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Synthesis, anticonvulsant and neurotoxicity of some novel 1,3,4-oxadiazole derivatives of phthalimide

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Abstract

A series of novel 1,3,4-oxadiazole derivatives of phthalimide (4a-j) were prepared in satisfactory yields and evaluated for their anticonvulsant and neurotoxicity studies. All the compounds were in good agreement with elemental analysis and spectral data. All the compounds were active in MES screen and less neurotoxic than phenytoin. Compound 4j having methoxy substitution at para position of the distal aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity.

Key words: Phthalimde, 1,3,4-oxadiazole, anticonvulsant activity, neurotoxicity.

INTRODUCTION

Epilepsy has been recognized as a neurological disorder, affecting a large section of people both male and female across the world. Every year approximately 250000 new cases are added to this figure. Many patients have seizures that are resistant to the available medical therapies. Newer drugs such as flupirtine [1], topiramate [2], zonisamide [3] and vigabatrin [4] have emerged as promising anticonvulsants. Despite introduction of these new drugs women of child bearing age and chronic patients face specific problems of neurotoxicity, symptoms of depression and CNS related ailments. Therefore, it is essential to search for newer chemical entities for the treatment of epilepsy. Pandeya has proposed the identifiable features for anticonvulsant activity like (i) hydrophobic aryl ring (ii) a hydrogen bonding domain (iii) an electron-donor group, and (iv) another distal hydrophobic site [5]. To test this hypothesis the size of the hydrophobic aryl ring has been varied.

Phthalidomide first synthesized as antihistaminic drug in 1954, was introduced as a sedative hypnotic drug in 1956 but withdrawn from the market because of its catastrophic teratogenicity. The teratogenic action of phthalidomide was due to the (*S*)-enantiomer. In the early 1960s, a new use was found for phthalimide as a sedative in patients suffering from lepromatous leprosy (*erythema nodosum leprosum*), an acute inflammatory manifestation of lepromatous leprosy. Phthalimide and *N*-substituted phthalimides are an important class of compounds because they posses important biological activities including anti-inflammatory activity [6], analgesic activity [7] and hypolipidemic activity [8]. 1,3,4-Oxadiazoles also possess very important biological activities like COX inhibitors [9], anticonvulsant [10], antimicrobial [11] and antifungal [12].

In our previous research on anticonvulsants, different moieties were selected for the synthesis of anticonvulsant agents e.g., sulphonamides [13], benzothiazoles [14] and coumarins [15]. In the present study, we reported herein the synthesis (scheme-1) and the possible anticonvulsant activity of 1,3,4-oxadiazole derivatives of phthalimides.

RESULTS AND DISCUSSION

1-{5-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-substituted phenyl) thioureas **(4a-j)** were synthesized by reacting phthalic anhydride with semicarbazide to form 1-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) urea **1** which was refluxed with hydrazine hydrate in presence of NaOH to form *N*-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) hydrazinecarboxamide **2**. In IR spectrum, bands at 3500 cm^{-1}, 3210 cm^{-1}, 1780-1720 cm^{-1} confirms the presence of NH, CONH and C=O groups respectively. The ^{1}H NMR spectra showed singlet at δ 2.5 for four NH protons, multiplet was observed at δ 7.6-7.98 with J = 10 Hz for four aromatic protons. The compound **2** was treated with cyanogen bromide to form cyclized product 2-[(5-amino-1,3,4-oxadiazol-2-yl) amino]-1*H*-isoindole-1,3(2*H*)-dione **3**. In IR spectrum bands at 1780-1720 cm^{-1}, 1382 cm^{-1}, 1271 cm^{-1} confirms the presence of C=O, C=N and C-O groups respectively. The ^{1}H NMR spectra showed singlet at δ 2.5 for one NH protons, multiplet at δ 7.8-8.07 with J =10 Hz for four aromatic protons, singlet at δ 11.54 for two NH protons. The final product **4a** was obtained by treating **3** with phenylisothiocyanate. Similarly other compounds of the series were obtained by reacting compound **3** with different phenylisothiocyantes. The synthesized compounds were characterized by elemental analysis, FT IR, ^{1}H NMR and mass spectroscopy. The FT IR spectrum revealed three bands for NH, C=O and C=SNH groups at 3500-3340 cm^{-1}, 1780-1720 cm^{-1} and 3200 cm^{-1} respectively. The ^{1}H NMR of confirmed the presence of Ar-H, NNH, CSNH, Ar-NH groups by multiplet at δ 7.1-8.18, singlet at δ 7.8-10.1, δ 8.1-11.8 and δ 8.7-10.9 respectively.

Anticonvulsant screening:

MES-Maximal electroshock seizure Test: Maximal electroshock seizures were elicited with a 60 cycle altering current of 50 mA intensity (5-7 times that necessary to elicit minimal electroshock seizures) delivered for 0.25 seconds via corneal electrodes. A drop of 0.9 % saline was instilled in the eye prior to application of the electrodes in order to prevent the death of the animal. Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and results are expressed as number of animal protected/number of animals tested.

NT-Neurotoxicity: The rotorod test was used to evaluate neurotoxicity. The animal was placed on a 3.2 cm diameter knurled rod rotating at 6 rpm. Normal mice can remain on a rod rotating at this speed indefinitely. Neurological toxicity is defined as the failure of the animal to remain on the rod for 1 min. and is expressed as number of animals exhibiting toxicity/number of animals tested. Anticonvulsant screening was undertaken by reported procedures [17] and the data are presented in (Table-1).

Behavioral test: The titled compounds (30 mg/kg) were screened for their behavioral effects using actophotometer according to the reported method [18]. Rats were placed inside the actophotometer after 30 min drug injection. The behavior of animals inside the photocell was recorded as a digital score. The control animal was administered 0.5 % MC. All the animal experimental protocols have met with the approval of the Institutional Animal Ethics Committee (IAEC).

The phthalimide derivatives of 1,3,4-oxadiazole were initially screened at three doses (30, 100 and 300 mg/kg) intraperitoneally in mice for anticonvulsant activity. All the compounds were active in MES test, making them useful for broad spectrum of seizure type. In MES test compounds with chloro substituent **(4b, 4c, 4d)** were all active at 300 mg/kg after 0.5 h and 4 h. Compounds with methyl substituent **(4e, 4f)** were also active at 300 mg/kg after 0.5 h and 4 h except the compound **(4g)** with para methyl group, which was active at 100 mg/kg after 0.5 h and at 300 mg/kg after 4 h. The compounds with methoxy substitution **(4h, 4i)** were active at 100 mg/kg after 0.5 h and at 300 mg/kg after 4 h except the compound **(4j)** with para methoxy substitution which showed protection at 30 mg/kg after 0.5 h and at 300 mg/kg after 4 h. In neurotoxicity screen, compounds **(4f, 4i and 4j)** with 3-methyl, 3-methoxy and 4-methoxy derivatives respectively showed toxicity at 300 mg/kg after 0.5 h but no toxicity after 4 h. The compound **(4c)** with 3-chloro substituent showed toxicity at dose of 300 mg/kg after 0.5 h and at 100 mg/kg after 4 h. Compound **(4g)** with 4-methyl substituent showed toxicity at dose of 100 mg/kg after 0.5 h and at 300 mg/kg after 4 h.

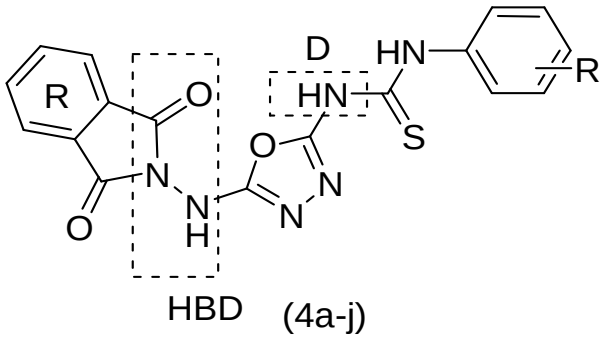


Fig-1: Pharmacophoric model of compounds (4a-j)

Basic structure of the compounds fulfilled all the pharmacophoric structural requirements (Fig-1). Presence of constituent like OCH_3 at distant phenyl ring especially at *para* position, showed highly potent activity in anti-MES screen. Presence of alkyl groups (CH_3) at distal aryl ring (ring B) has potent activity. It is now established fact that there are at least four parameters for anticonvulsant drugs (i) lipophilic domain (ii) distal aryl ring (hydrophobic centre) whose size

effects pharmacokinetic properties (iii) (CONH) acts as hydrogen donar (iv) an electron donar (C=N) system is also present. Hydrophobic size appears to govern the MES activity. If there is larger hydrophobic moiety, the MES activity is favored. These results confirm our observation and proposals for pharmacophore model and modifying the size of hydrophobic domain. The thioureido moiety was introduced in the structures to increase the lipophiolicity of the molecules.

Table -1: Anticonvulsant and neurotoxicity results of the titled compounds (4a-j)

Compd.	Intraperitonial injection in mice[a]			
	MES screen		Toxicity screen	
	0.5 h	4 h	0.5 h	4 h
4a	300	300	300	300
4b	300	300	300	300
4c	300	300	300	100
4d	300	300	300	300
4e	300	300	300	300
4f	300	300	300	-
4g	100	300	100	300
4h	100	300	300	300
4i	100	300	300	-
4j	30	300	300	-
Phenytoin[b]	30	30	100	100
Carbamazepine[b]	30	100	100	300
Phenobarbital[b]	100	30	100	300

[a] Doses of 30, 100 and 300 mg/kg were administered. The figure in the table indicates the minimum dose whereby bioactivity was demonstrated in half or more of the animals. The animals were examined 0.5 and 4 h after administration. The (-) indicates an absence of activity at maximum dose administered (300 mg/kg). [b]Data from references [19].

In behavioral despair test (Table-2), all the compounds except **(4d)** showed increased motor activity as indicated by actophotometer scores. The compound **(4e)** with 2-methyl substituent showed significant activity ($P<0.05$).The compounds **(4d)** with 4-chloro substituent showed maximum impairment with lowest actophotometer score 293.66 ± 21.691.

Distance mapping: The compounds **(4a-j)**, the (R-HBD = 8.766) of the titled compounds deviated from standard anticonvulsant drugs while as (R-D = 9.024) and (D-HBD = 3.846) were near to remacemide and lamotrigene values respectively (Table-3).

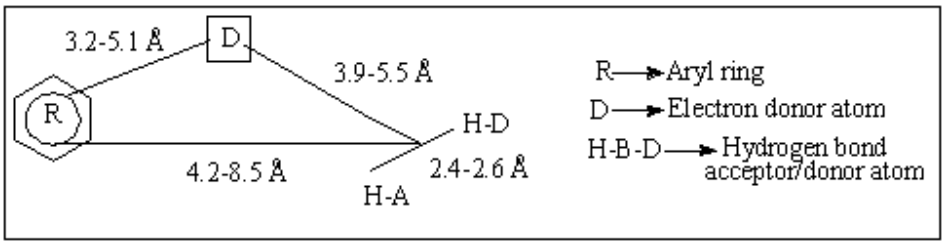


Table-2: Behavioral study on the titled compounds (4a-j) using actophotometer

Compound[a]	Score [b] (Time span 5 min)
Control	326.33 ± 24.428
4a	372.83 ± 32.641
4b	365.00 ± 33.441
4c	363.33 ± 30.732
4d	293.66 ± 21.691
4e	437.66 ± 27.865*
4f	430.83 ± 26.908
4g	432.50 ± 22.314
4h	385.66 ± 24.956
4i	375.83 ± 29.394
4j	397.16 ± 28.661
Phenytoin[c]	54 ± 4.560**

[a] The compounds were tested at a dose of 30 mg/kg (p.o).[b]Each score represents the mean ± S.E.M of six rats. The ANOVA (Dunnett's t-test) was used for the calculation of mean levels, [c] Tested at 5 mg/kg p.o., P<0.05, ** P< 0.01.*

Table-3: Distances range between the essential structure elements R, D and HBD

Compound	R-HBD[a]	R-D[a]	D-HBD[a]
Carbamazepine	6.517	3.931	5.554
Phenytoin	3.042	3.868	2.497
Lamotrigine	5.807	3.301	4.598
Zonisamide	4.058	5.651	6.729
Rufinamide	2.407	7.474	5.209
Dezinamide	4.481	5.909	2.948
Remacemide	3.211	9.811	6.635
Diazepam	4.793	4.827	1.49
Compounds (4a-j)	8.766	9.024	3.846

[a]Distance calculated for 3D optimized structures using ACD freeware 3D viewer 8.04 version

MATERIALS AND METHODS

General

All the solvents were of LR grade and were obtained from Merck and CDH. Melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography was performed on silica gel G (Merck). The FT-IR spectra were recorded in KBr pellets on a (BIO-RAD FTS 135) WIN-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker model DPX 300 FT NMR spectrometer in (DMSO-d_6) using tetramethylsilane (Me_4Si, TMS) as an internal standard. Mass spectra were recorded on a Jeol JMS-D instrument fitted with a JMS 2000 data system at 70 eV. The elemental analyses for C, H and N were within the limit of ±0.4% of the theoretical values. Male albino mice (CF-1 strain or Swiss, 18-258) were used as experimental animals and rats (Spraque-Dawley or Wistar, 100-150 g) were used as experimental animals. The tested compounds were suspended in 0.5 % methyl cellulose/water mixture or in polyethylene glycol (PEG).

1-(1, 3-Dioxo-1,3-dihydro-2H-isoindol-2-yl) urea **(1)** was synthesized by reported method [16].

N-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl) hydrazinecarboxamide **(2)**.

To an ethanolic solution of compound **1** (2.05 g, 0.01 mol), an equimolar quantity of hydrazine hydrate 99 % (0.5 mL, 0.01 mol), NaOH (0.4 g) was added to make the reaction mixture alkaline. The mixture was refluxed for 3 hours and cooled in ice. The product **2** was filtered under suction and recrystallized from ethanol. % Yield: 60; m. p.°C: 254; R_f: 0.4 ; FT-IR (KBr) cm^{-1}: 3500 (NH), 3210 (CONH), 1780-1720 (C=O, phthalimide), 1590, 1400 (phenyl); ^{1}H NMR (DMSO-d_6) δ ppm: 2.50 (s, 4H, NH, $CONHNH_2$, D_2O exchangeable); 7.60-7.98 (m, 4H, *J* = 10 Hz, Ar-H).

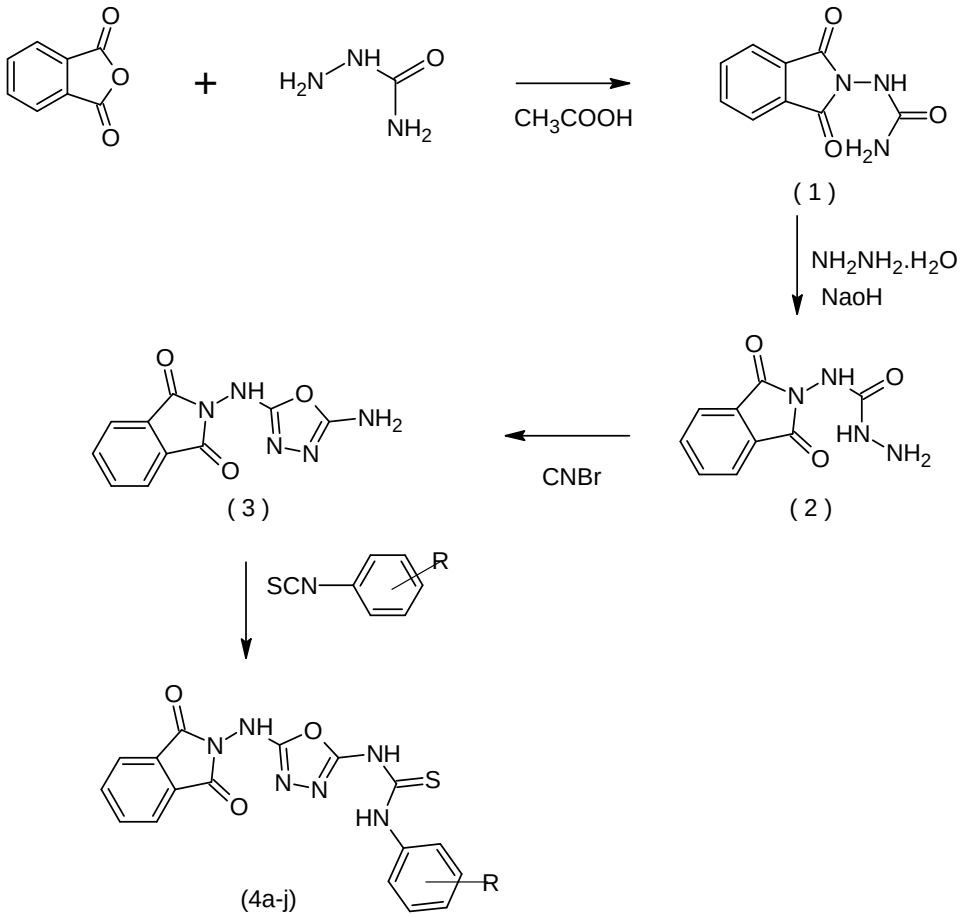
2-[(5-Amino-1,3,4-oxadiazol-2-yl) amino]-1H-isoindole-1,3 (2H)- dione **(3)**.

To an ethanolic solution of **2** (2.2 g, 0.01 mol) cyanogen bromide (1.06 g, 0.01 mol) was added. The reaction mixture was warmed at 55-60°C for 90 minutes. The resulting solution was cooled and neutralized with $NaHCO_3$. The solid **3** thus obtained was filtered, washed with water, dried and recrystallized from methanol. % Yield: 54; m. p.°C: 240; R_f: 0.43; FT-IR (KBr) cm^{-1}: 1780-1720 (C=O, phthalimide), 1382 (C=N, str.), 1271 (C-O, str.), 1590, 1400 (phenyl); ^{1}H NMR (DMSO-d_6) δ ppm: 2.50 (s, 1H, NNH, D_2O exchangeable), 7.89-8.07 (m, 4H, *J* = 10 Hz, Ar-H), 11.54 (s, 2H, NH_2).

1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-phenylthiourea **(4a).**

A mixture of **3** (2.5 g, 0.01 mol), phenylisothiocyanate (1.14 g, 0.01 mol) and methanol (50 mL) were refluxed on steam bath for 8 hours. It was then concentrated, cooled and kept overnight in refrigerator. The solid **4a** thus separated out was filtered, washed with petroleum ether, dried and recrystallized from ethanol. % Yield: 60; m. p.°C: 208; R_f: 0.53; FT-IR (KBr) cm^{-1}: 3500 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1650, 1690 (phenyl); ^{1}H NMR (DMSO-d_6) δ ppm: 7.3-7.8 (m, 9H, Ar-H), 7.8 (s, 1H, NNH, D_2O exchangeable), 8.1 (s, 1H, CSNH, D_2O exchangeable), 10.4 (s, 1H, Ar-NH, D_2O exchangeable); MS: m/z (%): 380 (100) [M^+].

Scheme-1



4a: R=H; **4b**: R=2-Cl; **4c**: R=3-Cl; **4d**: R=4-Cl; **4e**: R=2-CH_3; **4f**: R=3-CH_3; **4g**: R=4-CH_3; **4h**: R=2-OCH_3; **4i**: R=3-OCH_3; **4j**: R=4-OCH_3.

1-(2-Chlorophenyl)-3-{5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl} thiourea **(4b).**

FT-IR (KBr) cm^{-1}: 3400 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1660, 1680 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 7.2-8.0 (m, 8H, Ar-H, *J* = 10 Hz), 8.2 (s, 1H, NNH, D_2O exchangeable), 8.6 (s, 1H, CSNH D_2O exchangeable), 8.7 (s, 1H, Ar-NH, D_2O exchangeable); MS: m/z (%): 414 (100) [M^+].

1-(3-Chlorophenyl)-3-{5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl} thiourea **(4c).**

FT-IR (KBr) cm^{-1}: 3450 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide),1660, 1680 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 7.14-8.1 (m, 8H, Ar-H, *J* = 8 Hz), 8.2 (s, 1H, NNH, D_2O exchangeable), 9.5 (s, 1H, CSNH, D_2O exchangeable), 10.7 (s, 1H, Ar-NH, D_2O exchangeable); MS: m/z (%): 414 (100) [M^+].

1-(4-Chlorophenyl)-3-{5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl} thiourea **(4d).**
FT-IR (KBr) cm^{-1}: 3450 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1680 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 7.2-7.8 (m, 8H, Ar-H), 8.1 (s, 1H, NNH, D_2O exchangeable), 10.8 (s, 2H, Ar-NH, CSNH, D_2O exchangeable); MS: m/z (%): 414 (100) [M^+].

1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-(2-methylphenyl) thiourea **(4e).**
FT-IR (KBr) cm^{-1}: 3420 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1660, 1670, 1680 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 2.5 (s, 3H, CH_3), 7.18-8.16 (m, 8H, Ar-H), 10.1 (s, 1H, NNH, D_2O exchangeable), 11.8 (bs, 2H, Ar-NH, CSNH, D_2O exchangeable); MS: m/z (%): 394 (100) [M^+].

1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-(3-methylphenyl) thiourea **(4f).**
FT-IR (KBr) cm^{-1}: 3400 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1660 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 2.5 (s, 3H, CH_3), 6.9-8.1 (m, 8H, Ar-H), 8.16 (s, 2H, NNH, NHCS, D_2O exchangeable), 10.6 (s, 1H, Ar-NH, D_2O exchangeable); MS: m/z (%): 394 (100) [M^+].

1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-(4-methylphenyl) thiourea **(4g).**
FT-IR (KBr) cm^{-1}: 3340 (NH), 3200 (C=SNH),1780-1720 (C=O, phthalimide), 1660, 1680 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 2.5 (s, 3H, CH_3), 7.0-7.9 (m, 8H, Ar-H), 10.0 (s, 1H, NNH, D_2O exchangeable), 10.7 (bs, 2H, Ar-NH, CSNH, D_2O exchangeable); MS: m/z (%): 394 (100) [M^+].

1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-(2-methoxyphen -yl)thiourea **(4h).**
FT-IR (KBr) cm^{-1}: 3450 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1660, 1680 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 4.4 (s, 3H, OCH_3), 7.5-8.1 (m, 8H, Ar-H), 8.3 (s, 1H, NNH, D_2O exchangeable), 10.9 (bs, 2H, Ar-NH, CSNH, D_2O exchangeable); MS: m/z (%): 410 (100) [M^+].

1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-(3-methoxyphen -yl)thiourea **(4i).**
FT-IR (KBr) cm^{-1}: 3450 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1660, 1680 (phenyl); ^1H NMR (DMSO-d_6) δ ppm: 4.4 (s, 3H, OCH_3), 7.5-8.1 (m, 8H, ArH), 8.3 (s, 1H, NNH, D_2O exchangeable), 10.8 (bs, 2H, Ar-NH, CSNH, D_2O exchangeable); MS: m/z (%): 410 (100) [M^+].

1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-(4-methoxyphen -yl) thiourea **(4j).**
FT-IR(KBr) cm^{-1}: 3450 (NH), 3200 (C=SNH), 1780-1720 (C=O, phthalimide), 1660, 1680 (phenyl). ^1H NMR (DMSO-d_6) δ ppm: 4.4 (s, 3H, OCH_3), 7.4-8.1 (m, 8H, Ar-H), 8.3 (s, 1H, NNH, D_2O exchangeable), 10.9 (bs, 2H, Ar-NH, CSNH, D_2O exchangeable); MS: m/z (%): 410 (100) [M^+].

CONCLUSION

The presence of methoxy group in ring B causes more lipophilic character of the molecule. The lipophilic character was increased by the synthesis of alkoxy (methoxy derivative) at distal aryl ring. These compounds were assumed to be dealkylated after metabolism and alkoxy groups were replaced by hydrogen. The bioactivity in MES test exhibited by para methoxy substituent **(4j)** demonstrated that distal hydrophobic center could be made more lipophilic than phenyl ring. Distal hydrophobic center alters the bioavailibility of compounds. The present results have revealed that a number of phthalimide derivatives exhibit a range of activity in anticonvulsant screen with compound **(4j)** showing anti MES activity comparable to phenytoin.

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