IJPSR (2018), Volume 9, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 August, 2017; received in revised form, 10 October, 2017; accepted, 12 November, 2017; published 01 June, 2018

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NOVEL IMIDAZOLIDINE ANALOGUES AS POTENT ANTIDIABETIC AGENT

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Keywords:

Hydantoin, Knoevenagel condensation, Antidiabetic

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ABSTRACT: Imidazolidine are five-member heterocyclic compounds having two nitrogens in the ring. There are two carbonyls in the ring, one of them between the two nitrogens. The five positions of the ring are numbered and, as such, there are four points of functionality, one at the 1 position, one at the 3 position and two at the 5 position in their ring structure respectively and thus exhibiting potent as well as wide range of pharmacological activities. A series of, phenylene methylene hydantoin were synthesized. Benzaldehyde derivatives reacted with imidazolidine to yield the respective derivatives. This reaction follows the Knoevenagel condensation reaction mechanism by which ethanolamine abstract a proton from heterocyclic ring and a carbanion ion is generated. The structure of synthesize compounds were supported by IR, NMR and mass spectral data. The synthesized compounds were screened for their *in vitro* antidiabetic activity by α-amylase, α-glucosidase inhibition, glucose diffusion inhibitory test and the potential compounds tested for *in vivo* activity by blood glucose changes in type 2 diabetic rats.

INTRODUCTION: Diabetes mellitus is a group of metabolic diseases in which there is elevated blood sugar levels over a prolonged period of time [1]. Diabetes Mellitus is responsible for 25% of global deaths (WHO, 2015) Type 2 diabetes is caused by a decreased sensitivity of target cells to insulin accompanying serious, potentially life-threatening complications like atherosclerosis, retinopathy, neuropathy, foot problems, nephropathy [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(6).2287-92

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(6).2287-92

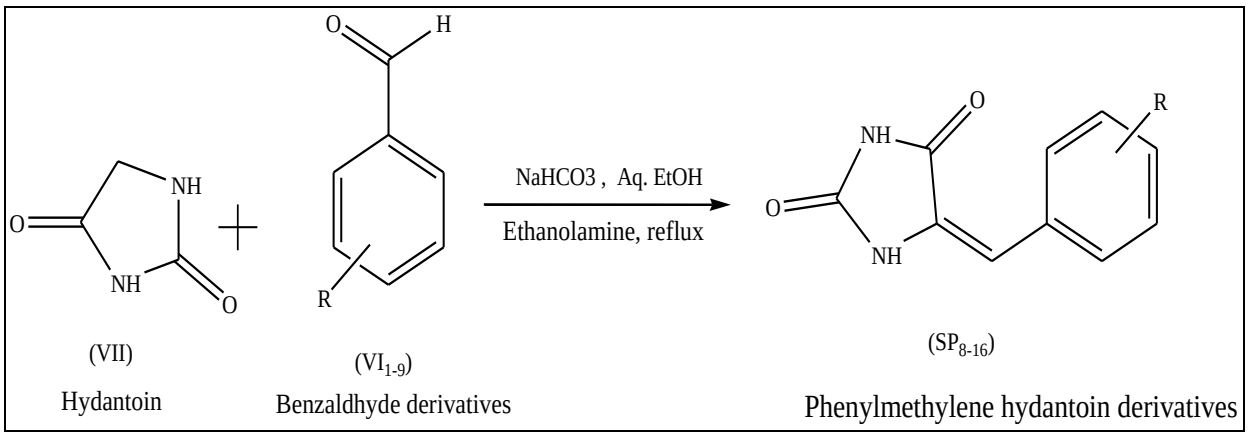
Glycogen synthase kinase-3β (GSK-3β) has recently emerged, in the field of medicinal chemistry, as one of the most attractive therapeutic targets for Type II diabetes. The full potential of GSK-3β inhibitors is yet to be realized and the number of drug candidates being developed by both academic centers and pharmaceutical companies has increased exponentially in the last few years [3 - 6].

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 serine [9], which prevents the enzyme from phosphorylating glycogen synthase. Unphospho-rylated glycogen synthase is active and able to synthesize glycogen [5, 6].

Unique activities revealed that GSK-3β a competitive target for the treatment of various human diseases such as type - 2 diabetes, [7] Alzheimer's disease (AD), [8] CNS disorders like manic depressive disorder and neurodegenerative diseases, [9] and chronic inflammatory disorders [10]. The search for GSK-3β inhibitors became a very active research trend for academic centers and pharmaceutical industry. Several structurally diverse compounds were reported to inhibit GSK-3β.

MATERIALS AND METHODS: All melting points (mp) measured in open capillary tube were uncorrected. FT-IR spectra were recorded on Perkin-Elmer spectrum Rx-I spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker II-400 NMR spectrophotometer (^{1}H, 400 MHz and ^{13}C, 100 MHz), using TMS as an internal standard in DMSO and $CDCl_3$. Chemical shifts are reported (δ) relative to TMS. Mass spectra were determined on Hitachi Perkin-Elmer RMU 6D mass spectrometer. Elemental analysis for C, H, and N were determined using the Perkin-Elmer 2400 CHN rapid analyzer. Chemicals were obtained from Merck, HiMedia and Loba chem and used without further purification. Streptozotocin and nicotinamide were procured from Himedia Laboratories, Mumbai, India. The estimation of biochemical parameters was carried out using kits (Primal Healthcare Limited, Lab Diagnostic Division, Mumbai, India). The pancreatic *α*-amylase was purchased from Sigma-Aldrich, USA. All other chemicals used in this study were analytical grade and purchased from Himedia Laboratories, Mumbai, India.

General Synthetic Procedure: Phenyl methylene hydantoin derivatives (SP_{1-9}) were prepared by reaction of benzaldehyde derivatives (VII) with hydantoin (VI) in the presence of ethanolamine. For the purpose, hydantoin (VI) (9.9 mM) was dissolved in 10 mL water at 70 °C with continuous stirring as shown in synthetic scheme. 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 substituted benzaldehyde (VII) in 4 mL ethyl alcohol was then added drop wise with continuous stirring. The reaction was kept under reflux for 8 - 10 hrs. The completion of reaction was monitored by TLC. After complete depletion of the substituted benzaldehyde (VII), the mixture was cooled and the precipitate was filtered and washed with ethanol / water (1:5).



SCHEME 1: SYNTHETIC SCHEME

Compound no.	R
SP_1	3,4,5-tri (OCH_3)
SP_2	3-OCH_3, 4-OH
SP_3	4-OH
SP_4	2-Cl
SP_5	4-Cl
SP_6	4-NO_2
SP_7	4-OH
SP_8	3-Cl
SP_9	3,4,5-tri (CH_3)

Characterisation of Synthesised Compounds:

5-(3, 4, 5-Trimethoxy benzylidene) hydantoin (SP_1): Yield 63.50% as a solid; mp 270 – 271 °C; UV (EtOH) λ_{max} (log ε) 272.5; IR (KBr) ν_{max}3328 (C-N str.), 3098 (C-O str.), 1763 (C=O str), (C=C str), 1653, 1590 (C=C str), 1042 (C-O str) cm^{-1}; ^1H NMR (DMSO) δ = 6.37 (s, 1H, ethylene CH), 6.84 (s, 2H, Ar-CH), 3.35 - 3.83 (m, 9H, methoxy CH_3); ^{13}CNMR ($CDCl_3$, 300 MHz): δ = 154.3, 124.9, 162.9, 122.6, 130.1, 102.8, 152.6, 138.2, 151.8, 102.2, 56.1, 55.3, 56.8; MS (EI) m/z: 277.1 (100.0%). Anal. Cacld for $C_{17}H_{10}FNO_3S_2$: C, 56.81; H, 2.80; F, 5.29; N, 3.90; O, 13.36; S, 17.84. Found: C, 56.81; H, 2.80; F, 5.29; N, 3.90; O, 13.36; S, 17.84.

5-(3-Methoxy-4-hydroxy benzylidene) hydantoin (SP_2): Yield 69.72% as a solid; mp 280 – 282 °C; UV(EtOH) λ_{max} (log ε) 306; IR (KBr) ν_{max} 3340 (C-OH str), 3229 (C-N str), 1714 (C=O str), 1647 (C=C str), 1558 (C=C str), 1000 (C-O str) cm^{-1}; ^1H NMR (DMSO) δ = 6.78 - 7.27 (m, 3H, aromatic CH), 6.35 (s, 1H, ethylene CH), 3.84 (s, 3H, methoxy CH_3), 4.68 (s, 1H, hydroxy OH); ^{13}CNMR ($CDCl_3$, 300 MHz): δ = 154.4, 124.7, 163.7, 122.4, 128.8, 112.0, 151.3, 144.9.0, 116.8, 120.1, 56.2; MS (EI) m/z: 234.2 (100.0%). Anal. Cacld. For $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07; O, 28.75. Found: C, 56.05; H, 5.02; N, 10.00; O, 28.70.

5- (4- Hydroxy benzylidene) hydantoin (SP_3): Yield 72.25 % as a solid; mp 239 – 240 °C; UV (EtOH) λ_{max} (log ε) 290.5; IR (KBr) ν_{max} 3383 (C-OH str), 3247 (C-N str), 1758 (C=O str), 1647 (C=C str), 1558 (C=C str), 1257 (C=S str) cm^{-1}; ^1H NMR (DMSO) δ = 6.82 - 7.33 (m, 3H, aromatic CH), 6.37 (s, 1H, ethylene CH), 3.73 (s, 3H, methoxy CH_3), 4.66 (s, 1H, hydroxy OH); ^{13}CNMR ($CDCl_3$, 300 MHz): δ = 153.5, 125.8, 162.8, 124.2, 129.7, 112.2, 152.1, 139.9, 117.3, 121.4, 57.8; MS (EI) m/z: 234.2 (100.0%). Anal. Cacld. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72; O, 23.51. Found: C, 58.80; H, 3.92; N, 13.70; O, 23.48.

5-(2-chloro benzylidene) hydantoin (SP_4): Yield 92.54% as a solid; mp 249 - 250 °C; UV (EtOH) λ_{max} (log ε) 293; IR (KBr) ν_{max} 1730 (C=O str), 1668 (C=C str), 1521 (C=C str), 1340 (NO_2str) cm^{-1}; ^1H NMR (DMSO) δ=9.37 (s, 1H, imide NH), 8.73 (s, 1H, ethylene H), 7.43 - 8.60 (m, 4H, aromatic CH), 5.57 (s, 1H, aromatic NH); ^{13}CNMR ($CDCl_3$, 300 MHz): δ = 124.7, 154.3, 164.8, 121.3, 130.2, 145.9, 120.9, 128.7, 134.3, 127.2; MS (EI) m/z: 233.2 (100.0%). Anal. Cacld. for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02; O, 27.45. Found: C, 51.45; H, 3.00; N, 18.00; O, 27.38.

5-(4-Chloro benzylidene) hydantoin (SP_5): Yield 88.20 % as a solid; mp 291 -2 92 °C; UV (EtOH) λ_{max} (log ε) 317; IR (KBr) ν_{max} 1758 (C=O str), 1647 (C=C str), 1558 (C=C str), 1257 (C=S str), 823 (C-Cl str) cm^{-1}; ^1H NMR (DMSO) δ = 9.23 (s, 1H, imide NH), 7.41-8.65 (m, 4H, aromatic CH), 6.73 (s, 1H, ethylene H), 5.43 (s, 1H, aromatic NH); ^{13}CNMR ($CDCl_3$, 300 MHz): δ = 124.5, 154.1, 163.8, 122.5, 134.1, 128.7, 128.9, 132.7, 127.9, 127.4; MS (EI) m/z: 223.6 (100.0%). Anal. Cacld. for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; Cl, 15.92; N, 12.58; O, 14.37. Found: C, 53.89; H, 3.11; Cl, 15.89; N, 12.48; O, 14.17.

5- (4- Nitro benzylidene) hydantoin (SP_6): Yield 85.20% as a solid; mp 289 – 290 °C; UV (EtOH) λ_{max} (log ε) 282; IR (KBr) ν_{max} 1730 (C=O str), 1668 (C=C str), 1521 (C=C str), 1340 (NO_2str) cm^{-1};^1H NMR (DMSO) δ = 9.17 (s, 1H, imide NH), 8.67 (s, 1H, ethylene H), 7.41 - 8.64 (m, 4H, aromatic CH), 5.67 (s, 1H, aromatic NH); ^{13}CNMR ($CDCl_3$, 300 MHz): δ = 123.6, 154.2, 164.8, 121.3, 130.2, 144.9, 120.5, 128.6, 133.8, 127.7; MS (EI) m/z: 232.7 (100.0%). Anal. Cacld. for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02; O, 27.45. Found: C, 51.45; H, 2.99; N, 17.98; O, 26.45.

5- (4- Hydroxy benzylidene) hydantoin (SP_7): Yield 70.52% as a solid; mp 274 – 275 °C; UV (EtOH) λ_{max} (log ε) 332.6; IR (KBr) ν_{max} 1758 (C=O str), 1647 (C=C str), 1558 (C=C str), 1257 (C=S str) cm^{-1}; ^1H NMR (DMSO) δ = 6.82 - 7.33 (m, 3H, aromatic CH), 6.37 (s, 1H, ethylene CH), 3.73 (s, 3H, methoxy CH_3), 4.66 (s, 1H, hydroxy OH); ^{13}CNMR ($CDCl_3$, 300 MHz): δ = 153.5, 125.8, 162.8, 124.2, 129.7, 112.2, 152.1, 139.9, 117.3, 121.4, 57.8; MS (EI) m/z: 234.2 (100.0%). Anal. Cacld. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72; O, 23.51.Found: C, 58.78; H, 3.795; N, 13.65; O, 23.48.

5- (3- Chloro benzylidene) hydantoin (SP_8): Yield 85.65% as a solid; mp 267 – 268 °C; UV (EtOH) λ_{max} (log ε) 385; IR (KBr) ν_{max} 1758 (C=O str), 1647 (C=C str), 1558 (C=C str), 1257 (C=S

str), 823 (C-Cl str) cm^{-1}; ^1H NMR (DMSO) δ = 9.21 (s, 1H, imide NH), 7.45 - 8.68 (m, 4H, aromatic CH), 6.76 (s, 1H, ethylene H), 5.53 (s, 1H, aromatic NH); $^{13}CNMR$ ($CDCl_3$, 300 MHz): δ = 124.3, 153.9, 163.2, 122.4, 134.2, 128.7, 128.9, 131.2, 127.9, 121.4; MS (EI) m/z: 223.2 (100.0%). Anal. Cacld. for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; Cl, 15.92; N, 12.58; O, 14.37. Found: C, 53.85; H, 3.08; Cl, 15.81; N, 12.38; O, 14.17.

5- (3, 4, 5-Trimethyl benzylidene) hydantoin (SP_9): Yield 63.50% as a solid; mp 270 – 272 °C; UV (EtOH) λ_{max}(log ε) 350; IR (KBr) ν_{max} 1738 (C=O str), 1675 (C=C str), 1594 (C=C str) cm^{-1}; ^1H NMR (DMSO) δ = 9.10 (s, 1H, imide NH), 7.45 (d, 2H, aromatic CH), 6.56 (s, 1H, ethylene H), 4.21 (s, 1H, Ar NH), 2.53 (m, 9H, CH_3); $^{13}CNMR$ ($CDCl_3$, 300 MHz): δ = 124.3, 154.9, 163.1, 122.4, 133.2, 123.7, 136.9, 135.2, 137.9, 121.9, 23.9, 18.5, 13.2; MS (EI) m/z: 233.1 (100.0%). Anal. Cacld. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17; O, 13.90. Found: C, 67.78; H, 6.09; N, 12.09; O, 13.87.

Biological Evaluation:

Inhibition Assay for α-Amylase Activity (DNSA): [10 – 14] A concentration of 5 mg/mL of synthesized compounds was prepared by dissolving in double distilled water and further diluted to produce different concentrations. A total of 500 µL of prepared compound solution and 500 µL of 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M sodium chloride) containing α-amylase solution (0.5 mg/mL) were incubated for 10 min at 25°C. After pre-incubation, 500 µL of 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M sodium chloride) was added to each tube at 5s intervals. This reaction mixture was then incubated for 10 minutes at 25 °C. DNSA colour reagent 1 mL was added to stop the reaction. These test tubes were then incubated in a boiling water bath for 5 min and cooled to room temperature. Finally this reaction mixture was again diluted by adding 10 mL distilled water following which absorbance was measured at 540 nm [15]. The percentage inhibition and 50% inhibitory concentration (IC_{50}) value was calculated using formula

Inhibition (%) = (control - test/control) / 100

Suitable reagent blank and inhibitor controls were simultaneously carried out. The results are depicted in **Table 1**.

TABLE 1: INHIBITION OF *α*-AMYLASE ENZYME ACTIVITY BY THE SYNTHESIZED COMPOUNDS

Treatment	% inhibition of enzyme activity at concentration (*µ*g/mL)						IC_{50} (*µ*g/mL)
	10	20	40	60	80	100	
SP_1	5.91 ± 0.40	14.03 ± 0.36	21.45 ± 0.42	47.32 ± 0.51	58.57 ± 0.58	70.41 ± 0.41	287.10
SP_2	20.82 ± 1.41	40.89 ± 0.34	53.21 ± 0.53	73.73 ± 0.67	80.94 ± 1.78	90.31 ± 0.67	3.53
SP_4	11.23 ± 0.32	22.73 ± 0.47	39.91 ± 0.69	54.48 ± 0.57	62.45 ± 1.01	79.04 ± 1.27	54.32
SP_5	10.43 ± 0.91	18.74 ± 0.42	29.08 ± 0.56	41.99 ± 1.14	58.06 ± 1.18	65.96 ± 0.74	140.89
SP_8	20.12 ± 1.01	40.99 ± 0.84	58.05 ± 0.77	76.73 ± 1.11	84.49 ± 0.96	91.17 ± 0.78	3.12
SP_9	14.32 ± 1.02	30.73 ± 1.21	43.23 ± 0.74	52.11 ± 0.72	67.66 ± 1.24	84.54 ± 0.25	10.35

The data represented as mean ± SD (n = 3)

Glucose Diffusion Inhibitory Test: The results of the glucose diffusion inhibitory test are given in **Table 2**. All tested compound showed significant inhibitory activity with SP_9 showing maximum inhibition to the diffusion of glucose and SP_7 showing least inhibition to the diffusion of glucose.

TABLE 2: EFFECT OF SYNTHESIZED COMPOUNDS ON DIFFUSION OF GLUCOSE OUT OF A BIO-MEMBRANE

Treatment	Concentration of glucose (mg/dL) at time (minutes)						Relative movement (%) at time (minutes)					
	30	60	90	120	150	180	30	60	90	120	150	180
Control	0.550±0.034	1.167±0.110	2.134±0.200	3.250±0.025	4.200±0.267	5.120±0.123						
SP_7	0.417±0.026	1.000±0.067	1.250±0.058	2.70±0.030	3.550±0.034	6.870±0.577	75.80	85.76	58.61	83.07	84.55	134.20
SP_9	0.34±0.045	0.74±0.045	1.20±0.120	2.54±0.67	3.01±0.089	4.21±0.290	61.80	63.40	56.23	78.15	71.40	76.05
Standard	0.164±0.11	0.442±0.032	1.333±0.108	2.43±0.042	3.632±0.019	4.86±0.301	38.31	44.17	60.53	80.04	89.74	96.12

The data represented as mean ± SEM (n = 3)

***In vivo* Hypoglycaemic Evaluation:**

Induction of Non- Insulin Dependent DM: The acclimatized animals were kept fasting for 24 h with water *ad libitum* and Alloxan Monohydrate (120 mg/kg i.p.) in normal saline was administered. After one hour of alloxan administration the animal's *ad libitum* 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 **Table 3**.

TABLE 3: 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] SP 01	41.13±17.13**	64.54±11.72***	69.70±12.23***
[b] SP 02	31.47±14.48**	59.44±5.88***	71.47±4.23***
[b] SP 03	31.23±14.44**	63.38±8.27***	74.53±6.14***
[b] SP 04	35.89±18.34**	54.30±8.21***	67.38±4.13***
[b] SP 05	36.05±17.25**	62.37±13.70***	72.16±4.59***
[b] SP 06	33.92±25.34*	59.65±10.56***	68.89±4.69***
[b] SP 07	28.05±13.22**	60.15±7.42***	69.23±7.11***
[b] SP 08	28.60±13.18**	63.07±8.97***	70.35±6.54***
[b] SP 09	25.60±13.17**	64.07±8.89***	71.39±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

***In vivo* Glycogen Content Determination Test:**

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 libitum* 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 6 hr before the drug administration. The animals were and their livers were immediately removed for glycogen **Table 4**.

TABLE 4: *IN VIVO* DATA OF INCREASE IN LIVER GLYCOGEN CONTENT OF TEST COMPOUNDS

S. no.	[b]Compound	[c]Increase in Liver Glycogen Content (mg)
1	[b] Control	0
2	[b] SP 01	72.80 ± 11.44**
3	[b] SP 02	117.76 ± 10.24**
4	[b] SP 03	111.01 ± 3.65**
5	[b] SP 04	60.64 ± 6.93**
6	[b] SP 05	116.03 ± 6.63***
7	[b] SP 06	62.39 ± 4.85**
8	[b] SP 07	70.26 ± 5.02***
9	[b] SP 08	112.01 ± 7.13**
10	[b] SP 09	122.01 ± 7.14**

RESULT AND DISCUSSION: The IR spectrum of the compounds (Der 01- Der 09) shows peaks C=O ketone stretching strong peaks in the range 1663 - 1751 cm^{-1}, C=C alkene stretching peaks in the range 1617 - 1675cm^{-1}, while C=C benzene stretching peaks fall between in the range 1521 - 1600 cm^{-1}. The IR spectrum of the compounds (Der 03, Der 05, Der 07, Der 08) shows peaks in the range 1074 - 1260 cm^{-1} for C=S thiocarbonyl stretching, compounds (Der 01, Der 02) shows peaks in the range 989 - 1172 cm^{-1} for C-O ether stretching, compounds (Der 02, Der 03, Der 07) shows peaks at 3295 cm^{-1} for O-H alcohol stretching, while compound (Der 04, Der 05, Der 08) shows peaks at 823 cm^{-1} for C-Cl alkyl halide stretching. Der 06 shows NO_2 stretching at 1340 cm^{-1}. The analogs were screened for their Inhibition Assay for α-Amylase activity, Glucose Diffusion Inhibitory Test, antidiabetic activity by alloxan induced tail tipping method and total liver glycogen.

CONCLUSION: In the present research work, an attempt has been made to synthesize phenyl methylene hydantoin derivatives, which are expected to have antidiabetic activity. All synthesized compounds shows characteristics absorption bands of the anticipated structure in infrared spectral study that confirm the functional group of synthesized compound. The structure of synthesize compounds were supported by IR, NMR and mass spectral data. All spectral data were in accordance with assumed structures. These all confirms the formation of the compound. The compounds (Der 01-Der 09) have shown

significant antidiabetic activity on oral administration. The results were calculated by measuring the mean ± SE and 'p' value. Synthesized compound shows decrease in blood glucose level in the range of 59.44 - 64.54% after 3 hr while 67.38 - 74.53% after 6 h.

Preliminary antidiabetic activity study and structure of hydantoin are unable to explain any SAR. The presented data support the notion that GSK-3β inhibitors are of pharmacotherapeutic interest for the pharmaceutical community and highlight essential aspects for the development of efficient, potent and selective GSK-3β inhibitors for management of diabetes mellitus with minimum side effect. The work may be further elaborated by substituting carboxylate or other negatively charged moiety along with benzyl or phenethyl on benzylidene ring system afford potent and selective GSK-3β inhibitors with minimum side effects.

ACKNOWLEDGEMENT: The authors are highly thankful to Principal, Indore Institute of Pharmacy, Indore and Dean, Suresh Gyan Vihar University, Jaipur for providing Necessary facilities to carry out this research.

CONFLICT OF INTEREST: Nil

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How to cite this article:
Prachand S, Gupta AK and Gilhotra R: Synthesis and biological activity of some novel imidazolidine analogues as potent antidiabetic agent. Int J Pharm Sci Res 2018; 9(6): 2287-92. doi: 10.13040/IJPSR.0975-8232.9(6).2287-92.