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Synthesis and evaluation of 1-(2-(Substituted benzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one as potential anticonvulsants

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ABSTRACT

*On the basis of pharmacophore model and essential parameters for anticonvulsant activity, a series of 1-[2-(substituted benzylidenhydrazinyl)acetyl]-3-(hydroxyimino)indolin-2-one (**4a-4n**) were designed and synthesized starting from isatin. The structures of synthesized compounds were confirmed by elemental and spectral analysis. All the compounds were evaluated for their anticonvulsant activity by MES induced seizure model and their neurotoxic effects by rotarod test. Most of the compounds showed moderate to good activity at the dose 30 and 100 mg/kg without neurotoxicity and produced neurotoxicity at 300 mg/kg.*

Key Words: Isatin, Isatin-3-oxime, Anticonvulsant activity, Neurotoxicity.

INTRODUCTION

Epilepsy is a condition of common synchronous neuronal discharge in the brain. According to epidemiological studies 1% of the population world wise is afflicted with this serious neurological disorder. It has been observed that 25% of the patients are inadequately controlled with the available antiepileptic drugs [1-3]. The anticonvulsants are a diverse group of pharmaceuticals which are used in the treatment of different types of epileptic seizures. They are also used in the treatment of bipolar disorder, thereby acting as mood stabilizers. The main work of anticonvulsant drugs is to suppress the hypersynchronous discharge of neurons that produce a seizure and also protect against possible excitotoxic effect that may result in brain damage. However, anticonvulsants themselves have been linked to lower IQ in children. Anticonvulsants moieties are often called antiepileptic drugs (abbreviated AEDs") or anti-seizure drugs (abbreviated "ASDs") [4-9].

Current AED_S produces a plethora of side effects including hepatotoxicity, drowsiness, ataxia, gastrointestinal disturbances, gingival hyperplasia, hirsutism and megaloblastic anaemia. Therefore, there is a need for synthesis of more effective and less toxic anticonvulsant drug. Isatin was found to have several biological activities like analgesic, anticancer, anticonvulsant, antifungal, anti-inflammatory, anti-HIV, antimicrobial, antioxidant, antiplasmodial, antitubercular, antiviral, spermicidal activity [10-21]. In these compounds the hydrophobic centre isatin, its oxime at position 3 and a carboxamide ($-CONH_2$) group are responsible for anticonvulsant activity. The parameters and pharmacophoric elements such as molecular weight, log P, hydrogen bond donor, hydrogen bond

acceptor, lipophilicity, and hydrophobic domain are essential for optimum anticonvulsant activity [22-23].The synthesized isatin derivatives possessed all the required pharmacophoric elements (Fig. 1).

Relation of Lead Compound with Anticonvulsant Activity

Important parameters which are necessary for anticonvulsant activity

Parameters	Rule of five	Lead compound
Mol. wt	≤ 500	323.22
log P	≤ 5 (all the existing Antiepileptic drug has log p in the range of 1.3-2.8)	2.18 (optimum value for CNS penetration 2.00)
Hydrogen bond donors	≤ 5 (expressed as the sum of OHs and NHs)	2
Hydrogen bond Acceptor	≤ 10 (expressed as the sum of Os and Ns)	4
Hydrogen bonding domain	necessary for binding to receptor mainly carboxamide (-CONH-)	one carbon introduces between this group (-$COCH_2NH$-)
Hydrophobic domain	necessary for lipophilicity	2 hydrophobic domains (Ar.)

MATERIAL AND METHODS

The melting points were determined by open capillaries method in a Hicon melting point apparatus and are uncorrected. The IR spectra of compounds were recorded on Perkin-Elmer infrared-283 FTIR spectrometer by KBr pellet technique. ^{1}H NMR spectra were recorded on Bruker DRX-300 (300 MHZ, FT NMR) spectrophotometer using TMS as an internal standard, and DMSO-d_6 as solvent. Mass spectrum was recorded on MICROTOF-Q II 10262 (BRUKER DATA ANALYSIS 4.0, Japan) under Electro Spray Ionization (ESI) technique. TLC was performed to monitor the reactions and to determine the purity of the products on a precoated aluminium plates using benzene and methanol (8:2) as a mobile phase. Iodine chamber and UV lamp were used for the visualization of TLC spots. The physicochemical parameters of the titled compounds are presented in Table1.

Procedure for the synthesis of isatin-3-oxime (1)

Hydroxylamine hydrochloride 10.4 g (0.15 mol) and sodium bicarbonate 12.6 g (0.15 mol) were dissolved in water (25 ml) and to this a separately prepared solution of isatin 7.35 g (0.05 mol) in ethanol (50 ml) was added dropwise at room temperature over 10 minutes. The reaction mixture was stirred at the same temperature for 16 hrs. Completion of reaction was monitored until the substrate disappeared by TLC. Ethanol was removed by reduced pressure and then the reaction was diluted with distill water and stirred for 10 min. Precipitate separated out, solvent was removed and residue was washed with cold water, filtered, dried and recrystallized from ethanol to give compound (**1**).

Procedure for the synthesis of 1-(2-chloroacetyl)-3-(hydroxyimino)indolin-2-one (2)

Freshly prepared sodium ethoxide was added to a solution of isatin-3-oxime 1.94 g (0.012 mol) in ethanol (60 ml). The reaction mixture was refluxed for 1hr and after that chloroacetyl chloride 6.89 g (0.061mol) was added and refluxed for 3 hrs. The product washed with water and recrystallized from ethanol to give compound **(2).**

Procedure for the synthesis of 1-(2-hydrazinylacetyl)-3-(hydroxyimino)indolin-2-one (3)

11.71g (0.05 mol) of compound (2) was dissolved in methanol and to this hydrazine hydrate 10 g (0.2 mol) was added and the reaction mixture was refluxed for 8 hrs. The completion of reaction was monitored by TLC. The solvent was removed and crude product recrystallized from ethanol to give compound **(3)** (4.9 g, 43.44%), m.p. 203-205^{o}C.

Procedure for the synthesis of 1-(2-(substituted benzylidenehydrazinyl) acetyl)-3-(hydroxyimino) indolin-2-one (4a-4n)

Equimolar quantity of compound **3** (0.008 mol) and different substituted benzaldehyde (0.008 mol) in methanol (60 ml) were refluxed on water bath for 9-34 hrs. The completion of reaction was monitored by TLC. Reaction mixture was cooled, filtered and the residue was recrystallized from ethanol/ethylacetate to give the product **(4a-4n)**.

Method of log P determination

Partition coefficient of synthesized compound between octanol and phosphate buffer was determine at room temperature by flask shake method. 10 ml of octanol and 10 ml of phosphate buffer were taken in a glass stoppered graduated tube and 5 mg of accurately weight compound was added. The mixture was then shaken with the help of

mechanical shaker for 24 hrs at room temperature and then transferred to a separating funnel and allowed to dynamic equilibrate for 6 hrs. The aqueous and octanol phases were separated and filtered through membrane filter and drug content in aqueous phase was analyzed by UV spectroscopy. Theoretical log P (calculated log P) for synthesized compounds was then compared with the experimental log P data. The values of CLog P is shown in table 1.

The spectral data of the synthesized compounds (4a-4n) are given as follows:

1-(2-(Benzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4a).
Yield 41.96%, mp 212^{o}C **FTIR (**ν, KBr, cm^{-1}**):** 3593 (O-H$_{str}$ of oxime), 3316 (N-H$_{str}$), 3087 (Ar-C-H$_{str}$), 2889 (Al C-H$_{str}$), 1714 (C=O$_{str.}$ of lactam), 1685 (C=O$_{str.}$ of $CH_2C=O$), 1668 (C=N$_{str}$ of NHN=C.), 1665 (C=N$_{str}$ of oxime), 1294 (C-N str), 942 (N-O$_{str}$ of NOH); **^{1}H NMR (δ, DMSO-*d*$_6$, ppm)**: 4.21 (s, 2H,CH_2),), 6.85-6.88 (d, 1H, Ar-H, *J*=9.0Hz), 6.92-7.00 (t, 1H, Ar-H, *J*=12.0Hz), 7.11-7.16 (t, 1H, Ar-H, *J*=7.5 Hz), 7.33-7.38 (t, 2H, Ar-H, *J*=7.5 Hz), 7.46-7.47 (d, 1H, Ar-H, *J*=3.0 Hz), 7.48-7.58 (t, 2H, Ar-H, *J*=15.0 Hz), 7.92-7.94 (d, 1H, Ar-H, *J*=6.0 Hz), 8.51(s, 1H, N=C-H), 10.54 (s, 1H, NH, D_2O exchangeable), 13.28 (s, 1H, NOH, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 322.11 (86) [M$^+$], 323.11 (16) [M+1]$^+$, 291.10, 158.02,133.07, 132.04, 116.05.

1-(2-(4-Chlorobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4b).
Yield 64.18%, m.p 238-240 ^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3595 (O-H$_{str}$. of oxime), 3317 (N-H$_{str}$.), 3089 (Ar C-H$_{str}$), 3025 (NC-H$_{str}$), 2890 (Al. C-H$_{str}$.), 1714 (C=O$_{str}$ of lactam), 1685 (C=O $_{str}$. of $CH_2C=O$), 1669 (C=N$_{str}$ of NHN=C), 1666 (C=N$_{str}$ of oxime), 1295 (C-N$_{str}$), 1179 (C-Cl$_{str}$.), 941 (N-O$_{str}$ of NOH), 827 (C-H$_{def}$ of *p*-disubstituted benzene); **^{1}H NMR (δ, DMSO-*d*$_6$, ppm)**: 4.32 (s, 2H, CH_2), 6.89-6.92 (d, 1H, Ar-H, *J*=9.0Hz), 7.00-7.06 (t, 1H, Ar-H, *J*=9.0 Hz), 7.31-7.34 (t, 1H, Ar-H, *J*=4.5 Hz), 7.34-7.36 (d, 2H, Ar-H, *J*=6.0 Hz), 7.41-7.45 (d, 2H, Ar-H *J*=12.0 Hz), 7.99-8.01 (d, 1H, Ar-H, *J*=6.0Hz), 8.62 (s, 1H, N=C-H), 10.69 (s,1H, NH, D_2O exchangeable), 13.29 (s, 1H, NOH, D_2O exchangeable); **Mass analysis:** MS (m/z): 189.03 (100), 356.07 (86) [M$^+$], 357.07 (16) [M+1]$^+$, 358.07 (27) [M+2]$^+$, 325.06, 167.03, 158.02, 132.04, 116.05.

1-(2-(3-Chlorobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4c).
Yield 62.68%, m.p 181-183^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3594 (O-H str. of oxime), 3317 (N-H str.), 3088 (Ar C-H$_{str}$), 3025 (NC-H$_{str}$), 2890 (Al str.), 171 (C=O$_{str}$ of lactam), 1686 (C=O$_{str}$ of $CH_2C=O$), 1669 (C=N$_{str}$ of NHN=C.), 1666 (C=N$_{str}$ of oxime), 1295 (C-N$_{str}$.), 1095 (C-Cl$_{str}$.), 941 (N-O$_{str.}$ of NOH), 692 (C-H$_{def}$. of *m*-disubstituted); **^{1}H NMR (δ, DMSO-*d*$_6$, ppm)**: 4.32 (s, 2H,CH_2), 6.86-6.89 (d, 1H, Ar-H, *J*=9.0 Hz), 7.01-7.04 (t, 1H, Ar-H, *J*=4.5 Hz), 7.31-7.39 (t, 1H, Ar.-H, *J*=12.0 Hz) 7.41-7.49 (t, 1H, Ar-H, *J*=12.0 Hz), 7.54-7.59 (t, 1H, Ar-H, *J*=7.5 Hz), 7.64-7.67 (d, 1H, Ar-H, *J*=9.0 Hz), 7.80 (s, 1H, Ar-H), 7.95-7.98 (d, 1H, Ar-H, *J*=9.0 Hz), 8.57 (s, 1H, N=C-H), 10.68 (s, 1H, NH, D_2O exchangeable), 13.29 (s, 1H, NO-H, D_2O exchangable); **Mass analysis :** MS (m/z): 189.03 (100), 356.07 (86) [M$^+$], 357.07 (16) [M+1]$^+$, 358.07 (27) [M+2]$^+$, 325.06, 321.09, 167.03, 158.02, 132.04, 116.05.

1-(2-(2-Chlorobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4d).
Yield 68.12%, m.p. 186-188 ^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3597 (O-H$_{str}$ of oxime), 3319 (N-H$_{str}$), 3090 (Ar C-H$_{str}$.), 3027 (NC-H$_{str}$), 2890 (Al$_{str}$), 1716 (C=O str. of lactam), 1687 (C=O$_{str}$ of $CH_2C=O$), 1670 (C=N str. of NHN=C.), 1666 (C=N$_{str}$. of oxime), 1297 (C-N$_{str}$), 1011 (C-Cl$_{str}$), 941 (N-O$_{str}$ of NOH), 756 (C-H$_{def}$ *o*-disubstituted); **^{1}H NMR (δ, DMSO-*d*$_6$, ppm)**: 4.32 (s, 2H, CH_2), 6.89-6.92 (d, 1H, Ar-H, *J*=9.0 Hz), 7.00-7.05 (t, 1H, Ar-H, *J*=7.5 Hz), 7.31-7.36 (m, 2H, Ar-H), 7.47-7.49 (d, 2H, Ar-H, *J*=6.0 Hz),7.50-7.52 (t, 1H, Ar-H, *J*=3.0 Hz), 7.98-8.01 (d, 1H, Ar-H, *J*=9.0 Hz), 8.62 (s, 1H, N=C-H), 10.69 (s, 1H, NH, D_2O exchangeable), 13.29 (s, 1H, NOH, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 356.07 (86) [M$^+$], 357.07 (16) [M+1]$^+$, 358.07 (27) [M+2]$^+$, 325.06, 321.09, 167.03, 158.02, 132.04, 116.05.

1-(2-(4-Nitrobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4e).
Yield 60.66%, m.p. 214-216 ^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3598 (O-H$_{str}$ of oxime), 3319 (N-H$_{str}$), 3091 (Ar C-H$_{str}$), 3028 (NC-H$_{str}$), 2893 (Al$_{str}$), 1717 (C=O str of lactam), 1687 (C=Ostr of $CH_2C=O$), 1671 (C=N str. of NHN=C), 1667 (C=N$_{str}$ of oxime), 1519 (asmmetric N=O$_{str}$), 1352.10 (symmetric N=O$_{str}$), 1298 (C-N$_{str}$), 941 (N-O$_{str}$ of NOH) 859 (C-H$_{def}$ *p*-disubstituted benzene); **^{1}H NMR (δ, DMSO-*d*$_6$, ppm)**: 4.53 (s, 2H,CH_2), 6.86-6.88 (d, 1H, Ar-H, *J*=6.0Hz), 6.99-7.03 (t, 1H, Ar-H, *J*=6.0 Hz), 7.32-7.37 (t, 1H, Ar-H, *J*=7.5 Hz), 7.78-7.79 (d, 2H, Ar-H, *J*=3.0 Hz), 7.99-8.02(d, 2H Ar-H, *J*=9.0Hz), 8.40-8.43 (d, 1H, Ar-H, *J*=9.0Hz), 9.14 (s, 1H, N=C-H), 10.68 (s, 1H, NH, D_2O exchangeable), 13.29 (s, 1H, NO-H, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 367.09 (86) [M$^+$], 368.09 (16) [M+1]$^+$, 336.08, 321.09, 178.06, 158.02, 132.04, 116.05.

1-(2-(3-Nitrobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4f).
Yield, 60.15%, m.p. 178-180^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3597 (O-H str. of oxime), 3317 (N-H str.), 3090 (aromatic C-$H_{str.}$), 3027 (NC-H_{str}), 2892 (Al C-H_{str}), 1716 (C=O_{str} of lactam), 1686 (C=O_{str} of CH_2C=O), 1670 (C=$N_{str.}$ of NHN=C.), 1667 (C=N_{str} of oxime), 1520 (asymmetric N=O_{str}), 1350 (symmetric N=O_{str}), 1298 (C-$N_{str.}$), 941 (N-$O_{str.}$ of NOH), 691 (C-$H_{def.}$ of *m*-disubstituted benzene); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 4.53 (s, 2H,CH_2), 6.86-6.89 (d, 1H, Ar-H, *J*=9.0 Hz), 6.99-7.04 (t,1H, Ar-H, *J*=7.5 Hz) 7.32-7.37 (t,1H, Ar-H, *J*=7.5 Hz), 7.71-7.76 (t, 1H, Ar-H,*J*=7.5 Hz), 7.90-7.92 (d, 1H, Ar-H, *J*=6.0Hz), 7.92-7.95 (d, 1H, Ar-H, *J*=9.0Hz), 8.18 (s,1H, Ar-H), 8.41-8.43 (d, 1H, Ar-H, *J*=6.0 Hz), 9.14 (s, 1H, N=C-H), 10.68 (s, 1H, NH, D_2O exchangeable), 13.29 (s, 1H, NOH, D_2O exchangeable); **Mass analysis:** MS (m/z): 189.03 (100), 367.09 (86) [M^+], 368.09 (16) [M+1]$^+$, 336.08, 321.09, 178.06,158.02, 132.04, 116.05.

1-(2-(2-Nitrobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4g).
Yield 62.38%, m.p. 196-198 ^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3598 (O-H str. of oxime), 3318 (N-H str.), 3090 (Ar C-H str.), 3027 (NC-H str.), 2892 (Al_{str}), 1718 (C=$O_{str.}$ of lactam), 1684 (C=O_{str} of CH_2C=O), 1671 (C=$N_{str.}$ of NHN=C.), 1668 (C=N_{str} of oxime), 1521 (asymmetric N=O_{str}), 1351 (symmetric N=O_{str}), 1299 (C-N_{str}), 941 (N-O_{str} of NOH), 752 (C-H_{def} of *o*-disubstituted benzene); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 4.53 (s, 2H,CH_2), 6.86-6.89 (d, 1H, Ar-H, *J*=9.0 Hz), 6.99-7.04 (t, 1H, Ar-H, *J*=7.5 Hz), 7.32-7.38 (t, 2H, Ar-H, *J*=9.0 Hz),7.75-7.77 (d, 2H, Ar-H, *J*=6.0 Hz),7.99-8.02 (d, 1H, Ar-H,*J*=9.0 Hz) 8.27-8.30 (d, 1H, Ar-H, *J*=9.0 Hz), 9.18 (s, 1H, N=C-H), 10.68 (s, 1H, NH, D_2O exchangeable), 13.29 (s, 1H, NO-H, D_2O exchangeable). **Mass analysis :** MS (m/z): 189.03 (100), 367.09 (86) [M^+], 368.09 (16) [M+1]$^+$, 336.08, 321.09, 178.06, 158.02, 132.04, 116.05.

1-(2-(4-Hydroxybenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4h).
Yield 58.68%, m.p. 160-162 ^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3593 (O-$H_{str.}$ of oxime), 3498 (O-$H_{str.}$ of phenol) 3317 (N-H str.), 3090 (Ar C-H str.), 3027 (NC-H_{str}), 2893 ($Al_{str.}$), 1716 (C=$O_{str.}$ of lactam), 1686 (C=O str. of CH_2C=O), 1671.34 (C=N str. of NHN=C.), 1665 (C=N str. of oxime), 1295 (C-N str.), 944 (N-O str. of NOH), 835 (C-H def. of *p*-disubstituted benzene); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 4.32 (s, 2H,CH_2), 6.85-6.87 (d, 1H, Ar-H, *J*=6.0 Hz), 6.92-6.95 (d,1H, Ar-H, *J*=9.0 Hz), 6.99-7.04 (t, 1H, Ar-H, *J*=7.5 Hz), 7.28-7.32 (d, 1H, Ar-H, *J*=12.0 Hz), 7.37-7.40 (d, 2H, Ar-H, 9.0 Hz), 7.96-7.99 (d,1-H, Ar-H, *J*=9.0 Hz), 9.09 (s, 1H, N=C-H), 10.69 (s, 1H NH, D_2O exchangeable), 10.83 (s, 1H, OH, D_2O exchangeable), 13.29 (s, 1H, NOH, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 338.10 (90) [M^+], 339.10 (18) [M+1]$^+$, 321.09, 307.09, 158.02, 149.07, 132.04, 116.05.

1-(2-(3-Hydroxybenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4i).
Yield 48.96%, m.p 122-124 ^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3594 (O-H_{str} of oxime), 3499 (O-H_{str} of phenol), 3319 (N-H_{str}), 3090 (Ar C-H_{str}), 3028 (NC-H_{str}), 2891 (aliphatic C-H_{str}), 1716 (C=O_{str} of lactam), 1687 (C=O_{str} of CH_2C=O), 1669 (C=N_{str} of NHN=C), 1667 (C=N_{str} of oxime), 1295 (C-N_{str}), 944 (N-O_{str} of NOH) 699 (C-H_{def} *m*-disubstituted benzene); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 4.32 (s, 2H, CH_2), 6.85-6.87 (d, 1H, Ar-H, *J*=6.0 Hz), 6.99 (s,1H, Ar-H), 6.99-7.04 (t, 3H, Ar- H, *J*=7.5 Hz), 7.24-7.35 (m, 2H, Ar-H), 7.95-7.99 (d,1H, Ar-H, *J*=12.0 Hz), 9.09 (s, 1H, N=C-H), 10.69 (s, 1H, NH, D_2O exchangeable), 10.80 (s,1H, OH, D_2O exchangeable), 13.30 (s, 1H, NO-H, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 338.10 (90) [M^+], 339.10 (18) [M+1]$^+$, 321.09, 307.09, 158.02, 149.07, 132.04, 116.05.

1-(2-(2-Hydroxybenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4j).
Yield 49.98%, mp. 164-166 ^{o}C. **FTIR (**ν, KBr, cm^{-1}**):** 3595 (O-H str. of oxime), 3499 (O-H str. of phenol) 3320 (N-H str.), 3092 (Ar C-H oxime), 3029 (NC-H_{str}), 2892 (Al C-H_{str}), 1717 (C=O_{str} of lactam), 1687 (C=O_{str} of CH_2C=O), 1671 (C=N_{str} of NHN=C.), 1668 (C=N_{str} of oxime), 1299 (C-N str.), 941 (N-O str. of NOH) 752 (C-H_{def} of *o*-disubstituted benzene); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 4.32 (s, 2H, CH_2), 6.85-6.87 (d, 1H, Ar-H, *J*=6.0 Hz), 6.89-6.91 (d,1H, Ar-H, *J*=6.0 Hz), 6.98-7.03 (m, 2H, Ar-H), 7.28-7.37 (m, 3H, Ar-H), 7.95-7.99 (d, 1H, Ar-H, *J*=12.0 Hz), 9.09 (s, 1H, N=C-H), 10.69 (s, 1H, NH, D_2O exchangeable), 10.80 (s,1H, OH, D_2O exchangeable), 13.30 (s, 1H, NOH, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 338.10 (90) [M^+], 339.10 (18) [M+1]$^+$, 321.09, 307.09, 158.02, 149.07, 132.04, 116.05.

1-(2-(4-Methoxybenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4k).
Yield 56.78%, mp. 196-198 ^{o}C; **FTIR (**ν, KBr, cm^{-1}**):** 3594.12 (O-H str. of oxime), 3317.24 (N-H str.), 3089 (aromatic C-H str.), 3025 (NC-H str.), 2892 (aliphatic C-H str.), 1716 (C=O str. of lactam), 1685 (C=$O_{str.}$ of CH_2C=O), 1669 (C=$N_{str.}$ of NHN=C.), 1666 (C=N_{str} of oxime), 1295 (C-N_{str}), 1045 (C-O-C_{str} of methoxy) 941 (N-O str. of NOH) 752 (C-H def. of *p*-disubstituted); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 3.87 (s, 3H, OCH_3), 4.20 (s,

2H,CH_2), 6.87-6.89 (d, 1H, Ar-H, *J*=6.0 Hz), 6.93-6.94 (d, 2H, Ar-H, *J*=3.0Hz) 7.01-7.10 (t, 1H, Ar-H, *J*=13.5 Hz), 7.29-7.32 (d, 2H, Ar-H, *J*=9.0 Hz), 7.32-7.37 (t, 1H, Ar-H, *J*=7.5 Hz), 7.93-7.95 (d, 1H, Ar-H, *J*=6.0 Hz), 8.47 (s, 1H, C=N-H), 10.68 (s, 1H, NH, D_2O exchangeable), 13.28 (s, 1H, NO-H, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 352.12 (86) [M^+], 353.12 (17) $[M+1]^+$, 321.11, 163.08, 158.02, 144.04, 132.04, 116.05.

1-(2-(3-Methoxybenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4l).
54.82%, m.p 190-192 ^oC. **FTIR (**ν, KBr, cm^{-1}**):** 3593 (O-H_{str} of oxime), 3316 (N-H_{str}), 3088 (Ar. C-H_{str}), 3024 (NC-H_{str}), 2891 (Al C-H_{str}), 1716 (C=O str. of lactum), 1684 (C=O_{str} of CH_2C=O), 1667 (C=N_{str} of NHN=C), 1664 (C=N str. of oxime), , 1294 (C-N_{str}), 1044 (C-O-C_{str} of methoxy), 941 (N-O_{str} of NOH), 780 (C-H_{def} of *m*-disubstitutedbenzene); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 3.37 (s,3H, OCH_3), 4.19 (s, 2H,CH_2), 6.86-6.88 (d, 1H, Ar-H, *J*=6.0 Hz), 6.93-6.96 (t, 1H, Ar-H, *J*=4.5 Hz), 7.04 (s, 1H, Ar-H), 7.04-7.09(t, 1H, Ar-H, *J*=7.5 Hz),7.32- 7.37 (m, 2H, Ar-H), 7.48-7.50 (d, 1H, Ar-H, *J*=6.0 Hz), 7.93-7.95 (d, 1H, Ar-H, *J*=6.0 Hz), 8.47 (s, 1H, N=C-H), 10.68 (s, 1H, NH, D_2O exchangeable), 13.28 (s, 1H, NO-H, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 352.12 (86) [M^+], 353.12 (17) $[M+1]^+$, 321.11, 163.08, 158.02, 144.04, 132.04, 116.06.

1-(2-(4-Fluorobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4m).
Yield 73.12%, m.p 216-218^oC. **FTIR (**ν, KBr, cm^{-1}**):** 3596 (O-H_{str} of oxime), 3320 (N-H_{str}), 3090 (Ar C-H_{str}), 3028 (NC-H_{str}), 2895.14 (Al C-H_{str}), 1721 (C=O_{str} of lactam), 1689 (C=O_{str} of CH_2C=O), 1672 (C=N_{str} of NHN=C.), 1668 (C=N_{str} of oxime), 1296 (C-N_{str}), 1164 (C-F_{str}), 951 (N-O_{str} of NOH), 840 (*p*-disubstituted benzene); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 4.23 (s, 2H,CH_2), 6.86-6.89 (d, 1H, Ar-H, *J*=9.0 Hz), 6.92-6.99 (t, 1H, Ar-H, *J*=10.5 Hz), 7.01-7.04 (d, 2H, Ar-H, *J*=9.0Hz), 7.32-7.37 (t, 1H, Ar-H, *J*=7.5 Hz), 7.75-7.78 (d, 2H, Ar-H. *J*=9.0 Hz), 7.93-7.95 (d, 1H, Ar-H, *J*=6.0 Hz), 8.72 (s, 1H, N=C-H), 10.61 (s, 1H, NH, D_2O exchangeable), 13.29 (s, 1H, NO-H, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 340.10 (86) [M^+], 341.10 (16) $[M+1]^+$, 342.10 (27) $[M+2]^+$, 321.11, 309.03, 158.02, 151.06, 132.04, 116.05.

1-(2-(4-*N*,*N*-Dimethylaminobenzylidenehydrazinyl)acetyl)-3-(hydroxyimino)indolin-2-one (4n).
Yield 64.86%, m.p. 178-180^oC. **FTIR (**ν, KBr, cm^{-1}**):** 3592 (O-H str. of oxime), 3315 (N-H str.), 3086 (aromatic C-H str.), 3022 (NC-H str.), 2893 (Al C-H_{str}), 1714 (C=O_{str} of lactam), 1683(C=O_{str} of CH_2C=O), 1665 (C=N_{str} of NHN=C), 1662 (C=N_{str} of oxime), , 1290 (Ar C-N_{str}), 1179 (Al C-N str.) 941 (N-O str. of NOH) 848 (C-H def. of *p*-disubstituted); **^{1}H NMR (δ, DMSO-d_6, ppm)**: 4.00 (s, 6H, $N(CH_3)_2$), 4.32 (s, 2H,CH_2), 6.85-6.87 (d, 2H, Ar-H, *J*=6.0 Hz), 6.91-6.98 (t, 1H, Ar-H, *J*=10.5 Hz), 7.01-7.04 (d, 1H, Ar-H, *J*=9.0 Hz), 7.28-7.34 (t,1H, Ar-H, *J*=9.0 Hz), 7.37-7.39 (d, 2H, Ar-H, *J*=6.0 Hz), 7.95-7.99 (d,1H, Ar-H, *J*=12.0 Hz), 8.57 (s, 1H, N=C-H), 10.69 (s, 1H, NH, D_2O exchangeable), 13.30 (s, 1H, NO-H, D_2O exchangeable); **Mass analysis :** MS (m/z): 189.03 (100), 365.15 (86) [M^+], 366.15 (16) $[M+1]^+$, 334.14, 321.09,176.11, 158.02, 132.04, 116.05.

Pharmacology
Albino rats (wistar strain) were used to predict anticonvulsant activity due to their physiological similarity with the human. The required number of animals was acclimatized to the experimental condition one day prior to initiation of biological activity. The animals were kept under standard conditions at an ambient temperature of 25±2 ^oC. The animals were obtained from Animal House of Rajiv Academy for Pharmacy, Mathura. All the experimental protocols were carried out with the permission from Institutional Animal Ethics Committee (IAEC), Registration no. is 882-ac/05/CPCSEA and date of registration is 03 Sep., 2011. Earthworms, *Phaeritima Posthuma*, due to its anatomical and physiological resemblance with the intestinal roundworm parasites of human beings were used in the present study. Both worms show undulating movement and protect evacuation against peristalsis of Gut.

Anticonvulsant Activity
Maximal Electroshock test (MES): Animals were fasted overnight, weighed, marked and classified into three groups namely control, standard and test group each group comprising of six rats. At the first day of experiment, the control group was administered with 30% v/v PEG400 aq. solution and to the standard group Phenytoin (30 mg/kg in 30% v/v PEG400) was administered intraperitoneally and test compounds were administered intraperitoneally to the test group at varying doses (30 mg/kg, 100 mg/kg and 300 mg/kg in 30% v/v PEG400). Next day the same procedure was followed for second and third group with other test compounds. After holding the animal properly, corneal electrodes were placed over the upper eye lid above the cornea and the prescribed current 150 mA for 0.2 seconds was given. Different stages of convulsions i.e. (a) the tonic flexion, (b) tonic extensor phase, (c) clonic convulsions, (d) stupor and (e) recovery or death were observed for each group. The time spent by the animal in each phase of convulsion was noted after dose administration of 0.5 and 4hrs.

The same procedure was repeated in all the animals of control and standard group. The reduction in time or abolition of different phase of MES-convulsions was noted [24]. Biological data of tested compounds have been reported in Table-**2**, **3, 4, 5 and 6**.

Neurotoxicity study

Minimal motor impairment was assessed in rats employing the rotorod test [25]. The rats were trained to stay on an accelerating rotorod rotating at 10 rpm. The rod diameter was 3.2 cm. Neurotoxicity was indicated by the inability of the rats to maintain equilibrium on the rod for at least 1min in each of the three trials. The data of neurotoxicity studies is given in Table **7.**

Anthelmintic Activity

All earthworms were of approximately equal size (≈3inch). They were collected from local place, washed and kept in water. Earthworms were divided into sixteen groups (4 each). The first group served as normal control which received 0.5% Tween 80 in distilled water. The second received the standard drugs i.e albendazole in aqueous Tween 80 (0.5%) solution at a dose level of 2 mg/ml and test groups received various doses of synthesized compounds (1, 2, 4 mg/ml) in Tween 80 (0.5%) and distilled water. Observations were made for the time taken to cause paralysis and death of individual worms for two hours. The paralyzing and death times were noted and their mean was calculated for triplicate sets. The death time was ascertained by placing the earthworm in warm water (50ºC), which stimulate the movement, if the worm was alive. The results of anthelmintic activity are shown in Table **8.**

RESULTS AND DISCUSSION

Chemistry

A series of 1-[2-(substituted benzylidenhydrazinyl) acetyl]-3-(hydroxyimino) indolin-2-one (**4a-4n**) were designed and synthesized according to scheme **1**. Isatin on treatment with hydroxylamine hydrochloride gave isatin-3-oxime **(1)** which on reaction with chloroacetyl chloride yielded 1-(2-chloroacetyl)-3-(hydroxyimino)indolin-2-one **(2)** which on further treatment with hydrazine hydrate produced 1-(2-hydrazinylacetyl)-3-(hydroxyimino)indolin-2-one **(3).** Condensation of **(3)** with various aromatic aldehydes afforded1-[2-(substitutedbenzylidenhydrazinyl) acetyl]-3-(hydroxyimino)indolin-2-one [**4a-4n].** The reactions were monitored by TLC on silica gel G plates and the final products were purified by recrystallization from ethanol/ ethylacetate.

The structures of synthesized compounds were confirmed by FTIR, ^{1}H NMR, EIMS spectral and elemental analysis and found different physical parameters (solubility, melting point).

Pharmacology

The anticonvulsant activity of synthesized compounds carried out under the Antiepileptic Drug Development (ADD) Program. Accordingly, the activity of the compounds investigated was classed with the following categories: active at doses of 100 mg/kg or less (class1) active at doses greater than 100 mg/kg (class2), inactive at 300 mg/kg. Rats were tested using the following doses 30, 100 and 300 mg/kg of compounds investigated.

Compounds were evaluated by Maximal Electroshock-induced seizures (MES test) and their neurotoxicity by rotorod test. Most of the compounds showed moderate to good activity at the dose 30, 100 mg/kg without neurotoxicity except compounds **4e**, **4f** and **4g**. Most of the compounds produced neurotoxicity at 300 mg/kg except **4n** which showed neurotoxicity at 100 mg/kg. The limited range of dose (30-100 mg/kg) for activity showed the concept of therapeutic window phenomena. Compound **4c** was found to be most potent compound having large range of dose for activity and produces less neurotoxicity at 300 mg/kg. Compounds **4e**, **4f** and **4g** (nitro substituted) showed poor or less activity due to low log P. The results are summarized in table 2 and 3 and their time period of abolishment of hind limbs. From the above results it was found that the chloro, fluoro derivatives exhibit better activity and the *m*-substituted derivative was found to possess more significant activity, alteration at *m*-position affect the activity. All the nitro substituted compounds showed poor activity due to low CNS penetration. The anticonvulsant activity profile depended on the distance between the aromatic moiety and imide nitrogen atom. The introduction of the fluoro and chloro ring proved to enhance the anticonvulsant activity.

Table 1. Physicochemical parameters of the titled compounds (4a-n)

Compd. No.	R	Mol. Formula	Mol. Wt	CLog P	R_f Value[a]	Elemental Analysis [% calcd. (% found)]		
						C	H	N
4a	H	$C_{17}H_{14}N_4O_3$	322.32	2.18	0.67	63.35 (63.31)	4.38 (4.35)	17.38 (17.36)
4b	4-Cl	$C_{17}H_{13}ClN_4O_3$	356.76	2.76	0.71	57.23 (57.21)	3.67 (3.65)	15.70 (15.68)
4c	3-Cl	$C_{17}H_{13}ClN_4O_3$	356.76	2.77	0.72	57.23 (57.22)	3.67 (3.67)	15.70 (15.69)
4d	2-Cl	$C_{17}H_{13}ClN_4O_3$	356.76	2.34	0.74	57.23 (57.24)	3.67 (3.69)	15.70 (15.71)
4e	4-NO_2	$C_{17}H_{13}N_5O_5$	367.32	0.94	0.77	55.59 (55.52)	3.57 (3.55)	19.07 (19.06)
4f	3-NO_2	$C_{17}H_{13}N_5O_5$	367.32	0.86	0.73	55.59 (55.56)	3.57 (3.52)	19.07 (19.04)
4g	2-NO_2	$C_{17}H_{13}N_5O_5$	367.32	0.79	0.79	55.59 (55.54)	3.57 (3.54)	19.07 (19.03)
4h	4-OH	$C_{17}H_{14}N_4O_4$	338.10	1.90	0.58	61.35 (61.34)	4.19 (4.15)	16.56 (16.51)
4i	3-OH	$C_{17}H_{14}N_4O_4$	338.10	1.91	0.63	61.35 (61.32)	4.19 (4.11)	16.56 (16.55)
4j	2-OH	$C_{17}H_{14}N_4O_4$	338.10	2.20	0.68	61.35 (61.30)	4.19 (4.14)	16.56 (16.54)
4k	4-OCH_3	$C_{18}H_{16}N_4O_4$	352.34	2.26	0.69	61.36 (61.38)	4.58 (4.54)	15.29 (15.24)
4l	3-OCH_3	$C_{18}H_{16}N_4O_4$	352.34	2.24	0.59	61.36 (61.32)	4.58 (4.56)	15.29 (15.27)
4m	4-F	$C_{17}H_{13}FN_4O_3$	340.31	2.19	0.65	60.00 (59.97)	3.85 (3.82)	16.46 (16.44)
4n	4-$N(CH_3)_2$	$C_{19}H_{19}N_5O_5$	365.39	2.50	0.57	62.46 (62.43)	5.24 (5.21)	19.17 (19.15)

[a]*Solvent system Benzene:Methanol (8:2)*

Table 2. Anticonvulsant activity of compounds (4a-4n) against MES induced seizures at a dose of 30 mg/kg after 0.5 h of drug administration

Compd. No.	Time (sec) in various phases of convulsion				
	Flexion	**Extensor**	**Clonus**	**Stupor**	**Recovery/Death**
4a	0	0	0	45.6±0.6***	R
ab	0	0	0	62.7±0.3***	R
4c	0	0	0	32.7±0.5***	R
4d	0	0	0	55.5±0.8***	R
4e	$3.3±0.3^{ns}$	$18.5±0.3^{ns}$	$31.5±0.4^{ns}$	199.6±0.6***	R
4f	3.7±0.3**	$18.5±0.3^{ns}$	36.5±0.6***	$208.8±0.2^{ns}$	R
4g	3.5±0.3***	$18.8±0.2^{ns}$	36.3±0.2***	198.6±0.3***	R
4h	2.3±0.3***	10.4±0.7***	32.3±0.3*	202.3±0.3***	R
4i	2.2±0.4***	9.2±0.4***	30.6±0.4***	140.4±0.7***	R
4j	2.3±0.4***	7.3±0.4***	30.8±0.3*	188.5±0.4***	R
4k	1.8±0.6***	8.8±0.2***	15.8±0.3***	165.2±0.6***	R
4l	1.5±0.3***	9.0±0.6***	14.3±0.6***	128.2±0.5***	R
4m	0	0	0	38.8±0.3***	R
4n	0	0	0	41.3±0.6***	R
Control	3.0±0.2	18.6±0.4	31.6±0.6	210±0.8	R
Phenytoin	0	0	0	0	R

*n=6; * P<0.05; ** P<0.01; *** P<0.001.; 0 indicates no convulsion*

Table 3. Anticonvulsant activity of compounds (4a-4n) against MES induced seizures at a dose of 30 mg/kg after 4 h of drug administration

Compd. No.	Time (sec) in various phases of convulsion				
	Flexion	**Extensor**	**Clonus**	**Stupor**	**Recovery/Death**
4a	0	0	0	32.6±0.6***	R
4b	0	0	0	61.8±0.3***	R
4c	0	0	0	30.8±0.2***	R
4d	0	0	0	55.1±0.7***	R
4e	$3.1±0.3^{ns}$	$18.1±0.4^{ns}$	30.8±0.4***	188.4±0.4***	R
4f	$3.3±0.8^{ns}$	$18.4±0.3^{ns}$	36.1±0.5***	206.8±0.6***	R
4g	$3.4±0.6^{ns}$	$18.5±0.8^{ns}$	35.9±0.4***	198.2±0.4***	R
4h	2.3±0.3***	10.1±0.4***	32.1±0.5***	106.4±0.7***	R
4i	2.1±0.6***	8.9±0.3***	30.1±0.6**	130.8±0.3***	R
4j	1.9±0.7***	7.1±0.6***	30.2±0.5**	186.2±0.3***	R
4k	1.6±0.8***	8.6±0.4***	15.3±0.8***	164.2±0.1***	R
4l	1.2±0.3***	8.3±0.6***	14.1±0.4***	136.5±0.5***	R
4m	0	0	0	38.2±0.6***	R
4n	0	0	0	40.6±0.6***	R
Control	3.0±0.2	18.6±0.4	31.6±0.6	210±0.8	R
Phenytoin	0	0	0	0	R

*n=6; * P<0.05; ** P<0.01; *** P<0.001.; 0 indicates no convulsion.*

The synthesized compounds were also screened for *in vitro* anthelmintic activity. Nitro and dimethylamine substituted derivatives showed potent anthelmintic activity. The compounds which show small death and paralyzing time called vermicide and compound **4f** may act as vermicide. The compounds which showed long duration of time for death and small time of duration for paralyzing and compound **4n** may act as better vermifuge.

In nitro derivatives *m*-substituted compounds were found to possess more potent anthelmintic activity. Worms paralyze due to hyperpolarization and in this activity there is no need to increase the lipophilicity.

Table 4. Anticonvulsant activity of compounds (4a-4n) against MES induced seizures at a dose of 100 mg/kg after 0.5 hr of drug administration

Compd. No.	Time (sec) in various phases of convulsion				
	Flexion	Extensor	Clonus	Stupor	Recovery/Death
4a	0	0	0	6.8±0.4***	R
4b	0	0	0	3.8±0.3***	R
4c	0	0	0	0	R
4d	0	0	0	4.1±0.8***	R
4e	3.1±0.3***	16.2±0.3***	30.1±0.2**	192.4±0.3***	R
4f	3.6±0.8^{ns}	16.4±0.8***	32.4±0.6*	196.8±0.6***	R
4g	3.5±0.5^{ns}	18.8±0.2***	36.3±0.2***	179.2±0.4***	R
4h	2.3±0.8***	10.4±0.7***	32.3±0.3*	106.4±0.7***	R
4i	2.2±0.6***	9.2±0.4***	30.6±0.4**	130.8±0.3***	R
4j	2.1±0.3***	7.3±0.4***	30.8±0.3***	186.2±0.3***	R
4k	1.8±0.6***	8.8±0.2***	15.8±0.3***	164.2±0.1***	R
4l	1.5±0.3	9±0.6***	14.3±0.6***	136.5±0.5***	R
4m	0	0	0	38.2±0.6***	R
4n	0	0	0	40.6±0.6***	R
Control	3.4±0.2	18.6±0.4	31.6±0.6	210±0.8	R
Phenytoin	0	0	0	114.4±0.2	R

*n=6; * P<0.05; ** P<0.01; *** P<0.001.; 0 indicates no convulsion*

Table 5. Anticonvulsant activity of compounds (4a-4n) against MES induced seizures at a dose of 100 mg/kg after 4 h of drug administration

Compd. No.	Time (sec) in various phases of convulsion				
	Flexion	Extensor	Clonus	Stupor	Recovery/Death
4a	0	0	0	5.8±0.3***	R
4b	0	0	0	2.1±0.6***	R
4c	0	0	0	0	R
4d	0	0	0	3.7±0.6***	R
4e	2.8±0.3***	18.1±0.6^{ns}	29.8±0.6*	190.8±0.6***	R
4f	2.1±0.6***	18.4±0.8^{ns}	31.2±0.6***	188.0±0.4***	R
4g	2.9±0.1***	16.2±0.3***	29.9±0.2**	167.2±0.8***	R
4h	1.8±0.8***	11.2±0.4***	29.2±0.4*	98.4±0.7***	R
4i	1.5±0.3***	8.6±0.2***	28.8±0.3***	120.6±0.8***	R
4j	1.2±0.3***	8.4±0.8***	26.2±0.9***	166.2±0.6***	R
4k	1.6±0.3***	6.2±0.8***	15.3±0.6***	146.2±0.6***	R
4l	1.2±0.8***	5.0±0.4***	12.4±0.6***	120.2±0.4***	R
4m	0	0	0	36.1±0.3***	R
4n	3.9±0.4***	18.9±0.3^{ns}	31.3±0.6**	228±0.9^{ns}	R
Control	3.1±0.6	18.9±0.3	30.8±0.3	226±0.8	R
Phenytoin	0	0	0	113.0.8	R

*n=6; * P<0.05; ** P<0.01; *** P<0.001.; 0 indicates no convulsion.*

Table 6. Anticonvulsant activity of compounds (4a-4n) against MES induced seizures at a dose of 300 mg/kg after 4 h of drug administration

Compd. No.	Time (sec) in various phases of convulsion				
	Flexion	Extensor	Clonus	Stupor	Recovery/Death
4a	3.6±0.4***	20.2±0.6***	32.9±0.3***	216.4±0.8***	R
4b	3.6±0.4***	21.2±0.8***	31.8±0.3^{ns}	215.8±0.3*	R
4c	2.8±0.3***	11.1±0.3***	21.3±0.6***	216.4±0.8***	R
4d	3.4±0.8***	20.8±0.8***	32.6±0.6***	220.2±0.4***	R
4e	3.6±0.8***	20.8±0.6***	33.4±0.6***	223.2±0.4***	R
4f	4.2±0.6**	24.2±0.2***	34.6±0.4***	219.3±0.3***	R
4g	3.8±0.3***	22.4±0.8***	32.2±0.6**	216.4±0.6***	R
4h	4.6±0.3***	25.6±0.3***	34.1±0.6***	218.6±0.5***	R
4i	3.9±0.4***	22.2±0.8***	32.6±0.6***	215.9±0.8**	R
4j	3.2±0.8^{ns}	21.3±0.3***	31.8±0.9^{ns}	213.6±0.7^{ns}	R
4k	3.2±0.9^{ns}	20.2±0.6***	31.7±0.3^{ns}	212.8±0.8^{ns}	R
4l	3.4±0.8^{ns}	21.8±0.6***	31.9±0.6*	214.6±0.6^{ns}	R
4m	3.1±0.2**	19.2±0.6^{ns}	31.2±0.6^{ns}	216.2±0.2**	R
4n	3.9±0.8***	23.1±0.2***	32.4±0.8***	226.2±0.2***	R
Control	3.3±0.4	18.2±0.8	30.9±0.6	212±0.9	R
Phenytoin	0	0	0	124.4±0.3	R

*n=6; * P<0.05; ** P<0.01; *** P<0.001.; 0 indicates no convulsion.*

Table 7. Neurotoxicity study of synthesized compound (4a-n) in rotorod test

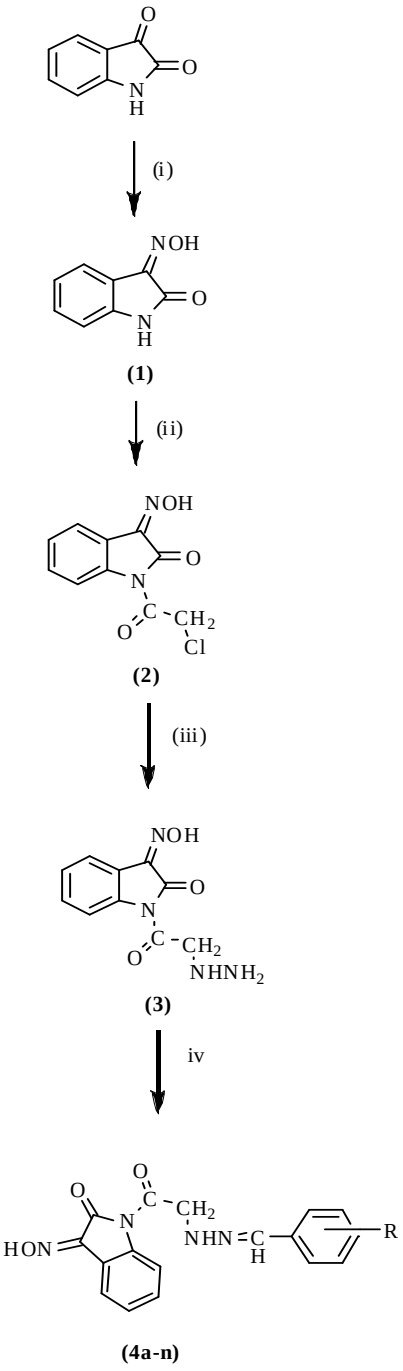
Compd. No.	Percent protection from neurotoxicity (rotorod test)					
	30 mg/kg		100 mg/kg		300 mg/kg	
	0.5 hr	4 hr	0.5 hr	4 hr	0.5 hr	4 hr
4a	100.0	100.0	100.0	100.0	0.0	25.0
4b	100.0	100.0	100.0	100.0	0.0	25.5
4c	100.0	100.0	100.0	100.0	50	75.0
4d	100.0	100.0	75.0	100.0	0.0	50.0
4e	100.0	75.0	50.0	25.0	0.0	25.0
4f	100.0	75.0	50.0	25.0	0.0	0.0
4g	100.0	75.0	75.0	50.0	0.0	0.0
4h	100.0	100.0	75.0	100.0	0.0	0.0
4i	100.0	100.0	100.0	100.0	0.0	0.0
4j	100.0	100.0	100.0	100.0	0.0	0.0
4k	100.0	100.0	100.0	100.0	0.0	0.0
4l	100.0	100.0	100.0	100.0	0.0	0.0
4m	100.0	100.0	100.0	100.0	0.0	50.0
4n	75.0	100.0	0.0	25.0	0.0	0.0

n=6; Percent toxicity was calculated by N/F×100 (N/F = number of animals active over the number tested at dose 30, 100 and 300 mg/kg)

Table 8. Anthelmintic activity of synthesized compound (4a-n)

Compd. No.	Time (in minutes)					
	For paralysis % Concentration (w/v)			For death % Concentration (w/v)		
	0.1%	0.2%	0.5%	0.1%	0.2%	0.5%
4a	27.66±0.57	26.83±1.70	23.58±0.38	41.92±0.62	39.87±0.53	41.91±0.14
4b	52.16±1.75	49.66±0.51	46.11±0.28	70.25±0.75	71±1.41	68.87±0.14
4c	48.83±0.62	45.50±0.50	46.58±1.28	59.91±0.38	64.41±0.52	62.58±0.38
4d	54.66±0.57	49.66±0.38	48.75±0.43	71.4±0.14	69.66±0.28	70.25±0.61
4e	18.33±0.57	16.66±0.38	17.58±0.38	25.50±0.52	23.91±1.12	25.83±0.14
4f	11.91±0.38	9.16±0.57	8.58±0.38	21.95±0.43	20.16±0.87	20.75±1.08
4g	20.66±0.57	19.41±0.52	17.58±0.38	31.91±0.14	30.08±0.07	29.83±1.01
4h	33.58±0.54	29.00±0.70	29.83±0.28	48.75±0.25	45.75±0.66	42.75±1.08
4i	30.08±1.29	26.75±0.35	24.83±0.76	56.83±0.28	54.66±0.43	53.66±1.52
4j	35.83±0.28	32.75±0.35	30.58±0.38	44.25±0.66	41.41±0.51	40.25±0.66
4k	43.33±1.01	40.37±1.2	36.91±0.14	60.5±0.70	54.75±0.43	50.91±1.01
4l	37.50±0.62	35.75±0.43	36.41±0.62	51.58±0.70	47.08±0.87	45.83±0.72
4m	56.16±0.57	53.58±0.38	51.16±1.04	89.50±0.72	81.25±0.66	79.16±0.72
4n	14.75±0.16	13±0.43	14.83±0.52	55.91±0.28	62.66±0.51	67.18±0.85
Standard	-	37.44±0.62	-	-	54.41±0.7	-

Scheme



Scheme 1: Synthesis of 1-(2-(substituted benzylidenehydrazinyl) acetyl)-3-(hydroxyimino) indolin-2-one (4a-4n) here (i) $NaHCO_3$, $NH_2OH.HCl$, RT; (ii) Chloroacetyl chloride, Sodium ethoxide, ethanol; (iii) Hydrazine hydrate, methanol; (iv) RPhCHO, Mathanol, reflux

CONCLUSION

From the present work it can be concluded that the compound **4a** can act as an emerging lead compound whose further molecular modification can improve the anticonvulsant activity. Any substitution that can increase the lipophilicity of the derivative can enhance the anticonvulsant activity. The derived compounds also showed a large therapeutic window thus can be regarded as safe but should be studied on the pre-clinical and clinical basis for more details. Similarly for the anthelmintic activity lipophilicity does not form the major factor influencing the activity.

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