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Full Paper

# Synthesis and Anticonvulsant Activity of Substituted-1,3-diazaspiro[4.5]decan-4-ones

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A series of novel spiroimidazolidinone derivatives **6a–d** and **8a–x** were synthesized and biologically evaluated for their anticonvulsant activity in the maximal electroshock seizure (MES) assay and the subcutaneous pentylenetetrazole (scPTZ) screening test. Compound **8w** was the most active derivative in the scPTZ screening test with an $ED_{50}$ value by about 5- and 83.6-fold lower than those of phenobarbital and ethosuximide as reference drugs, respectively. Most of the tested compounds exhibited moderate to weak activity in the MES screen test, except for **8a** which displayed 100% protection at 0.09 mmol/kg. Moreover, all the test compounds did not show any minimal motor impairment in the neurotoxicity test.

**Keywords:** Anticonvulsants / 1,3-Diazaspiro[4.5]decan-4-ones / Epilepsy

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## Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures [1]. These seizures are transient signs and/or symptoms of abnormal excessive neuronal activity in the brain [2]. Despite the introduction of many new antiepileptic drugs, estimates suggest that available antiepileptic drugs fail to control the seizures in about 20–30% of patients [3, 4]. Moreover, these medications are accompanied with severe adverse effects such as gingival hyperplasia, ataxia, megaloblastic anemia, and hepatotoxicity [5, 6]. Accordingly, there is an importunate demand for the development of new more effective and less toxic antiepileptic agents.

Rational studies find it difficult to discover new antiepileptic drugs due to insufficient information regarding molecular pathway of human epilepsy and complex mechanisms of action for the majority of available antiepileptic drugs [7]. Therefore, the development of new chemical entities having anticonvulsant activity is paramount and could be performed through the traditional screening investigations as well as the hybrid pharmacophoric approach [8]. This approach relies on the use of two or more pharmacophores, each with potential pharmacological activity to be combined in one molecule, aiming to produce candidates with better pharmacological profile.

Through literature survey, it was revealed that imidazolidin-4-ones represent an interesting class of compounds with respect to biological activity such as cholesterol-absorption inhibitors [9], antimalarials [10], and anxiolytics [11]. Also, certain imidazolidin-4-ones such as compound **I** (Fig. 1) exhibited anticonvulsant activity against maximal electroshock and PTZ-induced seizure tests [12]. It is worth noticing that one of the pharmacophoric groups inserted in

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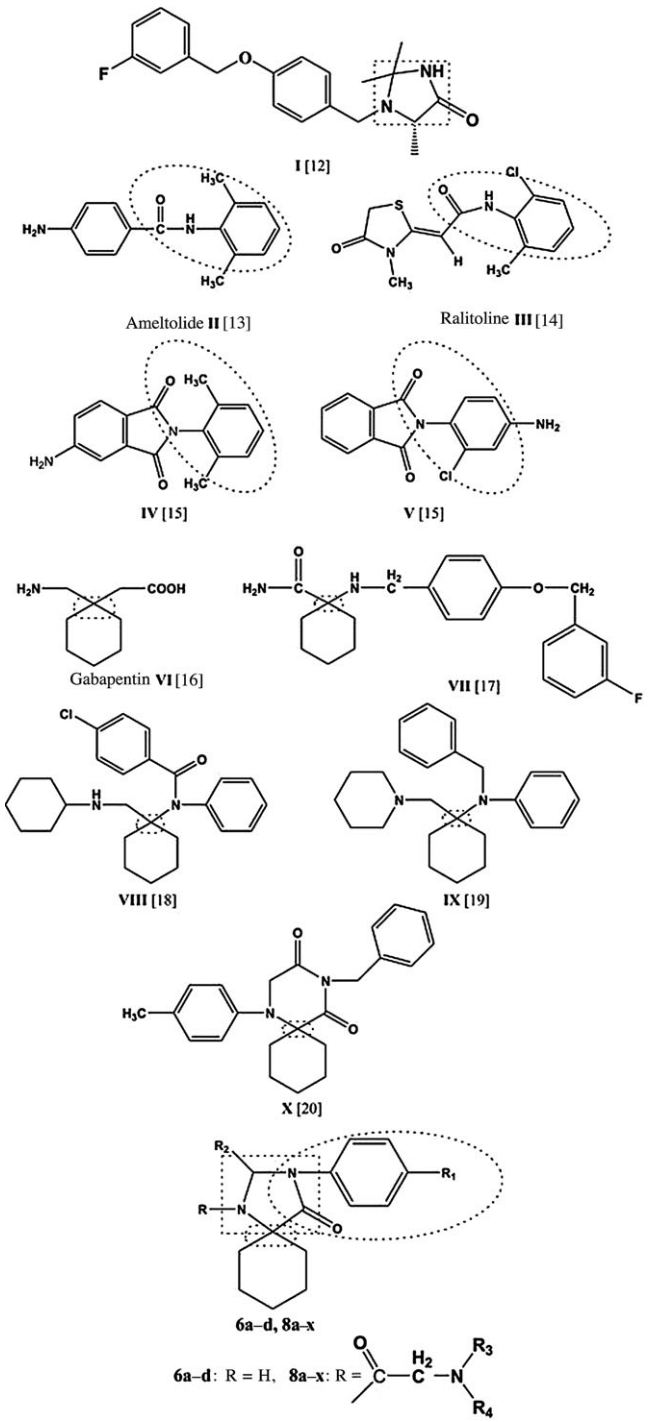


**Figure 1.** Reported anticonvulsant compounds and their structural relation to the target compounds **6a–d** and **8a–x**.

compounds studied for their anticonvulsant activity is the anilide moiety, for example, ameltolide (**II**) [13], ralitoline (**III**) [14], as well as some phthalimide derivatives **IV** and **V** [15] (Fig. 1) which exhibited potent anticonvulsant potential in maximal electroshock seizure (MES) test. Moreover, many geminally disubstituted cyclohexane derivatives have been proven to elicit anticonvulsant profile such as gabapentin (**VI**) [16]. In the same vein, Aboul-Enein et al. disclosed the preparation and the anticonvulsant potential of several geminally disubstituted cyclohexane derivatives **VII**,**VIII**, **XI**, and **X** in the PTZ and maximal electroshock-induced seizure tests [17–20]. In addition, it was reported that some compounds bearing the pharmacophoric aminoacyl moiety such as remacemide **XI** [21], safinamide **XII** [22], **XIII** [23], and **XIV** [24] possessed pronounced anticonvulsant profile (Fig. 2).

Based on the aforementioned considerations and in continuation of our research program on the design and synthesis of new anticonvulsant candidates, it was deemed valuable to prepare novel substituted-1,3-diazaspiro[4.5]-decan-4-ones having the general hybrid structures **6a–d** and **8a–x**. These newly synthesized compounds were evaluated for their anticonvulsant potential against maximal MES and the subcutaneous pentylenetetrazole (scPTZ) model in mice.

## Results and discussion

### Chemistry

The synthesis of the target compounds **6a–d** and **8a–x** and their intermediates is illustrated in Scheme 1. 1,3-Diazaspiro-[4.5]decane-2,4-dione (**2**) was synthesized from cyclohexanone (**1**) in the presence of potassium cyanide and ammonium carbonate in 50% ethanol according to the Bucherer–Bergs reaction [25]. The hydantoin **2** was subjected to hydrolysis under alkaline conditions for 72 h to yield 1-aminocyclohexanecarboxylic acid (**3**). Subsequently, protection of the amino acid **3** was successfully achieved using di-*tert*-butyl dicarbonate $(Boc)_2O$ in the presence of 3.8 M sodium hydroxide in THF to furnish the corresponding *N*-Boc derivative **4**. The desired 1-amino-*N*-substituted cyclohexanecarboxamides (**5a** and **5b**) were prepared by a previously described mixed anhydride coupling procedure which involved reaction of a *tert*-butoxycarbonyl (Boc)-protected amino acid with ethylchloroformate and an arylamine in the presence of triethylamine. Subsequent deprotection of the coupled product using dry HCl gas afforded the respective 1-amino-*N*-substituted cyclohexanecarboxamides (**5a** and **5b**). Cyclization of the latter compounds **5a** and **5b** was successfully accomplished by reacting with the appropriate aldehyde in absolute ethanol to give the respective target spiro secondary amines **6a–d**. The IR spectra showed NH bands of **6a–d** at 3291–3343 $cm^{-1}$. The formation of **6a** and **6b** was confirmed through the $^1H$ NMR spectra by the presence of $CH_2$ of the imidazolidine ring as a singlet at $\delta$ 4.77 and 4.69 ppm, respectively. Moreover, NH proton appeared at $\delta$ 2.07 and 1.99 ppm along with cyclohexyl protons and aromatic protons at $\delta$ 1.33–1.80 and 7.12–7.56 ppm, respectively. Meanwhile, in the substituted C-2 analogs **6c** and **6d** the CH proton appeared as a singlet at 5.97 and 5.95, respectively, and new signals were observed at the aromatic region. The $^{13}C$ NMR spectrum of **6a** revealed the

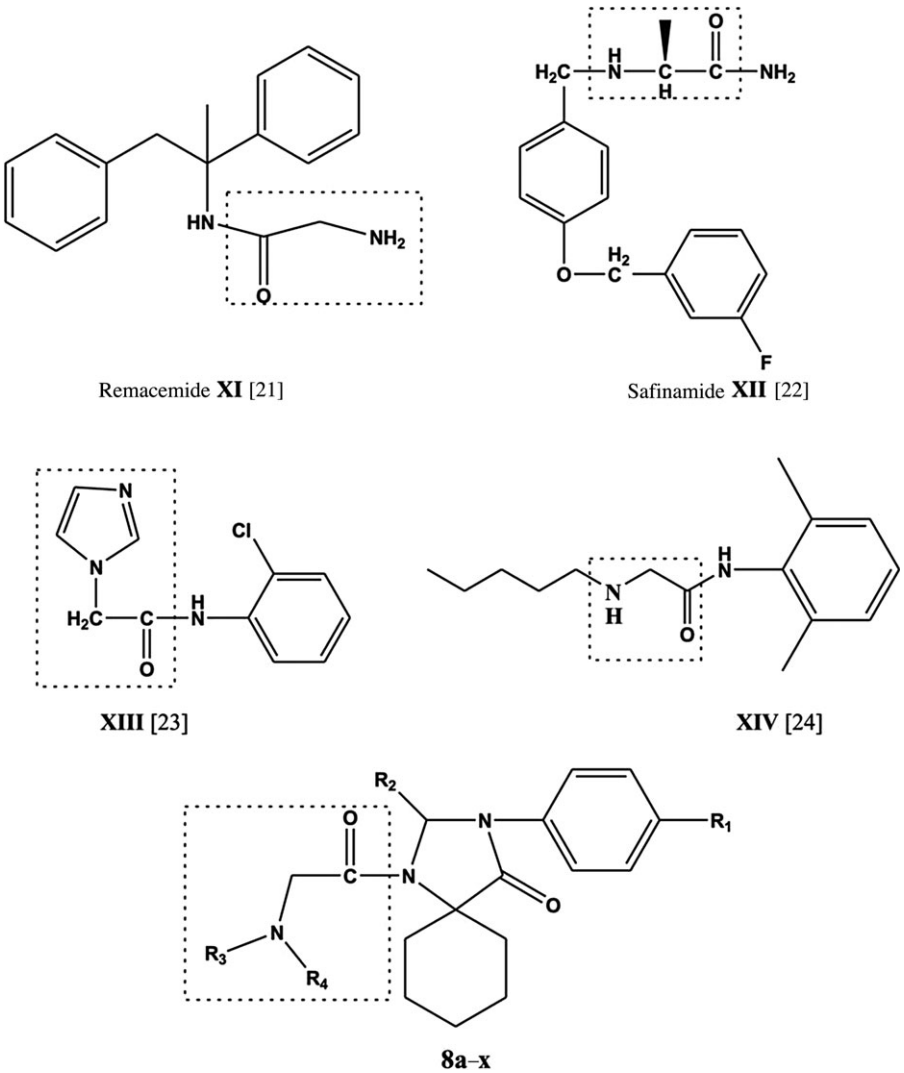


**Figure 2.** Structures of some anticonvulsants with the aminoacyl appendage and their structural relation to the target compounds **8a–x**.

presence of $CH_2$ at $\delta$ 62.38 ppm while in **6d** the CH carbon was observed downfield at $\delta$ 75.49 ppm. Subsequent chloroacetylation of **6a–d** was performed using chloroacetyl chloride in dry benzene in the presence of anhydrous potassium carbonate to obtain the corresponding chloroacetylated derivatives **7a–d**. The molecules **7a–d** showed the absence of NH in their IR and $^1$H NMR spectra as well as the existence of two carbonyl groups in $^{13}$C NMR spectra. Finally, the preparation of the target compounds **8a–x** was achieved by condensation of **7a–d** with the appropriate amine. The $^1$H NMR spectrum of the prototype compound **8a** displayed signals of ethyl group as triplet and quartet at $\delta$ 1.03–1.05 and 2.58–2.59 ppm, respectively. Also the protons of $CH_2$–C=O and $CH_2$–N appeared as singlet at $\delta$ 3.22 and 5.46 ppm, respectively. Moreover, the cyclohexyl and aromatic protons were observed at the expected chemical shifts at $\delta$ 1.3–2.76 and 7.16–7.57 ppm, respectively. The $^{13}$C NMR spectrum of **8a** confirmed the presence of 14 types of carbons where it displayed an upfield peak due to $CH_3$ of ethyl group at $\delta$ 11.78 ppm and the peak of $CH_2$ of ethyl group at $\delta$ 47.8 ppm. Furthermore, cyclohexyl carbons, $CH_2$–C=O, $CH_2$–N and aromatic carbons were found in their expected region as well as the carbonyl carbons which were observed downfield at $\delta$ 168.27 and 171.93 ppm. The structures of the new compounds in the present investigation were further confirmed by elemental analyses and the mass spectral data.

## Anticonvulsant activity

The use of predictable animal models is essential for the discovery of new bioactive candidates for treatment of epilepsy. The protocol given by the Epilepsy section of the National Institute of Neurological Disorders and Stroke

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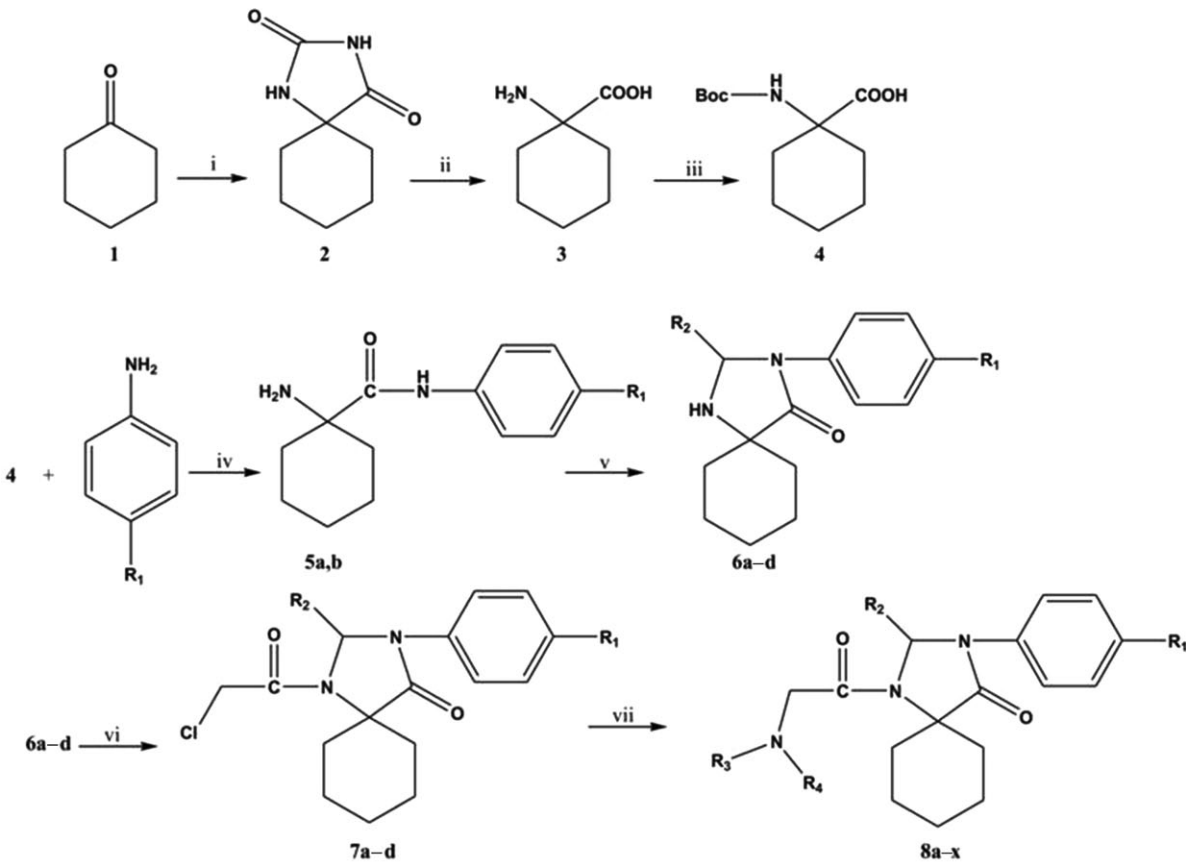


| No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|---|---|---|---|---|
| **6a** | H | H | – | | **6c** | H | phenyl | – | |
| **6b** | $CH_3$ | H | – | | **6d** | $CH_3$ | phenyl | – | |
| **8a** | H | H | $C_2H_5$ | $C_2H_5$ | **8m** | H | phenyl | $C_2H_5$ | $C_2H_5$ |
| **8b** | H | H | *n*-$C_3H_7$ | *n*-$C_3H_7$ | **8n** | H | phenyl | *n*-$C_3H_7$ | *n*-$C_3H_7$ |
| **8c** | H | H | pyrrolidin-1-yl | | **8o** | H | phenyl | pyrrolidin-1-yl | |
| **8d** | H | H | piperidin-1-yl | | **8p** | H | phenyl | piperidin-1-yl | |
| **8e** | H | H | morpholin-4-yl | | **8q** | H | phenyl | morpholin-4-yl | |
| **8f** | H | H | 1*H*-imidazol-1-yl | | **8r** | H | phenyl | 1*H*-imidazol-1-yl | |
| **8g** | $CH_3$ | H | $C_2H_5$ | $C_2H_5$ | **8s** | $CH_3$ | phenyl | $C_2H_5$ | $C_2H_5$ |
| **8h** | $CH_3$ | H | *n*-$C_3H_7$ | *n*-$C_3H_7$ | **8t** | $CH_3$ | phenyl | *n*-$C_3H_7$ | *n*-$C_3H_7$ |
| **8i** | $CH_3$ | H | pyrrolidin-1-yl | | **8u** | $CH_3$ | phenyl | pyrrolidin-1-yl | |
| **8j** | $CH_3$ | H | piperidin-1-yl | | **8v** | $CH_3$ | phenyl | piperidin-1-yl | |
| **8k** | $CH_3$ | H | morpholin-4-yl | | **8w** | $CH_3$ | phenyl | morpholin-4-yl | |
| **8l** | $CH_3$ | H | 1*H*-imidazol-1-yl | | **8x** | $CH_3$ | phenyl | 1*H*-imidazol-1-yl | |

**Scheme 1.** General method for the synthesis of the target compounds **6a–d** and **8a–x**. Reagents and conditions: (i) KCN, $(NH_4)_2CO_3$, 50% ethanol, 55°C, 24 h; (ii) $Ba(OH)_2$, $H_2O$, reflux, 72 h; (iii) $(Boc)_2O$, 3.8 M NaOH, THF, r.t., 15 h; (iv) a) $Et_3N$, EtOCOCl, THF, r.t., 18 h; b) HCl gas, DCM; (v) $R_2CHO$, ethanol, reflux, 18 h; (vi) $ClCH_2COCl$, anhyd. $K_2CO_3$, benzene, reflux, 18 h; (vii) appropriate amine, toluene, 90°C, 20 h.

(NINIDS) allotted the use of the standard procedure adopted by the Antiepileptic Drug Development (ADD) program named "the gold standard screen" [26], which includes three *in vivo* animal models: (i) the scPTZ screen, (ii) the MES screen, and (iii) the neurotoxicity screen. The scPTZ screen identifies compounds that elevate seizure threshold while MES screen evaluates the ability of the test compound to prevent seizure spread and the neurotoxicity identifies the minimal motor impairment. Moreover, compounds exhibited 100% protection against induced seizures were subjected to median effective dose ($ED_{50}$) evaluation.

The initial anticonvulsant activity (Phase I screening) of the newly synthesized compounds **6a–d** and **8a–x** expressed as % protection as well as their neurotoxicity are presented in Table 1. The obtained data revealed that all the compounds were effective in scPTZ screen while most of them were effective in MES screen. Concerning the scPTZ screen, in the 2-unsubstituted-3-aryl-1,3-diazaspiro[4.5]decan-4-ones series (**6a–b** and **8a–l**) where $R_2 = H$, compounds **6a** ($R_1 = H$) ($ED_{50} = 0.1$ mmol/kg), **8b** ($R_1 = H$, $R_3 = R_4 = n\text{-}C_3H_7$) ($ED_{50} = 0.064$ mmol/kg), **8c** ($R_1 = H$, $R_3$, $R_4$ = pyrrolidin-1-yl) ($ED_{50} = 0.058$ mmol/kg), **8f** ($R_1 = H$, $R_3$, $R_4$ = 1*H*-imidazol-1-yl) ($ED_{50} = 0.07$ mmol/kg), and **8l** ($R_1 = CH_3$, $R_3$, $R_4$ = 1*H*-imidazol-1-yl) ($ED_{50} = 0.07$ mmol/kg) were the most potent congeners in this series displaying 100% protection against PTZ-induced seizures at dose levels of 0.08–0.147 mmol/kg. These compounds were nearly equipotent or less potent than phenobarbital ($ED_{50} = 0.056$ mmol/kg) and most of them were more potent than ethosuximide ($ED_{50} = 0.92$ mmol/kg). Moreover, compounds **6b** ($R_1 = CH_3$), **8a** ($R_1 = H$, $R_3 = R_4 = C_2H_5$), **8e** ($R_1 = H$, $R_3$, $R_4$ = morpholin-4-yl), **8h** ($R_1 = CH_3$, $R_3 = R_4 = n\text{-}C_3H_7$), **8i** ($R_1 = CH_3$, $R_3$, $R_4$ = pyrrolidin-1-yl), and **8k** ($R_1 = CH_3$, $R_3$, $R_4$ = morpholin-4-yl) exerted anticonvulsant potential of 83% at dose levels of 0.11, 0.09, 0.092, 0.067, 0.078, and 0.08 mmol/kg, respectively. The different congeners of this series showed anticonvulsant activity in the following decreasing order: **8c** > **8b** > **8l** = **8f** > **6a** > **8h** > **8i** = **8k** > **8a** = **8e** > **6b** > **8d** = **8j** > **8g**.

In addition, in the 2-phenyl-3-aryl-1,3-diazaspiro[4.5]-decan-4-ones series (**6c–d** and **8m–x**) where $R_2$ = phenyl, compounds **6c** ($R_1 = H$) ($ED_{50} = 0.03$ mmol/kg), **8o** ($R_1 = H$, $R_3$, $R_4$ = pyrrolidin-1-yl) ($ED_{50} = 0.016$ mmol/kg), and **8w** ($R_1 = CH_3$, $R_3$, $R_4$ = morpholin-4-yl) ($ED_{50} = 0.011$ mmol/kg) showed 100% anticonvulsant protection compared to the reference drugs phenobarbital ($ED_{50} = 0.056$ mmol/kg) and ethosuximide ($ED_{50} = 0.92$ mmol/kg). Those compounds exhibited 1.8-, 3.5-, and 5-fold more potent anticonvulsant effect than phenobarbital as well as 30.6-, 57.5-, and 83.6-fold more potent than ethosuximide, respectively. On the other hand, **6d** ($R_1 = CH_3$), **8m** ($R_1 = H$, $R_3 = R_4 = C_2H_5$), **8n** ($R_1 = H$, $R_3 = R_4 = n\text{-}C_3H_7$), **8q** ($R_1 = H$, $R_3$, $R_4$ = morpholin-4-yl), **8r** ($R_1 = H$, $R_3$, $R_4$ = 1*H*-imidazol-1-yl), **8t** ($R_1 = CH_3$, $R_3 = R_4 = n\text{-}C_3H_7$), **8u** ($R_1 = CH_3$, $R_3$, $R_4$ = pyrrolidin-1-yl), and **8x** ($R_1 = CH_3$, $R_3$, $R_4$ = 1*H*-imidazol-1-yl) displayed 83% anticonvulsant activity at 0.087, 0.033, 0.035, 0.025, 0.033, 0.035, 0.046, and 0.032 mmol/kg dose levels, respectively. The anticonvulsant potential of the different congeners of this series was arranged in the following decreasing order: **8w** > **8o** > **6c** > **8q** > **8m** = **8n** = **8r** = **8t** = **8x** > **8u** > **6d** > **8s** = **8v** > **8p**.

Regarding the MES test, the dose which exerted the maximum anticonvulsant protection in the scPTZ screening has been selected. In this screening test, compound **8a** ($ED_{50} = 0.075$ mmol/kg) was the most active one. It exhibited 100% protection at dose 0.09 mmol/kg and possessed less potent effect than the reference drug diphenylhydantoin ($ED_{50} = 0.034$ mmol/kg) by about twofold. Compound **8d** ($R_1 = H$, $R_3$, $R_4$ = piperidin-1-yl) (0.092 mmol/kg) displayed 83% protection effect, while compounds **8c**, **8q**, and **8r** exhibited equipotent anticonvulsant effect of 66%. On the other hand, compounds **6c**, **8m**, and **8x** were devoid of anticonvulsant activity, meanwhile the rest of the compounds exhibited 16–50% protection (Table 1**)**.

Interestingly, in the neurotoxicity screen test, all the compounds did not show any minimal motor impairment at the maximum administrated dose.

It could be revealed from the scPTZ screening results that in the unsubstituted secondary amines (**6a–d**), compound **6c** was the most active one while removal of phenyl group from C-2 of the imidazolidine ring as in compounds **6a** and **6b** decreased the activity. Introduction of aminoacyl moeity on N-1 of the imidazolidine ring of **6a** and **6c** greatly affected the anticonvulsant activities in **8a–f** and **8m–r**. In the compounds having either diethylamino group or saturated heterocyclic amine, for example, pyrrolidine, piperidine, or morpholine, the presence of phenyl moeity on C-2 of the imidazolidine ring (**8m**, **8o**, **8p**, and **8q**) augmented the anticonvulsant activity against scPTZ-induced seizures more than the unsubstituted C-2 series (**8a**, **8c**, **8d**, and **8e**). Meanwhile, in the compounds having slightly longer aliphatic amine chain, that is, di-*n*-propylamino group or unsaturated heterocyclic amine, that is, imidazole moeity, the unsubstituted C-2 derivatives **8b** and **8f** were more active than the 2-phenyl analogs **8n** and **8r**. Also, upon introduction of the aminoacyl moeity to **6b** and **6d**, their 2-phenyl analogs **8s–w** were found to be more active than the C-2 unsubstituted ones **8g–k** except in the imidazole derivatives where **8l** is more potent than **8x**. From the above-mentioned data, it could be observed that in most derivatives the presence of phenyl group in C-2 enhanced the activity of the tested compounds in the scPTZ screen more than the unsubstituted ones. Concerning the relation between the substitution pattern in the anilide moeity of **6a–d** and the anticonvulsant activity against scPTZ screen, it was found that the introduction of methyl substitution at *para* position of the aromatic ring attenuated the activity from 100% in **6a** and **6c** to 83% in **6b** and **6d**, meanwhile the *p*-methyl substitution on the anilide moeity of **8a–x** does not clearly affect the anticonvulsant activity against scPTZ-induced seizures.

It was proven that PTZ-induced seizures could be controlled by drugs that reduce T-type $Ca^{2+}$ currents and also by those which enhance gamma amino butyric acid type A ($GABA_A$) receptor-mediated inhibitory neurotransmission [27–30]. As

**Table 1. Anticonvulsant activity and neurotoxicity of compounds 6a–d and 8a–x as well as the reference drugs against pentylenetetrazole and electro-induced seizures in adult male albino mice.**

| Compd. | Dose[a] mg/kg (mmol/kg) | Maximum % protection | | Neurotoxicity[b] | $ED_{50}$ mg/kg (confidence limits) $ED_{50}$ mmol/kg (confidence limits) |
|---|---|---|---|---|---|
| | | scPTZ | MES | | |
| **6a** | 34 (0.147) | 100 | 50 | 0/6 | 23 (27.67–19.12)<br>0.1 (0.12–0.083) |
| **6b** | 28 (0.11) | 83 | 16 | 0/6 | nd |
| **8a** | 31 (0.09) | 83 | 100 | 0/6 | 26 (28.29–23.89)[c]<br>0.075 (0.082–0.069) |
| **8b** | 30 (0.08) | 100 | 33 | 0/6 | 24 (26.29–21.90)<br>0.064 (0.071–0.059) |
| **8c** | 28 (0.08) | 100 | 66 | 0/6 | 20 (24.42–16.38)<br>0.058 (0.071–0.48) |
| **8d** | 33 (0.092) | 66 | 83 | 0/6 | nd |
| **8e** | 33 (0.092) | 83 | 16 | 0/6 | nd |
| **8f** | 37 (0.11) | 100 | 16 | 0/6 | 24 (28.86–19.96)<br>0.07 (0.085–0.059) |
| **8g** | 28 (0.078) | 50 | 50 | 0/6 | nd |
| **8h** | 26 (0.067) | 83 | 33 | 0/6 | nd |
| **8i** | 28 (0.078) | 83 | 16 | 0/6 | nd |
| **8j** | 36 (0.097) | 66 | 50 | 0/6 | nd |
| **8k** | 30 (0.08) | 83 | 16 | 0/6 | nd |
| **8l** | 32 (0.09) | 100 | 33 | 0/6 | 25 (28.53–21.91)<br>0.07 (0.081–0.062) |
| **6c** | 18 (0.058) | 100 | – | 0/6 | 9 (11.35–7.135)<br>0.03 (0.037–0.023) |
| **6d** | 28 (0.087) | 83 | 33 | 0/6 | nd |
| **8m** | 15 (0.033) | 83 | – | 0/6 | nd |
| **8n** | 15 (0.035) | 83 | 50 | 0/6 | nd |
| **8o** | 10 (0.023) | 100 | 50 | 0/6 | 7 (9.11–5.38)<br>0.016 (0.022–0.013) |
| **8p** | 16 (0.037) | 66 | 33 | 0/6 | nd |
| **8q** | 11 (0.025) | 83 | 66 | 0/6 | nd |
| **8r** | 14 (0.033) | 83 | 66 | 0/6 | nd |
| **8s** | 12 (0.028) | 66 | 33 | 0/6 | nd |
| **8t** | 16 (0.035) | 83 | 16 | 0/6 | nd |
| **8u** | 20 (0.046) | 83 | 33 | 0/6 | nd |
| **8v** | 12 (0.026) | 66 | 16 | 0/6 | nd |
| **8w** | 11 (0.024) | 100 | 50 | 0/6 | 5 (7.69–3.25)<br>0.011 (0.017–0.007) |
| **8x** | 14 (0.032) | 83 | – | 0/6 | nd |
| Phenobarbital | 30 (0.13) | 100 | – | nd | 13.2 (15.90–6.80)<br>0.056 (0.068–0.029) |
| Ethosuximide | 150 (1.06) | 100 | – | nd | 130 (150–111)<br>0.92 (1.06–0.78) |
| Diphenylhydantoin | 45 (0.16) | – | 100 | nd | 9.5 (7.8–11.6)<br>0.037 (0.03– 0.046) |

–, indicates the absence of anticonvulsant activity at the tested dose level; nd, not determined.
[a] The minimal dose which exerted the maximum anticonvulsant potential.
[b] Rotarod test: Number of animals exhibiting neurotoxicity/number of animals tested.
[c] $ED_{50}$ in MES screen.

mentioned above, as all the new screened compounds were found to control the seizures induced by PTZ, thus this result might speculate that these compounds probably exhibit their anticonvulsant potential through GABA activation or influence on $Ca^{2+}$ channels.

## Conclusion

The anticonvulsant potential of certain substituted-1,3-diazaspiro[4.5]decan-4-ones **6a–d** and **8a–x** was investigated. Most of the compounds displayed 50–100% anticonvulsant activity in the scPTZ screen at a dose range from 0.023 to 0.147 mmol/kg. The most potent compounds in the scPTZ screen were **8w** ($ED_{50} = 0.011$ mmol/kg), **8o** ($ED_{50} = 0.016$ mmol/kg), and **6c** ($ED_{50} = 0.03$ mmol/kg). They possessed more potent activities which reached 1.8-, 3.5-, and 5-fold than phenobarbital, and 30.6-, 57.5-, and 83.6-fold than ethosuximide, respectively. Compound **8a** is the only compound which exhibited 100% protection in the MES screen with an $ED_{50}$ of 0.075 mmol/kg. None of the test compounds showed any minimal motor impairment at the maximum administered dose in the neurotoxicity screen. These compounds could be regarded as promising candidates as antiepileptic drugs.

## Experimental

### Chemistry

Melting points (uncorrected) were determined by using Electrothermal Capillary melting point apparatus. Infrared (IR) spectra were recorded in KBr discs using a Jasco FT/IR-6100 spectrometer. $^1$H NMR and $^{13}$C NMR spectra were carried out on Jeol ECA 500 MHz spectrometer and Bruker 300 MHz using TMS as internal standard and chemical shift values were recorded in ppm on $\delta$ scale. EI/MS measurements were made using Thermo Scientific ISQ single quadrupole mass spectrometer at 70 eV ionization energy. Elemental analyses were carried out in Microanalytical Unit, National Research Centre and the results were within $\pm$0.4% of the theoretical value. Monitoring of reactions was achieved by TLC on silica gel plates (Merck, 60F 254) and visualization was performed by illumination with UV light source (254 nm). Column chromatography was carried out on silica gel 60 purchased from Merck.

*Synthesis of 1,3-diazaspiro[4.5]decane-2,4-dione (**2**)*
Prepared as reported in Ref. [25].

*Synthesis of 1-aminocyclohexanecarboxylic acid (**3**)*
Prepared as reported in Ref. [31].

*Synthesis of 1-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylic acid (**4**)*
To a solution of 40 mL, 3.8 M NaOH was added (9.4 g, 0.066 mol) of **3** and 50 mL tetrahydrofuran. The reaction mixture was cooled to 0–5°C and 14.5 g (0.066 mol) of di-*tert*-butyl dicarbonate $(Boc)_2O$ was added portionwise. The reaction mixture was stirred at room temperature for 15 h. The pH was adjusted to 3 with 2 M HCl, extracted with DCM, dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure to give 10.4 g (65%) yield of **4** as white solid, m.p. 176–178°C (Ref. [24], m.p. 177–178°C).

*General procedure for synthesis of 1-amino-N-substituted cyclohexanecarboxamides (**5a** and **5b**)*
A mixture of 4.86 g (0.02 mol) 1-[(*tert*-butoxycarbonyl)amino]-cyclohexanecarboxylic acid (**4**) and 2.02 g (0.02 mol) of triethylamine in 100 mL dry THF (100 mL) was stirred at 0–5°C. After stirring for 5 min, ethylchloroformate (2.16 g, 0.02 mol) was added in one portion and immediately a white precipitate formed. The reaction was allowed to proceed for an additional 20 min, then a solution of 0.02 mol of either aniline or *p*-toluidine in 20 mL THF was added dropwise. The reaction mixture was stirred for an additional 18 h at the ambient temperature and the precipitated triethylamine hydrochloride was filtered off. The residue formed after evaporation of solvent under reduced pressure was dissolved in 100 mL of DCM and subjected to deprotection using hydrogen chloride gas for 4 h followed by basification with 10% $Na_2CO_3$, extraction with DCM, and crystallization from a mixture of petroleum ether (40–60)/ethyl acetate to give **5a** and **5b** as white crystals.

*1-Amino-N-phenylcyclohexanecarboxamide (**5a**)*
M.p. 98–100°C; yield 65%; IR (KBr, $cm^{-1}$): 3402–3317 ($NH_2$), 3229 (NH) and 1672 (C=O, amide); MS (EI) *m/z* (%): 218 (21) ($M^+$+1), 98 (100); $^1$H NMR ($CDCl_3$): 1.24–2.02 (m, 12H, cyclohexyl protons, $NH_2$), 7.02–7.6 (m, 5H, $H_{ar.}$), 10.09 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$): 21.33, 25.29, 34.43 ($5CH_2$–cyclohexyl), 57.89 (C–cyclohexyl), 119.28, 123.79, 129, 138.35 (aromatic carbons), 176.4 (C=O, amide). Anal. calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.72; H, 8.13; N, 13.12.

*1-Amino-N-(4-methylphenyl)cyclohexanecarboxamide (**5b**)*
M.p. 102–104°C; yield 63%; IR (KBr, $cm^{-1}$): 3395–3334 ($NH_2$), 3218 (NH) and 1664 (C=O, amide); MS (EI) *m/z* (%): 233 (4) ($M^+$+1), 98 (100); $^1$H NMR ($CDCl_3$): 1.32–2.1 (m, 12H, cyclohexyl protons, $NH_2$), 2.31 (s, 3H, $CH_3$), 7.11–7.13 (d, $J = 7.5$ Hz, 2H, $H_{ar.}$), 7.5–7.52 (d, $J = 8$ Hz, 2H, $H_{ar.}$), 10 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$): 20.87, 21.29, 25.21, 34.4 ($5CH_2$–cyclohexyl, $CH_3$), 57.81 (C–cyclohexyl), 118.98, 129.13, 133.19, 135.75 (aromatic carbons), 175.98 (C=O, amide); Anal. calcd. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.02; H, 9.03; N, 12.00.

*General procedure for the synthesis of 3-aryl-1,3-diazaspiro[4.5]decan-4-one (**6a** and **6b**) and 2-phenyl-3-aryl-1,3-diazaspiro[4.5]decan-4-one (**6c** and **6d**)*
A mixture of 0.0128 mol of 1-amino-*N*-substituted cyclohexanecarboxamide**s 5a** or **5b**, 0.0141 mol of paraformaldehyde or benzaldehyde and one drop of piperidine in 25 mL

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absolute ethanol were refluxed overnight. The solvent was removed under vacuum, the residual oil was washed with a solution of aqueous sodium bisulphite, extracted with DCM, dried over $Na_2SO_4$, and evaporated under reduced pressure to give crude solid which was purified by column chromatography using silica gel as a stationary phase and a mixture of petroleum ether (40–60)/ethyl acetate (8:2) as a mobile phase.

*3-Phenyl-1,3-diazaspiro[4.5]decan-4-one (**6a**)*
White solid; m.p. 144–146°C; yield 80%; IR (KBr, $cm^{-1}$): 3303 (NH) and 1685 (C=O, amide); MS (EI) *m/z* (%): 230 (11) ($M^+$), 98 (100); $^1H$ NMR ($CDCl_3$): 1.55–1.75 (m, 10H, cyclohexyl protons), 2.07 (s, 1H, NH), 4.77 (s, 2H, $CH_2$–NH), 7.12–7.56 (m, 5H, $H_{ar.}$); $^{13}C$ NMR ($CDCl_3$): 21.71, 25.41, 31.88 ($5CH_2$–cyclohexyl), 62.38 ($CH_2$–NH), 63.45 (C–cyclohexyl), 118.73 ($CH_{ar}$), 124.5 ($CH_{ar}$), 129.09 ($CH_{ar}$), 138.23 ($C_{ar}$), 176.9 (C=O, amide). Anal. calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.90; H, 7.65; N, 11.93.

*3-(4-Methylphenyl)-1,3-diazaspiro[4.5]decan-4-one (**6b**)*
White solid; m.p. 158–160°C; yield 82%; IR (KBr, $cm^{-1}$): 3291 (NH) and 1679 (C=O, amide); MS (EI) *m/z* (%): 244 (12) ($M^+$), 98 (100); $^1H$ NMR ($CDCl_3$): 1.33–1.80 (m, 10H, cyclohexyl protons), 1.99 (s, 1H, NH), 2.31 (s, 3H, $CH_3$), 4.69 (s, 2H, $CH_2$–NH), 7.15–7.46 (m, 4H, $H_{ar.}$); $^{13}C$ NMR ($CDCl_3$): 20.92, 21.7, 25.37, 31.86 ($5CH_2$–cyclohexyl, $CH_3$), 62.46, 63.37 (C–cyclohexyl, $CH_2$–NH), 118.88, 129.51, 134.17, 135.66 (aromatic carbons), 176.72 (C=O, amide). Anal. calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.51; H, 7.91; N, 11.09.

*2,3-Diphenyl-1,3-diazaspiro[4.5]decan-4-one (**6c**)*
White solid; m.p. 114–116°C; yield 77%; IR (KBr, $cm^{-1}$): 3343 (NH) and 1686 (C=O, amide); MS (EI) *m/z* (%): 306 (26) ($M^+$), 187 (100); $^1H$ NMR ($CDCl_3$): 1.25–2.12 (m, 11H, cyclohexyl protons, NH), 5.97 (s, 1H, CH–NH), 7.22–7.34 (m, 10H, $H_{ar.}$); $^{13}C$ NMR ($CDCl_3$): 21.57, 21.79, 25.33, 31.55, 34.92 ($5CH_2$–cyclohexyl), 63.02, 75.45 (C–cyclohexyl, CH–NH), 122.26, 125.15, 127.07, 128.77, 129.14, 129.23, 137.4, 139.03 (aromatic carbons), 177.68 (C=O, amide). Anal. calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.13; H, 6.84; N, 8.99.

*3-(4-Methylphenyl)-2-phenyl-1,3-diazaspiro[4.5]decan-4-one (**6d**)*
White solid; m.p. 126–128°C; yield 73%; IR (KBr, $cm^{-1}$): 3305 (NH) and 1678 (C=O, amide); MS (EI) *m/z* (%): 320 (11) ($M^+$), 187 (100); $^1H$ NMR ($CDCl_3$): 1.39–2.15 (m, 11H, cyclohexyl protons, NH), 2.24 (s, 3H, $CH_3$), 5.95 (s, 1H, CH–NH), 7.04–7.06 (d, $J = 7.5$ Hz, 2H, $H_{ar.}$), 7.22–7.23 (d, $J = 8$ Hz, 2H, $H_{ar.}$), 7.3–7.4 (m, 5H, $H_{ar.}$); $^{13}C$ NMR ($CDCl_3$): 20.9, 21.53, 21.74, 25.29, 31.48, 34.88 ($5CH_2$–cyclohexyl, $CH_3$), 62.89 (C–cyclohexyl), 75.48 (CH–NH), 122.28, 127.05, 129.04, 129.12, 129.32, 134.73, 134.8, 139.14 (aromatic carbons), 177.59 (C=O, amide). Anal. calcd. for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.41; H, 7.91; N, 8.58.

*General procedure for synthesis of 1-(chloroacetyl)-3-aryl-1,3-diazaspiro[4.5]decan-4-ones (**7a** and **7b**) and 1-(chloroacetyl)-2-phenyl-3-aryl-1,3-diazaspiro[4.5]decan-4-ones (**7c** and **7d**)*
Chloroacetyl chloride (6.7 g, 0.06 mol) was added dropwise to a mixture of the appropriate amine **6a–d** (0.05 mol) and anhydrous $K_2CO_3$ (8.2 g, 0.06 mol) in 50 mL dry benzene at 0–5°C. The reaction mixture was refluxed for 18 h, after cooling to room temperature, the solvent was removed under vacuum washed with 10% $Na_2CO_3$, extracted with DCM, dried over anhydrous $Na_2SO_4$, evaporated under reduced pressure, and crystallized from a mixture of petroleum ether (40–60)/ethyl acetate to give **7a–d** as white crystals.

*1-(Chloroacetyl)-3-phenyl-1,3-diazaspiro[4.5]decan-4-one (**7a**)*
White crystals; m.p. 156–158°C; yield 79%; IR (KBr, $cm^{-1}$): 1678 (C=O, amide); MS (EI) *m/z* (%): 307 (42) ($M^+$+1), 309 (14), 271 (100); $^1H$ NMR ($CDCl_3$): 1.26–2.68 (m, 10H, cyclohexyl protons), 4.21 (s, 2H, $CH_2$–Cl), 5.3 (s, 2H, $CH_2$–N), 7.36–7.56 (m, 5H, $H_{ar.}$); $^{13}C$ NMR ($CDCl_3$): 21.78, 24.33, 29.74 ($5CH_2$–cyclohexyl), 42.45 ($CH_2$–Cl), 61.5, 64.43 (C–cyclohexyl, $CH_2$–N), 120.17, 125.95, 129.37, 136.33 (aromatic carbons), 163.48 (C=O, amide), 171.41 (C=O, amide). Anal. calcd. for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.41; H, 5.87; N, 8.99.

*1-(Chloroacetyl)-3-(4-methylphenyl)-1,3-diazaspiro[4.5]-decan-4-one (**7b**)*
White crystals; m.p. 156–158°C; yield 76%; IR (KBr, $cm^{-1}$): 1697 (C=O, amide) and 1669 (C=O, amide); MS (EI) *m/z* (%): 320 (2.71) ($M^+$), 322 (0.91), 91 (100); $^1H$ NMR ($CDCl_3$): 1.27–2.14 (m, 8H, cyclohexyl protons), 2.38 (s, 3H, $CH_3$), 2.71–2.75 (m, 2H, cyclohexyl protons), 4.06 (s, 2H, $CH_2$–Cl), 5.33 (s, 2H, $CH_2$–N), 7.23–7.51 (m, 4H, $H_{ar.}$); $^{13}C$ NMR ($CDCl_3$): 20.94, 21.73, 24.28, 29.7 ($5CH_2$–cyclohexyl, $CH_3$), 42.28 ($CH_2$–Cl), 61.60, 64.34 (C–cyclohexyl, $CH_2$–N), 120.24, 129.83, 133.68, 135.82 (aromatic carbons), 163.44 (C=O, amide), 171.34 (C=O, amide). Anal. calcd. for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.41; H, 6.42; N, 8.56.

*1-(Chloroacetyl)-2,3-diphenyl-1,3-diazaspiro[4.5]decan-4-one (**7c**)*
White crystals; m.p. 194–196°C; yield 77%; IR (KBr, $cm^{-1}$): 1684 (C=O, amide); MS (EI) *m/z* (%): 382 (3) ($M^+$), 384 (1), 28 (100); $^1H$ NMR ($CDCl_3$): 1.35–2.24 (m, 10H, cyclohexyl protons), 3..46–3.74 (m, 2H, $CH_2$–Cl), 6.52 (s, 1H, CH–N), 7.23–7.29 (m, 10H, $H_{ar.}$); $^{13}C$ NMR ($CDCl_3$): 22.04, 22.31, 24.39, 29.92, 31.49 ($5CH_2$–cyclohexyl), 43.64 ($CH_2$–Cl), 64.55, 75.73 (C–cyclohexyl, CH–N), 126.52, 127.32, 127.68, 129.21, 129.4, 130.18, 134.43, 137.56 (aromatic carbons), 164.71 (C=O, amide), 171.25 (C=O, amide). Anal. calcd. for $C_{22}H_{23}ClN_2O_2$: C, 69.01; H, 6.05; N, 7.32. Found: C, 68.72; H, 5.68; N, 7.14.

*1-(Chloroacetyl)-3-(4-methylphenyl)-2-phenyl-1,3-diazaspiro[4.5]decan-4-one (**7d**)*
White crystals; m.p. 174–176°C; yield 79%; IR (KBr, $cm^{-1}$): 1680 (C=O, amide); MS (EI) *m/z* (%): 396 (17) ($M^+$), 398 (5), 361

(100); $^1$H NMR ($CDCl_3$): 1.29–1.82 (m, 8H, cyclohexyl protons), 2.29 (s, 3H, $CH_3$), 2.93 (m, 2H, cyclohexyl protons), 3.5–3.81 (m, 2H, $CH_2$–Cl), 6.51 (s, 1H, CH–N), 6.94–7.35 (m, 9H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.07, 21.99, 22.24, 24.33, 29.98, 31.88 (5$CH_2$–cyclohexyl, $CH_3$), 43.54 ($CH_2$–Cl), 64.41, 75.21 (C–cyclohexyl, CH–N), 126.31, 127.27, 129.3, 129.79, 129.4, 130.04, 131.66, 137.66 (aromatic carbons), 164.65 (C=O, amide), 171.22 (C=O, amide). Anal. calcd. for $C_{23}H_{25}ClN_2O_2$: C, 69.60; H, 6.35; N, 7.06. Found: C, 69.45; H, 6.02; N, 6.81.

*General procedure for synthesis of 1-(aminoacetyl)-3-aryl-1,3-diazaspiro[4.5]decan-4-ones (**8a–l**) and 1-(aminoacetyl)-2-phenyl-3-aryl-1,3-diazaspiro[4.5]decan-4-ones (**8m–x**)*

A mixture of 0.002 mol of the chloroacetylated derivative **7a–d** and 0.01 mol of the appropriate amine in 40 mL toluene was heated at 90°C for 20 h. After cooling to room temperature, the solvent was removed under reduced pressure to give a residual oil which was washed with water and extracted with DCM to give the target compounds **8a–x** in crude form which were purified by crystallization or by column chromatography using silica gel as a stationary phase.

*1-[(Diethylamino)acetyl]-3-phenyl-1,3-diazaspiro[4.5]-decan-4-one (**8a**)*

Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 6:4 as a mobile phase, yield 75%, m.p. 98−100°C, IR (KBr, cm$^{-1}$): 1711 (C=O, amide) and 1646 (C=O, amide); MS (EI) *m/z* (%): 344 (0.75) ($M^+$+1), 86 (100); $^1$H NMR ($CDCl_3$): 1.03–1.05 (t, $J$ = 6.7 Hz, 6H, ($CH_2$–$CH_3$)$_2$), 1.3–2.06 (m, 8H, cyclohexyl protons), 2.58–2.59 (q, $J$ = 6.7 Hz, 4H, ($CH_2$–$CH_3$)$_2$), 2.71–2.76 (m, 2H, cyclohexyl protons), 3.22 (s, 2H,$CH_2$–C=O), 5.46 (s, 2H, $CH_2$–N), 7.16 (m, 1H, $H_{ar.}$), 7.36–7.57 (m, 4H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 11.78 (2$CH_2$–$CH_3$), 21.87, 24.42, 29.78 (5$CH_2$–cyclohexyl), 47.8 (2$CH_2$–$CH_3$), 58.95 ($CH_2$–C=O), 61.56, 64.12 (C–cyclohexyl, $CH_2$–N), 119.6, 125.4, 129.27, 136.85 (aromatic carbons), 168.27 (C=O, amide), 171.93 (C=O, amide). Anal. calcd. for $C_{20}H_{29}N_3O_2$: C, 69.94; H, 8.51; N, 12.23. Found: C, 69.59; H, 8.49; N, 12.02.

*1-[(Dipropylamino)acetyl]-3-phenyl-1,3-diazaspiro[4.5]-decan-4-one (**8b**)*

Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 7:3 as a mobile phase, yield 70%, m.p. 80−82°C, IR (KBr, cm$^{-1}$): 1714 (C=O, amide) and 1647 (C=O, amide); MS (EI) *m/z* (%): 371 (15) ($M^+$), 114 (100); $^1$H NMR ($CDCl_3$): 0.89–0.92 (t, $J$ = 7.5 Hz, 6H, ($CH_2$–$CH_2$–$CH_3$)$_2$), 1.33–1.35 (m, 1H, cyclohexyl proton), 1.47–1.55 (m, 4H, ($CH_2$–$CH_2$–$CH_3$)$_2$), 1.65–1.78 (m, 5H, cyclohexyl protons), 2.09–2.11 (m, 2H, cyclohexyl protons), 2.48–2.51 (t, $J$ = 7.5 Hz, 4H, ($CH_2$–$CH_2$–$CH_3$)$_2$), 2.76–2.82 (m, 2H, cyclohexyl protons), 3.27 (s, 2H,$CH_2$–C=O), 5.52 (s, 2H, $CH_2$–N), 7.19–7.22 (m, 1H, $H_{ar.}$), 7.39–7.42 (m, 2H, $H_{ar.}$), 7.59–7.61 (m, 2H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 11.98 (2$CH_2$–$CH_2$–$CH_3$), 19.98, 21.8, 24.35, 29.72 (2$CH_2$–$CH_2$–$CH_3$, 5$CH_2$–cyclohexyl) 56.54 (2$CH_2$–$CH_2$–$CH_3$), 60.64, 61.49, 64.04 ($CH_2$–C=O, $CH_2$–N, C–cyclohexyl), 119.64, 125.34, 129.18, 136.8 (aromatic carbons), 168.18 (C=O, amide), 171.88 (C=O, amide). Anal. calcd. for $C_{22}H_{33}N_3O_2$: C, 71.12; H, 8.95; N, 11.31. Found: C, 70.82; H, 9.15; N, 11.29.

*3-Phenyl-1-(pyrrolidin-1-ylacetyl)-1,3-diazaspiro[4.5]-decan-4-one (**8c**)*

Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 7:3 as a mobile phase, yield 60%, m.p. 112−114°C, IR (KBr, cm$^{-1}$): 1708 (C=O, amide) and 1660 (C=O, amide); MS (EI) *m/z* (%): 342 (5.43) ($M^+$+1), 84 (100); $^1$H NMR ($CDCl_3$): 1.23–2.06 (m, 12H), 2.14-2.75 (m, 6H) (cyclohexyl protons, pyrrolidine protons), 3.26 (s, 2H, $CH_2$–C=O), 5.35 (s, 2H, $CH_2$–N), 7.18–7.57 (m, 5H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.89, 23.79, 24.42, 29.88 (5$CH_2$–cyclohexyl, 2$CH_2$–pyrrolidine), 54.2 (2$CH_2$–pyrrolidine), 60.18, 61.34, 64.03 ($CH_2$–C=O, C–cyclohexyl, $CH_2$–N), 119.97, 125.6, 129.28, 136.69 (aromatic carbons), 167.63 (C=O, amide), 172.01 (C=O, amide). Anal. calcd. for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31. Found: C, 70.63; H, 8.21; N, 12.56.

*3-Phenyl-1-(piperidin-1-ylacetyl)-1,3-diazaspiro[4.5]-decan-4-one (**8d**)*

Crystallized from a mixture of petroleum ether (40–60)/ethyl acetate, yield 63%, m.p. 138−140°C, IR (KBr, cm$^{-1}$): 1706 (C=O, amide) and 1644 (C=O, amide); MS (EI) *m/z* (%): 356 (1.76) ($M^+$+1), 98 (100); $^1$H NMR ($CDCl_3$): 1.28–1.45 (m, 3H), 1.58–1.76 (m, 9H), 2.02–2.12 (m, 2H) (cyclohexyl protons and piperidine protons), 2.48 (br s, 4H, piperidine protons), 2.75–2.81 (m, 2H, cyclohexyl protons), 3.12 (s, 2H,$CH_2$–C=O), 5.43 (s, 2H, $CH_2$–N), 7.19–7.22 (m, 1H, $H_{ar.}$), 7.38–7.42 (m, 2H, $H_{ar.}$), 7.59–7.61 (m, 2H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.8, 23.88, 24.36, 25.92, 29.77 (5$CH_2$ cyclohexyl, 3$CH_2$ piperidine), 54.57 (2$CH_2$–piperidine), 61.33, 63.85, 64.03 ($CH_2$–C=O, $CH_2$–N and C–cyclohexyl), 119.74, 125.42, 129.19, 136.71 (aromatic carbons), 167.27 (C=O, amide), 171.88 (C=O, amide). Anal. calcd. for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 70.69; H, 8.53; N, 11.73.

*1-(Morpholin-4-ylacetyl)-3-phenyl-1,3-diazaspiro[4.5]-decan-4-one (**8e**)*

Crystallized from a mixture of petroleum ether (40–60)/ethyl acetate, yield 60%, m.p. 142−144°C, IR (KBr, cm$^{-1}$): 1710 (C=O, amide) and 1683 (C=O, amide); MS (EI) *m/z* (%): 358 (0.67) ($M^+$+1), 100 (100); $^1$H NMR ($CDCl_3$): 1.23–1.36 (m, 1H, cyclohexyl proton), 1.65–1.77 (m, 5H, cyclohexyl protons), 2.03–2.12 (m, 2H, cyclohexyl protons), 2.59 (s, 4H, morpholine protons), 2.74–2.8 (m, 2H, cyclohexyl protons), 3.18 (s, 2H, $CH_2$–C=O), 3.74–3.76 (t, $J$ = 4.5, 4H, morpholine protons), 5.38 (s, 2H, $CH_2$–N), 7.21–7.28 (m, 1H, $H_{ar.}$), 7.4–7.43 (m, 2H, $H_{ar.}$), 7.58–7.6 (m, 2H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.76, 24.32, 29.83 (5$CH_2$–cyclohexyl), 53.68 (2$CH_2$–morpholine), 61.24, 62.57, 64.11 ($CH_2$–C=O, $CH_2$–N, C–cyclohexyl), 66.71 (2$CH_2$–morpholine), 119.9, 125.64, 129.25, 136.53 (aromatic carbons), 166.29 (C=O, amide), 171.71 (C=O, amide). Anal. calcd. for $C_{20}H_{27}N_3O_3$: C, 67.20; H, 7.61; N, 11.76. Found: C, 67.48; H, 7.24; N, 11.57.

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*1-(1H-Imidazol-1-ylacetyl)-3-phenyl-1,3-diazaspiro[4.5]-decan-4-one (**8f**)*
Purified by column chromatography using a mixture of chloroform/ethyl acetate/methanol 7:5:1 as a mobile phase, yield 73%, m.p. 202−204°C, IR (KBr, $cm^{-1}$): 1705 (C=O, amide) and 1679 (C=O, amide); MS (EI) *m/z* (%): 338 (1.79) ($M^+$), 81 (100); $^1$H NMR ($CDCl_3$): 1.17–2.63 (m, 10H, cyclohexyl protons), 4.72 (s, 2H,$CH_2$–C=O), 5.22 (s, 2H, $CH_2$–N), 6.92 (s, 1H, imidazole), 7.02 (s, 1H, imidazole), 7.19–7.54 (m, 6H, $H_{ar.}$, imidazole); $^{13}$C NMR ($CDCl_3$): 21.78, 24.3, 30.02 (5$CH_2$–cyclohexyl), 48.77 (*$CH_2$*–C=O), 61.06, 64.5 (C–cyclohexyl, $CH_2$–N), 120.3, 120.49, 126.12, 129.43, 136.2, 138.18 (aromatic and imidazole carbons), 163.58 (C=O, amide), 171.28 (C=O, amide). Anal. calcd. for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56. Found: C, 67.67; H, 6.75; N, 16.78.

*1-[(Diethylamino)acetyl]-3-(4-methylphenyl)-1,3-diazaspiro[4.5]decan-4-one (**8g**)*
Crystallized from a mixture of petroleum ether (40–60)/ethyl acetate, yield 70%, m.p. 102−104°C, IR (KBr, $cm^{-1}$): 1706 (C=O, amide) and 1650 (C=O, amide); MS (EI) *m/z* (%): 358 (1.26) ($M^+$+1), 86 (100); $^1$H NMR ($CDCl_3$): 1.07–1.11 (t, $J$ = 6 Hz, 6H, ($CH_2$–*$CH_3$*)$_2$), 1.3–2.14 (m, 8H, cyclohexyl protons), 2.36 (s, 3H, $CH_3$), 2.59–2.65 (q, $J$ = 6 Hz, 4H, (*$CH_2$*–$CH_3$)$_2$), 2.76–2.8 (m, 2H, cyclohexyl protons), 3.25 (s, 2H,$CH_2$–C=O), 5.49 (s, 2H, $CH_2$–N), 7.21–7.51 (m, 4H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 7.3 (2$CH_2$–*$CH_3$*), 16.4, 17.37, 19.93, 25.28 (5$CH_2$–cyclohexyl, $CH_3$), 43.26 (2*$CH_2$*–$CH_3$), 54.74 (*$CH_2$*–C=O), 57.19, 59.54 (C–cyclohexyl, $CH_2$–N), 115.26, 125.23, 129.85, 130.66 (aromatic carbons), 163.89 (C=O, amide), 167.28 (C=O, amide). Anal. calcd. for $C_{21}H_{31}N_3O_2$: C, 70.55; H, 8.74; N, 11.75. Found: C, 70.25; H, 8.65; N, 11.52.

*1-[(Dipropylamino)acetyl]-3-(4-methylphenyl)-1,3-diazaspiro[4.5]decan-4-one (**8h**)*
Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 7:3 as a mobile phase, yield 63%, viscous oil, IR (KBr, $cm^{-1}$): 1682 (C=O, amide); MS (EI) *m/z* (%): 386 (1.52) ($M^+$+1), 114 (100); $^1$H NMR ($CDCl_3$): 0.83–0.86 (t, $J$ = 7.65 Hz, 6H, ($CH_2$–$CH_2$–*$CH_3$*)$_2$), 1.27–1.3 (m, 1H, cyclohexyl proton), 1.42–1.48 (m, 4H, ($CH_2$–*$CH_2$*–$CH_3$)$_2$), 1.65–1.72 (m, 5H, cyclohexyl protons), 2.09–2.11 (m, 1H, cyclohexyl protons), 2.29 (s, 3H, $CH_3$), 2.4–2.43 (t, $J$ = 7.65 Hz, 4H, (*$CH_2$*–$CH_2$–$CH_3$)$_2$), 2.71–2.75 (m, 2H, cyclohexyl protons), 3.19 (s, 2H, $CH_2$–C=O), 5.43 (s, 2H, $CH_2$–N), 7.15–7.43 (m, 4H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 12.11 (2$CH_2$–$CH_2$–*$CH_3$*), 20.05, 20.98, 21.89, 24.44, 29.76 (2$CH_2$–*$CH_2$*–$CH_3$, 5$CH_2$–cyclohexyl, $CH_3$), 56.54 (2*$CH_2$*–$CH_2$–$CH_3$), 60.81, 61.65, 64.02 (*$CH_2$*–C=O, $CH_2$–N, C–cyclohexyl), 119.79, 129.77, 134.25, 135.22 (aromatic carbons), 168.42 (C=O, amide), 171.8 (C=O, amide). Anal. calcd. for $C_{23}H_{35}N_3O_2$: C, 71.65; H, 9.15; N, 10.90. Found: C, 71.88; H, 9.43; N, 11.23.

*3-(4-Methylphenyl)-1-(pyrrolidin-1-ylacetyl)-1,3-diazaspiro[4.5]decan-4-one (**8i**)*
Crystallized from a mixture of petroleum ether (40–60)/ethyl acetate, yield 75%, m.p. 136−138°C, IR (KBr, $cm^{-1}$): 1713 (C=O, amide) and 1656 (C=O, amide); MS (EI) *m/z* (%): 355 (0.04) ($M^+$), 84 (100); $^1$H NMR ($CDCl_3$): 1.3–1.33 (m, 1H), 1.63–1.8 (m, 9H) (cyclohexyl protons, pyrrolidine protons), 2.07–2.09 (m, 2H, cyclohexyl protons), 2.33 (s, 3H, $CH_3$), 2.64 (br s, 4H, pyrrolidine protons), 2.75–2.79 (m, 2H, cyclohexyl protons), 3.3 (s, 2H,$CH_2$–C=O), 5.34 (s, 2H, $CH_2$–N), 7.18–7.19 (d, $J$ = 8 Hz, 2H, $H_{ar.}$), 7.45–7.46 (d, $J$ = 8 Hz, 2H, $H_{ar.}$), $^{13}$C NMR ($CDCl_3$): 20.88, 21.81, 23.75, 24.37, 29.82 (5$CH_2$–cyclohexyl, $CH_3$, 2$CH_2$–pyrrolidine), 54.05 (2$CH_2$–pyrrolidine), 59.90, 61.41, 63.89 (*$CH_2$*–C=O, C–cyclohexyl, $CH_2$–N), 120.07, 129.67, 134.08, 135.31 (aromatic carbons), 167.36 (C=O, amide), 171.73 (C=O, amide). Anal. calcd. for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 70.60; H, 7.97; N, 11.72.

*3-(4-Methylphenyl)-1-(piperidin-1-ylacetyl)-1,3-diazaspiro[4.5]decan-4-one (**8j**)*
Crystallized from a mixture of petroleum ether (40–60)/ethyl acetate, yield 60%, m.p. 156−158°C, IR (KBr, $cm^{-1}$): 1706 (C=O, amide) and 1654 (C=O, amide); MS (EI) *m/z* (%): 370 (1.5) ($M^+$+1), 98 (100); $^1$H NMR ($CDCl_3$): 1.31–1.45 (m, 3H), 1.6–1.77 (m, 9H), 2.05–2.13 (m, 2H) (cyclohexyl protons and piperidine protons), 2.35 (s, 3H, $CH_3$), 2.49 (br s, 4H, piperidine protons), 2.75–2.81 (m, 2H, cyclohexyl protons), 3.13 (s, 2H, $CH_2$–C=O), 5.4 (s, 2H, $CH_2$–N), 7.2–7.48 (m, 4H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 20.92, 21.82, 23.86, 24.38, 25.89, 29.8 (5$CH_2$ cyclohexyl, 3$CH_2$ piperidine, $CH_3$), 54.56 (2$CH_2$–piperidine), 61.46, 63.42, 64.01 (*$CH_2$*–C=O, $CH_2$–N, C–cyclohexyl), 119.92, 129.71, 134.13, 135.29 (aromatic carbons), 167.2 (C=O, amide), 171.74 (C=O, amide). Anal. calcd. for $C_{22}H_{31}N_3O_2$: C, 71.51; H, 8.46; N, 11.37. Found: C, 71.20; H, 8.12; N, 11.05.

*3-(4-Methylphenyl)-1-(morpholin-4-ylacetyl)-1,3-diazaspiro[4.5]decan-4-one (**8k**)*
Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 6:4 as a mobile phase, yield 62%, m.p. 182−184°C, IR (KBr, $cm^{-1}$): 1703 (C=O, amide) and 1650 (C=O, amide); MS (EI) *m/z* (%): 372 (0.28) ($M^+$+1), 100 (100); $^1$H NMR ($CDCl_3$): 1.29–1.32 (m, 1H, cyclohexyl proton), 1.63–1.76 (m, 5H, cyclohexyl protons), 2.03–2.08 (m, 2H, cyclohexyl protons), 2.34 (s, 3H, $CH_3$), 2.57 (s, 4H, morpholine protons), 2.72–2.78 (m, 2H, cyclohexyl protons), 3.16 (s, 2H,$CH_2$–C=O), 3.72–3.74 (t, $J$ = 4.5, 4H, morpholine protons), 5.36 (s, 2H, $CH_2$–N), 7.19–7.46 (m, 4H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 20.92, 21.78, 24.34, 29.84 (5$CH_2$–cyclohexyl, $CH_3$), 53.68 (2$CH_2$–morpholine), 61.35, 62.5, 64.04 (*$CH_2$*–C=O, $CH_2$–N, C–cyclohexyl), 66.71 (2$CH_2$–morpholine), 120.06, 129.74, 133.94, 135.5 (aromatic carbons), 166.28 (C=O, amide), 171.56 (C=O, amide). Anal. calcd. for $C_{21}H_{29}N_3O_3$: C, 67.90; H, 7.87; N, 11.31. Found: C, 67.53; H, 7.53; N, 11.18.

*1-(1H-Imidazol-1-ylacetyl)-3-(4-methylphenyl)-1,3-diazaspiro[4.5]decan-4-one (**8l**)*
Purified by column chromatography using a mixture of chloroform/ethyl acetate/methanol 7:5:1 as a mobile phase, yield 70%, m.p. 172−174°C, IR (KBr, $cm^{-1}$): 1704 (C=O, amide) and 1675 (C=O, amide); MS (EI) *m/z* (%): 352 (0.4) ($M^+$), 81

(100); $^1$H NMR ($CDCl_3$): 1.19–2.02 (m, 8H, cyclohexyl protons), 2.3 (s, 3H, $CH_3$), 2.6–2.62 (m, 2H, cyclohexyl protons), 4.75 (s, 2H,$CH_2$–C=O), 5.23 (s, 2H, $CH_2$-N), 6.94 (s, 1H, imidazole), 7.02 (s, 1H, imidazole), 7.16–7.18 (d, $J = 7.65$ Hz, 2H, $H_{ar.}$), 7.41–7.42 (d, $J = 7.65$ Hz, 2H, $H_{ar.}$), 7.52 (s, 1H, imidazole); $^{13}$C NMR ($CDCl_3$): 21.04, 21.8, 24.32, 30.04 ($CH_3$, 5$CH_2$–cyclohexyl), 48.87 ($CH_2$–C=O), 61.23, 64.5 (C–cyclohexyl, $CH_2$–N), 120.45, 120.66, 128.82, 129.95, 133.56, 136.07, 138.16 (aromatic and imidazole carbons), 163.56 (C=O, amide), 171.19 (C=O, amide). Anal. calcd. for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.87; H, 6.55; N, 15.78.

*1-[(Diethylamino)acetyl]-2,3-diphenyl-1,3-diazaspiro[4.5]-decan-4-one (**8m**)*

Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 6:4 as a mobile phase, yield 67%, m.p. 130−132°C, IR (KBr, $cm^{-1}$): 1690 (C=O, amide) and 1669 (C=O, amide); MS (EI) *m/z* (%): 420 (1.02) ($M^+$+1), 86 (100); $^1$H NMR ($CDCl_3$): 0.94–0.96 (t, $J = 6$ Hz, 6H, ($CH_2$–$CH_3$)$_2$), 1.4–2.25 (m, 8H, cyclohexyl protons), 2.50–2.56 (q, $J = 6$ Hz, 4H, ($CH_2$–$CH_3$)$_2$), 2.85–3.09 (m, 4H, cyclohexyl protons, $CH_2$–C=O), 7.01 (s, 1H, CH-N), 7.09–7.28 (m, 10H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 11.45 (2$CH_2$–$CH_3$), 22.11, 22.33, 24.4, 30.45, 31.72 (5$CH_2$–cyclohexyl), 46.63 (2$CH_2$–$CH_3$), 59.17 ($CH_2$–C=O), 64.03, 75.5 (C–cyclohexyl, CH–N), 126.48, 127.29, 128.77, 129.04, 129.35, 134.85, 138.33 (aromatic carbons), 169.59 (C=O, amide), 171.65 (C=O, amide). Anal. calcd. for $C_{26}H_{33}N_3O_2$: C, 74.43; H, 7.93; N, 10.02. Found: C, 74.12; H, 7.74; N, 9.85.

*2,3-Diphenyl-1-[(dipropylamino)acetyl]-1,3-diazaspiro[4.5]decan-4-one (**8n**)*

Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 7:3 as a mobile phase, yield 65%, m.p. 138−140°C, IR (KBr, $cm^{-1}$): 1691 (C=O, amide) and 1659 (C=O, amide); MS (EI) *m/z* (%): 447 (16) ($M^+$), 114 (100); $^1$H NMR ($CDCl_3$): 0.83–0.85 (t, $J = 6.4$ Hz, 6H, ($CH_2$–$CH_2$–$CH_3$)$_2$), 1.34–2.42 (m, 16H) (cyclohexyl protons, ($CH_2$–$CH_2$–$CH_3$)$_2$, ($CH_2$–$CH_2$–$CH_3$)$_2$), 2.77–2.93 (m, 4H) (cyclohexyl protons, $CH_2$–C=O), 7.05–7.3 (m, 11H, CH–N, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 10.21 (2$CH_2$–$CH_2$–$CH_3$), 17.99, 20.45, 24.56, 22.68, 28.38, 29.96 (2$CH_2$–$CH_2$–$CH_3$, 5$CH_2$–cyclohexyl), 53.87 (2$CH_2$–$CH_2$–$CH_3$), 59 ($CH_2$–C=O), 62.34, 75.33 (C–cyclohexyl, CH-N), 124.91, 125.49, 125.71, 127.07, 127.39, 127.65, 133.09, 136.56 (aromatic carbons), 168.04 (C=O, amide), 169.95 (C=O, amide). Anal. calcd. for $C_{28}H_{37}N_3O_2$: C, 75.13; H, 8.33; N, 9.39. Found: C, 74.81; H, 8.02; N, 8.99.

*2,3-Diphenyl-1-(pyrrolidin-1-ylacetyl)-1,3-diazaspiro[4.5]-decan-4-one (**8o**)*

Purified by column chromatography using a mixture of methylene chloride/ethyl acetate 7:1 as a mobile phase, yield 66%, m.p. 132−134°C, IR (KBr, $cm^{-1}$): 1699 (C=O, amide) and 1646 (C=O, amide); MS (EI) *m/z* (%): 418 (14.57) ($M^+$+1), 84 (100); $^1$H NMR ($CDCl_3$): 1.36–2.22 (m, 12H, cyclohexyl protons, pyrrolidine protons), 2.54 (s, 4H, pyrrolidine protons), 2.93–3.28 (m, 4H, cyclohexyl protons, $CH_2$–C=O), 7.08–7.25 (m, 11H, CH–N, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 22.12, 22.39, 23.79, 24.46, 30.1, 31.64 (5$CH_2$–cyclohexyl, 2$CH_2$–pyrrolidine), 53.76 (2$CH_2$–pyrrolidine), 60.42, 64.24, 75.66 ($CH_2$–C=O, C–cyclohexyl, CH–N), 126.30, 127.32, 127.6, 128.93, 129.07, 129.57, 134.78, 138.26 (aromatic carbons), 168.36 (C=O, amide), 171.63 (C=O, amide). Anal. calcd. for $C_{26}H_{31}N_3O_2$: C, 74.79; H, 7.48; N, 10.06. Found: C, 74.50; H, 7.10; N, 9.82.

*2,3-Diphenyl-1-(piperidin-1-ylacetyl)-1,3-diazaspiro[4.5]-decan-4-one (**8p**)*

Crystallized from a mixture of petroleum ether (40–60)/ethyl acetate, yield 50%, m.p. 150−152°C, IR (KBr, $cm^{-1}$): 1701 (C=O, amide) and 1658 (C=O, amide); MS (EI) *m/z* (%): 432 (2.88) ($M^+$+1), 98 (100); $^1$H NMR ($CDCl_3$): 1.24–1.46 (m, 3H), 1.6–1.79 (m, 8H), 2.09–2.17 (m, 1H), 2.24–2.26 (m, 4H), 2.39 (br s, 2H), 2.54–2.56 (m, 1H), 2.78–2.81 (m, 1H) (cyclohexyl protons and piperidinyl protons), 2.94–2.96 (m, 1H), 3.09–3.15 (m, 1H) ($CH_2$–C=O), 7.11–7.29 (m, 11H, CH–N, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.06, 22.07, 22.34, 23.9, 24.41, 26.03, 29.99, 31.6 (5$CH_2$–cyclohexyl, 3$CH_2$–piperidinyl), 54.09 (2$CH_2$–piperidinyl), 64.17, 64.47, 75.25 ($CH_2$–C=O, $CH_2$–N, C–cyclohexyl), 126.2, 127.22, 127.51, 128.76, 129.03, 129.38, 134.8, 138.22 (aromatic carbons), 168.63 (C=O, amide), 171.58 (C=O, amide). Anal. calcd. for $C_{27}H_{33}N_3O_2$: C, 75.14; H, 7.71; N, 9.74. Found: C, 75.23; H, 7.45; N, 9.50.

*2,3-Diphenyl-1-(morpholin-4-ylacetyl)-1,3-diazaspiro[4.5]-decan-4-one (**8q**)*

Crystallized from a mixture of petroleum ether (40–60)/ethyl acetate, yield 60%, m.p. 168−170°C, IR (KBr, $cm^{-1}$): 1707 (C=O, amide) and 1663 (C=O, amide); MS (EI) *m/z* (%): 434 (2) ($M^+$+1), 100 (100); $^1$H NMR ($CDCl_3$): 1.26–1.43 (m, 1H, cyclohexyl proton), 1.68–1.79 (m, 4H, cyclohexyl proton), 2.04–2.26 (m, 3H, cyclohexyl protons) 2.384 (br s, 2H, morpholine protons), 2.43 (br s, 2H, morpholine protons), 2.57–2.6 (m, 1H, cyclohexyl proton), 2.87–3.07 (m, 3H, cyclohexyl proton, $CH_2$–C=O), 3.71–3.79 (m, 4H, morpholine protons), 6.92 (s, 1H, CH–N), 7.07–7.29 (m, 10H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 22.06, 22.3, 24.38, 30.22, 31.56 (5$CH_2$–cyclohexyl), 53.39 (2$CH_2$–morpholine), 63.52, 64.15, 66.86, 75.63 ($CH_2$–C=O, $CH_2$–N, 2$CH_2$–morpholine, C–cyclohexyl), 126.35, 127.4, 127.6 128.92, 129.09, 129.59, 134.68, 138.08 (aromatic carbons), 167.85 (C=O, amide), 171.47 (C=O, amide). Anal. calcd. for $C_{26}H_{31}N_3O_3$: C, 72.03; H, 7.21; N, 9.69. Found: C, 71.75; H, 7.59; N, 9.62.

*2,3-Diphenyl-1-(1H-imidazol-1-ylacetyl)-1,3-diazaspiro[4.5]decan-4-one (**8r**)*

Purified by column chromatography using a mixture of chloroform/ethyl acetate/methanol 7:5:3 as a mobile phase followed by crystallization from mixture of ethyl acetate/isopropanol, yield 65%, m.p. 104−106°C, IR (KBr, $cm^{-1}$): 1682 (C=O, amide) and 1668 (C=O, amide); MS (EI) *m/z* (%): 414 (10) ($M^+$), 81 (100); $^1$H NMR ($CDCl_3$): 1.28–2.36 (m, 8H, cyclohexyl protons), 2.84–2.95 (m, 2H, cyclohexyl protons), 4–4.02 (m, 1H, $CH_2$–C=O), 4.65–4.68 (m, 1H, $CH_2$–C=O), 6.47 (s, 1H), 6.72 (s, 1H) (CH–N, imidazole proton), 7.02–7.36 (m, 12H, $H_{ar.}$,

imidazole); $^{13}$C NMR ($CDCl_3$): 22.07, 22.26, 24.3, 30.33, 31.48 ($5CH_2$–cyclohexyl), 49.68 (*$CH_2$*–C=O), 64.22, 75.66 (C–cyclohexyl, CH–N), 120.17, 126.67, 127.39, 127.91, 129.16, 129.31, 129.65, 130.45, 134.2, 137.43, 137.93 (aromatic and imidazole carbons), 164.87 (C=O, amide), 171.11 (C=O, amide). Anal. calcd. for $C_{25}H_{26}N_4O_2$: C, 72.44; H, 6.32; N, 13.52. Found: C, 72.11; H, 5.99; N, 13.32.

*1-[(Diethylamino)acetyl]-3-(4-methylphenyl)-2-phenyl-1,3-diazaspiro[4.5]decan-4-one (**8s**)*
Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 6:4 as a mobile phase, yield 61%, m.p. 102−104°C, IR (KBr, $cm^{-1}$): 1689 (C=O, amide); MS (EI) *m/z* (%): 433 (2.42) ($M^+$+1), 86 (100); $^1$H NMR ($CDCl_3$): 0.89–0.92 (t, $J = 6.7$ Hz, 6H, ($CH_2$–*$CH_3$*)$_2$), 1.29–2.11 (m, 8H, cyclohexyl protons), 2.28 (s, 3H, $CH_3$), 2.48–2.52 (t, $J = 6.7$ Hz, 4H (*$CH_2$*–$CH_3$)$_2$), 2.73–3.04 (m, 4H, cyclohexyl protons, $CH_2$–C=O), 6.87–7.24 (m, 10H, CH–N, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 11.49 ($2CH_2$–*$CH_3$*), 21.16, 22.17, 22.4, 24.47, 30.11, 31.69 ($5CH_2$–cyclohexyl, $CH_3$), 46.67 (*$2CH_2$*–$CH_3$), 59.09 (*$CH_2$*–C=O), 64.15, 76.93 (C–cyclohexyl, CH–N), 126.52, 127.37, 128.87, 129.44, 129.78, 132.07, 138.4 (aromatic carbons), 169.64 (C=O, amide), 171.77 (C=O, amide). Anal. calcd. for $C_{27}H_{35}N_3O_2$: C, 74.79; H, 8.14; N, 9.69. Found: C, 74.99; H, 8.35; N, 9.89.

*1-[(Dipropylamino)acetyl]-3-(4-methylphenyl)-2-phenyl-1,3-diazaspiro[4.5]decan-4-one (**8t**)*
Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 7:3 as a mobile phase, yield 62%, m.p. 114−116°C, IR (KBr, $cm^{-1}$): 1692 (C=O, amide) and 1670 (C=O, amide); MS (EI) *m/z* (%): 461 (0.04) ($M^+$), 114 (100); $^1$H NMR ($CDCl_3$): 0.81–0.84 (t, $J = 7.6$ Hz, 6H, ($CH_2$–$CH_2$–*$CH_3$*)$_2$), 1.32–2.48 (m, 19H) (cyclohexyl protons, ($CH_2$–*$CH_2$*–$CH_3$)$_2$, (*$CH_2$*–$CH_2$–$CH_3$)$_2$, $CH_3$), 2.78–3.05 (m, 4H) (cyclohexyl protons, $CH_2$–C=O), 6.9 (s, 1H, CH–N), 7.03–7.25 (m, 9H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 11.94 ($2CH_2$–$CH_2$–*$CH_3$*), 19.57, 21.14, 22.17, 22.37, 24.46, 30.17, 31.75 ($2CH_2$–*$CH_2$*–$CH_3$, $5CH_2$–cyclohexyl, $CH_3$), 55.66 (*$2CH_2$*–$CH_2$–$CH_3$), 59.56, 64.18, 75.63 (*$CH_2$*–C=O, C–cyclohexyl, CH–N), 126.53, 127.33, 128.91, 129.49, 129.79, 132.04, 137.47, 138.25 (aromatic carbons), 169.03 (C=O, amide), 171.61 (C=O, amide). Anal. calcd. for $C_{29}H_{39}N_3O_2$: C, 75.45; H, 8.52; N, 9.10. Found: C, 75.11; H, 8.95; N, 8.89.

*3-(4-Methylphenyl)-2-phenyl-1-(pyrrolidin-1-ylacetyl)-1,3-diazaspiro[4.5]decan-4-one (**8u**)*
Purified by column chromatography using a mixture of methylene chloride/ethyl acetate 7:1 as a mobile phase, yield 52%, m.p. 140−142°C, IR (KBr, $cm^{-1}$): 1703 (C=O, amide) and 1651 (C=O, amide); MS (EI) *m/z* (%): 432 (3.82) ($M^+$+1), 84 (100); $^1$H NMR ($CDCl_3$): 1.34–1.36 (m, 1H, cyclohexyl proton), 1.64–1.76 (m, 8H, cyclohexyl protons, pyrrolidine protons), 2.07–2.24 (m, 6H, $CH_3$, cyclohexyl protons), 2.45–2.54 (m, 5H, cyclohexyl proton, pyrrolidine protons), 2.93–3.12 (m, 3H, cyclohexyl proton, $CH_2$–C=O), 6.82–7.27 (m, 10H, CH–N, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.14, 22.15, 22.42, 23.78, 24.49, 30.54, 31.61 ($5CH_2$–cyclohexyl, $2CH_2$–pyrrolidine, $CH_3$), 53.74 ($2CH_2$–pyrrolidine), 60.9, 64.12, 75.63 (*$CH_2$*–C=O, C–cyclohexyl, CH–N), 126.24, 127.6, 128.88, 129.49, 129.7, 129.57, 132.09, 137.25, 138.45 (aromatic carbons), 168.84 (C=O, amide), 171.74 (C=O, amide). Anal. calcd. for $C_{27}H_{33}N_3O_2$: C, 75.14; H, 7.71; N, 9.74. Found: C, 75.16; H, 7.59; N, 9.57.

*3-(4-Methylphenyl)-2-phenyl-1-(piperidin-1-ylacetyl)-1,3-diazaspiro[4.5]decan-4-one (**8v**)*
Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 6:4 as a mobile phase, yield 60%, m.p. 148−150°C, IR (KBr, $cm^{-1}$): 1702 (C=O, amide) and 1657 (C=O, amide); MS (EI) *m/z* (%): 446 (7.7) ($M^+$+1), 98 (100); $^1$H NMR ($CDCl_3$): 1.27–1.47 (m, 3H), 1.61–1.79 (m, 8H), 2.12–2.15 (m, 1H), 2.23–2.25 (m, 4H) (cyclohexyl protons and piperidine protons), 2.27 (s, 3H, $CH_3$), 2.4 (br s, 2H), 2.54–2.57 (m, 1H), 2.81–2.87 (m, 1H) (cyclohexyl protons and piperidine protons), 2.95–2.97 (m, 1H), 3.04–3.3.06 (m, 1H) ($CH_2$–C=O), 6.95–7.29 (m, 10H, CH–N, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.07, 22.07, 22.34, 23.82, 24.42, 25.92, 30, 31.58 ($5CH_2$–cyclohexyl, $3CH_2$ piperidine), 54.04 ($2CH_2$–piperidine), 60.4, 64.16, 75.39 (*$CH_2$*–C=O, $CH_2$–N, C–cyclohexyl), 126.14, 127.53, 128.77, 129.36, 129.67, 132.07, 137.18, 138.32 (aromatic carbons), 168.43 (C=O, amide), 171.59 (C=O, amide). Anal. calcd. for $C_{28}H_{35}N_3O_2$: C, 75.47; H, 7.92; N, 9.43. Found: C, 75.16; H, 8.16; N, 9.26.

*3-(4-Methylphenyl)-1-(morpholin-4-ylacetyl)-2-phenyl-1,3-diazaspiro[4.5]decan-4-one (**8w**)*
Purified by column chromatography using a mixture of petroleum ether (40–60)/ethyl acetate 6:4 as a mobile phase, yield 63%, m.p. 154−156°C, IR (KBr, $cm^{-1}$): 1707 (C=O, amide) and 1644 (C=O, amide); MS (EI) *m/z* (%): 448 (0.32) ($M^+$+1), 100 (100); $^1$H NMR ($CDCl_3$): 1.37–1.78 (m, 6H, cyclohexyl protons), 2.06–2.25 (m, 3H, cyclohexyl protons), 2.28 (s, 3H, $CH_3$), 2.43 (br s, 2H, morpholine protons), 2.45 (br s, 2H, morpholine protons), 2.59–2.61 (m, 1H, cyclohexyl proton), 2.87–3.07 (m, 2H, $CH_2$–C=O), 3.74–3.8 (m, 4H, morpholine protons), 6.85 (s, 1H, CH–N), 6.93–7.31 (m, 9H, $H_{ar.}$);$^{13}$C NMR ($CDCl_3$): 21.07, 22.04, 22.29, 24.38, 30.14, 31.49 ($5CH_2$–cyclohexyl, $CH_3$), 53.24 ($2CH_2$–morpholine), 62.94, 64.24, 66.59, 75.76 (*$CH_2$*–C=O, $CH_2$-N, $2CH_2$–morpholine, C–cyclohexyl), 126.3, 127.41, 128.98, 129.64, 129.74, 131.86, 137.45, 138.09 (aromatic carbons), 167.69 (C=O, amide), 171.66 (C=O, amide). Anal. calcd. for $C_{27}H_{33}N_3O_3$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.17; H, 7.09; N, 9.21.

*1-(1H-Imidazol-1-ylacetyl)-3-(4-methylphenyl)-2-phenyl-1,3-diazaspiro[4.5]decan-4-one (**8x**)*
Purified by column chromatography using a mixture of chloroform/ethyl acetate/methanol 7:5:3 as a mobile phase followed by crystallization from a mixture of petroleum ether (40–60)/ethyl acetate, yield 63%, m.p. 150−152°C, IR (KBr, $cm^{-1}$): 1708 (C=O, amide) and 1672 (C=O, amide); MS (EI) *m/z* (%): 428 (1.15) ($M^+$), 81 (100); $^1$H NMR ($CDCl_3$): 1.32–2.11 (m, 8H, cyclohexyl protons), 2.26 (s, 3H, $CH_3$), 2.72–2.92 (m, 2H,

cyclohexyl protons), 4.11–4.62 (m, 2H,$CH_2$–C=O), 6.49 (s, 1H), 6.69 (s, 1H) (CH–N, imidazole), 6.92–6.93 (d, $J = 8$ Hz, 2H, $H_{ar.}$), 6.99 (s, 1H, imidazole), 7.05–7.06 (d, $J = 8$ Hz, 2H, $H_{ar.}$), 7.23 (s, 1H, imidazole), 7.28–7.37 (m, 5H, $H_{ar.}$); $^{13}$C NMR ($CDCl_3$): 21.04, 22, 22.2, 24.26, 30.33, 31.47 (5$CH_2$–cyclohexyl, $CH_3$), 49.67 ($CH_2$–C=O), 64.44, 76.28 (C-cyclohexyl, CH–N), 120.2, 126.43, 127.37, 128.73, 129.51, 129.83, 130.26, 131.49, 137.59, 137.77, 137.83 (aromatic and imidazole carbons), 164.77 (C=O, amide), 171.06 (C=O, amide). Anal. calcd. for $C_{26}H_{28}N_4O_2$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.67; H, 6.75; N, 12.89.

## Biological studies

*Materials*

*Animals:* Swiss male albino mice weighing 19–25 g were used for evaluation of the anticonvulsant and neurotoxicity of the target compounds **6a–d** and **8a–x**. Animals used in this study were purchased from the Animal House Colony of the National Research Centre, Cairo, Egypt. Animals were housed under standardized conditions of room temperature, relative humidity, light/dark cycle, and were allowed free access to water and standard mice laboratory chow throughout the whole experimental period. Procedures involving animals and their care were performed after the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals, "Canadian Council on Animal Care Guidelines, 1984". Additionally, all efforts were made to minimize animals suffering and to use only the number of animals necessary to produce reliable data.

*Drugs and chemicals:* Phenobarbital (Memphis Co. Pharm and Chem. Ind., Cairo, Egypt), ethosuximide (Pfizer Co., Giza, Egypt), diphenylhydantoin (Nasr Co., Giza, Egypt), Tween 80, and PTZ (Sigma, St. Loius, MO, USA) were used. Phenobarbital, ethosuximide, and PTZ were dissolved in physiologic saline solution. Diphenylhydantoin was dissolved in slightly alkalinized saline with 0.1 mmol potassaium hydroxide. Reference drugs and tested compounds were administered intraperitoneally (i.p.) in volumes of 0.1 mL/10 g of mice body weight.

*Methods*

Animals were allowed to acclimatize to laboratory conditions for one week before starting the experiments. Mice were randomly assigned to control, reference, and experimental groups consisting of six mice each. Each mouse was used only once. All the tested compounds were suspended in 7% Tween 80 as a vehicle.

*scPTZ test:* To determine the production of threshold or minimal clonic seizures, 85 mg/kg PTZ [32] was injected subcutaneously in a loose fold of skin on the back of the mice neck 30 min after individually i.p. injection of the reference drugs ethosuximide (150 mg/kg ≡ 1.06 mmol/kg) [20], phenobarbital (30 mg/kg ≡ 0.13 mmol/kg) [33], or one of the test compounds in the dose range of 4–37 mg/kg. Meanwhile, the control experiments were performed using the solvent alone. Each animal was placed in a single cage to minimize the stress [34] and observed for 30 min after PTZ administration, failure to observe even a threshold seizure (a single episode of clonic spasms of a least 5 s duration) was defined as protection [35].

*MES test:*Animals were randomly assigned to groups of six mice each. The first group served as the control group. The second group received the reference drug diphenylhydantoin at a dose of 45 mg/kg ≡ 0.16 mmol/kg and the other groups of mice received individually the test compounds by intraperitoneal injection with the dose that induces maximum protection in the PTZ test. Thirty minutes later, electroconvulsions were induced by a current (fixed current intensity of 25 mA, 0.2 s stimulus duration) delivered via ear clip [36] by a Rodent Shoker generator (current stimulator Type 221, Hugo Sachs Elektronik, Freiburg, Germany). The typical maximal seizure lasts approximately 22 s. Failure to extend the hind limbs to an angle with trunk greater than 90° is defined as protection [37].

*Neurotoxicity screen:* The neurotoxicity of the tested compounds was evaluated by adopting the rotarod test [38], which is designed to detect minimal neurological deficit. In this test, the animals were trained to maintain equilibrium on a rotating 1-inch diameter knurled plastic rod at a speed of 6 rpm for at least 1 min in each three trials using a rotarod device (UGO Basile, 47600, Varese, Italy). Only animals which fulfill this criterion were included in the experiment. The selected trained mice were classified into control and experimental groups ($n = 6$). The animals in the experimental groups were dosed (i.p.) with one of the test compounds at doses which exerted the maximal protection in the PTZ test. Thirty minutes later, the mice were placed again on the rotating rod and the neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least one min.

*Determination of the $ED_{50}$:* Anticonvulsant potential of the tested compounds was expressed in term of median effective dose ($ED_{50}$). Groups of mice were given range of doses of the test compound until at least three points were established in the range of 15–84% seizure protection. From the plot of these data, the respective $ED_{50}$ value and the confidence limits were calculated [39].

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