INTRODUCTION

According to the International League Against Epilepsy (ILAE), epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition [1]. The known potential causes of epilepsy include brain tumors, infections, traumatic head injuries, perinatal insults, developmental malformations, cerebrovascular diseases, febrile seizures and status epilepticus [2]. Even though significant advances have been made in epilepsy research, convulsions in 25% of epileptics are inadequately controlled by standard drug therapy [3].

In recent times several new drugs, for example, levetiracetam, felbamate, lamotrigine, gabapentin, and topiramate, have been approved to treat epilepsy. Although these drugs have been shown to be effective in epileptic syndromes in a number of patients, their efficacy does not appear to be superior to that of the established antiepileptic drugs. Currently, the main treatment for epileptic disorder is the long-term and consistent administration of anticonvulsant drugs (AEDs). Although over 30 AEDs are available, 25-30% of patients fail to achieve adequate seizure control, while others experience disturbing adverse effects of the treatment. As a result, intensive research efforts aim to find new, more effective and safer therapeutics [4]. Therefore, the ideal antiepileptic should prevent different types of seizures without producing side effects that affect adversely patients’ quality of life. Taking into consideration the above continued search for safer, more effective and possibly antiepileptogenic drugs is urgently necessary. The incomplete information on the pathogenesis of human epilepsy and the complex mechanism of action of majority antiepileptic drugs makes it difficult to use rational methodologies of discovery. Conceptually, there are two different methods of obtaining new anticonvulsants namely knowledge-based approaches and screening approaches [5, 6]. Knowledge-based approaches rely on the use of different pharmacophores that were established through the analysis of structural characteristics of clinically effective anticonvulsant active compounds. Serendipitous approaches involve a comprehensive screening process that utilizes rodent models.
screening programs employ mice and rats to assess efficacy against either electrically or chemically induced seizures [7, 8].

![Figure 1: Structure of different cyclic imides (a) 5-cyclic, (b) 6-cyclic, (c) 7-cyclic, (d) 8-cyclic imides.](image)

The SAR studies of clinically available AEDs and other anticonvulsant active compounds showed that most of these compounds included 5- or 6-member cyclic imides moiety in their molecules (Figure 1). Hydantoins, a class of cyclic imides, have been demonstrated to possess good anticonvulsant property [9-11]. Depending on the nature of substitution on the hydantoin ring, a wide range of other pharmacological properties, e.g., antihypertensive [12], herbicidal [13], antitumor [14], anti-HIV [15], antibacterial [16] and antiviral [17] activities, have also been identified.
A pharmacophore model has been put forward as a result of conformational investigations of the clinically established anticonvulsant drugs such as carbamazepine, phenytoin and mephenytoin [18, 19]. The suggested pharmacophore model for derivatives should have at least one aryl ring (R), one electron donor atom (D), and a second donor atom in close proximity to the NH group forming a hydrogen bond acceptor (HBA)/donor (HBD) units. The titled compounds (5-32) possessed all the required pharmacophoric elements (Figure 2) as the phenyl ring attached to the nitrogen moiety can be referred to the aryl ring (R - Lipophilic Aryl Ring), nitrogen of the hydantoin ring can acts as a hydrogen bond donor (HBD) and the amide keto group of the hydantoin ring acts as a hydrogen bond acceptor (HBA). The proposed hydantoins seems to resemble better with phenytoin. With this as

**Figure 2:** Anticonvulsant agents showing essential pharmacophoric elements present in their structure Hydrogen bond acceptor (HBA)/donor (HBD) units; Lipophilic aryl ring (Ar).
background, the present work highlights the importance of the synthesis of prototypes of diazaspirohydantoins and evaluation of their anticonvulsant activity.

**LITERATURE REVIEW**

Panayiotis *et al.* [20] have reported the preparation and biological evaluation of the substituted hydantoin and uracil rings. The authors have presented a series of novel, potent and selective human β₂ adrenoceptor agonists incorporating a hydantoin or a uracil ring on the right-hand side phenyl ring of (R)-salmeterol. The substituted hydantoins were prepared from the appropriate regioisomeric iodoaniline and ethyl isocyanatoacetate, base-hydrolysis of the resulting ester, followed by cyclisation under acidic conditions. The analogue was prepared from BOC-α-methyl-alanine and 3-iodoaniline, followed by cyclization with sodium hydride in DMF. The regioisomeric hydantoin was prepared by reaction of 3-iodophenylurea and ethyl chloroacetate in the presence of sodium hydride. Incorporation of a hydantoin or a uracil ring on the right-hand side phenyl ring of (R)-salmeterol has provided very potent and selective human β₂ adrenoceptor agonists. Hydantoins had long duration of action in vitro on guinea pig trachea, and in guinea pigs in vivo at its EC₉₀ 25µM. It had lower oral absorption than salmeterol in rats, and lower bioavailability than salmeterol in vivo in both rats and dogs. However, hydantoins were metabolised in human liver microsomes and hepatocytes to the active hydantoic acid, and no crystalline salts suitable for inhaled delivery were identified.

![Reaction Scheme](image)

Thirupathi *et al.* [21] have described the synthesis and screening of substituted (Z)-5-(N-benzylindol-3-ylmethylene)imidazolidine-2,4-diones. Aplysinsopsins are indole-derived marine natural products. The parent alysinsopsin was
isolated as the major metabolite of eight Indo-Pacific sponge species, which are representatives of the genera Thorecta [22, 23]. The appropriate substituted (Z)-5-(N-benzylindol-3-yl-methylene) imidazolidine-2,4-dione were synthesized via the commercially available indole-3-carboxaldehyde with various substituted benzyl halides under phase-transfer catalytic (PTC) conditions utilizing triethylbenzylammonium chloride and NaOH aqueous solution/ dichloromethane. Aldol condensation of the resulting product with hydantoin in the presence of ammonium acetate in acetic acid under microwave irradiation or under reflux conditions, afforded the corresponding substituted (Z)-5-(N-benzylindol-3-ylmethylene)imidazolidine-2,4-dione derivatives. The substituted (Z)-5-(N-benzylindol-3-ylmethylene)imidazolidine-2,4-dione analogs structurally related to aplysinopsin, and that incorporate a variety of substituents in both indole and N-benzyl moieties were synthesized under microwave irradiation and conventional heating methods. These analogs were evaluated for their anti-proliferative activity against MCF-7 and MDA-231 breast cancer cell lines, A549 and H460 lung cancer cell lines.

Jadwiga et al. [24] have reported the synthesis and biological evaluation of the substituted 5-arylidenehydantoins. The α-adrenoceptors, belonging to the earliest identified G-protein coupled adrenergic receptors family, have been and still are an important drug target because of their various physiological functions linked to their wide distribution in many mammalian tissues [25-27]. The 5-arylidenehydantoin derivatives were obtained within three-step synthesis accord. The initial step Knoevenagel condensation of the hydantoin with substituted benzaldehydes, leads to 5-arylidenehydantoins. In the next step, intermediates were alkylated by Mitsunobu reaction by the use of racemic oxiran-2-ylmethanol, triphenylphosphine and diethyl azodicarboxylate, with DMF as a solvent. The final compounds were obtained by N-alkylation of substituted phenylpiperazines with suitable oxiran derivatives under
microwave irradiation in solvent-free conditions. The series of compounds were assessed on their affinity for $\alpha$-adrenoceptors (ARs) and evaluated in functional bioassays for their antagonistic properties. Most of the compounds exhibited significant affinities for $\alpha$-ARs.

Recently, there is a growing interest in applying microwave energy to synthetic organic chemistry [28, 29]. The syntheses of 2,5-bis[(4-carboxyanilino) carbonyl] pyridine derivatives were reported by Khalil et al. [30]. Aromatic polyamides have already been noted for their high temperature resistance and excellent mechanical properties. They are also considered as difficult processable materials because of their insolubility in common organic solvents and too high glass transition temperatures. [31, 32]. Many approaches have been investigated in attempting to improve the solubility of aromatic polyamides include the addition of pendant groups to polymeric backbone, [33, 34] incorporation of bulky [35, 36] or flexible [37, 38] and heterocycles [39, 40] unit within the parent chain. Eight new polyamides containing azo moieties and hydantoin groups were synthesized under microwave irradiation using a domestic microwave oven from the polycondensation reactions of 4,40-azodibenzoyl chloride with eight different derivatives of 5,5-disubstituted hydantoin in the presence of a small amount of a polar organic medium such as o-cresol. The polycondensation proceeded rapidly, compared with the bulk polycondensation and the solution polycondensation and was completed between 7-12 min, producing a series of new polyamides.
Above chemical literature reveals that no researchers have reported the synthesis of title compounds and their derivatives. In this chapter, the author has presented the chemical biology of 1'-[2-(difluoromethoxy)benzyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione derivatives.

**EXPERIMENTAL**

**Materials and methods**

Melting points were determined in one end open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. The $^1$H NMR spectra were recorded on Bruker Avance -400 MHz NMR instrument using TMS as an internal standard and DMSO-$d_6$ as a solvent. Chemical shift are given in parts per million (δ-scale) and coupling constant are given in Hertz. Mass spectra were recorded on Perkin–Elmer LC-MS PE Sciei API/65 spectrophotometer. IR spectra recorded using KBr on 8400S Shimadzu Fourier Transform Spectrophotometer ($\nu_{\text{max}}$ in cm$^{-1}$). Silica gel column chromatography was performed using Merck 7734 silica gel (60-120 mesh), and Merck made TLC plate. Elemental analyses (C, H, and N) were undertaken with Perkin-Elmer model 240C analyzer.

**SYNTHESIS**

*Synthesis of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (I)*

A mixture of 8-azabicyclo[3.2.1]octan-3-one hydrochloride (4 g, 24.74 mmol), triethylamine (3.75 g, 37.12 mmol) and Boc anhydride (5.94 g, 27.22 mmol) in dry dichloromethane (40 mL) was stirred at room temperature for 16 h. After completion of the reaction (TLC), the reaction mixture was poured in to water and extracted with dichloromethane (3 x 40 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. The resulting crude product was recrystallized from hexane to get the pure product. White color solid: (5 g, 90 %); $^1$H NMR: 300 MHz, CDCl$_3$: δ 4.49 (s, 2H), 2.67 (s, 2H), 2.34 (d, $J = 15.72$ Hz, 2H), 2.09 (d, $J = 4.70$ Hz, 2H), 1.63 (d, $J = 12.37$ Hz, 2H), 1.51 (s, 9H), MS: m/z 225.3 (M$^+$), 226.3 (M+1).
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Synthesis of tert-butyl 2',5'-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxylate (2)

A mixture was prepared by dissolving tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (5 g, 22.2 mol) and ammonium carbonate (4.69 g, 48.82 mmol) in ethanol (25 mL) and water (25 mL). A solution of sodium cyanide (2.28 g, 46.60 mmol) in water (10 mL) was added drop wise and reaction mixture was stirred at room temperature for 24 h and heated to 50 ºC for 24 h and cooled to room temperature. After completion of the reaction (TLC), solid was filtered, washed with water (100 mL) and dried in vacuo to get hydantoin. White color solid: (5.1 g, 78%); ¹H NMR: 400 MHz, DMSO-$d_6$: δ 10.79 (s, 1H), 8.38 (s, 1H), 4.07 (s, 2H), 2.14 (s, 2H), 1.96 (t, J = 26.32 Hz, 4H), 1.57 (s, 2H), 1.41 (s, 9H); MS: m/z 295.3 (M⁺), 296.3 (M+1).

Synthesis of tert-butyl 1'-[4-(difluoromethoxy)benzyl]-2',5'-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxylate (3)

A mixture of tert-butyl 2',5'-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxylate (5.1 g, 17.26 mmol), anhydrous potassium carbonate (3.57 g, 25.90 mmol) and 1-(bromomethyl)-2-(difluoromethoxy)benzene(4.50 g, 18.99 mmol) in acetonitrile (50 mL), was refluxed for 6 h. The completion of the reaction was monitored by TLC, after being cooled to room temperature, then it was filtered. Filtrate was concentrated under vacuo to give the crude product which was purified by column chromatography over silica gel (60-120 mesh) using chloroform/methanol (9:1) as an eluent to get pure product. White color solid: (6.2 g, 81%); ¹H NMR: 400 MHz, DMSO-$d_6$: δ 8.80 (s, 1H), 7.33-7.34 (m, 1H), 7.19-7.19 (m, 2H), 7.07 (t, J = 14.56 Hz, 1H), 6.44 (s, 1H), 4.56 (s, 2H), 4.10 (s, 2H), 2.20 (s, 2H), 1.94-1.98 (m, 4H), 1.67 (d, J = 15.24 Hz, 2H), 1.41 (s, 9H); MS: m/z 451.2 (M⁺), 452.2 (M+1).

Synthesis of 1'-[4-(difluoromethoxy)benzyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (4)

Tert-butyl 1'-[4-(difluoromethoxy)benzyl]-2',5'-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxylate (6.2 g,13.73 mmol) was taken in
dioxane (30 mL) and cooled to 0 ºC. A volume of 60 mL of dioxane in HCl was added to it and allowed to stirred at room temperature for 4 h. After completion of the reaction (TLC), dioxane was removed under vacuum and the reaction mixture was neutralized with sodium carbonate solution, extracted with dichloromethane (3 x 60 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo to get pure product. White color solid : (3.9 g, 81%); ¹H NMR: 400 MHz, DMSO-d₆: δ 8.83 (s, 1H), 8.69 (s, 1H), 7.35-7.35 (m, 1H), 7.06-7.12 (m, 3H), 6.45 (s, 1H), 4.58 (s, 2H), 3.95 (s, 2H), 2.34 (d-d, J = 2.64 Hz, 2H), 2.18 (d-d, J = 6.36 Hz, 2H), 1.87-1.91 (m, 4H); MS: m/z 351.4 (M⁺), 352.4 (M+1).

**General procedure for the synthesis of azabicyclo spiro sulfonamides (5-19).**

A mixture of 8-(3,4-dimethylbenzoyl)-1'-[4-(difluoromethoxy)benzyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (100 mg 0.28 mmol), triethylamine (43.20 mg, 0.43 mmol) and sulfonyl chloride (0.31 mmol) in dichloromethane (4 mL) was stirred at room temperature for 16 h. After completion of the reaction (TLC), it was quenched with saturated sodium carbonate solution, extracted with dichloromethane (3 x 4 mL), dried over Na₂SO₄ and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica employing dichloromethane/methanol (9:1) as an eluent to obtain pure product.

**1'-[4-(difluoromethoxy)benzyl]-8-[(3,4-dimethylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (5).** White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.69 (s, 1H), 7.63 (s, 1H), 7.56 (d, J = 7.88 Hz, 1H), 7.35 (t, J = 7.88 Hz, 2H), 7.20 (q, J = 7.60 Hz, 2H), 7.06 (t, J = 18.04 Hz, 2H), 6.46 (s, 1H), 4.55 (s, 2H), 4.25 (s, 2H), 2.29 (s, 6H), 2.19 (q, J = 3.24 Hz, 2H), 1.82 (t, J = 7.60 Hz, 2H), 1.16-1.18 (m, 4H); MS: m/z 519.6 (M⁺), 520.6 (M+1); IR (KBr) 1650, 1340 cm⁻¹; Anal. calcd for C₂₅H₂₇F₂N₃O₅S: C, 57.79; H, 5.24; N, 8.09%; Found: C, 57.77; H, 5.21; N, 8.06%.

**1'-[4-(difluoromethoxy)benzyl]-8-[(2-methylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (6).** White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.80 (s, 1H), 7.92 (d, J = 7.92 Hz, 1H), 7.57 (d, J = 7.44 Hz, 1H), 7.40-7.41 (m, 2H), 7.33 (d, J = 7.76 Hz, 1H), 7.19 (t, J = 7.76 Hz, 2H),
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7.05 (t, J = 12.04 Hz, 1H), 6.47 (s, 1H), 4.55 (s, 2H), 4.17 (s, 2H), 2.62 (s, 3H), 2.05-2.07 (m, 4H), 1.81 (d, J = 14.20 Hz, 4H); MS: m/z 505.5 (M⁺), 506.5 (M+1); IR (KBr) 1652, 1344 cm⁻¹; Anal. calcd for C₂₄H₂₅F₂N₃O₅S: C, 57.02; H, 4.98; N, 8.31%; Found: C, 57.06; H, 4.99; N, 8.35%.

1'-[4-(difluoromethoxy)benzyl]-8-[(3-bromophenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (7). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.73 (s, 1H), 8.03 (s, 1H), 7.88-7.93 (m, 1H), 7.54-7.58 (m, 2H), 7.33-7.40 (m, 1H), 7.18-7.22 (m, 2H), 7.03-7.08 (m, 1H), 6.47 (s, 1H), 4.55 (s, 2H), 4.34 (s, 2H), 2.19 (q, J = 3.04 Hz, 2H), 1.87 (q, J = 13.28 Hz, 4H), 1.29 (t, J = 4.52 Hz, 2H); MS: m/z 570.4 (M⁺), 571.4 (M+1); IR (KBr) 1656, 1341 cm⁻¹; Anal. calcd for C₂₃H₂₂BrF₂N₃O₅S: C, 48.43; H, 3.89; N, 7.37%; Found: C, 48.41; H, 3.85; N, 7.36%.

1'-[4-(difluoromethoxy)benzyl]-8-[(2-fluorophenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (8). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.77 (s, 1H), 7.86 (t, J = 7.48 Hz, 1H), 7.73-7.75 (m, 1H), 7.33-7.50 (m, 3H), 7.19-7.20 (m, 2H), 7.32 (t, J = 16.88 Hz, 1H), 6.47 (s, 1H), 4.56 (s, 2H), 4.32 (s, 2H), 2.20 (d, J = 14.16 Hz, 1H), 2.00 (d, J = 8.36 Hz, 1H), 1.86 (d, J = 14.04 Hz, 2H), 1.52 (t, J = 4.40 Hz, 2H), 1.13-1.15 (m, 2H); MS: m/z 509.5 (M⁺), 510.5 (M+1); IR (KBr) 1653, 1340 cm⁻¹; Anal. calcd for C₂₃H₂₂F₃N₃O₅S: C, 54.22; H, 4.35; N, 8.25%; Found: C, 54.20; H, 4.32; N, 8.23%.

1'-[4-(difluoromethoxy)benzyl]-8-[(2,5-dimethylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (9). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.81 (s, 1H), 7.73 (s, 1H), 7.32-7.34 (m, 3H), 7.19 (q, J = 7.64 Hz, 2H), 6.98-6.98 (m, 1H), 6.46 (s, 1H), 4.54 (s, 2H), 4.16 (s, 2H), 2.56 (s, 3H), 2.44 (s, 3H), 2.02-2.14 (m, 4H), 1.81-1.91 (m, 4H); MS: m/z 519.7 (M⁺), 520.7 (M+1); IR (KBr) 1652, 1344 cm⁻¹; Anal. calcd for C₂₅H₂₇F₂N₃O₅S: C, 57.79; H, 5.24; N, 8.09%; Found: C, 57.75; H, 5.21; N, 8.07%.

1'-[4-(difluoromethoxy)benzyl]-8-[(4-methylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (10). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.81 (s, 1H), 7.92 (d, J = 7.92 Hz, 1H), 7.57 (d, J = 7.44 Hz, 1H), 7.40-7.41 (m, 2H), 7.33 (d, J = 7.76 Hz, 1H), 7.19 (t, J = 7.76 Hz, 2H),
7.05 (t, J = 12.04 Hz, 1H), 6.47 (s, 1H), 4.56 (s, 2H), 4.16 (s, 2H), 2.62 (s, 3H), 2.04-2.07 (m, 4H), 1.81 (d, J = 14.20 Hz, 4H); MS: m/z 505.5 (M^+), 506.5 (M+1); IR (KBr) 1651, 1343 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{25}\)F\(_2\)N\(_3\)O\(_5\)S: C, 57.02; H, 4.98; N, 8.31% ; Found: C, 57.03; H, 4.91; N, 8.28%.

1'-[4-(difluoromethoxy)benzyl]-8-[3-chlorophenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo [3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (11). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): δ 8.73 (s, 1H), 7.91 (s, 1H), 7.78-7.86 (m, 3H), 7.61-7.65 (m, 2H), 7.33-7.40 (m, 1H), 7.03-7.22 (m, 1H), 6.47 (s, 1H), 4.56 (s, 2H), 4.35 (s, 2H), 2.19 (q, J = 3.04 Hz, 2H), 1.83-1.86 (m, 4H), 1.23-1.28 (m, 2H); MS: m/z 525.96 (M^+), 527 (M+1); IR (KBr) 1655, 1342 cm\(^{-1}\); Anal. calcd for C\(_{23}\)H\(_{22}\)ClF\(_2\)N\(_3\)O\(_5\)S: C, 52.52; H, 4.22; N, 7.99% ; Found: C, 52.51; H, 4.24; N, 7.95%.

1'-[4-(difluoromethoxy)benzyl]-8-[4-fluoro-2-methylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (12). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): δ 8.81 (s, 1H), 7.96 (q, J = 5.80 Hz, 1H), 7.32-7.35 (m, 2H), 7.17-7.27 (m, 3H), 7.03-7.07 (m, 1H), 6.44 (s, 1H), 4.54 (s, 2H), 4.16 (s, 2H), 2.61 (s, 3H), 2.05-2.07 (m, 4H), 1.79-1.83 (m, 4H); MS: m/z 523.6 (M^+), 524.6 (M+1); IR (KBr) 1653, 1341 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{24}\)F\(_3\)N\(_3\)O\(_5\)S: C, 55.06; H, 4.62; N, 8.03% ; Found: C, 55.02; H, 4.60; N, 8.01%.

1'-[4-(difluoromethoxy)benzyl]-8-[4-methoxyphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (13). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): δ 8.70 (s, 1H), 7.76-7.77 (m, 2H), 7.33-7.35 (m, 2H), 7.03-7.18 (m, 3H), 6.45 (s, 1H), 4.55 (s, 2H), 4.24 (s, 2H), 3.74 (s, 3H), 2.19 (q, J = 3.20 Hz, 2H), 1.83 (q, J = 5.16 Hz, 4H), 1.24-1.27 (m, 2H); MS: m/z 521.5 (M^+), 522.5 (M+1); IR (KBr) 1650, 1343 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{25}\)F\(_2\)N\(_3\)O\(_6\)S: C, 55.27; H, 4.83; N, 8.06% ; Found: C, 55.25; H, 4.81; N, 8.03%.

1'-[4-(difluoromethoxy)benzyl]-8-[4-methylbenzyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (14). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): δ 8.70 (s, 1H), 7.77 (d, J = 8.24 Hz, 2H), 7.33-7.35 (m, 2H), 7.19-7.21 (m, 3H), 7.07 (s, 1H), 6.46 (s, 1H), 4.59 (s, 2H), 4.56 (s, 2H), 4.26 (s, 2H), 2.70 (q, J = 7.64 Hz, 2H), 2.21 (t, J = 10.92 Hz, 2H), 1.86 (t, J = 7.56 Hz, 4H),
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1.17 (t, J = 8.28 Hz, 3H); MS: m/z 519.6 (M⁺), 520.6 (M+1); IR (KBr) 1653, 1341 cm⁻¹; Anal. calcd for C₂₅H₂₇F₂N₃O₅S: C, 57.79; H, 5.24; N, 8.09% ; Found: C, 57.74; H, 5.21; N, 8.02%.

1'-[4-(difluoromethoxy)benzyl]-8-[(3-fluorophenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1] octane-3,4'-imidazolidine]-2',5'-dione (15). White color solid; ¹H NMR 400 MHz, DMSO-d₆: δ 8.73 (s, 1H), 7.74-7.74 (m, 3H), 7.33-7.37 (m, 2H), 7.07-7.22 (m, 3H), 6.46 (s, 1H), 4.55 (s, 2H), 4.34 (s, 2H), 2.19 (q, J = 3.28 Hz, 2H), 1.87 (q, J = 13.32 Hz, 4H), 1.30-1.31 (m, 2H); MS: m/z 509.5 (M⁺), 510.5 (M+1); IR (KBr) 1653, 1342 cm⁻¹; Anal. calcd for C₂₃H₂₂F₃N₃O₅S: C, 54.22; H, 4.35; N, 8.25% ; Found: C, 54.20; H, 4.32; N, 8.23%.

1'-[4-(difluoromethoxy)benzyl]-8-[(3,5-dimethylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (16). White color solid; ¹H NMR 400 MHz, DMSO-d₆: δ 8.71 (s, 1H), 7.47 (s, 2H), 7.32-7.33 (m, 2H), 7.18-7.22 (m, 2H), 7.06 (s, 1H), 6.41 (s, 1H), 4.55 (s, 2H), 4.27 (s, 2H), 2.34 (s, 6H), 2.20 (q, J = 2.92 Hz, 2H), 1.81-1.83 (m, 4H), 1.26 (t, J = 4.52 Hz, 2H); MS: m/z 519.7 (M⁺), 520.7 (M+1); IR (KBr) 1650, 1340 cm⁻¹; Anal. calcd for C₂₅H₂₇F₂N₃O₅S: C, 57.79; H, 5.24; N, 8.09% ; Found: C, 57.76; H, 5.20; N, 8.06%.

1'-[4-(difluoromethoxy)benzyl]-8-[(4-ethylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (17). White color solid; ¹H NMR 400 MHz, DMSO-d₆: δ 8.70 (s, 1H), 7.77 (d, J = 8.24 Hz, 2H), 7.33-7.35 (m, 2H), 7.19-7.21 (m, 3H), 7.07 (s, 1H), 6.46 (s, 1H), 4.56 (s, 2H), 4.26 (s, 2H), 2.70 (q, J = 7.64 Hz, 2H), 2.21 (t, J = 10.92 Hz, 2H), 1.86 (t, J = 7.56 Hz, 4H), 1.25 (q, J = 16.76 Hz, 2H), 1.17 (t, J = 8.28 Hz, 3H); MS: m/z 519.6 (M⁺), 520.6 (M+1); IR (KBr) 1653, 1341 cm⁻¹; Anal. calcd for C₂₅H₂₇F₂N₃O₅S: C, 57.79; H, 5.24; N, 8.09% ; Found: C, 57.75; H, 5.21; N, 8.02%.

1'-[4-(difluoromethoxy)benzyl]-8-[(3-methylphenyl)sulfonyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione (18). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.70 (s, 1H), 7.77 (d, J = 8.24 Hz, 2H), 7.33-7.35 (m, 2H), 7.19-7.21 (m, 3H), 7.07 (s, 1H), 6.46 (s, 1H), 4.56 (s, 2H), 4.26 (s, 2H), 2.70 (q, J = 7.64 Hz, 2H), 2.21 (t, J = 10.92 Hz, 2H), 1.86 (t, J = 7.56 Hz, 4H), 1.25 (q, J = 16.76 Hz, 2H), 1.17 (t, J = 8.28 Hz, 3H); MS: m/z 505.5 (M⁺), 506.5 (M+1); IR (KBr) 1653, 1341 cm⁻¹; Anal. calcd for C₂₃H₂₇F₂N₃O₅S: C, 57.79; H, 5.24; N, 8.09% ; Found: C, 57.75; H, 5.21; N, 8.02%.
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1652, 1343 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{25}\)F\(_2\)N\(_3\)O\(_5\)S: C, 57.02; H, 4.98; N, 8.31%; Found: C, 57.01; H, 4.94; N, 8.28%.

1’-[4-(difluoromethoxy)benzyl]-8-[(2-cyanobenzene)sulfonyl]-2’H,5’H-spiro[8-azabicyclo[3.2.1]octane-3,4’-imidazolidine]-2’,5’-dione (19). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): \(\delta\) 8.78 (s, 1H), 8.12-8.12 (m, 3H), 7.88-7.90 (m, 2H), 7.08-7.18 (m, 3H), 6.45 (s, 1H), 4.55 (s, 2H), 4.35 (s, 2H), 2.22 (d, \(J = 2.84\) Hz, 2H), 2.05 (d, \(J = 8.48\) Hz, 2H), 1.86 (d, \(J = 13.24\) Hz, 2H), 1.76 (d, \(J = 11.92\) Hz, 2H); MS: m/z 516.5 (M\(^+\)), 517.5 (M+1); IR (KBr) 1653, 1341 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{22}\)F\(_2\)N\(_4\)O\(_5\)S: C, 55.81; H, 4.29; N, 10.85%; Found: C, 55.78; H, 4.27; N, 10.82%.

**General procedure for the synthesis of azabicyclospirocarboxamide (20-32).**

A mixture of 8-(3,4-dimethylbenzoyl)-1’-[4-(difluoromethoxy)benzyl]-2’H,5’H-spiro[8-aza bicyclo[3.2.1]octane-3,4’-imidazolidine]-2’,5’-dione (100 mg 0.28 mmol), triethylamine (43.20 mg, 0.43 mmol) and isocyanate (0.31 mmol) in dichloromethane (4 mL) was stirred at room temperature for 16 h. After completion of the reaction (TLC), it was quenched with saturated sodium carbonate solution, extracted with dichloromethane (3 x 4 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. The formed crude product was purified by column chromatography on silica employing dichloromethane/methanol (9:1) as an eluent to obtain pure product.

1’-[4-(difluoromethoxy)benzyl]-N-[4-(methylsulfonyl)phenyl]-2’,5’-dioxospiro[8-azabicyclo [3.2.1]octane-3,4’-imidazolidine]-8-carboxamide (20). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): \(\delta\) 8.82 (s, 1H), 8.55 (s, 1H), 7.47 (d, \(J = 8.72\) Hz, 2H), 7.34 (t, \(J = 1.32\) Hz, 1H), 7.17-7.19 (m, 4H), 7.08 (t, \(J = 17.84\) Hz, 1H), 6.45 (s, 1H), 4.57 (s, 2H), 4.46 (s, 2H), 2.42 (s, 3H), 2.26 (q, \(J = 2.88\) Hz, 2H), 2.47 (d, \(J = 323.16\) Hz, 2H), 1.96 (d, \(J = 5.00\) Hz, 2H), 1.69 (d, \(J = 13.80\) Hz, 2H); MS: m/z 516.6 (M\(^+\)), 517.6 (M+1); IR (KBr) 3359, 1656 cm\(^{-1}\); Anal. calcd for C\(_{25}\)H\(_{27}\)F\(_2\)N\(_4\)O\(_4\)S: C, 58.13; H, 5.07; N, 10.85%; Found: C, 58.12; H, 5.05; N, 10.82%. 

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1'-[4-(difluoromethoxy)benzyl]-N-(3-fluorophenyl)-2',5'-dioxospiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (21). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): \(\delta\) 8.83 (s, 1H), 8.74 (s, 1H), 7.34-7.52 (m, 3H), 7.19-7.29 (m, 4H), 7.04-7.11 (m, 1H), 6.45 (s, 1H), 4.57 (s, 2H), 4.48 (s, 2H), 2.26 (q, \(J = 3.08\) Hz, 2H), 2.08 (t, \(J = 5.96\) Hz, 2H), 1.96 (t, \(J = 4.32\) Hz, 2H), 1.71 (d, \(J = 13.88\) Hz, 2H); MS: m/z 488.5 (M\(^+\)), 489.5 (M+1); IR (KBr) 3358, 1622 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{23}\)F\(_3\)N\(_4\)O\(_4\): C, 59.01; H, 4.75; N, 11.47%; Found: C, 59.04; H, 4.71; N, 11.45%.

1'-[4-(difluoromethoxy)benzyl]-N-(4-fluorophenyl)-2',5'-dioxospiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (22). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): \(\delta\) 8.56 (s, 1H), 7.51 (s, 1H), 7.47-7.50 (m, 2H), 7.32-7.37 (m, 1H), 7.18-7.22 (m, 2H), 7.18 (s, 3H), 6.45 (s, 1H), 4.56 (s, 2H), 4.44 (s, 2H), 2.25 (q, \(J = 4.00\) Hz, 2H), 2.06 (t, \(J = 6.36\) Hz, 2H), 1.94 (t, \(J = 4.28\) Hz, 2H), 1.68 (d, \(J = 13.88\) Hz, 2H); MS: m/z 488.5 (M\(^+\)), 489.5 (M+1); IR (KBr) 3361, 1629 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{23}\)F\(_3\)N\(_4\)O\(_4\): C, 59.01; H, 4.75; N, 11.47%; Found: C, 58.98; H, 4.73; N, 11.44%.

1'-[4-(difluoromethoxy)benzyl]-N-(2-chlorophenyl)-2',5'-dioxospiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (23). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): \(\delta\) 8.29 (s, 1H), 7.50 (s, 1H), 7.41-7.49 (m, 2H), 7.30-7.35 (m, 1H), 7.26-7.27 (m, 2H), 7.14-7.23 (m, 2H), 7.04-7.09 (m, 1H), 6.46 (s, 1H), 4.56 (s, 2H), 4.44 (s, 2H), 2.36 (q, \(J = 3.04\) Hz, 2H), 2.08 (d, \(J = 7.76\) Hz, 2H), 1.98 (d, \(J = 4.12\) Hz, 2H), 1.68 (d, \(J = 13.44\) Hz, 2H); MS: m/z 504.9 (M\(^+\)), 506 (M+1); IR (KBr) 3359, 1621 cm\(^{-1}\); Anal. calcd for C\(_{24}\)H\(_{23}\)Cl\(_2\)F\(_2\)N\(_4\)O\(_4\): C, 57.09; H, 4.59; N, 11.10%; Found: C, 57.06; H, 4.54; N, 11.08%.

1'-[4-(difluoromethoxy)benzyl]-N-(3-chlorophenyl)-2',5'-dioxospiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (24). White color solid; \(^1\)H NMR: 400 MHz, DMSO-\(d_6\): \(\delta\) 8.71 (s, 1H), 7.71 (s, 1H), 7.70 (d, \(J = 2.00\) Hz, 1H), 7.40-7.41 (m, 1H), 7.32-7.33 (m, 2H), 7.18-7.27 (m, 2H), 7.07 (t, \(J = 18.40\) Hz, 1H), 6.96-6.96 (m, 1H), 6.46 (s, 1H), 4.56 (s, 2H), 4.46 (s, 2H), 2.24 (q, \(J = 3.24\) Hz, 2H), 2.07 (t, \(J = 5.96\) Hz, 2H), 1.95 (t, \(J = 4.44\) Hz, 2H), 1.70 (d, \(J = 13.88\) Hz, 2H); MS: m/z 504.9 (M\(^+\)), 506 (M+1); IR (KBr) 3363, 1628 cm\(^{-1}\); Anal. calcd for
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C₂₄H₂₃ClF₂N₄O₄: C, 57.09; H, 4.59; N, 11.10%; Found: C, 57.08; H, 4.56; N, 11.09%.

1’-[4-(difluoromethoxy)benzyl]-N-(3-cyanobenzene)-2’,5’-dioxospiro[8-azabicyclo[3.2.1]octane-3,4’-imidazolidine]-8-carboxamide (25). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.59 (s, 1H), 7.51 (s, 1H), 7.47-7.50 (m, 2H), 7.32-7.37 (m, 1H), 7.18-7.22 (m, 2H), 7.18 (s, 3H), 6.45 (s, 1H), 4.56 (s, 2H), 4.44 (s, 2H), 2.25 (q, J = 4.00 Hz, 2H), 2.06 (t, J = 6.36 Hz, 2H), 1.94 (t, J = 4.28 Hz, 2H), 1.68 (d, J = 13.88 Hz, 2H); MS: m/z 495.5 (M⁺), 496.5 (M+1); IR (KBr) 3360, 1624 cm⁻¹; Anal. calcd for C₂₅H₂₃F₂N₅O₄: C, 60.60; H, 4.68; N, 14.13%; Found: C, 60.57; H, 4.62; N, 14.09%.

1’-[4-(difluoromethoxy)benzyl]-N-[4-(propan-2-yl)phenyl]-2’,5’-dioxospiro[8-azabicyclo[3.2.1]octane-3,4’-imidazolidine]-8-carboxamide (26). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.80 (s, 1H), 8.44 (s, 1H), 7.32-7.33 (m, 3H), 7.17-7.18 (m, 2H), 7.03-7.07 (m, 3H), 6.45 (s, 1H), 4.56 (s, 2H), 4.43 (s, 2H), 2.79 (t, J = 6.88 Hz, 1H), 2.39 (d, J = 2.68 Hz, 2H), 2.05 (t, J = 6.16 Hz, 2H), 1.94 (d, J = 5.00 Hz, 2H), 1.67 (d, J = 13.84 Hz, 2H), 1.16 (d, J = 6.84 Hz, 6H); MS: m/z 512.5 (M⁺), 513.5 (M+1); IR (KBr) 3356, 1631 cm⁻¹; Anal. calcd for C₂₇H₃₀F₂N₄O₄: C, 63.27; H, 5.90; N, 10.93%; Found: C, 63.25; H, 5.87; N, 10.91%.

1’-[4-(difluoromethoxy)benzyl]-N-[2-(propan-2-yl)phenyl]-2’,5’-dioxospiro[8-azabicyclo[3.2.1]octane-3,4’-imidazolidine]-8-carboxamide (27). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.78 (s, 1H), 8.44 (s, 1H), 7.31-7.33 (m, 1H), 7.16-7.17 (m, 2H), 7.01-7.08 (m, 2H), 6.76 (d, J = 6.96 Hz, 2H), 6.46 (s, 1H), 4.54 (s, 2H), 4.44 (s, 2H), 2.52 (q, J = 10.96 Hz, 2H), 2.25 (d, J =
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14.20 Hz, 2H), 2.01 (d, J = 22.20 Hz, 4H), 1.66 (d, J = 14.00 Hz, 2H), 1.24 (d, J = 7.52 Hz, 3H); MS: m/z 498.5 (M⁺), 499.5 (M+1); IR (KBr) 3356, 1629 cm⁻¹; Anal. calcd for C₂₆H₂₈F₂N₄O₄: C, 62.64; H, 5.66; N, 11.24%; Found: C, 62.61; H, 5.63; N, 11.20%.

I′-[4-(difluoromethoxy)benzyl]-N-phenyl-2',5'-dioxospiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (29). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.78 (s, 1H), 8.50 (s, 1H), 7.38-7.41 (m, 1H), 7.25-7.27 (m, 1H), 7.22 (s, 5H), 7.16-7.17 (m, 1H), 6.89-6.90 (m, 1H), 6.45 (s, 1H), 4.54 (s, 2H), 4.44 (s, 2H), 2.33 (t, J = 11.28 Hz, 2H), 2.05 (d, J = 7.72 Hz, 2H), 1.96 (d-d, J = 20.92 Hz, 2H), 1.66 (d, J = 14.12 Hz, 2H); MS: m/z 470.5 (M⁺), 471.5 (M+1); IR (KBr) 3355, 1624 cm⁻¹; Anal. calcd for C₂₄H₂₄F₂N₄O₄: C, 61.27; H, 5.14; N, 11.91%; Found: C, 61.27; H, 5.14; N, 11.91%.

I′-[4-(difluoromethoxy)benzyl]-N-(3-methylphenyl)-2',5'-dioxospiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (30). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.79 (s, 1H), 8.44 (s, 1H), 7.28-7.30 (m, 2H), 7.18-7.19 (m, 2H), 7.08-7.12 (m, 3H), 6.74-6.76 (m, 1H), 6.46 (s, 1H), 4.56 (s, 2H), 4.45 (s, 2H), 2.28 (t, J = 6.0 Hz, 2H), 2.24 (s, 3H), 2.06 (t, J = 5.92 Hz, 2H), 1.94 (t, J = 4.64 Hz, 2H), 1.68 (d, J = 13.80 Hz, 2H); MS: m/z 484.5 (M⁺), 485.5 (M+1); IR (KBr) 3361, 1628 cm⁻¹; Anal. calcd for C₂₅H₂₆F₂N₄O₄: C, 61.98; H, 5.41; N, 11.56%; Found: C, 61.93; H, 5.38; N, 11.52%.

I′-[4-(difluoromethoxy)benzyl]-N-(3,5-dimethylphenyl)-2',5'-dioxospiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (31). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.81 (s, 1H), 8.38 (s, 1H), 7.34-7.34 (m, 2H), 7.19-7.20 (m, 2H), 7.04-7.07 (m, 2H), 6.59-6.60 (m, 1H), 6.45 (s, 1H), 4.57 (s, 2H), 4.44 (s, 2H), 2.27 (t, J = 11.16 Hz, 2H), 2.24 (s, 3H), 2.18 (s, 3H), 2.07 (d, J = 7.84 Hz, 2H), 1.95 (d, J = 5.52 Hz, 2H), 1.68 (d, J = 13.76 Hz, 2H); MS: m/z 498.5 (M⁺), 499.5 (M+1); IR (KBr) 3359, 1632 cm⁻¹; Anal. calcd for C₂₆H₂₈F₂N₄O₄: C, 62.64; H, 5.66; N, 11.24%; Found: C, 62.60; H, 5.63; N, 11.19%.

I′-[4-(difluoromethoxy)benzyl]-N-(2-chloro-4,6-dimethylphenyl)-2',5'-dioxospiro[8-azabicyclo [3.2.1]octane-3,4'-imidazolidine]-8-carboxamide (32). White color solid; ¹H NMR: 400 MHz, DMSO-d₆: δ 8.78 (s, 1H), 8.34 (s, 1H), 7.34-7.34 (m, 2H), 7.19-
7.20 (m, 2H), 7.04-7.07 (m, 1H), 6.59-6.60 (m, 1H), 6.45 (s, 1H), 4.57 (s, 2H), 4.44 (s, 2H), 2.27 (t, $J = 11.16$ Hz, 2H), 2.22 (s, 3H), 2.16 (s, 3H), 2.07 (d, $J = 7.84$ Hz, 2H), 1.95 (d, $J = 5.52$ Hz, 2H), 1.68 (d, $J = 13.76$ Hz, 2H); MS: m/z 523.5 (M$^+$), 524.5 (M+1); IR (KBr) 3361, 1629 cm$^{-1}$; Anal. calcd for C$_{27}$H$_{27}$F$_2$N$_5$O$_4$: C, 61.94; H, 5.20; N, 13.38%; Found: C, 61.89; H, 5.18; N, 13.34%.

Pharmacology

Male albino mice (20-25 g) were used as experimental animals. The Institutional Animal Ethics Committee (IAEC) reviewed and approved all the animal procedures adopted. The animals were housed at an ambient temperature of 25±2 °C, in groups as required per metabolic cages and allowed them for free access to chow pellets and water. The light/dark cycle of 12 h: 12 h was maintained. All the synthesized test compounds were suspended in 30% polyethylene glycol (PEG 200).

Anticonvulsant screening

Anticonvulsant evaluations were undertaken using the reported procedures [41, 42]. Initially all the test compounds were administered i.p. in a volume of 0.01 mL/g body weight of mice at doses of 30, 100, 300 mg/kg to 1-6 animals. Anticonvulsant activity was assessed after 30 min and 4 h intervals of administration. Activity was established using the MES and scPTZ tests.

Neurotoxicity screen

Minimal motor impairment was measured in mice by the rotorod test [43]. Animals were divided in groups of 4 animals and trained to stay on accelerating rotorod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotorod for at least two consecutive periods of 90 s) were given an i.p. injection of the test compounds in doses of 30, 100 and 300 mg/kg. Neurological deficit was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. The dose at which animal fell off the rod, was determined.

Behavioural test
Some of the titled compounds (30 mg/kg) were screened for their behavioural effects using an actophotometer [44] at 30 min and 1 h after injection in each group of 6 animals. Animals were acclimatized to the dark environment 24 h before the test. The control administered was 30% PEG only. The behaviour of the animal inside the photocell was recorded as digital score. Increased score represented good behavioural activity.

**CNS depressant study**

The forced swim pool method reported earlier by Porsolt *et. al.* [45]. Mice (six animals in each group) were placed in chamber (diameter 45 cm, height 20 cm) containing water up to the height of 15 cm at 25 ± 2 ºC. Two swim sessions were conducted, an initial 15 min pre-test, followed by a 5 min test session 24 h later. The animals were administered an *i.p.* injection (30 mg/ kg) of the test compound 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which were necessary to keep its head above the surface) during 5 min was measured. This immobility reflected state of depression. Carbamazepine was used as a reference for comparison at a dose of 30 mg/kg (i.p., in PEG). The control animals were administered 30% PEG.

**RESULTS AND DISCUSSION**

**Chemical synthesis**

A systematic reaction pathway in the preparation of 1'-[2-(difluoromethoxy) benzyl]-2'H,5'H-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-dione derivatives is depicted in Scheme 1. The synthesis begins with protection of 8-azabicyclo[3.2.1]octan-3-one hydrochloride 1 using Boc anhydride in dry dichloromethane used as a solvent. Under Bucherer-Bergs condition, construction of azaspiro bicyclic hydantoin 3 was made [46, 47]. The reaction was carried out in aqueous ethanolic media using sodium cyanide and ammonium carbonate at heating temperature. The introduction of the substituent aryl groups at *N* position of hydantoin ring was achieved *via* selective *N*-alkylation reaction by reacting aryl halide in presence of potassium carbonate and acetonitrile solvent [48, 49]. Target key intermediates 5 was accomplished by deportection of Boc group from compound
4 with dioxane in HCl and followed by basification with sodium carbonate solution [50]. The aim of the step 5 was to introduce respective sulfonylchlorides / isocyanates at the N-position of azaspiro bicyclic moiety [51, 52] to lead the desired compounds 6 for SAR study. This was furnished by normal condensation reaction with good yield. The proton spectral data agree with respect to the number of protons and their chemical shifts with the proposed structures. The proton spectral data of the compound 4 shows resonance at δ 8.69 ppm (s, 1H, NH). In all the synthesized compounds (5-32), the above resonance disappeared, which confirmed the condensation between the amino group and carbonyl group. The formation of the hydantion ring was confirmed by $^1$H NMR, IR and Mass spectra. The chemical formula, physical data and yield of all the synthesized compounds are given in Table 1.

NMR and Mass spectra of the synthesized compounds are given at the end of this chapter.

**Scheme 1:** Synthetic pathway of targeted compounds 5-32.
Reagents and condition a) Boc anhydride, triethylamine, dichloromethane, rt, 16 h; b) ammonium carbonate, sodium cyanide, ethanol/water, rt, 24 h, 50 ºC, 24 h; c) anhydrous potassium carbonate, 1-(bromomethyl)-2-(difluoromethoxy)benzene, acetonitrile, reflux, 6 h; d) dioxane in HCl, rt 4 h; e) sodium carbonate solution, rt, 1 h; f) R= sulfonyl chloride/isocyanate, triethylamine, dichloromethane, rt, 16 h.

**Table 1:** Chemical formula, weight, Yield and Melting Point of the Compounds 5-32

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>weight (mg)</th>
<th>Yield (%)</th>
<th>m.p.(ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3,4-(H₃C)₂C₆H₅SO₂</td>
<td>102</td>
<td>69</td>
<td>216</td>
</tr>
<tr>
<td>6</td>
<td>2-H₃CC₆H₅SO₂</td>
<td>98</td>
<td>68</td>
<td>202</td>
</tr>
<tr>
<td>7</td>
<td>3-BrC₆H₅SO₂</td>
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<td>96</td>
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<td>9</td>
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<td>102</td>
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<td>4-H₃CC₆H₅SO₂</td>
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<td>20</td>
<td>4-H₃CSC₆H₄NHCO</td>
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<tr>
<td>32</td>
<td>2-Cl,3,5-(H₃C)₂C₆H₃NHCO</td>
<td>112</td>
<td>74</td>
<td>244</td>
</tr>
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</table>

**Pharmacology**

Some of the new derivatives obtained by the above mentioned procedure were undertaken for the initial anticonvulsant studies according to the anticonvulsant drug development (ADD) program protocol. The profile of anticonvulsant activity
was established after i.p. injections into mice and evaluated in the MES, scPTZ and neurotoxicity screens, using doses of 30, 100 and 300 mg/kg at two different time intervals. These data are presented in Table 2.

**Table 2:** Anticonvulsant and neurotoxicity screening of compounds. Evaluation of compounds in the mouse intraperitoneal MES, scPTZ and NT screens.\(^a\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>MES screen</th>
<th>PTZ screen</th>
<th>Neurotoxicity screen</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.5</td>
<td>4h</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
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<td>31</td>
<td>100</td>
<td>300</td>
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</tr>
<tr>
<td>32</td>
<td>100</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>phenytoin</td>
<td>30</td>
<td>30</td>
<td>×</td>
</tr>
<tr>
<td>Sodium valporate</td>
<td>×</td>
<td>×</td>
<td>300</td>
</tr>
</tbody>
</table>

\(^a\) doses of 30, 100 and 300 mg/kg of the compound were administered and the protection and neurotoxicity measured after 0.5 and 4 h. The figures indicate the
Hydantoin derivatives

Chapter 4

minimal dose required to cause protection or neurotoxicity in 50% or more of the animals. The dash (-) indicates the absence of anticonvulsant activity or neurotoxicity. × denotes not tested.

It is well documented that one of the important core fragments of anticonvulsants is defined by nitrogen heterocyclic system, usually lactam or imide, with attached phenyl or alkyl groups [53, 54]. This common template is found in the structures of first generation anticonvulsants such as mephenytoin or phenytoin [55-58]. At the present time, there are three in vivo models that are routinely used by most AED discovery programs. They include the MES and scPTZ models. Of these, the MES and scPTZ seizure models represent the two animal seizure models most widely used in the search for new AEDs [59, 60]. All of the titled compounds were evaluated initially in the MES and scPTZ, seizure models. The acute neurological toxicity (NT) was determined in the rotorod test. All the tested compounds showed protection against MES test indicative of their ability to inhibit the seizure spread. Compounds 17 and 19 showed protection against the MES model at 30 mg/kg while some other compounds that showed protection against the MES model at 100 mg/kg include 5, 6, 8, 9, 10, 11, 16, 17, 18, 23, 24 and 27 which showed activity at 0.5 h and 4.0 h periods indicating that drug is potent having a rapid onset of action and long duration of action, while 7, 12, 13, 14, 20, 21, 22, 25, 26, 28, 31 and 32 showed activity at 0.5 h only showing rapid onset and short duration of action. Compounds 19 and 30 showed activity only at 0.5 h, at high dose level of 300 mg/kg indicating that they have rapid onset and shorter duration of action with low potency.

All test compounds except 19 were found to be active in the scPTZ test, a test used to identify compounds that elevate seizure threshold. Compounds 12, 15 and 22 showed activity at a dose of 30 mg/kg while 5, 6, 8, 9, 10, 11, 13, 14, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 29, 30 and 31 showed activity at dose of 100 mg/kg comparable to sodium valproate. All the potent compounds are found to be short acting, except 5, 6, 9, 10, 11, 16 and 18 were found to be active at 4 h time interval at the dose of 100 mg/kg which was indicating their long duration of action.

Thus, the data from the MES and scPTZ tests revealed that 70% and 80%, respectively, of the compounds 5-32 had greater activity at the end of 0.5 h than after
4 h. Thus, in general, these compounds are short acting anticonvulsants. Secondly, the protection was afforded by 100% and 90% of the compounds in the MES and scPTZ screen respectively. In addition, 40% of compounds had greater activity in MES test rather than the scPTZ screen, while 50% of the compounds had equal activity on both models.

In neurotoxicity screen, compounds 6, 9, 10, 18, 23 and 27 did not show neurotoxicity in the maximum administered dose (300 mg/kg) and the remaining compounds were found to be less neurotoxic as compared to phenytoin.

**Table 3:** Behavioural study on some selected compounds using Actophotometer.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity score control (24 h prior)</th>
<th>Activity score post-treatment (locomotor activity score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>420 ± 15.56</td>
<td>47 ± 8.31, 52 ± 6.72</td>
</tr>
<tr>
<td>10</td>
<td>217 ± 24.43</td>
<td>55 ± 7.49, 39 ± 9.16</td>
</tr>
<tr>
<td>17</td>
<td>339 ± 28.72</td>
<td>219 ± 34.72, 310 ± 23.14</td>
</tr>
<tr>
<td>23</td>
<td>386 ± 19.61</td>
<td>370 ± 27.56, 379 ± 19.47</td>
</tr>
<tr>
<td>27</td>
<td>247 ± 17.58</td>
<td>104 ± 11.27, 212 ± 13.12</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>298 ± 32.23 NS</td>
<td>59 ± 4.92, 63 ± 6.37</td>
</tr>
</tbody>
</table>

*a The compounds were tested at a dose level of 100 mg/kg (i.p.).

*b Each score represents the mean ± SEM of six mice, significantly different from control at $P < 0.05$ & NS denote the non significant value (student’s t-test).

*c The compounds were tested at a dose level of 30 mg/kg (i.p.).

**Table 4:** CNS study on selected compounds in forced swim pool test

<table>
<thead>
<tr>
<th>Compound</th>
<th>Immobility time (s) Control (24 h prior)</th>
<th>Immobility time (s) Post-treatment (60 min after)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG</td>
<td>160.00 ± 13.37</td>
<td>173.50 ± 11.53 NS</td>
</tr>
<tr>
<td>6</td>
<td>148.17 ± 7.85</td>
<td>145.83 ± 9.65</td>
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<tr>
<td>10</td>
<td>139.53 ± 12.63</td>
<td>147.33 ± 4.55</td>
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<td>23</td>
<td>137.33 ± 10.81</td>
<td>151.50 ± 6.71</td>
</tr>
<tr>
<td>27</td>
<td>142.50 ± 9.35</td>
<td>148.17 ± 13.70 NS</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>143.33 ± 8.42</td>
<td>169.00 ± 11.63</td>
</tr>
</tbody>
</table>

*a Compounds were tested at a dose of 100 mg/kg (i.p.).

*b Control animals were administered PEG (i.p.).

*c Each value represents the mean ±SEM of six mice significantly different from the control at $P< 0.05$ (NS - not significant).

*d Tested at 30 mg/kg (i.p.).
Some selected compounds were evaluated for their CNS behavioural activity in mice using actophotometer and CNS depressant study using Porsolt’s forced swim pool test. The results are presented in Tables 3 and 4, respectively. In the behavioural study using actophotometer, the compound 23 showed no behavioural despair effect when compared to phenytoin as represented in Table 3. Compounds 17 and 27 showed decreased locomotor activity in the 30 min interval but did not show any significant behaviour despair effect in 1 h time period. All others were found to decrease behavioural activity of the animals. Among the compounds, the aryl derivative 6 exhibited activity. Similar results obtained in Porsolt’s swim pool test with compound 23 in which an increase in the slight immobility time by the compounds indicated the CNS depressant effect. Rest of the tested compounds showed no significant variation from control.

In the present study, the anticonvulsant activity of twenty eight newly synthesized spiroazahydantoins derivatives of sulfonamide and carboxamide were tested. For several decades, antiepileptic drug research has focused on identifying new potential drugs based on their anticonvulsant activity against single acute seizures induced by various stimulators. All established antiepileptic drugs have anticonvulsant activity. Thus, this test may, in some way distinguish the potential utility of compounds against different seizure types.

The author has synthesized two series of new N-substituted spiroazahydantoins derivatives having sulfonamide and carboxamide groups at phenyl ring. The results demonstrated that the anticonvulsant activity was in the order: sulfonamide>carboxamide. This is evident from the fact that five compounds in sulfonamide and two compounds in carboxamide series were more active compared to phenytoin.

A scrutiny for certain selected structures for active anticonvulsants has been shown to possess a hydrophobic unit (R), an electron donor group (D) and hydrogen donor acceptor unit (HBD). In the present study, a series of the active compounds possess all the requirements essential for anticonvulsant activity as proposed by Dimmock and others. Thus, our new proposal for a pharmacophore model includes not only three factors but also an additional hydrophobic binding site for bioactivity.
From the results of this study, the following structure-activity relationships could be derived. One hand, the substitution pattern at different position of the sulfonamide and carboxamide was compared further to increase structure-anticonvulsant activity relationship, the author has introduced the different substituent at aryl ring at different positions of aryl rings like simple phenyl ring, electron donating methyl group, moderated electronegative atom chlorine, more electronegative fluorine group and electron with-drawing cyano groups was examined. The results demonstrated that, the simple phenyl ring bearing compound 29 was moderately active. Similarly, the mild electronegative chlorine atom at different position ortho, meta and para on the phenyl ring bearing compounds 11, 23 and 24 and strong electronegative element (lipophilic groups) fluorine groups at different position ortho, meta and para on the phenyl ring bearing compounds 8, 12, 15, 21 and 22 showed moderate activity. The mild electron donating ethyl, isopropyl and methoxy group at different position ortho, meta and para on the phenyl ring bearing compounds 13, 17, 26, 27 and 28 showed moderate anticonvulsant activity. The influence of cyano electron withdrawing group at different position meta and para on the phenyl ring bearing compounds 19 and 25 practically reduces the anticonvulsant activity. The electron donating (hydrophobic) methyl group at different position ortho, meta and para on the phenyl ring bearing compounds 6, 9, 10, 18, 30 and 31 showed good anticonvulsant activity.

**CONCLUSION**

Considering the results of all the synthesized compounds, the following may be concluded. All of the compounds substituted with phenyl group at different position of hydantoin ring showed better anticonvulsant activity. The results demonstrated that the anticonvulsant activity was in the order: sulfonamide>carboxamide compared to phenytoin. Compounds 6, 9, 10, 18, 30 and 31 emerged as a prototype, being effective in ip MES screens and also exhibiting activity against scPTZ model of seizure. Some titled compounds exhibited lesser CNS depression and neurotoxicity compared to phenytoin/carbamazepine were evident from the CNS studies. The electron donating (hydrophobic) methyl groups at different position ortho, meta and para on the phenyl ring bearing compounds display maximum potent anticonvulsant activity. They may act as lead molecules for future investigations.
Figure 3: $^1$H NMR spectra of compound 5.

Figure 4: $^1$H NMR spectra of compound 8.
Figure 5: $^1$H NMR spectra of compound 12.

Figure 6: $^1$H NMR spectra of compound 17.
Figure 7: $^1$H NMR spectra of compound 22.

Figure 8: $^1$H NMR spectra of compound 30.
Figure 9: Mass spectra of compound 6.
Figure 10: Mass spectra of compound 11.
Figure 11: Mass spectra of compound 16.
Figure 12: Mass spectra of compound 23.
REFERENCES


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