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Synthesis and anticonvulsant activity of some ω-(1*H*-1-imidazolyl)-*N*-phenylalkanoic acid amide derivatives

Zeynep Aktürk [a], Fatma Kılıç [b], Kevser Erol [b], Varol Pabuçcuoğlu [a,*]

[a] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ege University Bornova, Izmir 35100, Turkey*
[b] *Faculty of Medicine, Osmangazi University, Department of Pharmacology, Eskişehir, Turkey*

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Abstract

In this study, 15 ω-(1*H*-imidazol-1-yl)-*N*-phenylacetamide, propionamide and butyramide derivatives having methoxyl, methyl, nitro and chloro in *ortho* position of *N*-phenyl ring or without any substituent have been realized by two-step synthesis. Their anticonvulsant activity was determined against seizures induced by maximal electroshock (MES). The most active compound in the series was 2-(1*H*-imidazol-1-yl)-*N*-(*o*-chlorophenyl)acetamide. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: Anticonvulsant; MES; Imidazole; Anilide

1. Introduction

Epilepsy is one of the most common neurological diseases. It is a chronic and often progressive disorder characterized by recurrent transient attacks which are caused by an abnormal discharge of cerebral neurons [1,2]. At least 50 million people worldwide are suffering from epilepsy, it being the second leading neurological disorder after stroke. Despite the optimal use of available antiepileptic drugs, the treatment is not satisfactory in preventing seizures completely [3–6]. The second handicap in treatment of epilepsy is the notable adverse effects of current antiepileptic drugs. Therefore, the need for safer and more effective new antiepileptic drugs is well known [1,6].

Numerous compounds are synthesized each year to determine anticonvulsant properties. One of the structures among the compounds studied for anticonvulsant activity is anilide nucleus. It is known that anilide function yields potent anticonvulsant compounds such as Ameltolide [7], Ralitoline [8], D2916 [9], certain *N*-phenylphthalimides [10,11] and *N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide [12] (Fig. 1). Structure–activity studies of anilide derivatives revealed that substitution pattern and nature of substituent(s) on *N*-phenyl ring is of vital importance for anticonvulsant activity [9,13]. It seems that *o*-substitution on *N*-phenyl ring is essential.

Üstünes et al., inspired by the structures of Denzimol and Nafimidone (Fig. 2), of which the clinical developments were stopped [14], have reported the anticonvul-

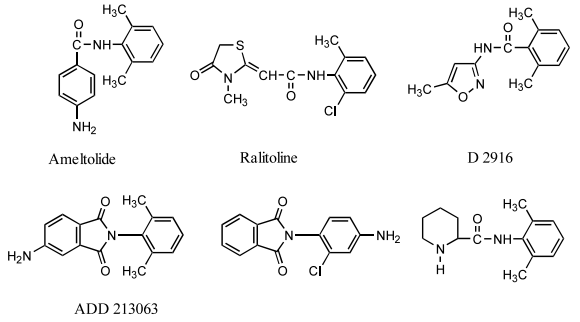

Fig. 1. Potent anticonvulsant compounds bearing anilide function.

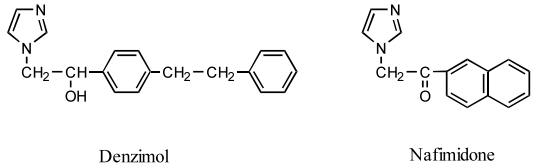

Fig. 2. Chemical structures of Denzimol and Nafimidone.

* Corresponding author.
E-mail address: papuccuogluv@pharm.ege.edu.tr (V. Pabuçcuoğlu).

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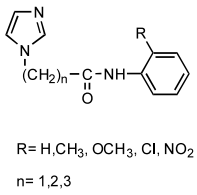


Fig. 3. Chemical structure of title compounds to be synthesized.

sant profiles of three compounds having the basic structures ω-(1*H*-imidazol-1-yl)-*N*-(*p*-tolyl)acetamide, propanamide and butyramide in a preliminary study [15]. According to their results, the anticonvulsant activities of these compounds against MES test were comparable to or less than that of phenobarbital. On the other hand, in a study on *N*-arylazole acetamide derivatives, Özkanli et al. stated that 2-(1*H*-imidazol-1-yl)-*N*-phenylacetamide shows anti-MES activity at 100 mg/kg dose in mice [16].

These findings have prompted us to refocus on ω-(1*H*-imidazol-1-yl)-*N*-phenylalkanoic acid amide derivatives to explore the possible effect of *o*-substitution on *N*-phenyl ring for anticonvulsant activity.

The compounds synthesized are presented in Fig. 3.

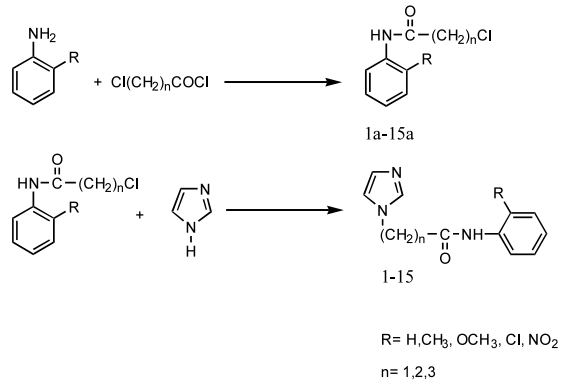
2. Chemistry

ω-(1*H*-Imidazol-1-yl)-*N*-(*o*-substitutedphenyl or phenyl)acetamides, propanamides and butyramides which were evaluated for anticonvulsant activity, were prepared by two-step synthesis. As illustrated in Scheme 1, in the first step, ω-chloroanilides were prepared by reacting ω-chloroacyl chloride with *o*-substituted anilines or aniline. In the second step, ω-chloroanilides were condensed with imidazole to furnish the title compounds **1**–**15** (Table 2). The title compounds except compound **1** are novel.

3. Experimental

3.1. Chemistry

Melting points were determined on a Buchi 510 Melting point apparatus and are uncorrected. The IR spectra of compounds were recorded as potassium bromide pellets on a Jasco FT/IR-400 spectrometer. The ^{1}H NMR spectra were recorded on a Bruker DPX-400 FT-NMR in $CHCl_3$-d_1 as solvent. Chemical shifts were reported in parts per million (δ). Mass spectra (EI) were measured on a Mikromass VG Platform-II spectrometer. Elemental analyses for C,H and N were performed by TUBİTAK Analytical Laboratory Ankara, Turkey. The analytical results for the elements were within $\pm 0.4\%$ of theoretical values.



Scheme 1. Synthesis of compounds.

3.1.1. Synthesis of ω-chloroanilide derivatives (*1a*–*15a*)

Aniline or *o*-substituted aniline (0.066 mol) was dissolved in 25 ml glacial acetic acid. ω-Chloroacyl chloride (2-chloroacetyl chloride, 3-chloropropionyl chloride and 4-chlorobutyryl chloride) (0.074 mol) was added dropwise to this solution while cooling in an ice-bath. The reaction mixture was stirred in ice-bath for 30 min and 1 h at room temperature. The mixture was poured into saturated sodium acetate solution. The precipitate was filtered, washed with cold water and purified by crystallization. Yields, melting points and ^{1}H NMR spectral data are presented in Table 1.

3.1.2. Synthesis of ω-(1H-1-imidazolyl)-N-phenylalkanoic acid amide derivatives (*1*–*15*)

ω-Chloroanilides (0.002 mol) and imidazole (0.01 mol) in a suitable solvent were refluxed under nitrogen (solvents and reflux times are listed in Table 2.). After the reaction was completed, solvent was removed under vacuo. Residue was dissolved in chloroform and washed with water twice. Organic phase, after drying over anhydrous sodium sulfate, evaporated to dryness. Residue was purified by crystallization (yields and melting points are given in Table 2.).

3.2. Pharmacology

All experiments for animal testing were approved by Osman Gazi University, School of Medicine, Animal Use and Care Committee. All compounds were tested for anticonvulsant activity with female albino mice weighing 25–35 g. The animals were housed in colony cages under standard laboratory conditions with free access to chow pellets and top water. Seizures were induced by means of 60 Hz current of 60 mA delivered through ear electrodes (Hugo Basile). The stimulus duration was 0.2 s and pulse width was 0.4. The criterion to indicate the convulsive response was the tonic extension of hind limbs. Eight animals were used in each group. All the compounds were dissolved in dimethyl sulfoxide (DMSO) and injected intraperi-

toneally to the animals at 100 and 30 mg/kg (only for compounds **8** and **10**) doses in approximately 0.1 ml volume. 0.1 ml DMSO were given to the control animals. The tests were performed 30 min after the injection of the compounds.

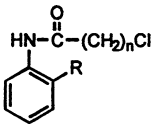
Minimal neurotoxicity was measured by using the rotarod test aparat (Commat MAY RR9612, Ankara, Turkey). Mice were placed on a 3.5 cm diameter knurled plastic rod rotating at 6 rpm after the administration of the compounds and their ability to maintain their balance was tested. Neurological deficit was indicated by the inability of the animal to maintain its equilibrium for 1 min on the rotating rod in each three trials [17]. Fisher's exact χ^2 test was used for statistical analysis.

4. Results

In this study, 15 ω-(1*H*-imidazol-1-yl)-*N*-phenylacetamide, propionamide and butyramide derivatives having methoxyl, methyl, nitro and chloro in *ortho* position of *N*-phenyl ring or without any substituent were obtained by two-step synthesis. Chemical structures of title compounds were confirmed by elemental analysis, ^{1}H NMR, IR and EIMS data.

In IR spectra, all title compounds had N–H and C=O stretching bands in the region of 3341–3103 and 1695–1665 cm^{-1}, respectively, indicating the presence of an anilide structure (Table 3). ^{1}H NMR spectra showed that aliphatic and aromatic protons resonated at expected frequencies and displayed similar splitting patterns for individual compound (Table 4). The chemical shifts of *N*-phenyl protons, in each compound, were relatively different depending on the nature of substituent. The structures of title compounds were further verified by EIMS spectra where the m/z values of molecular ion peaks were in complete agreement with the calculated molecular weight for individual compounds (Table 3). The mass spectra of chloro analogs **10**–**12**, also had the $[M + 2]^+$ ions which were less than 50% of the corresponding molecular ions as expected.

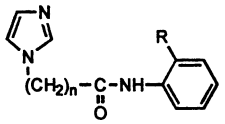
Table 1
Yields, melting points and ^{1}H NMR data of compounds **1a**–**15a**



Comp.	*n*	R	Yield (%)	m.p. (°C)	^{1}H NMR
1a	1	H	74	131–133 [a]	4.21 (s, 2H), 7.20 (td, 1H), 7.38 (td, 2H), 7.58 (dd, 2H), 8.52 (br.s, NH)
2a	2	H	43	113 [a]	2.83 (t, 2H), 3.89 (t, 2H), 7.15 (t, 1H), 7.34 (t, 2H), 7.54 (d, 2H), 7.58 (br.s, NH)
3a	3	H	44	59–61 [a]	2.21 (quin, 2H), 2.57 (t, 2H), 3.67 (t, 2H), 7.13 (t, 1H), 7.33 (t, 2H), 7.51 (br.s, NH), 7.52 (d, 2H)
4a	1	CH_3	59	106 [a]	2.33 (s, 3H), 4.25 (s, 2H), 7.15 (td, 1H), 7.23–7.26 (m, 2H), 7.90 (d, 1H), 8.10 (br.s, NH)
5a	2	CH_3	36	75 [a]	2.28 (s, 3H), 2.85 (t, 2H), 3.90 (t, 2H), 7.12 (t, 1H), 7.20–7.24 (m, 2H), 7.26 (br.s, NH), 7.73 (d, 1H)
6a	3	CH_3	39	73 [a]	2.22 (quin, 2H), 2.28 (s, 3H), 2.60 (t, 2H), 3.69 (t, 2H), 7.10–7.12 (m, 2H), 7.20–7.24 (m, 2H), 7.77 (d, 1H)
7a	1	OCH_3	88	61 [b]	3.93 (s, 3H), 4.21 (s, 2H), 6.93 (d, 1H), 7.00 (t, 1H), 7.12 (td, 1H), 8.36 (d, 1H), 8.96 (br.s, NH)
8a	2	OCH_3	88	78 [b]	2.88 (t, 2H), 3.91 (t, 2H), 3.91 (s, 3H), 6.90 (dd, 1H), 6.99 (td, 1H), 7.08 (td, 1H), 7.90 (br.s, NH), 8.39 (dd, 1H)
9a	3	OCH_3	97	75 [b]	2.23 (quin, 2H), 2.61 (t, 2H), 3.69 (t, 2H), 3.90 (s, 3H), 6.90 (dd, 1H), 6.97 (td, 1H), 7.06 (td, 1H), 7.83 (br.s, NH), 8.37 (d, 1H)
10a	1	Cl	56	70–71 [a]	4.26 (s, 2H), 7.12 (td, 1H), 7.32 (td, 1H), 7.42 (dd, 1H), 8.38 (dd, 1H), 8.96 (br.s, NH)
11a	2	Cl	47	82–83 [a]	2.92 (t, 2H), 3.91 (t, 2H), 7.08 (td, 1H), 7.30 (td, 1H), 7.40 (dd, 1H), 7.77 (br.s, NH), 8.39 (d, 1H)
12a	3	Cl	36	62–64 [a]	2.24 (quin, 2H), 2.66 (t, 2H), 3.70 (t, 2H), 7.07 (td, 1H), 7.30 (td, 1H), 7.39 (dd, 1H), 7.68 (br.s, NH), 8.37 (d, 1H)
13a	1	NO_2	45	83–86 [a]	4.27 (s, 2H), 7.28 (td, 1H), 7.71 (td, 1H), 8.27 (dd, 1H), 8.78 (dd, 1H), 11.37 (br.s, NH)
14a	2	NO_2	46	80–84 [a]	2.97 (t, 2H), 3.91 (t, 2H), 7.23 (td, 1H), 7.68 (td, 1H), 8.24 (dd, 1H), 8.80 (dd, 1H), 10.45 (br.s, NH)
15a	3	NO_2	40	61 [a]	2.25 (quin, 2H), 2.72 (t, 2H), 3.69 (t, 2H), 7.21 (td, 1H), 7.67 (td, 1H), 8.24 (dd, 1H), 8.79 (dd, 1H), 10.41 (br.s, NH)

[a] Ethanol/water.
[b] Ethyl acetate/hexane.

Table 2
Reflux times, yields, melting points and elemental analysis of title compounds



Comp.	*n*	R	Reflux time (h)	Yield (%)	m.p. (°C)	Empirical formula
1	1	H	1 [a]	49	139 [c]	$C_{11}H_{11}N_3O$
2	2	H	2 [b]	60	151–153 [c]	$C_{12}H_{13}N_3O$
3	3	H	1 [b]	68	128–132 [c]	$C_{13}H_{15}N_3O$
4	1	CH_3	2 [a]	31	169–171 [c]	$C_{12}H_{13}N_3O$
5	2	CH_3	5 [b]	44	119 [c]	$C_{13}H_{15}N_3O$
6	3	CH_3	20 [b]	43	68–70 [d]	$C_{14}H_{17}N_3O$
7	1	OCH_3	2 [a]	27	113 [d]	$C_{12}H_{13}N_3O_2$
8	2	OCH_3	2 [b]	29	93–96 [c]	$C_{13}H_{15}N_3O_2$
9	3	OCH_3	8 [b]	23	82–84 [d]	$C_{14}H_{17}N_3O_2$
10	1	Cl	2 [a]	60	159 [c]	$C_{11}H_{10}ClN_3O$
11	2	Cl	4 [b]	45	118 [c]	$C_{12}H_{12}ClN_3O$
12	3	Cl	20 [b]	51	93–94 [d]	$C_{13}H_{14}ClN_3O$
13	1	NO_2	3 [a]	60	166–168 [c]	$C_{11}H_{10}N_4O_3$
14	2	NO_2	3 [b]	60	131–133 [c]	$C_{12}H_{12}N_4O_3$
15	3	NO_2	4 [b]	54	118 [d]	$C_{13}H_{14}N_4O_3$

[a] Benzene.
[b] Toluene.
[c] Methanol/water.
[d] Ethyl acetate/hexane.

Table 3
IR and EIMS data of title compounds

Comp.	IR (cm^{-1})	EIMS *m*/*z* (% intensity)
1	3267–3137, 1670	202 (80, $M^+ + 1$), 201 (57, M^+), 174 (28), 82 (77), 81 (100), 54 (56).
2	3240–3122, 1685	216 (100, $M^+ + 1$), 215 (25, M^+), 96 (23), 95 (17), 81 (32), 68 (11), 54 (24).
3	3290–3110, 1680	230 (100, $M^+ + 1$), 229 (26, M^+), 162 (29), 137 (9), 110 (64), 109 (34), 95 (57), 82 (50), 81 (24), 54 (22).
4	3270–3115, 1665	216 (100, $M^+ + 1$), 215 (48, M^+), 120 (21), 107 (26), 106 (33), 91 (38), 82 (79), 81 (85), 54 (42).
5	3235–3105, 1685	230 (100, $M^+ + 1$), 229 (19, M^+), 123 (21), 107 (72), 106 (51), 96 (12), 95 (39), 81 (39), 69 (46), 68 (21), 54 (25).
6	3230–3104, 1685	244 (50, $M^+ + 1$), 243 (26, M^+), 137 (25), 110 (40), 109 (42), 107 (74), 106 (83), 95 (60), 82 (100), 81 (44), 69 (54), 54(34).
7	3270–3106, 1670	232 (94, $M^+ + 1$), 231 (64, M^+), 82 (100), 81 (81), 54 (31).
8	3220–3112, 1675	246 (52, $M^+ + 1$), 245 (29, M^+), 123 (87), 108 (100), 96 (78), 95 (42), 81 (62), 68 (38), 55 (38), 54 (41).
9	3230–3112, 1680	260 (99, $M^+ + 1$), 259 (32, M^+), 192 (30), 137 (10), 110 (57), 109 (40), 108 (71), 95 (58), 82 (100), 81 (37), 54 (31).
10	3255–3112, 1670	238 (24, $M^+ + 2$), 237 (17, $M^+ + 1$), 236 (70, M^+), 200 (45), 82 (63), 81 (100), 54 (53).
11	3230–3103, 1685	252 (32, $M^+ + 2$), 251 (17, $M^+ + 1$), 250 (96, M^+), 127 (18) 123 (4), 96 (9), 95 (12), 81 (46), 68 (16), 54 (49), 37 (34), 35 (100).
12	3270–3107, 1685	266 (30, $M^+ + 2$), 265 (20, $M^+ + 1$), 264 (91, M^+), 196 (31), 137 (27), 134 (26), 127 (52), 110 (100), 95 (93), 82 (71), 81 (41), 54 (38).
13	3341–3111, 1695	247 (21, $M^+ + 1$), 246 (7, M^+), 82 (45), 81 (100), 54 (74).
14	3140–3115, 1685	261 (5, $M^+ + 1$), 260 (1, M^+), 95 (9), 91 (20), 90 (22), 81 (57), 68 (25), 54 (100).
15	3235–3114, 1690	275 (7, $M^+ + 1$), 274 (2, M^+), 137 (15), 110 (14), 109 (11), 95 (64), 82 (31), 81 (52), 68 (12), 54 (74), 41 (100).

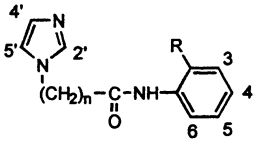
The anticonvulsant activities of the title compounds were determined against maximal electroshock seizures (MES) induced 30 min after administration of the compounds. For this purpose, each compound was, first, tested at 100 mg/kg dose level and the compounds displaying statistically significant activity were further tested at 30 mg/kg dose level. All the compounds at doses studied showed no neurotoxicity according to rotarod test. Preliminary screening results are presented in Table 5.

5. Discussion

The anticonvulsant activity results obtained from the MES test (Table 5) indicate that the acetamides, in general, are considerably more active than the propionamide and butyramide counterparts, and the nature of *o*-substituent on *N*-phenyl ring is an important factor in determining anticonvulsant potency. The most active compound in the series is 2-(1*H*-imidazol-1-yl)-*N*-(*o*-chlorophenyl)acetamide (**10**), followed by 2-(1*H*-imidazol-1-yl)-*N*-(*o*-methoxyphenyl)propionamide (**8**) as the second one.

Concerning acetamide derivatives, among the substituents studied, chloro is the only one that yields compound **10** with a higher anti-MES activity in comparison to unsubstituted acetamide derivative **1** (see Table 5). *o*-Tolyl derivative **4** in acetamide series shows no activity at 100 mg/kg dose, whereas 2-methyl or

Table 4
^{1}H NMR data of title compounds



Comp.	^{1}H NMR
1	4.85 (s, 2H, α-H), 7.09 (s, 1H, H-5′), 7.16 (t, 1H, $J = 7.4$, H-4), 7.23 (s, 1H, H-4′), 7.33 (t, 2H, $J = 7.9$, H-3 and H-5), 7.46 (d, 2H, $J = 7.9$, H-2 and H-6), 7.60 (s, 1H, H-2′), 7.78 (br.s, NH)
2	2.80 (t, 2H, $J = 6.3$, α-H), 4.37 (t, 2H, $J = 6.3$, β-H), 6.99 (s, 1H, H-5′), 7.03 (s, 1H, H-4′), 7.13 (t, 1H, $J = 7.4$, H-4), 7.32 (t, 2H, $J = 7.9$, H-3 and H-4), 7.34 (s, 1H, H-2′), 7.54 (d, 2H, $J = 8$, H-2 and H-6), 8.75 (br.s, NH).
3	2.21 (quin, 2H, $J = 6.6$, β-H), 2.34 (t, 2H, $J = 7$, α-H), 4.07 (t, 2H, $J = 6.3$, γ-H), 6.94 (s,1H, H-5′) 7.03 (s, 1H, H-4′), 7.09 (t, 1H, $J = 7.4$, H-4), 7.30 (t, 2H, $J = 7.9$, H-3 and H-5), 7.41 (s, 1H,H-2′) 7.59 (d, 2H, $J = 7.8$, H-2 and H-6), 9.65 (br.s, NH).
4	2.01 (s, 3H, CH_3), 4.87 (s, 2H, α-H), 6.9 (br.s, NH), 7.11 (s, 1H, H-5′), 7.11–7.27 (m, 2H, H-5 [a] and H-3), 7.23 (t, 1H, $J = 7.6$, H-4 [a]), 7.28 (s, 1H, H-4′), 7.68 (s, 1H, H-2′), 7.86 (d, 1H, $J = 8$, H-6).
5	2.17 (s, 3H, CH_3), 2.84 (t, 2H, $J = 6.3$, α-H), 4.40 (t, 2H, $J = 6.3$, β-H), 7.00 (s, 1H, H-5′), 7.05 (s, 1H, H-4′), 7.13 (t, 1H, $J = 7.4$, H-4 [a]), 7.18–7.23 (m, 2H, H-3 and H-5 [a]), 7.47 (s, 1H, H-2′), 7.60 (br.s, NH), 7.62 (d, 1H, $J = 7.9$, H-6).
6	2.19 (quin, 2H, $J = 6.8$, β-H), 2.24 (s, 3H, CH_3), 2.35 (t, 2H, $J = 6.9$, α-H), 4.06 (t, 2H, $J = 6.6$, γ-H), 6.93 (s, 1H, H-5′), 7.03 (s, 1H, H-4′), 7.11 (t, 1H, $J = 7.4$, H-4 [a]), 7.18–7.21 (m, 2H, H-3 and H-5 [a]), 7.43 (s, 1H, H-2′), 7.62 (d, 1H, $J = 7.8$, H-6), 8.15 (br.s, NH).
7	3.76 (s, 3H, OCH_3), 4.82 (s, 2H, α-H), 6.84 (dd, 1H, $J = 8.2$, 0.9, H-3), 6.96 (td, 1H, $J = 7.8$, 1.1, H-5 [a]), 7.07 (s, 1H, H-5′), 7.08 (td, 1H, $J = 7.8$, 1.5, H-4 [a]), 7.24 (s, 1H, H-4′), 7.62 (s, 1H, H-2′) 7.79 (br.s, NH), 8.29 (dd, 1H, $J = 8.0$, 1.4, H-6).
8	2.84 (t, 2H, $J = 6.5$, α-H), 3.86 (s, 3H, OCH_3), 4.40 (t, 2H, $J = 6.5$, β-H), 6.88 (dd, 1H, $J = 8.1$, 1.1, H-3), 6.97 (td, 1H, $J = 6.9$, 1.2, H-5 [a]), 6.99 (s, 1H, H-5′), 7.04 (s, 1H, H-4′), 7.06 (td, 1H, $J = 7.4$, 1.4, H-4 [a]), 7.54 (s, 1H, H-2′), 7.78 (br.s, NH), 8.32 (dd, 1H, $J = 8.0$, 1.4, H-6).
9	2.20 (quin, 2H, $J = 6.8$, β-H), 2.35 (t, 2H, $J = 7.0$, α-H), 3.78 (s, 3H, OCH_3), 4.08 (t, 2H, $J = 6.8$, γ-H), 6.89 (dd, 1H, $J = 8.1$, 1.1, H-3), 6.96 (s, 1H, H-5′), 6.97 (td, 1H, $J = 8.0$, 1.2, H-5 [a]), 7.06 (td, 1H, $J = 7.9$, 1.4, H-4 [a]), 7.08 (s, 1H, H-4′), 7.50 (s, 1H, H-2′), 7.78 (br.s, NH), 8.33 (dd, 1H, $J = 7.9$, 1.3, H-6).
10	4.88 (s, 2H, α-H), 7.10 (td, 1H, $J = 7.7$,1.4, H-5 [a]), 7.11 (s, 1H, H-5′), 7.28 (s, 1H, H-4′), 7.30 (td, 1H, $J = 7.8$, 1.3, H-4 [a]), 7.35 (dd, 1H, $J = 8.0$, 1.2, H-3), 7.64 (br.s, NH), 7.67 (s, 1H, H-2′), 8.33 (d, 1H, $J = 7.4$, H-6) 2.89 (t, 2H, $J = 6.4$, α-H), 4.40 (t, 2H, $J = 6.4$, β-H), 6.99 (s, 1H, H-5′), 7.05 (s, 1H, H-4′), 7.08 (t, 1H, $J = 7.8$, H-5 [a]), 7.28 (td, 1H, $J = 7.9$, 1.3, H-4 [a]), 7.37 (dd, 1H, $J = 7.5$, 1.0, H-3), 7.52 (s, 1H, H-2′), 7.91 (br.s, NH), 8.24 (d, 1H, $J = 8.1$, H-6).
11	2.89 (t, 2H, $J = 6.4$, α-H), 4.40 (t, 2H, $J = 6.4$, β-H), 6.99 (s, 1H, H-5′), 7.05 (s, 1H, H-4′), 7.08 (t, 1H, $J = 7.8$, H-5 [a]), 7.28 (td, 1H, $J = 7.9$, 1.3, H-4[a]), 7.37 (dd, 1H, $J = 7.5$, 1.0, H-3), 7.52 (s, 1H, H-2′), 7.91 (br.s, NH), 8.24 (d, 1H, $J = 8.1$, H-6).
12	2.22 (quin, 2H, $J = 6.8$, β-H), 2.41 (t, 2H, $J = 6.8$, α-H), 4.09 (t, 2H, $J = 6.8$, γ-H), 6.95 (s, 1H, H-5′), 7.05–7.09 (m, 1H, H-5 [a]), 7.08 (s, 1H, H-4′), 7.28 (td, 1H, $J = 7.9$, 1.4, H-4 [a]), 7.38 (dd, 1H, $J = 8.0$, 1.3, H-3), 7.50 (s, 1H, H-2′), 7.87 (br.s, NH), 8.27 (d, 1H, $J = 8.1$, H-6).
13	4.91 (s, 2H, α-H), 7.09 (t, 1H, $J = 1.2$, H-5′), 7.26 (t, 1H, $J = 1.1$, H-4′), 7.27 (td, 1H, $J = 7.8$, 1.4, H-4), 7.66 (s, 1H, H-2′), 7.69 (td, 1H, $J = 7.9$, 1.5, H-5), 8.22 (dd, 1H, $J = 8.5$, 1.5, H-3), 8.74 (dd, 1H, $J = 8.5$, 1.2, H-6), 10.43 (br.s, NH).
14	2.97 (t, 2H, $J = 6.3$, α-H), 4.43 (t, 2H, $J = 6.3$, β-H), 7.01 (d, 1H, $J = 1.2$, H-5′), 7.07 (s, 1H,H-4′), 7.23 (td, 1H, $J = 7.9$, 1.3, H-4), 7.57 (s, 1H, H-2′), 7.68 (td, 1H, $J = 7.9$, 1.5, H-5), 8.23 (dd, 1H, $J = 8.4$, 1.5, H-3), 8.74 (dd, 1H, $J = 8.5$, 1.0, H-6), 10.36 (br.s, NH).
15	2.24 (quin, 2H, $J = 7.0$, β-H), 2.49 (t, 2H, $J = 7.0$, α-H), 4.11 (t, 2H, $J = 7.0$, γ-H), 6.97 (s, 1H, H-5′), 7.09 (s, 1H, H-4′), 7.21 (td, 1H, $J = 7.9$, 1.1, H-4), 7.52 (s, 1H, H-2′), 7.67 (td, 1H, $J = 7.9$, 1.4, H-5), 8.22 (dd, 1H, $J = 8.5$, 1.2, H-3), 8.72 (d, 1H, $J = 8.5$, H-6), 10.36 (br.s, NH).

[a] Interchangeable.

Table 5
MES-test screening data in mice of title compounds

Comp.	100 mg/kg [a]	30 mg/kg [a]
1	5/8	
2	2/8	
3	2/8	
4	0/8	
5	2/8	
6	3/8	
7	5/8 *	
8	6/8 **	4/8 *
9	5/8 *	
10	7/8 **	6/8 **
11	1/8	
12	3/8	
13	5/8 *	
14	3/8	
15	2/8	

[a] Protected animals to tested animals.
* $P<0.05$.
** $P<0.01$.

2,6-dimethyl substitution on anilide structures were known to yield active anticonvulsant compounds [9,18]. Anti-MES activity of *o*-tolyl derivatives (**6**, **7**) in propionamide and butyramide series is increased gradually, but it is still lower than that of **1**. In propionamide and butyramide series, methoxyl is a unique substituent which leads to compounds **8** and **9** with slightly better or equal activity compared with **1**.

In conclusion, these results revealed that further detailed studies on this group of compounds are needed for determining substitution pattern and the nature of substituent(s) to optimize the anticonvulsant activity. Our effort will continue to do so.

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