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The Synthesis and Anticonvulsant Activity of some ω-Phthalimido-*N*-phenylacetamide and Propionamide Derivatives

In this study, by combining anilide and *N′,N′*-phthaloylglycinamide pharmacophores which are known to produce potent anticonvulsant compounds, sixteen ω-phthalimido-*N*-phenylacetamide and propionamide derivatives bearing substituents at positions 2 or 2,6 on *N*-phenyl ring have been synthesized. The structural confirmation of the title compounds was achieved by interpretation of spectral and analytical data. The anticonvulsant activity of the title compounds was determined against maximal electroshock seizure at 100 mg/kg dose level in mice. The preliminary screening results indicated that ω-phthalimido-*N*-phenylacetamide and propionamide nuclei have pronounced anticonvulsant activity against maximal electroshock seizure.

Keywords: Anticonvulsant; MES; Anilide; 2-Phthalimidoacetamide; 3-Phthalimidopropionamide

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Introduction

Electrophysiologically epileptic seizures are evoked by excessive neuronal discharge in the brain. Imbalance between inhibitory and excitatory processes followed by over-excitation in the brain leads to epileptic seizures [1]. Therefore, inhibition of excitation or enhancement of inhibition in the brain is the ultimate goal for anticonvulsive drug therapy. Thus, excitatory or inhibitory neurotransmission is the prevalent target for designing new anticonvulsants [2–4] GABAergic and glutamatergic systems and their receptor sites are the examples of such targets [1–3, 5]. It is also known that glycine is one of the most important inhibitory neurotransmitters in the brain. Meanwhile, it plays an important role as a "coagonist of glutamate" at glycine modulatory sites of NMDA receptors [1, 5]. Therefore, glycine is of importance as one of the starting points for the development of new anticonvulsants. Some of the glycine derivatives such as milacemide (*N*-pentylglycinamide), valrocemide (valproylglycinamide), and *N′,N′*-phthaloylglycinamide, are known to have potent anticonvulsant activity [6–8]. Salach et al. reported that *N′,N′*-phthaloylglycinamide and its *N*-alkyl analogs designed as probable prodrug of glycinamide have anticonvulsant activity on their own [8]. In a recent study conducted by Usifoh et al. the synthesis and anticonvulsant activity of *N*-alkyl amides of *N′,N′*-phthaloylglycine, *N′,N′*-phthaloyl-β-alanine and *N′,N′*-phthaloylGABA have been published [9]. They reported that phthaloylglycine *N*-monoalkylamides are more active than the corresponding derivatives containing GABA in maximal electroshock seizure (MES), and *N′,N′*-phthaloyl-β-alanine amides are essentially inactive. According to the authors "*N′,N′*-phthaloylglycine amides might represent a new class of antiepileptic drugs" [9].

Anilide is the other pharmacophore moiety known to produce potent anticonvulsant drugs such as ameltolide [4-amino-*N*-(2,6-dimethylphenyl)benzamide] [10], ralitoline [(*Z*)-*N*-(2-chloro-6-methylphenyl)-(3-methyl-4-oxothiazolidine-2-ylidene)acetamide] [11] and certain *N*-phenylphthalimides [12, 13]. Anti-MES activity of anilides is directly influenced by the nature and pattern of substitution on the *N*-phenyl ring. Optimum activity was found with small and lipophilic substituents at positions 2 or 2 and 6 of the *N*-phenyl ring [14-16]. These results encouraged us to combine anilide and phthaloylglycinamide pharmacophores to explore possible anti-MES-active 2-phthalimido-*N*-phenylacetamide derivatives as glycinamide analogs. Our literature survey revealed that certain 2-phthalimido-*N*-phenylacetamide derivatives with different substituents at position 2 and/or 3 and/or 4 of the *N*-phenyl ring have been evaluated once against pentylenetetrazole-induced convulsions [17]. To our knowledge this is the only report available about anticonvulsant activity of phthaloylglycinanilide in the literature.

In this study, we designed a group of 2-phthalimido-*N*-phenylacetamide and 3-phthalimido-*N*-phenylpropion-

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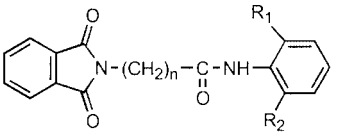
Full Paper



(1) n = 1, R_1 = R_2 = H
(2) n = 2, R_1 = R_2 = H
(3) n = 1, R_1 = Cl, R_2 = H
(4) n = 2, R_1 = Cl, R_2 = H
(5) n = 1, R_1 = CH_3, R_2 = H
(6) n = 2, R_1 = CH_3, R_2 = H
(7) n = 1, R_1 = OCH_3, R_2 = H
(8) n = 2, R_1 = OCH_3, R_2 = H
(9) n = 1, R_1 = $CH(CH_3)_2$, R_2 = H
(10) n = 2, R_1 = $CH(CH_3)_2$, R_2 = H
(11) n = 1, R_1 = Cl, R_2 = Cl
(12) n = 2, R_1 = Cl, R_2 = Cl
(13) n = 1, R_1 = CH_3, R_2 = CH_3
(14) n = 2, R_1 = CH_3, R_2 = CH_3
(15) n = 1, R_1 = Cl, R_2 = CH_3
(16) n = 2, R_1 = Cl, R_2 = CH_3

Figure 1. The title compounds designed.

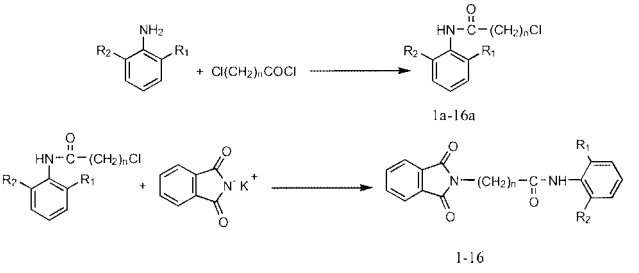
amide derivatives with substituents at positions 2 or 2 and 6 of the *N*-phenyl ring (Figure 1). Our aim was to investigate the anti-MES activity of ω-phthalimido-*N*-phenylacetamide and propionamide pharmacophore and the possible effects of the substitutions at positions 2 or 2 and 6 of the *N*-phenyl ring.

Results and discussion

Chemistry

In this study, sixteen ω-phthalimido-*N*-phenylacetamide and propionamide derivatives have been synthesized to evaluate anti-MES activity. The synthesis of the title compounds has been realized in two steps (Scheme 1). In the first step, ω-chloroanilides were prepared by reacting ω-chloroacyl chloride (2-chloroacetyl and 3-chloropropionyl chloride) with appropriately substituted anilines. In the second step, these intermediates were refluxed with phthalimide potassium salt in DMF according to the method reported by Schapira et al. [18]. The reflux times, yields and melting points are reported in Table 1. The structures of the title compounds were confirmed by spectral (IR, ^{1}H and ^{13}C NMR and EIMS) and elemental analysis (see Table 1, 2, and 3). The seven derivatives of the title compounds, namely **1** [17–19], **2** [20], **3** [17], **5** [17, 21], **7** [17], **13** [22] and **14** [23], were reported previously. However, except for compound 1 their detailed spectral data have not been described in the literature.

With regard to IR data, diagnostic vibrational bands were provided by anilide and phthalimide moieties. N-H and C=O stretching bands of anilide chromofore



Scheme 1. Synthesis of the compounds.

Table 1. Reflux time, yield, melting point and formula of title compounds.

Comp. No	Reflux Time (h)	Yield (%)	M.p. (°C)	Formula
1	4	73	224[a]	$C_{16}H_{12}N_2O_3$
2	5	69	188[b]	$C_{17}H_{14}N_2O_3$
3	3	76	234[c]	$C_{16}H_{11}ClN_2O_3$
4	5	73	194	$C_{17}H_{13}ClN_2O_3$
5	4	68	248[d]	$C_{17}H_{14}N_2O_3$
6	5	78	200	$C_{18}H_{16}N_2O_3$
7	4	87	202[e]	$C_{17}H_{14}N_2O_4$
8	5	57	166	$C_{18}H_{16}N_2O_4$
9	4	70	226	$C_{19}H_{18}N_2O_3$
10	5	55	167	$C_{20}H_{20}N_2O_3$
11	4	53	307	$C_{16}H_{10}Cl_2N_2O_3$
12	5	64	238	$C_{17}H_{12}Cl_2N_2O_3$
13	5	77	285–286[f]	$C_{18}H_{16}N_2O_3$
14	5	71	254[g]	$C_{19}H_{18}N_2O_3$
15	4	52	295	$C_{17}H_{13}ClN_2O_3$
16	5	41	227	$C_{18}H_{15}ClN_2O_3$

[a] 220–227 °C Ref [19], 232 °C Ref [17], 231 °C Ref [18].
[b] 193–194 °C Ref [20].
[c] 245 °C Ref [17].
[d] 242 °C Ref [17], 265-266 °C Ref [21].
[e] 240 °C Ref [17].
[f] 288–291 °C Ref [22].
[g] 253–254.5 °C Ref [23].

were observed between 3321–3242 cm^{-1} and 1650–1675 cm^{-1}, respectively. Two additional bands appeared at around 1770 and 1720 cm^{-1} in spectra indicating the presence of phthalimide carbonyl groups.

^{1}H NMR spectra of the title compounds were consistent with expected resonance signals in terms of

Table 2. IR and EIMS data of title compounds.

Comp. No	IR (cm^{-1})	EIMS m/z (% intensity)
1	3279, 1773, 1727, 1667	280 (M^+, 19), 160 (100), 132 (21), 104 (34), 93 (9), 92 (50), 76 (67)
2	3301, 1771,1725, 1655	294 (M^+, 8), 202 (18), 160 (11), 93 (100), 76 (29)
3	3255, 1770, 1728, 1667	316 ($[M+2]^+$, 2), 314 (M^+, 10), 279 (51), 160 (90), 159 (95), 132 (30), 126 (63), 104 (78), 99 (45), 90 (36), 83 (19), 77 (100)
4	3288, 1773, 1717, 1657	328 (M^+, 3), 293 (20), 202 (31), 160 (100), 126 (69), 104 (32), 99 (14), 76 (43)
5	3275, 1771, 1728, 1661	294 (M^+, 11), 160 (100), 133 (44), 106 (90), 104 (39), 91 (15), 78 (33) 76 (46)
6	3291, 1773, 1727, 1650	308 (M^+, 19), 202 (19), 160 (100), 107 (52), 106 (87), 104 (23), 76 (30)
7	3296, 1775, 1725, 1672	310 (M^+, 84), 161 (66), 160 (89), 132 (20), 123 (100), 108 (32), 104 (45), 85 (29), 83 (46), 76 (41)
8	3321, 1773, 1716, 1656	324 (M^+, 40), 202 (14), 160 (100), 123 (59), 122 (94), 108 (87), 106 (87), 104 (28), 92 (26), 80 (28), 75 (48)
9	3256, 1773, 1723, 1657	322 (M^+, 2), 162 (100), 160 (3), 132 (18), 117 (15), 104 (26), 82 (18), 76 (30)
10	3261, 1772, 1718, 1657	336 (M^+, 10), 202 (18), 162 (19), 160 (100), 134 (78), 120 (53), 104 (16), 91 (11), 85 (13), 82 (27), 76 (50)
11	3242, 1777, 1724, 1675	315 (2), 314 (4), 312 (7), 160 (100), 134 (6), 133 (21), 132 (19), 104 (41), 77 (37)
12	3246, 1770, 1705, 1665	329 (4), 327 (8), 202 (34), 163 (16), 160 (100), 132 (5), 130 (7), 76 (20)
13	3254, 1777, 1720, 1663	308(M^+, 8), 160 (100), 148 (81), 132 (22), 120 (52), 104 (43), 91 (19), 76 (52)
14	3271, 1772, 1721, 1653	322 (M^+, 20), 202 (31), 160 (100), 121 (88), 104 (16), 91 (11), 77 (16), 76 (23)
15	3251, 1774, 1726, 1672	330 ($[M+2]^+$, 2), 328 (M^+, 6), 160 (100), 141 (9), 140 (14), 132 (10), 104 (35), 82 (13), 77 (19), 76 (33)
16	3260, 1771, 1721, 1664	307 (60), 202 (23), 160 (100), 140 (46), 104 (21), 76 (43)

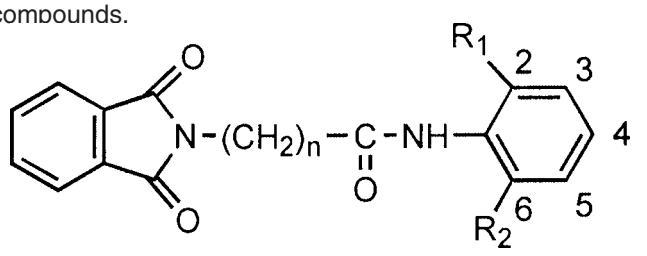
chemical shifts and integrations. The chemical shifts and splitting patterns of *N*-phenyl protons in each compound differed depending on the nature of the substituents and substitution patterns. In decoupled ^{13}C NMR spectra, the resonance signals did not account for the total number of carbon atoms in individual compounds, since as expected certain signals represent more than one carbon atom (Table 2).

The molecular ion peaks of the title compounds, except for compounds **11**, **12** and **16**, are in complete agreement with the calculated molecular weights. The aforementioned compounds **11**, **12** and **16** bearing chloro as a common substituent did not produce any molecular ion, but furnished $[M\text{-}Cl]^+$ ions derived by loss of one chlorine atom from the molecule. The main fragmentation seems to occur at the α-position of amide carbonyl (α-cleavage) to furnish ions derived from either the phthalimide or the anilide portion of the molecule. The m/z 160 ion $[C_9H_6NO_2]^+$ derived from the phthalimide portion through α-cleavage of amide results in the base peak of the title compounds, except for compounds **2**, **3**, **7** and **9** the base peaks of which were obviously derived from the aniline portion of the molecule.

Anticonvulsant activity

The anticonvulsant activity of the title compounds was evaluated against maximal electroshock seizures induced 0.5 or 4 h after administration of single dose levels (100 mg/kg) in mice. The Rotarod test was used to demonstrate the possible neurotoxicity. The anticonvulsant and neurotoxicity screening data are presented in Table 4. According to the rotarod test none

Table 3. NMR Data of title compounds.



Comp.	NMR
1	**^{1}H NMR:** 4.43 (*s*, 2H, CH_2), 6.98 (*td*, 1H, *J* = 7.4, 1.0, H-4), 7.19 (*td*, 2H, *J* = 7.6, 1.8, H-3 and H-5), 7.49 (*dd*, 2H, *J* = 7.6, 1.0, H-2 and H-6), 7.70−7.72 (*m*, 2H, Pht-H), 7.79−7.81 (*m*, 2H, Pht-H), 9.93 (*brs*, 1H, NH). **^{13}C NMR:** 41.6, 120.1, 124.1, 124.5, 129.7, 132.5, 135.5, 139.4, 165.6, 168.4.
2	**^{1}H NMR:** 2.97 (*t*, 2H, *J* = 7.3, α-CH_2), 4.23 (*t*, 2H, *J* = 7.3, β-CH_2),7.23 (*t*, 1H, *J* = 7.4, H-4), 7.46 (*t*, 2H, *J* = 7.9, H-3 and H-5), 7.76 (*d*, 2H, *J* = 7.8, H-2 and H-6), 7.97−8.00 (*m*, 2H, Pht-H), 8.03−8.06 (*m*, 2H, Pht-H), 9.93 (*brs*, 1H, NH). **^{13}C NMR:** 29.5, 30.4, 114.8, 118.2, 118.4, 123.6, 127.1, 129.3, 134.2, 162.8, 163.7.
3	**^{1}H NMR:** 4.59 (*s*, 2H, CH_2), 7.15 (*td*, 1H, *J* = 7.7, 1.4, H-4*), 7.27 (*td*, 1H, *J* = 7.3, 1.3, H-5*), 7.43 (*dd*, 1H, *J* = 8.0, 1.3, H-3), 7.80−7.86 (*m*, 3H, Pht-H and H-6), 7.88−7.91 (*m*, 2H Pht-H), 9.75 (*brs*, 1H, NH). **^{13}C NMR:** 41.4, 124.1, 127.0, 127.5, 128.4, 130.4, 132.6,135.2, 135.5, 166.3, 168.3.
4	**^{1}H NMR:** 2.80 (*t*, 2H, *J* = 7.0, α-CH_2), 3.97 (*t*, 2H, *J* = 7.0, β-CH_2), 7.10 (*td*, 1H, *J* = 7.7, 1.5, H-4*), 7.23 (*td*, 1H, *J* = 7.7, 1.4, H-5*), 7.35 (*dd*, 1H, *J* = 8.0, 1.4, H-3), 7.72 (*dd*, 1H, *J* = 7.9, 1.4, H-6), 7.76−7.79 (*m*, 2H,Pht-H), 7.80−7.84 (*m*, 2H,Pht-H), 9.39 (*brs*, N-H). **^{13}C NMR:** 35.2, 35.4, 123.9, 127.3, 127.6, 127.8, 128.1, 130.2, 132.6, 135.2, 135.6, 168.5, 169.9
5	**^{1}H NMR:** 2.21 (*s*, 3H, CH_3), 4.46 (*s*, 2H, CH_2), 7.03−7.09 (*m*, 2H, H-4 and H-5), 7.14 (*dd*, 1H, *J* = 7.3, 0.9, H-3), 7.34 (*dd*, 1H, *J* = 7.4, 1.0, H-6), 7.77−7.80 (*m*, 2H, Pht-H), 7.82−7.86 (*m*, 2H, Pht-H), 9.54 (*brs*, N-H). **^{13}C NMR:** 18.6, 41.4, 124.1, 125.9, 126.4, 126.9, 131.2, 132.6, 132.9, 135.5, 136.6, 165.9, 168.2.
6	**^{1}H NMR:** 2.13 (*s*, 3H, CH_3), 2.71 (*t*, 2H, *J* = 7.0, α-H), 3.94 (*t*, 2H, *J* = 7.1, β-H), 7.00 (*t*, 1H, *J* = 7.2, H-4), 7.08−7.10 (*m*, 2H, H-3 and H-5), 7.31 (*d*, 1H, *J* = 7.7, H-6), 7.75−7.77 (*m*, 2H, Pht-H), 7.80−7.82 (*m*, 2H, Pht-H), 9.26(*brs*, N-H). **^{13}C NMR:** 18.5, 35.4, 123.9, 126.0, 126.2, 126.7, 131.0, 132.6, 132.7, 135.2, 137.0, 168.5, 169.9
7	**^{1}H NMR:** 3.86 (*s*, 3H, OCH_3), 4.53 (*s*, 2H, CH_2), 6.82 (*t*, 1H, *J* = 7.7, H-5*), 6.94 (*dd*, 1H, *J* = 7.2, 1.0, H-3), 7.01 (*t*, 1H, *J* = 7.7, H-4*), 7.77−7.79 (*m*, 2H, Pht-H), 7.83−7.85 (*m*, 2H, Pht-H), 7.93 (*d*, 1H, *J* = 7.8, H-6), 9.40 (*brs*, N-H). **^{13}C NMR:** 41.6, 56.6, 112.2, 121.1, 122.7, 124.1, 125.6, 127.7, 132.5, 135.5, 150.5, 165.8, 168.4
8	**^{1}H NMR:** 2.89 (*t*, 2H, *J* = 7.4, α-H), 3.88 (*s*, 3H, OCH_3), 4.16 (*t*, 2H, *J* = 7.4, β-H), 6.89 (*dd*, 1H, *J* = 8.1, 1.3, H-3), 6.98 (*td*, 1H, *J* = 7.8, 1.3, H-5*), 7.07 (*td*, 1H, *J* = 7.8, 1.4, H-4*), 7.74-7.78 (m, 2H, Pht-H), 7.87−7.91 (*m*, 2H, Pht-H), 7.81 (*brs*, N-H), 8.37 (*d*, 1H, *J* = 7.6, H-6). **^{13}C NMR:** 35.2, 35.6, 56.4, 112.1, 121.0, 123.5, 123.9, 125.4, 127.9, 132.6, 135.2, 150.8, 168.5, 169.7
9	**^{1}H NMR:** 1.16 (*d*, 6H, *J* = 6.8, CH_3), 3.18−3.21 (*m*, 1H, CH), 4.46 (*s*, 2H, CH_2), 7.09 (*t*, 1H, *J* = 7.4, H-4*), 7.15 (*t*, 1H, *J* = 7.2, H-5*), 7.23 (*d*, 1H, *J* = 7.4, H-3**), 7.25 (*d*, 1H, *J* = 7.7, H-6**), 7.77−7.79 (*m*, 2H, Pht-H), 7.84-7.86 (*m*, 2H, Pht-H), 9.56 (*brs*, NH). **^{13}C NMR:** 18.6, 22.8, 73.7, 118.5, 121.1, 121.9, 122.0, 127.5, 129.4, 138.7, 161.0, 163.0.
10	**^{1}H NMR:** 1.04 (*d*, 6H, *J* = 6.8, CH_3), 2.71 (*t*, 2H, *J* = 6.9, α-H), 3.01−3.05 (*m*, 1H, CH), 3.93 (*t*, 2H, *J* = 6.9, β-H), 7.05−7.13 (*m*, 2H, H-4 and H-5), 7.17−7.22 (*m*, 2H, H-3 and H-6), 7.76−7.79 (*m*, 2H, Pht-H), 7.80−7.83 (*m*, 2H, Pht-H), 9.30 (*brs*, NH). **^{13}C NMR:** 24.0, 27.9, 35.2, 35.4, 123.9, 126.3, 126.5, 127.1, 127.9, 132.6, 135.2, 135.5, 144.2, 168.5, 169.9.

Table 3. (continued).

Comp.	NMR
11	**^{1}H NMR:** 4.30 (*s*, 2H, CH_2), 6.99 (*t*, 1H, *J* = 7.8, H-4), 7.15 (*d*, 2H, *J* = 8.1, H-3 and H-5), 7.54−7.57 (*m*, 2H, Pht-H), 7.61−7.64 (*m*, 2H, Pht-H), 9.82 (*brs*, NH). **^{13}C NMR:** 31.5, 124.1, 129.4, 130.3, 132.6, 133.2, 134.5, 135.5, 166.1, 168.2
12	**^{1}H NMR:** 2.79 (*t*, 2H, *J* = 7.4, α-H), 3.95 (*t*, 2H, *J* = 7.3, β-H), 7.11 (*t*, 1H, *J* = 8.1, H-4), 7.27 (*d*, 2H, *J* = 8.1, H-3 and H-5), 7.67−7.70 (*m*, 2H, Pht-H), 7.74−7.77 (*m*, 2H, Pht-H), 9.58 (*brs*, NH). **^{13}C NMR:** 34.1, 35.0, 123.8, 129.3, 130.0, 132.7, 133.7, 134.5, 135.2, 168.5, 169.3.
13	**^{1}H NMR:** 1.96 (*s*, 6H, CH_3), 4.24 (*s*, 2H, CH_2), 6.75-6.82 (*m*, 3H, H-3, H-4 and H-5), 7.55−7.57 (*m*, 2H, Pht-H), 7.62−7.64 (*m*, 2H, Pht-H), 9.23 (*brs*, NH). **^{13}C NMR:** 13.3, 35.7, 118.3, 121.9, 122.8, 127.3, 129.3, 129.6, 130.6, 160.1, 162.7
14	**^{1}H NMR:** 1.90 (*s*, 6H, CH_3), 2.59 (*t*, 2H, *J* = 7.3, α-H), 3.79 (*t*, 2H, *J* = 7.3, β-H), 6.76−6.83 (*m*, 3H, H-3, H-4 and H-5), 7.55−7.57 (*m*, 2H, Pht-H), 7.61−7.68 (*m*, 2H, Pht-H), 8.94 (*brs*, NH). **^{13}C NMR:** 13.4, 29.2, 29.8, 118.2, 121.7, 122.9, 127.2, 129.3, 130.1, 130.2, 130.5, 162.9, 163.5
15	**^{1}H NMR:** 2.17 (*s*, 3H, CH_3), 4.45 (*s*, 2H, CH_2), 7.07−7.10 (*m*, 2H, H-5* and H-4*), 7.16 (*dd*, 1H, *J* = 6.7, 2.7, H-3*), 7.72−7.75 (*m*, 2H, Pht-H), 7.79−7.82 (*m*, 2H, Pht-H), 9.60 (*brs*, NH). **^{13}C NMR:** 19.0, 41.0, 124.1, 127.8, 129.0, 129.9, 132.5, 132.7, 134.0, 135.4, 139.2, 165.9, 168.3
16	**^{1}H NMR:** 2.13 (*s*, 3H, CH_3), 2.80 (*t*, 2H, *J* = 7.6, α-H), 3.99 (*t*, 2H, *J* = 7.4, β-H), 7.01−7.03 (*m*, 2H, H-4 and H-5), 7.13 (*dd*, 1H, *J* = 7.4, 2.4, H-3), 7.75−7.77 (*m*, 2H, Pht-H), 7.65−7.67 (*m*, 2H, Pht-H), 9.05 (*brs*, NH). **^{13}C NMR:** 13.8, 29.2, 29.7, 118.1, 118.2, 122.1, 122.9, 124.0, 127.3, 128.2, 128.9, 129.2, 129.3, 133.6, 162.9, 163.8.

* Interchangeable.

of the compounds showed neurotoxicity at the applied dose. Preliminary screening results indicated that the title compounds have pronounced anti-MES activity. The derivatives bearing substituents at the *ortho* position on the *N*-phenyl ring in both acetamides and propionamides, except isopropyl substituted ones (compound **9** and **10**), provided better protection at 4 h than at 0.5 h. However, 2,6-disubstituted and 2-isopropyl substituted compounds did not follow similar trends and their activity did not differ significantly depending on the time of administration. The most active compounds in the acetamide series are compound **3** and compound **7**. The rest of the acetamide derivatives did not produce compounds superior to compound **1** which did not have any substituent on the *N*-phenyl ring. With regard to propionamide derivatives, the most active compound is compound **2** followed by compounds **6** and **10**. Surprisingly, in the propionamide series, the substituents studied did not create compounds with superior activity compared to the unsubstituted propionamide derivative (compound **2**). The compounds displaying statistically significant activity were **2**, **3**, **6**, **7** and **10** in both series. Compound **1**, **3**, **5** and **7** have been evaluated previously against pentylene-tetrazole-induced tonic-convulsions predicting activity on absence seizures. Compound **7**, one of the most active compounds against MES in this study, has been found inactive, and the others have shown 33% protection at 100 mg/kg dose level in frogs [17].

As mentioned in the introduction, Usifoh et al. reported that aliphatic amides of *N′,N′*-phthaloyl-β-alanine (corresponding to our propionamide derivatives) were essentially inactive in the MES test [9]. In contrast to this, our study revealed that *N*-phenyl substituted amides of *N′,N′*-phthaloyl-β-alanine nucleus have a definite anticonvulsant activity against MES.

Experimental

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 using a $CDCl_3$/DMSO-d_6 mixture (0.6 mL /4 drops) as solvent. 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.

Table 4. Anticonvulsant and neurotoxicity screening data of title compouds at 100 mg/kg dose in mice.

Comp	MES[a]		Toxicity[b]	
	0.5 h[c]	4 h[c]	0.5 h	4 h
1	1/4	3/4	0/4	0/4
2	3/4	8/8**	0/4	0/8
3	1/4	8/8**	0/4	0/8
4	2/4	3/4	0/4	0/4
5	2/4	3/4	0/4	0/4
6	2/4	7/8*	0/4	0/0
7	3/4	7/8*	0/4	0/4
8	2/4	2/4	0/4	0/4
9	3/4	3/4	0/4	0/4
10	3/4	7/8*	0/4	0/8
11	2/4	2/4	0/4	0/4
12	2/4	3/4	0/4	0/4
13	3/4	3/4	0/4	0/4
14	3/4	2/4	0/4	0/4
15	3/4	3/4	0/4	0/4
16	3/4	3/4	0/4	0/4

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

Synthesis of 2-chloro-N-phenylacetamides and 3-chloro-N-phenylpropionamides **1a**–**16a**

The intermediates were prepared according to the method reported in the literature [24]. 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 an ice-bath. The reaction mixture was stirred in the ice-bath for half an hour and one hour at 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).

Synthesis of 2-phthalimido-N-phenylacetamides and 3-phthalimido-N-phenylpropionamides **1**–**16**

According to the method reported in the literature [18], ω-chloro-*N*-phenylalkanamides (0.08 mol) and phthalimide potassium salt (0.12 mol) were refluxed in DMF. By monitoring with TLC, the reaction was terminated. The reaction mixture was poured into cold water. The precipitate was filtered and washed with water. After drying the precipitate was purified by crystallization from ethanol. Reflux times, % yields and melting points were reported in Table 1. The spectral data of compounds were reported in Table 2 and 3.

Anticonvulsant activity screening

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-hours light and dark schedule. Before the experiments mice were allowed 1 wk of adaptation. They were used only once. The experiments were performed between 9 and 12 am in the morning.

All title compounds were suspended in 0.5 % methylcellulose and injected intraperitoneally at 100 mg/kg doses. 0.1 mL methylcellulose was given intraperitoneally to control animals. The rotarod test was carried out to determine minimal neurotoxicity before the experiments. Maximal electroshock seizures (MES) were induced 0.5 h or 4 h after administration of title compounds, by application of a 60 Hz current of 60 mA and 0.4 pulse witdh for 0.2 s via ear electrodes by using a Ugo Basile electroshock device. The anticonvulsive activity of the compounds was evaluated by defining the abolition of the hind-leg tonic maximal extension component of the seizure [25]. Fisher's exact X^2 test was used for statistical analysis

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