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Synthesis and Pharmacological Evaluation of Novel 1′-[2-(Difluoromethoxy)benzyl]-2′*H*,5′*H*-spiro[8-azabicyclo[3.2.1]-octane-3,4′-imidazolidine]-2′,5′-diones and Their Derivatives

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A series of novel 1′-[2-(difluoromethoxy)benzyl]-2′*H*,5′*H*-spiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-2′,5′-dione substituted hydantoins (**5**–**32**) were synthesized using an appropriate synthetic route and characterized by elemental analysis and spectral data. The novel molecules were screened for anticonvulsant activity in mice by maximal electroshock (MES) and subcutaneous pentylenetetrazol (ScPTZ)-induced seizure tests. The neurotoxicity was assessed using the rotarod method. Compounds **9**, **10**, **18**, **30**, and **31** exhibited anticonvulsant potency against MES seizure and in the ScPTZ model, with lesser neurotoxicity. Some title compounds showed lesser central nervous system depression compared to phenytoin.

Keywords: Anticonvulsant / Isocyanate / Maximal electroshock / ScPTZ / Spirohydantoins

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Introduction

Epilepsy is a common neurologic affliction characterized by excessive temporary neuronal discharge that affects about 1% of the world's population [1] and it is affecting a large section of people, both male and female, throughout the world [2]. It is characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor, or autonomic phenomenon with or without loss of consciousness [3]. The known potential causes of epilepsy include brain tumors, infections, traumatic head injuries, developmental malformations, cerebrovascular diseases, febrile seizures, and status epilepticus [4]. Even though significant advances have been made in epilepsy research, convulsions in 25% of epileptics are inadequately controlled by standard drug therapy [5].

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. 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 of 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 [6, 7]. 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. Conventionally, most screening programs employ mice and rats to assess efficacy against either electrically or chemically induced seizures [8, 9].

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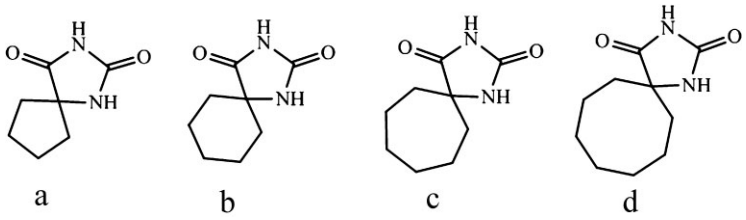


Figure 1. Structure of different cyclic imides (a) 5-cyclic, (b) 6-cyclic, (c) 7-cyclic, and (d) 8-cyclic imides.

The structure–activity relationship (SAR) studies of clinically available antiepileptic drugs and other anticonvulsant active compounds showed that most of these compounds included 5- or 6-member cyclic imides moiety in their molecules (Fig. 1). Hydantoins, a class of cyclic imides, have been demonstrated to possess good anticonvulsant property [10–12]. Depending on the nature of substitution on the hydantoin ring, a wide range of other pharmacological properties, e.g., antihypertensive [13], herbicidal [14], antitumor [15], anti-HIV [16], antibacterial [17], and antiviral [18] 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 [19, 20]. 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 hydrogen bond acceptor (HBA)/donor (HBD) units. The title compounds (**5–32**) possessed all the required pharmacophoric elements (Fig. 2) as the phenyl ring attached to the nitrogen moiety can be referred to as the aryl ring (R – lipophilic aryl ring), the nitrogen of the hydantoin ring can act as a HBD, and the amide keto group of the hydantoin ring can act as a HBA. The proposed hydantoins seems to resemble phenytoin. With this as background and in continuation of our research program on design and synthesis of new anticonvulsant agents [21–23], the present work highlights the importance of the synthesis of prototypes of diazaspirohydantoins and efficacy of their anticonvulsant activity.

Results and discussion

Chemistry

The synthetic pathway utilized 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 outlined as shown in Scheme 1. The synthesis begins with protection of 8-azabicyclo[3.2.1]octan-3-one hydrochloride **1** with di-*tert*-butyl dicarbonate using dry dichloromethane as a solvent. Under Bucherer–Bergs condition, azaspiro bicyclic hydantoin **3** was made [24, 25]. 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 [26, 27]. Target key intermediate **4** was accomplished by deprotection of *tert*-butyl carboxylate group from compound **3** with dioxane in HCl and followed by basification with sodium carbonate solution [28]. The aim of step **5** was to introduce respective sulfonylchloride/isocynates at the *N*-position of azaspiro bicyclic moiety [29, 30] to lead to the desired compounds (**5–32**) 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 hydantoin ring was confirmed by ^{1}H NMR, IR, and mass spectra. The chemical structures, physical data, and yield of all the synthesized compounds are given in Table 1.

Pharmacology

Some of the new derivatives obtained by the above-mentioned procedure were undertaken for the initial anticonvulsant studies by the anticonvulsant drug development (ADD) program protocol [31, 32]. The profile of anticonvulsant activity was established after i.p. injections into mice and evaluated in the maximal electroshock (MES), subcutaneous pentylenetetrazol (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.

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 [33, 34]. This common template is found in the structures of first-generation anticonvulsants such as mephenytoin or phenytoin [7, 35–37]. At the present time, there are two *in vivo* models that are routinely used by most AED discovery programs. They include the MES and scPTZ model.

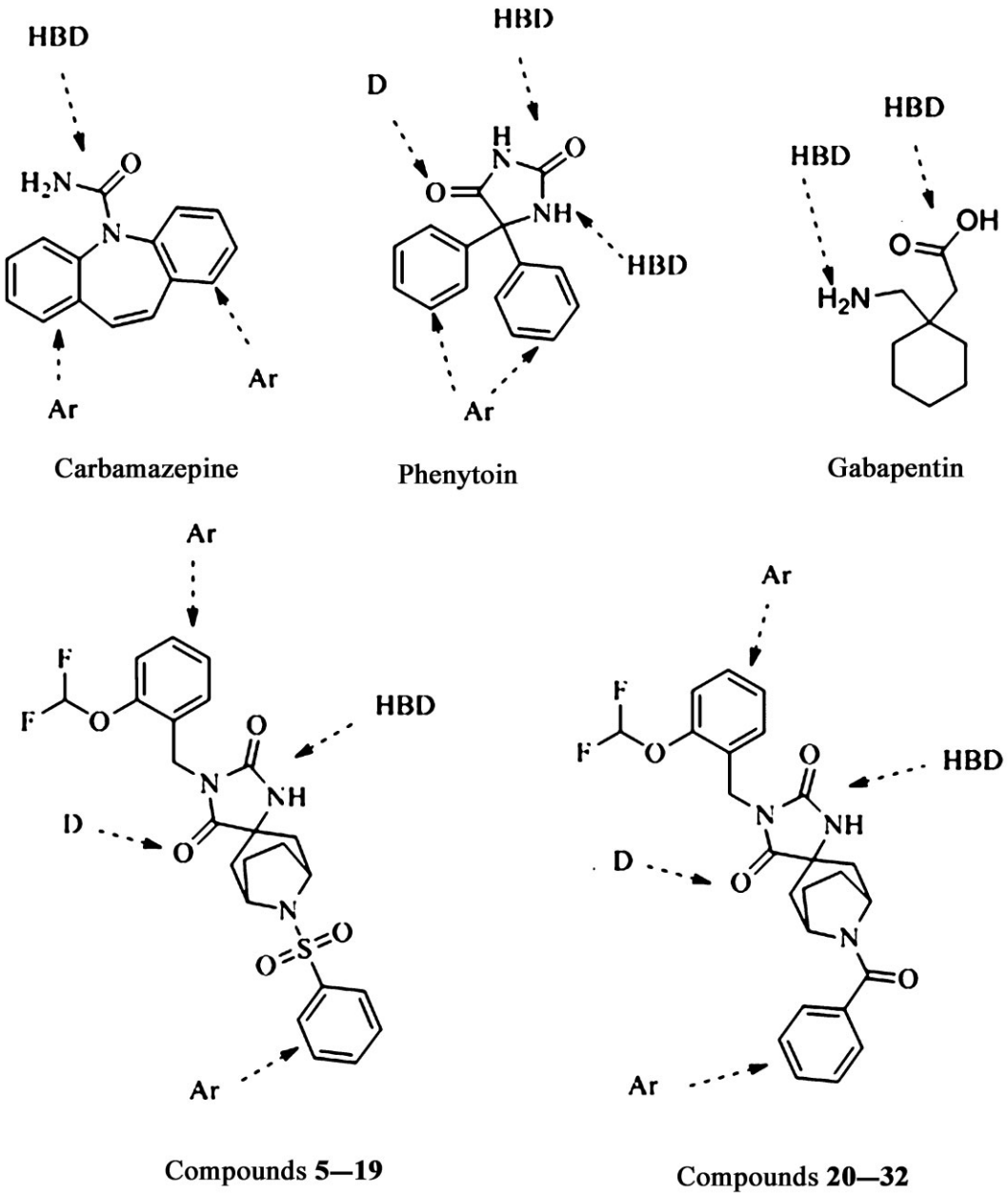
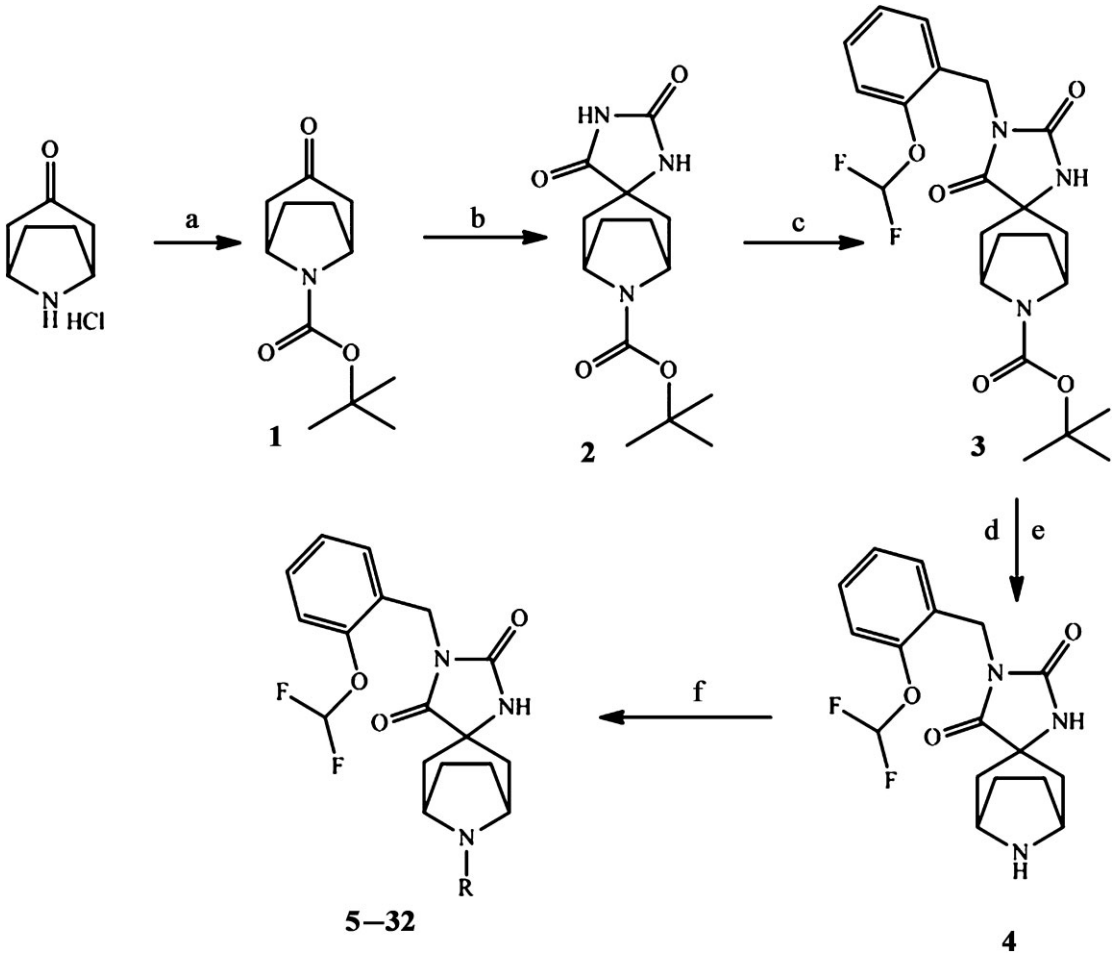


Figure 2. Anticonvulsant agents showing essential pharmacophoric elements present in their structure hydrogen bond donor (HBD) unit; lipophilic aryl ring (Ar), electron donor (D).

The MES and scPTZ seizure models represent the two animal seizure models most widely used in the search for new AEDs [38, 39]. All of the titled compounds were evaluated initially in the MES and scPTZ, seizure models. The acute neurological toxicity (NT) was determined in the rotarod test. All the tested compounds showed protection against MES test indicative of their ability to inhibit the seizure spread. Compounds **15** and **17** showed protection against the MES model at 30 mg/kg while some compounds that showed protection against the MES model at 100 mg/kg include **5**, **6**, **8**, **9**, **10**, **11**, **16**, **18**, **23**, **24**, and **27**, which showed activity at 0.5 and 4.0 h 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. Some of the compounds, i.e., **19** and **30**, showed activity only at 0.5 h, at



Scheme 1. General method for the synthesis of compounds **5–32**. Reagents and conditions: (a) Boc anhydride, triethylamine, dichloromethane, rt, 16 h; (b) ammonium carbonate, sodium cyanide, ethanol/water, rt, 24 h, 50°C, 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; and (f) R = sulfonyl chloride/isocyanate, triethylamine, dichloromethane, rt, 16 h.

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**, **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** that were found to be active at 4 h at the dose of 100 mg/kg, which indicated their long duration of action.

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.

Some selected compounds were evaluated for their CNS behavioral 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 behavioral study using actophotometer, the compound **23** showed no behavioral despair effect when compared to phenytoin as represented in Table 3. Compounds **17** and **27** did show decreased locomotor activity in the 30-min interval but did not show any significant behavior despair effect in 1-h time period. All others were found to decrease behavioral

Table 1. Chemical structures, weights, yields, and melting points of the compounds **5**–**32**.

Compound	R	Weight (mg)	Yield (%)	m.p. (°C)
5	3,4-$(H_3C)_2C_6H_3SO_2$	102	69	216
6	2-$H_3CC_6H_4SO_2$	98	68	202
7	3-$BrC_6H_4SO_2$	107	66	209
8	2-$FC_6H_4SO_2$	96	66	237
9	2,5-$(H_3C)_2C_6H_3SO_2$	102	69	205
10	4-$H_3CC_6H_4SO_2$	95	66	208
11	3-$ClC_6H_4SO_2$	92	61	201
12	4-F,2-$H_3CC_6H_3SO_2$	97	65	203
13	4-$H_3COC_6H_4SO_2$	103	71	222
14	4-$H_3CC_6H_4CH_2SO_2$	94	64	228
15	3- $FC_6H_4SO_2$	102	70	235
16	3,5-$(H_3C)_2C_6H_3SO_2$	97	66	218
17	4-$H_5C_2C_6H_4SO_2$	93	63	221
18	3-$H_3CC_6H_4SO_2$	98	68	210
19	2-$NCC_6H_4SO_2$	95	65	245
20	4-$H_3CSC_6H_4NHCO$	103	70	235
21	3-FC_6H_4NHCO	105	76	239
22	4-FC_6H_4NHCO	98	70	236
23	2-ClC_6H_4NHCO	106	74	232
24	3-ClC_6H_4NHCO	102	71	240
25	3-CNC6H4NHCO	99	70	238
26	4-$(H_3C)_2HCC_6H_4NHCO$	111	76	242
27	2-$(H_3C)_2HCC_6H_4NHCO$	108	74	237
28	3-$H_5C_2C_6H_4NHCO$	102	72	246
29	C_6H_5NHCO	73	73	237
30	3-$H_3CC_6H_4NHCO$	104	75	248
31	3,5-$(H_3C)_2C_6H_4NHCO$	107	75	252
32	2-Cl,3,5-$(H_3C)_2C_6H_3NHCO$	112	74	244

Table 2. Anticonvulsant and neurotoxicity screening of compounds.[a)]

	MES screen		PTZ screen		Neurotoxicity screen	
Compound	**0.5 h**	**4 h**	**0.5 h**	**4 h**	**0.5 h**	**4 h**
5	100	100	100	100	100	–
6	100	100	100	100	–	–
7	100	300	300	300	100	300
8	100	100	100	300	100	300
9	100	100	100	100	–	–
10	100	100	100	100	–	–
11	100	100	100	100	100	300
12	100	300	30	100	100	300
13	100	300	100	300	100	300
14	100	300	100	300	100	300
15	30	100	30	100	–	100
16	100	100	100	100	–	–
17	30	100	100	300	100	–
18	100	100	100	100	–	–
19	300	300	–	–	300	300
20	100	300	100	300	100	300
21	100	300	100	300	100	300
22	100	300	30	100	100	300
23	100	100	100	100	–	–
24	100	100	100	300	300	300
25	100	300	100	300	300	300
26	100	300	100	300	300	300
27	100	100	100	100	–	–
28	100	300	300	300	300	300
29	100	300	100	–	100	300
30	300	300	100	300	100	300
31	100	300	100	300	100	300
32	100	300	300	300	100	300
Phenytoin	30	30	×	×	100	100
Sodium valporate	×	×	300	–	–	–

Evaluation of compounds in the mouse intraperitoneal MES, scPTZ, and NT screens.

[a)] Doses of 30, 100, and 300 mg/kg of the compounds were administered and the protection and neurotoxicity measured after 0.5 and 4 h. The figures indicate the 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.

activity of the animals. Among the compounds, the aryl derivative **6** exhibited activity. Similarly, results were 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 past years, the discovery and development of anticonvulsant drugs have been the noticeable research fields. The search for new compounds combining strong anticonvulsant activity is in progress. Many sulfonamide and carboxamide derivatives have been discovered as potent anticonvulsant drugs and the SAR studies have been reported [40]. In the present study, the anticonvulsant activity of 28 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.

We synthesized a series of 28 new *N*-substituted spiroazahydantoins derivatives having different groups at phenyl ring. However, to know which series of compounds had better activity, we synthesized two series of compounds like sulfonamide and carboxamide; the results demonstrated that the anticonvulsant activity was in the order: sulfonamide > carboxamide. This is evident from the fact that five compounds in sulfonamide series and two compounds in carboxamide series were more active compared to phenytoin.

Certain selected structures for active anticonvulsants has been shown to possess a hydrophobic unit (R), an electron donor group (D), and hydrogen bond donor unit (HBD). In the

Table 3. Behavioral study on some selected compounds using actophometer.

Compound[a)]	Activity score control (24 h prior)	Post-treatment (locomotor activity score)[b)]	
		0.5 h after	1 h after
6	420 ± 15.56	47 ± 8.31	52 ± 6.72
10	217 ± 24.43	55 ± 7.49	39 ± 9.16
17	339 ± 28.72	219 ± 34.72	310 ± 23.14
23	386 ± 19.61	370 ± 27.56	379 ± 19.47
27	247 ± 17.58	104 ± 11.27	212 ± 13.12
Phenytoin[c)]	298 ± 32.23^{NS}	59 ± 4.92	63 ± 6.37

[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 $p < 0.05$, and NS denotes the non-significant value (Student's *t*-test).
[c)] The compounds were tested at a dose level of 30 mg/kg (i.p.).

present study, a series of the active compounds possess all the requirements essential for anticonvulsant activity as proposed by Dimmock et al. [31, 32]. 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 SARs could be derived. The substitution patterns at different position of sulfonamide and carboxamide were compared further to increase structure–anticonvulsant activity relationship; we introduced different substituents at different positions of aryl ring like simple phenyl ring, electron-donating methyl group, moderate electronegative atom chlorine, more electronegative fluorine group, and electron-withdrawing cyano groups. The results demonstrated that the simple phenyl ring bearing compound **29** was moderately active. Similarly, the moderate electronegative chlorine atom at different positions on the phenyl ring bearing compounds **11**, **23**, and **24** and more electronegative (lipophilic) fluorine groups at different positions on the phenyl ring bearing compounds **8**, **12**, **15**, **21**, and **22** showed moderate activity. The compounds **6**, **9**, **10**, **18**, **30**, and **31** bearing electron donating (hydrophobic) methyl group at different positions on the phenyl ring showed good anticonvulsant activity. The electron-donating ethyl, isopropyl, and methoxy groups at different positions on the phenyl ring bearing compounds **13**, **17**, **26**, **27**, and **28** showed moderate anticonvulsant activity. The influence of cyano groups at different positions on the phenyl ring bearing compounds **19** and **25** practically reduces the anticonvulsant activity.

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

Compound[a)]	Immobility time[b)] (s)	
	Control (24 h prior)	Post-treatment[c)] (60 min after)
PEG	160.00 ± 13.37	173.50 ± 11.53^{NS}
6	148.17 ± 7.85	145.83 ± 9.65
10	139.53 ± 12.63	147.33 ± 4.55
23	137.33 ± 10.81	151.50 ± 6.71
27	142.50 ± 9.35	148.17 ± 13.70^{NS}
Carbamazepine[d)]	143.33 ± 8.42	169.00 ± 11.63

[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.).

Conclusion

Considering the results of all the synthesized compounds, the following may be concluded. All of the compounds substituted with phenyl group at different positions 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 i.p. MES screens, and also exhibited activity against scPTZ model of seizure. Some titled compounds exhibited lesser CNS depression and neurotoxicity compared to phenytoin/carbamazepine, as evident from the CNS studies. The electron-donating (hydrophobic) methyl groups at different positions *ortho*, *meta*, and *para* on the phenyl ring bearing compounds display maximum potent anticonvulsant activity. They may act as lead molecules for future investigations.

Experimental

Materials

Melting points were determined in one end open capillary tubes on a Büchi 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 shifts are given in parts per million (δ-scale), and coupling constants are given in Hertz. Mass spectra were recorded on Perkin-Elmer LC–MS PE Sciex API/65 spectrophotometer. IR spectra were recorded using KBr on 8400S Shimadzu Fourier Transform spectrophotometer (ν_{max} in cm^{-1}). Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh), and Merck-made TLC plates. Elemental analysis (C, H, and N) was undertaken with Perkin-Elmer model 240C analyzer.

*Synthesis of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**1**)*

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 di-*tert*-butyl dicarbonate (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 into water and

extracted with dichloromethane (3 × 40 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was recrystallized from hexane to get the pure product. White color solid: (5 g, 90%); ^{1}H NMR (300 MHz, DMSO-d_6): 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).

*Synthesis of tert-butyl 2′,5′-dioxo-8H-spiro[8-azabicyclo-[3.2.1]octane-3,4′-imidazolidine]-8-carboxylate (**2**)*

A mixture of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (5 g, 22.2 mmol) and ammonium carbonate (4.69 g, 48.82 mmol) was taken 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 dropwise to the reaction mixture and it was stirred at room temperature for 24 h, to 50°C 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%); ^{1}H 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′-[2-(difluoromethoxy)benzyl]-2′,5′-dioxo-8H-spiro[8-azabicycle[3.2.1]octane-3,4′-imidazolidine]-8-carboxylate (**3**)*

A mixture of *tert*-butyl 2′,5′-dioxo-8*H*-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. After completion of the reaction (TLC) the reaction mixture was cooled to room temperature and filtered. Filtrate was concentrated *in 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%); ^{1}H 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 = 7.56 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 = 8.24 Hz, 2H), 1.41 (s, 9H); MS: m/z 451.2 (M^+), 452.2 (M+1).

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

tert-Butyl-1′-[2-(difluoromethoxy)benzyl]-2′,5′-dioxo-8*H*-spiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxylate (6.2 g, 13.73 mmol) was taken in dioxane (30 mL), cooled to 0°C. To the above reaction mixture dioxane in HCl (60 mL) was added and allowed to stir 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 × 60 mL), dried over Na_2SO_4 and concentrated *in vacuo* to get pure product. White color solid: (3.9 g, 81%); ^{1}H NMR (400 MHz, DMSO-d_6): 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, J = 2.64 Hz, 2H), 2.18 (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 azabicyclospiro-sulfonamides (**5**–**19**)*

A mixture of 8-(3,4-dimethylbenzoyl)-1′-[2-(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 sodium carbonate solution, extracted with dichloromethane (3 × 4 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica employing dichloromethane/methanol (9:1) as an eluent to obtain pure product.

*1′-[2-(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: (102 mg, 69%); m.p. = 216°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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, 1H), 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 $C_{25}H_{27}F_2N_3O_5S$: C, 57.79; H, 5.24; N, 8.09%; Found: C, 57.77; H, 5.21; N, 8.06%.

*1′-[2-(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: (98 mg, 68%); m.p. = 202°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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), 7.05 (t, J = 7.04 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 = 6.20 Hz, 4H); MS: m/z 505.5 (M^+), 506.5 (M+1); IR (KBr) 1652, 1344 cm^{-1}; Anal. calcd. for $C_{24}H_{25}F_2N_3O_5S$: C, 57.02; H, 4.98; N, 8.31%; Found: C, 57.06; H, 4.99; N, 8.35%.

*1′-[2-(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: (107 mg, 66%); m.p. = 209°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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 = 6.28 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 $C_{23}H_{22}BrF_2N_3O_5S$: C, 48.43; H, 3.89; N, 7.37%; Found: C, 48.41; H, 3.85; N, 7.36%.

*1′-[2-(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: (96 mg, 66%); m.p. = 237°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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 $C_{23}H_{22}F_3N_3O_5S$: C, 54.22; H, 4.35; N, 8.25%; Found: C, 54.20; H, 4.32; N, 8.23%.

*1′-[2-(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: (102 mg, 69%); m.p. = 205°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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 $C_{25}H_{27}F_2N_3O_5S$: C, 57.79; H, 5.24; N, 8.09%; Found: C, 57.75; H, 5.21; N, 8.07%.

*1′-[2-(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: (95 mg, 66%); m.p. = 208°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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 = 6.04 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 = 7.20 Hz, 4H); MS: m/z 505.5 (M^+), 506.5 (M+1); IR (KBr) 1651, 1343 cm^{-1}; Anal. calcd. for $C_{24}H_{25}F_2N_3O_5S$: C, 57.02; H, 4.98; N, 8.31%; Found: C, 57.03; H, 4.91; N, 8.28%.

*1′-[2-(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: (92 mg, 61%); m.p. = 201°C; ^{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+2); IR (KBr) 1655, 1342 cm^{-1}; Anal. calcd. for $C_{23}H_{22}ClF_2N_3O_5S$: C, 52.52; H, 4.22; N, 7.99%; Found: C, 52.51; H, 4.24; N, 7.95%.

*1′-[2-(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: (97 mg, 65%); m.p. = 203°C; ^{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 $C_{24}H_{24}F_3N_3O_5S$: C, 55.06; H, 4.62; N, 8.03%; Found: C, 55.02; H, 4.60; N, 8.01%.

*1′-[2-(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: (103 mg, 71%); m.p. = 222°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.76–7.77 (m, 2H), 7.33–7.33 (m, 1H), 7.18–7.20 (m, 3H), 7.03–7.18 (m, 2H), 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 $C_{24}H_{25}F_2N_3O_6S$: C, 55.27; H, 4.83; N, 8.06%; Found: C, 55.25; H, 4.81; N, 8.03%.

*1′-[2-(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: (94 mg, 64%); m.p. = 228°C; ^{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 = 7.92 Hz, 2H), 1.86 (t, J = 7.56 Hz, 4H), 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 $C_{25}H_{27}F_2N_3O_5S$: C, 57.79; H, 5.24; N, 8.09%; Found: C, 57.74; H, 5.21; N, 8.02%.

*1′-[2-(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: (102 mg, 70%); m.p. = 235°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.73 (s, 1H), 7.57–7.74 (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 = 6.32 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 $C_{23}H_{22}F_3N_3O_5S$: C, 54.22; H, 4.35; N, 8.25%; Found: C, 54.20; H, 4.32; N, 8.23%.

*1′-[2-(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: (97 mg, 66%); m.p. = 218°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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 $C_{25}H_{27}F_2N_3O_5S$: C, 57.79; H, 5.24; N, 8.09%; Found: C, 57.76; H, 5.20; N, 8.06%.

*1′-[2-(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: (93 mg, 63%); m.p. = 221°C; ^{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), 4.56 (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 (t, J = 8.28 Hz, 3H), 1.15 (q, J = 16.76 Hz, 2H); MS: m/z 519.6 (M^+), 520.6 (M+1); IR (KBr) 1653, 1341 cm^{-1}; Anal. calcd. for $C_{25}H_{27}F_2N_3O_5S$: C, 57.79; H, 5.24; N, 8.09%; Found: C, 57.75; H, 5.21; N, 8.02%.

*1′-[2-(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: (98 mg, 68%); m.p. = 210°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.67 (t, J = 7.24 Hz, 2H), 7.49 (t, J = 7.44 Hz, 2H), 7.35 (s, 1H), 7.18–7.19 (m, 2H), 7.09 (d, J = 7.28 Hz, 1H), 6.45 (s, 1H), 4.56 (s, 2H), 4.29 (s, 2H), 2.39 (s, 3H), 2.21 (q, J = 4.64 Hz, 2H), 1.84 (t, J = 2.12 Hz, 4H), 1.22–1.24 (m, 2H); MS: m/z 505.5 (M^+), 506.5 (M+1); IR (KBr) 1652, 1343 cm^{-1}; Anal. calcd. for $C_{24}H_{25}F_2N_3O_5S$: C, 57.02; H, 4.98; N, 8.31%; Found: C, 57.01; H, 4.94; N, 8.28%.

*1′-[2-(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: (95 mg, 65%); m.p. = 245°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 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 = 6.24 Hz, 2H), 1.76 (d, J = 2.92 Hz, 2H); MS: m/z 516.5 (M^+), 517.5 (M+1); IR

(KBr) 1653, 1341 cm^{-1}; Anal. calcd. for $C_{24}H_{22}F_2N_4O_5S$: 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 azabicyclospirocarboxamides **20–32***

A mixture of 8-(3,4-dimethylbenzoyl)-1′-[2-(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 isocyanate (0.31 mmol) in dichloromethane (4 mL) was stirred at room temperature for 16 h. The above general procedure was followed to get the pure compounds. Structure verification data for novel compounds (**5–32**) are documented in Supporting Information File.

*1′-[2-(Difluoromethoxy)benzyl]-N-[4-(methylsulfanyl)-phenyl]-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**20**)*

White color solid: (103 mg, 70%); m.p. = 235°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 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 = 7.84 Hz, 1H), 6.45 (s, 1H), 4.57 (s, 2H), 4.46 (s, 2H), 2.47 (d, J = 6.16 Hz, 2H), 2.42 (s, 3H), 2.26 (q, J = 2.88 Hz, 2H), 1.96 (d, J = 5.00 Hz, 2H), 1.69 (d, J = 6.80 Hz, 2H); MS: m/z 516.6 (M^+), 517.6 (M+1); IR (KBr) 3359, 1656 cm^{-1}; Anal. calcd. for $C_{25}H_{26}F_2N_4O_4S$: C, 58.13; H, 5.07; N, 10.85%; Found: C, 58.12; H, 5.05; N, 10.82%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(3-fluorophenyl)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**21**)*

White color solid: (105 mg, 76%); m.p. = 239°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 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 = 7.88 Hz, 2H); MS: m/z 488.5 (M^+), 489.5 (M+1); IR (KBr) 3358, 1622 cm^{-1}; Anal. calcd. for $C_{24}H_{23}F_3N_4O_4$: C, 59.01; H, 4.75; N, 11.47%; Found: C, 59.04; H, 4.71; N, 11.45%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(4-fluorophenyl)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**22**)*

White color solid: (98 mg, 70%); m.p. = 236°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 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 $C_{24}H_{23}F_3N_4O_4$: C, 59.01; H, 4.75; N, 11.47%; Found: C, 58.98; H, 4.73; N, 11.44%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(2-chlorophenyl)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**23**)*

White color solid: (106 mg, 74%); m.p. = 232°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 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), 4.40 (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 = 7.44 Hz, 2H); MS: m/z 504.9 (M^+), 506 (M+2); IR (KBr) 3359, 1621 cm^{-1}; Anal. calcd. for $C_{24}H_{23}ClF_2N_4O_4$: C, 57.09; H, 4.59; N, 11.10%; Found: C, 57.06; H, 4.54; N, 11.08%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(3-chlorophenyl)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**24**)*

White color solid: (102 mg, 71%); m.p. = 240°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 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 = 8.40 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 = 7.88 Hz, 2H); MS: m/z 504.9 (M^+), 506 (M+2); IR (KBr) 3363, 1628 cm^{-1}; Anal. calcd. for $C_{24}H_{23}ClF_2N_4O_4$: C, 57.09; H, 4.59; N, 11.10%; Found: C, 57.08; H, 4.56; N, 11.09%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(3-cyanobenzene)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**25**)*

White color solid: (99 mg, 70%); m.p. = 238°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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 = 7.88 Hz, 2H); MS: m/z 495.5 (M^+), 496.5 (M+1); IR (KBr) 3360, 1624 cm^{-1}; Anal. calcd. for $C_{25}H_{23}F_2N_5O_4$: C, 60.60; H, 4.68; N, 14.13%; Found: C, 60.57; H, 4.62; N, 14.09%.

*1′-[2-(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: (111 mg, 76%); m.p. = 242°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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), 6.37 (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 $C_{27}H_{30}F_2N_4O_4$: C, 63.27; H, 5.90; N, 10.93%; Found: C, 63.25; H, 5.87; N, 10.91%.

*1′-[2-(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: (108 mg, 74%); m.p. = 237°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.12 (s, 1H), 7.34–7.34 (m, 1H), 7.26–7.28 (m, 1H), 7.19–7.20 (m, 2H), 7.16–7.17 (m, 2H), 7.04–7.11 (m, 2H), 6.45 (s, 1H), 4.58 (s, 2H), 4.37 (s, 2H), 3.20–3.21 (m, 1H), 2.08 (t, J = 5.56 Hz, 2H), 1.97–1.98 (m, 4H), 1.65 (d, J = 7.88 Hz, 2H), 1.13 (d, J = 6.84 Hz, 6H); MS: m/z 512.5 (M^+), 513.5 (M+1); IR (KBr) 3359, 1626 cm^{-1}; Anal. calcd. for $C_{27}H_{30}F_2N_4O_4$: C, 63.27; H, 5.90; N, 10.93%; Found: C, 63.22; H, 5.86; N, 10.90%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(3-ethylphenyl)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**28**)*

White color solid: (102 mg, 72%); m.p. = 246°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.44 (s, 1H), 7.31–7.33 (m, 1H), 7.16–7.17 (m, 1H), 7.14 (d, J = 7.68 Hz, 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, $J = 7.96$ Hz, 2H), 2.25 (d, $J = 6.20$ Hz, 2H), 2.01 (d, $J = 7.20$ Hz, 4H), 1.66 (d, $J = 6.00$ 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 $C_{26}H_{28}F_2N_4O_4$: C, 62.64; H, 5.66; N, 11.24%; Found: C, 62.61; H, 5.63; N, 11.20%.

*1′-[2-(Difluoromethoxy)benzyl]-N-phenyl-2′,5′-dioxospiro-[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**29**)*

White color solid: (98 mg, 73%); m.p. = 237°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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, $J = 4.28$ Hz, 2H), 2.05 (d, $J = 7.72$ Hz, 2H), 1.96 (d, $J = 5.52$ Hz, 1H), 1.94 (d, $J = 8.76$ Hz, 1H), 1.66 (d, $J = 7.12$ Hz, 2H); MS: *m/z* 470.5 (M^+), 471.5 (M+1); IR (KBr) 3355, 1624 cm^{-1}; Anal. calcd. for $C_{24}H_{24}F_2N_4O_4$: C, 61.27; H, 5.14; N, 11.91%; Found: C, 61.27; H, 5.14; N, 11.91%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(3-methylphenyl)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**30**)*

White color solid: (104 mg, 75%); m.p. = 248°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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, $J = 2.60$ 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 $C_{25}H_{26}F_2N_4O_4$: C, 61.98; H, 5.41; N, 11.56%; Found: C, 61.93; H, 5.38; N, 11.52%.

*1′-[2-(Difluoromethoxy)benzyl]-N-(3,5-dimethylphenyl)-2′,5′-dioxospiro[8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-8-carboxamide (**31**)*

White color solid: (107 mg, 75%); m.p. = 252°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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, $J = 8.16$ 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, $J = 7.76$ Hz, 2H); MS: *m/z* 498.5 (M^+), 499.5 (M+1); IR (KBr) 3359, 1632 cm^{-1}; Anal. calcd. for $C_{26}H_{28}F_2N_4O_4$: C, 62.64; H, 5.66; N, 11.24%; Found: C, 62.60; H, 5.63; N, 11.19%.

*1′-[2-(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: (112 mg, 74%); m.p. = 244°C; ^{1}H NMR (400 MHz, DMSO-d_6): 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, $J = 8.16$ 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, $J = 7.76$ Hz, 2H); MS: *m/z* 532.5 (M^+), 534.5 (M+1); IR (KBr) 3361, 1629 cm^{-1}; Anal. calcd. for $C_{27}H_{27}F_2N_5O_4$: 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 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, and 300 mg/kg to one to six animals. Anticonvulsant activity was assessed after 30 min and 4 h of administration. Activity was established using the MES and scPTZ tests.

Neurotoxicity screen

Minimal motor impairment was measured in mice by the rotarod test [43]. Animals were divided in groups of four animals and trained to stay on the accelerating rotarod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod 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.

Behavioral test

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

CNS depressant study

The forced swim pool method was reported earlier by Porsolt et al. [45]. Mice (six animals in each group) were placed in a chamber (diameter 45 cm, height 20 cm) containing water up to the height of 15 cm at 25 ± 2°C. 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 that were necessary to keep its head above the surface) during the 5-min test period 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.

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