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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF NEW SPIROSUCCINIMIDES DIFFERENTLY SUBSTITUTED AT THE IMIDE NITROGEN ATOM

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Abstract: In the present study the series of spirosuccinimides with the aromatic ring at the imide nitrogen atom was synthesized. All the compounds were tested for their anticonvulsant activity in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens. The neurotoxic properties were determined applying the rotorod test (TOX). The most active were N-(2-methoxyphenyl)- [**V**] and N-(4-chlorophenylamino)-2-azaspiro[4.5]decane-1,3-dione **[XI]** that inhibited seizures at a dose of 100 mg/kg in the *sc*PTZ and MES tests, respectively. The other derivatives, namely N-(3-methoxyphenyl)- [VI], N-(1-phenylethyl)- [**VIII**], N-(diphenylmethyl)- [**IX**], N-(6-aminopyridin-2-yl)- [**XII**] 2-azaspiro[4.5]decane-1,3-diones, and the compounds with the methyl group at position-3 [**XIV, XVII**] or at position-4 [**XVIII**] of the cyclohexane ring showed anti-MES and/or anti-*sc*PTZ protections at doses of 300 mg/kg. The results obtained revealed that anticonvulsant activity depended on the substitution mode of the aromatic ring as well as the kind of spacer between imide nitrogen atom and aromatic system.

Keywords: anticonvulsant activity; spirosuccinimide; 2-azaspiro[4.5]decane-1,3-dione derivatives

In recent years, anticonvulsant activity of many 2-azaspiro[4.4]nonane- and [4.5]decane-1,3-diones (spirosuccinimides) with different substituents at the imide nitrogen atom have been described (1-4). These molecules were found to be active in the maximal electroshock (MES) and/or pentylenetetrazole (scPTZ) seizure tests, the most widely used seizure models for early identification of new anticonvulsants. The structure activity relationship studies conducted with these groups of compounds revealed that their efficacy depended highly on the size of the cycloalkyl system attached to the C3 spiro carbon atom and the kind of aromatic substituent at the nitrogen atom of pyrrolidine-2,5-dione ring. Moreover it was proven that the introduction of the methylene or imine linker between the endocyclic nitrogen atom and aromatic moiety increased anticonvulsant activity (5-10). Among these derivatives the most active were compounds **I**-**III** presented in Figure 1.

Based on these facts, in the present studies we have designed and synthesized a series of 2-azaspiro[4.5]decane-1,3-diones, 7-methyl-, and 8-methyl-2-azaspiro[4.5]decane-1,3-diones with differently substituted aromatic rings connected to the imide nitrogen atom directly or by methine, methylene or imine spacers.

The starting 1-carboxy-1-cyclohexane-, 1-carboxy-1-(3-methylcyclohexane)-, and 1-carboxy-1-(4-methylcyclohexane)- acetic acids were prepared as reported previously (11). The final compounds [**IV**-**XIX**] were obtained in a one-pot cyclization reaction of the prepared dicarboxylic acids and appropriately substituted phenylamine, 1-phenylethylamine, diphenylmethylamine, phenylhydrazine, benzylamine or aminopyridine, by heating them at ca. 190-200^{o}C for 1.5 h. The synthetic procedures are shown in Scheme 1.

The ^{1}H NMR spectra of the compounds synthesized were studied and revealed characteristic chemical shifts. The protons of cyclohexane rings were observed as multiplets within a range of δ 1.27-1.98 ppm [**IV**-**XIII**] and δ 1.22-2.10 ppm for compounds **XIV**-**XIX**. The imide protons were observed as quartets at δ 2.72 ppm [**V**, **VII**], as singlets ranging from δ 2.52 ppm to δ 3.15 ppm [**IV**, **VI**, **VIII**-**XVII**] or as doublets at δ 2.63 ppm [**XIX**] and δ 2.66 [**XVIII**]. For all the compounds with the -NH- linker [**X**, **XI**, **XV**-**XIX**], the amine protons were observed as broad singlets ranging from δ 6.08

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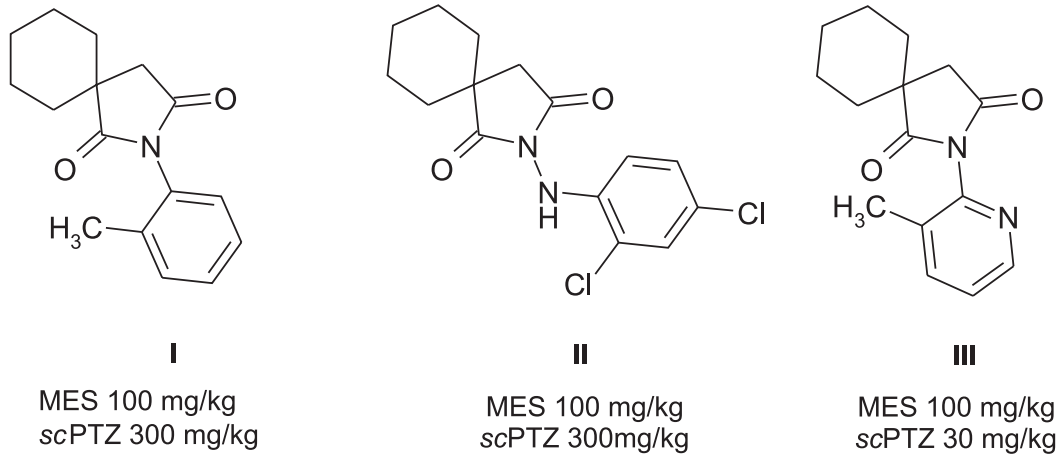
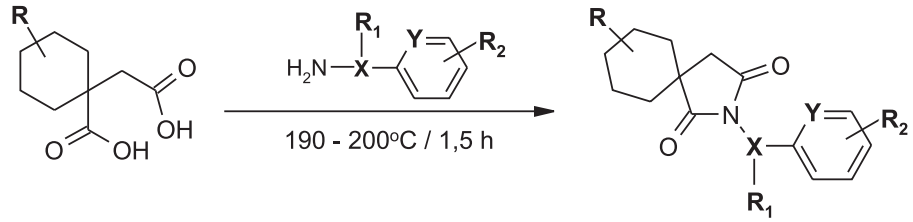


Figure 1. Structures of anticonvulsant active compounds **I**-**III**.



cmpd. **IV-XIX**

Compound	**R**	**X**	**R_1**	**Y**	**R_2**
IV	H	-	-	CH	2-NH_2
V	H	-	-	CH	2-OCH_3
VI	H	-	-	CH	3-OCH_3
VII	H	-	-	CH	2,5-OCH_3
VIII	H	CH	CH_3	CH	H
IX	H	CH	C_6H_5	CH	H
X	H	NH	-	CH	3-Cl
XI	H	NH	-	CH	4-Cl
XII	H	-	-	N	6-NH_2
XIII	H	-	-	N	5-CH_3
XIV	3-CH_3	CH_2	-	CH	2-CF_3
XV	3-CH_3	NH	-	CH	H
XVI	3-CH_3	NH	-	CH	2-CH_3
XVII	3-CH_3	NH	-	CH	4-CH_3
XVIII	4-CH_3	NH	-	CH	H
XIX	4-CH_3	NH	-	CH	4-CH_3

Scheme 1. Synthesis of compounds **IV** – **XIX**

Table 1. Physicochemical data for compounds **IV**-**XIX**.

Compd.	Molecular Formula/Weight	Yield % M.p.	Analysis (calculated/found)			R_f
			[°C]	%C	%H	%N
IV	$C_{15}H_{18}N_2O_2$ 258.32	62 193-195	69.83 69.77	7.03 6.88	10.89 10.69	0.68
V	$C_{16}H_{19}NO_3$ 273.33	68 139-141	70.40 70.71	7.02 6.90	5.13 5.31	0.83
VI	$C_{16}H_{19}NO_3$ 273.33	65 106-108	70.40 70.63	7.02 6.99	5.13 5.11	0.86
VII	$C_{17}H_{21}NO_4$ 303.36	67 105-107	67.39 67.60	6.55 6.80	4.62 4.91	0.88
VIII	$C_{17}H_{21}NO_2$ 273.38	70 63-65	74.79 70.49	7.75 7.32	5.13 5.18	0.92
IX	$C_{22}H_{23}NO_2$ 333.43	70 133-135	79.35 79.55	6.96 7.08	4.21 4.19	0.90
X	$C_{15}H_{17}N_2O_2Cl_1$ 292.76	68 174-176	61.70 61.42	5.85 6.00	9.56 9.78	0.70
XI	$C_{15}H_{17}N_2O_2Cl_1$ 292.76	58 178-180	61.70 61.94	5.85 5.60	9.56 9.28	0.72
XII	$C_{14}H_{17}N_3O_2$ 259.31	61 218-220	64.93 70.16	6.62 6.32	16.22 16.48	0.20
XIII	$C_{15}H_{18}N_2O_2$ 258.32	63 155-157	69.83 70.10	7.03 7.09	10.86 10.58	0.72
XIV	$C_{18}H_{20}NO_2F_3$ 339.35	66 103-105	63.78 63.68	5.95 6.11	4.13 4.28	0.92
XV	$C_{16}H_{20}N_2O_2$ 272.35	58 148-150	70.65 70.32	7.41 7.69	10.30 10.00	0.57
XVI	$C_{17}H_{22}N_2O_2$ 286.38	56 151-153	71.35 71.49	7.75 7.61	9.79 9.49	0.84
XVII	$C_{17}H_{22}N_2O_2$ 286.38	64 184-186	71.35 71.18	7.75 7.88	9.79 9.90	0.75
XVIII	$C_{16}H_{20}N_2O_2$ 272.35	62 165-167	70.65 70.79	7.41 7.23	10.30 10.12	0.60
XIX	$C_{17}H_{22}N_2O_2$ 286.38	59 163-165	71.35 71.53	7.75 7.91	9.79 9.58	0.80

ppm to δ 6.45 ppm. The proton of methine spacer [**VIII**, **IX**] was observed as a quartet at δ 5.42 ppm [**VIII**] or as singlet at δ 6.52 ppm [**IX**]. The resonance signals of aromatic protons were well separated and were observed within a range of δ 6.52-7.47 ppm. For the details see Tables 2 and 3.

EXPERIMENTAL

Chemistry

All the chemicals and solvents were purchased from Merck (Darmstadt, Germany) and were used without further purification. Melting points (m.p.) were determined in open capillaries on a Büchi 353 melting point apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. The purity of the compounds was confirmed by thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminium sheets (Merck; Darmstadt, Germany), using the developing systems: chloroform : acetone (9 : 1, v/v). Spots were detected by their absorption under UV light (λ = 254 nm) and by visualization with 0.05 mol I_2 in 10% HCl. The chemical structures were confirmed by elemental and spectral analyses (^{1}H NMR). ^{1}H NMR spectra were obtained on a Varian Mercury 300 MHz spectrometer (Varian Inc., Palo Alto, CA, USA), in $CDCl_3$, with TMS as an internal standard. Chemical shifts are reported in

Table 2. ^{1}H NMR data of compounds **IV**-**XIII**.

Compd.	^{1}H NMR δ (ppm)/ $CDCl_3$
IV	1.38-1.98 (10H, m, cyclohexane), 3.15 (2H, s, -CH_2-, imide), 4.20 (2H, brs., NH_2), 7.31-7.41 (2H, m, $H_{arom.}$), 7.70-7.73 (1H, m, $H_{arom.}$), 7.91-7.94 (1H, m, $H_{arom.}$)
V	1.33-1.97 (10H, m, cyclohexane), 2.72 (2H, q, -CH_2-, imide, *J* = 18.20 Hz), 3.74 (3H, s, OCH_3), 6.98-7.05 (2H, m, $H_{arom.}$), 7.16 (1H, dd, $H_{arom.}$, *J* = 7.69 Hz), 7.36-7.42 (1H, m, $H_{arom.}$)
VI	1.32-1.96 (10H, m, cyclohexane), 2.72 (2H, s, -CH_2-, imide), 3.81 (3H, s, OCH_3) 6.80-6.95 (3H, m, $H_{arom.}$), 7.36 (1H, t, $H_{arom.}$, *J* = 8.20 Hz)
VII	1.32-1.94 (10H, m, cyclohexane), 2.72 (2H, q, -CH_2-, imide, *J* = 17.95 Hz), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 6.68 (1H, t, $H_{arom.}$, *J* = 1.54 Hz), 6.93 (2H, d, $H_{arom.}$, *J* = 1.80 Hz)
VIII	1.27-1.81 (10H, m, cyclohexane), 1.84 (3H, s, -CH_3), 2.52 (2H, s, -CH_2-, imide), 5.42 (1H, dd, -CH-, *J* = 7.43 Hz), 7.28-7.37 (3H, m, $H_{arom.}$), 7.41-7.45 (2H, m, $H_{arom.}$)
IX	1.27-1.85 (10H, m, cyclohexane), 2.58 (2H, s, -CH_2-, imide), 2.67 (2H, s, imide), 6.04 (1H, brs, -NH-), 6.52-6.57 (2H, m, $H_{arom.}$), 6.77-6.80 (1H, m, $H_{arom.}$), 7.11 (1H, t, $H_{arom.}$, *J* = 7.82 Hz)
X	1.36-1.96 (10H, m, cyclohexane), 2.69 (2H, s, -CH_2-, imide), 6.13 (1H, brs, -NH-), 6.62-6.68 (1H, m, $H_{arom.}$), 6.70 (1H, t, $H_{arom.}$, *J* = 2.05 Hz), 6.94-6.98 (1H, m, $H_{arom.}$), 7.16 (1H, t, $H_{arom.}$, *J* = 8.08 Hz)
XI	1.36-1.95 (10H, m, cyclohexane), 2.67 (2H, s, -CH_2-, imide), 6.08 (1H, brs, -NH-), 6.68-6.72 (2H, m, $H_{arom.}$), 7.17-7.21 (2H, m, $H_{arom.}$)
XII	1.30-1.94 (10H, m, cyclohexane), 2.72 (2H, s, -CH_2-, imide), 4.75 (2H, brs, -NH_2), 6.52-6.59 (2H, m, $H_{pyridine}$), 7.54-7.60 (1H, m, $H_{pyridine}$)
XIII	1.32-1.97 (10H, m, cyclohexane), 2.34 (3H, s, -CH_3), 2.77 (2H, s, -CH_2- imide), 7.19 (1H, d, $H_{pyridine}$, *J* = 8,20 Hz), 7.34-7.67 (1H, m, $H_{pyridine}$), 8.47 (1H, dd, $H_{pyridine}$ *J* = 1.54 Hz)

Table 3. ^{1}H NMR data of compounds **XIV**-**XIX**.

Compd.	^{1}H NMR δ (ppm)/ $CDCl_3$
XIV	1.06 (3H, d, -CH_3, *J* = 5.85 Hz), 1.48-1.87 (9H, m, cyclohexane), 2.78 (2H, s, -CH_2-, imide), 4.74 (2H, s, -CH_2-), 7.06-7.09 (2H, m, $H_{arom.}$), 7.28-7.38 (2H, m, $H_{arom.}$)
XV	1.00 (3H, d, -CH_3, *J* = 6.05 Hz), 1.56-1.90 (9H, m, cyclohexane), 2.71 (2H, s, -CH_2-, imide), 6.14, (1H, brs, -NH-), 6.78-6.80 (2H, m, $H_{arom.}$), 7.01 (1H, t, $H_{arom.}$, *J* = 6.33 Hz), 7.28-7.31 (2H, m, $H_{arom.}$)
XVI	0.96 (3H, d, -CH_3, *J* = 5.90 Hz), 1.22-1.87 (9H, m, cyclohexane), 2.35 (3H, s, -CH_3), 2.69 (2H, s, -CH_2-, imide), 6.45 (1H, brs, -NH-), 6.89 (1H, t, $H_{arom.}$, *J* = 5.13 Hz), 6.92-7.12 (3H, m, $H_{arom.}$)
XVII	0.95 (3H, d, -CH_3, *J* = 5.90 Hz), 1.22-1.86 (9H, m, cyclohexane), 2.26 (3H, s, -CH_3), 2.65 (2H, s, -CH_2-, imide), 6.43 (1H, brs, -NH-), 6.68, (2H, t, H_{arom} *J* = 6.67 Hz), 7.03-7.06 (2H, m, $H_{arom.}$)
XVIII	1.04 (3H, d, -CH_3, *J* = 6.05 Hz), 1.51-2.10 (9H, m, cyclohexane), 2.66 (2H, d, -CH_2-, imide, *J* = 11.28 Hz), 6.11 (1H, brs, -NH-), 6.78-6.81, (2H, m, $H_{arom.}$), 6.99-7.04 (1H, m, $H_{arom.}$), 7.28-7.31 (2H, m, $H_{arom.}$)
XIX	0.94 (3H, d, -CH_3, *J* = 6.67 Hz), 1.43-2.04 (9H, m, cyclohexane), 2.26 (3H, s, -CH_3), 2.63 (2H, d, -CH_2-, imide, *J* = 11.28 Hz), 6.40 (1H, brs, -NH-), 6.68, (2H, d, $H_{arom.}$, *J* = 8.20 Hz), 7.03 (2H, d, $H_{arom.}$, *J* = 8.46 Hz)

δ values (ppm) and *J* values in Hertz (Hz). Signal multiplicities are represented by the following abbreviations: s (singlet), brs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet). Elemental analyses C, H, N were carried out with an Elementar Vario EL III (Hanau, Germany) and were within ± 0.4% of the theoretical values. The physicochemical data, yields, elemental analyses and R_f values for compounds **IV**-**XIX** are presented in Table 1. The ^{1}H NMR data are shown in Tables 2 and 3.

General procedure for the preparation of compounds **IV**-**XIX**

To a suspension of 1-carboxy-1-cyclohexane-, 1-carboxy-1-(3-methylcyclohexane)- or 1-carboxy-1-(4-methylcyclohexane)-acetic acids (0.01 mol) in 10 mL of water, the appropriately substituted phenylamine, 1-phenylethylamine, diphenylmethylamine, benzylamine, phenylhydrazines or 2-aminopyridine (0.01 mol) was gradually added. The mixture was heated in an oil bath with simultaneous distillation of water. The cyclization reaction was continued in

Table 4. Anticonvulsant screening project (ASP), results in mice for compounds **IV-XIX**.

Compd.	Intraperitoneal injection in mice[a]					
	MES[b]		*sc*PTZ[c]		NT[d]	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
IV	-	-	-	-	-	-
V	-	-	-	100[h]	300	-
VI[e]	300	-	300	-	300[g]	-
VII	-	-	-	-	300	-
VIII[f]	300	300	-	-	100	300
IX	-	-	-	300	-	-
X	-	-	-	-	-	-
XI	-	100	-	-	100	-
XII	300	-	-	-	300[g]	-
XIII	-	-	-	-	300	-
XIV	-	300	-	-	-	-
XV	-	-	-	-	-	-
XVI	-	-	-	-	300	-
XVII	-	-	300	-	-	-
XVIII	300	-	-	-	-	-
XIX	-	-	-	-	-	-

[a)] Doses of 30, 100 and 300 mg/kg were administrated. The values in the table indicate the minimum dose (mg/kg), whereby bioactivity was demonstrated. The dash (-) indicates an absence of activity at maximum dose administrated. [b)] Maximal electroshock test. [c)] Subcutaneous pentylenetetrazole test. [d)] Rotorod neurotoxicity screen. [e)] Compound **VI** was active at a dose of 100 mg/kg in MES and *sc*PTZ tests at 0.5 h. [f)] Compound **VIII** showed anti-MES protection at a dose of 100 mg/kg at 0.25 h and 1 h.
Response comments: [g] unable to grasp rotorod, [h] myoclonic jerks

190-200°C for 1.5 h. The crude products were crystallized from isopropanol to afford the desired compounds.

PHARMACOLOGY

Compounds **IV**-**XIX** were pharmacologically pre-evaluated within the Antiepileptic Drug Development (ADD) program (Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Rockville), by use of testing procedures which have been described elsewhere (12, 13).

Phase I studies involved three tests: maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and rotorod test for neurological toxicity (NT). Male albino mice (CF-1 strain) and male albino rats (Sprague–Dawley) were used as experimental animals. The animals were housed in metabolic cages and allowed free access to food and water. The compounds were suspended in 0.5% methylcellulose/water mixture.

The maximal electroshock test (MES)

In the MES screen, an electrical stimulus of 0.2 s in duration (50 mA in mice and 150 mA in rat at 60 Hz) is delivered *via* corneal electrodes primed with an electrolyte solution containing an anesthetic agent.

The subcutaneous pentylenetetrazole seizure test (*sc*PTZ)

This screen utilizes a dose of pentylenetetrazole (85 mg/kg in mice and 70 mg/kg in rats) that produces clonic seizures lasting for a period of at least five seconds in 97% (CD_{97}) of animals tested. At the anticipated time of testing the convulsant was administered subcutaneously.

All the compounds were injected intraperitoneally into mice at the dose levels of 30, 100, and 300 mg/kg with anticonvulsant activity and neurotoxicity assessment at 0.5 and 4 h after administration.

The neurological toxicity (NT)

This was induced by compound and was detected in mice or rats using standardized rotorod

test. Untreated control mice or rats, when placed on the rod, can maintain their equilibrium for a prolonged time period. The acute motor impairment can be demonstrated by the inability of animal to maintain equilibrium for a given time.

The results of preliminary screening for compounds **IV**-**XIX** are presented in Table 4.

RESULTS

Compounds **IV**-**XIX** revealed diversified anticonvulsant properties. Except **VI**, which was active both in MES and *sc*PTZ tests, the other active derivatives were effective only in the MES [**VIII**, **XI**, **XII**, **XIV** and **XVIII**] or *sc*PTZ [**V**, **IX**, **XVII**] test. The most active N-(2-methoxyphenyl)-2-azaspiro[4.5] decane-1,3-dione [**V**] inhibited pentylenetetrazole induced seizures at a dose of 100 mg/kg and 300 mg/kg (not indicated in Table 4) at 4 h, whereas its 3-methoxy analogue [**VI**] was effective in the MES and scPTZ tests at a dose of 300 mg/kg at 0.5 h. The presence of the second methoxy group at position-5 of the aromatic ring yielded inactive compound **VII**. Furthermore, introduction of the -CH- linker between imide nitrogen atom and phenyl ring [**VIII**, **IX**] increased activity. The anticonvulsant efficacy of compounds mentioned above depended on the kind of second substituent at the -CH- group. In case of methyl phenyl substituents [**VIII**], anti-MES activity was observed at a dose of 300 mg/kg at 0.5 h and 4 h. Additionally, **VIII** showed protection at a dose of 100 mg/kg at 0.25 h and 1 h in the MES test. The replacement of the methyl group into second phenyl substituent [**IX**] made the compound active in the *sc*PTZ screen at a dose of 300 mg/kg at 4 h. The change of the -CH- spacer to -NH- bridge and the introduction of chloro atom to aromatic ring at position-4 in compound **XI**, resulted in the activity in the MES test at a dose of 100 mg/kg at 4 h. Surprisingly, the 3-Cl analogue [**X**] was found inactive. Among the N-pyridin-2-yl derivatives [**XII**, **XIII**], only N-(6-aminopyridyn-2-yl)-2-azaspiro[4.5]decane-1,3-dione [**XII**] protected animals in the MES test at a dose of 300 mg/kg at 0.5 h. Introduction of the methyl group into the cyclohexane ring at position-3 [**XIV-XVII**] or at position-4 [**XVIII-XIX**] made the compounds less active. In this series, N-(2-trifluoromethyl-benzyl)-7-methyl-2-azaspiro[4.5]decane-1,3-dione [**XIV**] exhibited anti-MES activity at a dose of 300 mg/kg at 4 h, whereas N-[(4-methylphenyl)-amino]-7-methyl-2-azaspiro [4.5]decane-1,3-dione [**XVII**] was active in the *sc*PTZ test at a dose of 300 mg/kg. The *ortho*-methyl analogue [**XVI**] was devoid of activity in both tests applied. It was in contrast to earlier experiments indicating that the presence of different substituents at the position-2 of the aryl ring is important for the anticonvulsant activity (5-7).

The change of position of methyl group in spirocyclohexane ring from position-3 to -4, did not influence the anticonvulsant activity. Among the *para*-methyl derivatives only **XVIII** showed anti-MES protection at a dose of 300 mg/kg at 0.5 h.

In the neurotoxicity screen, compounds **VIII** and **XI** were toxic at a dose of 100 mg/kg, whereas the other derivatives **V-VII**, **XII**, **XIII** and **XVI** were found to be toxic at a dose of 300 mg/kg. Compounds **IV**, **IX**, **X**, **XIV**, **XV** and **XVII-XIX** were devoid of neurotoxicity at the maximum dose administrated (300 mg/kg). The mice were unable to grasp rotorod after administration of **VI** and **XII** (300 mg/kg at 0.5 h). Compound **V**, effective in the *sc*PTZ test, induced myoclonic jerks at the same dose in which the anticonvulsant activity was observed.

In conclusion, the results obtained revealed that a number of new N-substituted spirosuccinimides were moderately effective in the MES or scPTZ screens, however, none of them was more potent than the compounds presented in Figure 1 used as the lead structures. There were no clear structure-activity relationships but it is justified to claim that all modifications presented in this paper decreased the anticonvulsant activity in relation to similar molecules obtained earlier.

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