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Research Article

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Synthesis, Docking Analysis and Anticonvulsant Activity of Substituted Hydrazone and 1,3,4-Oxadiazole Derivatives

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ABSTRACT

A series of 3-Phenyl-acrylic acid [1-(substituted-phenyl)-ethylidene]-hydrazide and 2-(substituted-phenyl)-2-methyl-5styryl-2, 3-dihydro-[1,3,4]oxadiazole were synthesize and evaluated for anticonvulsant activity. All compounds were docked on to (PDB ID: 4COF). Compound characterization carried out by IR, H^1NMR, and Mass spectroscopy. All Compounds showed activity in the range of 40-90% comparison to Phenytoin. H-9, H10, O-9, and O-10 possess good significant activity. Compound 3-Phenyl-acrylic acid (2-oxo-1,2-diphenyl-ethylidene)-hydrazide(H-9) was the most active compound in docking study having Least Binding energy -7.4 Kcal/mol with Amino acid residues Ala 322, Ala 327, Cys 320, Glu 330, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319, Val 324. MES (ED50=20.11) tests.

Keywords: 1,3,4 Oxadiazole; Docking; Human gamma-aminobutyric acid receptor (PDB ID: 4COF); Anticonvulsant

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INTRODUCTION

Hydrazone and 1,3,4-Oxadiazole derivatives are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological applications. A large number of 1,3,4-oxadiazole derivatives have been found to exhibit various biological activities such as Anti-Inflammatory [1,2], Antimicrobial [3,4], Anticancerous [5], Anticonvulsant [6,7], Anti tubercular activity [8], Hypoglycemic activity [9], Enzyme inhibitors [10]. In present investigation six hydrazones and six 1,3,4-Oxadiazoles have been synthesized. All synthesized hydrazone and 1,3,4-oxadiazole derivatives screened in-silico and in vivo for anti-convulsant activity.

MATERIALS AND METHODS

The chemicals used for the experimental work were commercially procured from various chemical units- E. Merck India Ltd., CDH, S.D. Fine Chem. Ltd. Sigma Aldrich Ltd. The silica gel G (60-120 mesh) used for analytical chromatography (TLC) was obtained from E. Merck India Ltd. UV spectra were recorded on a UV- Visible Spectrophotometer Pharma spec-1700 (SHIMADZU). The IR spectra of compounds were recorded in KBr on Perkin Elmer FTIR BX-2 spectrophotometer. The proton magnetic resonance spectra (^{1}H NMR) were recorded on Bruker 300MHz instrument in $CDCl_3$ / DMSO-d_6 using tetramethylsilane [$(CH_3)_4Si$] (TMS) as internal standard. The 2D structure construction, energy minimization and geometry optimization of the penetration enhancer were carried out by using ChemDraw Ultra 7.0 and Chem3D Pro 7.0 (CambridgeSoft 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 energy minimization was carried out to minimum RMS Gradient of 0.100, with step interval of 2.0 Fs and frame interval of 10. For

docking study AutoDock Vina PyRx- Python Prescription 0.8 has been used into the 3D structure of the catalytic site of human gamma-aminobutyric acid receptor (PDB ID: 4COF).

EXPERIMENTAL SECTION

Molecular Docking Study

To identify potential anticonvulsant lead compounds among substituted hydrazones and 1,3,4-oxadiazoles, the 2D structure construction, energy minimization and geometry optimization of the penetration enhancer were carried out. The docking studies of 12 novel substituted hydrazones and 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 amino butyric acid receptor (PDB ID: 4COF). Parameter of docking study for 4COF Grid center are +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 (Tables 1 and 2) (Figure 1).

Table 1: Human gamma amino butyric acid receptor 4COF

S. No	Compound code	Least Binding energy Kcal/mol	Amino acid residues enveloped
1	H7	-6.1	Ala 318, Ala 322, Met 293, Phe 316, Phe 323, Ser 297, Trp 315, Val 290, Val 319
2	H8	-6.2	Ala 318, Ala 322, Met 293, Phe 316, Phe 323, Ser 297, Trp 315, Val 290, Val 319
3	H9	-7.4	Ala 322, Ala 327, Cys 320, Glu 330, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319, Val 324
4	H10	-7	Ala 322, Ala 327, Cys 320, Glu 330, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319, Val 324
5	H11	-6	Ala 318, Ala 322, Met 296, Phe 316, Phe 323, Ser 297, Trp 315, Val 290, Val 319
6	H12	-6.2	Ala 318, Ala 322, Met 293, Phe 316, Phe 323, Ser 297, Trp 315, Val 290, Val 319
7	O7	-6.7	Ala 322, Ala 327, Cys 320, Leu 291, Phe 323, Ser 326, Thr 294Val 287, Val 324
8	O8	-6.6	Ala 322, Ala 327, Cys 320, Leu 291, Phe 323, Ser 326, Thr 294Val 287, Val 324
9	O9	-7.1	Ala 322, Ala 327, Cys 320, Leu 291, Phe 323, Ser 326, Thr 283, Thr 294, Val 284, Val 287, Val 319, Val 324
10	O10	-7.1	Ala 322, Ala 327, Leu 291, Phe 323, Ser 326, Thr 283, Thr 288, Val 284, Val 287, Val 324
11	O11	-6.5	Ala 322, Ala 327, Cys 320, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 324
12	O12	-6.7	Ala 322, Ala 327, Cys 320, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319, Val 324

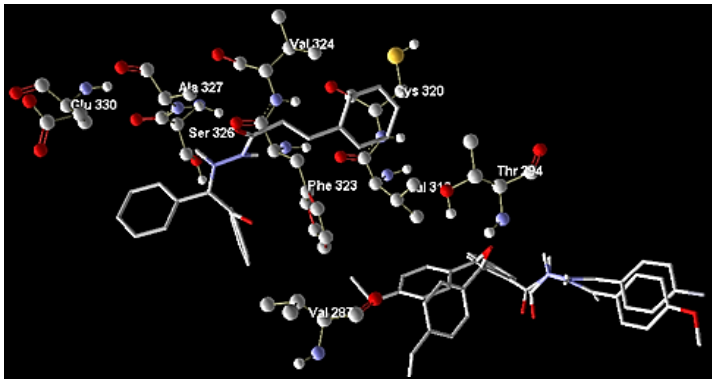


Figure 1: Receptor 4COF with atoms interacting with individual best selected compounds

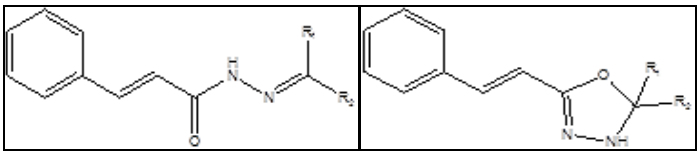
Synthesis of (E)-methyl cinnamate

A mixture of cinnamic acid **(**0.01 M), 100 ml of ethanol and 1ml of sulphuric acid were refluxed for 6 hrs. After cooling the solution, the product obtained was collected by filtration and recrystallized from ethanol. 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: 0.80, Yield: 67%, M.p.: 35-37°C.

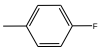
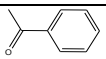
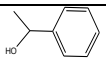
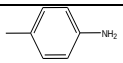
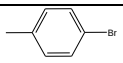
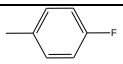
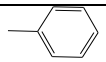
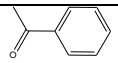
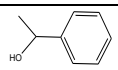
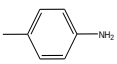
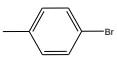
Synthesis of (E)-cinnamohydrazide

A mixture of (E)-methyl cinnamate and hydrazine hydrate (0.02 mol) was refluxed in dry ethanol (25 ml) 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: 0.82, Yield: 71%, M.p.: 236-238°C.

Table 2: Molecular docking study

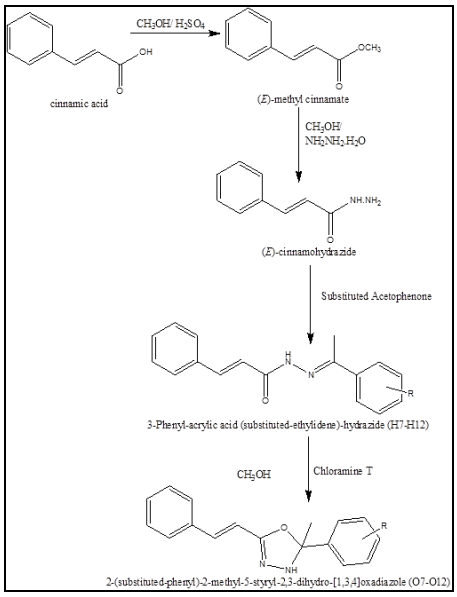


Hydrazone **1,3,4-Oxadiazole**

S. No.	Substitutions			Rf Value	% yield	Melting Point °C	Mol. Wt. (Calculated)
	Compound No.	R_1	R_2				
1	H-7	CH_3		0.70	72	196-198	282.31
2	H-8	CH_3		0.76	67	167-169	264.32
3	H-9	$-C_6H_5$		0.82	66	179-181	354.40
4	H-10	CH_3		0.80	75	184-186	356.42
5	H-11	CH_3		0.82	60	177-179	279.34
6	H-12	CH_3		0.70	64	183-185	242.04
7	O-7	CH_3		0.80	63	170-172	283.14
8	O-8	$-C_6H_5$		0.82	67	191-193	265.14
9	O-9	$-C_6H_5$		0.78	70	163-164	355.14
10	O-10	CH_3		0.80	58	152-154	357.16
11	O-11	CH_3		0.76	64	210-212	280.34
12	O-12	CH_3		0.82	67	170-171	343.22

Synthesis of 3-Phenyl-acrylic acid [1-(substituted-phenyl)-ethylidene]-hydrazide (H-7 to O12)

A solution of (E)-cinnamohydrazide (0.01 mole) in glacial acetic acid (20 ml) and various substituted acetophenone was added and mixture was heated under reflux for about 4 hrs. Cool the solid precipitate obtained on pouring onto crushed ice, washed with water, filtered and recrystallized with ethanol to give final product.



Scheme 1: Synthesis of 2-(substituted-phenyl)-2-methyl-5styryl-2,3-dihydro-[1,3,4]oxadiazole

Synthesis of 2-(substituted-phenyl)-2-methyl-5styryl-2,3-dihydro-[1,3,4]oxadiazole(O-7 to O12)

3-Phenyl-acrylic acid [1-(substituted-phenyl)-ethylidene]-hydrazide (0.01 mole) was dissolved in ethanol and chloramines T (0.05 mole) was added to it. The solution was refluxed for 4 hrs; 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.

***In-vivo* Anticonvulsant Activity**

All synthesized compounds H-7 to H12 and O-7 to O12 were screened through maximum electroshock seizures (MES) in male Wister rats (180–220 g). Maximum electroshock of 150 mA current for 0.2 seconds was given through ear electrodes to various groups of rat after dose administration of 50 mg/kg of test compounds; Phenytoin 50 mg/kg was used as standard. MES produce various phases of convulsions i.e., Flexion, Extension, Clonus and Stupor. The duration of tonic extension of hind limb was used as end point. i.e., prevention or decrease in the duration of hind limb extension was considered as protective action.

RESULT AND DISCUSSION

3-Phenyl-acrylic acid [1-(4-fluoro-phenyl)-ethylidene]-hydrazide(H-7)

Mol. Formula $C_{17}H_{15}FN_2O$, IR (KBr, cm^{-1}) υ: 1477.85 (C=C), 3247.50 (NH), 1697.01(C=O), 1310.08 (C=N), 1256.52(C-F), ^{1}HNMR (CDCl3, 400 MHz): δ 7.27-7.03 (m, 9H, Ar-H), 7.13(s, ^{1}H, -NH), 6.11-6.04 (d,2H,CH=CH), 1.99(s, 3H, CH_3), Mass : m/z: (M+1) $^+$283.14, Anal. Calcd/Found: C, 72.32/ 72.30; H, 5.36/5.29; N, 9.92/9.90.

3-Phenyl-acrylic acid (1-phenyl-ethylidene)-hydrazide (H-8)

Mol. Formula $C_{17}H_{16}N_2O$, IR (KBr, cm^{-1}) υ: 1666.90 (C=C); 3165.04 (NH), 1622.37(C=O), 1446,72 (C=N), 3015.79(C-H), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 5.87(d, 2H, CH=CH), 7.260-8.33(m, 9H, Ar-H), 9.99(s, 1H, NH'), 2.54(s, 1H, -CN-CH), 3.170(s, ^{1}H,C-Cl), Mass : m/z: (M+1) $^+$265.31, Anal. Calcd/ Found: C, 77.25/77.22; H, 6.10/6.09; N, 10.60/10.58.

3-Phenyl-acrylic acid (2-oxo-1,2-diphenyl-ethylidene)-hydrazide(H-9)

Mol. Formula $C_{23}H_{18}N_2O_2$, IR (KBr, cm^{-1}) υ: 1524.43 (C=C), 3435.33 (NH), 1668.53(C=O), 1385.11 (C=N), 3019.56(C-H), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.85-7.14(m, 15H, Ar-H), 7.68(s,1H,-NH), 6.21-6.00(d,2H, CH=CH), Mass : m/z: (M+1) $^+$355.87, Anal. Calcd/ Found: C, 77.95/77 .91; H, 5.12, 5.10; N, 7.90/ 7.86.

3-Phenyl-acrylic acid (2-hydroxy-1,2-diphenyl-ethylidene)-hydrazide(H-10)
Mol. Formula $C_{23}H_{20}N_2O_2$, , IR (KBr, cm^{-1}) υ: 1477.85 (C=C), 3247.50 (NH), 1697.01(C=O), 1310.08 (C=N), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.85-7.16(m,15H,Ar-H), 7.68(s,1H,-NH), 6.21-6.00(d,2H, CH=CH), 5.10(s,1H,-OH), Mass : m/z: (M+1) $^+$357.14, Anal. Calcd/ Found: C, 77.51/77 .50; H, 5.66/, 5.60; N, 7.86/7.82.

3-Phenyl-acrylic acid [1-(4-amino-phenyl)-ethylidene]-hydrazide(H-11)
Mol. Formula $C_{17}H_{17}N_3O$, IR (KBr, cm^{-1}) υ: 1487.54 (C=C); 3308.49 (NH); 1655.21(C=O); 1353.11 (C=N); 3204.35 (C-NH_2), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.27-6.58(m,9H,Ar-H), 7.13(s,1H,-NH), 6.11-6.06(d,2H, CH=CH), 3.67(s,2H,-NH_2), 2.12(s,3H,CH_3), Mass : m/z: (M+1) $^+$280.32, Anal. Calcd/ Found: C, 73.10/73 .09; H, 6.13/6.10; N, 15.04/15.00.

3-Phenyl-acrylic acid [1-(4-bromo-phenyl)-ethylidene]-hydrazide (H-12)
Mol. Formula $C_{17}H_{15}BrN_2O$, IR (KBr, cm^{-1}) υ: 3358.77 (NH); 1615.52 (C=O); 1596.32 (C=C); 1392.14 (C=N); 1163.95 (C-Br), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.27-6.58(m,9H,Ar-H), 7.13(s,1H,-NH), 6.11-6.06(d,2H, CH=CH), 2.02(s,3H,CH_3), Mass : m/z: (M+1) $^+$343.05, Anal. Calcd/ Found: C, 59.49/59.45; H, 4.41/4.36; N, 8.16/8.19.

2-(4-fluoro-phenyl)-2-methyl-5styryl-2,3-dihydro-[1,3,4]oxadiazole(O-7)
Mol. Formula $C_{17}H_{15}FN_2O$, IR (KBr, cm^{-1}) υ: 1566.70 (C=C); 3403.84 (NH); 1188.31(C-O-C); 1311.91 (C=N); 1202.74(C-F), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.27-7.03 (m, 9H, Ar-H), 7.13(s, 1H,- NH), 6.11-6.04 (d,2H,-CH=CH),1.92(s, 3H, -CH_3), Mass : m/z: (M+1) $^+$283.14, Anal. Calcd/ Found: C, 72.32/72.30; H, 5.36/5.34; N, 9.92/9.90.

2-Methyl-2-phenyl-5styryl-2,3-dihydro-[1,3,4]oxadiazole(O-8)
Mol. Formula $C_{17}H_{16}N_2O$, IR (KBr, cm^{-1}) υ: 1597.76 (C=C); 3434.36 (NH); 1279.35 (C-O-C); 1390.04 (C=N), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.27-7.03 (m, 9H, Ar-H), 7.13(s, 1H,- NH), 6.11-6.04 (d,2H,-CH=CH-),1.92(s, 3H, -CH_3), Mass : m/z: (M+1) $^+$265.14, Anal. Calcd/ Found: C, 77.25/77.22; H, 6.10/6.09; N, 10.60/10.59;

Phenyl-(2-phenyl-5styryl-2,3-dihydro-[1,3,4]oxadiazol-2-yl)-methanone (O-9)
Mol. Formula $C_{23}H_{18}N_2O_2$, IR (KBr, cm^{-1}) υ: 1524.43 (C=C); 3435.33 (NH); 1215.44 (C-O-C); 1385.11 (C=N); 1668.53 (C=O), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.85-7.14 (m, 15H, Ar-H), 7.67(s, 1H,- NH), 6.21-6.09 (d,2H,-CH=CH-), Mass : m/z: (M+1) $^+$355.14, Anal. Calcd/ Found: C, 77.95/77.92; H, 5.12/5.10; N, 7.90/7.89.

Phenyl-(2-phenyl-5-styryl-2,3-dihydro-[1,3,4]oxadiazol-2-yl)-methanol (O-10)
Mol. Formula $C_{23}H_{20}N_2O_2$, IR (KBr, cm^{-1}) υ: 1597.76 (C=C); 3434.36 (NH); 1279.35 (C-O-C); 1390.04 (C=N),^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.33-7.16 (m, 15H, Ar-H), 6.79(s, 1H,- NH), 6.33-6.28 (d,2H,-CH=CH-),5.21(s, 1H, -OH),1.53(s, 1H, -CH-), Mass : m/z: (M+1) $^+$357.16, Anal. Calcd/ Found: C, 77.51/77.50; H, 5.66/5.61; N, 7.86/7.80.

4-(2-methyl-5-styryl-2,3-dihydro-[1,3,4]oxadiazol-2-yl)-phenylamine (O-11)
Mol. Formula $C_{17}H_{17}N_3O$, IR (KBr, cm^{-1}) υ: 1656.27 (C=C); 3479.09 (NH); 1122.51(C-O-C); 1312.11 (C=N); 3290.09 (C-NH_2), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 6.58-7.26 (m, 9H, Ar-H), 7.13(s, 1H,- NH), 6.04-6.11 (d,2H,-CH=CH-),3.67(s, 2H, -NH_2),1.92(s, 3H, -CH_3), Mass : m/z: (M+1) $^+$280.34, Anal. Calcd/ Found:C, 73.10/73.08; H, 6.13/6.11; N, 15.04/15.00.

2-(4-Bromo-phenyl)-2-methyl-5-styryl-2,3-dihydro-[1,3,4]oxadiazole (O-12)
Mol. Formula $C_{17}H_{15}BrN_2O$, IR (KBr, cm^{-1}) υ: 1596.32 (C=C); 3358.77 (NH); 1215.52 (C-O-C); 1392.14 (C=N); 1163.95 (C-Br), ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.47-7.05 (m, 9H, Ar-H), 7.13(s, 1H, -NH), 6.10-6.03 (d,2H,-CH=CH-),1.91(s, 3H, -CH_3), Mass : m/z: (M+1) $^+$343.22 Anal. Calcd/ Found: C, 59.49/59.42; H, 4.41/4.39; N, 8.16/8.12.

Chemistry
The title compounds were prepared according to the synthetic strategy described in Scheme 1. A mixture of cinnamic acid (0.01 M), 100 ml of ethanol and 1ml of sulphuric acid were refluxed for 6 hrs to produce(E)-methyl cinnamate. (E)-Methyl cinnamate and hydrazine hydrate (0.02 mol) was refluxed in dry ethanol (25 ml) for 14 hours and found (E)-cinnamohydrazide. 3-Phenyl-acrylic acid [1-(substituted-phenyl)-ethylidene]-hydrazide (0.01 moles) was dissolved in ethanol and chloramines T (0.05 moles) was added to it to give 2-(substituted-phenyl)-2-methyl-

5styryl-2,3-dihydro-[1,3,4]oxadiazole. The structure of newly synthesized compounds was confirmed by spectral and analytical data. The IR spectra of newly synthesized compounds revealed NH, C=N and C-O-C (oxadiazole) peaks near 3358, 1392 and 1279 cm^{-1}, respectively. The 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.

Anticonvulsant Activity

Among the all 12 best selected compounds with code H-9 was found in best conformation with least binding energy -7.4, other compounds H-10, O-7,O-8, O-9, O10, O11 and O12 were also comparable in their conformation and least binding energies. The compound O-9 having envelop of Amino acid residues are Ala 322, Ala 327, Cys 320, Glu 330, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319, Val 324. All Compounds showed activity in the range of 40-90% comparison to Phenytoin (Table 3). While test compounds H-9 possess flexion 5.53 ± 0.42, Extensor 2.5 ± 0.22 and O-9, Clonus 13.33 ± 0.42, Stupor 17.33 ± 0.4 and Recovery 112.67 ± 1.53.

Table 3: Activity in the range of 40-90% comparison to phenytoin

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 H9	5.53 ± 0.42**	2.5 ± 0.22**	13.33 ± 0.42**	17.33 ± 0.42**	112.67 ± 1.53**
IV	Test O10	6.33 ± 0.42**	4.16 ± 0.35**	13.12 ± 0.30**	17.0 ± 0.35**	113.35 ±1.50**
V	Test O9	5.66 ± 0.42**	4.83 ± 0.47**	13.16 ± 0.30**	17.5 ± 0.42**	113.50 ±1.57**
VI	Test H10	6.5 ± 0.56*	5.16 ± 0.47*	13.5 ± 0.42*	17.83 ± 0.60*	114.66 ± 1.65*
VII	Test O12	5.83 ± 0.47**	5.5 ± 0.42*	13.80 ± 0.60*	13.83 ± 0.60**	113.65 ± 1.60**
VIII	Test O7	7.66 ± 0.55*	5.83 ± 0.30*	14.16 ± 0.30*	18.5 ± 0.99*	115.70 ± 2.0*
IX	Test O8	8.16 ± 0.47	6.5 ± 0.42	14.5 ± 0.99*	19.0 ± 1.18*	116.01 ± 2.21*
X	Test O11	8.66 ± 0.49	7.0 ± 0.26	15.0 ± 1.06*	19.83 ± 1.27	117.25 ± 2.69*
XI	Test H12	8.72 ± 0.42	7.2 ± 0.26	15.6 ± 1.18	19.5 ± 0.99	119.65 ± 1.65*
XII	Test H8	8.83 ± 0.42	7.5 ± 0.30	15.83 ± 0.60	20.0 ± 0.35	120.6 ± 1.53*
XIII	Test H7	9.0 ± 0.49	7.86 ± 0.30	16.5 ± 0.42	22.5 ± 0.60	120.6 ± 1.65*
XIV	Test H11	9.5 ± 0.47	8.0 ± 0.42	16.9 ± 1.18	22.85 ± 0.99	126.85 ± 1.57

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

CONCLUSION

Twelve 3-Phenyl-acrylic acid [1-(substituted-phenyl)-ethylidene]-hydrazide(H-7) and 2-(substituted-phenyl)-2-methyl-5styryl-2,3-dihydro-[1,3,4]oxadiazoles were synthesized and docking analysis carried out for anticonvulsant activity. All Compounds showed activity in the range of 40-90% comparison to Phenytoin. H-9, H10, O-9, and O-10 possess good significant activity. Compound 3-Phenyl-acrylic acid (2-oxo-1,2-diphenyl-ethylidene)-hydrazide(H-9) was the most active compound in docking study having Least Binding energy -7.4 Kcal/mol with Amino acid residues Ala 322, Ala 327, Cys 320, Glu 330, Leu 291, Phe 323, Ser 326, Thr 294, Val 287, Val 319, Val 324. MES (ED50=20.11) tests.

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