Acta Pharmaceutica Turcica
XLIII (3,4) (161-163) 2001

ANTICONVULSANT ACTIVITY OF SOME SUBSTITUTED 1,3,4-THIADIAZOLES

BAZI SÜBSTİTÜE 1,3,4-TİYADİAZOLLERİN ANTİKONVÜLSAN AKTİVİTESİ

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Some 5-[4-(benzoylamino)phenyl]-2 substituted amino-1,3,4-thiadiazoles have been synthesized previously in our laboratory. The structures of these compounds were elucidated using UV, IR and Mass spectroscopic methods besides elemental analyses. In the present work, the structures of these compounds have also been supported by ^{1}H-NMR and their anticonvulsant activities against pentylenetetrazole induced seizures in male and female Albino Swiss mice have been investigated. All the compounds showed protections ranging from 10 to 60% at a dose of 100 mg.kg^{-1} and among them, 2-allylamino-5-[4-(benzoylamino)phenyl]-1,3,4-thiadizole was found to posses significant protection against pentylenetetrazole shock.

Daha önceki bir çalışmamızda, bazı 5-[4-(benzoilamino)fenil]-2-substitüe amino-1,3,4-tiyadiazol türevleri sentezlenmişti. Bu bileşiklerin yapıları, elementel analiz yanında UV, IR ve kütle spektroskopisi yardımıyla aydınlatılmıştı. Bu çalışmada, bileşiklerin yapıları ^{1}H-NMR bulguları ile de desteklenmiş ve antikonvulsan aktiviteleri, erkek ve dişi Albino Swiss farelerde pentilentetrazole karşı araştırılmıştır. Bütün bileşikler 100 mg.ml^{-1} dozda %10-60 koruma göstermiş ve bileşiklerden 2-allilamino-5-[4-(benzoilamino)fenil]-1,3,4-tiyadiazolün pentilentetrazol şokuna karşı belirgin koruma sağladığı bulunmuştur.

Key words: *Anticonvulsant activity; 2,5-disubstituted-1,3,4-thiadiazoles*

Anahtar kelimeler: *Antikonvülsan aktivite; 2,5-disübstitüe-1,3,4-tiyadiazoller*

Introduction

In a previous paper the synthesis and structural elucidations (UV, IR, MS) of some 5-[4-(benzoylamino)phenyl]-2-substituted amino-1,3,4-thiadiazoles have been described (1). Several investigators have reported that some substituted 1,3,4-thiadiazoles have possessed significant anticonvulsant properties (2-4). In the view of these observations, this paper describes the ^{1}H-NMR data and anticonvulsant activities of some new compounds against pentylenetetrazole induced seizures in male and female Albino Swiss mice.

Materials and methods

^{1}H-NMR were recorded on a Brucker AVANC-DPX 400 and Brucker AC 200 L spectrometers. The structures of the compounds investigated for their anticonvulsant activity are presented in the figure.

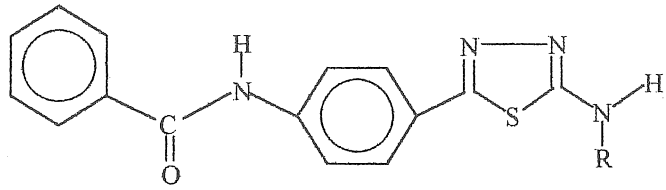
5-[4-(Benzoylamino)phenyl]-2-methylamino-1,3,4-thiadiazole trihydrate **(1a):** ^{1}H-NMR (200 MHz) (DMSO-d_6/TMS) δ ppm: 2.36 (s, 3H, NH-$\underline{CH_3}$); 5.03 (s, 6H, H_2O), 7.53-7.63 (m, 3H, $\underline{H}_{benzoyl}$ 3,4,5), 7.79 (d, 2H, $\underline{H}_{phenyl}$ 3,5); 7.94 (d, 2H, $\underline{H}_{phenyl}$ 2,6); 7.98 (d, 2H, $\underline{H}_{benzoyl}$ 2,6); 8.58 (s, 1H, N$\underline{H}$-CH_3); 10.47 (s, 1H, CON$\underline{H}$).

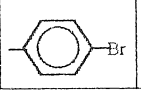
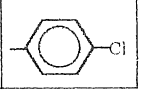
5-[4-(Benzoylamino)phenyl]-2-ethylamino-1,3,4-thiadiazole dihydrate **(1b)**: ^{1}H-NMR (200 MHz) (DMSO-d_6/TMS) δ ppm: 1.22 (t, 3H, CH_2-$\underline{CH_3}$); 3.37 (q, 2H, $\underline{CH_2}$-CH_3); 4.23 (s, 4H, H_2O); 7.53-7.64 (m, 3H, $\underline{H}_{benzoyl}$ 3,4,5), 7.76 (d, 2H, $\underline{H}_{phenyl}$ 3,5); 7.94 (d, 2H, $\underline{H}_{phenyl}$ 2,6); 7.98 (d, 2H, $\underline{H}_{benzoyl}$ 2,6); 8.22 (s, 1H, N$\underline{H}$-CH_2); 10.44 (s, 1H, CON$\underline{H}$).

2-Allyl-amino-5-[4-(benzoylamino)phenyl] 1,3,4-thiadiazole **(1c)**: ^{1}H-NMR (200 MHz) (DMSO-d_6/TMS) δ ppm: 3.97 (t, 2H, $\underline{CH_2}$-CH); 5.17 (d, 1H, CH=C$\underline{H_2}$ cis J:10.4); 5.29 (d, 1H,

* Correspondence

Fig. Structures of the compounds tested for anticonvulsant activity (abbreviations as described in the text).



Comp.	1a	1b	1c	1d	1e	1f	1g	1h
R	$-CH_3$	$-C_2H_5$	$-CH_2CH=CH_2$	$-C_6H_{11}$	$-CH_2CH_2C_6H_5$	$-C_6H_5$		

CH=CH$_2$ trans J:17.10); 5.92-5.98 (m, 1H, CH=CH$_2$); 7.53-7.63 (m, 3H, H$_{benzoyl}$ 3,4,5), 7.76 (d, 2H, H$_{phenyl}$ 3,5); 7.91 (d, 2H, H$_{phenyl}$ 2,6); 7.98 (d, 2H, H$_{benzoyl}$ 2,6); 8.06 (t, 1H, NH-CH$_2$); 10.42 (s, 1H, CONH).

5-[4-(Benzoylamino)phenyl]-2-cyclohexylamino-1,3,4-thiadiazole (**1d**): ^{1}H-NMR (200 MHz) (DMSO-d$_6$/TMS) δ ppm: 1.19-1.99 (m, 10H, H$_{cyclohexyl}$); 3.56 (s, 1H, H$_{cyclohexyl}$); 7.53-7.68 (m, 3H, H$_{benzoyl}$ 3,4,5); 7.73 (d, 2H, H$_{phenyl}$ 3,5); 7.81 (s, 1H, NH); 7.90 (d, 2H, H$_{phenyl}$ 2,6); 7.97 (d, 2H, H$_{benzoyl}$ 2,6); 10.18 (s, 1H, CONH).

5-[4-(Benzoylamino)phenyl]-2-phenethylamino-1,3,4-thiadiazole (**1e**): ^{1}H-NMR (200 MHz) (DMSO-d$_6$/TMS) δ ppm: 2.94 (t, 2H, CH$_2$CH$_2$); 3.57 (q, 2H, CH$_2$CH$_2$); 7.23-7.34 (m, 5H, H$_{phenyl}$); 7.53-7.62 (m, 3H, H$_{benzoyl}$ 3,4,5); 7.75 (d, 2H, H$_{phenyl}$ 3,5); 7.93 (d, 2H, H$_{phenyl}$ 2,6); 7.97-7.99 (m, 3H, H$_{benzoyl}$ 2,6 and NHCH$_2$); 10.43 (s, 1H, CONH).

5-[4-(Benzoylamino)phenyl]-2-phenylamino-1,3,4-thiadiazole (**1f**): ^{1}H-NMR (200 MHz) (DMSO-d$_6$/TMS) δ ppm: 7.02 (t, 1H, H$_{phenyl}$ 4); 7.36 (t, 1H, H$_{benzoyl}$ 4); 7.51-7.68 (m, 6H, H$_{benzoyl}$ 3,5, H$_{phenyl}$ 3,5, H$_{phenyl}$ 2,6); 7.83-8.05 (m, 6H, H$_{benzoyl}$ 2,6, H$_{phenyl}$ 2,6, H$_{phenyl}$ 3,5); 10.45 (s, 2H, CONH, NH).

5-[4-(Benzoylamino)phenyl]-2-(4-bromophenyl) amino-1,3,4-thiadiazole (**1g**): ^{1}H-NMR (200 MHz) (DMSO-d$_6$/TMS) δ ppm: 7.53-7.63 (m, 5H, H$_{benzoyl}$ 3,4,5 and H$_{4\text{-bromophenyl}}$ 2,6); 7.66 (d, 2H, H$_{4\text{-bromophenyl}}$ 3,5); 7.86 (d, 2H, H$_{phenyl}$ 3,5); 7.95-8.00 (m, 4H, H$_{benzoyl}$ 2,6, H$_{phenyl}$ 2,6); 10.48 (s, 1H, CONH); 10.62 (s, 1H, NH).

5-[4-(Benzoylamino)phenyl]-2-(4-chlorophenyl) amino-1,3,4-thiadiazole (**1h**): ^{1}H-NMR (200 MHz) (DMSO-d$_6$/TMS) δ ppm: 7.42 (d, 2H, H$_{4\text{-chlorophenyl}}$ 2,6); 7.53-7.64 (m, 3H, H$_{benzoyl}$ 3,4,5); 7.72 (d, 2H, H$_{4\text{-chlorophenyl}}$ 3,5); 7.86 (d, 2H, H$_{phenyl}$ 2,6); 7.95-8.00 (m, 4H, H$_{benzoyl}$ 2,6, H$_{phenyl}$ 2,6); 10.48 (s, 1H, CONH); 10.62(s,1H,NH).

Anticonvulsant activity: The anticonvulsant activities of the compounds were determined against pentylenetetrazole-induced seizures in Albino Swiss mice of either sex weighing 20-30 g. They were housed in groups of 15 and acclimated to their environment for at least 2 days prior to the experiments. The animals were allowed free access to pellet and water before the tests. The test compounds were suspended in 5% aqueous gum acacia and were administered to a group of 10 animals at a dose of 100 mg.kg^{-1} intraperitoneally. 2 hours after the administration, mice were injected 90 mg.kg^{-1} pentylenetetrazole subcutaneously. This dose of pentylenetetrazole has been shown not only to produce convulsions in almost all untreated mice, but also to exhibit 100% mortality during the 24 hours period in the control group. The mice were observed for the next 60 mins for seizures. Animals devoid of a threshold convulsion were considered protected. The mortalities within 24 hours were also recorded. All pharmacological data were evaluated according to Litchfield and Wilcoxon (5).

Results and discussion

The structures of the previously synthesized compounds (1) were supported by the ^{1}H-NMR spectroscopic method in this research. The ^{1}H-NMR spectrum of compounds **1a-h** showed singlets at 10.18-10.48 ppm and 7.81-10.62 ppm corresponding to the secondary amide N-H and secondary amine N-H protons respectively. Furthermore other protons were observed in the expected field as in accordance with the literature (6-8).

The synthesized compounds were evaluated for anticonvulsant activity against pentylenetetrazole induced seizures in male and female Albino Swiss mice (9,10). The initial pharmacological screening of **1a-h** led to the results presented in the table. All

Table. Results of anticonvulsant activity against pentylenetetrazole shock.

Compounds	1a	1b	1c	1d	1e	1f	1g	1h
Protection(%)	20	20	60	30	20	10	30	40
Mortality(%)	80	80	40	70	80	90	70	60

the compounds showed 10-60 % anticonvulsant activities against pentylenetetrazole schock. The maximum protection was observed with **1c** which possessed allylamino group at position 2 of thiadiazole nucleus. Replacement of the allyl group by a phenyl ring resulted with the decrease of anticonvulsant activity. However, the presence of chlorine or bromine at position 4 of the phenyl ring caused an increase in the anticonvulsant activity.

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Accepted: 15.11.2000