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SYNTHESIS AND ANTICONVULSANT EVALUATION OF SOME N-SUBSTITUTED PHTHALIMIDES

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Abstract: Two series of phthalimides – one possessing an N-phenoxyalkyl moiety substituted at position 3 or 4 of the phenyl ring (**1**-**9**) and the other of N-alkenyl or alkinyl phthalimides (**10**-**18**) – were synthesized, evaluated for anticonvulsant activity and had their *in silico* lipophilicity estimated using computer programs. The anticonvulsant activity of phthalimides containing an unsaturated substituent at the phthalimide nitrogen was superior to that of the N-phenoxyalkyl phthalimides. Alkinyl derivative **10** emerged as the most active (in MES and ScMet tests) of all the compounds tested. A correlation between anticonvulsant activity and *in silico* estimated lipophilicity was not observed.

Keywords: phthalimides, anticonvulsant activity, structure-activity relationships, lipophilicity

Epilepsy is a relatively common neurological condition affecting 0.5-1% of the world's population. The classical antiepileptic drugs comprise phenytoin, phenobarbital, carbamazepine, ethosuximide, valproic acid and various benzodiazepines still widely utilized in the treatment of the various forms of epilepsy. In recent years several new drugs have been employed, e.g. felbamate, fosphenytoin, gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin and zonisamide. However, about 25% of patients are resistant to the available medical therapies. All the currently approved antiepileptic drugs have dose-related toxicity and idiosyncratic side effects (1). Antiepileptic drugs belong to many different classes of chemical compounds and act *via* various mechanisms (2). This makes it difficult to identify a common pharmacophore.

Among the compounds tested for anticonvulsant activity are phthalimide derivatives (3-5). Based on the structure-activity relationships for 4-aminobenzamide derivatives (especially ameltolide) and thalidomide, Vamecq et al. studied N-phenyl phthalimide derivatives as rigidified analogues of ameltolide and designed the 4-amino-N-(2,6-dimethylphenyl)phthalimide model and subsequent phthalimide pharmacophore without the 4-amino group in the phthaloyl moiety (Fig. 1) (5). Similarly to ameltolide, N-phenylphthalimide derivatives exhibit a phenytoin-like profile i.e. they are quite potent in the maximal electroshock seizure (MES) test and are inactive in the subcutaneous pentylenetetrazole (ScMet) test.

Marona and Kieć-Kononowicz found some anticonvulsant compounds among the 2-N-(phthalimido)-1-alkyl esters of aromatic and heterocyclic acids (4). The highest activity was shown by isomer R of 2-N-(phthalimido)-1-butyl-(4-benzyloxy)benzoate (Fig. 2).

This study indicated that a rigid phenyl ring substituted at the phthalimide nitrogen atom is not an essential element for anticonvulsant activity. In our research we synthesized two series of phthalimides: those possessing an N-phenoxyalkyl moiety substituted at position 3 or 4 of the phenyl ring and a series of N-alkenyl or alkinyl phthalimides. We evaluated their anticonvulsant activity and estimated their lipophilicity *in silico* using computer programs. The target compounds were synthesized using two methods: by conventional alkylation of phthalimide with appropriate bromides under phase-transfer conditions (compounds **1**-**9**, **11**, Scheme 1) (6) and, by using the Mitsunobu reaction, from appropriate alcohols and phthalimide in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (compounds **10**, **12-18,** Scheme 3) (7). Phenoxyalkyl bromides were prepared from the corresponding phenols using the standard procedure (Scheme 2).

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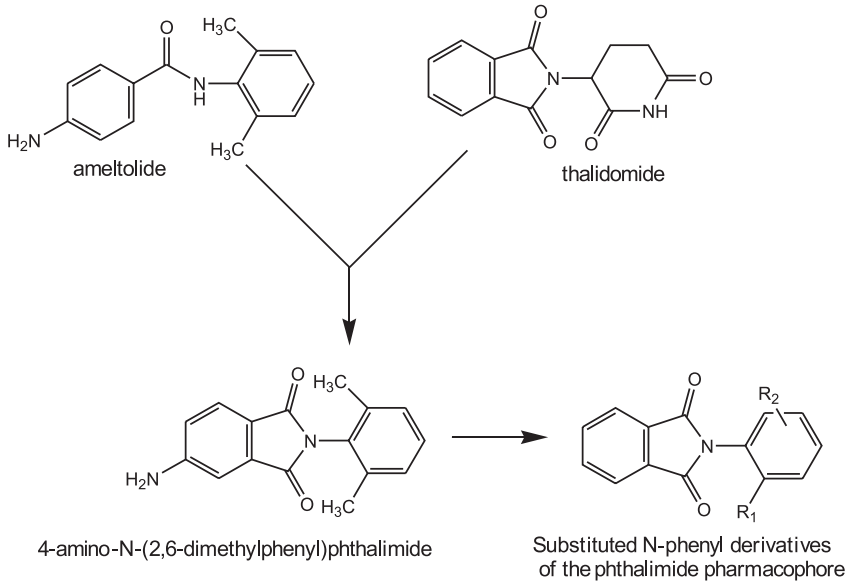


Figure 1. Anticonvulsant compounds designed from ameltolide and thalidomide

Compounds **1**-**3**, **7**, **8**, **12**-**15** and **18** were unknown in the literature to date, but the other compounds (**4**-**6**, **9**-**11** and **16**-**17**) were described as intermediate products in the synthesis of amines, used in the preparation of the final compounds. Compounds **4**-**6**, **9**, **11**, **16** and **17** were obtained by the reaction of appropriate bromides (comp. **4**-**6**, **9**, **11**) or chlorides (**16**, **17**) and potassium phthalimide in anhydrous THF. Compound **10** was obtained by the reaction of 4-pentynol with phthalimide under Mitsunobu reaction conditions. Physicochemical data for all the compounds is given in Table 3.

The anticonvulsant properties of the compounds obtained were evaluated by the Antiepileptic Drug Development Program, Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institute of Health in Bethesda, USA. Phase I of these screenings included two major convulsant tests: maximal electroshock (MES) and subcutaneous pentylenetetrazole (ScMet), as well as a toxicity screen (Tox). The MES test is a model for generalized tonic-clonic (grand-mal) seizures, whereas the ScMet test is a model which primarily identifies compounds that raise the seizure threshold. The neurological toxicity was evaluated in mice using the rotorod test. The pharmacological data are given in Tables 1 and 2.

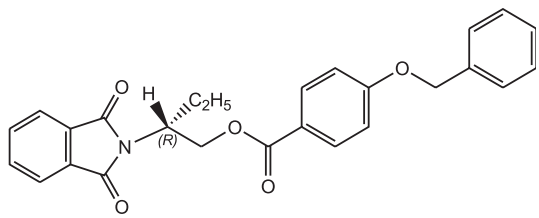
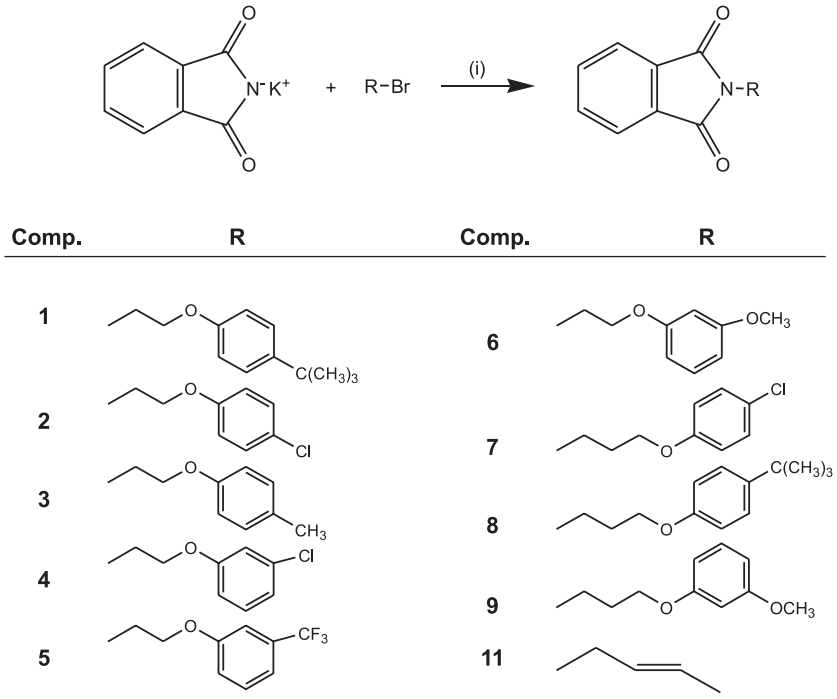


Figure 2. The most active compound among the 2-N-(phthalimido)-1-alkyl esters of aromatic and heterocyclic acids (4)

EXPERIMENTAL

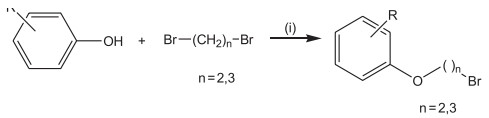
General methods

All the melting points were measured in glass capillary tubes using Mel-Temp Laboratory Devices Inc. USA apparatus, and are uncorrected. TLC analysis was conducted on Al sheets with a 0.2 mm layer of silica gel ($60F_{254}$ Merck). ^{1}H NMR spectra were recorded on a Varian Mercury-VX instrument at 300 MHz using TMS as an internal standard in DMSO-d_6 (for comp. **1**-**9**) or $CDCl_3$ (for comp. **10**-**18**). Elemental analyses were performed on an Elemental Vario-EL III apparatus. Reagents: phthalimide, potassium phthalimide, TEBA, triphenylphosphine, DEAD, 1,2-dibromoethane, 1,3-dibromopropane and solvents were commercial reagents (Aldrich, Fluka). The theoretical values of logP were calculated using the Pallas ($logP_{PALLAS}$) and clogP programs.



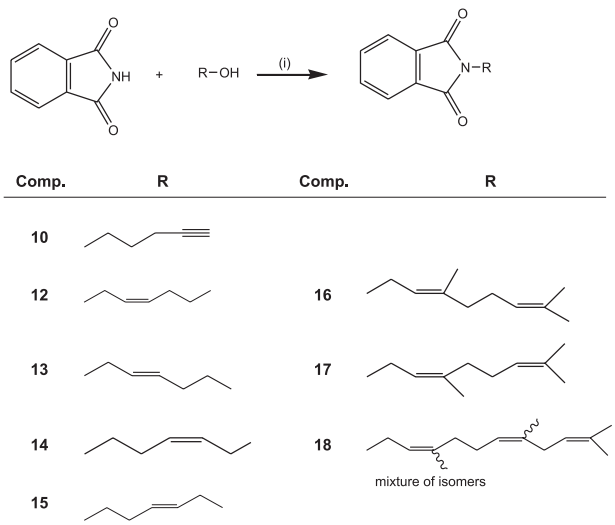
Reagents and conditions: (i) K_2CO_3, TEBA, acetone, 6 h reflux

Scheme 1. Synthesis of N-substituted phthalimides from bromides



Reagents and conditions: (i) sodium n-propanolate, 3 h at 60ºC, 3 h reflux

Scheme 2. Synthesis of phenoxyalkyl bromides



Reagents and conditions: (i) DEAD, $(Ph)_3P$, THF (anhydr.)

Scheme 3. Synthesis of N-substituted phthalimides by the Mitsunobu reaction

Table 1. Anticonvulsant and neurotoxicity screening data for phenoxyalkyl phthalimides (**1**-**9**)

Compd. no.	Dose [mg/kg]	Activity					
		MES[a]		ScMet[b]		Tox[c]	
		0.5h	4h	0.5	4	0.5	4
1	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 2/5	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2
2	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2
3	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2
4	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2
5	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 1/8 1/4	0/2 0/4 0/2
6	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2
7	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2
8	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2
9	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 0/8 0/4	0/2 0/4 0/2

[a] Number of animals protected/number of animals tested in the MES test.
[b] Number of animals protected/number of animals tested in the ScMet test.
[c] Number of animals exhibiting toxicity/number of animals tested in the rotorod test.

Chemistry

General synthetic procedure for the preparation of N-substituted phthalimides from bromides (**1-9**, **11**)

A mixture of potassium phthalimide (10 mmol), K_2CO_3 (30 mmol), and benzyltriethylammonium chloride (TEBA) (1 mmol) in 50 mL of acetone was refluxed for 40 min. An appropriate bromide (10 mmol) in 10 mL of acetone was added dropwise and refluxed for additional 6 h. The precipitate was filtered and the solvent was evaporated under reduced pressure. The residue was washed twice with 2% NaOH solution and water and purified by column chromatography (eluent: CH_2Cl_2) to afford pure N-substituted phthalimide. Compounds **1**-**6**, **8** and **9** were also crystallized from ethanol.

General synthetic procedure for the preparation of bromides

Bromides for the synthesis of compounds **1**-**9** were obtained from appropriate phenols and an excess of 1,2-dibromoethane (**1**-**6**) or 1,3-dibromopropane (**7**-**9**) by heating for 6 h (3 h at 60°C, 3 h reflux) in sodium n-propanolate. Unpurified raw materials were used for further synthesis. The bromide for the synthesis of **11** was commercially available.

General procedure for the preparation of N-substituted phthalimides from alcohols (**10**, **12-18**)

A mixture of phthalimide (15 mmol), triphenylphosphine (15 mmol), and an appropriate alcohol (15 mmol) in 10 mL of dry THF was cooled to 0°C. Diethyl azodicarboxylate (DEAD) (15 mmol) in 10 ml of dry THF was slowly added dropwise (30 min); the reaction mixture was then allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue suspended in Et_2O. The precipitate was filtered, the solvent was evaporated and the residue was purified by column chromatography (eluent: CH_2Cl_2) to afford pure N-substituted phthalimide.

Table 2. Anticonvulsant and neurotoxicity screening data for unsaturated phthalimides (**10**-**18**)

Compd. no.	Dose [mg/kg]	Activity					
		MES[a]		ScMet[b]		Tox[c]	
		0.5h	4h	0.5	4	0.5	4
10	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	2/3	1/3	0/1	0/1	0/8	0/4
	300	1/1	1/1	1/1	0/1	4/4	1/2
11	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	1/1	0/1	0/1	0/1	2/4	0/2
12	30	0/1	0/1	0/1	0/1	0/4	0/2
	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
13	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	0/1	0/1	0/1	0/1	1/4	0/2
14	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	1/8	0/4
	300	1/1	0/1	1/1	0/1	2/4	0/2
15	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	1/8	0/4
	300	0/1	0/1	0/1	0/1	3/4	0/2
16	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	1/8	1/4
	300	0/1	0/1	0/1	0/1	2/4	0/2
17	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	0/1	0/1	0/1	0/1	2/4	0/2
18	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	2/8	0/4
	300	0/1	0/1	0/1	0/1	1/4	0/2

[a] Number of animals protected/number of animals tested in the MES test.
[b] Number of animals protected/number of animals tested in the ScMet test.
[c] Number of animals exhibiting toxicity/number of animals tested in the rotorod test.

Pharmacology

The anticonvulsant properties of the compounds obtained were evaluated by the Antiepileptic Drug Development Program, Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institute of Health in Bethesda, USA. Preliminary screenings in this program included two major convulsant tests: maximal electroshock (MES) and subcutaneous pentylenetetrazole (ScMet), as well as a toxicity screen (Tox). Compounds were injected intraperitoneally into mice as suspensions in 0.5% methylcellulose at three dosage levels (30, 100 and 300 mg/kg) 30 min or 4 h before evaluation of their activity in these tests. The MES were elicited by a 60 Hz alternating current at 50 mA delivered for 0.2 s via corneal electrodes. A drop of 0.9% NaCl solution was instilled in each eye prior to application of the electrodes. The abolition of the hindlimb tonic extension component of the seizure was defined as protection in the MES test. The ScMet test was conducted by administering 85 mg/kg of pentylenetetrazole dissolved in 0.9% NaCl solution into the posterior midline of mice. A minimal time of 30 min subsequent to the *s.c.* administration of pentylenetetrazole was used for seizure detection. Neurotoxicity was measured in mice by the rotorod test. The details of the testing procedures have been published (8).

Lipophilicity

The log *P* values of the compounds tested were calculated using two programs with different algorithms: clog *P* – the fragmental approach (9) and Pallas 3.1.1.2 – the combined atomic-fragmental approach (10).

Table 3. Physicochemical and spectral data of compounds **1-18**

Comp. no.	Formula Molecular mass	Yield [%]	m. p. [°C]	R_f	Elemental analyses [%]		^{1}H NMR δ [ppm]*
					calc.	found	
1	$C_{20}H_{21}NO_3$ 323.39	56.4	80-82	0.60 A	C: 74.28 H: 6.54 N: 4.33	C: 74.16 H: 6.56 N: 4.21	1.19 (s, 9H, 3×CH_3), 3.93 (t, 2H, *J* = 5.6 Hz, N-CH_2), 4.16 (t, 2H, *J* = 5.6 Hz, OCH_2), 6.76-6.79 (m, 2H, Ph 2,6-H), 7.20-7.23 (m, 2H, Ph 3,5-H), 7.80-7.88 (m, 4H, Pht 3,4,5,6-H)
2	$C_{16}H_{12}ClNO_3$ 301.72	88,7	140	0.53 A	C: 63.69 H: 4.01 N: 4.64	C: 63.40 H: 4.33 N: 4.58	3.93 (t, 2H, *J* = 5.6 Hz, N-CH_2), 4.19 (t, 2H, *J* = 5.9 Hz, OCH_2), 6.87-6.92 (m, 2H, Ph 2,6-H), 7.24-7.28 (m, 2H, Ph 3,5-H), 7.81-7.88 (m, 4H, Pht 3,4,5,6-H)
3	$C_{17}H_{15}NO_3$ 281.31	49.8	128-131	0.52 A	C: 72.58 H: 5.37 N: 4.98	C: 72.69 H: 5.38 N: 4.71	2.17 (s, 3H, CH_3), 3.92 (t, 2H, *J* = 5.6 Hz, N-CH_2), 4.14 (t, 2H,, *J* = 5.9 Hz, OCH_2) 6.73-6.76 (m, 2H, Ph 2,6-H), 7.00-7.03 (m, 2H, Ph 3,5-H), 7.80-7.88 (m, 4H, Pht 3,4,5,6-H)
4	$C_{16}H_{12}ClNO_3$ 301.72	59.8	92-94 85-87 (11)	0.49 A	C: 63.69 H: 4.01 N: 4.64	C: 63.44 H: 4.39 N: 4.88	3.93 (t, 2H, *J* = 5.6 Hz, N-CH_2), 4.22 (t, 2H, *J* = 5.9 Hz, OCH_2), 6.83-6.87 (m, 1H, Ph 6-H), 6.93-6.96 (m, 2H, Ph 2,4-H), 7.22-7.27 (m, 1H, Ph 5-H), 7.80-7.89 (m, 4H, Pht 3,4,5,6-H)
5	$C_{17}H_{12}F_3NO_3$ 335.28	44.8	98-100 98 (12)	0.61 A			3.96 (t, 2H, *J* = 5.6 Hz, N-CH_2), 4.29 (t, 2H, *J* = 5.6 Hz, OCH_2), 7.17-7.27 (m, 3H, Ph 2,4,6-H), 7.47 (m, 1H, Ph 5-H), 7.81-7.88 (m, 4H, Pht 3,4,5,6-H)
6	$C_{17}H_{15}NO_4$ 297.31	80.8	110-112 114-115 (11)	0.52 A	C: 68.67 H: 5.08 N: 4.71	C: 68.20 H: 5.19 N: 4.94	3.68 (s, 3H, OCH_3), 3.93 (t, 2H, *J* = 5.6 Hz, N-CH_2), 4.17 (t, 2H, *J* = 6.2 Hz, OCH_2), 6.41-6.48 (m, 3H, Ph 2,4,6-H), 7.12 (t, 1H, *J* = 8.2 Hz, Ph 5-H), 7.80-7.88 (m, 4H, Pht 3,4,5,6-H)
7	$C_{17}H_{14}ClNO_3$ 315.75	44.3	110-112	0.58 A	C: 64.66 H: 4.47 N: 4.44	C: 64.43 H: 4.57 N: 4.54	2.03 (qu, 2H, *J* = 6.2 Hz, CH_2-CH_2-CH_2), 3.74 (t, 2H, *J* = 6.7 Hz, N-CH_2),3.98 (t, 2H, *J* = 5.9 Hz, OCH_2), 6.77-6.82 (m, 2H, Ph 2,6-H), 7.22-7.27 (m, 2H, Ph 3,5-H), 7.78-7.86 (m, 4H, Pht 3,4,5,6-H)
8	$C_{21}H_{23}NO_3$ 337.41	46.4	96-98	0.60 A	C: 74.75 H: 6.87 N: 4.15	C: 74.73 H: 6.88 N: 4.07	1.21 (s, 9H, 3×CH_3), 2.02 (q, 2H, *J* = 6.2 Hz, CH_2-CH_2-CH_2), 3.74 (t, 2H, *J* = 6.7 Hz, N-CH_2), 3.95 (t, 2H, *J* = 5.9 Hz, OCH_2), 6.69-6.71 (m, 2H, Ph 2,6-H), 7.20-7.23 (m, 2H, Ph 3,5-H), 7.79-7.86 (m, 4H, Pht 3,4,5,6-H)
9	$C_{18}H_{17}NO_4$ 311.33	51.5	106-108 68-71 (13)	0.44 A	C: 69.44 H: 5.50 N: 4.50	C: 69.41 H: 5.51 N: 4.46	2.03 (qu, 2H, *J* = 6.4 Hz, CH_2-CH_2-CH_2), 3.65 (s, 3H, OCH_3), 3.74 (t, 2H, *J* = 6.7 Hz, N-CH_2), 3.97 (t, 2H, *J* = 5.6 Hz, OCH_2), 6.27-6.28 (m, 1H, Ph 2-H), 6.34-6.37 (m, 1H, Ph 4-H), 6.43-6.47 (m, 1H, Ph 6-H), 7.07-7.12 (t, 1H, *J* = 8.2 Hz, Ph 5-H), 7.79-7.86 (m, 4H, Pht 3,4,5,6-H)
10	$C_{13}H_{11}NO_2$ 213.23	31.2 87-89 (14)	85	0.69 A			1.78 (q, 2H, *J* = 7.0 Hz, N-CH_2-CH_2-), 2.23 (m, 2H, CH_2-C≡CH), 3.32 (s, 1H, C≡C*H*), 3.65 (t, 2H, *J* = 7.0 Hz, N-CH_2), 7.81-7.88 (m, 4H, Pht 3,4,5,6-H)

Table 3. cont.

Comp. no.	Formula Molecular mass	Yield [%]	m. p. [°C]	R_f	Elemental analyses [%]		^{1}H NMR δ [ppm]
					calc.	found	
11	$C_{12}H_{11}NO_2$ 201.22	81.1 78.5-79.5 (15)	60	0,59 B			1.70 (d, 3H, *J* = 6.8 Hz, CH_3), 4.23-4.26 (m, 2H, N-CH_2), 5.50-5.84 (m, 2H, C*H*=C*H*), 7.70-7.76 (m, 2H, Pht 4,5-H), 7.83-7.90 (m, 2H, Pht 3,6-H),
12	$C_{14}H_{15}NO_2$ 229.27	90,7	oil	0.61 B			0.95 (t, 3H, *J* = 7.1 Hz, CH_3), 1.45 (q, 2H, *J* = 7.4 Hz, C$H_2$$CH_2CH_3$), 2.25 (q, 2H, *J* = 7.4 Hz, C$H_2$$CH_3$), 4.31 (d, 2H, *J* = 5.8 Hz, N-CH_2), 5.38-5.46 (m, 1H, CH=C*H*-CH_2-CH_3), 5.54-5.63 (m, 1H, N-CH_2-C*H*=CH), 7.68-7.72- (m, 2H, Pht 4,5-H), 7.81-7.84 (m, 2H, Pht 3,6-H),
13	$C_{14}H_{15}NO_2$ 229.27	76,8	60-61	0,60 B			0.85 (t, 3H, *J* = 7.2 Hz, CH_3), 1.36 (sc, 2H, *J* = 7.4 Hz, CH_2-CH_3), 1.97 (q, 2H, *J* = 7.2 Hz, CH_2-CH_2-CH_3), 4.22 (d, 2H, *J* = 6.1 Hz, N-CH_2), 5.44-5.54 (m, 1H, CH=C*H*-CH_2-CH_2), 5.68-5.78 (m, 1H, N-CH_2-C*H*=CH), 7.67-7.72- (m, 2H, Pht 4,5-H), 7.81-7.85 (m, 2H, Pht 3,6-H),
14	$C_{14}H_{15}NO_2$ 229.27	59.1	oil	0.60 B			0.85 (t, 3H, *J* = 7.4 Hz, CH_3), 1.93-2.03 (m, 2H, C$H_2$$CH_3$), 2.40-2.47 (m, 2H, N-$CH_2CH_2$) 3.71 (t, 2H, *J* = 7.1 Hz, N-CH_2), 5.27-5.49 (m, 2H, C*H*=C*H*), 7.66-7.72 (m, 2H, Pht 4,5-H), 7.79-7.85 (m, 2H, Pht 3,6-H)
15	$C_{14}H_{15}NO_2$ 229.27	81,2	49-50	0,60 B			0.85 (t, 3H, *J* = 7.4 Hz, CH_3), 1.88-1.98 (m, 2H, CH_2-CH_3), 2.36 (q, 2H, *J* = 6.6 Hz, N-CH_2-CH_2), 3.71 (t, 2H, *J* = 7.2 Hz, N-CH_2), 5.31-5.41 (m, 1H, CH=C*H*-CH_2-CH_3), 5.44-5.53 (m, 1H, N-CH_2-CH_2-C *H*=CH), 7.68-7.71 (m, 2H, Pht 4,5-H), 7.81-7.84 (m, 2H, Pht 3,6-H),
16	$C_{18}H_{21}NO_2$ 283.36	74,2	59-60 60-61.5 (16)	0.83 A			1.55 (s, 3H, C=C(CH_3)(CH_2CH_2)), 1.62 (s, 3H, C=C(CH_3), 1.82 (s, 3H, C=C(CH_3), 1.95-2.10 (m, 4H, =CHCH_2CH_2CH=C), 4.27 (d, 2H, *J* = 7.1 Hz, N-CH_2), 5.03, (t, 2H, *J* = 6.4 Hz, C*H*=C(CH_3)$_2$), 5.26 (t, 1H, *J* = 6.1 Hz, N-CH_2C*H*=C), 7.67-7.72 (m, 2H, Pht 4,5-H), 7.81- 7.84 (m, 2H, Pht 3,6-H),
17	$C_{18}H_{21}NO_2$ 283.36	52.9	59-60 59-60.5 (16)	0.83 A			1.63 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.07-2.29 (m, 4H, CH_2CH_2-CH=C), 4.26 (d, 2H, *J* = 7.1 Hz, N-CH_2), 5.16, (t, 2H, *J* = 6.9 Hz, C*H*=C(CH_3)$_2$), 5.27 (t, 1H, *J* = 6.6 Hz, N-CH_2C*H*=C), 7.66-7.71 (m, 2H, Pht 4,5-*H*), 7.79-8.85 (m, 2H, Pht 3,6-*H*)
18	$C_{23}H_{29}NO_2$	61.0	oil	0.62 B			1.55-1.82 (m, 12H, 4xCH_3), 1.90-2.10 (m, 8H, 4 x CH_2), 4.26 (d, 2H, *J* = 7.15 Hz, N-CH_2), 5.02-5.07 (m, 2H, 2 × C*H*=), 5.23-5.28 (m, 1H, N-CH_2-C*H*=), 7.64-7.70 (m, 2H, Pht 4,5-H), 7.78-7.84 (m, 2H, Pht 3,6-H)

A: toluene : acetone (40:3, v/v); B: dichloromethane
* Ph – phenyl, Pht – phthalimide

Table 4. Predicted log P values for compounds **1**-**18**

Compd. no.	$logP_{Pallas}$	clogP	ASP
1	3.15	4.36	2
2	2.95	3.21	3
3	2.65	3.14	3
4	2.84	3.21	3
5	2.96	3.57	3
6	2.41	2.53	3
7	3.25	3.31	3
8	3.87	4.46	3
9	2.48	2.63	3
10	1.34	1.90	1
11	1.29	2.05	2
12	2.97	2.88	3
13	2.97	2.88	3
14	2.97	2.74	2
15	2.97	2.74	3
16	4.30	3.75	3
17	4.30	3.75	3
18	6.56	5.27	3

The ASP classification is: 1 – anticonvulsant activity at doses of 100 mg/kg or less; 2 – anticonvulsant activity at doses greater than 100 mg/kg; 3 – compound inactive at 300 mg/kg.

RESULTS AND DISCUSSION

Among the unsaturated derivatives, only compound **12** was devoid of activity in both of the convulsant tests and showed no neurotoxicity at any of the doses studied. In contrast, all of the phenoxyalkyl phthalimides were inactive in the MES test and the majority of them did not exhibit neurotoxicity at doses of up to 300 mg/kg (compounds **2**, **3**, **4**, **6**, **7**, **8**, **9**). Only compound **5** showed neurotoxicity at doses of 100 and 300 mg/kg at 30 min after administration. Anti-MES activity of 300 mg/kg at 30 min was recorded for compounds **10**, **11** and **14**, but all of them exhibited neurotoxicity at the same or lower dose. Only compound **10** showed anticonvulsant activity in this test at a dose of 100 mg/kg at 30 min and 4 h and exhibited a lesser degree of neurotoxicity (300 mg/kg; 30 min, 4 h). The most neurotoxic of the compounds investigated were **14**, **15**, **16** and **18** (100 mg/kg, 300 mg/kg; 30 min). Compound **16** was toxic at a dose of 100 mg/kg at both the investigated time points (30 min, 4 h). In the ScMet test only compounds **1**, **10** and **14** were active at the highest dose (300 mg/kg) after 30 min. Only compound **1** was active in this model and devoid of neurotoxicity.

The log *P* values calculated for the compounds obtained vary from 1.29 to 6.56. It is known that compounds expected to act in the CNS should possess log P ~2. The predicted log P value for **10**, the most active compound, is 1.34 (Pallas) and 1.90 (clogP). The log *P* values for compounds **1**, **11** and **14**, belonging to ASP group 2, vary from 1.29 to 4.36. Also in the same range are the log P values for the compounds that are devoid of activity.

CONCLUSIONS

Two series of phthalimides – one possessing an N-phenoxyalkyl moiety substituted at position 3 or 4 of the phenyl ring (**1**-**9**) and the other, a series of N-alkenyl or alkinyl phthalimides (**10**-**18**) – were obtained and their anticonvulsant activity was examined.

The anticonvulsant activity of phthalimides containing an unsaturated substituent at the phthalimide nitrogen was superior to that of the N-phenoxyalkyl phthalimides. This suggests that the rigid-

ity of the molecule influences the activity of this group of compounds. Alkynyl derivative **10** emerges as the most active (MES and ScMet tests) of all the compounds tested. The activity of the unsaturated phthalimides depended on the length and configuration of the alkenyl chain. Activity was shown by derivatives possessing a limited chain length (up to 6 carbon atoms). The results obtained showed that the *cis* configuration of the alkenyl chain was more beneficial to activity than the *trans* configuration (**14**→**13**). Among the compounds containing a phenoxyalkyl substituent only the *p-tert*-butylphenoxyethyl derivative was active. Here the length of the alkyl linker was critical for activity since the propyl derivative (**8**) showed a lack of activity in comparison to the ethyl one (**1**). Compounds possessing the phenoxyalkyl substituent showed lower neurotoxicity in comparison to unsaturated derivatives. A correlation between anticonvulsant activity and *in silico* estimated lipophilicity was not observed.

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