Anticonvulsant Profiles of Certain New 6-Aryl-9-substituted-6,9-diazaspiro-[4.5]decane-8,10-diones and 1-Aryl-4-substituted-1,4-diazaspiro[5.5]undecane-3,5-diones

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Abstract: Synthesis and anticonvulsant potential of certain new 6-aryl-9-substituted-6,9-diazaspiro[4.5]decane-8,10-diones (6a–l) and 1-aryl-4-substituted-1,4-diazaspiro[5.5]undecane-3,5-diones (6m–x) are reported. The intermediates 1-[(aryl)(cyanomethyl)amino]cycloalkanecarboxamides (3a–f) were prepared via adopting Strecker synthesis on the proper cycloalkanone followed by partial hydrolysis of the obtained nitrile functionality and subsequent N-cyanomethylation. Compounds 3a–f were subjected to complete nitrile hydrolysis to give the respective carboxylic acid derivatives 4a–f which were cyclized under mild conditions to give the spiro compounds 5a–f. Ultimately, compounds 5a–f were alkylated or aralkylated to give the target compounds 6a–i and 6m–u. On the other hand, compounds 6j–l and 6v–x were synthesized from the intermediates 5a–f through
alkylation, dehydration and finally tetrazole ring formation. Anticonvulsant screening of the target compounds 6a–x revealed that compound 6g showed an ED50 of 0.0043 mmol/kg in the scPTZ screen, being about 14 and 214 fold more potent than the reference drugs, Phenobarbital (ED50 = 0.06 mmol/kg) and Ethosuximide (ED50 = 0.92 mmol/kg), respectively. Compound 6e exhibited an ED50 of 0.019 mmol/kg, being about 1.8 fold more potent than that of the reference drug, Diphenylhydantoin (ED50 = 0.034 mmol/kg) in the MES screen. Interestingly, all the test compounds 6a–x did not show any minimal motor impairment at the maximum administered dose in the neurotoxicity screen.

**Keywords:** cycloalkanones; Strecker synthesis; alkylation; spiro compounds; tetrazole; anticonvulsant

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### 1. Introduction

Epilepsy is a group of neurological disorders characterized by excessive abnormal bioelectrical functions of the brain leading to recurrent unprovoked seizures [1,2]. It affects about 1% of the global population with the majority of cases being in the developing countries [3]. Estimates suggest that approximately 20%–30% of patients are not adequately controlled by the available antiepileptic medications [4,5]. Furthermore, the clinically used antiepileptics display serious side effects such as ataxia, hepatotoxicity, gingival hyperplasia and megaloblastic anaemia [6–8]. Therefore, there is a substantial need for novel, more effective and more selective antiepileptic agents with lesser side effects.

Diketopiperazines (DKPs) are the smallest cyclic peptides known, commonly biosynthesized from amino acids by a large variety of organisms [9]. They are privileged structures for the discovery of new lead compounds. They display attractive chemical characteristics, such as resistance to proteolysis, mimicking of peptidic pharmacophoric groups, conformational rigidity and donor as well as acceptor groups for hydrogen bonding which might influence interactions with biological targets [10].

DKPs include 2,3-DKPs, 2,5-DKPs and 2,6-DKPs (3-aza-glutarimides). Although various methods and synthetic protocols are reported for the synthesis of 2,6-DKPs, there is a paucity of information on their induced biological profiles, including anticonvulsant, antiviral and anticancer activities [2,11–13].

Incorporation of lipophilic moieties in the scaffold of new bioactive chemical entities could improve their anticonvulsant potential. Accordingly, cyclohexane and/or cyclopentane moieties were embedded in the skeleton of the new 2,6-DKP derivatives 6a–x aiming to enhance their anticonvulsant activity. On the other hand, the tetrazole moiety is a bioisostere of carboxylic acid functionality and it is an integrated part in the construction of certain anticonvulsants [14,15]. Therefore, compounds 6j–l and 6v–x, bearing a tetrazole moiety, were synthesized and screened for their anticonvulsant potential.

Our research group has previously reported the synthesis and anticonvulsant activity of certain 1-alkyl-1,4-diaza[4.5]decane and [5.5]undecane-3,5-diones [16] as ring expanded hydantoins which are one of the well known classical families of anticonvulsants. As an extension of this study, we describe herein the synthesis and anticonvulsant profile of certain new 6-aryl-9-substituted-6,9-diaza[4.5]decane-8,10-diones (6a–l) and 1-aryl-4-substituted-1,4-diaza[5.5]undecane-3,5-diones (6m–x) aiming to get new anticonvulsant biocandidates.
2. Results and Discussion

2.1. Chemistry

Syntheses of the target compounds 6a–x and their intermediates are depicted in Schemes 1–3. Thus, cyclopentanone and/or cyclohexanone were allowed to react with the appropriate commercially available aniline derivative and potassium cyanide in glacial acetic acid under Strecker synthesis conditions to give the respective nitrile derivatives 1a–f. The nitrile group of compounds 1a–f was subjected to hydrolysis under acidic conditions using sulfuric acid at ambient temperature to yield the amide derivatives 2a–f. Subsequently, cyanomethylation of the secondary amine moiety of compounds 2a–f was successfully achieved using potassium cyanide, paraformaldehyde and formaldehyde to furnish the corresponding compounds 3a–f (Scheme 1).

Scheme 1. Synthesis of compounds 1–3a–f. Reagents and conditions: (i) KCN, glacial acetic acid, RT, 24 h; (ii) Conc. H2SO4, RT, 48 h; (iii) KCN, formaldehyde 37% solution, paraformaldehyde, 60 °C-RT, 3–18 h.

| 1–3 | n | R1 |
|-----|---|----|
| a   | 0 | H  |
| b   | 0 | 4-CH3|
| c   | 0 | 4-OCH3|
| d   | 1 | H  |
| e   | 1 | 4-CH3|
| f   | 1 | 4-OCH3|

The target compounds 6a–i and 6m–u as well as their intermediates 4a–f and 5a–f were obtained as portrayed in Scheme 2. Thus, the nitrile moiety in compounds 3a–f was hydrolysed via reflux in sodium hydroxide solution to yield the corresponding carboxylic acid derivatives 4a–f. Cyclization of the latter compounds 4a–f was successfully realized using ethylenediamine in 4 N HCl solution to give the respective spiro compounds 5a–f according to our previously developed procedure [16]. The imide functionality of compounds 5a–f was alkylated under phase transfer catalysis conditions using the appropriate alkyl/aralkyl halide to give the target compounds 6a–i and 6m–u.
Scheme 2. Synthesis of compounds 4a–f, 5a–f, 6a–i and 6m–u.

Reagent and conditions: (i) NaOH, reflux, 24 h; (ii) Ethylenediamine, 4N HCl, reflux, 24 h; (iii) BrCH2COOCH3 or ClCH2C6H5 or BrCH2CH2C6H5, acetone, tetrabutylammoniumbromide, reflux, 7 h.

The synthesis of the intermediates 7a–f and 8a–f as well as the target compounds 6j–l and 6v–x were successfully achieved as illustrated in Scheme 3. Synthesis of compounds 6j–l and 6v–x was commenced with the reaction of compounds 5a–f with chloroacetamide to give the corresponding compounds 7a–f. Dehydration of compounds 7a–f using trifluoroacetic anhydride furnished the respective penultimate cyanomethyl derivatives 8a–f. Elaboration of the cyano group of compounds 8a–f to the tetrazolyl moiety was acquired using sodium azide in the presence of aluminium chloride to yield the desired compounds 6j–l and 6v–x.
Scheme 3. Synthesis of compounds 7a–f, 8a–f, 6j–l and 6v–x. Reagents and conditions: (i) Acetone, K₂CO₃, tetrabutylammonium bromide, reflux 7 h; (ii) Trifluoroacetic anhydride, THF, cooling, 0–5 °C, 2 h, ammonium bicarbonate; (iii) NaN₃, AlCl₃, cooling then reflux 24 h.

2.2. Anticonvulsant Activity

The test compounds 6a–x were subjected to preliminary anticonvulsant evaluation (Phase I screening) according to the protocol given by the Epilepsy Section of the National Institute of Neurological Disorders and Stroke (NINIDS) using the standard procedure adopted by the Antiepileptic Drug Development (ADD) program [17]. Those include the ‘gold standard’ screens, namely subcutaneous Pentylenetetrazole (scPTZ) screen and the maximal electroshock seizure (MES) screen. The former screen identifies compounds that elevate seizure threshold while the latter one measures the ability of the test compound to prevent seizure spread. Compounds exhibited 100% protection against induced seizures, were subjected to median effective dose (ED₅₀) estimation and minimal motor impairment (neurotoxicity) evaluation.

It has been indicated that PTZ-induced seizures can be prevented by drugs that reduce T-type Ca²⁺ currents such as Ethosuximide and also by drugs that enhance gamma amino butyric acid type A (GABAA) receptor-mediated inhibitory neurotransmission such as Phenobarbital [18].

The results of the initial anticonvulsant screening of the test compounds 6a–x are given in Table 1. The evaluation indicated that, all the compounds were effective in scPTZ screen while most of them were effective in MES screen. scPTZ screen showed that, compound 6g (R¹ = 4-OCH₃ and R² = -CH₂COOCH₃) was the most potent congener in the cyclopentane series 6a–l, displaying 100% protection against PTZ-induced seizure at dose level of 0.0086 mmol/kg as compared with Phenobarbital (0.13 mmol/kg) and Ethosuximide (1.06 mmol) which were used as reference standards.

Meanwhile, compound 6b (R¹ = H, R² = CH₂-Ph) and compound 6d (R¹ = 4-CH₃, R² = -CH₂COOCH₃) exerted equal anticonvulsant activity (100% protection) at a dose level of 0.018 mmol/kg. Moreover,
all compounds of the cyclopentane series 6a–l were more potent than the reference drugs as they showed the same anti-seizure profile (100% protection) at lower doses on molecular bases (Table 1). The different congeners of this series showed anticonvulsant potential in the following decreasing order:

\[ 6g > 6b = 6d > 6i > 6a > 6e > 6f > 6k > 6c > 6j > 6l > 6h \]

**Table 1.** Anticonvulsant potential (scPTZ and MES screens) of compounds 6a–x as well as the reference standards, Phenobarbital, Ethosuximide and Diphenylhydantoin in adult male albino mice.

| Compound Nr. | Dose (mmol/kg) * | % Protection scPTZ | % Protection MES |
|--------------|------------------|--------------------|-----------------|
| 6a           | 0.0280           | 100                | 50              |
| 6b           | 0.0180           | 100                | 50              |
| 6c           | 0.0570           | 100                | 60              |
| 6d           | 0.0180           | 100                | 50              |
| 6e           | 0.0320           | 100                | 100             |
| 6f           | 0.0320           | 100                | 60              |
| 6g           | 0.0086           | 100                | 60              |
| 6h           | 0.1300           | 100                | 60              |
| 6i           | 0.0230           | 100                | 33              |
| 6j           | 0.0600           | 100                | 20              |
| 6k           | 0.0350           | 100                | 40              |
| 6l           | 0.0780           | 100                | 0               |
| 6m           | 0.0360           | 100                | 33              |
| 6n           | 0.1400           | 100                | 66              |
| 6o           | 0.2700           | 100                | 50              |
| 6p           | 0.1400           | 100                | 0               |
| 6q           | 0.0690           | 100                | 80              |
| 6r           | 0.0310           | 100                | 0               |
| 6s           | 0.0350           | 100                | 0               |
| 6t           | 0.0310           | 100                | 0               |
| 6u           | 0.2500           | 83.3               | 33              |
| 6v           | 0.0470           | 100                | 60              |
| 6w           | 0.0560           | 100                | 40              |
| 6x           | 0.0320           | 100                | 60              |
| Phenobarbital | 0.1300         | 100                | -               |
| Ethosuximide  | 1.0600          | 100                | -               |
| Diphenylhydantoin | 0.1600    | -                  | 100             |

* The minimal dose which exhibits the maximum anticonvulsant activity; The dash (-) indicates the absence of anticonvulsant activity at the tested dose level.

Regarding the cyclohexane series 6m-x, compounds 6r (R\(^1\) = 4-CH\(_3\), R\(^2\) = -CH\(_2\)CH\(_2\)Ph) and 6t (R\(^1\) = 4-OCH\(_3\), R\(^2\) = -CH\(_2\)Ph) exhibited the highest anticonvulsant potential with 100% protection against PTZ-induced seizures in mice at the same dose level of 0.031 mmol/kg. Meanwhile, compound 6o (R\(^1\) = H, R\(^2\) = -CH\(_2\)CH\(_2\)Ph) and compound 6u (R\(^1\) = 4-OCH\(_3\), R\(^2\) = -CH\(_2\)CH\(_2\)Ph) require high doses to achieve the 100% protection (0.27 and 0.25 mmol/kg, respectively).
The different congeners of the cyclohexane series $6m$–$x$ showed a decrease in the anticonvulsant potential in the following decreasing order:

$$6r = 6t > 6x > 6s > 6m > 6v > 6w > 6q > 6n = 6p > 6u > 6o$$

Concerning the MES test, the dose which exerted 100% anticonvulsant protection in the scPTZ screening has been selected. In this screening test, all of the compounds showed protection in half or more of the tested mice after 0.5 h post administration except compounds $6i$, $6j$, $6k$, $6m$, $6u$ and $6w$. On the other hand, compounds $6l$, $6p$, $6r$, $6s$ and $6t$ were devoid from anticonvulsant activity. Meanwhile, $6e$ ($R^1 = 4$-CH$_3$, $R^2 = -$CH$_2$Ph) exhibited 100% protection at dose level of 0.032 mmol/kg being more potent than the reference drug, Diphenylhydantoin, which exerted the same protection at a dose level of 0.16 mmol/kg. It is worthwhile to mention that, compound $6e$ displayed 100% protection against both scPTZ and MES-induced seizures in mice.

Compounds showed 100% protection in scPTZ and/or MES screens, were subjected to median effective dose (ED$_{50}$) estimation as well as to minimal motor impairment (neurotoxicity) evaluation. Table 2 summarizes ED$_{50}$ of the selected test compounds along with their neurotoxicity evaluation. Compound $6g$ gave an ED$_{50}$ of 0.0043 mmol/kg $\equiv$ 1.5 mg/kg in the scPTZ screen being about 14 and 214 fold more potent than the reference drugs, Phenobarbital (ED$_{50}$ = 0.06 mmol/kg $\equiv$ 13.2 mg/kg) and Ethosuximide (ED$_{50}$ = 0.92 mmol/kg $\equiv$ 130 mg/kg), respectively. In the MES screen, only compound $6e$ showed 100% protection against induced seizures with ED$_{50}$ of 0.019 mmol/kg $\equiv$ 7.0 mg/kg being about 1.8 fold more potent than that of the reference drug, Diphenylhydantoin (ED$_{50}$ = 0.034 mmol/kg $\equiv$ 9.5 mg/kg [19]). Interestingly, all the test compounds did not show any minimal motor impairment at the maximum administered dose in the neurotoxicity screen.

**Table 2.** Median effective dose (ED$_{50}$, mg/kg) of compounds $6a$–$t$ and $6v$–$x$ exhibiting 100% protection against scPTZ-induced seizures and their neurotoxicity in adult male albino mice using Phenobarbital and Ethosuximide as reference standards.

| Compound Nr. | ED$_{50}$ (Confidence Limits) | Neurotoxicity * |
|--------------|-------------------------------|-----------------|
| $6a$         | 4.5 (6.85–2.96)               | 0/6             |
| $6b$         | 2.5 (3.56–1.76)               | 0/6             |
| $6c$         | 11.5 (13.66–9.68)             | 0/6             |
| $6d$         | 2.4 (4.10–1.40)               | 0/6             |
| $6e$ **      | 6.0 (7.95–4.53)               | 0/6             |
| $6f$         | 2.5 (2.84–2.20)               | 0/6             |
| $6g$         | 1.5 (2.40–0.94)               | 0/6             |
| $6h$         | 19.0 (25.24–14.30)            | 0/6             |
| $6i$         | 4.2 (6.82–2.59)               | 0/6             |
| $6j$         | 13.5 (15.38–11.85)            | 0/6             |
| $6k$         | 6.5 (8.44–4.27)               | 0/6             |
| $6l$         | 16.5 (19.65–13.85)            | 0/6             |
| $6m$         | 4.0 (6.92–2.31)               | 0/6             |
| $6n$         | 25.0 (33.35–18.74)            | 0/6             |
| $6o$         | 35.0 (66.42–18.44)            | 0/6             |
| $6p$         | 24.0 (32.24–17.87)            | 0/6             |
| $6q$         | 10.0 (13.67–7.32)             | 0/6             |
Table 2. Cont.

| Compound Nr. | ED$_{50}$ (Confidence Limits) | Neurotoxicity * |
|--------------|-------------------------------|----------------|
| 6r           | 4.0 (6.14–2.60)               | 0/6            |
| 6s           | 6.0 (8.79–4.09)               | 0/6            |
| 6t           | 6.0 (8.44–4.27)               | 0/6            |
| 6v           | 6.5 (11.89–3.55)              | 0/6            |
| 6w           | 12.0 (15.42–9.34)             | 0/6            |
| 6x           | 6.0 (11.00–3.27)              | 0/6            |
| Phenobarbital| 13.2 (15.90–6.80)             | ND             |
| Ethosuximide | 130.0 (111–150)               | ND             |

* Rotarod test: number of animals exhibiting neurotoxicity/number of animals tested; ** ED$_{50}$ in MES screen = 7.0 mg/kg; ND: not determined.

3. Experimental Section

3.1. Chemistry

All melting points were determined using Electrothermal Capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin film (for oils) in NaCl discs or as KBr pellets (for solids) with JASCO FT/IR-6100 spectrometer and values are represented in cm$^{-1}$. $^1$H-NMR (500 MHz) and $^{13}$C-NMR (125 MHz) spectra were carried out on Jeol ECA 500 MHz spectrometer using TMS as internal standard and chemical shift values were recorded in ppm on $\delta$ scale. The $^1$H-NMR data were represented as follows: chemical shifts, multiplicity (s. singlet, d. doublet, t. triplet, m. multiplet, br. broad), number of protons, and type of protons. The $^{13}$C-NMR data were represented as chemical shifts and type of carbons. Mass spectral data were obtained with electron impact (EI) ionization technique at 70 eV from a Finnigan Mat SSQ-7000 Spectrometer. Elemental analyses were carried out in Microanalytical Units at National Research Centre and Cairo University. Silica gel TLC (thin layer chromatography) cards from Merck (silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for thin layer chromatography. Visualization was performed by illumination with UV light source (254 nm). Column chromatography was carried out on silica gel 60 (0.063–0.200 mm) obtained from Merck.

3.1.1. General Procedure for the Synthesis of 1-(Arylamino)cycloalkanecarbonitriles (1a–f)

A solution of potassium cyanide (9.75 g, 0.15 mol) in water (25 mL) was added drop-wise to a solution of cycloalkanone (0.15 mol) and the appropriate aniline derivative (0.15 mol) in glacial acetic acid (75 mL). The reaction mixture was stirred mechanically at room temperature for 24 h. The precipitated product was filtered off, washed with water, dried and recrystallized from petroleum ether (40–60 °C) to afford 1a–f. The spectral data of compounds 1a–f were consistent with the published ones (cited below).

1-(Phenylamino)cyclopentanecarbonitrile (1a) [20]. Yield: 92%; white solid, m.p. 60 °C.

1-[(4-Methylphenyl)amino]cyclopentanecarbonitrile (1b) [21]. Yield: 89%; buff solid, m.p. 56 °C.

1-[(4-Methoxyphenyl)amino]cyclopentanecarbonitrile (1c) [22]. Yield: 80%; brown solid, m.p. 132 °C.
1-(Phenylamino)cyclohexanecarbonitrile (1d) [23]. Yield: 75%; white solid, m.p. 74–76 °C.

1-[(4-Methylphenyl)amino]cyclohexanecarbonitrile (1e) [24]. Yield: 75%; yellowish white solid, m.p. 76–78 °C.

1-[(4-Methoxyphenyl)amino]cyclohexanecarbonitrile (1f) [24]. Yield: 84.5%; buff solid, m.p. 76 °C.

3.1.2. General Procedure for the Synthesis of 1-(Arylamino)cycloakanecarboxamides (2a–f)

The appropriate nitrile derivative 1a–f (0.125 mol) was dissolved in cold concentrated sulfuric acid (20 mL). After remaining at room temperature for 48 h, the reaction mixture was poured over crushed ice and rendered alkaline with 25% ammonium hydroxide solution. The precipitated amide was filtered off, washed with water, dried and recrystallized from ethanol to give 2a–f. The spectral data of compounds 2a–f were consistent with the published ones (cited below).

1-(Phenylamino)cyclopentanecarboxamide (2a) [25]. Yield: 90%; white solid, m.p. 166 °C.

1-[(4-Methylphenyl)amino]cyclopentanecarboxamide (2b) [26]. Yield: 85%; buff solid, m.p. 120 °C.

1-[(4-Methoxyphenyl)amino]cyclopentanecarboxamide (2c) [27]. Yield: 50%; buff solid, m.p. 90–93 °C.

1-(Phenylamino)cyclohexanecarboxamide (2d) [24]. Yield: 85%; white solid, m.p. 148 °C.

1-[(4-Methylphenyl)amino]cyclohexanecarboxamide (2e) [27]. Yield: 85%; white solid, m.p. 154 °C.

1-[(4-Methoxyphenyl)amino]cyclohexanecarboxamide (2f) [27]. Yield: 75%; buff solid, m.p. 110 °C.

3.1.3. General Procedure for the Synthesis of 1-[(Aryl)(cyanomethyl)amino]cycloakanecarboxamides (3a–f)

Paraformaldehyde (1.52 g, 0.05 mol) was added to a solution of the appropriate 1-(arylamino)cycloakanecarboxamides (2a–f) (0.05 mol) in glacial acetic acid (30 mL). A solution of potassium cyanide (3.9 g, 0.06 mol) was added drop-wise to the stirred and cooled (15 °C) reaction mixture. The temperature was raised gradually to 45 °C over 30 min and was maintained at 50–60 °C for 3 h. After cooling to 35 °C, a 37% formaldehyde solution (5 mL) was added and the reaction mixture was stirred at room temperature for 18 h. Water (30 mL) was added, the reaction mixture was cooled and neutralized with 10% sodium carbonate solution. The precipitated product was extracted with CH₂Cl₂ (3 × 50 mL), washed with water (2 × 30 mL), dried (Na₂SO₄) and evaporated under vacuum to give the anticipated compounds 3a–f. The crude 3a–f were pure enough to be used in the following step without any further purification. The spectral data of compounds 3a–f were consistent with the published ones (cited below).

1-[(Cyanomethyl)(phenyl)amino]cyclopentanecarboxamide (3a) [16]. Yield: 78%; pale yellow viscous oil.
1-[(Cyanomethyl)(4-methylphenyl)amino]cyclopentanecarboxamide (3b) [16]. Yield: 86.6%; pale yellow viscous oil.

1-[(Cyanomethyl)(4-methoxyphenyl)amino]cyclopentanecarboxamide (3c) [16]. Yield: 80%; pale yellow viscous oil.

1-[(Cyanomethyl)(phenyl)amino]cyclohexanecarboxamide (3d) [16]. Yield: 85%; yellowish white solid, m.p. 135 °C.

1-[(Cyanomethyl)(4-methylphenyl)amino]cyclohexanecarboxamide (3e) [16]. Yield: 95%; buff solid, m.p. 83 °C.

1-[(Cyanomethyl)(4-methoxyphenyl)amino]cyclohexanecarboxamide (3f) [16]. Yield: 97%; buff solid, m.p. 103 °C.

3.1.4. General Procedure for the Synthesis of [(Aryl)(1-carbamoylcycloalkyl)amino]acetic Acids (4a–f)

A mixture of the appropriate cyanomethyl derivative 3a–f (0.01 mol) and NaOH (0.48 g, 0.012 mol) in 50% aqueous ethanol (25 mL) was stirred under reflux for 18 h, until complete evolution of ammonia was ceased. The ethanol was removed by evaporation under vacuum. The residue was extracted with ethyl acetate (2 × 15 mL) and the aqueous layer was acidified with 2 N HCl. The acidic layer was extracted with ethyl acetate (3 × 15 mL), dried (Na2SO4) and evaporated under reduced pressure to yield compounds 4a–f. The crude 4a–f were pure enough to be used in the following step without any further purification. The spectral data of compounds 4a–f were consistent with the published ones (cited below).

[(1-Carbamoylcyclopentyl)(phenyl)amino]acetic acid (4a) [16]. Yield: 85%; white solid, m.p. 120–121 °C.

[(1-Carbamoylcyclopentyl)(4-methylphenyl)amino]acetic acid (4b) [16]. Yield: 80%; yellowish white solid, m.p. 118 °C.

[(1-Carbamoylcyclopentyl)(4-methoxyphenyl)amino]acetic acid (4c) [16]. Yield: 70%; buff solid, m.p. 105 °C.

[(1-Carbamoylcyclohexyl)(phenyl)amino]acetic acid (4d) [16]. Yield: 70%; white solid, m.p. 186 °C.

[(1-Carbamoylcyclohexyl)(4-methylphenyl)amino]acetic acid (4e) [16]. Yield: 80%; buff solid, m.p. 188 °C.

[(1-Carbamoylcyclohexyl)(4-methoxyphenyl)amino]acetic acid (4f) [16]. Yield: 70%; buff solid, m.p. 163 °C.
3.1.5. General Procedure for the Synthesis of 6-Aryl-6,9-diazaspiro-[4.5]decane-8,10-diones (5a–c) and 1-Aryl-1,4-diazaspiro[5.5]undecane-3,5-diones (5d–f)

4 N HCl (40 mL, 0.16 mol) was added to a solution of the appropriate carboxylic acid derivative 4a–f (0.01 mol) and ethylenediamine (3.61 g, 0.06 mol) in dioxan (60 mL). The reaction mixture was refluxed under stirring for 18 h. The solvent was evaporated in vacuo and the residue was neutralized (pH 6–7) with 5% NaHCO3 solution till no effervescence occured, extracted with CH2Cl2 (3 × 20 mL), dried (Na2SO4) and the organic layer was evaporated under reduced pressure to give compounds 5a–f. The crude 5a–f were pure enough to be used in the following step without any further purification. The spectral data of compounds 5a–f were consistent with the published ones (cited below).

6-Phenyl-6,9-diazaspiro[4.5]decane-8,10-dione (5a) [16]. Yield: 50%; white solid, m.p. 73–74 °C.

6-(4-Methylphenyl)-6,9-diazaspiro[4.5]decane-8,10-dione (5b) [16]. Yield: 60%; white solid, m.p. 88 °C.

6-(4-Methoxyphenyl)-6,9-diazaspiro[4.5]decane-8,10-dione (5c) [16]. Yield: 50%; buff solid m.p. 60 °C.

1-Phenyl-1,4-diazaspiro[5.5]undecane-3,5-dione (5d) [16]. Yield: 80%; white solid, m.p. 162 °C.

1-(4-Methylphenyl)-1,4-diazaspiro[5.5]undecane-3,5-dione (5e) [16]. Yield: 85%; white solid, m.p. 183 °C.

1-(4-Methoxyphenyl)-1,4-diazaspiro[5.5]undecane-3,5-dione (5f) [16]. Yield: 60%; buff solid, m.p. 110 °C.

3.1.6. General Procedure for the Synthesis of 6-Aryl-9-substituted-6,9-diazaspiro-[4.5]decane-8,10-diones (6a–i) and 1-Aryl-4-substituted-1,4-diazaspiro[5.5]undecane-3,5-diones (6m–u)

To a mixture of the appropriate diketopiperazine derivative 5a–f (0.01 mol) in acetone (100 mL), was added the proper alkylation agent (0.07 mol), namely methyl bromoacetate, benzyl chloride or phenethylbromide in the presence of K2CO3 (0.01 mol) and a catalytic amount of tetrabutylammonium bromide (0.001 mol) as a phase transfer catalyst. The reaction mixture was heated under reflux for 7 h, cooled to room temperature, filtered and the filtrate was evaporated under vacuum. The residue was purified using column chromatography (chloroform:ethyl acetate, 9:1) to furnish the target compounds 6a–i and 6m–u.

Methyl 2-(8,10-dioxo-6-phenyl-6,9-diazaspiro[4.5]decane-9-yl)acetate (6a). Yield: 65%; yellow viscous oil; IR (KBr, ν, cm−1) absence of NH band at 3100 and exhibited bands at 1752 (carbonyl ester), 1720, 1685 (imide carbonyls), 609, 557; 1H-NMR (CDCl3) δ ppm 1.80 (br.s, 4H, 2 × CH2, cyclopentyl), 2.00–2.37 (m, 4H, 2 × CH2, cyclopentyl), 3.76 (s, 3H, COOCH3), 4.32 (s, 2H, O=C-CH2-N), 4.58 (s, 2H, N-CH2-COO), 7.02–7.32 (m, 5H, Har); 13C-NMR (CDCl3) δ ppm 25.08, 36.25 (4 × CH2, cyclopentyl), 40.12 (CH2-COOCH3), 52.59, 56.59 (O=C-CH2-N, COOCH3), 69.65 (Cq), 124.82,
128.48, 129.32 (CH ar.), 148.71 (Car.), 169.91, 170.11, 176.18 (3 × C=O); MS (EI) m/z (%): 316.2 ([M]+, 17), 91 (100), 172.2 (90); Anal. Calcd for C17H20N2O4 (316.35): C, 64.54%; H, 6.37%; N, 8.86%. Found: C, 64.51%; H, 6.15%; N, 8.66%.

9-Benzyl-6-phenyl-6,9-diazaspiro[4.5]decane-8,10-dione (6b). Yield: 60%; Yellow viscous oil; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1725, 1678 (imide carbonyls), 604, 555; ¹H-NMR (CDCl₃) δ ppm 1.79–2.30 (m, 8H, 4 × CH₂, cyclopentyl), 4.27 (s, 2H, O=C-CH₂-N), 5.10 (s, 2H, CH₂-C₆H₅), 6.85–6.86 (m, 2H, H ar.), 7.05–7.17 (m, 3H, H ar.), 7.30–7.34 (m, 5H, H ar.); ¹³C-NMR (CDCl₃) δ ppm 25.50, 36.70 (4 × CH₂, cyclopentyl), 42.6 (CH₂-C₆H₅), 56.91 (O=C-CH₂-N), 67.27 (Cq), 124.71, 126.96, 127.49, 128.21, 128.40, 129.42 (CH ar.), 136.81, 148.76 (2 × Car.), 170.33, 176.00 (2 × C=O); MS (EI) m/z (%): 334.3 ([M]+, 15), 91 (100), 77.1 (40); Anal. Calcd. for C₂₁H₂₂N₂O₂ (334.41): C, 75.42%; H, 6.63%; N, 8.38%. Found: C, 75.32%; H, 6.61%; N, 8.17%.

9-Phenethyl-6-phenyl-6,9-diazaspiro[4.5]decane-8,10-dione (6c). Yield: 71.5%; yellow viscous oil; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1725, 1677 (carbonyl imides), 575, 500; ¹H-NMR (CDCl₃) δ ppm 1.77 (br.s, 4H, 2 × CH₂, cyclopentyl), 1.96 (s, 2H, CH₂, cyclopentyl), 2.25 (s, 2H, CH₂, cyclopentyl), 2.85 (t, 2H, J = 7.5 Hz, CH₂-C₆H₅), 4.09 (t, 2H, J = 7.5 Hz, CH₂-CH₂-C₆H₅), 4.24 (s, 2H, O=C-CH₂-N), 6.95–7.12 (m, 3H, H ar.), 7.26–7.32 (m, 7H, H ar.); ¹³C-NMR (CDCl₃) δ ppm 25.05, 33.92 (4 × CH₂, cyclopentyl), 36.59, 40.53 (CH₂-C₆H₅, CH₂-CH₂-C₆H₅), 56.92 (O=C-CH₂-N), 63.71 (Cq), 124.53, 124.62, 126.52, 128.45, 128.61, 129.05 (CH ar.), 138.27, 148.82 (2 × Car.), 170.03, 175.97 (2 × C=O); MS (EI) m/z (%): 348.23 ([M]+, 22), 91 (100), 172.1 (65), 229 (65); Anal. Calcd. for C₂₂H₂₄N₂O₂ (348.44): C, 75.38%; H, 6.94%; N, 8.04%. Found: C, 75.41%; H, 6.91%; N, 8.23%.

Methyl 2-(8,10-dioxo-6-(4-methylphenyl)-6,9-diazaspiro[4.5]decane-9-yl)acetate (6d). Yield: 79%; yellow viscous oil; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1752 (carbonyl ester), 1722, 1686 (imide carbonyls), 607, 564; ¹H-NMR (CDCl₃) δ ppm 1.73–1.77 (br.s, 4H, 2 × CH₂, cyclopentyl), 1.96 (s, 2H, CH₂, cyclopentyl), 2.25 (s, 2H, CH₂, cyclopentyl), 2.85 (t, 2H, J = 7.5 Hz, CH₂-C₆H₅), 4.23 (s, 2H, O=C-CH₂-N), 6.95–7.12 (m, 2H, H ar.), 7.05 (d, 2H, J = 8.6 Hz, H ar.), 7.26–7.32 (m, 3H, H ar.); ¹³C-NMR (CDCl₃) δ ppm 21.31 (CH₃), 25.62, 36.85 (4 × CH₂, cyclopentyl), 40.16 (CH₂-COOCH₃), 52.53, 56.89 (O=C-CH₂-N, COOCH₃), 69.81 (Cq), 124.90, 130.57, (CH ar.), 134.56, 146.22 (2 × Car.), 170.17, 176.01 (2 × C=O); MS (EI) m/z (%): 330.24 ([M]+, 24), 105.1 (100), 186.2 (53); Anal. Calcd. for C₁₈H₂₂N₂O₄ (330.38): C, 65.44%; H, 6.71%; N, 8.48%. Found: C, 65.21%; H, 6.63%; N, 8.38%.

9-Benzyl-6-(4-methylphenyl)-6,9-diazaspiro[4.5]decane-8,10-dione (6e). Yield: 90%; colourless viscous oil; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1725, 1678 (imide carbonyls), 634, 582; ¹H-NMR (CDCl₃) δ ppm 1.75–1.91 (m, 8H, 4 × CH₂, cyclopentyl), 2.23 (s, 3H, CH₃), 3.75 (s, 3H, COOCH₃), 4.23 (s, 2H, O=C-CH₂-N), 4.65 (s, 2H, CH₂-COOCH₃), 6.91 (d, 2H, J = 8.6 Hz, H ar.), 7.05 (d, 2H, J = 8.6 Hz, H ar.), 7.25 (d, 2H, J = 8.6 Hz, H ar.); ¹³C-NMR (CDCl₃) δ ppm 20.85 (CH₃), 25.12, 36.85 (4 × CH₂, cyclopentyl), 40.16 (CH₂-COOCH₃), 52.53, 56.89 (O=C-CH₂-N, COOCH₃), 69.81 (Cq), 124.90, 130.57, (CH ar.), 134.56, 146.22 (2 × Car.), 170.17, 176.01 (2 × C=O); MS (EI) m/z (%): 364.26 ([M]+, 28), 91 (100), 105 (98); Anal. Calcd. for C₂₂H₂₄N₂O₃ (364.44): C, 72.50%; H, 6.64%; N, 7.69%. Found: C, 72.43%; H, 6.75%; N, 7.81%.
6-(4-Methylphenyl)-9-phenethyl-6,9-diazaspiro[4.5]decane-8,10-dione (6f). Yield: 71.2%; yellow viscous oil; IR (KBr, v, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1725, 1678 (imide carbonyls), 2.20–2.27 (m, 3H, CH₃), 2.84 (t, J = 7.7 Hz, 2H, CH₂-C₆H₅), 4.04 (t, 2H, J = 7.7 Hz, CH₂-CH₂), 4.16 (s, 2H, O=C-CH₂-N), 7.21 (d, 2H, J = 6.7 Hz, Har.), 7.24 (d, 2H, J = 6.7 Hz, Har.), 7.25–7.26 (m, 5H, Har.); ¹³C-NMR (CDCl₃) δ ppm 20.83 (CH₃), 25.09, 34.08 (4 × CH₂, cyclopentyl), 36.59, 40.58 (CH₂-C₆H₅, CH₂-CH₂-C₆H₅), 56.90 (O=C-CH₂-N), 69.88 (Cq), 124.63, 126.56, 128.68, 128.68, 129.13 (CH₃), 134.40, 138.39, 146.30 (3 × Car.), 170.30, 176.18 (2 × C=O); MS (EI) m/z (%): 362.2 ([M]+, 15), 81(100); Anal. Calcd. for C₂₃H₂₇N₂O₂ (362.46): C, 76.21%; H, 7.23%; N, 7.73%. Found: C, 76.02%; H, 7.15%; N, 7.89%.

Methyl 2-(6-(4-methoxyphenyl)-8,10-dioxo-6,9-diazaspiro[4.5]decan-9-yl)acetate (6g). Yield: 71.4%; yellow viscous oil; IR (KBr, v, cm⁻¹) absence of NH band at 3100 and exhibited bands 1752 (carbonyl ester), 1720, 1685 (imide carbonyls), 3.82 (s, 6H, COOCH₃, OCH₃), 4.25 (s, 2H, O=C-CH₂-N), 4.61 (s, 2H, CH₂-COOCH₃), 6.83 (d, 2H, J = 9.0 Hz, Har.), 7.12 (d, 2H, J = 9.0 Hz, Har.); ¹³C-NMR (CDCl₃) δ ppm 24.95, 36.24 (4 × CH₂, cyclopentyl), 40.19 (CH₂-COOCH₃), 51.97, 52.44, 55.45 (O=C-CH₂-N, COOCH₃, OCH₃), 70.68 (Cq), 114.40, 114.99 (CH₃), 133.40, 157.42, 169.69, 170.59, 176.19 (3 × C=O); MS (EI) m/z (%): 346.23 ([M]+, 17), 121.14 (100), 77.1 (29); Anal. Calcd. for C₁₈H₂₂N₂O₅ (346.38): C, 62.42%; H, 6.40%; N, 8.09%. Found: C, 62.22%; H, 6.35%; N, 8.22%.

9-Benzyl-6-(4-methoxyphenyl)-6,9-diazaspiro[4.5]decane-8,10-dione (6h). Yield: 90%; yellow viscous oil; IR (KBr, v, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1725, 1678 (imide carbonyls), 6.67 (d, 2H, J = 8.5 Hz, Har.), 6.75 (d, 2H, J = 8.5 Hz, Har.), 7.28–7.39 (m, 5H, Har.); ¹³C-NMR (CDCl₃) δ ppm 25.58, 36.40 (4 × CH₂, cyclopentyl), 39.0 (CH₂-C₆H₅), 42.63 (O=C-CH₂-N), 55.48 (OCH₃), 73.15 (Cq), 114.40, 114.99, 126.50, 127.54, 128.18 (CH₃), 135.47, 136.78, 141.35 (3 × Car.), 170.43, 172.47 (2 × C=O); MS (EI) m/z (%): 364.2 (100), 91 (85); Anal. Calcd. for C₂₂H₂₄N₂O₃ (364.44): C, 72.50%; H, 6.64%; N, 7.96%. Found: C, 72.33%; H, 6.46%; N, 7.79%.

6-(4-Methoxyphenyl)-9-phenethyl-6,9-diazaspiro[4.5]decane-8,10-dione (6i). Yield: 90%; yellow viscous oil; IR (KBr, v, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1722, 1687 (imide carbonyls), 6.68 (d, 2H, J = 9.0 Hz, Har.), 6.79 (d, 2H, J = 9.0 Hz, Har.), 7.28–7.39 (m, 5H, Har.); ¹³C-NMR (CDCl₃) δ ppm 24.94, 36.40 (4 × CH₂, cyclopentyl), 39.0 (CH₂-C₆H₅), 42.63 (O=C-CH₂-N), 55.41 (OCH₃), 73.15 (Cq), 114.27, 114.96, 126.50, 127.54, 128.18 (CH₃), 135.47, 136.78, 141.35 (3 × Car.), 170.43, 172.47 (2 × C=O); MS (EI) m/z (%): 378.24 ([M]+, 40), 121 (100); Anal. Calcd. for C₂₃H₂₆N₂O₃ (378.46): C, 72.99%; H, 6.92%; N, 7.40%. Found: C, 72.66%; H, 6.99%; N, 7.58%.

9-Benzyl-6-(4-methoxyphenyl)-6,9-diazaspiro[4.5]decane-8,10-dione (6j). Yield: 90%; yellow viscous oil; IR (KBr, v, cm⁻¹) absence of NH band at 3100 and exhibited bands 1725, 1678 (imide carbonyls), 6.68 (d, 2H, J = 9.0 Hz, Har.), 6.79 (d, 2H, J = 9.0 Hz, Har.), 7.28–7.39 (m, 5H, Har.); ¹³C-NMR (CDCl₃) δ ppm 24.94, 36.40 (4 × CH₂, cyclopentyl), 39.0 (CH₂-C₆H₅), 42.63 (O=C-CH₂-N), 55.41 (OCH₃), 73.15 (Cq), 114.27, 114.96, 126.50, 128.17, 129.00 (CH₃), 135.47, 136.78, 141.35 (3 × Car.), 170.43, 172.47 (2 × C=O); MS (EI) m/z (%): 364.22 ([M]+, 17), 121.14 (100), 77.1 (29); Anal. Calcd. for C₂₂H₂₄N₂O₃ (364.44): C, 72.50%; H, 6.64%; N, 7.96%. Found: C, 72.33%; H, 6.46%; N, 7.79%.
Methyl 2-(3,5-dioxo-1-phenyl-1,4-diazaspiro[5.5]undecane-4-yl)acetate (6m). Yield: 78%; white solid m.p. 118 °C; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1760 (carbonyl ester), 1726, 1675 (imide carbonyls), 633, 588; ¹H-NMR (CDCl₃) δ ppm 1.41–2.00 (m, 10H, 5 × CH₂, cyclohexyl), 3.72 (s, 3H, COOCH₃), 4.11 (s, 2H, O=C-CH₂-N), 4.56 (s, 2H, CH₂-COOCH₃), 7.12–7.25 (m, 5H, CH₃); ¹³C-NMR (CDCl₃) δ ppm 20.46, 25.52, 31.48 (5 × CH₂, cyclohexyl), 40.19 (CH₂-COOCH₃), 59.11 (O=C-CH₂-N), 60.59 (Cq), 126.01, 127.28, 129.36 (CH₃, 147.95 (C₆H₅), 168.46, 170.56, 176.27 (3 × C=O); MS (EI) m/z (%): 330.1 ([M]+, 80), 186.2 (100), 91.1 (49); Anal. Calcd. for C₁₈H₂₂N₂O₄: C, 65.44%; H, 6.71%; N, 8.48%. Found: C, 65.52%; H, 6.68%; N, 8.31%.

4-Benzyl-1-phenyl-1,4-diazaspiro[5.5]undecane-3,5-dione (6n). Yield: 80%; colourless viscous oil; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1725, 1678 (imide carbonyls), 634, 582; ¹H-NMR (CDCl₃) δ ppm 1.48–1.97 (m, 10H, 5 × CH₂, cyclohexyl), 4.11 (s, 2H, O=C-CH₂-N), 5.03 (s, 2H, CH₂-C₆H₅), 6.86 (s, 2H, CH₃), 6.86–7.13 (m, 5H, CH₃), 7.38–7.39 (m, 5H, CH₃); ¹³C-NMR (CDCl₃) δ ppm 20.53, 25.63, 31.57 (5 × CH₂, cyclohexyl), 42.66, 55.37 (CH₂-C₆H₅, O=C-CH₂-N), 60.71 (Cq), 125.84, 127.08, 128.52, 129.17, 129.31, 129.76 (CH₃, 136.94, 148.06 (2 × C₆H₅), 170.94, 176.42 (2 × C=O); MS (EI) m/z (%): 348.2 ([M]+, 100), 186.2 (70), 91.1 (58); Anal. Calcd. for C₂₂H₂₄N₂O₂ (348.44): C, 75.83%; H, 6.94%; N, 8.04%. Found: C, 75.78%; H, 6.88%; N, 8.27%.

4-Phenethyl-1-phenyl-1,4-diazaspiro[5.5]undecane-3,5-dione (6o). Yield: 64.5%; buff solid, m.p. 138 °C; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1720, 1681 (imide carbonyls), 592, 555; ¹H-NMR (CDCl₃) δ ppm 1.48–1.96 (m, 10H, 5 × CH₂, cyclohexyl), 2.87 (t, 2H, J = 7.6 Hz, CH₂-C₆H₅), 4.08 (s, 2H, CH₂-C₆H₅), 4.12 (s, 2H, O=C-CH₂-N), 6.99–7.00 (m, 2H, CH₃), 7.23–7.29 (m, 8H, CH₃); ¹³C-NMR (CDCl₃) δ ppm 20.57, 25.63, 31.56 (5 × CH₂, cyclohexyl), 34.12, 40.61 (CH₂-C₆H₅, CH₂-C₆H₅), 55.36 (O=C-CH₂-N), 60.48 (Cq), 125.78, 126.61, 128.56, 129.12, 129.40 (CH₃), 138.39, 148.20 (2 × C₆H₅), 170.74, 176.56 (2 × C=O); MS (EI) m/z (%): 362.2 ([M]+, 100), 243.1 (90), 186.1 (70), 91.1 (48); Anal. Calcd. for C₂₃H₂₆N₂O₄ (362.46): C, 76.21%; H, 7.23%; N, 7.73%. Found: C, 76.41%; H, 7.42%; N, 7.91%.

Methyl 2-(3,5-dioxo-1-(4-methylphenyl)-1,4-diazaspiro[5.5]undecane-4-yl)acetate (6p). Yield: 75%; white solid, m.p. 156–158 °C; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1752 (carbonyl ester), 1726, 1675 (imide carbonyls), 619, 523; ¹H-NMR (CDCl₃) δ ppm 1.49–1.98 (m, 10H, 5 × CH₂, cyclohexyl), 2.28 (s, 3H, CH₃), 2.87 (s, 3H, CH₃), 3.77 (s, 3H, COOCH₃), 3.79 (s, 2H, O=C-CH₂-N), 4.58 (s, 2H, CH₂-COOCH₃), 7.07 (s, 4H, CH₃); ¹³C-NMR (CDCl₃) δ ppm 20.94, 21.15, 31.53 (5 × CH₂, cyclohexyl), 24.35 (CH₃), 40.19 (CH₂-COOCH₃), 52.48, 54.98 (O=C-CH₂-N, CH₂-COOCH₃), 60.79 (Cq), 127.08, 129.99 (CH₃), 135.81, 145.32 (2 × C₆H₅), 168.48, 170.64, 176.30 (3 × C=O); MS (EI) m/z (%): 344.2 ([M]+, 50), 200.1 (100), 105(37), 91.1(29); Anal. Calcd. for C₁₉H₂₄N₂O₄ (344.4): C, 66.26%; H, 7.02%; N, 8.13%. Found: C, 66.17%; H, 7.25%; N, 8.31%.

4-Benzyl-1-(4-methylphenyl)-1,4-diazaspiro[5.5]undecane-3,5-dione (6q). Yield: 70%; white solid m.p. 110 °C; IR (KBr, ν, cm⁻¹) absence of NH band at 3100 and exhibited bands at 1717, 1673 (imide carbonyls), 615, 516; ¹H-NMR (CDCl₃) δ ppm 1.47–1.87 (m, 10H, 5 × CH₂, cyclohexyl), 1.92 (s, 3H, CH₃), 4.07 (s, 2H, O=C-CH₂-N), 5.07 (s, 2H, CH₂-C₆H₅), 6.92 (d, 2H, J = 7.5 Hz, CH₃), 7.30 (d, 2H,
J = 7.5 Hz, Har.), 7.38-7.40 (m, 5H, Har.); $^{13}$C-NMR (CDCl$_3$) $\delta$ ppm 20.57, 20.89, 31.60 (5 $\times$ CH$_2$, cyclohexyl), 25.62 (CH$_3$), 42.66 (CH$_2$-C$_6$H$_5$), 55.31 (O=C-CH$_2$-N), 60.91 (Cq), 126.91, 127.61, 128.49, 128.68, 129.19 (CH$_{ar}$), 129.90 130.16, 145.41 (3 $\times$ Car.), 170.99, 176.41 (2 $\times$ C=O); MS (EI) m/z (%): 362.3 ([M]$^+$, 84), 91.1 (100), 200.2 (93); Anal. Calcd. for C$_{23}$H$_{26}$N$_2$O$_2$ (362.46): C, 76.21%; H, 7.23%; N, 7.73%. Found: C, 76.31%; H, 7.19%; N, 7.75%.

1-(4-Methylphenyl)-4-phenethyl-1,4-diazaspiro[5.5]undecane-3,5-dione (6r). Yield: 59%; white solid, m.p. 92 °C; IR (KBr, $\nu$, cm$^{-1}$) absence of NH band at 3100 and exhibited bands at 1719, 1674 (imide carbonyls), 597, 559; $^1$H-NMR (CDCl$_3$) $\delta$ ppm 1.48–1.94 (m, 10H, 5 $\times$ CH$_2$, cyclohexyl), 2.25 (s, 3H, CH$_3$), 2.87 (t, $J$ = 7.7 Hz, 2H, CH$_2$-C$_6$H$_5$), 4.04 (s, 2H, C$_6$H$_2$-CH$_2$-C$_6$H$_5$), 4.06 (s, 2H, O=C-CH$_2$-N), 7.04 (d, 2H, $J$ = 8.4 Hz, Har.), 7.28 (d, 2H, $J$ = 8.4 Hz, Har.), 7.29–7.30 (m, 5H, Har.); $^{13}$C-NMR (CDCl$_3$) $\delta$ ppm 20.61, 20.91, 25.63 (5 $\times$ CH$_2$, cyclohexyl), 31.58 (CH$_3$), 34.12, 40.58 (CH$_2$-C$_6$H$_5$, CH$_2$-CH$_2$-C$_6$H$_5$), 55.32 (O=C-CH$_2$-NH$_2$), 60.63 (Cq), 126.58, 126.72, 128.53, 129.10, 129.97 (CH$_{ar}$), 135.53, 138.44, 145.56 (3 $\times$ Car.), 170.81, 176.58 (2 $\times$ C=O); MS (EI) m/z (%): 376.25 ([M]$^+$, 70), 257.23 (100); Anal. Calcd. for C$_{24}$H$_{28}$N$_2$O$_2$ (376.49): C, 76.56%; H, 7.50%; N, 7.44%. Found: C, 76.33%; H, 7.75%; N, 7.29%.

Methyl 2-(1-(4-methoxyphenyl)-3,5-dioxo-1,4-diazaspiro[5.5]undecan-4-yl)acetate (6s). Yield: (53.5%); yellow viscous oil; IR (KBr, $\nu$, cm$^{-1}$) absence of NH band at 3100 and exhibited bands at 1752 (carbonyl ester), 1626, 1675 (imide carbonyls), 619, 523; $^1$H-NMR (CDCl$_3$) $\delta$ ppm 1.07–1.47 (m, 10H, 5 $\times$ CH$_2$, cyclohexyl), 3.61 (s, 3H, COOCH$_3$), 3.73 (s, 3H, OCH$_3$), 4.22 (s, 2H, O=C-CH$_2$-N), 4.64 (s, 2H, CH$_2$-COOCH$_3$), 6.75 (d, 2H, $J$ = 8.6 Hz, Har.), 7.04 (d, 2H, $J$ = 8.6 Hz, Har.); $^{13}$C-NMR (CDCl$_3$) $\delta$ ppm 22.88, 25.51, 32.94 (5 $\times$ CH$_2$, cyclohexyl), 37.70 (CH$_2$COOCH$_3$), 51.84, 52.10 (O=C-CH$_2$-N, CH$_2$COOCH$_3$), 55.24 (OCH$_3$), 67.64 (Cq), 113.38, 127.76 (CH$_{ar}$), 141.72, 156.29 (2 $\times$ Car.), 168.2, 170.13, 178.70 (3 $\times$ C=O); MS (EI) m/z (%): 360 ([M]$^+$, 0.5), 218.2 (100), 77 (5); Anal. Calcd. for C$_{19}$H$_{24}$N$_2$O$_5$ (360.40): C, 63.32%; H, 6.71%; N, 7.77%. Found: C, 63.33%; H, 6.81%; N, 7.91%.

1-(4-Methoxyphenyl)-4-benzyl-1,4-diazaspiro[5.5]undecane-3,5-dione (6t). Yield: 63%; yellow viscous oil; IR (KBr, $\nu$, cm$^{-1}$) absence of NH band at 3100 and exhibited bands at 1725, 1675 (imide carbonyls), 615, 516; $^1$H-NMR (CDCl$_3$) $\delta$ ppm 1.41–1.90 (m, 10H, 5 $\times$ CH$_2$, cyclohexyl), 2.28 (s, 3H, OCH$_3$), 4.16 (O=C-CH$_2$-N), 4.94 (s, 2H, CH$_2$-C$_6$H$_5$), 6.67 (d, 2H, $J$ = 7.6 Hz, Har.), 6.90 (d, 2H, $J$ = 7.6 Hz, Har.), 7.23–7.29 (m, 5H, Har.); $^{13}$C-NMR (CDCl$_3$) $\delta$ ppm 20.80, 25.59, 36.66 (5 $\times$ CH$_2$, cyclohexyl), 42.66 (CH$_2$-C$_6$H$_5$), 56.84, 59.07 (O=C-CH$_2$-N, OCH$_3$), 69.94 (Cq), 114.35, 124.97, 127.53, 128.46, 128.87 (CH$_{ar}$), 129.782, 136.89, 145.56 (3 $\times$ Car.), 170.62, 176.18 (2 $\times$ C=O); MS (EI) m/z (%): 378.4 ([M]$^+$, 7), 91.12 (100); Anal. Calcd. for C$_{23}$H$_{26}$N$_2$O$_3$ (378.46): C, 72.99%; H, 6.92%; N, 7.40%. Found: C, 72.75%; H, 6.78%; N, 7.52%.

1-(4-Methoxyphenyl)-4-phenethyl-1,4-diazaspiro[5.5]undecane-3,5-dione (6u). Yield: 66.5%; yellow viscous oil; IR (KBr, $\nu$, cm$^{-1}$) absence of NH band at 3100 and exhibit bands at 1725, 1685 (imide carbonyls), 671, 538; $^1$H-NMR (CDCl$_3$) $\delta$ ppm 1.23–2.05 (m, 10H, 5 $\times$ CH$_2$, cyclohexyl), 2.81 (s, 2H, CH$_2$-C$_6$H$_5$), 3.72 (s, 3H, OCH$_3$), 3.77(s, 2H, CH$_2$-CH$_2$-C$_6$H$_5$), 4.20 (s, 2H, O=C-CH$_2$-N), 6.80–6.81 (m, 5H, Har.), 7.13 (s, 4H, Har.); $^{13}$C-NMR (CDCl$_3$) $\delta$ ppm 22.78, 22.99, 32.11 (5 $\times$ CH$_2$, cyclohexyl), 32.78, 38.02 (CH$_2$-C$_6$H$_5$, CH$_2$-CH$_2$-C$_6$H$_5$), 55.52, 55.70 (O=C-CH$_2$-N, OCH$_3$), 68.20 (Cq),
113.66, 114.60, 117.64, 127.65, 128.23 (CH ar.), 138.23, 140.11, 157.74 (3 × C ar.), 170.22, 176.11 (2 × C=O); MS (EI) m/z (%): 392.39 ([M]+, 14), 105 (60); Anal. Calcd. for C24H28N2O3 (392.49): C, 73.44%; H, 7.19%; N, 7.14%. Found: C, 73.59%; H, 7.15%; N, 7.24%.

3.1.7. General Procedure for the Synthesis of 2-(6-Aryl-8,10-dioxo-6,9-diazaspiro[4.5]decan-9-yl)acetamides (7a–c) and 2-(1-Aryl-3,5-dioxo-1,4-diazaspiro[5.5]undecan-4-yl)acetamides (7d–f)

Chloroacetamide (6.55 g, 0.07 mol) was added to a cold solution of the appropriate cyclized compound 5a–f in acetone (100 mL) in the presence of K2CO3 (1.38 g, 0.01 mol) and a catalytic amount of tetrabutylammonium bromide (0.32 g, 0.001 mol) as a phase transfer catalyst. The reaction mixture was heated under reflux for 7 h. The reaction mixture was filtered off and acetone was evaporated under reduced pressure to give compounds 7a–f. The crude 7a–f were purified via recrystallization from ethanol.

2-(8,10-Dioxo-6-phenyl-6,9-diazaspiro[4.5]decan-9-yl)acetamide (7a). Yield: 95%; yellowish white solid m.p. 104 °C; IR (KBr, ν, cm−1) exhibited bands at 3383.14, 3180.62 (NH2), 1674.21, 1647.21, 1614 (3 × C=O); 1H-NMR (CDCl3) δ ppm 1.75–1.96 (m, 6H, 3 × CH2, cyclopentyl), 2.35 (br.s, 2H, CH2-cyclopentyl), 4.05, 4.44 (2 × s, 4H, O=C-CH2-N, CH2-C=O), 5.97 (s, 2H, NH2), 6.51 (s, 3H, H ar.); 13C-NMR (CDCl3) δ ppm 25.23, 36.73 (4 × CH2, cyclopentyl), 41.36 (CH2-C=O), 56.67 (O=C-CH2-N), 69.83 (Cq), 124.83, 129.30, 131.03 (CH ar.), 148.58 (Car.), 169.08, 169.20, 176.02 (3 × C=O); MS (EI) m/z (%): 301.26 ([M]+, 7), 77.11 (100); Anal. Calcd. for C16H19N3O3 (301.34): C, 63.77%; H, 6.36%; N, 13.94%. Found: C, 63.79%; H, 6.35%; N, 13.92%.

2-(8,10-Dioxo-6-(4-methylphenyl)-6,9-diazaspiro[4.5]decan-9-yl)acetamide (7b). Yield: 98%; yellowish white solid m.p. 120 °C; IR (KBr, ν, cm−1) exhibited bands at 3383.14, 3197.98 (NH2), 1658.78, 1639.49, 1616.35 (3 × C=O); 1H-NMR (CDCl3) δ ppm 1.31–1.93 (m, 8H, 4 × CH2, cyclopentyl), 3.73 (s, 3H, CH3), 3.99, 4.48 (2 s, 4H, O=C-CH2-N, CH2-C=O), 6.14 (s, 2H, NH2), 6.78 (d, 2H, J = 8.7 Hz, H ar.), 7.18 (d, 2H, J = 8.6 Hz, H ar.); 13C-NMR (CDCl3) δ ppm 20.55, 31.52 (4 × CH2, cyclopentyl), 25.51 (CH3), 41.37 (CH2-C=O), 55.45 (O=C-CH2-N), 61.26 (Cq), 114.48, 128.67 (CH ar.), 140.59, 157.7 (2 × Car.), 169.56, 171.05, 176.44 (3 × C=O); MS (EI) m/z (%): 317.28 ([M + 2]+, 16), 121.16 (100); Anal. Calcd. for C17H19N3O3 (315.34): C, 63.77%; H, 6.36%; N, 13.94%. Found: C, 63.79%; H, 6.35%; N, 13.92%.

2-(8,10-Dioxo-6-(4-methoxyphenyl)-6,9-diazaspiro[4.5]decane-9-yl)acetamide (7c). Yield: 98%; yellowish white solid m.p. 73 °C; IR (KBr, ν, cm−1) exhibited bands at 3383.93, 3294.42 (NH2), 1658.78, 1639.49, 1616.35 (3 × C=O); 1H-NMR (CDCl3) δ ppm 1.02–1.47 (m, 4H, 2 × CH2, cyclopentyl), 1.68–2.26 (m, 4H, 2 × CH2, cyclopentyl), 3.77 (s, 3H, OCH3), 4.10, 4.13 (2 × s, 4H, O=C-CH2-N, CH2-C=O-N), 6.41 (s, 2H, NH2), 6.80 (d, 2H, J = 7.5 Hz, H ar.), 7.05 (d, 2H, J = 7.5 Hz, H ar.); 13C-NMR (CDCl3) δ ppm 23.87, 36.40 (4 × CH2, cyclopentyl), 42.05 (CH2-C=O), 55.66 (O=C-CH2-N, OCH3), 70.27 (Cq), 114.35, 126.88 (CH ar.), 141.71, 157.07 (2 × Car.), 169.26, 169.29, 176.12 (3 × C=O); MS (EI) m/z (%): 331.3 ([M]+, 0.44), 67.17 (100); Anal. Calcd. for C17H21N3O4 (331.37): C, 67.62%; H, 6.39%; N, 12.68%. Found: C, 67.61%; H, 6.37%; N, 12.65%.
2-(3,5-Dioxo-1-phenyl-1,4-diazaspiro[5.5]undecan-4-yl)acetamide \((\text{7d})\). Yield: 97%; yellowish white solid m.p. 110 °C; IR (KBr, ν, cm\(^{-1}\)) exhibited bands at 3385.07, 3188.3 (NH\(_2\)), 1670, 1647.2, 1618.2 (3 × C=O); \(^1\)H-NMR (CDCl\(_3\)) δ ppm 1.18–2.01 (m, 10H, 5 × CH\(_2\), cyclohexyl), 4.07, 4.47 (2 × s, 4H, O=C-CH\(_2\)-N, CH\(_2\)-C=O), 6.66 (s, 2H, NH\(_2\)), 7.08-7.13 (m, 5H, H\(_{\text{ar.}}\)); \(^1^3\)C-NMR (CDCl\(_3\)) δ ppm of 24.03, 25.07, 33.15 (5 × CH\(_2\), cyclohexyl), 53.85, 54.93 (CH\(_2\)-C=O, O=C-CH\(_2\)-N), 58.92 (Cq), 127.34, 129.07, 129.3 (CH\(_{\text{ar.}}\)), 147.97 (C\(_{\text{ar.}}\)), 169.45, 169.78, 171.27 (3 × C=O); MS (EI) \(m/z\) (%): 315.26 ([M]+, 4.7), 58.17 (51), 100.2 (100); Anal. Calcd. for C\(_{17}\)H\(_{21}\)N\(_3\)O\(_3\) (315.37): C, 64.74%; H, 6.71%; N, 13.32%. Found: C, 64.77%; H, 6.73%; N, 13.35%.

2-(3,5-Dioxo-1-(4-methylphenyl)-1,4-diazaspiro[5.5]undecan-4-yl)acetamide \((\text{7e})\). Yield: 94%; yellowish white solid m.p. 100 °C; IR (KBr, ν, cm\(^{-1}\)) exhibited bands at 3456.14, 3383.14 (NH\(_2\)), 1662.6, 1647.2, 1614.4 (3 × C=O); \(^1\)H-NMR (CDCl\(_3\)) δ ppm of 1.32–1.57 (m, 10H, 5 × CH\(_2\), cyclohexyl), 2.18 (s, 3H, CH\(_3\)) 3.94, 4.50 (2 × s, 4H, O=C-CH\(_2\)-N, CH\(_2\)-C=O), 5.97, 6.58 (2 × s, 2H, NH\(_2\)), 6.98–7.29 (m, 4H, H\(_{\text{ar.}}\)); \(^1^3\)C-NMR (CDCl\(_3\)) δ ppm 20.35, 22.86, 23.49 (5 × CH\(_2\), cyclohexyl), 25.44 (CH\(_3\)), 41.36 (CH\(_2\)-C=O), 41.50, 42.14 (CH\(_2\)-C=O, O=C-CH\(_2\)-N), 56.39 (OCH\(_3\)), 70.43 (Cq), 127.16, 135.49 (CH\(_{\text{ar.}}\)), 129.41, 145.36 (2 × C\(_{\text{ar.}}\)), 169.0, 169.50, 176.29 (3 × C=O); MS (EI) \(m/z\) (%): 329.32 ([M]+, 50), 257.28 (40), 100.16 (100), 142.18 (63); Anal. Calcd. for C\(_{18}\)H\(_{23}\)N\(_3\)O\(_3\) (329.39): C, 65.63%; H, 7.04%; N, 12.76%. Found: C, 65.66%; H, 7.12%; N, 12.78%.

2-(3,5-Dioxo-1-(4-methoxyphenyl)-1,4-diazaspiro[5.5]undecan-4-yl)acetamide \((\text{7f})\). Yield: 97%; buff solid, m.p. 94 °C; IR (KBr, ν, cm\(^{-1}\)) exhibited bands at 3383.14, 3186.4 (NH\(_2\)), 1678.07, 1670.35, 1654.92 (3 × C=O); \(^1\)H-NMR (CDCl\(_3\)) δ ppm 1.80–2.38 (m, 10H, 5 × CH\(_2\), cyclohexyl), 4.03 (s, 3H, OCH\(_3\)), 4.28, 4.51 (2s, 4H, O=C-CH\(_2\)-N, CH\(_2\)-C=O), 7.01 (d, 2H, \(J = 8.4\) Hz, H\(_{\text{ar.}}\)), 7.08 (d, 2H, \(J = 8.4\) Hz, H\(_{\text{ar.}}\)) 7.26 (s, 2H, NH\(_2\)); \(^1^3\)C-NMR (CDCl\(_3\)) δ ppm 21.25, 25.19, 36.51 (5 × CH\(_2\), cyclohexyl), 41.50, 42.14 (CH\(_2\)-C=O, O=C-CH\(_2\)-N), 56.39 (OCH\(_3\)), 70.43 (Cq), 124.64, 129.81 (CH\(_{\text{ar.}}\)), 135.25, 145.33 (2 × C\(_{\text{ar.}}\)), 169.04, 169.76, 175.66 (3 × C=O); MS (EI) \(m/z\) (%): 315.28 ([M-OCH\(_3\)]+, 13), 105.14 (100), 287.31(10); Anal. Calcd. for C\(_{18}\)H\(_{23}\)N\(_3\)O\(_4\) (345.39): C, 62.59%; H, 6.71%; N, 12.17%. Found: C, 62.57%; H, 6.74%; N, 12.19%.

### 3.1.8. General Procedure for the Synthesis of 2-(6-Aryl-8,10-dioxo-6-phenyl-6,9-diazaspiro[4.5]decan-9-yl)acetonitriles \((\text{8a}–\text{c})\) and 2-(1-Aryl-3,5-dioxo-1,4-diazaspiro[5.5]undecan-4-yl)acetonitriles \((\text{8d}–\text{f})\)

Trifluoroacetic anhydride (6.61 g, 0.03 mol) was added to a solution of the appropriate amide \(\text{7a}–\text{f}\) (0.02 mol) in THF (40 mL) at 0–5 °C. The reaction mixture was stirred at room temperature for 2 h (monitored by TLC). Ammonium bicarbonate (12.43 g, 0.16 mol) was added portion-wise during 5–10 min. and the reaction mixture was stirred at room temperature for a further 45 min., concentrated under vacuum, washed with water (2 × 20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried (Na\(_2\)SO\(_4\)) and evaporated under reduced pressure to afford compounds \(\text{8a}–\text{f}\). The crude compounds \(\text{8a}–\text{f}\) were purified using column chromatography (chloroform:ethyl acetate, 9:1).

2-(8,10-Dioxo-6-phenyl-6,9-diazaspiro[4.5]decan-9-yl)acetonitrile \((\text{8a})\). Yield: 97%; yellowish white solid m.p.70 °C; IR (KBr, ν, cm\(^{-1}\)) absence of amidic NH\(_2\) and exhibited bands at 2848.86 (CN), 1743.65, 1687.71 (2 × C=O); \(^1\)H-NMR (CDCl\(_3\)) δ ppm 1.20–2.30 (m, 8H, 4 × CH\(_2\), cyclopentyl), 4.25,
4.64 (2 × s, 4H, O=C-CH2-N and CH2-CN), 6.68–7.27 (m, 5H, Har.); 13C-NMR (CDCl3) δ ppm 25.18, 26.33 (4 × CH2, cyclopentyl), 29.54 (CH2-CN), 56.61 (O=C-CH2-N), 69.70 (Cq), 114.36 (CN), 124.60, 124.91, 129.27 (CHar.), 148.29 (Car.), 169.36, 175.26 (2 × C=O); MS (EI) m/z (%): 283.25 ([M]+, 25), 91.09 (100), 243.23 (15); Anal. Calcd. for C18H17N3O2 (283.33): C, 67.83%; H, 6.05%; N, 14.83%.

Found: C, 67.85%; H, 6.15%; N, 14.82%.

2-(8,10-Dioxo-6-(4-methylphenyl)-6,9-diazaspiro[4.5]decane-9-yl)acetonitrile (8b). YIELD: 90%; yellowish white solid m.p. 82 °C; IR (KBr, ν, cm−1) absence of amidic NH2 and exhibited bands at 2226.71 (CN), 1735.93, 1689.64 (2 × C=O); 1H-NMR (CDCl3) δ ppm 1.26–1.79 (m, 8H, 4 × CH2, cyclopentyl), 2.34 (s, 3H, CH3), 4.09 (s, 2H, O=C-CH2-N), 4.71 (s, 2H, CH2-CN), 6.80 (d, 2H, J = 8.6 Hz, Har.), 6.90 (d, 2H, J = 8.6 Hz, Har.); 13C-NMR (CDCl3) δ ppm 20.51, 29.69 (2 × CH2, cyclopentyl), 26.26 (CH3), 29.54 (CH2-CN), 54.87 (O=C-CH2-N), 61.33 (Cq), 114.46 (CN), 127.97, 128.69 (CHar.), 140.16, 157.65 (2 × Car.), 170.66, 175.48 (2 × C=O); MS (EI) m/z (%): 299.26 ([M + 2]+, 16), 121.15 (100); Anal. Calcd. for C17H19N3O2 (297.35): C, 68.67%; H, 6.44%; N, 14.13%. Found: C, 68.68%; H, 6.42%; N, 14.15%.

2-(8,10-Dioxo-6-(4-methoxyphenyl)-6,9-diazaspiro[4.5]decane-9-yl)acetonitrile (8c). Yield: 77%; yellow viscous oil; IR (KBr, ν, cm−1) absence of amidic NH2 and exhibited bands at 2310.70 (CN), 1743.65, 1629.85 (2 × C=O); 1H-NMR (CDCl3) δ ppm 1.27–1.55 (m, 4H, 2 × CH2, cyclopentyl), 1.79–2.21 (m, 4H, 2 × CH2, cyclopentyl), 3.77 (s, 3H, OCH3), 4.13 (s, 2H, O=C-CH2-N), 4.78 (s, 2H, CH2-CN), 6.89 (d, 2H, J = 7.5 Hz, Har.), 6.97 (d, 2H, J = 7.5 Hz, Har.); 13C-NMR (CDCl3) δ ppm 26.19, 38.30 (2 × CH2, cyclopentyl), 29.06 (CH2-CN), 54.87 (O=C-CH2-N), 56.16 (OCH3), 65.11 (Cq), 114.62 (CN), 127.98, 131.32 (CHar.), 142.62, 157.30 (2 × Car.), 169.54, 175.16 (2 × C=O); MS (EI) m/z (%): 312.43 ([M − 1]+, 4), 57.15 (100); Anal. Calcd. for C17H19N3O3 (313.35): C, 65.16%; H, 6.11%; N, 13.41%. Found: C, 65.14%; H, 6.13%; N, 13.42%.

2-(3,5-Dioxo-1-phenyl-1,4-diazaspiro[5.5]undecane-4-yl)acetonitrile (8d). Yield: 90%; yellow viscous oil; IR (KBr, ν, cm−1) absence of amidic NH2 and exhibited bands at 2254.79 (CN), 1735.9, 1705.07 (2 × C=O); 1H-NMR (CDCl3) δ ppm 1.18 (s, 4H, 2 × CH2, cyclohexyl), 1.45–2.01 (m, 8H, 4 × CH2, cyclohexyl), 4.09 (s, 2H, O=C-CH2-N), 4.69 (s, 2H, CH2-CN), 6.89 (d, 2H, J = 7.5 Hz, Har.), 6.97 (d, 2H, J = 7.5 Hz, Har.); 13C-NMR (CDCl3) δ ppm 25.01, 29.07, 29.25 (5 × CH2, cyclohexyl), 29.44 (CH2-CN), 54.22 (O=C-CH2-N), 60.85 (Cq), 114.29 (CN), 128.95, 129.33, 129.64 (CHar.), 147.36 (Car.), 169.76, 175.30 (2 × C=O); MS (EI) m/z (%): 297.28 ([M]+, 6), 257.2 (4), 77.14 (100); Anal. Calcd. for C17H19N3O2 (297.35): C, 65.16%; H, 6.11%; N, 13.41%. Found: C, 65.14%; H, 6.13%; N, 13.42%.

2-(3,5-Dioxo-1-(4-methylphenyl)-1,4-diazaspiro[5.5]undecane-4-yl)acetonitrile (8e). Yield: 94.5%; yellowish white solid m.p. 120–122 °C; IR (KBr, ν, cm−1) absence of amidic NH2 and exhibited bands at 1888.31 (CN), 1741.72, 1989.6 (2 × C=O); 1H-NMR (CDCl3) δ ppm 1.28 (s, 2H, CH2, cyclohexyl), 1.45–2.01 (m, 8H, 4 × CH2, cyclohexyl), 2.32 (s, 3H, CH3), 4.16 (s, 2H, O=C-CH2-N), 4.74 (s, 2H, CH2-CN), 6.91 (d, 2H, J = 7.0 Hz, Har.), 7.15 (d, 2H, J = 7.0 Hz, Har.); 13C-NMR (CDCl3) δ ppm 22.70 (CH3), 23.06, 24.76, 25.36 (5 × CH2, cyclohexyl), 31.33 (CH2-CN), 54.92 (O=C-CH2-N), 60.98 (Cq), 114.23 (CN), 129.77, 130.24 (CHar.), 136.09, 144.74 (2 × Car.), 169.89, 175.37 (2 × C=O); MS (EI)
m/z (%): 311.27 ([M]+, 16), 91.15 (100); Anal. Calcd. for C_{18}H_{21}N_{3}O_{2} (311.38): C, 69.43%; H, 6.80%; N, 13.49%. Found: C, 69.44%; H, 6.81%; N, 13.47%.

2-(3,5-Dioxo-1-(4-methoxyphenyl)-1,4-diazaspiro[5.5]undecan-4-yl)acetonitrile (8f). Yield: 75%; brown viscous oil; IR (KBr, ν, cm⁻¹) absence of amidic NH₂ and exhibited bands at 2260.57 (CN), 1687.71, 1676.14 (2 × C=O); ¹H-NMR (CDCl₃) δ ppm 1.76–2.06 (m, 10H, 5 × CH₂, cyclohexyl), 3.75 (s, 3H, OCH₃), 4.27 (s, 2H, O=C-CH₂-N), 4.69 (s, 2H, CH₂-CN), 6.91 (d, 2H, J = 7.8 Hz, Hₘₐr.), 7.04 (d, 2H, J = 7.8 Hz, Hₘₐr.); ¹³C-NMR (CDCl₃) δ ppm 20.41, 26.23, 31.40 (5 × CH₂, cyclohexyl), 29.75 (CH₂-CN), 54.86 (O=C-CH₂-N), 61.37 (OCH₃) 68.26 (Cq), 114.72 (CN), 127.82, 128.09 (CHₘₐr.), 140.19, 157.88 (2 × Cₘₐr.), 170.13, 175.43 (2 × C=O); MS (EI) m/z (%): 327.23 ([M]+, 85), 121.11 (100), 287.22 (20); Anal. Calcd. for C_{18}H_{21}N_{3}O_{3} (327.38): C, 66.04%; H, 6.47%; N, 12.84%. Found: C, 66.13%; H, 6.49%; N, 12.85%.

3.1.9. General Procedure for the Synthesis of 6-Aryl-9-(1H-tetrazol-5-yl)methyl)-6,9-diazaspiro[4.5]decane-8,10-diones (6j–l) and 1-Aryl-4-((1H-tetrazol-5-yl)methyl)-1,4-diazaspiro[5.5]undecane-3,5-diones (6v–x)

Anhydrous AlCl₃ (13.3 g, 0.1 mol) was added to a cold dry THF (200 mL) under stirring during 10 min. Thereafter, NaN₃ (28.9 g, 0.45 mol) was added portion-wise through 10 min. The appropriate penultimate nitrile derivative 8a–f was added and the reaction mixture was stirred under refluxed for 24 h. After cooling, the reaction mixture was filtered and the filtrate was evaporated under vacuum. The crude residues were purified through column chromatography (chloroform:ethyl acetate, 9:1) to give the ultimate respective compounds 6j–l and 6v–x.

6-Phenyl-9-((1H-tetrazol-5-yl)methyl)-6,9-diazaspiro[4.5]decane-8,10-dione (6j). Yield: 71%; colorless viscous oil; IR (KBr, ν, cm⁻¹) exhibited band at 3419 (NH) and disappearance of CN band; ¹H-NMR (CDCl₃) δ ppm 1.11–2.23 (m, 8H, 4 × CH₂, cyclopentyl), 4.22 (s, 2H, O=C-CH₂-N), 5.14 (s, 2H, O=C-CH₂-N), 6.75–7.07 (m, 5H, Hₘₐr.), 7.37 (s, 1H, NH); ¹³C-NMR (CDCl₃) δ ppm 25.15, 29.77 (4 × CH₂, cyclopentyl), 38.86 (N-CH₂-tetrazole), 56.70 (O=C-CH₂-N), 69.98 (Cq), 124.92, 129.42, 132.50 (CHₘₐr.), 148.48 (Cₘₐr.), 153.55 (C=N-tetrazole), 170.55, 176.06 (2 × C=O); MS (EI) m/z (%): 326.43 ([M]+, 33), 327.27 (100); Anal. Calcd. for C_{16}H_{18}N_{6}O_{2} (326.35): C, 58.88%; H, 5.56%; N, 25.75%. Found: C, 58.66%; H, 5.51%; N, 25.72%.

6-(4-Methylphenyl)-9-((1H-tetrazol-5-yl)methyl)-6,9-diazaspiro[4.5]decane-8,10-dione (6k). Yield: 61%; yellow viscous oil; IR (KBr, ν, cm⁻¹) exhibited band at 3419 (NH) and disappearance of CN band; ¹H-NMR (CDCl₃) δ ppm 1.47 (s, 3H, CH₃), 1.51–1.56 (m, 4H, 2 × CH₂, cyclopentyl), 1.77 (br.s, 4H, 2 × CH₂ cyclopentyl), 3.91 (s, 2H, O=C-CH₂-N), 4.10 (s, 2H, N-CH₂-tetrazole), 5.21 (s, 1H, NH), 6.83 (d, 2H, J = 6.0 Hz, Hₘₐr.), 7.12 (d, 2H, J = 6.0 Hz, Hₘₐr.); ¹³C-NMR (CDCl₃) δ ppm 25.38 (CH₃), 30.02, 34.84 (4 × CH₂, cyclopentyl), 50.98 (N-CH₂-tetrazole), 55.59 (O=C-CH₂-N), 60.89 (Cq), 125.36, 128.92 (CHₘₐr.), 140.92, 151.94 (2 × Cₘₐr.), 157.55 (C=N-tetrazole), 168.93, 170.71 (2 × C=O); MS (EI) m/z (%): 340.29 ([M]+, 0.5), 121.14 (100); Anal. Calcd. for C_{17}H_{20}N_{6}O_{2} (340.38): C, 59.99%; H, 5.92%; N, 24.69%. Found: C, 59.74%; H, 5.82%; N, 24.67%.
6-(4-Methoxyphenyl)-9-((1H-tetrazol-5-yl)methyl)-6,9-diazaspiro[4.5]decane-8,10-dione (6l). Yield: 63.3%; yellow viscous oil; IR (KBr, ν, cm\(^{-1}\)) exhibited band at 3421.72 (NH) and disappearance of CN band; \(^1\)H-NMR (CDCl\(_3\)) δ ppm 1.47 (br.s, 6H, 3 × CH\(_2\), cyclopentyl), 2.19 (br.s, 2H, CH\(_2\) cyclopentyl), 3.73 (s, 3H, OCH\(_3\)), 3.80 (s, 2H, O=C-CH\(_2\)-N), 4.21 (s, 2H, N-CH\(_2\)-tetrazole), 6.64 (s, 1H, NH), 6.99 (d, 2H, J = 6.0 Hz, Har.), 7.25 (d, 2H, J = 6.0 Hz, Har.); \(^13\)C-NMR (CDCl\(_3\)) δ ppm 23.08, 30.43 (4 × CH\(_2\), cyclopentyl), 51.01 (N-CH\(_2\)-tetrazole), 55.83 (O=C-CH\(_2\)-N), 59.45 (OCH\(_3\)), 61.02 (Cq), 128.49, 132.02 (CH\(_{\text{ar.}}\)), 140.0, 152.0 (2 × Car.), 159.96 (C=N-tetrazole), 160.01, 169.1 (2 × C=O); Anal. Calcd. for C\(_{17}\)H\(_{20}\)N\(_6\)O\(_3\) (356.38): C, 57.29%; H, 5.66%; N, 23.58%. Found: C, 57.11%; H, 5.64%; N, 23.38%.

1-Phenyl-4-((1H-tetrazol-5-yl)methyl)-1,4-diazaspiro[5.5]undecane-3,5-dione (6v). Yield: 75%; yellow viscous oil; IR (KBr, ν, cm\(^{-1}\)) exhibited band at 3400 (NH) and disappearance of CN band; \(^1\)H-NMR (CDCl\(_3\)) δ ppm 0.87 (br.s, 2H, CH\(_2\) cyclohexyl), 1.18–1.98 (m, 8H, 4 × CH\(_2\), cyclohexyl), 4.09 (s, 2H, O=C-CH\(_2\)-N), 5.03 (s, 2H, N-CH\(_2\)-tetrazole), 7.05–7.13 (m, 5H, H\(_{\text{ar.}}\) and 1H, NH); \(^13\)C-NMR (CDCl\(_3\)) δ ppm 13.58, 25.37, 31.36 (5 × CH\(_2\), cyclohexyl), 55.01 (N-CH\(_2\)-tetrazole), 58.88 (O=C-CH\(_2\)-N), 60.77 (Cq), 125.93, 127.15, 129.38 (CH\(_{\text{ar.}}\)), 147.86 (C\(_{\text{ar.}}\)), 153.74 (C=N-tetrazole), 170.57, 175.98 (2 × C=O); MS (EI) \(m/z\) (%): 340.29 ([M]+, 3), 77.13 (100); Anal. Calcd. for C\(_{17}\)H\(_{20}\)N\(_6\)O\(_2\) (340.38): C, 59.99%; H, 5.92%; N, 24.69%. Found: C, 59.78%; H, 5.91%; N, 24.68%.

1-(4-Methylphenyl)-4-((1H-tetrazol-5-yl)methyl)-1,4-diazaspiro[5.5]undecane-3,5-dione (6w). Yield: 61%; yellow viscous oil; IR (KBr, ν, cm\(^{-1}\)) exhibited band at 3419.79 (NH) and disappearance of CN band; \(^1\)H-NMR (CDCl\(_3\)) δ ppm 1.47 (s, 3H, CH\(_3\)), 1.51–1.59 (m, 6H, 3 × CH\(_2\), cyclohexyl), 2.14 (br.s, 4H, 2 × CH\(_2\) cyclohexyl), 4.09 (s, 2H, O=C-CH\(_2\)-N), 4.30 (s, 2H, N-CH\(_2\)-tetrazole), 6.65 (s, 1H, NH), 7.16 (d, 2H, J = 6.0 Hz, Har.), 7.19 (d, 2H, J = 6.0 Hz, Har.); \(^13\)C-NMR (CDCl\(_3\)) δ ppm 22.66, 31.50, 34.94 (5 × CH\(_2\), cyclohexyl), 29.74 (CH\(_3\)), 45.801 (N-CH\(_2\)-tetrazole), 50.95 (O=C-CH\(_2\)-N), 60.73 (Cq), 127.83, 130.13 (CH\(_{\text{ar.}}\)), 140.10, 145.92 (2 × C\(_{\text{ar.}}\)), 151.94 (C=N-tetrazole), 168.82, 170.42 (2 × C=O); MS (EI) \(m/z\) (%): 354.7 ([M]+, 3), 105.17 (100); Anal. Calcd. for C\(_{18}\)H\(_{22}\)N\(_6\)O\(_2\) (354.41): C, 61.00%; H, 6.26%; N, 23.71%. Found: C, 61.15%; H, 6.22%; N, 23.61%.

1-(4-Methoxyphenyl)-4-((1H-tetrazol-5-yl)methyl)-1,4-diazaspiro[5.5]undecane-3,5-dione (6x). Yield: 66%; buff solid, m.p 73 °C; IR (KBr, ν, cm\(^{-1}\)) exhibited band at 3419 (NH) and disappearance of CN band; \(^1\)H-NMR (CDCl\(_3\)) δ ppm 1.18–1.88 (m, 10H, 5 × CH\(_2\), cyclohexyl), 3.75 (OCH\(_3\)), 4.20 (s, 2H, O=C-CH\(_2\)-N), 5.29 (s, 2H, N-CH\(_2\)-tetrazole), 6.73 (d, 2H, J = 7.0 Hz, Har.), 6.95 (d, 2H, J = 7.0 Hz, Har.), 7.19 (s, 1H, NH); \(^13\)C-NMR (CDCl\(_3\)) δ ppm 20.71, 25.04, 32.60 (5 × CH\(_2\), cyclohexyl), 36.59 (N-CH\(_2\)-tetrazole), 41.32 (O=C-CH\(_2\)-N), 56.50 (OCH\(_3\)), 70.07 (Cq), 127.79, 129.88 (CH\(_{\text{ar.}}\)), 134.86, 145.77 (2 × C\(_{\text{ar.}}\)), 153.48 (C=N-tetrazole), 170.73, 176.09 (2 × C=O); MS (EI) \(m/z\) (%): 340.3 ([M-OCH\(_3\)]+, 5), 105.17 (100); Anal. Calcd. for C\(_{18}\)H\(_{22}\)N\(_6\)O\(_3\) (370.41): C, 58.37%; H, 5.99%; N, 22.69%. Found: C, 58.32%; H, 5.79%; N, 22.54%.
3.2. Anticonvulsant Activity

3.2.1. Materials

Animals: The anticonvulsant activity of the target compounds 6a–x was tested on Swiss strain adult male albino mice weighing 19–25 g. Animals were obtained from the Animals House Colony of the National Research Centre, Cairo, Egypt. Animals were housed in polypropylene cages under the standard conditions of light (12 h light/dark cycle) and temperature (23 ± 2 °C), and were allowed free access to water and maintained on a daily standard schedule of laboratory diet. 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. for Pharm & Chem. Ind., Cairo, Egypt), Ethosuximide (Pfizer Co., Giza, Egypt), Diphenylhydantoin (Nasr Co., Giza, Egypt), Tween 80 and Pentylenetetrazole (Sigma, St. Louis, MO, USA) were used. Ethosuximide, Phenobarbital and Pentylenetetrazole (PTZ) were dissolved in physiologic saline solution, Diphenylhydantoin was dissolved in saline that was alkalinized slightly with 0.1 mmol potassium hydroxide. Reference drugs and tested compounds were administered intraperitoneally (i.p) in volumes of 0.1 mL/10 g of mice body weight.

3.2.2. Methods

After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to control, reference and tested experimental groups consisting of 6 mice. Each mouse was used only once and all tests were performed between 09:00 a.m. and 04:00 p.m. All the tested compounds were suspended in 7% Tween 80 as a vehicle.

Subcutaneous Pentyleneteterazole (scPTZ)-induced Seizures Test [28]: A PTZ dose of 85 mg/kg administered subcutaneously to mice causes seizures in more than 97% of the animals. This is called the convulsive dose 97 (CD97). The control experiments were performed using the solvent alone. The other groups each received individually the reference drugs Ethosuximide (150 mg/kg ≡ 1.06 mmol/kg) [29] and/or Phenobarbital (30 mg/kg ≡ 0.13 mmol/kg) [30] or one of the test compounds in graded doses, 6a–1 (1.5–50 mg/kg), 6m–x (6–100 mg/kg). Thirty minutes later Pentylenetetrazole was administered subcutaneously in a loose fold of skin on the back of the neck in a dose of 85 mg/kg. Each animal was observed for 30 min after PTZ administration, failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) was defined as protection [31]

Maximal Electroshock Seizure (MES) Test [32]: Animals were randomly assigned to groups of 6 mice each. The first group served as the control group. The second group received Diphenylhydantoin (45 mg/kg) as a reference drug and the other groups of animals received the test compounds individually by intraperitoneal injection with the dose which induces 100% protection in the Pentylenetetrazole 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 electrodes by a Rodent Shocker generator (constant-current stimulator Type 221, Hugo Sachs Elektronik, Freiburg, Germany).
The maximal seizures typically consist of a short period of initial tonic flexion and a prolonged period of tonic extension (especially of the hind limbs) followed by terminal clonus. The typical seizure lasts approximately 22 s. Failure to extend the hind limbs to an angle with trunk greater than 90° is defined as protection [33].

**Neurotoxicity** [34]: This test 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 rev/min for at least 1 min in each of three trials using a rotarod device (UGO Basile, 47600, Varese, Italy). Only animals that fulfill this criterion were included in the experiment. The selected trained animals were classified into control and experimental groups. The animals in the experimental groups were given the reference drug or one of the test compounds via i.p. route at doses which exerted 100% protection in the PTZ test; meanwhile, the control group received the vehicle. 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 1 min.

3.2.3. Determination of the ED$_{50}$

Anticonvulsant activity of the test compounds was expressed in term of median effective dose (ED$_{50}$) that is, the dose of drug required to produce the required biological response in 50% of animals. For determination of the ED$_{50}$, groups of 8 mice were given a range of i.p. 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 [18].

4. Conclusions

The anticonvulsant potential of certain new 6-aryl-9-substituted-6,9-diazaspiro[4.5]decane-8,10-diones (6a–l) and 1-aryl-4-substituted-1,4-diazaspiro[5.5]undecane-3,5-diones (6m–x) was described. The title compounds 6a–x showed good anticonvulsant activity especially in the scPTZ screen. Compound 6g displayed an ED$_{50}$ of 0.0043 mmol/kg in the scPTZ screen being about 14 and 214 fold more potent than the reference drugs, Phenobarbital and Ethosuximide, respectively. Compound 6e exhibited an ED$_{50}$ of 0.019 mmol/kg being about 1.8 fold more potent than that of the reference drug, Diphenylhydantoin in the MES screen. None of the test compounds exhibited any minimal motor impairment at the maximum administered dose in the neurotoxicity screen.

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Author Contributions

Mohamed N. Aboul-Enein, Aida A. El-Azzouny, Mohamed I. Attia and Fatma Ragab conceived the study, designed the work, contributed in the strategy of the chemistry part, performed interpretation of the analytical data of the prepared compounds, prepared the manuscript and revised it for publication. Yousreya A. Maklad designed the pharmacological part, contributed in performing pharmacology experiments and revised the manuscript. Mona E. Aboutabl participated in conducting pharmacology experiments. Walaa H. A. Abdel-Hamid synthesized all compounds and participated in conducting pharmacology experiments.

Conflicts of Interests

The authors declare no conflict of interest.

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