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SYNTHESIS, CHARACTERIZATION AND *IN VIVO* ANTICONVULSANT AND NEUROTOXICITY SCREENING OF SCHIFF BASES OF PHTHALIMIDE

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Abstract: A series of Schiff bases of phthalimide **(4a-l)** were prepared in satisfactory yields and evaluated for their anticonvulsant and neurotoxicity activities. The structures of 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 **4l** having nitro substitution at *ortho* position of the distal aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity.

Keywords: phthalimide, Schiff base, MES test, neurotoxicity

Epilepsy has been recognized as a neurological disorder, affecting a large section of people, both male and female, across the world. Every year, approximately 0.25 million new cases are added to this population. Many patients have seizures that are resistant to the available medical therapies. Newer drugs such as topiramate (1), zonisamide (2) and vigabatrin (3) 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 et al. has proposed the identifiable structural 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 (4). To test this hypothesis the size of the hydrophobic aryl ring has been varied.

Thalidomide, first synthesized as antihistaminic drug in 1954, was introduced as a sedative hypnotic drug in 1956 but withdrawn from the market because of its catastrophic teratogenicity.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 thalidomide was due to the (*S*)-enantiomer. In the early 1960s, a new use was found for thalidomide as a sedative in patients suffering from lepromatous leprosy (*erythema nodosum leprosum*), an acute inflammatory manifestation of lepromatous leprosy. In recent years, N^4-phthalimide derivatives have emerged as structurally novel anticonvulsants (5). Phthalimide and *N*-substituted phthalimides are an important class of compounds because they possess important biological activities including anti-inflammatory activity (6), analgesic activity (7) and hypolipidemic activity (8).

In our previous research on anticonvulsants, different moieties were selected for the synthesis of anticonvulsant agents e.g., sulfonamides (9), benzothiazoles (10) and coumarin (11). In the present study, we report herein the synthesis and the possible anticonvulsant activity of Schiff bases of phthalimide.

EXPERIMENTAL

All the solvents were of LR grade and were obtained from Merck, CDH and S. D. Fine Chemicals. 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 and ^{13}C-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, 18–25 g) were used as experimental animals. The tested compounds were suspended in 0.5% methylcellulose/water mixture or in polyethylene

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glycol (PEG). All the structures of the compounds were drawn with the help of ACD Chemsketch (freeware).

MES – Maximal electroshock seizure test

Maximal electroshock seizures were elicited with a 60 cycle altering current of 50 mA intensity (5–7 times that is necessary to elicit minimal electroshock seizures) delivered for 0.25 s *via* corneal electrodes of electro-convulsometer. A drop of 0.9% saline was instilled in the animal 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 by rotorod

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 one minute and is expressed as a number of animals exhibiting toxicity/number of animals tested. Anticonvulsant screening was undertaken by reported procedures (12) and the data are presented in Table 1. All the animal experimental protocols have met the approval of the Institutional Animal Ethics Committee (IAEC).

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzoic acid (**1**)

p-Aminobenzoic acid (PABA, 1.0 g, 1.29 mmol) and phthalic anhydride (1.0 g, 6.75 mmol) dissolved in glacial acetic acid (10 mL) were refluxed for 4 h. The *N*-substituted phthalimide separated out on cooling. A nearly white powder appeared that was filtered through a Buchner funnel and washed twice with water (30 mL) to give product **1**. Yield: 91%; m.p.: 250–252°C; R_f: 0.7 (benzene : acetone, 7:3 v/v); FT-IR (KBr, cm^{-1}): 3547 (OH); 1782–1748 (C=O), 1428 (N-C=O), 1380 (C-N-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.7–8.0 (m, 8H, Ar-H), 13.0 (s, 1H, RCOOH); MS (m/z): 267.2 [M^+].

Ethyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzoate (**2**)

Compound **1** (5.34 g, 0.02 mol) was dissolved in absolute ethanol (18 mL, 0.5 mol) and 2.7 mL of conc. H_2SO_4 was added. The mixture was refluxed for 4 h, then it was concentrated, cooled and poured into ice-cooled water. The solid **2** thus separated out was

Table 1. Anticonvulsant and neurotoxicity results of the title compounds (**4a-l**).

Compd.	Intraperitonial injection in mice[a]			
	MES screen		Toxicity screen	
	0.5 h	4 h	0.5 h	4 h
4a	300	300	300	-
4b	300	300	300	-
4c	100	300	100	300
4d	300	-	-	300
4e	300	-	300	300
4f	300	300	300	-
4g	300	300	300	-
4h	100	300	100	300
4i	300	300	300	-
4j	300	300	300	-
4k	300	-	300	300
4l	100	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. (–) indicates an absence of activity at maximum dose administered (300 mg/kg).[b]Data from reference (13).

filtered, dried and recrystallized from ethanol. Yield: 70%; m.p.:130–132°C; R_f: 0.8 (benzene : acetone, 8:2 v/v); FT-IR (KBr, cm^{-1}): 3547 (OH), 1782–1748 (C=O), 1428 (N-C=O), 1380 (C-N-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.5 (t, 3H, CH_3), 3.2 (m, 2H, CH_2), 7.8–8.1 (m, 8H, Ar-H); MS (m/z): 295.2 [M^+].

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzohydrazide (**3**)

Compound **2** (2.95 g, 0.01 mol) and hydrazine hydrate 99% (1 mL, 0.02 mol) were refluxed in absolute ethanol (50 mL) for 20 h. The mixture was concentrated, cooled and poured into ice-cold water. The solid **3** thus separated out was filtered, dried and recrystallized from ethanol. Yield: 70%; m.p.: 150–152°C; R_f: 0.67 (benzene : acetone, 7:3 v/v); FT-IR (KBr, cm^{-1}): 1782–1748 (C=O), 1428 (N-C=O), 1380 (C-N-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.5 (s, 2H, NH_2), 6.91–8.17 (m, 8H, Ar-H), 9.5 (s, 1H, CONH); MS (m/z): 281.2 [M^+].

General method of synthesis of 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-[(substituted phenyl)methylene]benzohydrazides (4a-l)

Compound **3** (2.81 g, 0.01 mol) and 4-hydroxybenzaldehyde (1.22 g, 0.01 mol, or equivalent amount of other carbonyl compound) in glacial acetic acid (2 mL) were refluxed in methanol (50 mL) for 8 h. Product **4** was obtained by pouring the reaction mixture into ice-cold water. After filtration, it was crystallized from ethanol.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-[(4-hydroxyphenyl)methylene]benzohydrazide (**4a**)

Yield: 70%; m.p: 275–277°C; R_f: 0.78 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3677 (OH), 3110 (CONH), 3000 (C-H arom.), 2700 (N=CH), 2365 (C=NH), 1656 (C=O), 1604 (C-N), 1509 (C=C), 790 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 6.8–7.8 (m, 12H, Ar-H), 8.1 (s, 1H, Ar-OH), 9.5 (s, 1H, CONH), 10.6 (s, 1H, N=CH-Ar); ^{13}C-NMR ($CDCl_3$, δ, ppm): 116.0 ($C_{25,}$ C_{27}), 121.7 ($C_{11, 15}$), 126.4 (C_{23}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12,}$ C_{14}), 129.8 (C_{13}), 130.6 ($C_{24, 28}$), 132.0, ($C_{3, 4}$), 132.3 ($C_{7,}$ C_8), 136.1 (C_{10}), 142.9 (C_{22}), 160.8 (C_{26}), 162.9 (C_{18}), 167.1($C_{2, 5}$); MS (m/z): 385.1 [M^+], 239, 146.02, 135.06, 104.03; Analysis: for $C_{22}H_{15}N_3O_4$ calcd. C 68.57, H 3.92, N 10.90%; found: C 68.30, H 3.93, N 10.94 %.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-(3,4-dimethoxyphenyl)methylenebenzohydrazide (**4b**)

Yield:75%; m.p.: 280–282°C; Rf: 0.70 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3110 (CONH), 3000 (C-H arom.), 2700 (N=CH), 2200 (C=NH), 1623 (C=O), 1510 (C=C), 754 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.3 (s, 6H, 2´OCH_3),7.0 (m, 11H, Ar-H), 9.5 (s, 1H, CONH), 10.7 (s, 1H, N=CH-Ar); ^{13}C-NMR ($CDCl_3$ δ, ppm): 56.1 ($C_{29, 30}$), 114.3 (C_{24}), 115.4 (C_{27}), 121.7 ($C_{11, 15}$), 122.5 (C_{28}), 127.1 (C_{23}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 132.0, ($C_{3, 4}$), 132.3 ($C_{7, 8}$), 136.1 (C_{10}), 142.9 (C_{22}), 149.9 (C_{25}), 152 (C_{26}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 429.4 [M^+], 179.08, 146.02, 104.03; Analysis: for $C_{24}H_{19}N_3O_5$ calcd. C 67.13, H 4.46, N 9.79%; found: C 67.33, H 4.45, N 9.75 %.

4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-N'-(3-nitrophenyl)methylenebenzohydrazide (**4c**)

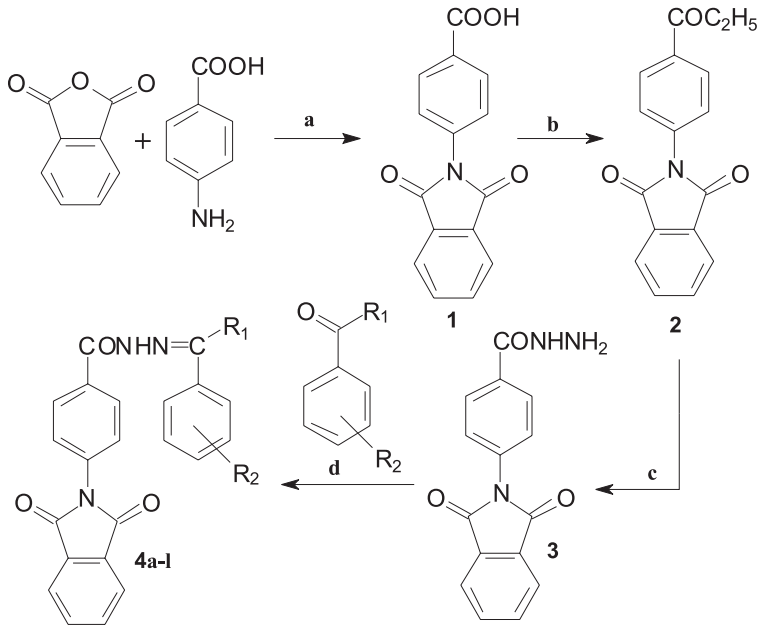
Yield: 60%; m.p.: 210–212°C; R_f: 0.65 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3110 (CONH), 3000 (C-H arom.), 2700 (N=CH), 2200 (C=NH), 1623 (C=O), 1510 (C=C), 754 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.6–8.4 (m, 12H, Ar-H), 11.3 (s, 1H, N=CH-Ar); ^{13}C-NMR ($CDCl_3$ δ, ppm): 121.7 ($C_{11, 15}$), 122.8 (C_{24}), 126.1 (C_{26}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 ($C_{13, 27}$), 132.0, ($C_{3, 4}$), 132.3 ($C_{7, 8}$), 134.1 (C_{23}), 135.5 (C_{28}), 136.1 (C_{10}), 142.9 (C_{22}), 148.8 (C_{25}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 414 [M^+], 164.05, 146.02, 105.03; Analysis: for $C_{22}H_{14}N_4O_5$ calcd. C 63.77, H 3.41, N 13.52%; found: C 63.57, H 3.42, N 13.56%.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-(2-hydroxyphenyl)methylene]benzohydrazide (**4d**)

Yield: 65%; m.p.: 270–272°C; R_f: 0.60 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3677 (OH), 3110 (CONH), 3000 (C-H arom.), 2700 (N=CH), 2363 (C=NH), 1623 (C=O), 1488 (C=C), 751 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 6.9–7.4 (m, 12H, Ar-H), 8.0 (s, 1H, Ar-OH), 8.7 (s, 1H, CONH), 11.2 (s, 1H, N=CH-Ar); ^{13}C-NMR ($CDCl_3$ δ, ppm): 116.0 (C_{25}), 118.5 (C_{23}), 121.5 (C_{27}), 121.7 ($C_{11, 15}$), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 130.6 (C_{28}), 132.0 ($C_{3, 4}$), 132.3 ($C_{7, 8}$),132.5 (C_{26}), 136.1 (C_{10}), 142.9 (C_{22}), 161.0 (C_{24}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 385 [M^+], 146.02, 135.06, 104.03; Analysis: for $C_{22}H_{15}N_3O_4$ calcd. C 69.17, H 4.29, N 10.52%; found: C 69.37, H 4.30, N 10.56%.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-1-(4-hydroxyphenyl)ethylidene]benzohydrazide (**4e**)

Yield: 70%; m.p.: 265–267°C; R_f: 0.75 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3678 (OH), 3100 (CONH), 3000 (C-H arom.), 2364 (C= NH), 1657 (C=O), 1514 (C=C), 1440 (C-N), 833 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.2 (s, 3H, CH_3), 6.8–7.7 (m, 12H, Ar- H), 8.1 (s, 1H, Ar-OH), 9.3 (s, 1H, Ar-CONH); ^{13}C-NMR



Scheme 1. (a) CH_3COOH, reflux 4 h; (b) absolute EtOH, conc. H_2SO_4, reflux 4 h; (c) NH_2NH_2. H_2O, EtOH, reflux, 20 h. (d) glacial acetic acid, MeOH, reflux 8 h. **4a**: R_1 = H, R_2 = 4-OH; **4b**: R_1 = H, R_2 = 3,4 $(OCH_3)_2$; **4c**: R_1 = H, R_2 = 3-NO_2; **4d**: R_1 = CH_3, R_2 = 2-OH; **4e**: R_1 = CH_3, R_2 = 4-OH; **4f**: R_1 = CH_3, R_2 = 4-CH_3; **4g**: R_1 = CH_3, R_2 = 4-Cl; **4h**: R_1 = CH_3, R_2 = 4-NO_2; **4i**: R_1 = CH_3, R_2 = 4-OCH_3; **4j**: R_1 = CH_3, R_2 = 2,4-$(Cl)_2$; **4k**: R_1 = CH_3, R_2 = 2-OH, 3-OCH_3; **4l**: R_1 = CH_3, R_2 = 2-NO_2

($CDCl_3$ δ, ppm): 19.5 (C_{22a}), 116.0 ($C_{25, 27}$), 121.7 ($C_{11, 15}$), 126.6 (C_{23}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 130.6 ($C_{24, 28}$), 132.0, ($C_{3, 4}$), 132.3 ($C_{7, 8}$), 136.1 (C_{10}), 142.9 (C_{22}), 160 (C_{26}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 399.3 [M^+], 149.07, 146.02, 105.03; Analysis: for $C_{23}H_{17}N_3O_4$ calcd. C 69.17, H 4.29, N 10.52%; found: C 68.97, H 4.30, N 10.48%.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-1-(4-methylphenyl)ethylidene]benzohydrazide (**4f**)

Yield: 65%; m.p.: 205–207°C; R_f: 0.67 (toulene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3110 (CONH), 3000 (C-H arom.), 2700 (N=CH), 2200 (C=NH), 1623 (C=O), 1510 (C=C), 754 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.5 (s, 3H, CH_3); 7.4–6.9 (m, 12H, Ar-H), 8.7 (s, 1H, CONH), 11.2 (s, 1H, N=CH-Ar); ^{13}C-NMR ($CDCl_3$ δ, ppm): 19.5 (C_{22a}), 121.7 ($C_{11, 15}$), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.1 ($C_{24, 27, 28}$), 129.5 (C_{25}), 129.8 (C_{13}), 131 (C_{23}), 132.0 ($C_{3,}C_4$), 132.3 ($C_{7, 8}$), 136.1 (C_{10}), 140.7 (C_{26}), 142.9 (C_{22}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 397 [M^+], 147.09, 146.02, 105.03; Analysis: for $C_{23}H_{17}N_3O_3$ calcd. C 72.53, H 4.82, N 10.57%; found: C 72.73, H 4.83, N 10.60%.

N'-1-(4-chlorophenyl)ethylidene]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzohydrazide (**4g**)

Yield: 75%; m.p.: 180–182°C; R_f: 0.73 (toluene: ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3100 (CONH), 3000 (C-H arom.), 1657 (C=O), 1606 (C=C), 1489 (C-N), 790 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.2 (s, 3H, CH_3), 6.8–7.7 (m, 12H, Ar-H), 9.3 (s, 1H, Ar-CONH); ^{13}C-NMR ($CDCl_3$, δ, ppm): 19.5 (C_{22a}), 121.7 ($C_{11, 15}$), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 128.9 ($C_{25, 27}$), 129.8 (C_{13}) 130.6 ($C_{24, 28}$), 132.0 ($C_{3, 4}$), 132.1 (C_{23}), 132.3 ($C_{7,}C_8$), 136.1 (C_{10}), 136.6 (C_{26}), 142.9 (C_{22}), 162.9 (C_{18}) 167.1 ($C_{2, 5}$); MS (m/z): 417 [M^+], 167.04, 146.02, 105.03; Analysis: for $C_{23}H_{16}ClN_3O_3$ calcd. C 66.11, H 3.86, N 10.06%; found: C 66.33, H 3.87, N 10.02%.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-1-(4-nitrophenyl)ethylidene]benzohydrazide (**4h**)

Yield: 80%; m.p.: 220–222°C; R_f: 0.77 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3100 (CONH), 3000 (C-H arom.), 2700 (N=CH-CH_3), 2360 (C=NH), 1663 (C=O), 1338 (C=C), 751 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.5 (s, 3H, CH_3), 7.4–8.3 (m, 12H, Ar-H), 10.8 (bs, 1H, Ar-CONH); ^{13}C-NMR ($CDCl_3$ δ, ppm): 19.5 (C_{22a}), 121.7 ($C_{11, 15}$), 124.0 (C_{27}), 124.1 (C_{25}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 130.1 ($C_{24, 28}$), 132.0 ($C_{3, 4}$), 132.3 ($C_{7, 8}$), 136.1 (C_{10}), 140.1 (C_{23}), 142.9 (C_{22}), 150.2 (C_{26}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 428.3 [M^+], 178.06, 146.02, 105.03; Analysis: for $C_{23}H_{16}N_4O_5$ calcd. C 64.48, H 3.76, N 13.08%; found: C 64.68, H 3.75, N 13.12%.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-1-(4-methoxyphenyl) ethylidene]benzohydrazide (**4i**)

Yield: 80%; m.p.: 190–192°C; R_f: 0.68 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3110 (CONH), 3000 (C-H arom.), 2700 (N=CH-CH_3), 2343 (C=NH), 1654 (C=O), 1506 (C=C), 1253 (C-O), 834 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.8 (s, 3H, CH_3), 2.3 (s, 3H, OCH_3), 7.0–7.5 (m, 12H, Ar-H), 9.5 (s, 1H, CONH), 10.7 (s, 1H, N=CH-Ar); ^{13}C-NMR ($CDCl_3$ δ, ppm): 19.5 (C_{22a}), 55.8 (C_{29}), 114.4 ($C_{25, 27}$), 121.7 ($C_{11, 15}$), 126.3 (C_{23}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 130.0 (C_{28}), 130.2 (C_{24}), 132.0 ($C_{3, 4}$), 132.3 ($C_{7,} C_8$), 136.1 (C_{10}), 162.9 ($C_{18, 26}$), 167.1 ($C_{2, 5}$), 168.7 (C_{22}); MS (m/z): 413 [M^+], 163.09, 105.03, 16.02; Analysis: for $C_{24}H_{19}N_3O_4$ calcd. C 69.72, H 4.63, N 10.16%; found: C 69.92, H 4.64, N 10.20%.

N'-1-(2,4-dichlorophenyl)ethylidene]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzohydrazide (**4j**)

Yield: 60%; m.p.: 200–202°C; R_f: 0.77 (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3110 (CONH), 3000 (C-H arom.), 2700 (N=C-CH_3), 2343 (C=NH), 1701 (C=O), 1470 (C=C), 810 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.5 (s, 3H, CH_3), 7.4–8.1 (m, 11H, Ar-H), 10.9 (bs, 1H, CONH); ^{13}C-NMR ($CDCl_3$ δ, ppm): 121.7 ($C_{11, 15}$), 127.0 (C_{27}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 130.5 (C_{25}), 132.0, ($C_{3, 4}$), 132.1 (C_{28}), 132.3 ($C_{7, 8}$), 135.3 ($C_{23, 24}$), 136.1 (C_{10}), 138.0 (C_{26}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$), 168.0 (C_{22}); MS (m/z): 452 [M^+], 201, 146.02, 105.03; Analysis: for $C_{23}H_{15}Cl_2N_3O_3$ calcd. C 61.08, H 3.34, N 9.29%; found: C 61.27, H 3.35, N 9.25%.

N'-1-(2-hydroxy,3-methoxyphenyl)ethylidene]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzohydrazide (**4k**)

Yield: 75%; m.p.: 275–277°C; R_f: 0.72 (toluene : ethylacetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3110 (CONH), 3000 (C-H arom.), 2700 (N=C-CH_3), 1653 (C=O), 1507 (C=C), 668 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.2 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 6.9–7.5 (m, 11H, Ar-H), 8.5 (s, 1H, CONH), 8.9 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$ δ, ppm): 56.1 (C_{29}), 118 (C_{26}), 119.0 (C_{23}), 127.6 (C_9), 121.7 ($C_{11, 15}$), 122.5 (C_{27}), 122.9 (C_{28}), 127.6 (C_6), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 132.0, ($C_{3, 4}$), 132.3 ($C_{7,} C_8$),136.1 (C_{10}), 142.9 (C_{22}), 150.0 (C_{24}), 151.5 (C_{25}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 429 [M^+], 179.08, 146.02, 105.03; Analysis: for $C_{24}H_{19}N_3O_5$ calcd. C 69.17, H 4.29, N 10.52%; found: C 69.34, H 4.30, N 10.56%.

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-N'-1-(2-nitrophenyl)ethylidene]benzohydrazide (**4l**)

Yield: 70%; m.p.: 215–217°C; R_f: 0.8 (toluene : ethylacetate : formic acid, 5:4:1 v/v/v); IR (KBr, cm^{-1}): 3100 (CONH), 3000 (C-H arom.), 2700 (N=CH), 1683 (C=O), 1330 (C=C), 818 (=C-H); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.7 (s, 3H, CH_3), 7.0–8.3 (m, 12H, Ar-H), 10.8 (bs, 1H, Ar-CONH); ^{13}C-NMR ($CDCl_3$ δ, ppm): 121.7 ($C_{11, 15}$), 124 (C_{25}), 127.6 ($C_{6, 9}$), 127.7 ($C_{12, 14}$), 129.8 (C_{13}), 130.1 (C_{28}), 132.0, ($C_{3, 4}$), 132.1 (C_{26}), 132.3 ($C_{7,} C_8$), 135 ($C_{23, 27}$), 136.1 (C_{10}), 142.9 (C_{22}), 147 (C_{24}), 162.9 (C_{18}), 167.1 ($C_{2, 5}$); MS (m/z): 428 [M^+], 178.06, 146.02, 105.03; Analysis: for $C_{23}H_{16}N_4O_5$ calcd. C 64.48, H 3.76, N 13.08%; found: C 64.28, H 3.75, N 13.12%.

RESULTS AND DISCUSSION

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-*N*'-(substitutedphenyl)methylene/ethylidene benzohydrazides **(4a-l)** were synthesized by reacting phthalic anhydride with p-aminobenzoic acid (PABA) to form 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) benzoic acid **1**. In the IR spectrum, bands at 3547, 1782–1748, 1428 and 1380 cm^{-1} confirm the presence of OH, C=O, NCO and N-C groups, respectively. The ^{1}H-NMR spectra showed multiplet at δ 7.7–8.0 ppm for eight aromatic protons. The carboxylic acid proton was observed at δ 13.02 ppm. Compound **1** was refluxed with absolute alcohol in the presence of conc. H_2SO_4 to form ethyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzoate **2**. In the IR spectrum, bands at 1782–1748, 1428 and 1380 cm^{-1} confirm the presence of C=O, NCO and N-C groups, respectively. The ^{1}H-NMR spectra showed multiplet at δ 7.8–8.1 ppm for eight aromatic protons. Multiplet at δ 3.2 ppm for two methylene protons and triplet at δ 2.5 ppm for three methyl protons were observed. Compound **2** was treated with hydrazine hydrate to form 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzohydrazide **3**. In the IR spectrum, bands at 1782–1748, 1428 and 1380 cm^{-1} confirm the presence of C=O, NCO and N-C groups, respectively. The ^{1}H-NMR spectra showed singlet at δ 2.5 ppm for two NH protons, singlet at δ 4.1 ppm for one CONH proton and multiplet at δ 6.9–8.17 ppm for eight aromatic protons. Hydrazide **3** was treated with 4-hydroxybenzaldehyde to obtain the final product **4a** and similarly other compounds of the series were obtained by reacting hydrazide **3** with different carbonyl compounds. The synthesized compounds were characterized by elemental analysis, FT IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. The IR spectrum

revealed the following bands for N=CH, C=O, C-NH groups at 2700, 1701–1623 and 2365–2000 cm^{-1}, respectively. The ^{1}H-NMR spectra of **4a-l** confirm the presence of Ar-H, CONH and N=CH protons by showing signals at δ: 6.8–8.3, 8.5–10.9 and δ 10.6–11.3 ppm, respectively.

The Schiff bases with phthalimide pharmacophore were evaluated for anticonvulsant and neurotoxic properties. Anticonvulsant screening was performed using MES test at three doses (30, 100 and 300 mg/kg). All the Schiff bases of phthalimides were active in the MES test at a dose of 300 mg/kg, indicative of their ability to prevent seizure spread. At a dose of 100 mg/kg, compounds that showed protection in half or more of the tested mice were **4c, 4h** and **4l**. Compounds **4d, 4e** and **4k** showed protection at a dose of 300 mg/kg after 0.5 h but did not showed protection after 4 h interval. Other compounds of the series showed protection at a dose of 300 mg/kg after both 0.5 h and 4 h. In the neurotoxicity screen, compounds **4a, 4b, 4f, 4g, 4i, 4j** and **4l** showed the neurotoxicity only up to 0.5 h. All the compounds showed neurotoxicity at a higher dose level 300 mg/kg except **4c** and **4h**, which showed toxicity at 100 mg/kg. All the compounds were less neurotoxic than phenytoin.

CONCLUSION

The evaluation of compounds indicates the importance of the size of the group at the carbimino carbon atom. Replacement of the hydrogen atom on the carbimino carbon atom by methyl group is leading to an increase in the size at this position of the molecule and has shown a change in activity. This modification may increase the anticonvulsant activity because of additional van der Walls bonding or alternately steric impedance to alignment at the binding site causing lower activity or its loss. The attachment of distal aryl ring to the proximal aryl ring increases the van der Walls bonding at the binding site and increases potency. The distal aryl ring at carbimino terminal (benzylidene ring) is essential for the pharmacokinetic properties of compounds since the variation in the substitution at the distal aryl ring was found to affect biological activity. During metabolism, the distal aryl ring is expected to be p-hydroxylated. Introduction of nitro substitution showed protection at 100 mg/kg at 0.5 h as compared to methyl, chloro and hydroxy substitution at distal aryl ring which showed protection at 300 mg/kg at 0.5 h in MES test. Compound **4l** with nitro substitution at *ortho* position of distal aryl ring have emerged as the most promising anticonvulsant agent with low neurotoxicity.

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