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Substituted biphenyl ethanones as antidiabetic agents: synthesis and in-vivo screening

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Abstract : A series of biphenyl derivatives were synthesized and evaluated for hypoglycemic activity using alloxan induced diabetic mice model and oral glucose tolerance test. Biphenyl derivatives, VMNS 2a-2o were prepared by condensation of 1-biphenyl-4-yl-2-chloroethanone with different substituted aryl alcohols while few substituted aryl alcohols were prepared by some established procedures. Biphenyls were selected due to their favorable interaction with the active site of the receptor. Compounds VMNS 2b, 2c, 2e, 2f, 2i, 2m and 2n showed significant decrease in serum glucose level comparable to the standard. On the basis of the results of acute study, compounds VMNS 2b, 2c, 2e, 2f, 2i, 2m and 2n were selected and evaluated for subacute study for 28 days and oral glucose tolerance test (OGTT). Acute oral toxicity studies were also carried out as per the OECD guidelines 425.
Key Words: Diabetes; Hypoglycemia; Biphenyls

Introduction

The complex metabolic syndrome, diabetes mellitus, is a major human health concern the world over and is estimated to affect 300 million people by the year 2025.[1] Although our understanding of the disease progressed considerably in recent years, very few viable alternative therapeutic agents were developed since the chance discovery of sulfonylurea class of drugs during World War II followed later, by the biguanides.[2-6]

Although treatment with highly active thiazolidinedione (TZD)[7] class of drugs has significantly improved the clinical situation, suffers with adverse side effects of hepatotoxicity, weight gain and edema. The prevalence and rising incidence of diabetes emphasized the need to explore the new molecular targets and strategies to develop novel antihyperglycemic agents. One such strategy is to design and synthesize inhibitors for protein tyrosine phosphatase 1B (PTP 1B), which is a legitimate target for the treatment of Type 2 diabetes by attenuating insulin resistance.

PTP 1B inhibitors could potentially ameliorate insulin resistance and normalizes plasma glucose and insulin without inducing hypoglycemia and could be potential pharmacological agents for the treatment of obesity and T2DM. In recent years, interest in the development of small molecule PTP 1B inhibitors has dramatically intensified.[8]

This paper reports the synthesis and structural characteristics of several biphenyl ethanones. These compounds were evaluated for their hypoglycemic activity after oral administration at dose of 30mg/kg in alloxan induced diabetic mice. Blood glucose level were measured and compared with control taking pioglitazone (30mg/kg) as a standard. Oral glucose tolerance test (OGTT) was performed for some selected compounds of the series. Acute oral toxicity studies were also carried out as per OECD guidelines in swiss albino mice.

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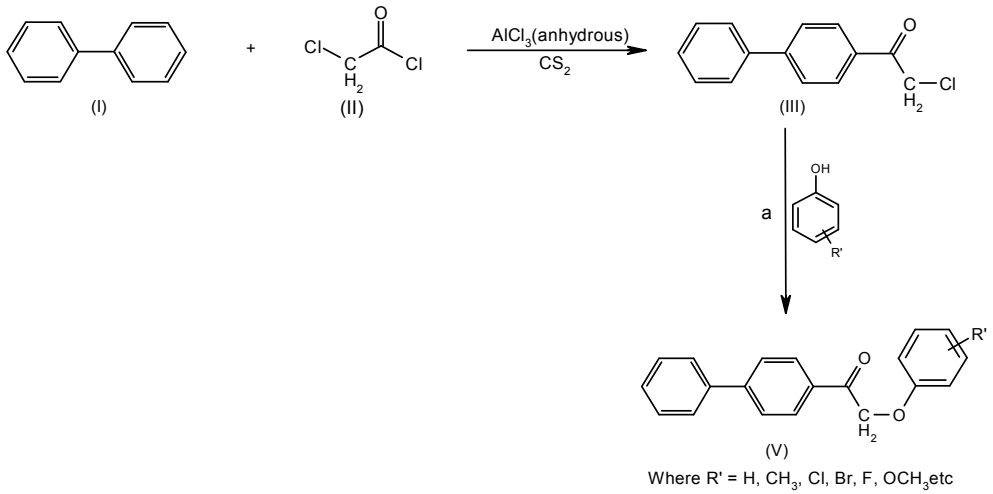
Materials and Methods

Chemistry

Melting points were determined on a open capillary melting point apparatus and are uncorrected. All chemicals used in this study were purchased from Aldrich Co. (Milwaukee, Wl, USA). In order to find the purity and homogeneity of synthesized compounds, thin layer chromatography was carried out on silica gel plates with a fluorescent indicator and the Rf values were calculated. IR spectra were recorded from KBr pellets on

JASCO FT-IR 5300 and *SHIMADZU – FTIR3100* spectrophotometer. ^{1}H-NMR spectra were obtained with "VARIAN-NMR 300 *MERCURY*" spectrometer with TMS as an internal standard. Chemical shifts were reported as δ (ppm) values.



Scheme 1 Synthetic steps used in the preparation of biphenyl (I) derivatives. II: chloroacetyl chloride; III: 1-biphenyl-4-yl-2-chloroethanone; IV: substituted biphenyl ethanones. a: K_2CO_3, acetonitrile, reflux.

Synthesis

Preparation of 1-biphenyl-4-yl-2-chloroethanone

In a 250 ml three necked flask provided with a dropping funnel, a mechanical stirrer and a reflux condenser, 1.54 g (0.01mol) of biphenyl, 1.33 g (0.01mol) of finely powdered anhydrous aluminum chloride and 35 ml of anhydrous carbon disulphide was placed. The dropping funnel was charged with 0.8 ml (0.01mol) of pure chloroacetyl chloride and closed with a calcium chloride guard tube. The mixture was heated on a water bath until gentle reflux commenced and chloroacetyl chloride was added dropwise, the addition product made its appearance as a curdy mass when about three quarters of the chloroacetyl chloride was added, the reaction mixture was refluxed gently for an hour. The reaction mixture was cooled and poured slowly and with stirring on to crushed ice to which hydrochloric acid had been added. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was re-crystallized from methanol.

Yield: 85%, m.p.: 124-126°C, R_f: 0.55 (4.5:0.5 benzene : ethyl acetate, v/v)

IR: 3034 (Ar-CH), 2908 (-CH), 1699 (-CO), 1602 (Ar-C=C), 767 (-CCl)

^{1}H-NMR ($CDCl_3$): 7.409-8.038 (s,d,m, 9H, Ar-H), 4.735 (s, 2H, $-CH_2$).

Preparation of substituted biphenyl ethers

General procedure: In a 250 ml RBF, 1-biphenyl-4-yl-2-chloroethanone (2.30 g, 0.01 mol) was dissolved in 30 ml of acetonitrile. To this solution, 0.01 mol of substituted aryl alcohols and 0.01 mol of anhydrous potassium carbonate was added. The resulting reaction mixture was then refluxed for 24 hrs. Acetonitrile was distilled out at the end of the reflux period; the reaction mixture was cooled and poured onto 60 ml of water, to obtain the final compound as solid crystals. The compound was filtered, washed with water, dried and re-crystallized from methanol

Antidiabetic Activity

Animals and Treatment

Swiss Albino mice of either sex weighing between 25 ± 5g were obtained from national toxicological centre, Pune. Animals were housed under standard condition of temperature (25 ± 2°C), 12h/12h light dark cycles and fed with standard pelleted diet (Chakan oil mills, Sangli) and water was given ad libitum. All the study protocols related to antidiabetic activity testing were approved from the Institutional Animal Ethics Committee and the ethical clearance was obtained from the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Mice were kept on overnight fasting and water was given *ad libitum*. Blood samples were collected by retro orbital plexus technique (ROP) and the initial fasting serum glucose (SG) was estimated by enzymatic colorimetric method i.e glucose oxidase peroxidase (GOD/POD) method using kit obtained from Accurex Biomedicals, Mumbai. The animals showing optimum, SG 80-120 mg/dl, were selected and injected with alloxan (70 mg/kg) i.v. After 48 hrs, the blood was withdrawn and SG was estimated. The animals showing SG levels above 200 mg/dl were selected for study and divided into experimental groups of 6 animals each.

Hypoglycemic Activity:

Acute Study: The synthesized compounds were screened for hypoglycemic activity in vivo by alloxan induced diabetic mice model.[9,10,11] For acute study animals were fasted

overnight and the fasting SG, 0hr, levels were calculated. Now the compounds were administered at a fixed dose of 30mg/kg body weight orally (homogenized suspension in 0.5% carboxy methyl cellulose (CMC) and permissible amounts of Tween 80). Animals of vehicle treated group were given an equal amount of 0.5% CMC and those of control group were kept as such. Blood samples were removed from all animals at 2, 4, 6 and 24 hrs and percentage change in SG was calculated.

Subacute Study: Study animals were fasted overnight and the fasting SG, 0day, levels were calculated. Now the compounds VMNS 2b, 2c, 2e, 2f, 2i, 2m and 2n were administered at a fixed dose of 30mg/kg orally (homogenized suspension in 0.5% CMC and permissible amounts of Tween 80) for 21days at a fixed time. After 21days treatment was stopped and animals were left for a rest period of 7days. Animals of vehicle treated group were given an equal amount of 0.5% CMC and those of control group were kept as such. During study blood samples were removed from all animals at 7, 14, 21 and 28 days and percentage change in SG was calculated.

The data obtained were analyzed by one-way ANOVA followed by Dunnett test.[12] The results were expressed as mean ± standard error of mean (SEM) for each group, $p<0.01$ was considered as statistically significant.

Oral glucose tolerance test:

This test was performed after 21 days of treatment of diabetic animals with test compounds and standard at a dose of 30mg/kg. The animals were kept on fasting overnight. The compounds VMNS 2b, 2c, 2e, 2f, 2i, 2m, 2n and standard were administered at a fixed dose of 30mg/kg orally. Animals of vehicle treated group were given an equal amount of 0.5% CMC and those of control group were kept as such and SG was estimated immediately, that is considered as 0min. After half an hour of drug administration and SG estimation (0min), glucose (2.5g/kg) was administered orally to the animals and further SG was estimated at 30, 60, 90 and 120min.

Results and discussion

Chemistry

Different substituted 1-biphenyl-4-yl-2-chloroethanones have been synthesized as per scheme 1. In the first step, synthesis of 1-biphenyl-4-yl-2-chloroethanone (III) was carried out using biphenyl (I) and chloroacetyl chloride (II) in the presence of anhydrous aluminium chloride. 1-Biphenyl-4-yl-2-chloroethanone was condensed with different substituted aryl alcohols to get finally substituted 1-biphenyl-4-yl-2-ethanone derivatives (VMNS 2a-2o). The structures of synthesized compounds were confirmed by chromatographic and spectral analysis. The physicochemical characteristics of synthesized compounds are summarized in Table 1.

1-Biphenyl-4-yl-2-phenoxy-ethanone (VMNS2a):

IR: 3059, 2916 (Ar-CH), 2849 (-CH), 1691 (-CO), 1601 (Ar-C=C), 1224 (C-O-C)

^{1}H-NMR ($CDCl_3$): 6.974-8.073 (m, 14H, Ar-H), 5.288 (s, 2H, $-CH_2$).

1-Biphenyl-4-yl-2-(4-bromo-phenoxy)-ethanone (VMNS2b):

IR: 3054(Ar-CH), 2917 (-CH), 1698 (-CO), 1601 (Ar-C=C), 1201 (C-O-C), 863 (-CBr).

^{1}H-NMR ($CDCl_3$): 6.98-8.17 (m, 13H, Ar-H), 5.38 (s, 2H, $-CH_2$).

1-Biphenyl-4-yl-2-(4-chloro-phenoxy)-ethanone (VMNS2c):

IR: 3061(Ar-CH), 2847 (-CH), 1689 (-CO), 1601 (Ar-C=C), 1236 (C-O-C), 763 (-CCl).

^{1}H-NMR ($CDCl_3$): 6.69-8.12 (m, 13H, Ar-H), 5.39 (s, 2H, $-CH_2$).

1-Biphenyl-4-yl-2-(4-fluoro-phenoxy)-ethanone (VMNS2d):

IR: 3082 (Ar-CH), 2849 (-CH), 1699 (-CO), 1593 (Ar-C=C), 1230 (C-O-C), 987 (-CF)

^{1}H-NMR ($CDCl_3$): 6.97-8.19 (m, 13H, Ar-H), 5.43 (s, 2H, $-CH_2$).

1-Biphenyl-4-yl-2-(4-nitro-phenoxy)-ethanone (VMNS2e):

IR: 3052 (Ar-CH), 2792 (-CH), 1712 (-CO), 1580 (Ar-C=C), 1198 (C-O-C).

^{1}H-NMR ($CDCl_3$): 6.56-8.23 (m, 13H, Ar-H), 5.12 (s, 2H, $-CH_2$).

1-Biphenyl-4-yl-2-p-tolyloxy-ethanone (VMNS2f):

IR: 3047, 3023 (Ar-CH), 2857 (-CH), 1697 (-CO), 1601 (Ar-C=C), 1214 (C-O-C).

^{1}H-NMR (DMSO-*d6*): 6.96-7.98 (m,13H, Ar-H), 5.02 (s, 2H, $-CH_2$), 2.46 (s, 3H, $-CH_3$).

1-Biphenyl-4-yl-2-o-tolyloxy-ethanone (VMNS2g):

IR: 3057, 3034 (Ar-CH), 2851,2731 (-CH), 1687 (-CO), 1604 (Ar-C=C), 1238 (C-O-C).

^{1}H-NMR (DMSO-*d6*): 6.89-8.10 (m,13H, Ar-H), 5.07 (s, 2H, $-CH_2$), 2.32 (s, 3H, $-CH_3$).

1-Biphenyl-4-yl-2-m-tolyloxy-ethanone (VMNS2h):

IR: 3066, 3029 (Ar-CH), 2916 (-CH), 1691 (-CO), 1601 (Ar-C=C), 1226 (C-O-C).

^{1}H-NMR (DMSO-*d6*): 6.63-8.15 (m, 13H,Ar-H), 5.11 (s, 2H, $-CH_2$), 2.42 (s, 3H, $-CH_3$).

1-Biphenyl-4-yl-2-(2,6-dimethyl-phenoxy)-ethanone (VMNS2i):

IR: 3061 (Ar-CH), 2945, 2910 (-CH), 1699 (-CO), 1602 (Ar-C=C), 1197 (C-O-C).

^{1}H-NMR (DMSO-*d6*): 6.91-8.075 (m,12H,Ar-H), 2.455 (s,6H,$-CH_3$), 4.456 (s,2H,$-CH_2$)

Mass: 316 (M^+), 181 (100).

2-(4-Acetyl-phenoxy)-1-biphenyl-4-yl-ethanone (VMNS2j):

IR: 3115 (Ar-CH), 2945,2986 (-CH), 1745, 1693 (-CO), 1602 (Ar-C=C), 1236 (C-O-C).

^{1}H-NMR ($CDCl_3$): 6.96-8.095 (m, 13H, Ar-H), 5.385 (s, 2H, $-CH_2$).

2-(2-Acetyl-phenoxy)-1-biphenyl-4-yl-ethanone (VMNS2k):

IR: 3059 (Ar-CH), 2916, 2847 (-CH), 1672 (-CO), 1601 (Ar-C=C), 1263 (C-O-C).
^{1}H-NMR (DMSO-*d6*): 6.88-8.12 (m, 13H, Ar-H), 5.35 (s, 2H, -CH_2).

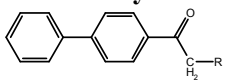
2-(2-Biphenyl-4-yl-2-oxo-ethoxy)-[1,4]-naphthoquinone (VMNS2l):
IR: 3103,3042 (Ar-CH), 2926 (-CH), 1716, 1683 (-CO), 1602 (Ar-C=C), 1248 (C-O-C).
^{1}H-NMR (DMSO-*d6*): 6.58-8.22 (s, d, t, 14H, Ar-H), 5.15 (s, 2H, -CH_2).

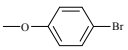
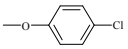
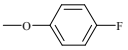
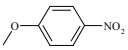
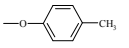
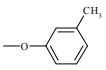
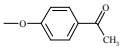
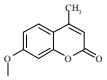
4-(2-Biphenyl-4-yl-2-oxo-ethoxy)-chromen-2-one (VMNS2m):
IR: 3072 (Ar-CH), 2945 (-CH), 1720, 1689 (-CO), 1594 (Ar-C=C), 1232 (C-O-C).
^{1}H-NMR ($CDCl_3$): 6.820-8.071 (s, d, t,13H,Ar-H), 5.405 (s,2H,-CH_2), 6.146 (s,1H,-CH)
.

7-(2-Biphenyl-4-yl-2-oxo-ethoxy)-4-methyl-chromen-2-one (VMNS2n):
IR: 3067 (Ar-CH), 2914, 2849 (-CH), 1728, 1701 (-CO), 1610 (Ar-C=C), 1203 (C-O-C)
^{1}H-NMR ($CDCl_3$): 6.820-8.071 (s, d, t, 12H, Ar-H), 2.404 (s, 3H, -CH_3), 5.405 (s, 2H, -CH_2), 6.146 (s, 1H, -CH)

1-Biphenyl-4-yl-2-(quinolin-8-yloxy)-ethanone (VMNS2o):
IR: 3059.38 (Ar-CH), 2984.15 (-CH), 1595.27 (C-C), 2224.13 (-CCN)
^{1}H-NMR (DMSO-*d6*): 6.93-8.84 (m, 13H, Ar-H), 4.96 (s, 2H, -CH_2).

Table 1 Physicochemical characteristics and structures of VMNS 2a-2o



Compd Code	R	Mol. Formula	% Yield	M.P.
VMNS2a		$C_{20}H_{16}O_2$	82%	93-95°C
VMNS2b		$C_{20}H_{15}BrO_2$	79.01%	250-252°C
VMNS2c		$C_{20}H_{15}ClO_2$	80%	150-152°C
VMNS2d		$C_{20}H_{15}FO_2$	80%	140-142°C
VMNS2e		$C_{20}H_{16}NO_4$	59.58%	144-146°C
VMNS2f		$C_{21}H_{18}O_2$	68%	98-102°C
VMNS2g		$C_{21}H_{18}O_2$	77%	102-104°C
VMNS2h		$C_{21}H_{18}O_2$	77%	101-103°C
VMNS2i		$C_{22}H_{20}O_2$	81%	100-102°C
VMNS2j		$C_{22}H_{18}O_3$	81%	135-137°C
VMNS2k		$C_{22}H_{18}O_3$	78%	130-132°C
VMNS2l		$C_{24}H_{16}O_4$	81.52%	128-130°C
VMNS2m		$C_{23}H_{16}O_4$	79.77%	168-172°C
VMNS2n		$C_{24}H_{18}O_4$	77%	180-182°C
VMNS2o		$C_{23}H_{17}NO_2$	73.75%	188-190°C

*alloxan induced diabetic mice model.

Antidiabetic Activity

Antihyperglycemic effect on SG level in alloxan induced diabetes: The results of antihyperglycemic activity of all the synthesized compounds and pioglitazone are summarized in Table 2. Oral administration of compounds VMNS 2b, 2c, 2e, 2f, 2i, 2m and 2n (30mg/kg) reduced serum glucose level in diabetic mice significantly (P<0.001) compared to vehicle treated group while others exhibited moderate to no hypoglycemic activity at 2, 4, 6 and 24hr. Continous treatment with VMNS 2e, 2f, 2i, 2m and 2n for 7, 14, 21 days showed significant (P<0.05 to <0.001) decrease in SG while others showed insignificant or no decrease in SG levels as shown in Table 3.

We did not analyze whether the hypoglycemic effects of our compounds were derived from a PTP 1B inhibition, since we did not evaluate their direct effect or binding affinities to the PTP 1B. However since these ligands show a chemical structure derived from core biphenyl, our results suggest that these compounds may have some effects through the PTP 1B.

Table 2 Effect of VMNS 2a-2o (30mg/kg) on SG in diabetic mice (acute study)

Compd	%Change in SG			
	2hr	4hr	6hr	24hr
Control	1.13±0.17	2.11±0.05	2.61±1.37	-0.15±1.92
Vehicle	5.06±1.02	9.60±3.09	8.92±4.36	1.37±2.96
Pio	-32.11±9.68***	-21.22±9.59**	-10.63±6.37	-11.11±2.50
VMNS2a	-20.37±3.42**	-22.17±3.34***	-26.11±3.24*	-23.76±2.50***
VMNS2b	-48.57±9.54***	-44.19±12.00***	-54.38±8.98***	-52.38±5.98***
VMNS2c	-37.69±2.96***	-24.14±5.00***	-17.15±3.66***	-15.55±9.07***
VMNS2d	-29.36±3.28***	-32.85±2.83***	-31.06±3.73***	-13.00±3.50
VMNS2e	-50.92±9.22***	-68.16±6.24***	-76.14±5.19***	-26.67±10.60***
VMNS2f	-51.18±9.04***	-48.52±8.13***	-31.66±5.40***	-14.95±4.74***
VMNS2g	-27.75±2.42*	-24.26±3.47***	-31.35±2.72***	-20.37±2.85**
VMNS2h	-25.99±4.08**	-27.77±3.52**	-12.14±9.79*	-8.75±11.30
VMNS2i	-30.68±4.26**	-27.44±8.34***	-52.31±6.11***	-29.55±13.69***
VMNS2j	-24.16±3.82**	-11.24±5.19	-15.88±4.83**	2.17±4.38
VMNS2k	-1.37±2.84	4.08±6.37	11.55±2.83	14.76±7.43
VMNS2l	-12.37±5.51	-27.14±2.44***	-20.30±2.72***	-10.76±7.46
VMNS2m	-29.53±3.20***	-23.51±2.69***	-20.57±1.85***	-15.98±4.88*
VMNS2n	-28.21±6.02***	-22.81±3.38***	-45.09±9.68***	-17.44±6.27**
VMNS2o	-16.73±14.22**	-16.74±14.55***	-9.78±11.00***	-15.98±8.22**

Values are mean ± S.E.M, n=6 in each group; Statistical analysis by one way ANOVA followed by Dunnet test using Graphpad Instat software. (*** P < 0.001) (** P < 0.01), (* P < 0.05)

Table 3 Effect of VMNS 2b, 2c, 2e, 2f, 2i, 2m and 2n (30mg/kg) on SG in diabetic mice (Subacute study).

Compd	% Change in SG			
	7day	14day	21day	after 7days rest period
Control	1.00±1.32	-1.15±2.18	-2.93±1.65	1.89±3.19
Vehicle	5.09±1.60	3.39±2.21	7.38±1.55	9.52±3.37
Pio	-10.68±3.20	-18.95±4.12	-51.55±3.40***	-43.66±3.29***
VMNS2b	-6.27±4.95	-22.59±6.50*	-19.75±5.76**	-14.29±3.77*
VMNS2c	-19.01±7.31*	-15.77±8.33	-40.31±6.59***	-34.94±5.03***
VMNS2e	-17.43±3.68*	-34.91±3.51***	-43.55±3.69***	-37.06±6.75***
VMNS2f	-21.18±2.85*	-23.80±5.55*	-50.87±3.99**	-41.99±4.00***
VMNS2i	-24.65±5.38**	-24.06±4.67*	-52.08±6.03***	-35.72±4.73***
VMNS2m	-20.46±4.44*	-36.61±5.88***	-53.05±3.21***	-31.71±5.55***
VMNS2n	-23.79±5.77*	-32.05±5.72**	-61.69±3.40***	-45.03±5.41***

Values are mean ± S.E.M, n=6 in each group; Statistical analysis by one way ANOVA followed by Dunnet test using Graphpad Instat software. (*** P < 0.001) (** P < 0.01), (* P < 0.05)

Body weight: Administration of vehicle in diabetic mice resulted in gradual decease in body weight during the period of 28 days. All the treatments (VMNS 2b, 2c, 2e, 2f, 2i, 2m, 2n or pioglitazone) could reverse alloxan-induced weight loss in mice after 7th, 14th, 21st and 28th day of treatments up to certain extent (Fig. 1).

OGTT: It was found that pretreatment of the animals with synthesized compounds VMNS 2b, 2c, 2e, 2f, 2i, 2m and 2n and pioglitazone improved the glucose tolerance, decreasing the blood glucose in alloxan induced diabetic mice. Although most of the compounds showed significant ($P<0.001$) glucose tolerance at 120min, but at 60min and 90min only VMNS 2c, 2e, 2f and 2m showed significant ($P<0.01$) decrease in SG level compared to vehicle treated group (Fig. 2). Treatment of nondiabetic mice with VMNS 2b, 2e, 2i and 2m also produced some glucose tolerance but not significant. (Fig. 3)

Acute oral toxicity: Single dose (55mg/kg p.o) of all the compounds (VMNS2a-2o) did not have any toxic effects. The animals were alive, healthy and active during the observation period of 14days. Use of AOT 425 software was made to obtain higher doses for LD_{50} determination as per OECD guidelines. In case of all the compounds computer programme suggested doses 55, 175, 550 and 2000 mg/kg after the previous result. The results indicated that dose up to 2000mg/kg was non lethal.

Conclusion

Several biphenyl ethers were prepared in fair to good yields. The hypoglycemic activity of biphenyl derivatives was evaluated by alloxan induced diabetic mice model. Biological activity was expressed in terms of percent change in SG level. Most of the synthesized compounds showed hypoglycemic activity but a few of them have shown significant decrease in SG level. Pretreatment with some of the compounds increased the glucose tolerance among diabetic animals, while others have shown medium activity. LD_{50} indicated safety profile of compounds. In conclusion, the biphenyl ethers show potent alternatives to some of the existing antidiabetic agents acting via PTP 1B.

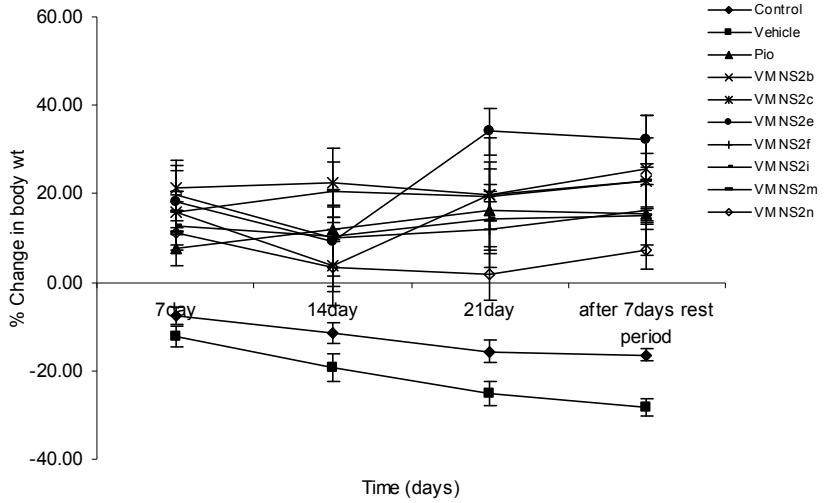


Fig. 1 Effect of VMNS2b,2c,2e,2f,2i,2m and 2n on % change in body wt in diabetic mice

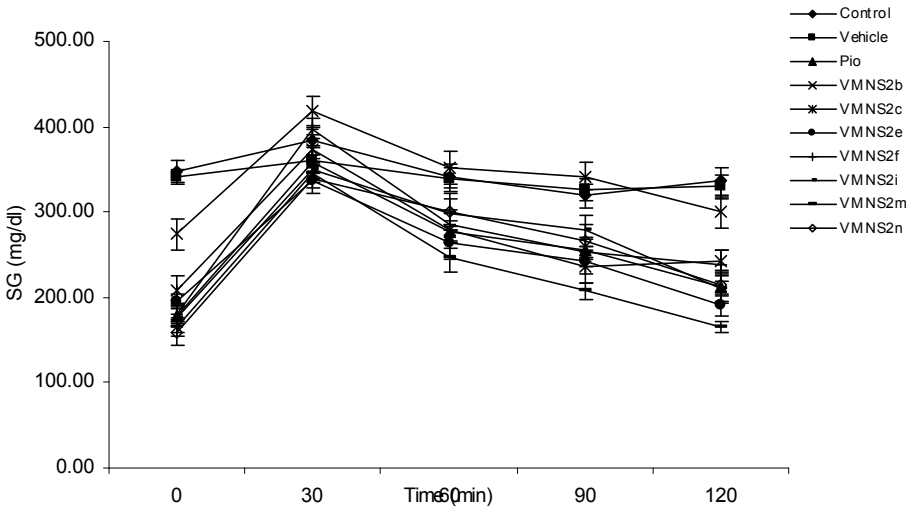


Fig. 2 Effect of VMNS 2b, 2c, 2e, 2f, 2i, 2m and 2n on OGTT in diabetic mice

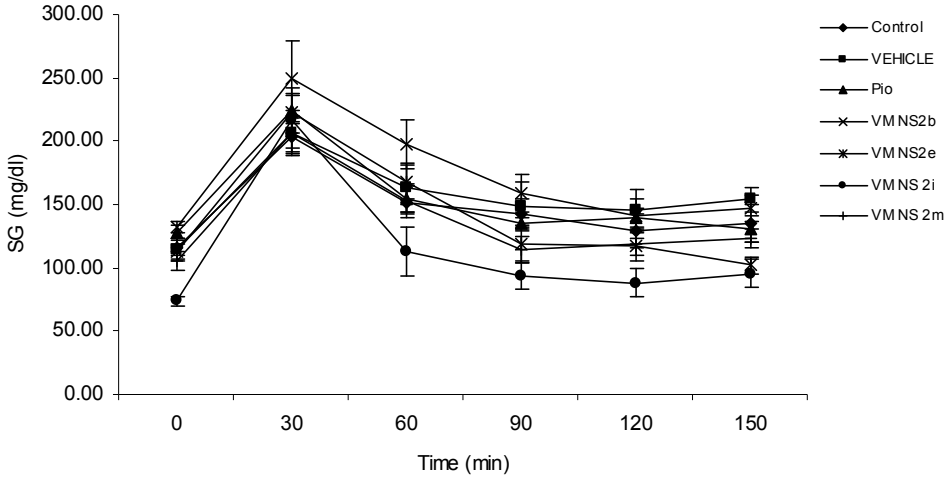


Fig. 3 Effect of VMNS 2b, 2e, 2i and 2m on OGTT in non diabetic mice

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