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DESIGN AND SYNTHESIS OF NOVEL HYDRAZONES OF ETHYL3-AMINO-4-HYDROXYBENZOATE AS PROMISING ANTICONVULSANT AGENTS

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Keywords:

Substituted hydrazide-hydrazone, Anticonvulsants, Rotarod, Lipophilicity

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ABSTRACT: A series of hydrazide-hydrazones (3a-o) have been synthesized by the reaction of acid hydrazide (2) which is obtained from 4-carbomethoxy-2-aminophenol with aromatic acid through multi-steps. The bioactivities of the final compounds were tested with MES and *sc*PTZ methods. The CNS toxicity was studied by the rotarod experiment. Based on the results, compounds 3d and 3o were found to be most active at 30 $mgkg^{-1}$ in the MES test with prolonged duration of action; they exhibited activity comparable to standard drugs phenytoin and carbamazepine. Compounds 3f, 3j and 3m exposed toxicity (300 $mgkg^{-1}$) at 0.5 h of the time period and compounds 3i, 3n and 3o exhibited late toxicity after 4.0 h as compared to carbamazepine. The rest of the compounds did not face toxicity at a maximum dose level (300 $mgkg^{-1}$). This study shows that increased lipophilicity is directly related to the anticonvulsant activity. Further studies need to be carried out on other seizure tests and models of epilepsy to ascertain the precise mechanism of action of these molecules.

INTRODUCTION: Epilepsy is a cerebrum issue described by frequency of more than one epileptic seizure with persistent tendency to produce further epileptic assaults connected with neurobiological, mental, sociological, economic, and cultural influences [1, 2].

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It has now become the severe syndrome, which accounts for about 1-2% of the world's problem of ailments [3], affecting nearly 40-50 million of manhood with the common of cases existence in developing nations [4, 5].

Each year nearly 0.25 million new cases are added to this digit [5, 6]. It was reported that the occurrence of epilepsy is greater in rural (1.9%) as related to the urban people (0.6%) [7, 8]. In spite of the fact that the ideal use of existing antiepileptic drugs, 30% of patients with epilepsy proceed [9] and others experience the seizure control just to the detriment of deplorable prescription-related reactions, for

example, CNS hindrances, a plastic iron deficiency, hepatic distress [10]. Up till now, 30-40% of patients are impervious to the current drugs [5]. Right now, accessible AEDs stifle seizures, yet don't resolve the pathophysiological procedure fundamental a patient's epilepsy, nor do they keep the advancement of seizures in patients without epilepsy however at high hazard, for example, the individuals who endure genuine brain damage [11]. The restrictions with accessible medications tinted the prerequisite for advancing more up to date wide-extending and increasingly drug protection outline [12, 13]. However, the advancement of the few new antiepileptics tranquilizes, the treatment of epilepsy as yet difficult [14]. Benzoxazole and their derivatives have been reported to elicit such activities [15-18]. In addition, hydrazide-hydrazones derivatives also exhibit potent antimicrobial [19, 20], anti-tubercular [21, 22], anti-fungal [23, 24], anti-inflammatory [25, 26], anticancer [27], antidepressant [28] and anticonvulsant [29-32] activities. For anti-convulsant action, the predictable pharmacophore model was proposed during the study of semi-carbazones [33, 34] according to which four necessary binding sites **Fig. 1**. These sites are

- An aryl binding location (A) with halogen substituent preferably at *para* position.
- Hydrogen bonding domain (HBD).
- An electron donor group (D) and
- Additional hydrophobic/hydrophilic position (C) controlling the pharmacokinetic properties of the antiepileptic drugs.

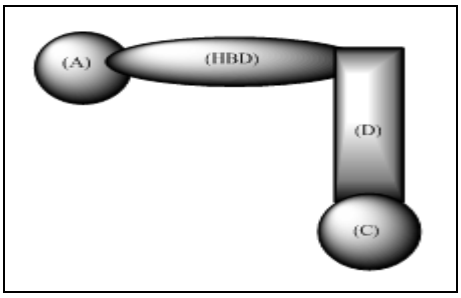


FIG. 1: PROPOSED PHARMACOPHORE MODEL FOR ANTICONVULSANT ACTION

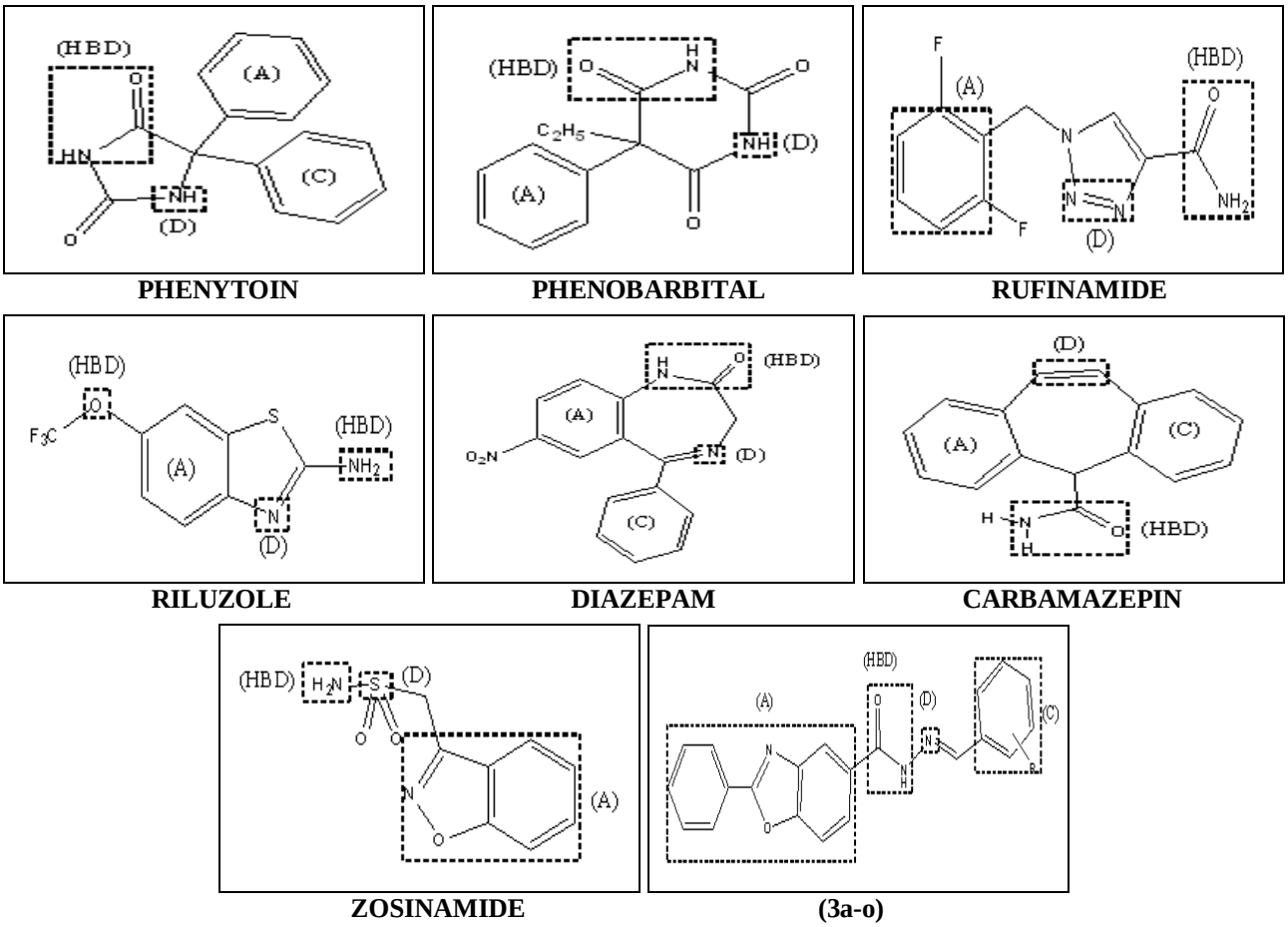


FIG. 2: STRUCTURE OF PROPOSED UNIVERSAL PHARMACOPHORE MODEL OF THE PREPARED MOLECULES AND REPORTED MEDICINES

The above moieties are found in the chemical structures of conventional antiepileptic drugs. The synthesized molecules possessed all the required pharmacophores **Fig. 2** such as benzoxazole ring a hydrophobic aryl ring (A), –NHC=O hydrogen bonding domain (HBD), =N– an electron donor atom (D) and phenyl as distal aryl ring (C). Encouraged by these results and in furtherance of our endeavors in making different bioactive candidates, we have joined a 2-substituted benzoxazole nucleus by substituted aryl substituent of the hydrazone subunit on the anticonvulsant activity.

MATERIALS AND METHODS:

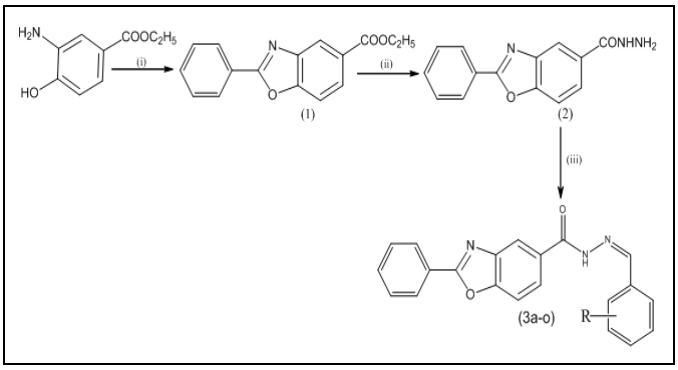
Chemistry: Perkin-Elmer model 240 analyzer was used for elemental analysis. The FT-IR spectra of the compounds were obtained in KBr by the FT-IR spectrophotometer (BIO-RADFTS). Bruker 300MHz and 400 Ultra Shield^{TM} instrument using DMSO/d_6 with TMS as internal standard was used to record ^{1}H- NMR spectrum. Mass spectra of the compounds were noted on UPLC-MS/MS (WATERS, Mass Lynx version 4.1) spectrometer. The melting points recorded on digital melting point apparatus which are unchecked. Thin-layer chromatography plates (Merk) was used to determine the completion of the reaction in different solvent systems. Visualization was made with ultraviolet light. All chemicals and solvents (Spectrochem and CDH) were purified before using them. The spectral records of the new molecules are presented in experimental protocols.

Synthesis:

Synthesis of methyl 2-(3-chlorophenyl)-1,3-benzoxazole-5-carboxylate (1) and their hydrazide (2): These compounds were synthesized from 4-carbomethoxy-2-aminophenol according to the method from the literature [35, 36].

General Procedure for Synthesis of benzoxazole hydrazide-hydrazones (3a-o): An equimolar quantity of the substituted aromatic aldehydes and compound 2 (0.01 mol) was refluxed for 8-10 h in alcoholic condition with a catalytic amount of glacial acetic acid. The reaction mixture concentrated to half of the volume transferred in freeze water and the precipitate found was cleaned and desiccated the precipitate in a desiccator, was recrystallized from alcoholic medium to get solid (3a). The other compounds (3b-o) were also getting by the same technique [37, 38].

The preparation of the compounds is displayed **Scheme 1**.



SCHEME 1: CHEMICALS AND CONDITION: (I) BENZOIC ACIDS, ABS. ETHANOL, REFLUX; (II) HYDRAZINE HYDRATE, ABS. ETHANOL, REFLUX; (III) SUBSTITUTED AROMATIC ALDEHYDES, GAA, REFLUX

2- phenyl- N'- [(E)- phenylmethylidene]- 1, 3-benzoxazole-5-carbohydrazide (3a): Yield 55%; m.p. 130-132 °C; IR (KBr, cm^{-1}): 3321 (NH), 3021 (CH str), 1691 (C=O), 1600 (C=N). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.55 (s, 1H, NH), 8.35 (s, 1H, CH=), 7.40-8.12 (m, 13H-Ar). Mass m/z: 342 (M+1). Anal Calcd for $C_{21}H_{15}N_3O_2$: C, 74.03; H, 4.11; N, 12.23; Found: C, 73.89; H, 4.43; N, 12.31.

N'- [(E)-(2-chlorophenyl)methylidene]-2-phenyl-1, 3-benzoxazole-5-carbohydrazide (3b): Yield 67%; m.p. 145-147 °C; IR (KBr, cm^{-1}): 3201 (NH), 3058 (CH str), 1669(C=O), 1592 (C=N), 721 (C-Cl). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.51 (s, 1H, NH), 8.45 (s, 1H, CH=), 7.41-8.21 (m, 12H-Ar). Mass m/z: 376 (M+1). Anal calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.50; H, 3.65; N, 11.21; Found: C, 67.12; H, 3.75; N, 11.18.

N'- [(E)-(3-chlorophenyl) methylidene]-2-phenyl-1,3-benzoxazole-5-carbohydrazide (3c): Yield 65%; m.p. 145-147 °C; IR (KBr, cm^{-1}): 3223 (NH), 3033 (CH str), 1676 (C=O), 1599 (C=N), 726 (C-Cl). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.64 (s, 1H, NH), 8.34 (s, 1H, CH=), 7.56-8.07 (m, 12H-Ar). Anal calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.50; H, 3.65; N, 11.21; Found: C, 67.12; H, 3.75; N, 11.18.

N'- [(E)-(4-chlorophenyl)methylidene]-2-phenyl-1, 3- benzoxazole-5-carbohydrazide (3d): Yield 71%; m.p. 140-142 °C; IR (KBr, cm^{-1}): 3198 (NH),

3001 (CH str), 1668 (C=O), 1611 (C=N), 718 (C-Cl). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.61 (s, 1H, NH), 8.39 (s, 1H, CH=), 7.44-8.19 (m, 12H-Ar). Anal calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.50; H, 3.65; N, 11.21; Found: C, 67.12; H, 3.75; N, 11.18.

N'-[(E)-(2-bromophenyl) methylidene]-2-phenyl-1, 3-benzoxazole- 5- carbohydrazide (3e): Yield 45%; m.p. 150-152 °C; IR (KBr, cm^{-1}): 3278 (NH), 3076 (CH str), 1671 (C=O), 1607 (C=N), 591 (C-Br). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.44 (s, 1H, NH), 8.30 (s, 1H, CH=), 7.66-8.01 (m, 12H-Ar). Mass m/z: 420 (M+1). Anal calcd for $C_{21}H_{14}BrN_3O_2$: C, 60.11; H, 3.41; N, 10.09; Found: C, 60.02; H, 3.36; N, 10.00.

N'-[(E)-(4-bromophenyl) methylidene]-2-phenyl-1, 3-benzoxazole- 5- carbohydrazide (3f): Yield 51%; m.p. 150-152 °C; IR (KBr, cm^{-1}): 3300 (NH), 3034 (CH str), 1677 (C=O), 1601 (C=N), 598 (C-Br).^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.46 (s, 1H, NH), 8.39 (s, 1H, CH=), 7.49-8.18 (m, 12H-Ar). Anal calcd for $C_{21}H_{14}BrN_3O_2$: C, 60.11; H, 3.41; N, 10.09; Found: C, 60.02; H, 3.36; N, 10.00.

N'- [(E)- (2- hydroxyphenyl) methylidene]- 2-phenyl- 1, 3-benzoxazole-5-carbohydrazide (3g): Yield 76%; m.p. 140-142 °C; IR (KBr, cm^{-1}): 3321 (NH), 3316 (OH str), 3057 (CH str), 1711 (C=O), 1613 (C=N). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.41 (s, 1H, NH), 9.44 (s, 1H, OH), 8.77 (s, 1H, CH=), 7.41-8.29 (m, 12H-Ar). Mass m/z: 358 (M+1). Anal calcd for $C_{21}H_{15}N_3O_3$: C, 70.44; H, 4.00; N, 11.79; Found: C, 70.58; H, 4.23; N, 11.76.

N'- [(E)- (4- hydroxyphenyl) methylidene]- 2-phenyl-1, 3-benzoxazole-5-carbohydrazide (3h): Yield 70%; m.p. 145-147 °C; IR (KBr, cm^{-1}): 3307 (NH), 3298 (OH str), 3037 (CH str), 1691 (C=O), 1611 (C=N). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.40 (s, 1H, NH), 9.41 (s, 1H, OH), 8.68 (s, 1H, CH=), 7.46-8.51 (m, 12H-Ar). Mass m/z: 358 (M+1). Anal calcd for $C_{21}H_{15}N_3O_3$: C, 70.44; H, 4.00; N, 11.79; Found: C, 70.58; H, 4.23; N, 11.76.

N'- [(E)-(3-nitrophenyl)methylidene]-2-phenyl-1, 3-benzoxazole-5-carbohydrazide (3i): Yield 65%; m.p. 170-172 °C; IR (KBr, cm^{-1}): 3211 (NH), 3051 (CH str), 1696 (C=O), 1609 (C=N), 1518 (NO_2). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.52 (s, 1H, NH), 8.48 (s, 1H, CH=), 7.40-8.30 (m, 12H-Ar). Anal calcd for $C_{21}H_{14}N_4O_4$: C, 65.10; H, 3.46; N, 14.34; Found: C, 65.28; H, 3.65; N, 14.50.

N'- [(E)-(4-nitrophenyl)methylidene]-2-phenyl-1, 3- benzoxazole- 5- carbohydrazide (3j): Yield 60%; m.p. 175-177 °C; IR (KBr, cm^{-1}): 3201 (NH), 3066 (CH str), 1701 (C=O), 1590 (C=N), 1511 (NO_2). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.52 (s, 1H, NH), 8.48 (s, 1H, CH=), 7.40-8.30 (m, 12H-Ar). Anal calcd for $C_{21}H_{14}N_4O_4$: C, 65.10; H, 3.46; N, 14.34; Found: C, 65.28; H, 3.65; N, 14.50.

N'- [(E)- (2, 6- dichlorophenyl)methylidene]-2-phenyl-1, 3-benzoxazole-5-carbohydrazide (3k): Yield 75%; m.p. 160-162 °C; IR (KBr, cm^{-1}): 3222(NH), 3081 (CH str), 1698 (C=O),1600 (C=N), 713 (C-Cl). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.34 (s, 1H, NH), 8.41 (s, 1H, CH=), 7.47-8.26 (m, 11H-Ar). Anal Calcd for $C_{21}H_{13}Cl_2N_3O_2$: C, 61.23; H, 3.41; N, 10.31; Found: C, 61.48; H, 3.19; N, 10.24.

N'- [(E)-(2-chloro-5-nitrophenyl)methylidene]-2-phenyl-1, 3-benzoxazole-5-carbohydrazide (3l): Yield 40%; m.p. 185-187 °C; IR (KBr, cm^{-1}): 3262 (NH), 3077 (CH str), 1694 (C=O), 1601 (C=N), 701 (C-Cl). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.47 (s, 1H, NH), 8.52 (s, 1H, CH=), 7.41-8.33 (m, 11H-Ar). Mass m/z: 421 (M+1). Anal calcd for $C_{21}H_{13}ClN_4O_4$: C, 60.11; H, 3.23; N, 13.00; Found: C, 59.94; H, 3.11; N, 13.31.

N'- [(E)- (2-fluorophenyl)methylidene]-2-phenyl-1, 3-benzoxazole-5-carbohydrazide (3m): Yield 55%; m.p. 140-142 °C; IR (KBr, cm^{-1}): 3245 (NH), 3043 (CH str), 1677 (C=O),1621 (C=N), 1215 (C-F). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.40 (s, 1H, NH), 8.71 (s, 1H, CH=), 7.55-8.54 (m, 12H-Ar). Mass m/z: 360 (M+1). Anal calcd for $C_{21}H_{14}FN_3O_2$: C, 70.12; H, 3.78; N, 12.01; Found: C, 70.19; H, 3.93; N, 11.69.

***N*'- [(*E*)- (2-bromo-5-fluorophenyl)methylidene]-2-phenyl-1,3-benzoxazole-5-carbohydrazide(3n):** Yield 50%; m.p. 145-147 °C; IR (KBr, cm^{-1}): 3229 (NH), 3065 (CH str), 1699 (C=O), 1611 (C=N), 1218 (C-F), 598 (C-Br). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.44 (s, 1H, NH), 8.56 (s, 1H, CH=), 7.51-8.39 (m, 11H-Ar). Anal calcd for $C_{21}H_{13}BrFN_3O_2$: C, 57.32; H, 3.12; N, 9.43; Found: C, 57.55; H, 2.99; N, 9.59.

N'- [(E)- (4-bromo-2-fluorophenyl)methylidene]-2-phenyl-1,3-benzoxazole-5-carbohydrazide(3o): Yield 55%; m.p. 140-142 °C; IR (KBr, cm^{-1}): 3309 (NH), 3067 (CH str), 1709 (C=O), 1610(C=N), 1215 (C-F), 590 (C-Br). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.44 (s, 1H, NH), 8.56 (s, 1H, CH=), 7.51-8.39 (m, 11H-Ar). Anal calcd for $C_{21}H_{13}BrFN_3O_2$: C, 57.32; H, 3.12; N, 9.43; Found: C, 57.55; H, 2.99; N, 9.59.

Biological Activity:

Anticonvulsant Screening: All the compounds were tested for their antiepileptic actions via *sc*PTZ and MES methods. MES, scPTZ, and rotarod assessments can be used in extraordinary screening, as displayed through the National Institute of Health Anticonvulsant Screening Program [39, 40]. All compounds were suspended in polyethylene glycol and experiments were done on mice (20-25 g), obtained from the Institutional Animal Ethics committee, R.V. Northland Institute, Dadri, Greater Noida, Uttar Pradesh, India, under the proposal number RVNI/IAEC/2017/05. The anticonvulsant potential and neurotoxicity results are reported in **Table 2**.

Maximal Electroshock (MES) Test: A 60 Hz alternating current of 50 mA intensity for 0.2 s through corneal clips evoked maximal seizures in mice, effects were measured at 0.5 and 4 h afterward drug administration (30, 100 and 300 mg/kg). As a result, a reflection of tonic and clonic spasms looking throughout the seizure was noted [39, 40].

Subcutaneous Pentylenetetrazole Seizure (scPTZ) Test: *sc*PTZ were injected *i.p.*at 75 mg/kg which produce seizures in mice. The animals were noticed for 30 min later the dose of test analogs. Safety against the spread of seizures at least 5 s duration was defined as the protection against clonic spasm [41].

Minimal Motor Impairment Test: In mice, the minimal motor or neurological interference was tested by rotorod method [42]. Failure of treated mice to keep the balance for at least 1 min in two consecutive trials on a slowly rotating plastic rod (10 rpm) having a diameter of 2.3 cm was used as the endpoint indicating motor impairment.

Lipophilicity Determination: The biological effects of new chemical entities acting on CNS, depends on the lipophilic character was measured by established procedure [43]. Conversely, it was found that compounds having maximum potency if they have an ideal lipophilic character *i.e.* lop ≈ 2. In the present work, we linked the calculated log P value that was determined via chloroform phosphate buffer technique [44] with bioactivities of the novel hydrazide-hydrazones.

RESULTS AND DISCUSSION: Preparation of novel hydrazide-hydrazones (3a-o) was carried shown in **Scheme 1**. Compounds 1 and 2 are proficiently synthesized in good yields. Hydrazide of benzoxazole (2) was prepared *via* the reaction of methyl 3-amino-4-hydroxybenzoate with benzoic acid followed by treatment with hydrazine hydrate. The obtained hydrazide was refluxed for 8-10 h with suitable aromatic aldehydes to form novel hydrazones (3a–o). Thin-layer chromatography was used to decide the completion of the reaction. All prepared compounds are novel and their anticonvulsant activities have not been stated in the literature. The physical parameters of new candidates are presented in **Table 1**. Structural interpretation of all the synthesized entities has been established on the source of spectral methods. In general, ^{1}H- NMR spectra of most analogs showed distinctive singlet signs for =CH and NH moieties have been observed on δ 8.34–8.77 ppm and δ 10.34–10.64 ppm, respectively. IR spectra of most compounds showed absorption band at around 3321-3198, 3071-3029 and 1691-1659 cm^{-1} confirming the existence of NH, CH, C=N and C=O correspondingly. Both findings successfully confirmed the synthesis of hydrazide-hydrazones of methyl 3-amino-4-hydroxybenzoate.

All synthesized compounds were tested for their antiepileptic actions *via sc*PTZ and MES methods, and rotarod tests can be used to detect neurological deficit [65, 66]. All compounds were suspended in polyethylene glycol and experiments were done on albino mice (20–25 g). In **Table 2** the anticonvulsant potential and neurotoxicity effects are reported. Phenytoin and carbamazepine drugs were used as reference drugs for comparison. In the anticonvulsant screening, every compound indicated empowering action except 3a, 3g and 3h. In the MES test, compounds 3d and 3o were observed to be very dynamic at 0.5 h time interval at 30 $mgkg^{-1}$ dose level, were exposed to have a fast

beginning and extended period of effects, characteristic of their capacity to avoid seizure attack. Compounds that showed protection at a moderate level against the MES model at 100 $mgkg^{-1}$ include 3f, 3i, 3j, 3l and 3n. The compounds 3d, 3f, 3i, 3j, 3n and 3o indicated effects 0.5 and 4.0 h time intervals.

TABLE 1: PHYSICAL PARAMETERS OF SUBSTITUTED HYDRAZONES (3a-o)

Code no.	R	Mol. formula[a]		M.P[b] (°C)	Log *P*[c]	R_f[d] Value
3a	H	$C_{21}H_{15}N_3O_2$	341	130-132	0.77	0.88
3b	2-Cl	$C_{21}H_{14}ClN_3O_2$	375	145-147	1.12	0.76
3c	3-Cl	$C_{21}H_{14}ClN_3O_2$	375	145-147	1.27	0.87
3d	4-Cl	$C_{21}H_{14}ClN_3O_2$	375	140-142	2.17	0.82
3e	2-Br	$C_{21}H_{14}BrN_3O_2$	420	150-152	1.59	0.67
3f	4-Br	$C_{21}H_{14}BrN_3O_2$	420	150-152	2.03	0.67
3g	2-OH	$C_{21}H_{15}N_3O_3$	357	140-142	1.01	0.71
3h	4-OH	$C_{21}H_{15}N_3O_3$	357	145-147	0.95	0.87
3i	3-NO_2	$C_{21}H_{14}N_4O_4$	386	170-172	2.02	0.90
3j	4-NO_2	$C_{21}H_{14}N_4O_4$	386	175-177	2.07	0.87
3k	2,6-dichloro	$C_{21}H_{13}Cl_2N_3O_2$	410	160-162	1.71	0.70
3l	2Cl-5NO_2	$C_{21}H_{13}ClN_4O$	420	185-187	1.95	0.76
3m	2-F	$C_{21}H_{14}FN_3O_2$	359	140-142	1.82	0.71
3n	2Br-5F	$C_{21}H_{13}BrFN_3O_2$	438	145-147	1.91	0.65
3o	4Br-2F	$C_{21}H_{13}BrFN_3O_2$	438	140-142	2.20	0.69

[a]Solvent of crystallization — ethanol. [b]Melting point of the compounds at their decay. [c]Log *P* was deliberate by absorbance records, chloroform/phosphate buffer at 28 °C. [d]Solvent system — benzene:acetone (8:2, v/v), benzene:ethanol (2:0.5, v/v), toluene:ethylacetate: formic acid (5:4:1, v/v/v).

TABLE 2: *IN-VIVO* ANTICONVULSANT AND MOTOR IMPAIRMENT SCREENING OF SUBSTITUTED HYDRAZONES (3a-o)

Code no.	*i.p.* administration in mice[a]				Neurotoxicity screen[a]	
	MES screen		*sc*PTZ screen			
	0.5h	4h	0.5h	4h	0.5h	4h
3a	–	–	–	–	×	×
3b	300	–	–	–	×	×
3c	300	–	–	–	×	×
3d	30	300	300	–	–	–
3e	300	–	–	–	×	×
3f	100	300	300	–	300	–
3g	–	–	–	–	×	×
3h	–	–	–	–	×	×
3i	100	300	300	–	–	300
3j	100	300	300	–	300	–
3k	300	–	–	–	–	–
3l	100	–	–	–	×	×
3m	–	–	300	300	300	–
3n	100	300	–	300	–	300
3o	30	300	300	300	–	300
Phenytoin[b]	30	30	–	–	100	100
Carbamazepine[b]	30	100	100	300	300	300

[a]Test compounds were injected to mice (30, 100 and 300 $mgkg^{-1}$). The data in the table show the lowest dose whereby effects were established in half or more of the mice. The mice were observed 0.5 and 4 h after the administration of test compounds. The dash (–) designates absence of effect at higher dosage (300 $mgkg^{-1}$) and cross (×) signifies not tested. Propylene glycol (0.1 ml, *i.p.*) was used as a control solvent. [b]Statistics from reference [40, 45].

In this way, the larger part of the candidates demonstrated empowering antiepileptic effects at half an hour showed that they have a fast beginning and smaller period of action. In chemo shock examination, some compounds like 3d, 3f, 3i, 3j, 3m, and 3o exhibited anticonvulsant effects at the maximum dose (300 $mgkg^{-1}$) at 0.5 h time interval showing that rapid start and small action. Two compounds 3m and 3n indicated the safety of seizure spread in both time intervals at 300 $mgkg^{-1}$. In rotarod motor impairment test, compound 3f, 3j and 3m exposed toxicity (300 $mgkg^{-1}$) at 0.5 h of

the time period and compound 3i, 3n and 3o exhibited late toxicity after 4.0 hrs as compared to carbamazepine. However, the rest of the compounds did not face any toxicity at a higher dose level (300 $mgkg^{-1}$). Conversely, all the tested compounds were minimal lethal as compared to phenytoin (100 $mgkg^{-1}$). Compounds 3d and 3o were observed to be increasingly lipophilic having powerful anticonvulsant action. Molecules like 3a, 3b, 3c, 3g and 3h were exceptionally less lipophilic and were littler or insignificant effects. The remaining compounds were also lipophilic, having some potency.

Reviewing the effects of all derivatives, the resulting structural activity relationship was noted. It was observed that the hydrazone analogs containing a halogen group/s displayed the highest actions as compare to hydroxyl and nitro groups. The place of the substituents on the aromatic nucleus is significantly liable for the anticonvulsant action, the order is *para*>*meta*>*ortho*.

CONCLUSION: This study reports that the syntheses of various benzoxazole having hydrazide-hudrazones and were interpreted based on instrumentation methods. All compounds screened for anticonvulsant action by standard procedure MES and *sc*PTZ and exhibited good to moderate effects.

In the preliminary screening compounds 3d, 3f, 3i, 3j, 3n, and 3o were observed to be very dynamic at both time intervals, were exposed to have a fast beginning and extended period of effects, characteristic of their capacity to avoid seizure attack. Compounds 3d and 3o showed protection at a maximum level against the MES model at 30 $mgkg^{-1}$, were also found to display powerful actions against *sc*PTZ model as compared to reference drug carbamazepine and phenytoin.

From the results it has been noticed that the effect is due to the existence of promising basic moiety *viz*. aryl ring with hydrophobic moiety, hydrogen bonding domain -NHC=O group, electron donor =N– atom, electron-withdrawing group and another aryl group as a hydrophobic site. Even an increase in the lipophilicity of the prepared compounds achieves the same level of effects. Hence, compounds 3d and 3o reasonable very active, revealing defense in all screened against seizures models with a minimum role to the motor impairment and appeared as lead compounds in this series. One can assume that the para substituent ring might increase the interaction with the receptor. Additionally, the 3f, 3i, 3j and 3n turn out as a potential contender for further study.

In conclusion, it might be speedily reason that the substitution plan in the aryl ring impacts the action along with the toxicity of the distinctive substituted hydrazones.

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