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Synthesis and anticonvulsant activity of some ω-(1*H*-imidazol-1-yl)-*N*-phenylacetamide and propionamide derivatives

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Abstract

In this study, eight new ω-(1*H*-imidazol-1-yl)-*N*-phenylacetamide and propionamide derivatives having 2,6-dimethyl, 2,6-dichloro, 2-chloro-6-methyl and 2-isopropyl substitutions on *N*-phenyl ring were synthesized to evaluate anticonvulsant activity against maximal electroshock test. The most active compounds in the series were the derivatives bearing 2-isopropyl and 2,6-dimethyl substituents on *N*-phenyl ring.

Keywords: Anticonvulsant; MES; Imidazole; Anilide; Rotamer

1. Introduction

Epilepsy, one of the most common neurological diseases, is characterized by epileptic seizures, which are evoked by unexpected, high-level neuronal discharges in the brain [1]. Since the anticonvulsant agents currently used in the treatment of epilepsy have certain disadvantages such as notable adverse effects and inefficient therapy in some seizure types, a clear need for safer and more effective antiepileptic drugs is well known [1–3]. Therefore, the development of new antiepileptic drugs with approved therapeutic properties is an important challenge for medicinal chemists.

One of the structures among the compounds studied for anticonvulsant activity is anilide nucleus [4–15]. Ameltolide [16], ralitoline [17] and some phthalimide derivatives [12,18], are the examples of anilide analogs with potent anticonvulsant activity in maximal electroshock (MES) test (Fig. 1). The structure–activity studies on benzanilide derivatives indicated that 2,6-dimethyl or 2-ethyl substitution on *N*-phenyl ring yielded the most active compounds in MES test [6–10]. Lepage et al. [5] reported similar findings on *N*-phenylizoxazolecarboxamide and *N*-isoxazolylbenzamide series as anticonvulsant agents. The authors have confirmed the importance of 2,6-disubstitutions on *N*-phenyl ring by small, lipophilic, non-hydrogen bonding groups for anticonvulsant activity [5]. On the other hand, the structure–activity studies on *N*-phenylphthalimide derivatives, which is originally designed by hybridization of ameltolide and phenytoin, revealed that anti-MES activity is directly influenced by the substitutions of the *N*-phenyl ring, in which small, lipophilic substituents at 2 or 2 and 6 positions furnished compounds with optimal anti-MES activity [13,14].

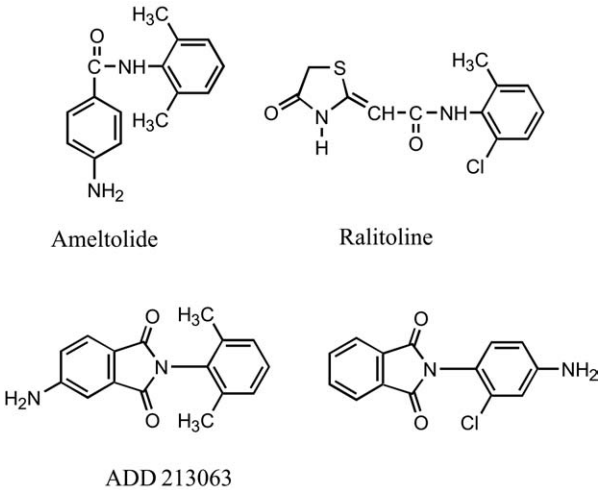

Fig. 1. Potent anticonvulsant compounds bearing anilide function.

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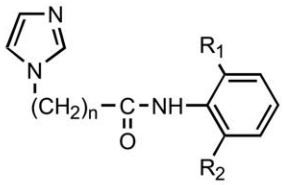


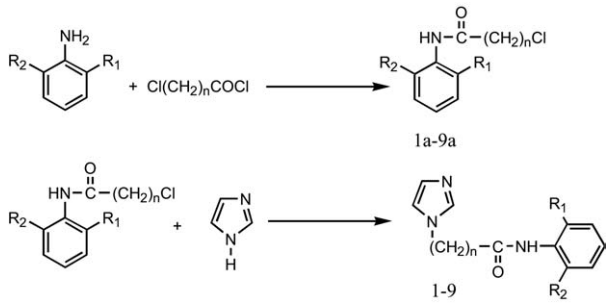
(**1**) n=1, R_1=Cl, R_2= H
(**2**) n=1, R_1= $CH(CH_3)_2$, R_2= H
(**3**) n=2, R_1= $CH(CH_3)_2$, R_2= H
(**4**) n=1, R_1= CH_3, R_2= CH_3
(**5**) n=2, R_1= CH_3, R_2= CH_3
(**6**) n=1, R_1=Cl, R_2= Cl
(**7**) n=2, R_1=Cl, R_2= Cl
(**8**) n=1, R_1=Cl, R_2= CH_3
(**9**) n=2, R_1=Cl, R_2= CH_3

Fig. 2. Chemical structure of title compounds to be synthesized.

In our recent publication, we reported the anti-MES activity of 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 [19]. According to the results obtained in this study, the acetamides, in general, were considerably more active than the propionamide and butyramide counterparts, and concerning acetamide derivatives, among the substituent studied, chloro was the only one that yields compound (compound **1** in Fig. 2) with a higher anti-MES activity in comparison to unsubstituted acetamide derivative of which anticonvulsant activity is originally reported by Özkanlı et al. [20]. These results encouraged us to investigate the possible effect of disubstitution or mono bulky substitution at *ortho* position(s) of *N*-phenyl ring in ω-(1*H*-imidazol-1-yl)-*N*-phenylacetamide and propionamide derivatives in terms of anti-MES activity (Fig. 2).

2. Chemistry

The title compounds evaluated for anti-MES activity were prepared by two-step synthesis. As illustrated in Scheme 1, in the first step, reacting 2-chloroacetyl and 3-chloropropionyl chlorides with appropriately substituted anilines yielded ω-chloroanilides. In the second step, those intermediates were condensed with imidazole to furnish the title compounds. The title compounds except compound **1** are novel.



Scheme 1. Synthesis of the compounds.

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 NMR spectra were recorded on a Bruker DPX-400 FT-NMR. Chemical shifts were reported in parts per million (δ). *J* values were given in Hz. Mass spectra (EI) were measured on a Mikromass VG Platform-II spectrometer. Elemental analyses (C, H and N) were performed by TUBITAK Analytical Laboratory Ankara, Turkey. The analytical results for the elements were within ±0.4% of theoretical values.

3.1.1. Synthesis of ω-chloroanilide derivatives (*1a–9a*)

The intermediates were prepared according to the method reported in the literature [21]. For this purpose, appropriately substituted aniline (0.066 mol) was dissolved in 25 ml glacial acetic acid. 2-Chloroacetyl chloride or 3-chloropropionyl chloride (0.074 mol) was added dropwise to this solution while cooling in ice-bath. The reaction mixture was stirred in ice-bath for 0.5 and 1 h in room temperature. The mixture was poured into saturated sodium acetate solution. The precipitate was filtered, washed with cold water and purified by crystallization (ethanol/water). Yields, melting points and ^{1}H NMR spectral data are presented in Table 1.

3.1.2. Synthesis of ω-(1H-imidazol-1-yl)-N-phenylacetamide and propionamide derivatives (*1–9*)

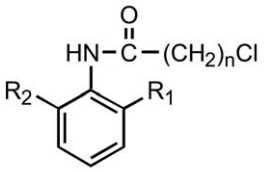
ω-chloroanilides (0.002 mol) and imidazole (0.01 mol) in 20 ml benzene (for compound **3**, 10 ml toluene) were refluxed under nitrogen (reflux times are listed in Table 2.). After the reaction was completed, solvent was removed under vacuo. Residue was dissolved in chloroform and washed with water twice. Organic phase, after drying over anhydrous sodium sulfate, evaporated to dryness. Residue was crystallized from water (yields and melting points are given in Table 2).

3.2. Pharmacology

Osmangazi University, School of Medicine, Animal Use and Care Committee approved all experiments for animal testing. Male albino mice weighing 25–35 g were used. Laboratory temperature was maintained at 20 ± 1 °C under conditions of a 12-h light and dark schedule. Before experimentations, mice were allowed 1 week of adaptation. They were used only once. The experiments were made between 9 and 12 h in the morning.

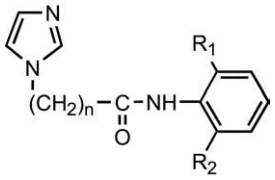
All title compounds were suspended in 0.5% methylcellulose and injected intraperitoneally to the animals at 100 mg/kg doses; 0.1 ml methylcellulose was given intraperitoneally to the control animals. Rotarod test was carried

Table 1
Yields, melting points and ^{1}H NMR data of compounds **2a–9a**



Comp.	n	R_1	R_2	Yield(%)	M.p (°C)	^{1}H NMR ($CDCl_3$)
2a	1	Pr^i	H	91	78	1.30 (*d*, 6H, *J*= 6.8), 3.03-3.08 (*m*, 1H), 4.28 (*s*, 2H), 7.24-7.34 (*m*, 2H), 7.34 (*dd*, 1H, *J*= 7.0, 2.4), 7.80 (*dd*, 1H, *J*= 7.3, 2.0), 8.55 (*brs*, N-H)
3a	2	Pr^i	H	94	66	1.27 (*d*, 6H, *J*= 6.8), 2.87 (*t*, 2H, *J*= 6.3), 3.05-3.12 (*m*, 1H), 3.91 (*t*, 2H, *J*= 6.3), 7.22-7.24 (*m*, 2H), 7.32-7.34 (*m*, 1H), 7.37 (*brs*, N-H), 7.63-7.66 (*m*, 1H)
4a	1	Me	Me	77	145	2.27 (*s*, 6H), 4.29 (*s*, 2H), 7.12-7.18 (*m*, 3H), 7.66 (*brs*, N-H)
5a	2	Me	Me	49	126	2.28 (*s*, 6H), 2.88 (*t*, 2H, *J*=6.2), 3.94 (*t*, 2H, *J*=6.2), 6.87 (*brs*, N-H), 7.09-7.17 (*m*, 3H)
6a	1	Cl	Cl	83	172	4.30 (s, 2H), 7.26 (d, 1H, J= 8.1), 7.42 (d, 2H, J= 8.1), 8.32 (brs, N-H)
7a	2	Cl	Cl	51	142	2.95 (*t*, 2H, *J*=6.4), 3.93 (*t*, 2H, *J*=6.4), 7.12 (*brs*, N-H), 7.22 (*d*, 1H, *J*= 8.1), 7.40 (*d*, 1H, *J*= 8)
8a	1	Cl	Me	60	136	2.31 (*s*, 3H), 4.29 (*s*, 2H), 7.19-7.21 (*m*, 2H), 7.31-7.34 (*m*, 1H), 7.85 (*brs*, N-H)
9a	2	Cl	Me	56	98	2.31 (*s*, 3H), 2.92 (*t*, 2H, *J*=6.4), 3.93 (*t*, 2H, *J*=6.4), 7.07 (*brs*, N-H), 7.16-7.20 (*m*, 2H), 7.29-7.31 (*m*,1H).

Table 2
Reflux times, yields, melting points and formula of title compounds **2–9**



Comp.	n	R_1	R_2	Reflux Time (h)	Yield (%)	m.p. (°C)	Formula
2	1	Pr^i	H	3	78	115	$C_{14}H_{17}N_3O$
3	2	Pr^i	H	2	73	89-90	$C_{15}H_{19}N_3O$
4	1	Me	Me	1	82	160	$C_{13}H_{15}N_3O$
5	2	Me	Me	8	82	110	$C_{14}H_{17}N_3O$
6	1	Cl	Cl	1	66	180	$C_{11}H_9Cl_2N_3O$
7	2	Cl	Cl	4	82	158	$C_{12}H_{11}Cl_2N_3O$
8	1	Cl	Me	2	76	140	$C_{12}H_{12}ClN_3O$
9	2	Cl	Me	9	57	84	$C_{13}H_{14}ClN_3O$

out to determine minimal neurotoxicity before the experiments. MES seizures were induced 0.5 or 4 h after administration, by application of a 60 Hz current of 60 mA and 0.4 pulse width for 0.2 s via ear electrodes by using Ugo Basile electroshock device. The anticonvulsive activity of the compounds was evaluated by defining as the abolition of the hind-leg tonic maximal extension component of the seizure [22]. Fisher's exact χ^2-test was used for statistical analysis.

4. Results and discussion

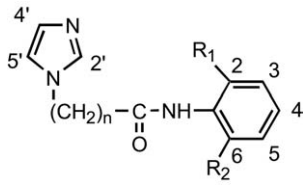
In this study, eight new ω-(1*H*-imidazol-1-yl)-*N*-phenylacetamide and propionamide derivatives having 2,6-dimethyl, 2,6-dichloro, 2-chloro-6-methyl and 2-isopropyl substitutions on *N*-phenyl ring were synthesized to evaluate anticonvulsant activity against MES test. 2–(1*H*-imidazol-1-yl)-*N*-(2-chlorophenyl)acetamide (compound **1**) was also synthesized for comparison. Chemical structures of title compounds were confirmed by elemental analysis, ^{1}H, ^{13}C NMR, IR and EIMS data (Tables 3, 4). The spectral data of compound **1** was consistent with those reported [19].

Intermediates (compounds **1a–9a**) were verified by IR (data not presented) and ^{1}H NMR analysis (Table 1). An intriguing feature in the ^{1}H NMR spectra of propionamide intermediates was the appearance of certain minor signals of which patterns resemble the major ones. Meanwhile, there was an increase in integration of resonances at aromatic

Table 3
IR and EIMS data of title compounds **2–9**

Compound	IR (cm^{-1})	EIMS *m/z* (% intensity)
2	3117, 1680	243 (18, M^+), 175 (18), 162 (47), 148 (15), 146 (12), 117 (12), 82 (69), 81 (100), 77 (17), 54 (34)
3	3168–3112, 1676	257 (24, M^+), 174 (11), 148 (12), 146 (26), 135 (31), 132 (25), 123 (21), 120 (38), 118 (46), 117 (49), 115 (13), 97 (19), 95 (77), 90 (58), 81 (100), 68 (82), 65 (16), 54 (74)
4	3246, 1664	229 (12, M^+), 147 (14), 133 (11), 119 (31), 104 (16), 91 (20), 81 (100), 76 (20), 55 (19), 53 (19)
5	3480, 1658	243 (9, M^+), 228 (21), 120 (100), 105 (26), 95 (41), 90 (24), 81 (49), 68 (55), 65 (10), 54 (44)
6	3442–3104, 1673	269 (2, M^+), 234 (37), 173 (13), 160 (12), 81 (100), 62 (15), 55 (22), 52 (76)
7	3486–3117, 1670	283 (9, M^+), 248 (24), 234 (14),173 (10), 163 (10), 162 (14), 161 (22), 160 (43), 132 (10), 122 (32), 95 (36), 88 (13), 82 (48), 80 (50), 69 (16), 68 (52), 62 (20), 54 (100)
8	3240, 1671	249 (8, M^+), 214 (46), 153 (17), 146 (18), 139 (23), 103 (23), 81 (100), 76 (49), 54 (57), 51 (30).
9	3242, 1662	263 (9, M^+), 228 (46), 159 (13), 142 (12), 141 (32), 140 (58), 124 (16), 122 (24), 105 (19), 103 (28), 95 (67), 89 (10), 81 (92), 77 (62), 68 (100), 54 (93)

Table 4
NMR data of title compounds **2–9**



Comp.	NMR
2	**^{1}H NMR ($CDCl_3$):** 1.03 (*d*, 6H, *J*= 6.8, 2xCH_3), 2.48-2.51 (*m*, 1H, CH), 4.78 (*s*, 2H, CH_2), 6.95 (*brs*, N-H), 7.01 (*s*, 1H, H-5'), 7.11-7.19 (*m*, 4H, H-3, H-4, H-5, H-4'), 7.57 (*s*, 1H, H-2'), 7.68 (*d*, 1H, *J*= 7.1, H-6)
	^{13}C NMR ($CDCl_3$): 23.2, 28.4, 50.9, 120.1, 124.9, 126.1, 126.8, 127.1, 131.2, 133.4, 138.5, 141.1, 165.8
3	**^{1}H NMR (DMSO-d_6):** 1.06 (*d*, 6H, *J*= 6.8, 2xCH_3), 2.81 (*t*, 2H, *J*=6.6, α-H), 2.90-3.01 (*m*, 1H, CH), 4.26 (*t*, 2H, *J*=6.6, β-H), 6.87 (*s*, 1H, H-5'), 7.12-7.18 (*m*, 4H, H-3, H-4, H-5, H-4'), 7.28 (*d*, 1H, *J*=7.5, H-6), 7.59 (*s*, 1H, H-2'), 9.39 (*brs*, N-H)
	^{13}C NMR ($CDCl_3$): 23.7, 28.3, 38.8, 43.4, 119.8, 126.3, 126.5, 126.7, 127.3, 128.7, 129.6, 133.9, 137.5, 142.8, 169.1
4	**^{1}H NMR (DMSO-d_6):** 2.12 (*s*, 6H, 2xCH_3), 4.90 (*s*, 2H, CH_2), 6.90 (*s*, 1H, H-5'), 7.04-7.06 (*m*, 3H, H-3, H-4, H-5), 7.16 (*s*, 1H, H-4'), 7.64 (*s*, 1H, H-2'), 9.57 (*brs*, N-H)
	^{13}C NMR ($CDCl_3$): 18.7, 18.9, 50.4, 120.2, 128.1, 128.7, 129.5, 130.8, 133.1, 135.5, 138.4, 165.8
5	**^{1}H NMR (DMSO-d_6):** 2.00 (*s*, 6H, 2xCH_3), 2.82 (*t*, 2H, *J*=6.6, α-H), 4.27 (*t*, 2H, *J*=6.6, β-H), 6.88 (*s*, 1H, H-5'), 7.01-7.04 (*m*, 3H, H-3, H-4, H-5), 7.16 (*s*, 1H, H-4'), 7.59 (*s*, 1H, H-2'), 9.30 (*brs*, N-H)
	^{1}H NMR ($CDCl_3$): 2.09 (*s*, 6H, 2xCH_3, min.), 2.12 (s, 6H, 2xCH_3), 2.32 (*t*, 2H, *J*=6.3, α-H, min), 2.85 (*t*, 2H, *J*=6.3, α-H), 4.27 (*t*, 2H, *J*=6.3, β-H, min), 4.40 (*t*, 2H, *J*=6.4, β-H), 6.99-7.11 (*m*, 6H, H-3, H-4, H-5, H-4', H-5' and N-H), 7.13-7.15 (*m*, 1H, min.), 7.44 (*s*, 1H, min), 7.52 (*s*, 1H, H-2')
	^{13}C NMR ($CDCl_3$): 18.6, 18.5 (min), 34.3 (min), 37.9, 42.4 (min), 43.4, 119.5 (min), 119.6, 127.8, 128.5, 129 (min), 129.1, 129.6, 129.7 (min), 134.2, 135.7, 137.1 (min), 137.5, 137.7 (min), 168.5, 172.1 (min)
6	**^{1}H NMR ($CDCl_3$):** 4.87 (*s*, 2H, CH_2), 7.12 (*s*, 1H, H-5'*), 7.14 (*s*, 1H, H-4'*), 7.21 (*t*, 1H, *J*=8.1, H-4), 7.38 (*d*, 2H, *J*=8.1, H-3, H-4), 7.55 (*s*, 1H, H-2'), 8.36 (*brs*, N-H)
	^{13}C NMR ($CDCl_3$): 50.6, 120.2, 128.9, 129.6, 131.2, 131.5, 134.3, 138.5, 165.6
7	**^{1}H NMR ($CDCl_3$+DMSO-d_6):** 2.85 (*t*, 2H, *J*=6.3, α-H), 4.31 (*t*, 2H, *J*=6.4, β-H), 6.95 (*s*, 2H, H-4', H-5'), 7.10 (*t*, 1H, *J*=8.0, H-4), 7.28 (*d*, 2H, *J*=8.1, H-3, H-5), 7.47 (*s*, 1H, H-2'), 8.95 (*brs*, N-H)
	^{1}H NMR (DMSO-d_6): 2.86 (*t*, 2H, *J*=6.7, α-H), 4.28 (*t*, 2H, *J*=6.7, β-H), 6.88 (*s*, 1H, H-5'), 7.18 (*s*, 1H, H-4'), 7.35 (t, 1H, *J*=7.8, H-4), 7.52 (*d*, 2H, *J*=8.1, H-3, H-5), 7.62 (*s*, 1H, H-2'), 9.96 (*brs*, N-H)
	^{13}C NMR ($CDCl_3$+DMSO-d_6): 32.4, 38.1, 114.6, 123.7, 124.0, 124.4, 128.2, 129.5, 132.6, 164.1
8	**^{1}H NMR ($CDCl_3$):** 2.20 (*s*, 3H, CH_3), 4.84 (*s*, 2H, CH_2), 7.09-7.24 (*m*, 6H, H-3, H-4, H-5, H-4', H-5', N-H), 7.61 (*s*, 1H, H-2')
	^{13}C NMR ($CDCl_3$): 19.0, 50.1, 120.5, 122.1, 127.6, 128.8, 129.5, 130.0, 132.2, 132.3, 138.4 166.2
9	**^{1}H NMR (DMSO-d_6):** 2.00 (*s*, 3H, CH_3), 2.85 (*t*, 2H, *J*=6.6, α-H), 4.28 (*t*, 2H, *J*=6.6, β-H), 6.88 (*s*,1H, H-5'), 7.18-7.22 (*m*, 3H, H-4, H-5, H-4'), 7.33 (*dd*, 1H, *J*= 2.9, 6.6, H-3'), 7.62 (*s*, 1H, H-2'), 9.64 (*brs*, N-H)
	^{13}C NMR ($CDCl_3$): 19.0, 37.6, 43.4, 119.9, 122.1, 124.0, 127.6, 128.5, 129.4, 133.2, 135.4, 138.6, 169.3.

* Interchangeable.

region, which correspond to the minor signal/major signal ratio. The highest minor/major ratio was observed in compound **5a** (1/4) followed by compounds **3a** (1/7), **7a** (1/11) and **9a** (1/11), respectively. Those minor signals (not reported) would be due to the two different rotamer formation (i.e. E/Z rotamers in seconder amides) in $CDCl_3$. In order to clarify the situation, high temperature ^{1}H NMR spectra were recorded for compounds **3a, 5a** and **7a**, since recording low or high temperature spectra in ^{1}H NMR experiments are important in confirmation of intramoleculer motions [23,24]. For compounds **3a** and **7a**, the major and minor signals combined at coalescence temperature (343 and 335 K, respectively) and the signals and integrations matched the expected ones, confirming the rotamer formation. However, in compound **5a**, some major and minor signals, although becoming broader, still remained uncombined at the highest temperature permitted by $CDCl_3$ (343 K). This result indicated that the intramoleculer rotation barrier in compound **5a** was higher than those for compounds **3a** and **7a**.

Concerning the title compounds, they had N–H and C=O stretching bands in the region of 3486–3112 and 1658–1680 cm^{-1}, respectively, indicating the presence of an anilide structure (Table 3). In acetamide series, ^{1}H NMR spectra confirmed the presence of expected proton signals with relevant splitting patterns and integrations. However, in propionamide series, ^{1}H NMR spectra recorded in $CDCl_3$ (except compound **7** of which the spectrum recorded in $CDCl_3$–DMSO-d_6 mixture), displayed additional unexpected minor signals due to two different rotamers, as is the case in propionamide intermediates. The highest minor/major ratio observed for compound **5** (1/3) followed by compounds **3** (1/5) and **9** (1/8), respectively. Major and detectable minor rotamer signals in $CDCl_3$ for compound **5** were summarized at Table 4 as an example. High temperature ^{1}H NMR experiments were run for compound **5** which display the highest rotamer ratio. By gradually heating up to point permitted by $CDCl_3$, converging methyl signals were combined at 335 K. In this coalescence temperature for methyl signals, triplets of methylene protons became broader and they were not combined even at 343 K as seen in corresponding intermediate **5a**. In NMR experiments, solvent polarity dependent behavior of rotamer mixtures is quite well known [23–25]. So, we

decided to record the ^{1}H NMR spectra of aforementioned title compounds (compounds **3, 5, 7** and **9**) in DMSO-d_6. The minor signals observed in spectra in $CDCl_3$ disappeared when DMSO-d_6 was used (Table 4). This result also accounted for the absence of minor signals in compound **7**. This solvent dependent behavior obviously indicated that title compounds with propionamide derivative, existed as two different rotamer in $CDCl_3$. The rotamer formation could be related with restricted rotation of amide N–CO bond, which is known to produce E/Z rotamer [23–25]. Disubstitution at 2,6 position or mono but bulky substitution at 2 position of *N*-phenyl ring in propionamide derivatives trigger the rotamer formation by additional steric stress, since *ortho* monosubstitution of *N*-phenyl ring in propionamide series did not produce any rotameric mixture in $CDCl_3$ in early study related with our recent publication [19]. DMSO-d_6, as a hydrogen acceptor polar solvent, could favor the single rotamer by stabilizing it with hydrogen bond formation [25].

Decoupled ^{13}C NMR spectra of title compounds did not accounted for the total number of carbon atoms in individual ones as expected, since the certain resonance signals represent more than one carbon atom. Compound **5** conferred additional weak signals in ^{13}C spectrum due to the high rotamer ratio (Table 4).

The structures of the 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. The compounds having chloro substituent (compounds **6–9**) have relatively small molecular ions whereas the $[M\text{-}Cl]^+$ ions derived by loss of chlorine were more intense (Table 3).

The anticonvulsant activity of the title compounds was evaluated against MES seizures induced by 0.5 and 4 h after administration at a single dose level (100 mg/kg). None of the compounds showed neurotoxicity according to the rotarod test at dose studied. Preliminary screening results are presented in Table 5.

The results indicated that the acetamides, in generally, were more active than the propionamide counterparts. The compounds displaying statistically significant activity were **2, 3** and **4**. In acetamide series, in terms of *ortho* substitution of *N*-phenyl ring, 2-isopropyl and 2-chloro substitutions yielded the most active compounds at 0.5 h and the rest of the substituents studied, namely 2,6-dimethyl, 2,6-dichloro and 2-chloro-6-methyl, produced compounds with equal activity (see Table 5). This activity trend changed at 4 h and 2-isopropyl and 2,6-dimethyl substitution afforded the most active derivatives in the series. Surprisingly, the anti-MES activity of compound **1** was decreased considerably at 4 h, indicating possible pharmacokinetic intervention. In propionamide series, 2-isopropyl derivative was the most active one at 0.5 and 4 h after administration. Considered the results at 4 h, the most active compounds in both series were compounds **2** and **4** followed by compound **3** (Table 5). 2-Methyl substitution on *N*-phenyl in acetamide series was reported to yield inactive compound at 100 mg/kg dose level [19]. On the contrary, 2,6-dimethyl substitution yielded very active acetamide derivative at same dose level in this study. These results revealed that 2,6-dimethyl or 2-isopropyl substitution on *N*-phenyl ring in the acetamide derivatives studied optimize the anti-MES activity at 4 h after administration and isopropyl group seems to give superior result than dimethyl substitution in both series. This finding is consistent with the earlier reports on benzanilide derivatives which indicate the importance of 2-ethyl and 2,6-dimethyl substitution in terms of anti-MES activity [6–10]. It can be speculated that the increase in activity depending on 2-isopropyl and 2,6-dimethyl, but not 2-methyl, substitutions would be due to conformational preferences determined by the substituent(s) of *N*-phenyl ring, as reported by Bailleux et al. [14]. Those conformational preferences would keep the molecule in a state that may support the desired interactions (e.g. receptor site) or provide the beneficial interventions (e.g. delayed enzymatic inactivation), which may account for the decrease in activity of compound **1** at 4 h after administration.

Table 5
Anticonvulsant and neurotoxicity screening data of title compounds at 100 mg/kg dose in mice

Compound	MES [a]		Toxicity [b]	
	0.5 h [c]	4 h [c]	0.5 h	4 h
1	4/4	5/8	0/4	0/8
2	4/4	8/8 **	0/4	0/8
3	4/4	7/8 *	0/4	0/8
4	3/4	8/8 **	0/4	0/8
5	2/4	2/4	0/4	0/4
6	3/4	3/4	0/4	0/4
7	2/4	1/4	0/4	0/4
8	3/4	2/4	0/4	0/4
9	3/4	2/4	0/4	0/4

** $P < 0.01$, * $P < 0.05$.
[a] Protected animals to tested animals.
[b] Animals exhibited neurotoxicity to tested animals.
[c] Control group: 6/8.

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