Full Paper

Synthesis and Anticonvulsant Activity of Some *N*-Phenyl-2-phtalimidoethanesulfonamide Derivatives

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In this study, inspired by the structures of the taltrimide, 2-phthalimidoethanesulphonamide, and the anilide pharmacophore known to be synthetically produced anticonvulsant compounds, fifteen *N*-phenyl-2-phtalimidoethanesulfonamide derivatives bearing substituents with diverse electronic and hydrophobic features on *N*-phenyl ring were 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 in mice at a dose level of 100 mg/kg. The preliminary screening results indicated that the exchange of the *N*-isopropyl moiety for an *N*-phenyl ring in the taltrimide molecule abolished the anticonvulsant activity. However, introducing certain substituents, such as nitro, methyl, and chloro, into the *N*-phenyl ring lead to more active compounds in comparison to the unsubstituted derivatives.

Keywords: Anticonvulsant / MES / *N*-Phenyl-2-phtalimidoethanesulfonamide / Taurine / Taltrimide

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Introduction

Epilepsy requires long-term efficient therapy without unwanted side effects, so the development of new anti-epileptic drugs (AEDs) with approved therapeutic properties is as an important challenge for medicinal chemistry, since epilepsy is one of the most common neurological diseases [1 – 3]. Clinically available AEDs have certain disadvantages such as notable adverse effects and inefficient therapy in some seizure types [3, 4]. The need for new anti-epileptic drugs with different modes of action than those of the available ones seems essential for satisfactory results [4].

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Abbreviations: anti-epileptic drugs (AEDs); maximal electroshock seizure (MES); anticonvulsant screening project (ASP)

The inhibition of excitation or enhancement of inhibition in the brain is the ultimate goal for anticonvulsant drug therapy, since the imbalance between inhibitory and excitatory processes followed by over-excitation in the brain leads to epileptic seizure [3, 5, 6]. Therefore, the inhibitor amino acids in the central nervous system become the natural prevalent targets for designing new anticonvulsants [7].

Besides the major inhibitor amino acids GABA and glycine, taurine, as an inhibitor amino acid, modulates the excitatory and inhibitory neurotransmission leading to enhanced inhibition [8 – 10]. Taurine is known to have anti-epileptic activity, but it has clinically no application yet [8, 11]. Its hydrophilic nature leading to uncertain pharmacokinetics prevents its use for therapeutic purposes [8]. Attempts for more lipophilic taurine analogs yielded *N*-isopropyl-2-phthalimidoethane sulfonamide, a potent anticonvulsant compound known as taltrimide [8, 12, 13]. In animal experiments, the anticonvulsive effects of taltrimide (in both tests of MES and PST) have

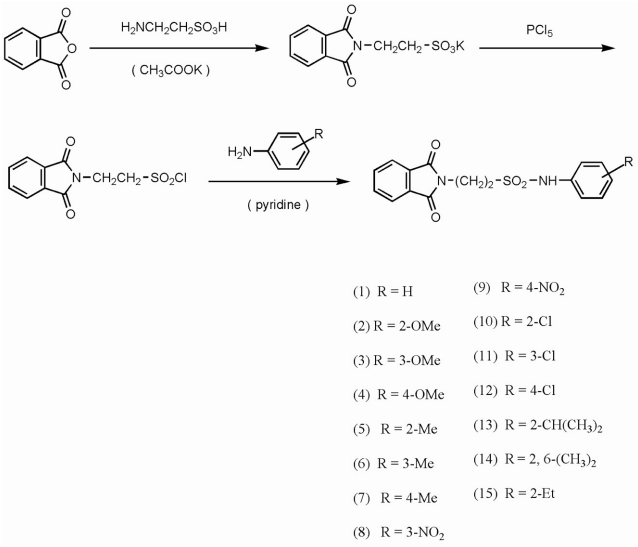
not been confirmed in clinical studies, and during the taltrimide treatment, the frequency of seizures has been increased indicating the possible proconvulsive behavior [14]. On the other hand, in a recent study, *N*-valproyltaurinamide has been reported as promising AED candidate for further experimental epilepsy models [15].

The data summarized above encourage us to investigate the *N*-phenyl derivatives of 2-phthalimidotaurinamide as potential anticonvulsants since the anilide pharmacophore with small and lipophilic substituents on the *N*-phenyl ring is known to produce potent anticonvulsants [16 – 18].

Results and discussion

Chemistry

In this study, fifteen *N*-phenyl-2-phtalimidoethanesulfonamide derivatives have been synthesized to evaluate anti-MES activity. The synthesis of the title compounds was performed in three steps according to the method reported by Winterbottom *et al*. [19]. As illustrated in Scheme 1, in the first step, the reaction of 2-aminoethane sulfonic acid (taurine) with phthalic anhydride and potassium acetate in acetic acid solution furnished 2-phthalimidoethanesulfonic acid potassium salt. In the second step, potassium salt was transformed to the corresponding sulfonyl chloride derivative with phosphorus pentachloride. The reactions of sulfonyl chloride deriv-



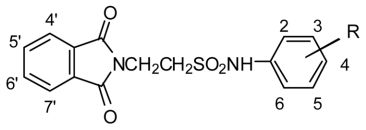
Scheme 1. Synthesis of the presented compounds.

Table 1. Yield, melting point, formula, IR, and API-MS data of title compounds.

Comp	Yield (%)	Mp (°C)	Formula	IR (cm^{-1})	API-MS m/z (% intensity)
1	60	136 – 138[a]	$C_{16}H_{14}N_2O_4S$	3248, 1768, 1699, 1362, 1142	331 (1, $[M+1]^+$), 174 (100)
2	19	154	$C_{17}H_{16}N_2O_5S$	3265, 1771, 1716, 1370, 1147	362 (2, $[M+2]^+$), 361 (10, $[M+1]^+$), 174 (100)
3	25	118	$C_{17}H_{16}N_2O_5S$	3244, 1770, 1700, 1362, 1143	361 (6, $[M+1]^+$), 174 (100)
4	12	142[b]	$C_{17}H_{16}N_2O_5S$	3252, 1776, 1718, 1359, 1146	362 (6, $[M+2]^+$), 361 (31, $[M+1]^+$), 297 (100)
5	43	174	$C_{17}H_{16}N_2O_4S$	3278, 1770, 1716, 1365, 1149	345 (3, $[M+1]^+$), 174 (100)
6	15	122	$C_{17}H_{16}N_2O_4S$	3266, 1775, 1702, 1366, 1147	345 (3, $[M+1]^+$), 174 (100)
7	21	165[c]	$C_{17}H_{16}N_2O_4S$	3326, 1773, 1721, 1369, 1143	346 (5, $[M+2]^+$), 345 (22, $[M+1]^+$), 174 (100)
8	25	222	$C_{16}H_{13}N_3O_6S$	3270, 1774, 1707, 1525, 1390, 1346, 1153	376 (6, $[M+1]^+$), 270 (100)
9	32	208[d]	$C_{16}H_{13}N_3O_6S$	3201, 1772, 1707, 1519, 1362, 1336, 1147	376 (1, $[M+1]^+$), 174 (100)
10	20	162	$C_{16}H_{13}ClN_2O_4S$	3249, 1773, 1717, 1399, 1148	366 (0.2, $[M+2]^+$), 365 (1, $[M+1]^+$), 174 (100)
11	31	128	$C_{16}H_{13}ClN_2O_4S$	3268, 1764, 1711, 1367, 1148	366 (0.4, $[M+1]^+$), 365 (2, $[M+1]^+$), 174 (100)
12	53	150[e]	$C_{16}H_{13}ClN_2O_4S$	3321, 1773, 1719, 1367, 1143	366 (1, $[M+2]^+$), 365 (3, $[M+1]^+$), 174 (100)
13	13	144	$C_{19}H_{20}N_2O_4S$	3267, 1770, 1713, 1365, 1144	373 (13, $[M+1]^+$), 174 (100)
14	18	189	$C_{18}H_{18}N_2O_4S$	3278, 1775, 1719, 1363, 1140	359 (10, $[M+1]^+$), 174 (100)
15	18	128	$C_{18}H_{18}N_2O_4S$	3312, 1769, 1700, 1366, 1140	359 (5, $[M+1]^+$), 174 (100)

[a] 141°C from etanol, Ref [19].
[b] 148 – 149°C from aqueous acetic acid, Ref [19].
[c] 168 – 170°C from ethanol, Ref [19].
[d] 214.5 – 215.5°C from aqueous acetic acid, Ref [19].
[e] 154 – 155°C from aqueous acetic acid, Ref [19].

Table 2. NMR data of title compounds.



Compound	NMR
1	^{1}H NMR ($CDCl_3$) δ 7.86 (2H, *dd*, *J*= 2.7, 5.5 Hz, H-4′, H-7′), 7.73 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-5′, H-6′), 7.25–7.33 (4H, *m*, H-2, H-3, H-5, H-6), 7.15–7.17 (1H, *m*, H-4), 7.07 (*brs*, NH), 4.08 (2H, *t*, *J*= 5.9 Hz, α-CH_2), 3.45 (2H, *t*, *J*= 5.9 Hz, β-CH_2) ppm.
2	^{1}H NMR ($CDCl_3$) δ 7.84 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-4′, H-7′), 7.72 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-5′, H-6′), 7.53 (1H, *dd*, *J*= 1.6, 7.8 Hz, H-3*), 7.16 (*brs*, NH), 7.12 (1H, *td*, *J*= 1.6, 7.8 Hz, H-4**), 6.94 (1H, *t*, *J*= 7.8 Hz, H-5**), 6.89 (1H, *d*, *J*= 8.1 Hz, H-6*), 4.14 (2H, *t*, *J*= 6.2 Hz, α-CH_2), 3.91 (3H, *s*, OCH_3), 3.41 (2H, *t*, *J*= 6.2 Hz, β-CH_2) ppm.
5	^{1}H NMR ($CDCl_3$) δ 7.85 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-4′, H-7′), 7.73 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-5′, H-6′), 7.46 (1H, *d*, *J*= 7.8 Hz, H-3*), 7.21–7.18 (2H, *m*, H-5**, H-6*), 7.06 (1H, *t*, *J*= 7.4 Hz, H-4**), 6.65 (*brs*, NH), 4.12 (2H, *t*, *J*= 6.0 Hz, α-CH_2), 3.53 (2H, *t*, *J*= 6.2 Hz, β-CH_2), 2.43 (3H, *s*, CH_3) ppm.
8	^{1}H NMR (DMSO-d_6) δ 10.55 (*brs*, NH), 7.96–7.95 (1H, *m*, H-4), 7.91–7.88 (1H, *m*, H-6), 7.8 (4H, *m*, H-4′, H-5′, H-6′, H-7′), 7.59–7.57 (2H, *m*, H-2, H-5), 3.95 (2H, *t*, *J*= 7 Hz, α-CH_2), 3.55 (2H, *t*, *J*= 7.2 Hz, β-CH_2) ppm.
9	^{1}H NMR ($CDCl_3$) δ 8.19 (2H, *d*, *J*= 9 Hz, H-3, H-5′), 7.86 (2H, *dd*, *J*= 3.1, 6.25 Hz, H-4, H-7′), 7.76 (2H, *dd*, *J*= 3.1, 5.6 Hz, H-5′, H-6′), 7.64 (*brs*, NH), 7.41(2H, *dd*, *J*= 1.95, 8.97 Hz, H-2, H-6), 4.07 (2H, *t*, *J*= 5.9 Hz, α-CH_2), 3.55 (2H, *t*, *J*= 5.9 Hz, β-CH_2) ppm.
10	^{1}H NMR ($CDCl_3$) δ 7.85 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-4′, H-7′), 7.73 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-5′, H-6′), 7.66 (1H, *dd*, *J*= 1.6, 8.2 Hz, H-3), 7.39 (1H, *dd*, *J*= 1.6, 8.19 Hz, H-6), 7.3–7.26 (1H, *m*, H-4*), 7.22 (*brs*, NH), 7.09 (1H, *td*, *J*= 1.6, 7.8 Hz, H-5*), 4.18 (2H, *t*, *J*= 6.2 Hz, α-CH_2), 3.49 (2H, *t*, *J*= 6.2 Hz, β-CH_2) ppm.
14	^{1}H NMR ($CDCl_3$) δ 7.88 (2H, *dd*, *J*= 2.7, 5.5 Hz, H-4′, H-7′), 7.74 (2H, *dd*, *J*= 3.1, 5.5 Hz, H-5′, H-6′), 7.10–7.09 (3H, *m*, H-3, H-4, H-5), 6.26 (*brs*, NH), 4.35 (2H, *t*, *J*= 6.24 Hz, α-CH_2), 3.54 (2H, *t*, *J*= 6.24 Hz, β-CH_2), 2.41 (6H, *s*, CH_3) ppm.

* Interchangeable

ative and appropriated anilines in the third step yielded the title compounds. The structures of the title compounds were confirmed by spectral (IR, ^{1}H-NMR, and APCI (atmospheric pressure chemical ionization)-MS) and elemental analysis. The yields, melting points, and formulas of title compounds are reported in Table 1. The title compounds except compound **1**, **4**, **7**, **9**, and **12**, which were reported as potential antibacterials and antimalarials by Winterbottom *et al*., are novel [19]. Taltrimide was also synthesized according to the method reported in the literature and its spectral data is consistent with the data reported [20].

The presence of vibrational bands resulting from phthalimide and sulfonamide moieties are the confirmative frequencies for title compounds in the IR spectra (Table 1). C=O stretching bands of phthalimide moiety were observed between 1700–1776 cm^{-1} as a doublet arising from the vibrational interaction [21]. N-H and SO_2 stretching bands providing the confirmation of sulfonamide group were detected between 3201–3326 and 1140–1399 cm^{-1}, respectively.

^{1}H-NMR data of title compounds were totally in agreement with the expected resonance signals in terms of chemical shifts and integrations. Depending on the nature of the substituents and substitution patterns on *N*-phenyl ring, the aromatic protons were observed in different chemical shifts with expected splitting patterns. The representative examples of NMR data of the title compounds are summarized at Table 2.

The mass spectra of the title compounds were recorded according to the APCI technique and interpreted for the positive ionization (Table 1). The $[M+H]^+$ ions of the title compounds were in complete agreement with the calculated molecular weights. The main fragmentation seems to occur at the sulfonamide function to give the m/z 238 ion $[C_{10}H_8NO_4S]^+$ and m/z 174 ion $[C_{10}H_8NO_2]^+$ as base peaks in title compounds except compounds **4** and **8**.

Pharmacology

According to the Anticonvulsant Screening Project (ASP), two convulsant test, maximal electroshock (MES) and pentylenetetrazole (ScPTZ), are used for primary evaluation for anticonvulsant activity and the rotarod test is for primary toxicity screening. The MES test is a model for generalized tonic-clonic seizures and represents those compounds, which prevent seizure spread [22]. Since taltrimide and anticonvulsant anilides are more active in the MES test, the anticonvulsant activity of title compounds was evaluated against maximal electroshock seizures induced 0.5 or 4 h after administration of single dose level (100 mg/kg) in mice. The rotarod test was used for determining possible neurotoxicity. The anticonvul-

Table 3. Anticonvulsant and neurotoxicity screening data of title compounds at 100 mg/kg dose in mice.

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

[a] Protected animals to tested animals.
[b] Animals exhibited neurotoxicity to tested animals.
[c] $p < 0.05$.

sant and neurotoxicity screening data are presented in Table 3.

The replacement of *N*-isopropyl with *N*-phenyl ring in taltrimide molecule (compound **1**) abolished the anticonvulsant activity. Introducing small lipophilic substituents on the *N*-phenyl ring in compound **1** provided limited contribution to anticonvulsant activity depending on the nature and the position of the substituents. The activity screening data revealed that compounds **8** and **10** are more and compound **14** is equal active at 0.5 h in comparison to taltrimide. Under the set of studied substituents on *N*-phenyl ring, chloro in *ortho* position and nitro in *meta* position gave the best results at 0.5 h producing more active compounds than taltrimide (compounds **8** and **10**). Their activity was diminished at 4 h. On the other hand, positive contribution of methyl group to anticonvulsant activity became apparent in compounds **5** and **14** at 4 h. A similar situation was observed with compound **9** having a nitro substituent on *para* position at 4 h. Those compounds except compound **14** were inactive at 0.5 h. One methyl substitution in the *ortho* position increased the neurotoxicity dramatically leading to the most neurotoxic compound in the series (compound **5**), whereas dimethyl substitution did not follow a similar pattern (compound **14**). None of the compounds synthesized presented equal activity to taltrimide at 4 h.

In a recent study, the 2-phthalimido-*N*-phenylpropanamide nucleus has been reported to have anticonvulsant activity against MES test without any neurotoxicity [23]. Exchanging the carbonyl group with sulfonyl in the 2-phthalimido-*N*-phenylpropanamide nucleus leads to *N*-phenyl-2-phtalimidoethanesulfonamide derivatives. The results obtained in this study revealed that such non-classic isosteric replacement not only reduced the anticonvulsant activity but also increased the neurotoxicity.

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The authors have declared no conflict of interest.

Experimental

Chemistry

Melting points were determined on a Büchi 510 melting point apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. The IR spectra of compounds were recorded as a potassium bromide pellets on a Jasco FT/IR-400 spectrometer (Jasco, Tokyo, Japan). The NMR spectra were recorded on a Varian AS 400 Mercury Plus NMR (Varian Inc., Palo Alto, CA, USA). Chemical shifts were reported in parts per million (δ). *J* values were given in Hz. Mass spectra (APCI; atmospheric pressure chemical ionization) were measured on an Agilent 1100 MSD spectrometer (Agilent, Palo Alto, CA, USA). Elemental analyses (C, H and N) were performed by TUBITAK Analytical Laboratory Ankara, Turkey.

Synthesis of the potassium salt of 2-phthalimidoethanesulfonic acid

A suspension of 1.36 mol of taurine and 1.45 mol of anhydrous potassium acetate in 475 mL of acetic acid was refluxed for ten minutes, then, 1.45 mol of phthalic anhydride was added. The reaction mixture was refluxed with stirring for additional two and half hour. At the end of the reaction, a white precipitation was formed. After cooling in an ice-bath with continued stirring, the white product was filtered off, washed with acetic acid followed by alcohol, and purified by crystallization from water.

Synthesis of 2-phthalimidoethanesulfonyl chloride

The potassium salt of 2-phthalimidoethanesulfonic acid (0.015 mol) was suspended in 22 mL of benzene. The excess of benzene (approximately 4 mL) was removed under vacuum. Phosphorus pentachloride (0.0132 mol) of was added to the mixture and refluxed by stirring for one hour. After adding another 0.0132 mol of phosphorus pentachloride, the reaction was continued to reflux for an additional one and a half hour. The reaction mixture was evaporated to dryness. The residue was washed with cold water. The crude product was crystallized from dichloromethane : ethanol mixture (1 : 1).

Synthesis of N-phenyl-2-phthalimidoethanesulfonamide derivatives

2-Phthalimidoethanesulfonyl chloride (0.01 mol) was added in portions to 0.01 mol of the aniline dissolved in 0.1 mol of dry pyridine by cooling in an ice bath. After treating the mixture in an ice bath for half an hour and stirring the mixture at room temperature for an additional half hour. The mixture was poured into dilute hydrochloric acid solution. The precipitated product, after washing with water, was crystallized from acetic acid : water mixture (1 : 1).

Pharmacology

Eskisehir Osmangazi University, School of Medicine, Animal Use and Care Committee approved all the experiments for animal testing. Male swiss albino mice weighing 30–40 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 one week 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 to the animals at 100 mg/kg doses. Methylcellulose 0.1 mL was given intraperitoneally to the control animals. The rotarod test was carried out to determine minimal neurotoxicity before the experiments. Maximal electroshock seizures (MES) were induced 0.5 or 4 h after administration of the title compounds, 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 (Ugo Basile, Italy). The anticonvulsive activity of the compounds was evaluated by defining as the abolition of the hind-leg the tonic maximal extension component of the seizure [24]. Fischer's exact $\chi 2$ test was used for statistical analysis.

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