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

BAZI SÜBSTİTÜE 1,3,4-TİYADİAZOLLERİN ANTİKONVULSAN 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 ¹H-NMR and their anticonvulsant activities against pentylentetrazole 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-thiadiazole was found to posses significant protection against pentylentetrazole shock.

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

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 ¹H-NMR data and anticonvulsant activities of some new compounds against pentylentetrazole induced seizures in male and female Albino Swiss mice.

Materials and methods

¹H-NMR were recorded on a Brucker AVANCE-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-(Benzyolamino)phenyl]-2-methylamino-1,3,4-thiadiazole trihydrate (1a): ¹H-NMR (200 MHz) (DMSO-d₆/TMS) δ ppm: 2.36 (s, 3H, NH-CH₃); 5.03 (s, 6H, H₂O), 7.53-7.63 (m, 3H, H₃ benzoyl 3,4,5), 7.79 (d, 2H, H₃phenyl 3,5), 7.94 (d, 2H, H₃ phenyl 2,6), 7.98 (d, 2H, H₃benzoyl 2,6), 8.58 (s, 1H, NH-CH₃); 10.47 (s, 1H, CONH).

5-[4-(Benzyolamino)phenyl]-2-ethylamino-1,3,4-thiadiazole dihydrate (1b): ¹H-NMR (200 MHz) (DMSO-d₆/TMS) δ ppm: 1.22 (t, 3H, CH₃-CH₂), 3.37 (q, 2H, CH₂-CH₂), 4.23 (s, 4H, H₂O); 7.53-7.64 (m, 3H, H₃ benzoyl 3,4,5), 7.76 (d, 2H, H₃ phenyl 3,5), 7.94 (d, 2H, H₃ phenyl 2,6), 8.22 (s, 1H, NH-CH₃); 10.44 (s, 1H, CONH).

2-allylamino-5-[4-(benzyolamino)phenyl] 1,3,4-thiadiazole (1c): ¹H-NMR (200 MHz) (DMSO-d₆/TMS) δ ppm: 3.97 (t, 2H, CH₂-CH₂), 5.17 (d, 1H, CH=CH₂ cis J:10.4); 5.29 (d, 1H,
Fig. Structures of the compounds tested for anticonvulsant activity (abbreviations as described in the text).

\[
\begin{array}{|c|c|c|c|c|c|c|c|}
\hline
\text{Comp.} & l\text{a} & l\text{b} & l\text{c} & l\text{d} & l\text{e} & l\text{f} & l\text{g} & l\text{h} \\
\hline
R & -\text{CH}_3 & -\text{C}_2\text{H}_5 & -\text{CH}_2\text{CH} = \text{CH}_2 & -\text{C}_6\text{H}_{11} & -\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5 & -\text{C}_6\text{H}_5 & -\text{OBr} & -\text{OCl} \\
\hline
\end{array}
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CH=CH_2 trans J=17.10; 5.92-5.98 (m, 1H, CH=CH_2); 7.53-7.63 (m, 3H, H_benzyl 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-[(Benzoylamino)phenyl]-2-cyclohexylamino-1,3,4-thiadiazole (1d): ¹H-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-[(Benzoylamino)phenyl]-2-phenethylamino-1,3,4-thiadiazole (1e): ¹H-NMR (200 MHz) (DMSO-d_6/TMS) δ ppm: 2.94 (t, 2H, CH_2CH_2); 3.57 (q, 2H, CH_2CH_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-[(Benzoylamino)phenyl]-2-phenylamino-1,3,4-thiadiazole (1f): ¹H-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).

5-[(Benzoylamino)phenyl]-2-(4-bromophenyl)amino-1,3,4-thiadiazole (1g): ¹H-NMR (200 MHz) (DMSO-d_6/TMS) δ ppm: 7.53-7.63 (m, 5H, H benzoyl 3,4,5 and H_4-bromophenyl 2,6); 7.66 (d, 2H, H_4-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-[(Benzoylamino)phenyl]-2-(4-chlorophenyl)amino-1,3,4-thiadiazole (1h): ¹H-NMR (200 MHz) (DMSO-d_6/TMS) δ ppm: 7.42 (d, 2H, H_4-chlorophenyl 2,6); 7.53-7.64 (m, 3H, H benzoyl 3,4,5); 7.72 (d, 2H, H_4-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 pentylentetrazole-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⁻³ pentylentetrazole subcutaneously. This dose of pentylentetrazole 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 ¹H-NMR spectroscopic method in this research. The ¹H-NMR spectrum of compounds l₁ₐ-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 pentylentetrazole induced seizures in male and female Albino Swiss mice (9,10). The initial pharmacological screening of l₁ₐ-h led to the results presented in the table. All
Table. Results of anticonvulsant activity against pentylenetetrazole shock.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>1d</th>
<th>1e</th>
<th>1f</th>
<th>1g</th>
<th>1h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protection(%)</td>
<td>20</td>
<td>20</td>
<td>60</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Mortality(%)</td>
<td>80</td>
<td>80</td>
<td>40</td>
<td>70</td>
<td>80</td>
<td>90</td>
<td>70</td>
<td>60</td>
</tr>
</tbody>
</table>

the compounds showed 10-60 % anticonvulsant activities against pentylenetetrazole shock. The maximum protection was observed with 1c which possessed allylamino group at position 2 of thia diazole 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.

References

Accepted: 15.11.2000