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Synthesis and anticonvulsant activity of new N-1′,N-3′-disubstituted-2′*H*,3*H*,5′*H*-spiro-(2-benzofuran-1,4′-imidazolidine)-2′,3,5′-triones

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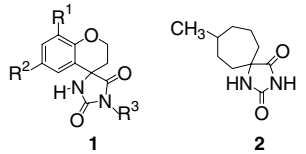
Abstract—Thirteen new N-1′,N-3′-disubstituted-2′*H*,3*H*,5′*H*-spiro-(2-benzofuran-1,4′-imidazolidine)-2′,3,5′-triones were synthesized and their pharmacological activity determined with the objective to better understand their SAR for anticonvulsant activity. The anticonvulsant effects of these compounds were evaluated by standard pentylenetetrazol (scPTZ test) and maximum electroshock seizure (MES test) models in mice. Most of the compounds showed ability to protect against the pentylenetetrazol-induced convulsions. Compound **3o** (the *N*-1′-*p*-nitrophenyl, *N*-3′-ethyl derivative) in the *N*-1′-aryl, *N*-3′-alkyl disubstituted series exhibited maximum activity with ED_{50} of 41.8 mg/kg in scPTZ convulsion model.

Epilepsy, characterized by the periodic and unpredictable occurrence of seizures, is the most prevalent neurological disorder, affecting approximately 50 million people worldwide.[1,2] 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, felbamate, lamotrigine, gabapentin, and topiramate, have been approved to treat epilepsy.[4] 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, there is need for new antiepileptic drugs with greater efficacy and fewer side effects. Most of the compounds with anticonvulsant activity contain a cyclic ureide ring system.[5,6] Phenytoin, a hydantoin, represents one of the important anticonvulsant drugs in the treatment of the generalized convulsion and psychomotor seizures since its discovery over six decades ago.[5,7] Since then many hydantoin analogs have been synthesized and shown to have anticonvulsant activity. Spirohydantoins, 5,5-(cyclic hydrocarbon) hydantoins were also synthesized and reported for their antiepileptic activity,[5] Figure 1. Compounds of the type **1** were found to be similar or more effective than diphenylhydantoin and methylphenylhydantoin to a stimulus test,[8] while compound **2** has sedative, hypnotic, and anticonvulsant properties.[9]

In a previous paper,[10] from our laboratory it was shown that oxidation of N-1,N-3-disubstituted urea–ninhydrin cycloadducts with sodium periodate leads to products



1 **2**

R^1, R^2 = H, halogen
R^3 = H, alkyl

Figure 1. Spirohydantoins with antiepileptic activity.

Keywords: 2′*H*,3*H*,5′*H*-spiro-(2-benzofuran-1,4′-imidazolidine)-2′,3,5′-triones anticonvulsants; Spirohydantoins; Ninhydrin; N,N′-substituted ureas; Sodium periodate.
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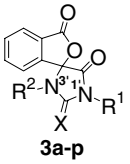
which were assigned benzodiazocine structure. However, crystallographic studies[11] have revealed that they are spirohydantoins of the type **3**, Scheme 1. In the homologous series of these compounds bearing dimethyl (**3a**, R^1, $R^2 = CH_3$), diethyl (**3b**, R^1, $R^2 = C_2H_5$), and diallyl (**3c**, R^1, $R^2 = CH_2–CH=CH_2$), the diethyl (**3b**) was the most active with ED_{50} of 190 mg/kg in scPTZ test. In this research, a series of new N-1′,N-3′-disubstituted, 2′*H*,3*H*,5′*H*-spiro-(2-benzofuran-1,4′-imidazolidine)-2′,3,5′-triones (**3d**–**p**) Scheme 1, were synthesized to better understand the SAR of these compounds. Substituents were selected in order to determine the optimum chain length of the nitrogen substituents and to increase the lipophilicity of the spirohydantoins to make them more permeable to the blood–brain barrier (BBB). The anticonvulsant effects of these compounds have been evaluated through subcutaneous pentylenetetrazol (scPTZ)-induced convulsions and maximal electroshock (MES) tests. It emerges that the *p*-nitrophenyl derivative, compound **3o** in the *N*-1′-aryl, *N*-3′-alkyl series, is the most active in scPTZ animal model.

The designed compounds were synthesized according to Scheme 2. All the compounds, **3d**–**p**, were prepared from the corresponding disubstituted ureas. Commercially unavailable ureas **6h**–**p** were prepared by reaction of the corresponding alkylamine with the appropriately substituted phenylisocyanate or phenylisothiocyanate. The indeno-[1,2-*d*]-imidazole intermediates (**7d**–**p**) were readily prepared by refluxing the disubstituted ureas (**6d**–**p**) with ninhydrin in benzene for 1 h. These were then oxidized to spirohydantoins **3d**–**p** in good yields with sodium periodate by previously reported methods.[10] The structures were assigned on the basis of infrared, NMR, mass spectra, and X-ray crystallography.[12]



3a-p

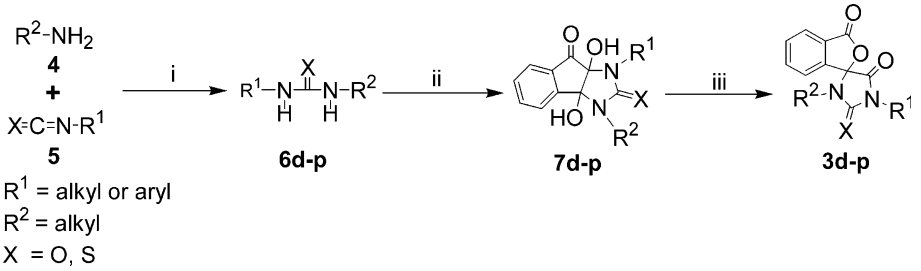
Compd	R^1	R^2	X
3a*	CH_3	CH_3	O
3b*	C_2H_5	C_2H_5	O
3c*	allyl	allyl	O
3d	CH_3	C_2H_5	O
3e	*n*-C_3H_7	*n*-C_3H_7	O
3f	*n*-C_4H_9	*n*-C_4H_9	O
3g	*i*-C_3H_7	*i*-C_3H_7	O
3h	*cyclo*-C_6H_{11}	*cyclo*-C_6H_{11}	O
3i	C_6H_5	CH_3	O
3j	C_6H_5	CH_3	S
3k	*p*-F-C_6H_4	CH_3	O
3l	*p*-CF_3-C_6H_4	CH_3	O
3m	C_6H_5	C_2H_5	O
3n	*p*-F-C_6H_4	C_2H_5	O
3o	*p*-NO_2-C_6H_4	C_2H_5	O
3p	*p*-OCH_3-C_6H_4	C_2H_5	O

Scheme 1. The structure of designed compounds. *Previously synthesized and reported by Sarra et al.[10]

The anticonvulsant activities of the synthesized compounds were determined[13] through the evaluation of the ability of the compounds to protect mice against convulsions induced by PTZ[14,15] (scPTZ test) and electroshock[14,16] (MES test) as two routine models. Phenobarbital and phenytoin were taken as the reference compounds in the scPTZ and MES models, respectively.

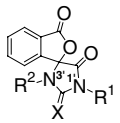
As shown in Table 1, compound **3e** with a three-carbon chain at N-3′ position is approximately two and half times more active than parent compound **3b** (the diethyl analog) in scPTZ model and also showed protection in MES model. But, increasing the chain length to four carbons (**3f**) resulted in decreased activity in both scPTZ and MES tests. Also, decreasing the length of the alkyl group by one-carbon at N-1′ (**3d**) results in substantial loss in activity in both scPTZ and MES models. Replacement of the straight chain propyl group with the branched isopropyl (**3g**) group or bulky cyclohexane ring (**3h**) abolishes the activity in both the anticonvulsant models. The activity was regained by replacement of the alkyl group at the N-1′ position with a phenyl ring (**3i**). These results suggest that the length of the alkyl chain is critical at the N-3′ position of the spirohydantoin and there is tolerance up to a three-carbon alkyl group only. Bulk tolerance is not very critical at N-1′ position of the ring as compound **3i** which has a phenyl ring, shows substantial activity in scPTZ test.

The oxygen of the C=O group at C-2′ is thought to be involved in H-bonding, since there is decrease in activity when the carbonyl group in compound **3i** is replaced by a thiocarbonyl (**3j**), which is in agreement with the reported SAR for hydantoins.[17] Substitution of a small lipophilic group like fluorine (**3k**) at the *para* position of the *N*-1′-phenyl ring of **3i** resulted in increased activity in both scPTZ and MES. However, substitution with CF_3 (**3l**) at the *para* position resulted in substantial de-



Scheme 2. The synthesis of **3d**–**p**. Reagents and conditions: (i) dry THF, 0 °C; (ii) ninhydrin, C_6H_6, reflux, 1 h; (iii) $NaIO_4$, EtOH, 12–16 h.

Table 1. Anticonvulsant test results (ED_{50}) in mice of the synthesized compounds



3b and 3d-p

Compound	R^1	R^2	X	milog P[f]	ED_{50}[a,b]	
					scPTZ test	MES test
3b	C_2H_5	C_2H_5	O	1.457	190[c]	–
3d	CH_3	C_2H_5	O	1.081	+	–
3e	*n*-C_3H_7	*n*-C_3H_7	O	2.462	78.5 (63.7–96.7)	>100
3f	*n*-C_4H_9	*n*-C_4H_9	O	3.581	>100	+
3g	*i*-C_3H_7	*i*-C_3H_7	O	2.051	+	–
3h	*cyclo*-C_6H_{11}	*cyclo*-C_6H_{11}	O	4.516	–	–
3i	C_6H_5	CH_3	O	2.403	96.8 (70.1–133.9)	+
3j	C_6H_5	CH_3	S	2.943	+	–
3k	*p*-F-C_6H_4	CH_3	O	2.566	87.1 (65.6–123.8)	>100
3l	*p*-CF_3-C_6H_4	CH_3	O	3.298	>100	>100
3m	C_6H_5	C_2H_5	O	2.779	54.8 (19.0–162.4)	81 (13–530)
3n	*p*-F-C_6H_4	C_2H_5	O	2.942	85.8 (40.7–181.0)	>100
3o	*p*-NO_2-C_6H_4	C_2H_5	O	2.738	41.8 (39.2-44.5)	–
3p	*p*-OCH_3-C_6H_4	C_2H_5	O	2.835	82.5 (61.8–110.0)	+
Phenobarbital					20[d] (16)[e]	–
Phenytoin					–	8.1[d] (9)[e]

[a] ED_{50} values are in mg/kg of test drug delivered intraperitoneally and measured at 0.5 h. The time of peak effect was not determined.
[b] $n = 3$, numbers in parentheses are 95% confidence intervals.
[c] Previously synthesized and published data (Sarra et al.10). '–' means not active up to 300 mg/kg. '+' denotes activity at 300 mg/kg but ED_{50} could not be determined.
[d] Experimental ED_{50} value.
[e] Literature ED_{50} value.
[f] Partition coefficient values calculated by Molinspiration® interactive log P calculator.

crease in anticonvulsant activity, possibly due to its increased bulk. Increasing the chain length to two carbons at N-3′ position (**3m**) resulted in increased activity, when compared to the N-3′ methyl compound (**3i**), in agreement with previous SAR of linear chain substituents.[9] Introducing the *p*-nitrophenyl group as the R^1-substituent resulted in compound **3o** having the best activity in scPTZ test with ED_{50} of 41.8 mg/kg, five times more potent than the parent compound **3b**, but abolished its activity in MES test.

Electron-donating groups like methoxy (**3p**) at the 4 position of the phenyl ring cause a slight decrease in activity compared to **3m** but was not significant. Unfortunately, further increasing the chain length to three carbons at N-3′ engendered very high toxicity (data not shown). Based on the calculated log P values shown in Table 1 the compounds showing significant activity in scPTZ model have partition coefficient values in the range of 2.4–3.0 compared to that of the lead compound **3b** (log $P = 1.457$). Although the drug levels in cerebrospinal fluid (CSF) or brain concentrations were not measured, higher log P values for the new series suggest that there is correlation between activity and lipophilicity.

In summary, several new N-1′, N-3′-disubstituted phthalidyl spirohydantoins were synthesized and shown to have appreciable anticonvulsant activity. Among the compounds tested **3e**, **3i**, **3k**, **3m**, **3n**, and **3o** displayed significant anticonvulsant activity against the scPTZ test with most ED_{50} values in the narrow range of 78–97 mg/kg. In the dialkyl series, based on the SAR, an unbranched, unsaturated alkyl chain up to three carbons is essential for protection, with di-*n*-propyl derivative (**3e**) exhibiting strongest activity. Compound **3o**[18] (the *N*′-3′-ethyl-*N*-1′-*p*-nitrophenyl derivative) in the *N*-1′-aryl-*N*-3′-alkyl disubstituted series exhibited maximum activity with an ED_{50} of 41.8 mg/kg which is five times more potent than the parent compound (**3b**) in the scPTZ test. It should be noted all of these compounds are prepared as racemic mixtures and no attempt has been made to resolve the enantiomers. Most compounds were not significantly active in the MES assay.

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12. X-ray coordinates of compound **3i** have been deposited with the Cambridge Crystallographic Data Centre and the deposition number is CCDC 608866.
13. Compounds **3d**–**p**, positive controls or vehicle (DMSO) were administered intraperitoneally 30 min before the subcutaneous injection of PTZ, 80 mg/kg, or administration of electroshock (50 mA for 0.2 s). Occurrences of clonic seizure for more than 5 s and hind limb tonic extensor component were recorded in scPTZ and MES, respectively. Experiments were done in triplicates and the ED_{50} values were determined by non-linear regression analysis and reported as the mean value with 95% confidence intervals.
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18. Spectroscopic data for **3o**. IR (KBr) *v*: 1799, 1783, 1738, 1520 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6) δ: 1.039 (3H, t, J = 7.2 Hz), 3.160 (1H, sextet, J = 7.2 Hz), 3.397 (1H, sextet, J = 7.3 Hz), 7.880 (1H, t, J = 7.5 Hz), 7.907 (2H, d, J = 8.7 Hz), 7.995 (1H, t, J = 7.6 Hz), 8.097 (1H, d, J = 7.6 Hz), 8.221 (1H, d, J = 7.7 Hz), 8.417 (2H, d, J = 8.9 Hz). ^{13}C NMR (400 MHz; DMSO-d_6) δ: 14.06, 35.23, 92.20, 124.15, 124.66, 125.74, 126.74, 132.55, 135.80, 136.67, 140.52, 146.47, 152.79, 165.5, 166.42. *m/z*: 367 ($M^{\cdot+}$), 323, 175, 160, 131, 104, 90, 76, 50. Anal. Calcd for $C_{18}H_{13}N_3O_6$: C, 58.87; H, 3.56; N, 11.44. Found: C, 58.63; H, 3.56; N, 11.45.