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Synthesis, Anticonvulsant and Neurotoxicity Evaluation of Some Newer *N*-(2-benzoylbenzofuran-3-yl)-3-(substituted)-propanamide Analogs

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Abstract: A series of 12, *N*-(2-benzoylbenzofuran-3-yl)-3-(substituted)-propanamide analogs was designed and synthesized to meet the pharmacophore requirement essential for anticonvulsant activity. All the compounds were characterized by IR, ^{1}H NMR and mass spectral data followed by their anticonvulsant evaluation according to the Antiepileptic Drug Development Program (ADD) protocol. The present study has proved the hypothesis concerning the pharmacophore model with essential binding sites. *N*-(2-benzoylbenzofuran-3-yl)-3-(4-(2-fluorophenyl)piperazin-1-yl) propanamide, **6h** was found to be the most active compound in both maximal electroshock seizure (MES) and subcutaneous metrazol (scMET) seizure test at 30 and100 mg/kg respectively at 0.5 and 4.0 h.

Keywords: Amides, anticonvulsant agents, benzofuran, maximal electroshock seizure (MES), neurotoxicity, subcutaneous metrazol (scMET) seizure.

INTRODUCTION

Epilepsy is one of the central nervous system (CNS) disorders characterized by recurrent seizures. More than 60 million people are inflicted globally according to epidemiological studies and every year approximately 0.25 million new cases are added to this figure [1, 2]. It is roughly estimated that 28-30 % of patients are resistant to the available antiepileptic drugs (AEDs). Despite the development of several new AEDs the treatment of epilepsy still remains inadequate, and the patients suffer from a lot of specific problems like neurotoxicity, depression and other CNS related diseases [3, 4]. Moreover, many AEDs have serious side effects and lifelong medication may be required [5,6]. This enforced the search for newer chemical entities for the effective treatment of epilepsy. Literature survey revealed that amides are compounds, having a wide range of biological applications and anticonvulsant activity [7-11]. Some of the amide analogs in clinical phase of development are harkoseride, NW-1015, remacemide, soretolide, NPS 1776, rufinamide, NW-1015, retigabine, etc. (Fig. **1**) [12]. Dimmock *et al*. and Pandeya *et al*. proposed a hypothetical pharmacophore model for the anticonvulsant activity of semicarbazones, which consists of hydrophobic aryl binding site, a hydrogen-bonding region, an electron donor acceptor system, and a distal hydrophobic site [13-15]. The proposed pharmacophore model for anticonvulsant activity for the title compounds for *in vivo* interaction with macromolecules is shown in Fig. **2**.

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In our study *N*-(2-benzoylbenzofuran-3-yl)-3-(substituted) propanamides (**6a-l**) were synthesized and evaluated for anticonvulsant activity to test this hypothesis. Benzofuran, a versatile heterocyclic hydrophobic molecule possessing preliminary anticonvulsant activity has been selected for the hydrophobic binding site [16-21]. Benzofuran propanamides were condensed with different amines (piperidine and piperazine) with the hope to potentiate the anticonvulsant activity with lesser or limited toxicity.

MATERIALS AND METHODS

Chemistry

The melting points of the compounds were determined in open glass capillary on a Veego melting point apparatus (India) and are uncorrected. ^{1}H-NMR spectra were recorded on Bruker model DRX-300 NMR spectrometer (chemical shift in ppm) in $CDCl_3$ using tetra methylsilane (TMS) as an internal reference. Chemical shifts were reported in parts per million (ppm, δ) and the signals were described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Elemental analysis (C, H, and N) was conducted with a Perkin-Elmer model 2400 analyzer, and all analyses were found to be consistent with theoretical values (within 0.4%) unless indicated. IR spectra were recorded in Perkin-Elmer model spectroscope by preparing KBr pellets for the synthesized compounds. The reaction was monitored by thin layer chromatography (TLC) on silica gel G (Qualigens) coated plates using cyclohexane: ethyl acetate (8:2) as mobile phase. Iodine chamber and UV lamp were used for the visualization of the TLC spots.

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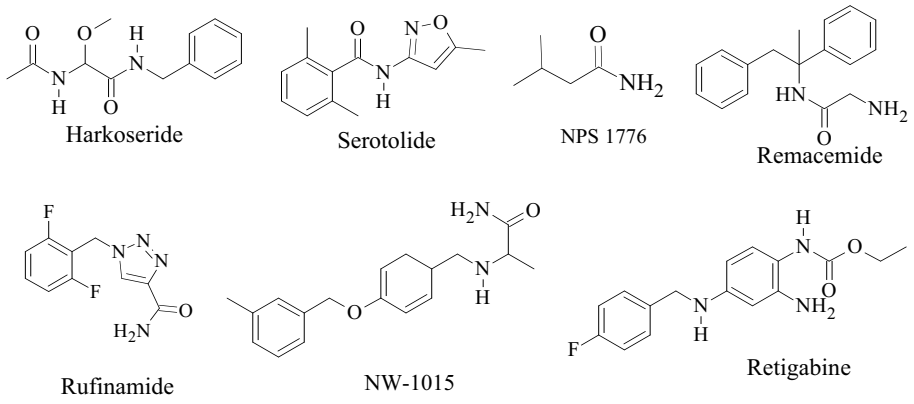


Fig. (1). Anticonvulsant agents containing amide in clinical phase of development.

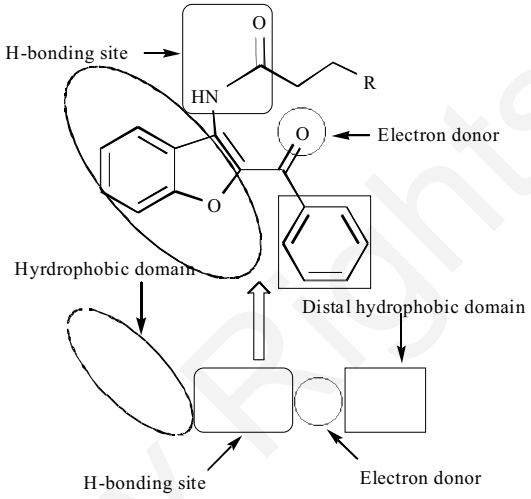


Fig. (2). Proposed pharmacophore model for anticonvulsant activity: hydrophobic aryl binding site; hydrogen-bonding region; electron donor group; distal hydrophobic site.

Synthesis of 2-(2-oxo-2-phenylethoxy)benzonitriles (3)

A mixture of 2-hydroxybenzonitrile (10 mmol), 2-bromo-1-phenyl-ethan-1-one (11 mmol) and potassium carbonate (1.5 g, 15 mmol) in DMF (20 ml) was stirred at room temperature for 2 h. The mixture was then poured into water (100 ml), the insoluble portion was filtered off, washed with water and recrystallized with ethanol to give 2-(2-oxo-2-phenylethoxy)benzonitriles (**3**) [22].

Synthesis of 2-benzoyl-1-benzofuran-3-amines (4)

Sodium methoxide (0.55 g, 10 mmol) was added to solution of **3** (10 mmol) in methanol (20 ml) and the mixture was stirred at room temperature for 30 min. The mixture was then poured into water (25 ml), the insoluble portion was filtered off, washed with water and recrystallized from ethanol to obtain **4** [22].

Synthesis of *N*-(2-benzoylbenzofuran-3-yl)-3-chloropropanamide (5)

A mixture of 2-benzoyl-1-benzofuran-3-amines (**4**) (0.02mol) and 3-chloropropionyl chloride (5ml) in dioxane was refluxed for 30 min. and then was poured into ice water with stirring. The solid, was separated, dried and recrystallized from absolute ethanol as colorless needles, **5** [21].

Synthesis of *N*-(2-benzoylbenzofuran-3-yl)-3-(substituted) propanamide (6a-l)

To a solution of *N*-(2-benzoylbenzofuran-3-yl)-3-chloropropanamide (**5**, 1 mmol) in dioxane (10 ml), different amines (2 mmol) were added and stirred at room temperature for 24 h. The reaction mixture was evaporated to dryness in vacuum. Residue was suspended in water (25 ml) and extracted with chloroform (2x25 ml). The organic layer (chloroform) was separated and evaporated to obtain the title compounds **6a-l**. The physical constants of the compounds are given in Table **1**.

N-(2-benzoylbenzofuran-3-yl)-3-(piperidin-1-yl) propanamide (6a)

IR (cm^{-1}) KBr: 3432.4 (amide NH_{str}), 2925.0 (Ar CH_{str}), 2812.0 (aliphatic CH_{str}), 1718.6 (benzoyl $C{=}O_{str}$), 1681.2 (amide $C{=}O_{str}$), 1446.4 (Ar $C{=}C_{str}$); ^{1}H NMR ($CDCl_3$): (δ, ppm) 1.52-1.63 (m, 4H, H_{-3} and H_{-5} of piperidine), 1.59 (d, 2H, H_{-4} of piperidne), 2.36-2.58 (m, 4H, H_{-2} and H_{-6} of piperidine), 2.51 (t, 2H, $COCH_2$), 3.66 (t, *J*= 7.2 Hz, 2H,

CH_2 β to -CO), 7.28-8.30 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 376.45 (M^+), 377.16 (M^++1). Cal/Ana: [C (73.38) 73.52 H (6.43) 6.34 N (7.44) 7.76].

N-(2-benzoylbenzofuran-3-yl)-3-(2-methylpiperidin-1-yl) propanamide (6b)

IR (cm^{-1}) KBr: 3440.2 (amide NH_{str}), 2924.0 (Ar CH_{str}), 2809.0 (aliphatic CH_{str}), 1716.2 (benzoyl $C=O_{str}$), 1690.4 (amide $C=O_{str}$), 1450.0 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 1.12 (d, *J*= 9.3 Hz, 3H, CH_3 piperidine), 1.44-1.53 (m, 2H, H_{-4} of piperidine), 1.58-1.33 (m, 4H, H_{-3} and H_{-5} of piperidine), 2.29 (t, *J*= 6 Hz, 2H, $COCH_2$), 2.42-2.53 (m, 3H, H_{-2} and H_{-6} of piperidine), 2.64 (t, *J*= 7.2 Hz, 2H, CH_2 β to -CO), 7.27-8.29 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 390.46 (M^+), 391.35 (M^++1). Cal/Ana: [C (73.82) 73.67 H (6.71) 6.87 N (7.17) 7.34].

N-(2-benzoylbenzofuran-3-yl)-3-(4-methylpiperidin-1-yl)propanamide (6c)

IR (cm^{-1}) KBr: 3432.4 (amide NH_{str}), 2923.0 (Ar CH_{str}), 2816.0 (aliphatic CH_{str}), 1712.2 (benzoyl $C=O_{str}$), 1689.6 (amide $C=O_{str}$), 1454.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 0.98 (d, *J*= 8.4 Hz, 3H, CH_3 piperidine), 1.34-1.60 (m, 4H, H_{-3} and H_{-5} of piperidine), 1.65 (m, 1H, H_{-4} of piperidine), 2.43-2.52 (m, 4H, H_{-2} and H_{-6} of piperidine), 2.48 (t, 2H, $COCH_2$), 3.63 (t, *J*= 9.9 Hz, 2H, CH_2 β to -CO), 7.29-8.29 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 390.31 (M^+), 391.16 (M^++1). Cal/Ana: [C (73.82) 73.48 H (6.71) 6.89 N (7.17) 7.23].

N-(2-benzoylbenzofuran-3-yl)-3-(2,6-dimethylpiperidin-1-yl) propanamide (6d)

IR (cm^{-1}) KBr: 3283.1 (amide NH_{str}), 2922.4 (Ar CH_{str}), 2819.6 (aliphatic CH_{str}), 1713.2 (benzoyl $C=O_{str}$), 1683.5 (amide $C=O_{str}$), 1465.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 1.12 (d, 6H, 2xCH_3 piperidine), 1.32-1.59 (m, 4H, H_{-3} and H_{-5} of piperidine), 1.45-1.54 (m, 2H, H_{-4} of piperidine), 2.28 (t, *J*= 7.2 Hz, 2H, $COCH_2$), 2.41-2.53 (m, 2H, H_{-2} and H_{-6} of piperidine), 2.65 (t, 2H, CH_2 β to -CO), 7.26-8.28 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 404.56 (M^+), 405.34 (M^++1). Cal/Ana: [C (74.23) 74.45 H (6.98) 6.72 N (6.93) 6.76].

N-(2-benzoylbenzofuran-3-yl)-3-(4-methylpiperazin-1-yl) propanamide (6e)

IR (cm^{-1}) KBr: 3281.1 (amide NH_{str}), 2918.4 (Ar CH_{str}), 2817.6 (aliphatic CH_{str}), 1718.2 (benzoyl $C=O_{str}$), 1681.5 (amide $C=O_{str}$), 1466.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 2.25 (s, 3H, aliphatic CH_3), 2.37 (s, 8H, CH_2 of piperazine), 2.51 (t, *J*= 7.2 Hz, 2H, $COCH_2$), 3. 66 (t, *J*= 7.6 Hz, 2H, CH_2 β to -CO), 7.28-8.30 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.00 (s, 1H, NH); Mass (m/z) 391.48 (M^+), 392.61 (M^++1). Cal/Ana: [C (70.57) 70.37 H (6.44) 6.68 N (10.73) 10.89].

N-(2-benzoylbenzofuran-3-yl)-3-(4-ethylpiperazin-1-yl) propanamide (6f)

IR (cm^{-1}) KBr: 3442.4 (amide NH_{str}), 2927.0 (Ar CH_{str}), 2810.0 (aliphatic CH_{str}), 1713.6 (benzoyl $C=O_{str}$), 1686.4 (amide $C=O_{str}$), 1451.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 1.251 (t, *J*= 8.4 Hz, 3H, $-CH_2CH_3$), 2.11-2.51 (m, 8H, CH_2 of piperazine), 2.41 (q, *J*= 5.8 Hz, 2H, $-CH_2CH_3$), 2.50 (t, *J*= 5.7 Hz, 2H, $COCH_2$), 3.66 (t, *J*= 7.2 Hz, 2H, CH_2 β to -CO), 7.27-8.30 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 405.46 (M^+), 406.34 (M^++1). Cal/Ana: [C (71.09) 71.06 H (6.71) 6.56 N (10.36) 10.46].

N-(2-benzoylbenzofuran-3-yl)-3-(4-(furan-2-carbonyl) piperazin-1-yl) propanamide (6g)

IR (cm^{-1}) KBr: 3287.1 (amide NH_{str}), 2924.4 (Ar CH_{str}), 2815.6 (aliphatic CH_{str}), 1714.4 (benzoyl $C=O_{str}$), 1690.5 (amide $C=O_{str}$), 1463.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 2.51 (t, *J*= 6 Hz, 2H, $COCH_2$), 2.52 (t, *J*= 7 Hz, 4H, H_{-2} and H_{-6} of piperazine), 3.20 (t, 4H, H_{-3} and H_{-5} of piperazine), 3.65 (t, *J*= 5.6 Hz, 2H, CH_2 β to -CO), 6.82 (t, *J*= 7.2 Hz, 1H, $H_{-4'}$ of furan), 7.28 (d, 1H, $H_{-3'}$ of furan), 7.28-8.31 (m, 4H, C*H* benzofuran, 5H, Ar-H), 8.08 (d, *J*= 4.8 Hz, 1H, $H_{-5'}$ of furan), 10.00 (s, 1H, NH); Mass (m/z) 471.56 (M^+), 472.61 (M^++1). Cal/Ana: [C (68.78) 68.71 H (5.34) 5.67 N (8.91) 8.65].

N-(2-benzoylbenzofuran-3-yl)-3-(4-(2-fluorophenyl) piperazin-1-yl) propanamide (6h)

IR (cm^{-1}) KBr: 3287.1 (amide NH_{str}), 2925.4 (Ar CH_{str}), 2816.6 (aliphatic CH_{str}), 1712.4 (benzoyl $C=O_{str}$), 1692.5 (amide $C=O_{str}$), 1459.4 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 2.50 (t, *J*= 6.6 Hz, 2H, $COCH_2$), 3.45 (s/br, 8H, CH_2 of piperazine), 3.65 (t, *J*= 7.2 Hz, 2H, CH_2 β to -CO), 6.62-7.05 (m, 4H, Ar-H), 7.28-8.30 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 471.46 (M^+), 472.56 (M^++1). Cal/Ana: [C (71.32) 71.23 H (5.56) 5.73 N (8.91) 8.76].

N-(2-benzoylbenzofuran-3-yl)-3-(4-pyridin-2-yl)piperazin-1-yl) propanamide (6i)

IR (cm^{-1}) KBr: 3283.1 (amide NH_{str}), 2920.4 (Ar CH_{str}), 2817.6 (aliphatic CH_{str}), 1700.4 (benzoyl $C=O_{str}$), 1692.5 (amide $C=O_{str}$), 1463.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 2.51 (t, *J*= 6 Hz, 2H, $COCH_2$), 3.44 (t, *J*= 7.2 Hz, H_{-2} and H_{-6} of piperazine), 3.63 (m, H_{-3} and H_{-5} of piperazine), 3.64 (m, 2H, CH_2 β to -CO), 6.62-7.09 (m, 4H, pyridinyl), 7.26-8.27 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.00 (s, 1H, NH); Mass (m/z) 454.56 (M^+), 455.36 (M^++1). Cal/Ana: [C (71.35) 71.67 H (5.77) 5.45 N (12.33) 12.27].

N-(2-benzoylbenzofuran-3-yl)-3-(dipropylamino) propanamide (6j)

IR (cm^{-1}) KBr: 3284.1 (amide NH_{str}), 2932.4 (Ar CH_{str}), 2823.6 (aliphatic CH_{str}), 1710.6 (benzoyl $C=O_{str}$), 1688.5 (amide $C=O_{str}$), 1463.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$): (δ, ppm) 0.90 (t, *J*= 7.8 Hz, 6H, 2x-$CH_2CH_2CH_3$), 1.46 (m, 4H, 2x-$CH_2CH_2CH_3$), 2.46 (m, 4H, 2x-$CH_2CH_2CH_3$), 2.50 (m, 2H, $COCH_2$), 3.66 (t, 2H, CH_2 β to -CO), 7.27-8.30 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 392.46 (M^+), 393.56 (M^++1). Cal/Ana: [C (73.44) 73.67 H (7.19) 7.34 N (7.14) 7.23].

N-(2-benzoylbenzofuran-3-yl)-3-(cyclohexyl(methyl)amino) propanamide (6k)

IR (cm^{-1}) KBr: 3287.1 (amide NH_{str}), 2926.4 (Ar CH_{str}), 2822.6 (aliphatic CH_{str}), 1711.2 (benzoyl $C=O_{str}$), 1694.5 (amide $C=O_{str}$), 1462.2 (Ar $C=C_{str}$); ^1H NMR ($CDCl_3$):

(δ, ppm) 1.11-1.21 (m, 4H, H_{-3} and H_{-5} of cyclohexyl), 1.33-1.57 (m, 4H, $H_{-2'}$ and $H_{-6'}$ of cyclohexyl), 1.47-1.50 (m, 2H, $H_{-4'}$ of cyclohexyl), 2.25 (s, 3H, N-CH_3), 2.50 (m, 2H, $COCH_2$), 2.56 (m, 1H, $H_{-1'}$ of cyclohexyl), 3.66 (t, 2H, CH_2 β to -CO), 7.26-8.31 (m, 4H, C*H* benzofuran, 5H, Ar-H), 10.00 (s, 1H, NH) ; Mass (m/z) 404.46 (M^+), 405.35 (M^++1). Cal/Ana: [C (74.23) 74.56 H (6.98) 6.67 N (6.93) 6.74].

N-(2-benzoylbenzofuran-3-yl)-3-morpholinopropanamide (6l)

IR (cm^{-1}) KBr: 3278.1 (amide NH_{str}), 2917.4 (Ar CH_{str}), 2817.6 (aliphatic CH_{str}), 1705.6 (benzoyl C=O_{str}), 1684.5 (amide C=O_{str}), 1463.2 (Ar C=C_{str}); ^{1}H NMR ($CDCl_3$): (δ, ppm) 2.36 (t, *J*= 7.2 Hz, 4H, N-CH_2 of morpholine), 2.51 (t, *J*= 6.6 Hz, 2H, $COCH_2$), 3.64 (t, *J*= 7.6 Hz, 4H, O-CH_2 of morpholine), 3.66 (t, *J*= 5.6 Hz, 2H, CH_2 β to -CO), 7.26-8.30 (m, 4H, CH benzofuran, 5H, Ar-H), 10.01 (s, 1H, NH); Mass (m/z) 378.45 (M^+), 379.29 (M^++1). Cal/Ana: [C (69.83) 69.53 H (5.86) 5.69 N (7.40) 7.34].

PHARMACOLOGY

Anticonvulsant Activity

The anticonvulsant activity of the title compounds (**6a-l**) was undertaken according to the Antiepileptic Drug Development Program (ADD) protocol [23-27].

Maximal Electroshock Seizure (MES)

The tests were based on MES convulsions, 60 Hz alternating current of 50 mA in mice was delivered for 0.2 s by pinnal electrodes. The mice were tested at various (0.5 and 4 h) intervals following doses of 30, 100 and 300 mg/kg of test compound given by i.p. injection of a volume of 0.05 ml. An animal is considered protected from MES-induced seizure upon abolition of the hind limb tonic extensor component of the seizure [23-25].

Subcutaneous Metrazole-induced Seizure (scMET)

Subcutaneous injection of the metrazol produces clonic seizures in laboratory animals. scMET test detects the ability of a test compound to raise the seizure threshold of an animal and thus protects it from exhibiting a clonic seizure. Animals were pre-treated with various doses of the test compound (in a similar manner to the MES test, although a dose of 50 mg/kg (p.o.) is the standard for scMET). An animal is considered protected from scMET induced seizure upon absence of episode of clonic spasms of the fore and/or hind limbs, jaws, or vibrissae, for approximately 3-5 second [26].

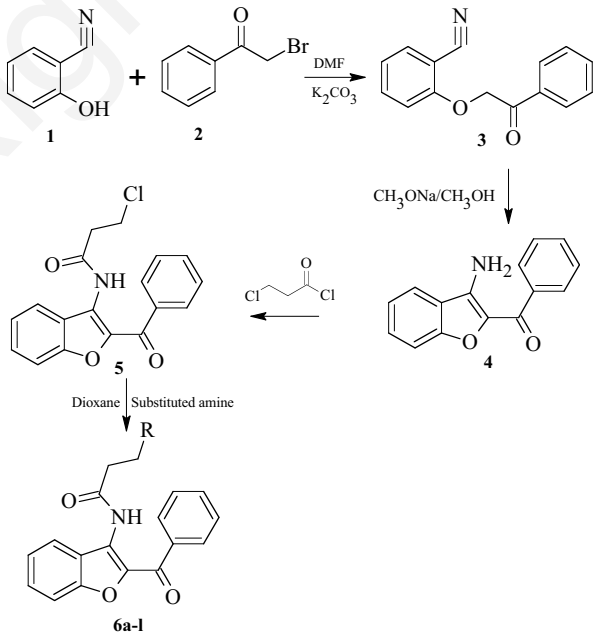
Neurotoxicity (NT) Screening

Activity of the drug interfering with motor coordination was checked by rotorod test. The mice (20-25 g) were trained to stay on the knurled plastic rod of diameter 3.2 cm that rotated with 10 rpm. Normal mice can maintain their equilibrium on a rotating rod for long periods of time. The test compounds were injected i.p. at doses of 30, 100 and 300 mg/kg. Neurotoxicity of compounds was indicated by inability of the animal to maintain equilibrium on the rod for at least one minute in each of three trials [27].

RESULTS AND DISCUSSION

Chemistry

N-(2-Benzoylbenzofuran-3-yl)-3-(substituted)propanamide analogs (**6a–l**) described in this study are shown in Table **1** and the reaction sequences for their synthesis are summarized in Scheme **1**. In the initial step, 2-hydroxybenzonitrile (**1**) and 2-bromo-1-phenylethan-1-one (**2**) were stirred in dimethyl formamide (DMF) containing anhydrous potassium carbonate at room temperature for 2 h to obtain the intermediate 2-(2-oxo-2-phenylethoxy)benzonitrile (**3**). In the subsequent step, compound **3** was stirred with sodium methoxide in methanol for 0.5 h to obtain 2-benzoyl-1-benzofuran-3-amines (**4**), which was further refluxed with 3-chloropropionyl chloride to obtain *N*-(2-benzoylbenzofuran-3-yl)-3-chloropropanamide (**5**). In the final step, the intermediate compound, **5** was mixed with substituted amine in dioxane and stirred at room temperature for 24 h to obtain the title compounds (**6a-l**). The yields of the title compounds were obtained ranging from 65 % to 84 % after recrystallization with absolute ethanol. The completion of reactions was monitored by TLC using mobile phase cyclohexane: ethylacetate (8:2) and purity was checked by elemental analyses.

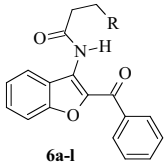


Scheme (1). Protocol for the synthesis of *N*-(2-Benzoylbenzofuran-3-yl)-3-(substituted)propanamide analogs.

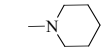
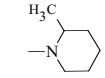
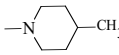
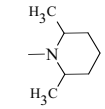
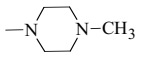
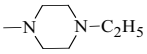
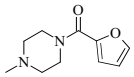
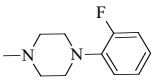
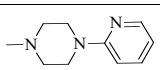
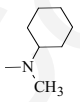
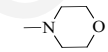
Pharmacology

MES test is a proven method to check generalized tonic-clonic seizure and to identify clinical candidates that prevent seizure. The anticonvulsant activity of the compounds is given in Table **2**. All the synthesized compounds showed significant anticonvulsant activity. Compound **6h** and **6j** exhibited highest protection in MES seizure test similar to that of the standard drug, phenytoin. Compound **6g** and **6l** exhibited the lowest protection in MES seizure. Rest of the compounds showed variable activity between these values.

Table 1. Physical constants of *N*-(2-benzoylbenzofuran-3-yl)-3-(substituted) propanamide analogs (6a-l).



6a-l

Compound	R	Mp (°C)	Yield (%)	R_f* Value
6a		198-200	65	0.48
6b		169-171	82	0.52
6c		219-221	75	0.53
6d		228-230	78	0.45
6e		192-194	68	0.69
6f		213-215	80	0.65
6g		183-185	69	0.51
6h		209-211	73	0.42
6i		203-205	84	0.46
6j		157-159	66	0.63
6k		168-170	70	0.54
6l		175-177	67	0.32

*Cyclohexane: ethyl acetate (8:2).

From the data it is clear that the 4-(2-fluorophenyl)piperazin-1-yl (**6h**), and *N,N*-dipropylamino (**6j**) substituents produced significant protection in MES seizure while the substituents viz. (4-pyridin-2-yl)piperazin-1-yl (**6i**), 2-methylpiperidin-1-yl (**6b**), 4-methylpiperidin-1-yl (**6c**), 2,6-dimethylpiperidin-1-yl (**6d**), cyclohexyl(methyl)amino (**6k**), piperidin-1-yl (**6a**), 4-methylpiperazin-1-yl (**6e**), and 4-ethylpiperazin-1-yl (**6f**) produced protection in MES seizure in descending order. The substituent morpholino (**6l**), and 4-(furan-2-carbonyl)piperazin-1-yl (**6g**) produced the least protection in MES seizure. The ED_{50} of synthesized compounds ranged between 23.4 and 78.0 mg/kg. In the scMET seizure compound **6h** showed maximum activity but associated with neurotoxicity at 100 mg/kg, and the compounds **6d**, **6f**, and **6i** showed activity between 100 and 300 mg/kg and rest of the compounds were inactive at the maximum dose of 300 mg/kg. The compound **6h** was further evaluated in the MES test and neurotoxicity (toxicity) after oral administration to mice at 30 mg/kg (Table **3**), showed 25% protection at 0.25 h, 50% protection at 0.5h. & 1.0 h, while 25% protection at 2.0 h. The SAR was explored for the compounds and found that compounds contain benzofuran as hydrophobic aryl ring, an amide linkage as hydrogen bonding domain, oxygen (O) as an electron donor while a distant hydrophobic site responsible for metabolism is essential which was fulfilled by phenyl group. The compounds containing the 4-(2-fluorophenyl) piperazin-1-yl (**6h**), 4-(pyridin-2-yl)piperazine (**6i**), *N,N*-dipropylamino (**6j**), *N,N*-methylcyclohexyl-amino (**6k**) substituents were equipotent in MES and produced maximum activity. The compounds containing

Table 2. Anticonvulsant activity of *N*-(2-benzoylbenzofuran-3-yl)-3-(substituted) propanamide analogues (6a-l).

Compound	MES		*ED_{50} (mg/kg)	ScMET		Neurotoxicity	
	0.5 h	4.0 h		0.5 h	4.0 h	0.5 h	4.0 h
6a	30	100	36.5	-	-	100	300
6b	30	30	31.6	-	-	100	100
6c	30	30	31.6	-	-	100	100
6d	30	30	31.6	300	300	100	100
6e	100	100	56.7	-	-	300	-
6f	100	100	51.3	100	300	300	-
6g	100	300	78.0	-	-	300	-
6h	30	30	23.4	100	100	100	100
6i	30	30	31.6	300	300	100	100
6j	30	30	23.4	-	-	100	100
6k	30	30	31.6	-	-	100	100
6l	100	300	65.3	-	-	300	300
Phenytoin	30	30	10.3	-	-	100	100
Carbamazepine[a]	30	100	-	100	300	100	300
Sodium Valproate[a]	-	-	-	300	-	-	-

*ED_{50} was calculated using XLSOFT (Evaluation Ver. 2012.2.01) on the basis of maximum effect observed at 0.5 h.
MES, maximal electroshock; scMET, subcutaneous metrazol.
[a]Activity reported [14].
Doses of 30, 100 and 300 mg/kg were prepared in PEG400 and were administered i.p. The animals were examined 0.5 and 4 h after injections were made.

Table 3. Evaluation of compound, 6h in the MES test and toxicity after oral administration to rat.

Compound	Oral administration to rat (30 mg/kg)				
	0.25 h	0.5 h	1.0 h	2.0 h	4.0 h
MES (**6h**)	1/4	2/4	2/4	1/4	0/4
Toxicity	0/4	0/4	0/4	0/4	0/4

4-ethylpiperidin-1-yl (**6f**) and 4-methylpiperazin-1-yl (**6e**) substituents are equipotent in MES while substituents containing furan-2-yl(4-piperazin-1-yl) methanone (**6g**) and 4-morpholino (**6l**) are equipotent. The compounds with substituent 2,6-dimethylpiperidine (**6d**) and 4-(pyridin-2-yl)piperazine (**6i**) are equipotent in scMET.

CONCLUSION

All the compounds were synthesized in satisfactory yield and a few compounds showed significant anticonvulsant activity. The compound **6h** showed maximum activity and would be considered as lead for further optimization as anticonvulsant agent.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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