"GREEN PHARMACOPHORE-GUIDED DESIGN OF EUGENOL CONJUGATED 2,5-DISUBSTITUTED-1,3,4-OXADIAZOLE SEMICARBAZONES AS PROMISING HERBAL ANTIEPILEPTIC AGENTS"

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Abstract

Due to the drawbacks of the present treatments, such as insufficient seizure control and dose-related side effects, the development of safer and more effective antiepileptic drugs continues to be a significant issue. In this work, a 2,5-disubstituted-1,3,4-oxadiazole nucleus was integrated with a natural green product scaffold, eugenol , to create novel semicarbazone derivatives using a rational drug design approach. The 1,3,4-oxadiazole ring was added to improve biological stability and maximize pharmacodynamic interactions, while eugenol was chosen as a bioactive precursor due to its proven pharmacological potential and favorable safety profile. Based on known pharmacophoric requirements for anticonvulsant effectiveness, such as hydrogen-bonding capacity, electron-donating properties, and hydrophobic aryl contacts, the semicarbazone moiety was added. A multistep synthesis route was used to design and create a variety of eugenol - coupled 2 , 5- di-substituted -1,3,4-oxadiazole semicarbazones. Standard methods such as mass spectroscopy, NMR, and infrared were used to confirm the synthetic compounds' molecular design. Using suitable experimental seizure models (MES) and the Rotarod test for neurotoxicity ,the newly synthesized compounds were assessed for their antiepileptic potential .The hybridization of a natural eugenol scaffold with oxadiazole and semicarbazone pharmacophores appears to be a viable strategy for the development of novel antiepileptic agents, as several compounds demonstrated encouraging anticonvulsant effects with improved safety profiles when compared to conventional therapy. These results suggest that 1,3,4-oxadiazole semicarbazones generated from eugenol could be viable lead compounds for additional development and optimization in antiepileptic medication research.

Keywords: 1,3,4-Oxadiazoles , Semicarbazones , Eugenol , Anticonvulsant activity
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Introduction

Epilepsy is the second most common neurological ailment, affecting over 51 million individuals globally. Many patients do not experience seizure control despite the optimal use of current antiepileptic medications, and those who do only do so at the expense of severe dose-related toxicity and unusual side effects that range in severity from mild brain impairment to death from aplastic anemia or hepatic failure [1]. These data highlight the pressing need for the creation of novel antiepileptic medications with increased effectiveness and fewer adverse effects.

Aryl semicarbazones have become a structurally new class of compounds having anticonvulsant activity throughout the past 22 years [2,3]. However, a number of studies have documented the anticonvulsant properties of quinazolines [6,7] and 1,3,4-thiadiazoles[4,5]. Therefore, the synthesis of test compounds with semicarbazide moiety, 1,3,4-thiadiazole, and quinazoline rings for their possible anticonvulsant efficacy was intriguing. Conformational studies of clinically proven anticonvulsant medications including phenytoin, lamotrigine, and phenobarbital [8] have led to the development of a pharmacophore model **(Figure.1)**. Four essential binding sites make up this semicarbazone-based pharmacophore model: (i) an aromatic hydrophobic binding site (A); (ii) a hydrogen bonding domain (HBD); (iii) an electron donor group (D); and (iv) another hydrophobic-hydrophilic site controlling the anticonvulsant's pharmacokinetic characteristics (C) **(Figure.2)**. Our research team has

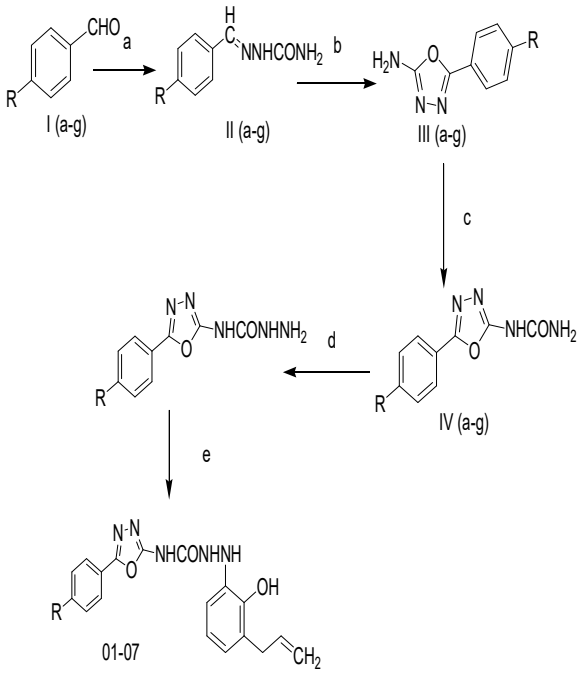
demonstrated in previous investigations on this pharmacophoric model that one of the key factors for anticonvulsant efficacy is the presence of a halogen-substituted aryl group close to the semicarbazone moiety [3,5].

Experimentation

Chemistry

E. Merck (Germany), Fisher Scientific (India), Himedia (India), and Spectro chem Pvt. Ltd. (India) provided all of the chemicals and solvents used in this investigation. Melting points are uncorrected and were calculated using the open capillary method. A Perkin Elmer IR spectrophotometer (KBr discs) (Perkin Elmer, Beaconsfield, UK) was used to record the IR spectra; a Bruker DRX-300 NMR spectrometer (DMSO-d6, TMS) (Bruker Bioscience, Billerica, MA, USA) was used to record the NMR spectra; and a Micromass Quattro II triple-quadrupole mass spectrometer (methanol) was used to record the electrospray mass spectrometer (Micromass, Manchester, UK).

The synthetic approach outlined in Reaction Scheme-I was used to create the title compounds. The synthesis strategy's initial step involves reacting semicarbazide hydrochloride with various aromatic aldehydes [I(a–g)] to create 4-substituted benzaldehyde semicarbazones [II(a–g)]. [II(a–g)] were oxidatively cyclized with bromine in the presence of CH3COOH to produce 2-amino-5-aryl-1,3,4-oxadiazoles [III(a–g)]. 1-[5-(4-substitutedphenyl)-1,3,4-oxadiazol-2-yl]-urea [IV(a–g)] was produced by reacting [III(a–g)] with sodium cyanate in the presence of CH3COOH.[9] By reacting [IV(a–g)] with hydrazine hydrate in the presence of sodium hydroxide, hydrazine carboxamides [V(a–g)] were created. The penultimate stage was combining eugenol with [V(a-g)] in the presence of ethanol and acetic acid to create final compounds 1–7.



Compound No.	(R)
I-a	H
I-b	Cl
I-c	OCH_3
I-d	NO_2
I-e	F
I-f	CH_3
I-g	OH

Reaction Scheme 1 : Synthesis of eugenol based 2 , 5 - disubstitued 1,3,4-Oxadiazole analogues (1–7).

Reagents and conditions: (a) $H_2NNHCONH_2 \cdot HCl$, CH_3COONa **(b)** Br_2, CH_3COOH, 45 min stirring ; **(c)** NaCNO , CH_3COOH ; **(d)** $NH_2NH_2 \cdot H_2O$, EtOH, NaOH, 6–8 hrs reflux ; **(e)** Eugenol , glacial acetic acid, ethanol, 1 hrs to 1.5 hrs reflux .

The general synthesis process for semicarbazones of 4-substituted benzaldehyde [II(a-g)]- This approach was used to synthesis the necessary semicarbazones. After dissolving semicarbazide HCl (0.02 mol) and crystalline sodium acetate (0.04 mol) in 18–20 milliliters of water, aldehyde (0.02 mol) was added and thoroughly shaken. If the mixture was turbid, acetone-free alcohol was added until a clear solution was achieved. The mixture was then agitated for a few minutes before being left to stand. The crystals were filtered out, washed with a little cold

water, and then recrystallized from water, methanol, or ethanol, either by themselves or diluted with water.[10].

Compounds: II(a) yield 66.7 % , m.p. 209-211 **°C** ; **II(b)** yield 77.5 % , m.p. 230-232 **°C ; II(c)** yield 69.2 % , m.p. 209-211**°C ; II(d)** yield 72.4 % m.p. 197-199 **°C ; II(e)** yield 67.3 % , m.p. 214-216 **°C ; II(f)** yield 73.5 % m.p. 235-237 **°C ; II(g)** yield 66.5 % ,m.p. 226-228 **°C** , **IR (KBr)** : 3079.34 (Aromatic C-H), 1606.32 & 1526.36 (Aromatic C=C str), 3460.22 (Secondary amine N-H str), 1696.25 (Imine C-N str), 1658.35 (Amide group C=O str), 3672.24 (Amide group N-H str), 856.48 (Aromatic ring C-H def) .

The general synthesis process of 2-amino-5-aryl-1,3,4-oxadiazole[III(a-g)] -

This approach was used to synthesis the necessary 1.3.4-oxadiazole. In a round-bottomed flask with a separating funnel for the addition of bromine, 70–80 ml of CH3COOH was used to dissolve semicarbazone (0.02 mol) and sodium acetate (0.04 mol). While stirring magnetically, bromine (1.4 ml in 10 ml of CH3COOH) was gradually added. The mixture was dumped onto crushed ice after 45 minutes of stirring. The resultant material was removed from ethanol, dried, and then recrystallized.[11].

Compounds: III(a) yield 72.5 % , m.p. 219-221 **°C** ; **III(b)** yield 68.2 % , m.p. 202-204 **°C ; III(c)** yield 74.2 % , m.p. 189-191 **°C ; III(d)** yield 69.2 % m.p. 208-210 **°C ; III(e)** yield 66.2 % , m.p. 214-216 **°C ; III(f)** yield 77.2 % m.p. 209-211 **°C ; III(g)** yield 69.2 % ,m.p. 220-222 **°C. IR (KBr)** : 1085.24 (1,3,4-oxadiazole C-O str), 1656.25 (1,3,4-oxadiazole C-N str), 1505.32 & 1608.15 (Aromatic C=C str), 757.82 (Primary amine N-H str)

The general synthesis process of 1-(5-para substituted phenyl-1,3,4-oxadiazol-2-yl)urea [IV(a-g)] - In 20–50 ml of CH3COOH diluted to 100 ml with distilled water, the proper 2-amino-5-para substituted phenyl-1,3,4-oxadiazole (0.02 mol) was dissolved. Stirring, an equimolar amount of sodium cyanate was added to 40–50 milliliters of warm water. The precipitates were collected by filtration, cleaned with cold water, and recrystallized from 90% aqueous ethanol after the reaction mixture was let to stand for a few hours in an ice bath.[12]

Compounds: IV(a) yield 66.2 % , m.p. 234-236 **°C** ; **IV(b)** yield 67.2 % , m.p. 273-275 **°C ; IV(c)** yield 59.5 % , m.p. 242-244 **°C ; IV(d)** yield 63.2 % m.p. 189-191 **°C ; IV(e)** yield 57.2 % , m.p. 251-253 **°C ; IV(f)** yield 70.8 % m.p. 234-236 **°C ; IV(g)** yield 69.3 % ,m.p. 229-231 **°C IR (KBr)** : 1108.36 (1,3,4-oxadiazole C-O str), 1659.29 (1,3,4-oxadiazole C-N str),1608.33 (Aromatic C=C str), 754.48 (Primary amine N-H str) , 3073.29 (Aromatic C-H str) , 1689.14 (Amide C-O str) , 3473.23 (Amide N-H str) , **ESMS(Methanol)** m/z 204.76 ($[M+H]^+$).

The general synthesis process of 4-(5-para substituted phenyl–1,3,4 - oxadiazol-2-yl) semicarbazide [V(a-g)] – In 60–70 milliliters of ethanol, IV(a–g) (0.02 mol) was dissolved. An equimolar solution of hydrazine hydrate in 10 milliliters of water was added to this, and 8 grams of NaOH pellets were added to make the reaction mixture alkaline. After heating the contents to reflux for six to eight hours, they were cooled in an ice bath. 90% ethanol was used to filter and recrystallize the resulting product **[V(a-g)]**.[13]

Compounds: V(a) yield 72.2 % , m.p. 239 - 241 **°C** ; **V(b)** yield 68.2 % , m.p. 264-266 **°C ; V(c)** yield 69.4 % , m.p. 233-235 **°C ; V(d)** yield 70.4 % m.p. 164-166 **°C ; V(e)** yield 65.3 % , m.p. 280-282 **°C ; V(f)** yield 62.4 % m.p. 253-255 **°C ; V(g)** yield 58.5 % ,m.p. 254-256 **°C , IR (KBr)** : 1095.25 (1,3,4-oxadiazole C-O str), 1677.55 (1,3,4-oxadiazole C-N str) , 1529.35 (Aromatic C=C str), 748.59 (Primary amine N-H str) , 3076.18 (Aromatic C-H str) , 3467.45 (Amide N-H str) , **ESMS(Methanol)** m/z 219.70 ($[M+H]^+$) , **^{1}HNMR δ (ppm)** (DMSO-d_6,TMS) 7.3 -7.4 (ArH) , 6.04 (**δ**,1H, NHCONHN)

The general synthesis process of 2-(3-allyl-2hydroxyphenyl)-N-(5-(p-alkyl)-1,3,4-oxadiazol-2-yl)hydrazine-1-carboxamide

50 milliliters of 95% ethanol were used to dissolve an equimolar amount of [V(a-g)] and eugenol (0.02 mol). Glacial acetic acid was then added to the reaction mixture to bring its pH between 4 and 5. After refluxing for 45 minutes to 1.5 hours, the liquid was chilled in an ice bath. The precipitates were filtered, dried, and recrystallized from 95% aqueous ethanol after the solution was poured over broken ice to cause crystallization.[14]

Compound (01): Pale yellow Colour , %Yield 47 % , m.p. 227-229 **°C,** Rf value. 0.35 ; **IR (KBr)** : 1131.55 (1,3,4-oxadiazole C-O str), 1705.85 (1,3,4-oxadiazole C-N str) , 1508.62 & 1609.67 (Aromatic C=C str) , 1672.56 (Eugenol C=C str (allyl)) , 1876.65 (Carbonyl C=O str) , 2932.65 { Eugenol C-H str (allyl)} , 1261.85 (Eugenol C-O str) , 3402.55 (Eugenol O-H str) , 3466.88 (Amide N-H str) , **^{1}HNMR δ (ppm)** (DMSO-d_6,TMS) 7.22-7.43 (Ar-H) , 6.05 (**δ**,1H,NHCONHN) ,1.75 {**δ**,1H, CH3,

C(CH2)CH3}, 7.2 (**δ**,1H, NHCONHN), 5.27 {**δ**,1H, CH (Terpene)}, 2.01, 1.98{**δ**,1H, CH2 (Terpene)}.

Compound (02): Cream Colour , %Yield 57 % ; **M.P** 241-243**°C ; Rf value** 0.44 **; IR (KBr)** : 827.38 (C-H def para aromatic) . 744.44 (Ar-Cl str) , 1132.58 (1,3,4-oxadiazole C-O str), 1658.88 (1,3,4-oxadiazole C-N str) , 1735.24 (Amide C=O str) , 1613.33 (Eugenol C=C str (allyl)), 2933.55 { Eugenol C-H str (allyl)} , 1260.65 (Eugenol C-O str) , 3403.65 (Eugenol O-H str) , 3468.28 (Amide N-H str) , **^{1}HNMR δ (ppm)** (DMSO-d_6,TMS) 7.34-7.54 (Ar-H) , 6.10 (**δ**,1H,NHCONHN) ,1.73 {**δ**,1H, CH3, C(CH2)CH3}, 7.03 (**δ**,1H, NHCONHN), 5.45 {**δ**,1H, CH (Terpene)}, 2.25, 1.83{**δ**,1H, CH2 (Terpene)}.

Compound (03): Dark cream Colour , yield 45 % , m.p. 157-159 **°C ,** Rf value. 0.41 **; IR (KBr)** : 1132.44 (1,3,4-oxadiazole C-O str), 1262.56 (C-O str Methoxy group), 1654.34 (1,3,4-oxadiazole C-N str) , 1696.56 (Amide C=O str), 1616.84 (Eugenol C=C str (allyl)), 2935.65 { Eugenol C-H str (allyl)} , 1333.25 (Eugenol C-O str) , 3406.62 (Eugenol O-H str) , 3464.89 (Amide N-H str) , **^{1}HNMR δ (ppm)** (DMSO-d_6,TMS) 7.33-7.44 (Ar-H) , 6.04 (**δ**,1H,NHCONHN) , 1.75 {**δ**,1H, CH3, C(CH2)CH3}, 7.07 (**δ**,1H, NHCONHN), 5.25 {**δ**,1H, CH (Terpene)}, 2.24{**δ**,1H, CH2 (Terpene)}.

Compound (04) Dark yellow Colour, %Yield 41 % m.p. 271-273 **°C ,** Rf value. 0.60 **; IR (KBr)** : 1135.48 (1,3,4-oxadiazole C-O str), 1532.35 (N-O str Nitro group), 1657.36 (1,3,4-oxadiazole C-N str), 1617.84 & 1511.14 (Aromatic C=C str), 1694.55{ C-O str (Amide group), 1266.53 (Eugenol C-O str) , 2937.63 { Eugenol C-H str (allyl)}, 1647.66 {Eugenol C=C str (allyl)} , 3408.64 (Eugenol O-H str), 3468.86 (Amide N-H str) ; **^{1}HNMR δ (ppm)** (DMSO-d_6,TMS) 8.27 (**δ**,1H, NO2) , 1.75 {**δ**,1H,CH3,C(CH2)CH3}, 7.06 (**δ**,1H,NHCONHN), 5.25 { **δ**,1H, CH(Terpene)}, 2.24 { **δ**,1H, CH2 (Terpene)}

Solubility: Approximate 100 mg of synthesized compounds taken in solvent. The solubility of synthesized compounds is shown in table-1.

Table-1, The solubility profile of synthesized compounds

Compound.	**H2O**	**Hot H2O**	**Et OH**	**Me OH**	**C6H6**	**CHCl3**	**GA**	**5 % HCl**
1	-	-	++	++	-	+	++	-
2	-	-	+	+	+	++	+++	+
3	-	-	+	+	-	++	++	-
4	-	-	+	+	-	+	+++	-
5	-	-	++	++	+	++	++	-
6	-	-	+	+	-	++	++	+
7	-	-	+	+	-	++	++	-

Where (-) Insoluble, (+) slightly soluble, (++) sparingly soluble, (+++) freely Soluble

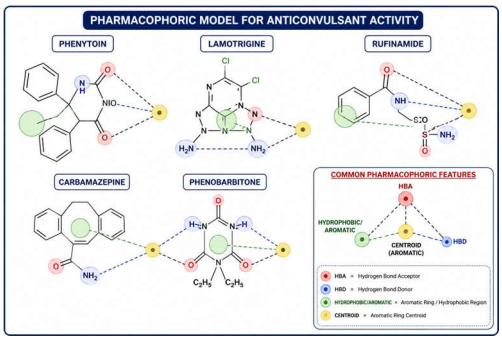


Figure 1. Pharmacophoric Structural Features In Standard Drugs :

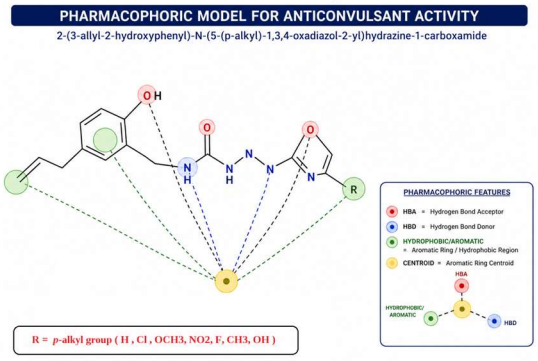


Figure 2. Pharmacophoric Structural Features In Title Compounds:

Table 2 : Anticonvulsant and Neurotoxicity Screening of Eugenol based 2,5-disubstituted-1,3,4-oxadiazoles .

Compound [a]	**MES screening [b]**		***Sc* PTZ screening [b]**		**NT screening [b]**	
	0.5 hr	**4.0 hrs**	**0.5 hr**	**4.0 hrs**	**0.5 hr**	**4.0 hrs**
1	-	300	-	-	-	300
2	10	30	-	30	-	-

	0	0		0		
3	-	-	-	-	300	-
4	100	300	100	300	-	-
5	100	300	-	300	-	300
6	-	-	-	-	300	-
7	100	300	-	300	-	-
Phenytoin	50	50	-	-	100	100
Carbamazepine	30	100	100	300	100	300
Na Valproate	300	-	300	-	-	-
Ethosuximide	-	-	100	300	-	-

Abbreviations : MES = maximal electroshock seizure ; *sc*PTZ = subcutaneous pentylene -tetrazole ; NT= neurotoxicity.

[a] 50, 100 and 300 mg/kg of doses were administered ip in the animals . The data in the table indicates the minimal dose where by biological activity was demonstrated in half or more of the animals. The activity was measured after 0.5 and 4.0 h of dose administration of test compounds. The sign—(dash) represents an absence of activity at maximum dose administered (300 mg/kg).

[b] Mice were employed in this biological evaluation.

Table 3 : Anticonvulsant evaluation of compounds after oral administration in rats

Compound	**Oral Adminstration in Rats [a]**									
	MES Screening					**NT Screening**				
	0.5 hr	**1 hr**	**1.5 hrs**	**2 hrs**	**4 hrs**	**0.5 hr**	**1 hr**	**1.5 hrs**	**2 hrs**	**4 hrs**
2	++++	++++	+++	++	++	-	-	-	+	-
4	++++	+++	+++	+++	+++	-	-	-	-	-
7	+++	+++	+++	++	+	-	+	-	-	-
Phenytoin	++++	++++	+++	+++	+	-	-	-	-	-

[a] The compounds were administered in a dose of 50 mg/kg. The elaborations of symbols is as follows: ++++ : activity in 75–100% of rats; +++ : activity in 50–75% of rats; ++ : activity in 25–50% of rats; + : activity in 0–25% of rats; — (dash): no activity or neurotoxicity.

Male albino mice (Swiss, 25–30g) and rats (Wistar,150–200g) were used to determine the antiepileptic potential [15-16] of test substances. Two models, maximal electroshock seizure (MES) and subcutaneous pentylene-tetrazole (sc PTZ), were used to determine the anticonvulsant activity. The rotarod test was used to screen for acute neurological toxicity in mice.[17]. The anticonvulsant potential of all the generated compounds was evaluated by intra peritoneal (ip) injection at doses of 50, 100, and 300 mg/kg. According to the findings, 72% of compounds 1-2, 4, 5, and 7 were active in the MES evaluation, while 55% of compounds 2, 4, 5, and 7 were active in the scPTZ test. These findings demonstrate that some drugs have MES selectivity (Tables 2 and 3). After 4 hours, all of the compounds—aside from 3 and 6—showed biological activity in either MES or sc PTZ, suggesting that the test compounds are slow-acting anticonvulsants. It is important to note that in the rotarod test, only 57% of the test compounds—that is, 1, 3, 5, and 6—were shown to be neurotoxic.

Due to the test compounds' low molecular weight and great lipid solubility, eugenol was added as a moiety. By altering the activity of GABA receptors, they can therefore get through the blood-brain barrier and influence the central nervous system. The current research' findings demonstrated the high potency of compounds with groups like hydroxy and nitro on distant phenyl rings in MES and scPTZ tests. However, substituting these groups on the distant phenyl ring with methyl or methoxy groups has produced molecules with less anticonvulsant efficacy. When the structure and biological activity of the compounds were compared, it was discovered that the compound with nitro substitution had the highest activity and the compound with methyl substitution the lowest. Among all test compounds, in terms of their substitutents, structure activity relationship may be summarized as follows: NO_2 > Cl > OH > F > H > OCH_3 > CH_3 . SAR of test compounds was found quite convincing with earlier reports.[18-23]

The title compounds were designed and synthesized while keeping in mind that a number of clinically active anticonvulsants possess a heteroatomic system of nitrogen with one phenyl rings and at least one carbonyl group in their structure. The structure of the title compounds 01–07 satisfied all the pharmacophoric structural requirements that is,

presence of 5-{4-substituted-phenyl}-1,3,4-oxadiazol-2-yl moiety as hydrophobic portion, -NH as electron donor system, and another hydrophobic distal hydrocarbon moiety in the form of eugenol might be responsible for controlling the anticonvulsant's pharmacokinetic characteristics. Thus, these findings confirmed the long-established four binding site hypothesis for semicarbazones. In the present study 2- (3-allyl-2-hydroxyphenyl)-N-(5-(p-nitro)-1,3,4-oxadiazol-2-yl)hydrazine-1-carboxamide {compound– 4} emerged out as the most active compound showing considerable activity in maximal electroshock seizure (at 100 mg/kg after 0.5 h and at 300mg/kg after 4.0 h), sub-cutaneous pentylene-tetrazole model (at 100 mg/kg after 0.5 h and at 300 mg/kg after 4.0 h) with out any neurotoxicity (up to 300 mg/kg after 4.0 h).

Conclusion

In order to satisfy the structural requirements required for anticonvulsant efficacy, a series of new 2-(3-allyl-2hydroxyphenyl)-N-(5-(p-alkyl)-1,3,4-oxadiazol-2-yl)hydrazine-1-carboxamide {01-07} were produced. It was discovered that the semicarbazones based on eugenol have more anticonvulsant action. Our findings confirmed that a pharmacophoric model with four binding sites is necessary for anticonvulsant efficacy.

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