_{10}N_2O_4$): Practical yield and M.P. of the compound was found to be 62.82% and 253-256°C respectively.

The λ_{max} of the compound was determined in methanol and it was found to be 344.4 nm. Der 05 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.82 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1714 (C=O ketone), 1647 (C=C alkene), 1558 (C=C benzene), 1000 (C-O ether); MS, m/z: 233.1[M-H]$^-$;

^{1}H NMR (DMSO): 6.35 δ (s, 1H, -CH-), 6.78-7.27 δ (m, 2H, Ar-H), 3.84 δ (m, 9H, -OCH_3), 4.68 (s, 1H, -OH).

Der 06 ($C_{10}H_6ClNOS_2$): Practical yield and M.P. of the compound was found to be 69% and 217-220°C respectively.

The λ_{max} of the compound was determined in methanol and it was found to be 334.5 nm. Der 06 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.70 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1668 (C=O ketone), 1617 (C=C alkene), 1583 (C=C benzene), 1257 (C=S thiocarbonyl), 823 (C-Cl alkyl halide).

Der 07 ($C_{11}H_9NO_2S_2$): Practical yield and M.P. of the compound was found to be 70.56% and 242-246°C respectively.

The λ_{max} of the compound was determined in methanol and it was found to be 352 nm. Der 07 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.54 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1663 (C=O ketone), 1617 (C=C alkene), 1589 (C=C benzene), 1246 (C=S thiocarbonyl), 1172 (C-O ether).

Der 08 ($C_{10}H_6N_2O_3S_2$): Practical yield and M.P. of the compound was found to be 78% and 234-238°C respectively.

The λ_{max} of the compound was determined in methanol and it was found to be 357.5 nm. Der 08 is soluble in DMSO, DMF, Ethanol, Acetone and Methanol and shows R_f value 0.62 in chloroform: ethanol (9:1) solvent system.

IR (FTIR) cm^{-1}: 1674 (C=O ketone), 1623 (C=C alkene), 1600 (C=C benzene), 1260 (C=S thiocarbonyl), 1337 (NO_2 nitro).

2.3. Biological Activity

2.3.1. In-Vivo Biological Evaluation

Solution
Alloxan monohydrate (1gm) was dissolved in chilled saline and mixed properly up to 100 mL by saline in cold condition to prevent decomposition.

Method
*Induction of Non- Insulin Dependent DM***:** The acclimatized animals were kept fasting for 24h with water *ad libitm* and Alloxan Monohydrate (120 mg/Kg i.p.) in normal saline was administered. After one hour of alloxan administration the animal's a*d libitm* were given 5% dextrose solution through feeding bottle, for a day, to overcome the early hypoglycemic phase. The blood glucose regulator was monitored after alloxination by withdrawing a drop of blood from the tail vein by tail tipping method. The blood was dropped on the Dextrostrix Reagent Pad. The strip was inserted into microprocessor Digital Blood Glucometer and readings were noted.

*Experimental Design***:** 10 group having 6 rats in each group.

Group 1: Diabetic control (Alloxan induced)
Group 2: Reference standard (Rosiglitazone 4 mg/kg body weight)
Group 3: Der 01 compound (25 mg/kg body weight for acute study)
Group 4: Der 02 compound (25 mg/kg body weight for acute study)
Group 5: Der 03 compound (25 mg/kg body weight for acute study)
Group 6: Der 04 compound (25 mg/kg body weight for acute study)
Group 7: Der 05 compound (25 mg/kg body weight for acute study)
Group 8: Der 06 compound (25 mg/kg body weight for acute study)
Group 9: Der 07 compound (25 mg/kg body weight for acute study)
Group 10: Der 08 compound (25 mg/kg body weight for acute study)

The test compounds were administered orally as acacia suspension (2%). The blood glucose level was monitored at different times 0 h, 1h, 3h, and 6h respectively.

Table 2: Antidiabetic Activities of Synthesized Compounds

Compound	Decrease in Blood Glucose Level Mg/DL		
	[c]1h	[c]3h	[c]6h
Control	4.27±0.61	8.18±1.90	17.29±2.17
[a] Standard	16.54±9.97*	50.24±24.81**	58.42±19.21*
[b] Der 01	41.13±17.13**	64.54±11.72***	69.70±12.23***
[b] Der 02	31.47±14.48**	59.44±5.88***	71.47±4.23***
[b] Der 03	31.23±14.44**	63.38±8.27***	74.53±6.14***
[b] Der 04	35.89±18.34**	54.30±8.21***	67.38±4.13***
[b] Der 05	36.05±17.25**	62.37±13.70***	72.16±4.59***
[b] Der 06	33.92±25.34*	59.65±10.56***	68.89±4.69***
[b] Der 07	28.05±13.22**	60.15±7.42***	69.23±7.11***
[b] Der 08	28.60±13.18**	63.07±8.97***	70.35±6.54***

[a]4 mg/kg body weight dose; [b]25 mg/kg body weight dose; [c] mean ± S.E.M. (n=6); ***P<0.001; **P<0.01; *P<0.05

2.3.2. In-Vivo Glycogen Content Determination Test

(A) Preparation of test solution

The effect of test compound on liver glycogen content of Albino rats was investigated. The test compounds were administered orally as acacia suspension (2%). Dose: 25 mg/kg of body weight was used.

(B) Determination of Liver Glycogen

Six-week old female Albino rats with average weight of 200 g were used for this investigation. The animals were randomized and fed ad libitm with standard food and water except when fasting was needed in the course of the study. All animals were housed in the same conditions and separated randomly to nine groups. Eight groups (three rats/group) used to investigate test compound were administered orally with the 25 mg/kg dose of test compound and one group was kept as control. On the day of the experiment, food and water were removed 6h before the drug administration. The animals were and their livers were immediately removed for glycogen determination. Liver glycogen content was determined quantitatively following a reported procedure. Briefly, livers were removed immediately after the animals sacrificed and were homogenized using a homogenizer with appropriate volume of 5% trichloroaceticacid over 5 min. The homogenate was centrifuged at 3000 rpm for 5 min. The supernatant fluid was taken and filtered using acid-washed filter paper, and the residues were homogenized again with another volume of 5% trichloroaceticacid over 1-3 min to ensure better extraction of glycogen. The glycogen of 1.0 mL of this filtrate was precipitated using ethanol (95%, 5 mL), incubated in water bath at 37-40ºC for 3h, and centrifuged at 3000 rpm for 15 min. The clear liquid is gently decanted from the packed glycogen, and the tubes were allowed to drain in an inverted position for 10 min. The glycogen was dissolved in distilled water (2 mL) and mixed with 10 mL of the anthrone reagent (0.05% anthrone, 1.0% thiourea in 72% H_2SO_4). The mixture was incubated in boiling water over 30 min, and subsequently, the absorbance was spectrophotometric ally

measured at 620 nm by a UV-Vis spectrophotometer. Blank and standard solutions were prepared by adding 10 mL of anthrone reagent to 2 mL of water and to 2 mL of glucose solution containing 0.1 mg of glucose in saturated benzoic acid, respectively.

The liver glycogen content is estimated using the following formula:

Amount (mg) of glycogen liver tissue
= (DU/DS) × (Volume of Extract (mL)/Weight of Liver Tissue (g)) ×0.09
Where, DU is the absorbance of the unknown sample and DS is the absorbance of the standard.

Table 3: *In-vivo* Data of Increase in Liver Glycogen Content of Test Compounds

S. No.	[b]Compound	[c]Increase in Liver Glycogen Content (mg)
	[b] Control	0
	[b] Der 01	72.80±11.44**
	[b] Der 02	117.76±10.24**
	[b] Der 03	111.01±3.65**
	[b] Der 04	60.64±6.93**
	[b] Der 05	116.03±6.63***
	[b] Der 06	62.39±4.85**
	[b] Der 07	70.26±5.02***
	[b] Der 08	112.01±7.13**

[b]25 mg/kg body weight dose; [c] mean ± S.E.M. (n=3); ***P<0.001; **P<0.01; *P<0.05

3. Results and Discussion

Synthesized hydantoin & rhodanine analogs were screened for their antidiabetic activity by alloxan induced tail tipping method. The study was carried out in ten different groups of rats of either sex. Rosiglitazone (4 mg/kg body weight) was used as a standard drug. Compounds (Der01-Der08) at 25 mg/kg body weight shown significant (P<0.001) decreasing in blood glucose levels. Synthesized compound shows decrease in blood glucose level in the range of 59.44-64.54% after 3h while 67.38-74.53% after 6h. The compounds were also tested for change in hepatic glycogen content. Der 02, Der 03, Der 05 and Der 08 increased hepatic glycogen content 117.76, 111.01, 116.04 and 112.02 mg/gm liver weight respectively while compounds Der 01, Der 04 Der 06 and Der 07 cause increased in hepatic glycogen content in range of 60-72 mg/gm liver weight. Preliminary study revealed that hydantoin analogs are more potent than rhodanine analogs. Nitrobenzylidene derivatives of hydantoin and rhodanine have comparable activity. Primary structure activity relationship revealed that 4-N, N-dimethylamine, 4-Nitro and 4-hydroxy groups favours for the activity while trisubstituted benzylidene analogs having low potency. The plot of antidiabetic & GSK-3β inhibitory activity of test compounds were shown in fig. 8, fig. 9 & fig. 10 respectively. The plot shows significant decrease in blood glucose level by test compounds as compare to control & standard. The bar graph shown the GSK-3β inhibitory activity of test compound by significant increase in hepatic glycogen content by test compounds as compare to control.

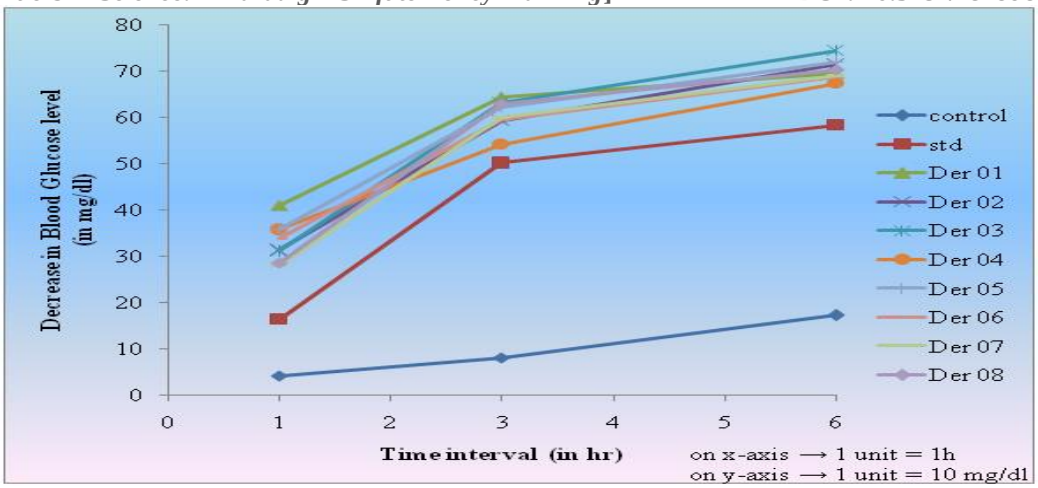


Figure 8: A plot of decrease in blood glucose level v/s time for test compounds

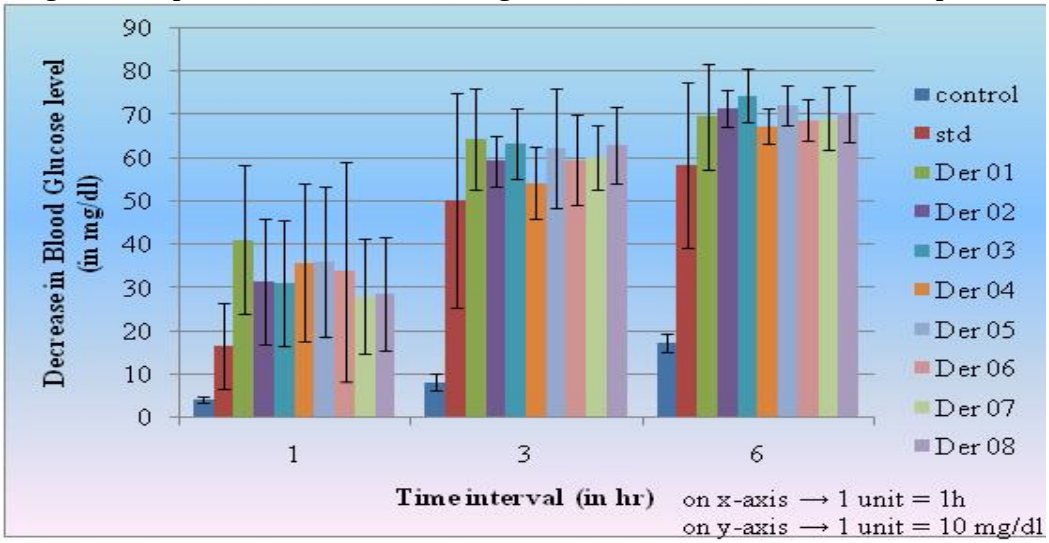


Figure 9: The bar graph of antidiabetic activity of test and standard compounds

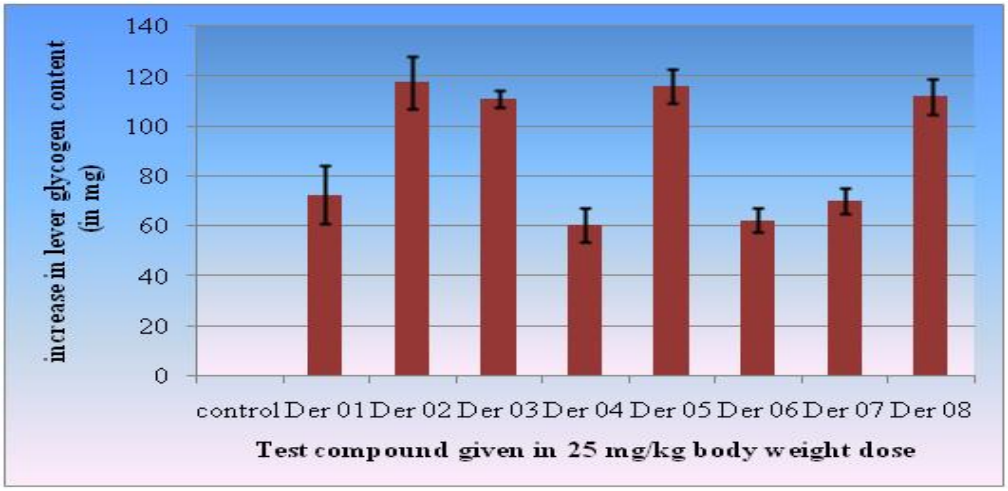


Figure 10: A bar graph of increase in liver glycogen level by test compounds

4. Conclusion

In the present research work, an attempt has been made to synthesize phenylmethylenehydantoin & phenylmethylenerhodanine derivatives are antidiabetic agents.

Synthesized compound shows decrease in blood glucose level in the range of 59.44-64.54% after 3h while 67.38-74.53% after 6h. Study shows significant increase in liver glycogen content ranging from 60.64-117.76 mg per gm liver weight. The hydantoin analogs are more potent than rhodanine analogs. **Nitrobenzylidene derivatives of hydantoin and rhodanine have comparable** activity.

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References

[1] Khanfar, A. M.; Bilal, A. A.; Mudit, M.; Kaddoumi A.; Khalid A. E., Bioorg. Med. Chem., 2009, 17, 6032–6039.
[2] Sivaprakasama, P.; Aihua, X.; Robert, J. D., Bioorg. Med. Chem., 2006, 14, 8210–8218.
[3] Denise, M. F.; David, K., Dev. Biol., 2000, 225, 471–479.
[4] Vats, R. K.; Kumar, V.; Kothari, A.; Mital, A.; Ramachandran, U., Curr. Sc., 2005, 88, 241-249.
[5] Pattan, S. R.; Suresh, C.; Pujar, V. D.; Reddy, V. V. K.; Rasal, V. P.; Koti, B. C., Indian J. Chem., 2005, 44B, 2404-2408.
[6] Sheelagh, F.; Philip, C., Biochem. J., 2001, 359, 1-16.
[7] Laurent, M.; Marc, F.; Paul, G., Trends Pharmacol. Sci., 2004, 25, 471-480.
[8] Li, S.; Ngoc, T.; Flora, T.; Herald, A.; Pter, H.; Gerald, M.; Cho, T., J. Med. Chem., 1998, 41, 2588-2603.
[9] Bastaki, S., Int. J. Diabetes Metabolism, 2005, 13, 111-134.
[10] Ballard, A.M., Clin. Diabetes, 2000.
[11] Gerald, I. S., J. Clin. Invest. 2000, 106, 171-176.
[12] Modi, P., Curr. Drug Discov. Tech., 2007, 4, 39-47.
[13] Clifford, J. B.; Caroline, D., Br. J. Cardiol., 2003, 10,128–136.
[14] Sarabu, R.; Tilley, J., Annu. Rep. Med. Chem., 2005, 40, 167-178.
[15] Hendrik, S.; Rainer, M.; Marcus, G.; Yoan, F.; Olivier, L.; Thomas, L.; Simone, K.; Alexander, L.; Ulrike, B.; Cord, D.; Laurent M.; Matthias, A.; Conrad, K., J. Med. Chem., 2008, 51, 2196–2207.
[16] Ana, M.; Mercedes, A.; Ana, C.; Concepcion, P.; Francisco, J. M., J. Med. Chem., 2002, 45, 1292-1299.

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