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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF A SERIES OF N-SUBSTITUTED BICYCLO [2.2.1] HEPT-5-ENE-2,3-DICARBOXIMIDES

JOLANTA OBNISKA[a], ROMAN LESYK[b], DYMYTRO ATAMANYUK[b], and KRZYSZTOF KAMIŃSKI[a]

[a] Department of Pharmaceutical Chemistry, Medical College of the Jagiellonian University, 9 Medyczna Str., 30-688 Kraków, Poland
[b] Department of Pharmaceutical, Organic and Bioorganic Chemistry, the Danylo Halytsky Lviv National Medical University, 69 Pekarska Str., 79-010 Lviv, Ukraine

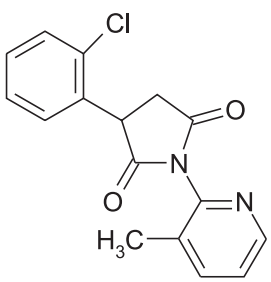
Abstract: As part of our study, a series of *N*-phenyl- and N-benzyl-bicyclo [2.2.1] hept-5-ene-2,3-dicarboximides [**III-XVI**], structurally related to the previously described N-phenyl- or N-pirydyl-3-arylpyrrolidine-2,5-dione [**I**, **II**], were synthesized and tested for their anticonvulsant activity in the maximum electroshock seizure (MES) and metrazole seizure threshold (sc. MET) tests. The most potent in the maximum electroshock seizure (MES) test were compounds with methyl [**III**] and chloro [**XI**] substituents at position -2 of the aromatic ring, whereas of all the synthesized compounds, only N-(2-methoxybenzyl)-bicyclo [2.2.1] hept-5-ene-2,3-dicarboximide [**XII**] was active in the sc. MET. Compounds with substituents at position -3 or -4 of the aromatic ring were found to be less active [**V**, **VI**, **XIII** and **XIV**], or devoid of activity [**VII**, **IX**, **XV** and **XVI**]. In contrast, the N-(4-chlorophenyl)-bicyclo [2.2.1] hept-5-ene-2,3-dicarboximide [**VIII**] at a dose of 100mg/kg was active in the MES test.

Keywords: N-phenyl- and N-benzyl-bicyclo [2.2.1] hept-5-ene-2,3-dicarboximides; succinimide; pyrrolidine-2,5-dione; anticonvulsant activity

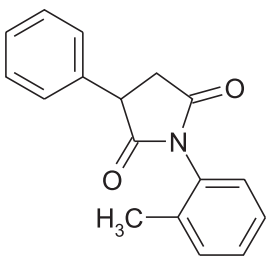
Epilepsy is a chronic neurological disorder characterized by seizures that result from a sudden, disorderly depolarisation of neurons in the brain (1). Many patients with epilepsy fail to effectively control their seizure, despite of optimal usage of the available antiepileptic drugs. In other patients, such a control is possible at the expense of significant toxic side-effects (2). Therefore, new anticonvulsant drugs with enhanced efficacy and minimal side-effects need to be developed.

One of the classes of compounds with well documented anticonvulsant activity are succinimide derivatives (3-7), and their 3-spirocycloalkyl analogues (8-10). Structure-activity relationship studies show that the anticonvulsant properties of this class are associated with the presence of carbonyl groups, important for hydrogen binding, as well as with lipophilic aryl portion facilitating penetration of the blood-brain barrier (11-13). This aromatic fragment is connected with imide moiety at position -3 and/or at the imide nitrogen atom.

In our earlier study we described anticonvulsant activity of a great number of succinimides with different substituents at the nitrogen atom and at position -3 of pyrrolidine-2,5-dione ring (14-16). The most promising were compounds with an aromatic ring at position -3 of the imide moiety, and a pyridyl, or phenyl substituent at the imide nitrogen atom. It was also found that the kind and position of substituents in the aromatic area had a significant effect on the activity of those compounds. (17, 18). The structures of the active compounds are presented below:



comp. **I**
ASP class 1 (30mg/kg MES)



comp. **II**
ASP class 1 (30mg/kg MES)

The obtained results prompted us to synthesize a variety of N-phenyl- [**III**-**IX**] and N-benzyl- [**X**--**XVI**] analogues of bicyclo [2.2.1] hept-5-ene-2,3-dicarboximide in which succinimide is a basic structure. We assumed that such modification, as well as introduction of different substituents to the aryl ring would yield compounds with more potent anticonvulsant activity.

The final dicarboximides [**III**-**XVI**] were synthesized using standard literature methods (4, 19, 20) as outline in Scheme 1. This reaction was performed by treatment of bicyclo [2.2.1] hept-5-ene-2,3-dicarboxylic anhydride with an appropriate phenyl or benzylamine, and further heating of obtained solid residues with acetic anhydride and sodium acetate at 90-95^{0}C for 1 h.

^{1}H NMR spectra of the synthesized compounds were studied.

The ^{1}H NMR spectra of the investigated compounds revealed a few characteristic chemical shifts (see Tables 2 and 3). The chemical shifts of the norbornane protons H_a in all the compounds were shown as multiplets within the range δ 1.51-1.87 ppm. The resonance signals of protons of the norbornane ring H_b, and H_c appeared as multiplets within the range δ 3.25-3.57 ppm. The signals of double bond (H_d) protons were observed as a doublet of triplets within the range δ 6.32-6.36ppm [**IV**] and as triplets ranging from δ 5.89 ppm to δ 6.35 ppm [**III**, **V**-**XVI**]. The protons of the -CH_2- group appeared as singlets at δ 4.45-4.68 ppm [**X**-**XVI**]. The resonance signals of -CH_3 protons were recorded as doublets within the range δ 2.08-2.17 ppm for compounds with the methyl group at the *ortho* position of the aryl ring [**III**, **IV**], and as singlets at δ 2.39 ppm [**VII**] and δ 2.34 [**XV**] for the *para* isomers. The protons of the -OCH_3 group of compounds **XII** and **XVI** appeared as singlets at δ 3.86ppm and δ 3.81ppm, respectively. The resonance signals of aromatic protons [**III**-**XVI**] were well-separated and were observed ranging from δ 6.80ppm to δ 7.66 ppm. Their position depend on the kind of substituents in the aryl ring. For the details see Tables 2 and 3.

The ^{1}H-NMR spectral data supported the chemical structure of compounds **III**-**XVI**.

EXPERIMENTAL

Chemistry

Melting points (m. p. ^{0}C) were determined with an Electrothermal digital melting point apparatus and are uncorrected. The chemical structure of the obtained compounds was confirmed by elemental and spectral analyses. ^{1}H NMR spectra (in $CDCl_3$) were obtained in a Varian Mercury spectrometer working at 300 MHz. Chemical shifts were described as parts per million (δ ppm) from $(CH_3)_4Si$ (TMS) as an internal standard. Signal multiplicities are represented by the following abbreviations: s (singlet), d (doublet), dd (doublet of doublets), td (triplet of doublets), t (triplet), dt (doublet of triplets), m (multiplet).

Elemental analyses for C, H, N were within ± 0.4% of the theoretical values.

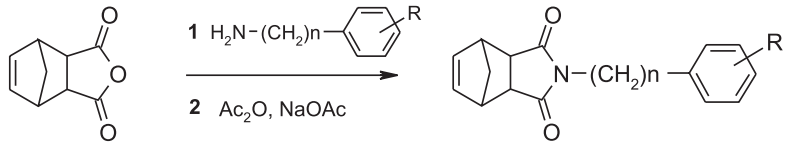
The purity of the compounds was checked by thin–layer chromatography (TLC) performed on Merck silica gel GF_{254} aluminium sheets using the following developing systems: A) chloroform: acetone (9: 1), B) ethyl acetate: hexane (3: 7). Spots were detected under UV light (λ = 254 nm).

GENERAL PROCEDURE FOR THE PREPARATION OF N-PHENYL AND N-BENZYL BICYCLO [2.2.1] HEPT-5-ENE-1,3-DICARBOXIMIDES [**III**-**XVI**].

To a solution of bicyclo [2.2.1] hept-5-ene-2,3-dicarboxylic anhydride (0.01 mole) in ethyl acetate (10 mL) an appropriately substituted phenyl- or benzyl- amine (0.01 mole) in ethyl acetate (10 mL) was added and left at room temperature for 12 h. After that time, crystalline products were formed. The obtained solid residues were filtered and crystallized from isopropanol. The final dicarboximides [**III**--**XVI**] were prepared by heating of the above residues with an acetic anhydride (10 mL) and a catalytic amount of anhydrous sodium acetate (0.5 g) in a water bath for 1 h. After that time, the products were cooled and ice water was added. The mixtures were left overnight in a refrigerator. The crude products were filtered and purified by crystallization from methanol. The physicochemical data, yields, elemental analyses and R_f values are presented in Table 1. The ^{1}H NMR spectral data are shown in Tables 2 and 3.

Pharmacology

All the obtained compounds 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), Bethesda) using the test procedures described elsewhere (21, 22). Phase I studies of the investigated compounds involved three tests: maximal electroshock (MES), subcutaneous metrazole (sc. MET) and a rotarod test for neurological toxicity (TOX).



comp. **III - XVI**

Comp. **III-IX** n=0

No.	III	IV	V	VI	VII	VIII	IX
R	2-CH_3	2-CH_3 5-Cl	3-Cl	3-CF_3	4-CH_3	4-Cl	4-F

Comp. **X-XVI** n=1

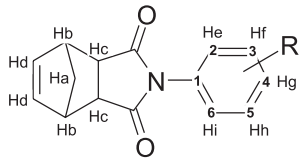
No.	X	XI	XII	XII	XIV	XV	XVI
R	H	2-Cl	2-OCH_3	4-Cl	4-F	4-CH_3	4-OCH_3

Table 1. Physicochemical and analytical data for compounds **III-XVI**

No.	Molecular Formula Weight	Yield % M.p. [C]	Analysis			R_f[b]
			%C	%H	%N	
III	$C_{16}H_{15}O_2N_1$ 253.30	41 133-135	75.63 75.87	5.97 6.15	5.53 5.43	0.78 A 0.24 B
IV	$C_{16}H_{14}O_2N_1Cl_1$ 287.75	47 208-210	66.79 66.52	4.90 5.00	4.87 4.78	0.79 A 0.26 B
V	$C_{15}H_{12}O_2N_1Cl_1$ 273.72	48 177-179	65.82 65.52	4,42 4.71	5.12 5.03	0.78 A 0.28 B
VI	$C_{16}H_{12}O_2N_1F_3$ 307.28	43 198-200	62.54 62.52	3.94 4.13	4.56 4.46	0.79 A 0.20 B
VII	$C_{16}H_{15}O_2N_1$ 253.30	50 169-171	75.87 75.71	5.97 6.27	5.53 5.49	0.74 A 0.39 B
VIII	$C_{15}H_{12}O_2N_1Cl_1$ 273.72	41 169-171	65.82 66.01	4.42 4.69	5.12 5.06	0.67 A 0.25 B
IX	$C_{15}H_{12}O_2N_1F_1$ 257.27	46 187-189	70.03 69.79	4.40 4.86	5.44 5.39	0.72 A 0.32 B
X	$CH_{15}O_2N_1$ 253.30	48 90-91	75.87 75.94	5.97 6.16	5.53 5.50	0.81 A 0.40 B
XI	$C_{16}H_{14}O_2N_1Cl_1$ 287.75	39 142-144	66.79 66.76	4.90 5.12	4.87 4.83	0.86 A 0.36 B
XII	$C_{17}H_{17}O_3N_1$ 283.33	42 143-144	72.07 72.00	6.05 6.32	4.94 4.89	0.81 A 0.25 B
XIII	$C_{16}H_{14}O_2N_1Cl_1$ 287.75	48 105-107	66.79 66.69	4.90 5.09	4.87 4.80	0.74 A 0.37 B
XIV	$C_{16}H_{14}O_2N_1F_1$ 271.23	40 93-95	70.84 70.50	5.20 5.46	5.16 5.03	0.84 A 0.36 B
XV	$C_{17}H_{17}O_2N_1$ 267.33	43 110-112	76.38 76.44	6.41 6.50	5.24 5.14	0.86 A 0.36 B
XVI	$C_{17}H_{17}O_3N_1$ 283.33	45 119-121	72.07 72.23	6.05 6.25	4.94 4.92	0.76 A 0.29 B

[a] Yields calculated from acetic anhydride.
[b] Solvents : A- chloroform : acetone (9 : 1), B- ethyl acetate : n-hexane (3 : 7)

Table 2. ^{1}H NMR data of compounds **III-IX**



No.	R	^{1}H NMR δ(ppm) / $CDCl_3$
III	2-CH_3	1.62-1.87 (2H, m, H_a), 2.12-2.16 (3H, d, -CH_3, *J*=9.35Hz), 3.48-3.56 (4H, m, $2H_b$, $2H_c$), 6.33-6.35 (2H, t, H_d, *J*=1.65Hz), 6.88-7.02 (1H, dd, H_g, *J*=7.56Hz), 7.23-7.36 (3H, m, H_f, H_h, H_i)
IV	2-CH_3 5-Cl	1.62-1.87 (2H, m, H_a), 2.08-2.17 (3H, d, -CH_3, *J*=9.07Hz), 3.48-3.56 (4H, m, $2H_b$, $2H_c$), 6.32-6.36 (2H, dt, H_d, *J*=1.65 Hz), 6.87-7.04 (1H, dd, H_g, *J*=2.20Hz), 7.21-7.32 (2H, m, H_f, H_i)
V	3-Cl	1.60-1.85 (2H, m, H_a), 3.43-3.56 (4H, m, $2H_b$ $2H_c$), 6.29-6.30 (2H, t, H_d, *J*=1.78 Hz), 7.05-7.12 (1H, m, H_g), 7.19-7.20 (1H, dd, H_h, *J*=1.37Hz), 7.30-7.42 (2H, m, H_e, H_i)
VI	3-CF_3	1.64-1.86 (2H, m, H_a), 3.47-3.57 (4H, m, $2H_b$, $2H_c$), 6.30-6.32 (2H, t, H_d, *J*= 1.92Hz), 7.38-7.39 (1H, d, H_g, *J*=1.37Hz), 7.41-7.47 (1H, m, H_h), 7.56-7.66 (2H, m, H_e, H_i)
VII	4-CH_3	1.60-1.84 (2H, m, H_a), 2.39 (3H, s,-CH_3), 3.42-3.55 (4H, m, $2H_b$, $2H_c$), 6.28-6.30 (2H, t, H_d, *J*=1.79Hz), 7.02-7.05 (2H, dd, H_f, H_h, *J*=1.94Hz), 7.24-7.29 (2H, d, H_e, H_i, *J*=7.97Hz)
VIII	4-Cl	1.61-1.84 (2H, m, H_a), 3.45-3.57 (4H, m, $2H_b$, $2H_c$), 6.27-6.29 (2H, t, H_d, *J*=1.92Hz), 7.10-7.15 (2H, m, H_f, H_h), 7.40-7.45 (2H, m, H_e, H_i)
IX	4-F	1.62-1.85 (2H, m, H_a), 3.46-3.56 (4H, m, $2H_b$, $2H_c$), 6.28-6.29 (2H, t, H_d, *J*=1.78Hz), 7.11-7.17 (4H, m, arom.)

The MES test is a model for generalized tonic--clonic seizures. In this test, an electrical stimulus of 0.2 s in duration (50 mA in mice at 60 Hz) is delivered *via* corneal electrodes. Mice are tested for 0.5 and 4 h with the following doses: 30, 100, 300 mg/kg of tested compound.

The sc. MET is a model for compounds that raise a seizure threshold. In sc. MET test a dose of metrazole (85 mg/kg in mice) was administrated subcutaneously. This produces clonic seizures during a period of least 5 seconds in 97% of tested animals. The tested compounds are administrated intraperitoneally, suspended in 0.5% methylcellulose at doses of 30, 100, 300 mg/kg.

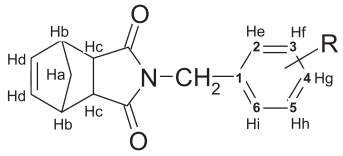
Neurotoxicity, induced by tested compounds, is detected in mice using a rotarod test. Untreated control mice, when placed on a 6 r. p. m. rotation rod can maintain their equilibrium for a prolonged time. Neurotoxicity is indicated by the inability of mouse maintaining equilibrium for one min in each of the three successive trials.

Phase I is a qualitative assay involving a small number of mice (1-4). The compounds were classified into the following categories: anticonvulsant activity at 100 mg/kg or less (class 1), anticonvulsant activity at doses higher than 100 mg/kg (class 2), compounds inactive at 300 mg/kg (class 3). The results are shown in Tables 4 and 5.

RESULTS

As part of our study, we investigated the conversion of the aryl system of the earlier obtained compounds **I** and **II** to the norbornane moiety, as well as the substitution mode in the aryl ring of N--benzyl- and N-phenyl-bicyclo [2.2.1] hept-5-ene--2,3-dicarboximides. Taking account of our earlier experiments, introduction of substituents into 2 position of the aryl ring should enhance the activity. Such an effect was observed for both electron-donating 2-CH_3 [**III**] and electron-attracting 2-Cl [**XI**] substituents which were active at a dose of 100 mg/kg (2/3 and 3/3 of the animals protected after 0.5 h) in the MES test. Compound **XII** with the 2-OCH_3 group was also ascribed to ASP class 1, but as the only one of the whole series, was active at a dose of 100 mg/kg (1/5 of the animals protected after 0.5 h) in the sc. MET test, and inhibited elec-

Table 3. ^{1}H NMR data of compounds **X**-**XVI**



No.	R	^{1}H NMR δ (ppm) / $CDCl_3$
X	H	1.52-1.74 (2H, m, H_a), 3.25-3.52 (4H, m, $2H_b$, $2H_c$), 4.52 (2H, s, -CH_2-), 5.92-5.93 (2H, t, H_d, *J*=1.80Hz), 7.28-7.34 (5H, m, arom.)
XI	2-Cl	1.58-1.81 (2H, m, H_a), 3.34-3.51 (4H, m, $2H_b$, $2H_c$), 4.68 (2H, s, -CH_2-), 6.14-6.16 (2H, t, H_d, *J*=1.92Hz), 7.19-7.23 (3H, m, H_g, H_h, H_i), 7.35-7.38 (1H, m, H_f)
XII	2-OCH_3	1.56-1.79 (2H, m, H_a), 3.32-3.52 (4H, m, $2H_b$, $2H_c$), 3.86 (3H, s, -OCH_3), 4.60 (2H, s, -CH_2-), 6.10-6.12 (2H, t, H_d, *J*=1.79 Hz), 6.84-6.89 (2H, m, H_f, H_h), 7.07-7.10 (1H, dd, H_i, *J*=1.65Hz), 7.21-7.27 (1H, td, H_g, *J*=1.65Hz)
XIII	4-Cl	1.53-1.75 (2H, m, H_a), 3.27-3.52 (4H, m, $2H_b$, $2H_c$), 4.47 (2H, s, -CH_2-), 5.91-5.92 (2H, t, H_d, *J*=1.78Hz), 7.26-7.28 (4H, m, arom.)
XIV	4-F	1.52-1.74 (2H, m, H_a), 3.26-3.52 (4H, m, $2H_b$, $2H_c$), 4.48 (2H, s, -CH_2-), 5.89-5.90 (2H, t, H_d, *J*=1.92 Hz), 6.96-7.02 (2H, m, H_f, H_h), 7.30-7.36 (2H, m, H_e, H_i)
XV	4-CH_3	1.52-1.74 (2H, m, H_a), 2.34 (3H, s, -CH_3), 3.26-3.52 (4H, m, $2H_b$, $2H_c$), 4.48 (2H, s, -CH_2-), 5.93-5.95 (2H, t, H_d, *J*=1.92Hz), 7.09-7.12 (2H, d, H_f, H_h, *J*=7.97Hz), 7.21-7.24 (2H, m, H_e, H_i)
XVI	4-OCH_3	1.51-1.73 (2H, m, H_a), 3.25-3.40 (4H, m, $2H_b$, $2H_c$), 3.81 (3H, s, -OCH_3), 4.45 (2H, s, -CH_2-), 5.90-5.91 (2H, t, H_d, *J*=1.78Hz), 6.80-6.85 (2H, d, H_f, H_h, *J*=8.80Hz), 7.27-7.29 (2H, m, H_e, H_i)

trically provoked seizures (MES) at a dose of 300 mg/kg (1/1 of the animals protected after 0.5 h). The introduction of a chloro substituent into position -5 of compound **III** yielded an inactive derivative **IV**. Compounds with the 3-Cl [**V**], and the 3-CF_3 [**VI**] group were less active (ASP class 2), probably due to an unfavorable distance between the electron-attracting atoms and carbonyl oxygen. As anticipated, the introduction of substituents into position -4 of the aryl ring gave inactive compounds [**VII**, **IX**, **XV**, **XVI**]. Surprisingly enough, an increased anticonvulsant activity (MES) was observed in the case of the 4-Cl derivatives **VIII** and **XIII**, which were potent at doses of 100 and 300 mg/kg (2/3 and 1/1 of the animals protected after 4 h, respectively) [**VIII**], and at a dose of 300 mg/kg (1/1 of the animals protected after 0.5 h) [**XIII**]. In the series of N-benzyl derivatives, the unsubstituted compound **X** and its 4-F analogue **XIV** were only slightly active at a dose of 300 mg/kg (1/1 of the animals protected after 0.5 and 4 h respectively) in the MES test.

In a neurological toxicity screening test, all the inactive compounds [**IV**, **VII**, **IX**, **XV** and **XVI**] were non-toxic at a dose of 300 mg/kg. The mice were unable to grasp the rotarod after administration of compounds **X**-**XIV** at a dose of 300 mg/kg after 0.5 h. Additionally, after administration of compounds with 3-CF_3 [**VI**], 4-Cl [**XIII**] and 4-F [**XIV**] substituents, the animals had clonic seizures and muscle spasms.

In conclusion, our investigation has shown that the replacement of the aryl ring in our earlier synthesized 3-arylpyrrolidine-2,5-dione derivatives with a norbornane moiety connected with the succinimide at 3 and 4 carbon atoms causes deterioration of their anticonvulsant properties, probably due to the rigidity of the molecule. Surprisingly, of all the tested N-phenyl- and N-benzyl-bicyclo [2.2.1] hept-5-ene-2,3-dicarboximide derivatives [**III**-**XVI**], none was more active than the previously obtained series to which compounds **I** and **II** belong. In summary, no additional studies with this group of N-substituted bicyclo [2.2.1] hept-5-ene-2,3-dicarboximides are planned for in future.

Table 4. Anticonvulsant screening project (ASP) phase I test in mice for N–phenyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide derivatives (**III**-**IX**)

Comp.	Dose mg/kg	MES[a] 0,5h	MES[a] 4h	sc.MET[b] 0,5h	sc.MET[b] 4h	TOX[c] 0,5h	TOX[c] 4h	ASP[d] Class
III	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	2/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	0/1	0/1	1/4	0/2	
IV	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	1/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
V	30	0/1	0/1	0/1	1/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	1/4	
	300	0/1	0/1	0/1	1/1	2/4	1/2	
VI	30	0/1	0/1	0/1	0/1	0/4[34]	1/2	2
	100	0/3	0/3	0/1	1/1	3/8[23, 34]	0/4	
	300	0/1	1/1	0/1	0/1	4/4[22, 23,34]	2/2[34]	
VII	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
VIII	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	0/3	2/3	0/1	0/	0/8	0/4	
	300	0/1	1/1	0/1	0/0	1/4	2/2	
IX	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	

[a)] Maximal electroshock test (number of animals protected/ number of animals tested); [b)] Subcutaneous metrazole test; [c)] Rotarod toxicity (number of animals exhibiting toxicity/ number of animals tested).
[d)] The classification are as follows: active at 100 mg/kg or less (class 1), anticonvulsant activity at a dose greater than 100 mg/kg (class 2), inactive at 300 mg/kg (class 3).
Response comments:[3]death following continuous seizure, [14]unable to grasp rotarod, [22]continuous seizure activity; [23]clonic seizures, [34]muscle spasms.

Table 5. Anticonvulsant screening project (ASP) phase I test in mice for N–benzyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide derivatives (**X**-**XVI**)

Comp.	Dose mg/kg	MES[a] 0,5h	MES[a] 4h	sc.MET[b] 0,5h	sc.MET[b] 4h	TOX[c] 0,5h	TOX[c] 4h	ASP[d] Class
X	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	1/1	0/1[22]	0/1	3/4[14,34]	0/2	
XI	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	3/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	1/1	0/1	0/1	3/4[14]	0/2	
XII	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	0/3	0/3	1/5	0/1	0/8	0/4	
	300	1/1	0/1	1/1	0/1	4/4[14]	0/2	
XIII	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	1/1	0/1	0/1	4/4[14, 23,34]	0/2	
XIV	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	1/8[14]	0/4	
	300	1/1	1/1	0/1[22]	0/1	4/4[14, 23,34]	0/2	
XV	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
XVI	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	

[a)], [b)], [c)], [d)], and response comments see Table 4.

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REFERENCES

1. Pastalos P. N.: Curr. Opin. CNS Invest. Drugs, 5, 549 (1999).
2. Brodi M. J.: Lancet, 336, 93 (1990).
3. Chen G., Portman R., Ensor C. R., Bratton A. C.: J. Pharmacol. Exp. Ther. 103, 54 (1951).
4. Hudkins R. L., DeHaven-Hudkins D. L., Doukas P.: Bioorg. Med. Chem. Lett. 7, 979 (1997).
5. Estrada E., Pena A.: Bioorg. Med. Chem. 8, 2755 (2000).
6. Sigler M., Strassburg H. M., Boenigk H. E.: Seizure, 10, 120 (2001).
7. Carter M. D., Stephenson V. C., Weaver D. F.: J. Mol. Struct. 638, 57 (2003).
8. Traver M. L, Nicholson J. M, Scott K. R.: J. Pharm. Sci. 74, 785 (1985).
9. Scott K. R, Moore J. A, Zalusky T. B., Nicholson., J. M., Lee J. A. M.: J. Med. Chem. 28, 413 (1985).
10. Alexander M. S., Stables J. P, Ciechanowicz--Rutkowska M, Hursthouse M. B., Hibbs D. E., Edafiogho I. O., Moore V. A, Scott K. R.: Eur. J. Med. Chem. 31, 787 (1996).
11. Wong G. M., Andrews P. R.: J. Med. Chem. 29, 562 (1986).
12. Wong G. M., Defina J. A., Andrews P. R: Eur. J. Med. Chem. 24, 323 (1989).
13. Duke N. E. C., Codding P.: J. Med. Chem. 35, 1806 (1992).
14. Obniska J., Kulig K., Zejc A.: Acta Pol. Pharm. -Drug Res. 55 (1998).
15. Obniska J., Zagórska A.: Il Farmaco 58, 1227 (2003).
16. Obniska J., Zejc A.: Acta Pol. Pharm.-Drug Res. 60, 383 (2003).
17. Obniska J., Zejc A., Karolak-Wojciechowska J.: Il Farmaco, 54, 423 (1999).
18. Obniska J., Zejc A., Zagórska A.: Acta Pol. Pharm.-Drug Res. 59, 209 (2002).
19. Mehta N. B., Phillips A. P., Fu F., Brooks R. E.: J. Med. Chem. 6, 1012 (1960).
20. Lebrun S., Couture A., Deniau E., Grandclaudon.: in Tetrahedron: Asymmetry. 14, 2628 (2003).
21. Krall R. L., Penry J. K, White B. G., Kupferberg H. J., Swinyar E. A.: Epilepsia 19, 409 (1978).
22. Kupferberg K. R.: Epilepsia 30 (Suppl.), 51 (1989).

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