INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

IN-SILICO AND *IN-VIVO* STUDY OF NEW 2-(4-SUBSTITUTED-PHENYL)-5-(3-PHENYL-PROPENYL) -[1,3,4]OXADIAZOLE DERIVATIVES AS ANTIDIABETIC AND ANTICONVULSANT

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ABSTRACT

A series of 2-(3,5-Dimethoxy-benzoyl)-benzoic acid (Substituted-benzylidene)-hydrazide were synthesized and evaluated for antidiabetic and anticonvulsant activity. Molecular docking study were perform on human gamma-aminobutyric acid receptor (PDB ID: 4COF) and Glycogen Phosphorylase B (PDB ID: 1H5U). Synthesized compounds were characterized by ^{1}HNMR, IR, Mass and elemental analysis. *In-silico* Compound O-16 and O-17 show good Gabaergic activity with least mean binding energy -6.2 and O-13, O-14 and O-17 show antidiabetic activity with least mean binding energy -7.9, -8.4 and -7.3 respectively. *In-vivo* study test compounds were administered at 35mg/kg oral dose. The compound O-13, O-14 and O-17 lower the serum glucose level on day 14, have good antidiabetic activity. The test compound O-16 and O-17 indicate reduction of all stage convulsions as compare to standard.

Keywords: Anticonvulsant, Antidiabetic, docking, oxadiazole, 1H5U, 4COF.

INTRODUCTION

1,3,4-oxadiazole nucleus have been reported a very important nucleus in organic and medicinal chemistry and more widely studied by researchers because of its versatile chemical and biological properties[1]. Specifically compounds having 1,3,4-oxadiazole nucleus are known to exhibit unique anticonvulsant activity[2] and antidiabetic[3,4,5] activity. Different ring or substitution on oxadiazole moiety possess a verity of biological activity such as anti-inflammatory[6,7], antitubercular[8], antihypertensive[9] and antidiarrheal[10] activity. There are several route of synthesis of 1,3,4-oxadiazoles as it can be synthesized by condensation of aldehyde and aroylhydrazone in presence of acetic anhydride[11], condensation of various alkyl hydrazides with substituted aromatic acid in presence of $POCl_3$ yielded respective 2-alkyl- 5aryl- 1,3,4-oxadiazole [12-15]. In the view of their good biological activity it is worthwhile to synthesized 1,3,4-oxadiazole derivatives.

MATERIAL AND METHODS

All the chemicals were commercially obtained from E. Merck India Ltd., CDH, S.D. Fine Chem. Ltd. Sigma Aldrich Ltd. the compounds purity and completion of reaction is checked by TLC using E. Merck 0.25mm silica gel plates, visualization was accomplished on UV-Visible Spectrophotometer Pharma spec-1700 (SHIMADZU). The melting points were determine on Bio Technics India, melting point apparatus and were uncorrected. The IR spectra of compounds were recorded by using KBr disc on Perkin Elmer FTIR BX-2 spectrophotometer.1H NMR spectra were recorded on Bruker 400MHz instrument in $CDCl_3$ / DMSO-d_6 using tetramethylsilane [$(CH_3)_4Si$] (TMS) as internal standard. The mass spectra were recorded on a LC-MSD-Trap-SL (jeol GCmate spectrometer). The elemental analysis was recorded on EURO

VECTOR EA 3000. Docking study was performed on EXHZ Version 1.4 and Auto Dock 4.0 on Fedora Linux WS 3.0.

Experimental

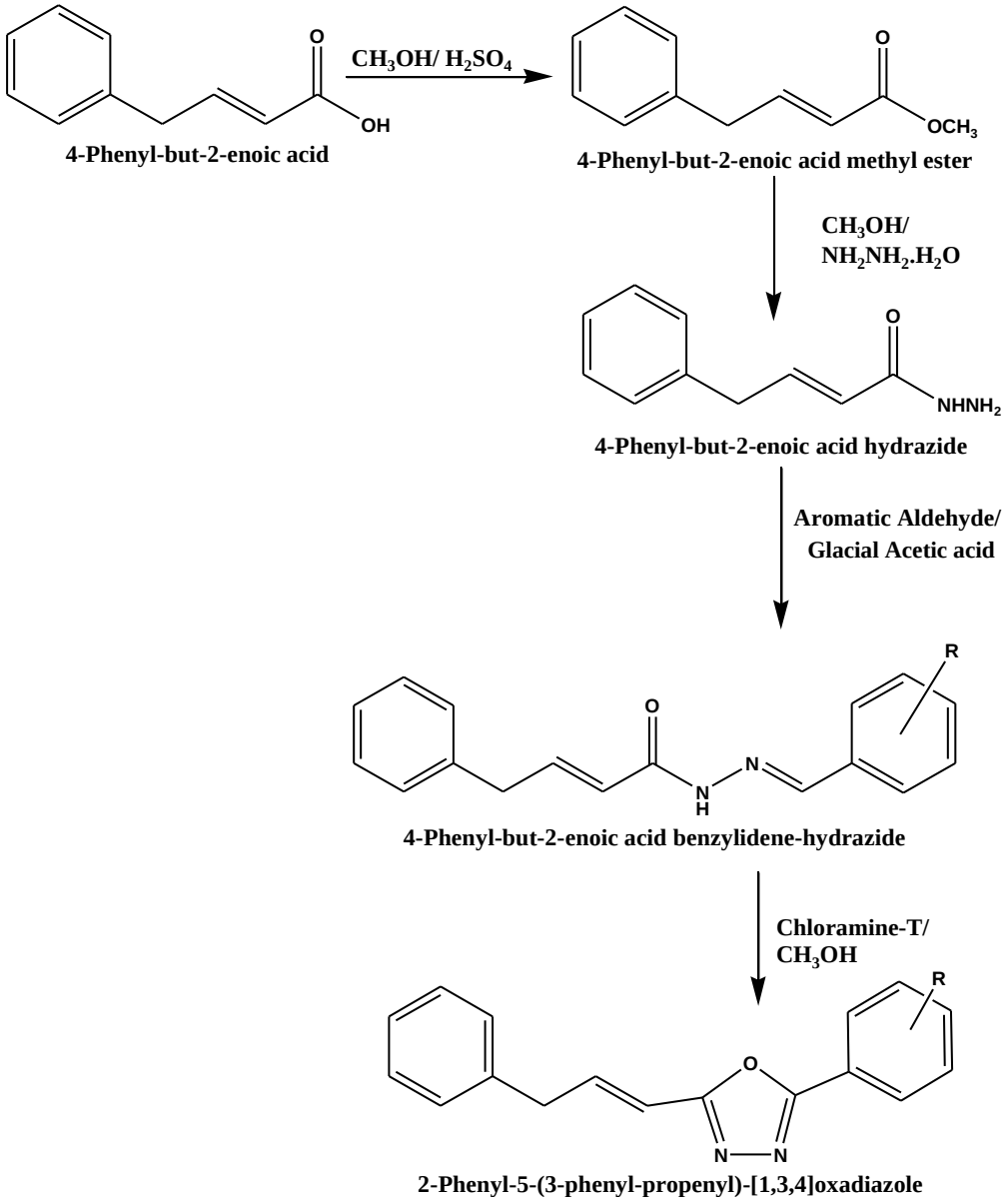
Molecular Docking Study

To identify potential anticonvulsant and anti-diabetic lead compounds The 2D structure construction, energy minimization and geometry optimization were carried out by using Chem Draw Ultra 7.0 and Chem3D Pro 7.0 (Cambridge Soft Corporation, 100 Cambridge Park Drive, Cambridge MA, 02140 USA) on an Intel(R) Core(TM) 2 Duo Central Processing Unit T6670 @ 2.20 GHz and 4.00 GB of RAM, running the Windows 7 Home Basic, 64-bit compatible operating system. The docking studies of all substituted 1,3,4-oxadiazole derivatives have been performed with the AutoDock Vina PyRx- Python Prescription 0.8. into the 3D structure of the catalytic site of **human gamma-aminobutyric acid receptor** (PDB ID: 4COF) and **Glycogen Phosphorylase B** (PDB ID: 1H5U). The Parameter of docking study for **4COF** Gridcenter are as: +3.2771 -1.1140 +139.3007 XYZ-coordinates respectively, the dimensions for xyz 88.8313 84.8868 121.3119 (À) angstrom and Algorithm used is Lamarckian genetic algorithm, for **1H5U** Gridcenter as: +28.4330 +21.1060 +31.7483 XYZ-coordinates respectively, the dimensions for xyz 80.8988 70.3496 75.7681 (À) angstrom and Algorithm used is Lamarckian genetic algorithm.

Table 1: Docking study data of synthesized compounds with least mean binding energy and amino acid residues enveloped

S. No	Compound code	Receptor 4COF		Receptor 1H5U	
		Least Binding energy Kcal/mol	Amino acid residues enveloped	Least Binding energy Kcal/mol	Amino acid residues enveloped
1	**O13**	-6.0	Ala 322, Ala 327,Cys 320, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319,Val 324	-7.9	Ala 383, Arg 292, Asn 133, Asn 282, Asn 284, Asp 283, Asp 339, Glu 88, Glu 287, Glu 296, Glu 385, Gly134, Gly 135, Gly 137,Gly 288,His 341,His 377, Leu 136,Phe 285, Phe 286,Thr 378,Trp 387,Tyr 280
2	**O14**	-6.1	Ala 322, Ala 327, Leu 291, Phe 323, Ser 326, Thr 288, Val 287, Val 324	-8.4	Ala 383, Arg 292, Asn 133, Asn 282, Asn 284, Asp 283, Asp 339, Glu 88, Glu 287, Glu 296, Glu 385, Gly 288,His 341,His 377, Leu 136,Phe 285, Phe 286,Thr 378,Trp 387,Tyr 280
3	**O15**	-6.1	Ala 322, Ala 327,Cys 320, Glu 330,Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319,Val 324	-6.0	Ala 383, Arg 292, Asn 133, Asn 282, Asn 284, Asp 283, Asp 339, Glu 88, Glu 287, Glu 296, Glu 385, Gly134, Gly 135, Gly 137,Gly 288,His 341,His 377, Leu 136,Lys 289, Phe 285, Phe 286,Thr 378,Trp 387,Tyr 280
4	**O16**	-6.2	Ala 322, Ala 327,Cys 320, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319,Val 324	-1.6	Ala 383, Arg 292, Asn 133, Asn 282, Asn 284, Asp 283, Asp 339, Glu 88, Glu 287, Glu 296, Glu 385, Gly134, Gly 135, Gly 137,Gly 288,His 341,His 377, Leu 136,Lys 289,Phe 285, Phe 286,Thr 378,Trp 387,Tyr 280
5	**O17**	-6.2	Ala 322, Ala 327,Cys 320,Glu 330, Leu 291, Phe 323, Ser326, Thr 294, Val 287, Val 319,Val 324	-7.3	Ala 383, Arg 292, Asn 133, Asn 282, Asn 284, Asp 283, Asp 339, Glu 88, Glu 287, Glu 296, Glu 385, Gly134, Gly 135, Gly 137,Gly 288,His 341,His 377, Leu 136,Lys 289,Phe 285, Phe 286,Thr 378,Trp 387,Tyr 280
6	**O18**	-6.0	Ala 318, Ala 322,Met 293, Phe 316, Phe 323, Ser 397, Ser 326,Trp 315, Val 287, Val 390,Val 319	-5.2	Ala 383, Arg 292, Asn 133, Asn 282, Asn 284, Asp 283, Asp 339, Glu 88, Glu 287, Glu 296, Glu 385, Gly134, Gly 135, Gly 137,Gly 288,His 341, Leu 136,Lys 289,Phe 285, Phe 286,Trp 387,Tyr 280

Scheme



4-Phenyl-but-2-enoic acid

4-Phenyl-but-2-enoic acid methyl ester

4-Phenyl-but-2-enoic acid hydrazide

4-Phenyl-but-2-enoic acid benzylidene-hydrazide

2-Phenyl-5-(3-phenyl-propenyl)-[1,3,4]oxadiazole

Synthesis of 4-phenyl-but-2-enoic acid methyl ester

A mixture of 4-phenyl-but-2-enoic acid **(**0.01M), 100ml of ethanol and 1ml of sulphuric acid were refluxed for 6 hrs. After cooling the solution, the product obtained was collected by separating funnel. The completion of the reaction was checked on precoated silica gel G plates using chloroform: methanol (9:1) as an elutent and observed under UV light. R_f: 0.78, Yield: 61%.

Synthesis of 4-phenyl-but-2-enoic acid hydrazide

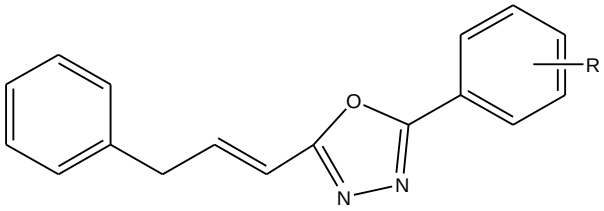
A mixture **of** 4-phenyl-but-2-enoic acid methyl ester and hydrazine hydrate (0.02 mol) was refluxed in dry ethanol (25ml) for 14 hours. After completion of reaction it was cooled, poured onto crushed ice, the solid so obtained was filtered off, washed with water and recrystallized from ethanol. R_f: 0.76, Yield: 70%, M.p.: 198-200^{o}C.

Synthesis of 4-Phenyl-but-2-enoic acid (substituted-benzylidene)-hydrazide (H-13 to H-18)

A solution of 4-phenyl-but-2-enoic acid hydrazide (0.01mole) in glacial acetic acid (20ml) and various substituted aromatic aldehyde was added and mixture was heated under reflux for 4 hrs. Cool the solid precipitate obtained on pouring onto crushed ice, washed with water, filtered and recrystallized to give final product.

Synthesis of 2-(4-substituted-phenyl)-5-(3-phenyl-propenyl)-[1,3,4]oxadiazole (O-13 to O-18)

4-Phenyl-but-2-enoic acid (substituted-benzylidene)-hydrazide (0.01 mole) was dissolved in ethanol and chloramines- T (0.05mole) was added to it. The solution was refluxed for 4hrs, sodium chloride which separated out during the course of reaction was filtered off. Excess ethanol was completely remove from the filtrate by boiling on a water bath, leaving behind a solid mass, which was crystallized from ethanol.



1,3,4-Oxadiazole

Compound No.	O-13	O-14	O-15	O-16	O-17	O18
Substitution (R)	-OH	-H	$-OCH_3$	$-N(CH_3)$	-Cl	$-NO_2$

BIOLOGICAL EVALUATION

Anticonvulsant activity

Anticonvulsant activity of the synthesized compounds O-13 to O-18 was determined by their ability to provide protection from convulsions in albino mice. Supra maximal electroshock of current intensity of 150 mA, for 0.2 s duration was given to the various groups of mice after administration of 50 mg/kg of test compounds oral dose; phenytoin sodium (50 mg/kg) was used as a standard. The abolition of the hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity.

Antidiabetic Activity

All the synthesized compounds O-13 to O-18 were evaluated for anti-diabetic activity of alloxan induced type-II diabetic rats. The healthy wistar albino rats of either sex between the age of 2-3 months and weighing 150mg/kg were used for this study. Alloxan monohydrate was freshly prepared and administered by i.p route within 5 min of preparation to prevent degradation. To prevent hypoglycemic shock 5% glucose solution was given for 72 hrs. Animals had access to feed and water. Glucose was estimated for development of hyperglycemia by fasting serum glucose estimation 72hr after Alloxan monohydrate injection. Animals were fasted again for 14hrs before blood collection. Rats which were found to have fasting serum glucose level of above 200mg/dl at 72 hr were diabetic and considered for the study. The test compounds were administered at 35mg/kg oral dose in 0.25% w/v CMC solution.

Rats were separated and divided into eight different groups for experimental study, with each group containing six animals. Group I was treated as normal/vehicle control animals received 1% PEG orally. Group II to group VII alloxan as well as synthesized compounds (35mg /kg body weight per orally) individually. Group VIII alloxan as well as Glibenclamide 5 mg /kg body weight per orally (standard).

Blood samples were collected from the fasted animals prior to treatment with above scheduled and after administration, at weekly intervals till the end of study.

4-[5-(3-Phenyl-propenyl)-[1,3,4]oxadiazol-2-yl]-phenol (O-13)

Mol. Formula $C_{16}H_{14}N_2O_2$, R_f: 0.80, Yield: 63%, M.p.: 190-191 ^oC**,** IR (KBr, cm^{-1}) υ:3373.33(OH), 1603.62 (C=C), 1158.45 (C-O-C), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.71-6.96 (m, 9H, Ar-H), 6.21-6.18(m, 1H,- CH=), 6.08-6.07(d,1H,-CH=CH-),4.66(s, 1H, -OH), 3.44(d,2H,-CH_2), Anal. Calcd/Found: C, 73.37/73.33; H, 5.07/5.08; N, 10.07/10.50.

2-Phenyl-5-(3-phenyl-propenyl)-[1,3,4]oxadiazole (O-14)

Mol. Formula $C_{16}H_{14}N_2O$, R_f: 0.78, Yield: 53.2%, M.p.: 180-181 ^oC, IR (KBr, cm^{-1}) υ: 1664.63 (C=C), 1207.18 (C-O-C), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.72-6.97 (m, 10H, Ar-H), 6.21-6.18(m, 1H,- CH=), 6.08-6.07(d,1H,-CH=CH-),3.43-3.42(d, 2H, -CH_2-), Anal. Calcd/ Found: C, 77.84/77.83; H, 5.38/5.35; N, 10.68/1069.

2-(4-Methoxy-phenyl)-5-(3-phenyl-propenyl)-[1,3,4]oxadiazole (O-15)

Mol. Formula $C_{17}H_{16}N_2O_2$, R_f: 0.76, Yield: 45.1%, M.p.: 140-141^oC, IR (KBr, cm^{-1}) υ: 2960.31 (-OCH_3),1588.19 (C=C), 1211.04 (C-O-C), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.71-6.96 (m, 9H, Ar-H), 6.21-6.18(m, 1H,- CH=), 6.08-6.07(d,1H,=CH-),3.82(s, 3H, -OCH_3),

3.43(d,2H,CH_2), Anal. Calcd/ Found: C, 73.95/73.93; H, 5.52/5.56; N, 9.589.59.

Dimethyl-{4-[5-(3-phenyl-propenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amine (O-16)
Mol. Formula $C_{18}H_{19}N_3O$, R_f: 0.77, Yield: 39%, M.p.: 161-162^oC, IR (KBr, cm^{-1}) υ:1624.14 (C=C), 1558.42(C=N), 1030.13(C-O-C), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.72-6.97 (m, 9H, Ar-H), 6.21-6.18(m, 1H,- CH=), 6.08-6.07(d,1H,-CH=CH-), 3.43-3.42(d, 2H, -CH_2-), 2.93(s,6H,N(CH_3)$_2$), Mass : m/z: (M+1) $^+$305.09, Anal. Calcd/ Found: C, 74.73/74.92; H, 6.27/6.29; N,13.76/13.79.

2-(4-Chloro-phenyl)-5-(3-phenyl-propenyl)-[1,3,4]oxadiazole (O-17)
Mol. Formula $C_{16}H_{13}ClN_2O$, R_f: 0.82, Yield: 54%, M.p.: 179-180 ^oC, IR (KBr, cm^{-1}) υ: 1555.21 (C=C), 1200.52(C-O-C), 1088.66(C-Cl), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.72-6.96 (m, 9H, Ar-H), 6.21-6.18(m, 1H,- CH=), 6.08-6.07(d,1H,-CH=CH-),3.44-3.43(d, 2H, -CH_2), Anal. Calcd/ Found: C, 64.81/64.84; H, 4.42/4.54; N, 9.44/9.46.

2-(4-Nitro-phenyl)-5-(3-phenyl-propenyl)-[1,3,4]oxadiazole (O-18)
Mol. Formula $C_{16}H_{13}N_3O_3$, R_f: 0.79, Yield: 49.6%, M.p.: 201-202 ^oC, IR (KBr, cm^{-1}) υ: 1607.59 (C=C), 1501.55 (-NO_2), 1240.10 (C-O-C), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.72-6.96 (m, 9H, Ar-H), 6.21-6.18 (m, 1H, CH=), 6.08-6.07 (d,1H, =CH), 3.44-3.43 (d, 2H, -CH_2), Anal. Calcd/Found: C, 66.44/66.46; H, 4.62/4.65; N, 13.67/13.70.

Chemistry
The synthesized compounds O-13 to O-18 were confirmed by recording their IR, ^{1}HNMR and mass spectra. All the compounds were characterized after recrystallization by appropriate solvents. A mixture of 4-phenyl-but-2-enoic acid (0.01M), 100ml of ethanol and 1ml of sulphuric acid were refluxed for 6 hours to produce 4-phenyl-but-2-enoic acid methyl ester. 4-phenyl-but-2-enoic acid methyl ester and hydrazine hydrate (0.02 mol) was refluxed in dry ethanol (25ml) for 14 hours and 4-phenyl-but-2-enoic acid hydrazide was obtained. 4-Phenyl-but-2-enoic acid (substituted-benzylidene)-hydrazide (0.01 mole) was dissolved in ethanol and chloramines-T (0.05mole) was added to it to give 4-[5-(substituted-propenyl)-[1,3,4]oxadiazol-2-yl]-phenol.
The IR spectra of newly synthesized compounds revealed N-H, C=N and C-O-C (oxadiazole) peaks near 3358, 1392 and 1279 cm-1, respectively. The ^{1}H-NMR spectra, shows respective protons of synthesized compounds showed the peaks for -CH_3, -CH=CH-,NH and aromatic protons near δ 1.91, 6.21-6.09, 7.3 and 6.58 -8.3, respectively. The mass fragmentation for the compounds describes by m/z peaks of some derivatives. Elemental analysis given appropriate place is not more than deviated from 0.4% calculated value.

Anticonvulsant Activity

Table 2: Measurement of anti anti-convulsant activity

Group	Treatment	Flexion	Extensor	Clonus	Stupor	Recovery
I	Control	9.16±0.47	13.66±0.55	18.83±0.47	38.83±0.60	195.16± 4.82
II	Standard	4.16± 0.47**	0.86± 0.09**	9.33± 0.49**	17.5± 0.42**	92.17±1.26**
III	Test O14	6.64± 0.42*	5.26± 0.22*	13.33± 0.42*	18.34± 0.42*	126.67±1.53*
IV	Test O15	6.76±0.42*	5.66±0.35*	14.78±0.30*	19.12±0.35*	132.34±1.50*
V	Test O16	5.66± 0.42*	4.83± 0.47*	13.16± 0.30*	17.5± 0.42*	113.50±1.57**
VI	Test O17	6.5 ±0.56*	5.16± 0.47*	13.75± 0.42*	17.83± 0.60*	129± 1.65*

All values expressed as mean ± SEM (n=6). *P ≤ 0.05, **P≤ 0.01, ***P≤ 0.001 as compared with control (One- way ANOVA followed by Dunnett's test).

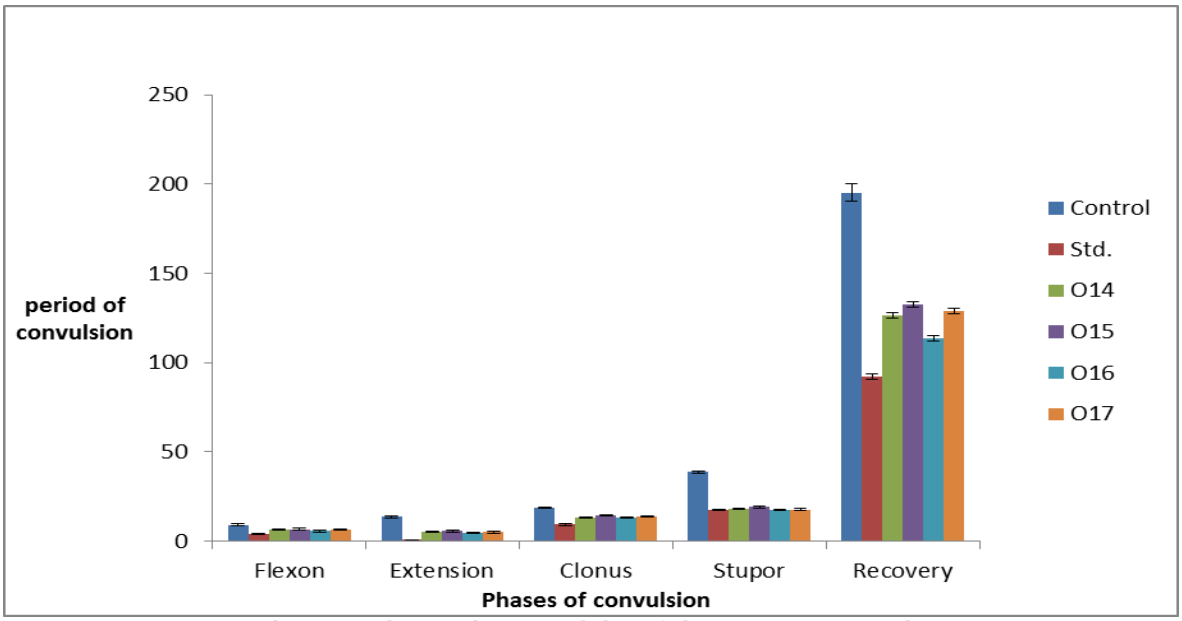


Fig. 1: Anticonvulsant activity of the test compounds

The compound-14, O-15, O-16 and O-17 was found in best conformation with least mean binding energy-6.1, -6.1, -6.2 and -6.2 respectively. The compounds O-14 to O-17 shows a variant 40-90% anti convulsant activity compared Phenytoin as standard drug.

Antidiabetic Activity

Table 3: Measurement of Fasting Blood Glucose Level changes

Group	Fasting Blood Glucose Concentration (mg/ml)			
	Day 1	Day 5	Day 10	Day 14
Diabetic control	211.5 ± 2.66	203.8 ± 1.9	247.3 ± 2.67	287.2 ± 2.49
Standard	225.7 ± 2.10	156.6 ± 2.39**	147.6 ± 3.64**	123.6 ± 2.74**
O13	307.83 ± 3.58	253.4 ± 7.54	202.4 ± 4.86	141.8 ± 3.42**
O14	306.6 ± 4.02	265.4 ± 12.26	217.6 ± 9.67	178.5 ± 6.41*
O17	307.83 ± 3.58	250.4 ± 4.26	211.5 ± 2.66	190.9 ± 2.85*

All values expressed as mean ± SEM (n=6). *P ≤ 0.05, **P≤ 0.01, ***P≤ 0.001 as compared with control (One- way ANOVA followed by Dunnett's test).

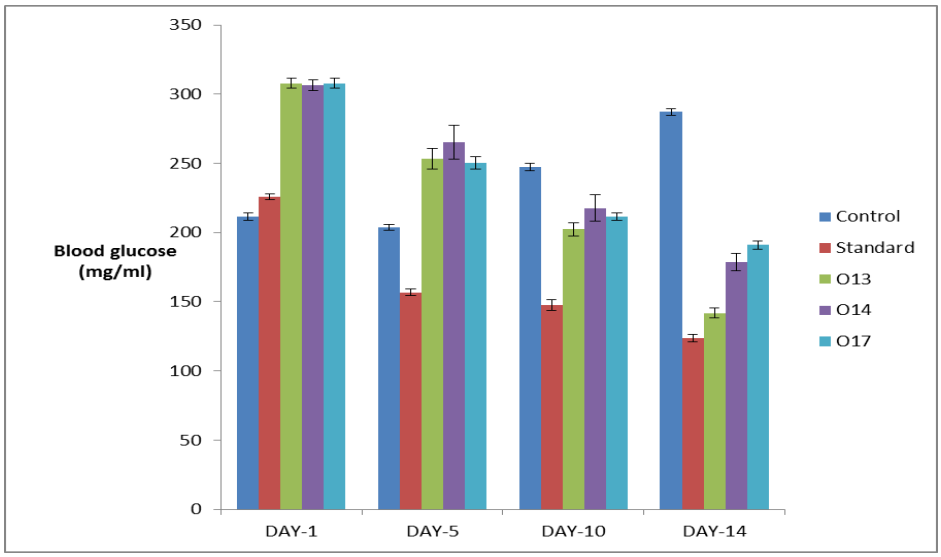


Fig. 2: Effect of compounds on blood glucose level in rat

The Docking study reveals that compounds O13, O14 and O-17 shows best conformation with least mean binding energy -7.9, -8.4 and -7.3 respectively. The compound O-13, O-14 and O-17 start the lowering of serum glucose level from day 5th. The compound O-13 show maximums lowering of serum glucose level on

day 14th have good antidiabetic activity as compared to standard Glibenclamide.

CONCLUSION

Among all synthesized compounds dimethyl-{4-[5-(3-phenyl-propenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amine and 2-(4-Chloro-phenyl)-5-(3-phenyl-propenyl)-[1,3,4]oxadiazole shows best in confirmation and exhibit maximum anticonvulsant activity. The compound 4-[5-(3-Phenyl-propenyl)-[1,3,4]oxadiazol-2-yl]-phenol shows good antidiabetic activity as compared to standard.

ACKNOWLEDGEMENT

This work was supported by S D College of Pharmacy & vocational Studies for providing research facility and animal house facility. Author is also thankful to CDRI and Roorkee IIT for analytical facility.

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