Synthesis and Anticonvulsant Activities of Some New Dioxolane Derivatives

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Summary

In this study, ten 2-acetylnaphtalene derivatives with a dioxolane structure were synthesized and screened for their anticonvulsant activities. Dioxolane derivatives were prepared by the reaction with appropriate ethanone, glycol and p-toluensulphonic acid. The structures of the compounds were elucidated by IR, 'H-NMR and elemental analysis. Anticonvulsant activities of the compounds were determined by maximal electroshock seizure (MES) test and subcutaneous metrazol (scMet) test, rotarod toxicity test was used for the assessment of neurological deficits. According to the activity studies compound 6 was found neurotoxic, compounds, 1, 4, 5, 7-9 were found protective against MES and 7-10 were found protective against ScMet. Compounds 2 and 3 were found inactive.

Key words

- 2-Acetylnaphthalene derivatives
- Antiepileptic drugs
- Dioxolanes, anticonvulsant activity, synthesis

Zusammenfassung


Die neurologische Toxizität wurde im Rotarod-Test ermittelt. Die Verbindungen 1, 4, 5, 7-9 waren im MES-Test wirksam, Verbindungen 7-10 zeigten Wirkung im Metrazol-Test. Die Verbindungen 2 und 3 erwiesen sich als unwirksam.

1. Introduction

The search for new antiepileptic drugs is one of the popular areas of drug investigation since uncontrolled seizures, drug side effects and toxicity are still the main problems of the therapy with existing drugs [1-3]. Arylalkylimidazoles is one of the structurally distinct groups and nafimidone and denzimol (see structure formulas) are two representatives of this class [4-8].

According to the previous structure-activity relationship studies, the most desirable anticonvulsant activity appeared with a lipophilic aryl group and oxygen containing small substituent in the alkyene bridge and imidazole ring [4-6]. These and our previous studies [9, 11] on these imidazole containing anticonvulsant drugs have prompted us to study some arylalkylimidazoles having dioxolane group as the alkyene bridge between aryl group and azole ring.

This study describes the synthesis of dioxolane derivatives having 2-naphthyl as an aryl group and having imidazole, pyrazole, 1,2,4-triazole, benzimidazole and benzotriazole rings as an azole group see structure formula) and their anticonvulsant activity.

The structures of the compounds were confirmed by IR, 1H-NMR and elemental analysis. Anticonvulsant activities of the compounds were examined by maximal electroshock (MES) and subcutaneous metrazol (ScMet.) tests. The compounds were suspended in 30 % aqueous of PEG 400 and administered intraperitoneally in a volume of 0.01 mg/kg at body weight to the mice. Seizure assays and neurotoxicity were determined by rotated toxicity test according to the phase I tests of the Antiepileptic Drug Development (ADD) programme which were developed by the National Institute of Neurological and Communicative Disorders and Stroke [2, 13].

2. Materials and methods

2.1. Chemistry

All chemicals used in this study were supplied by E. Merck (Darmstadt, Germany) and Aldrich (Steinheim, Germany). Melting points were determined with a Thomas Hoover capillary melting point apparatus (Philadelphia, PA, USA) and are uncorrected. IR spectra (KBr disc) were recorded on a Perkin Elmer FT-IR spectrophotometer 1720 X (Beaconsfield, UK), 1H-NMR spectra were recorded on a Bruker AC 400 MHz FT NMR spectrometer using tetramethylsilane internal standard and dimethylsulfoxide-d6. All chemical shifts were reported as δ (ppm) values. The purity of the compounds was controlled by thin-layer chromatography (Merck, silicagel, HF254+366 type 60, 0.25 mm. The elemental analyses (C, H, N) were performed on Leco CHNS 932 (Leco Coop, St. Joseph, MI, USA) analyzer by the Scientific and Technical Research Council of Turkey Instrumental Analysis Laboratories (Ankara, Turkey) and were within ± 0.4 % of the theoretical values.

2.1.1. Synthesis of α-bromo-2-acetylnaphthalene

α-Bromo-2-acetylnaphthalene were synthesized according to the Immediata's method by the treatment of 0.1 mol 2-acetyl naphthalene and 5 ml bromine in 100 ml acetic acid [12].

2.1.2. Synthesis of 1-(2-naphthyl)-2-(imidazolyl and/or pyrazolyl and/or benzimidazolyl)-1-ethanone hydrochloride

To a stirred, ice-cooled solution of the appropriate amine (imidazole or pyrazole) (0.03 mol) in 10 ml of DMF was added dropwise α-bromo-2-acetylnaphthalene (0.01 mol) in 5 ml of DME. The mixture was stirred for 2 h at 0 °C and kept overnight at room temperature. The solution was poured into cold water and stirred for 2 h. The resulting base precipitated and was filtered off, washed with water and dissolved in benzene. The benzene solution was dried (azeotroped), filtered and treated with gas HCl. The precipitated salt was crystallized from methanol [9].

2.1.3. Synthesis of 1-(2-naphthyl)-2-(1,2,4-triazolyl and/or benzotriazolyl)-1-ethanone

The appropriate amine (0.01 mol) was added to the solution of metallic sodium in dried methanol; α-bromo-2-acetyl naphthalene (0.01 mol) was added in portions to this solution. The mixture was heated for 6 h under reflux; methanol was evaporated. The crude product was crystallized from benzene [9].

2.1.4. General synthesis of dioxolane derivatives

A mixture of ethanone derivatives (0.02 mol), ethylene glycol (or propylene glycol) (0.04 mol) and p-toluene sulphonic acid (0.04 mol) in 50 ml toluene was heated overnight under reflux through a Dean-stark trap. The cooled mixture was treated with ethyl acetate and poured into excess aqueous potassium carbonate and the organic phase was separated and dried. The hydrochloride salt was precipitated by the addition of ethereal HCl until precipitation was just complete. The precipitated salt was filtered off and crystallized from methanol-ethyl acetate [4].

2.2. Pharmacology

Stimulator (Grass S88, Grass Instruments, USA), constant current unit (Grass SCUJA), corneal electrode were used for the evaluation of anticonvulsant activity. All synthesized com-

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pounds were administered i.p. as 30 % aqueous polyethylene glycol (PEG) 400 suspensions. Twelve Swiss albino male mice (20 ±2 g) (mice were obtained from the Refik Saydam Hfizissláh Institute Animal Care Unit in our laboratory according to the NINCDS-ADD programme [13]) were used for each compound. Control animals received 30 % aqueous PEG 400. The compounds were tested for their anticolvulsant activity against MES and Sc Met. induced seizures and rotarod toxicity test was performed for neurological toxicity according to the phase I tests of the ADD programme [13]. Pentetrazole was administered s.c. into the back of the neck. The rotarod toxicity test was performed on a 1 inch diameter knurled wooden rod, rotating at 6 rpm.

2.1. MES test
Maximal electroshock seizures were elicited with a 60 cycle alternating current of 50 mA intensity (5-7 times that necessary to elicit minimal electroshock seizures) delivered for 0.2 s via corneal electrodes. A drop of 0.9 % saline was applied onto the eye prior to application of the electrodes in order to prevent the death of the animal. Abolition of the hind limb tonic extension component of the seizure was defined as protection.

2.2. ScMet. test
85 mg/kg of pentetrazole (producing seizures in greater than 95 % of mice) was administered as a 0.5 % solution subcutaneously into the posterior midline. The animal was observed for 30 min. Failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) was defined as protection.

2.3. Toxicity
The rotarod test was used to evaluate neurotoxicity. The animal was placed on a 1 inch diameter knurled wooden rod rotating at 6 rpm. Normal mice remain on a rod rotating at this speed indefinitely. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min.

3. Results
α-Bromo-2-acetyl-naphthalene was prepared by reacting 2-acetylnaphthalene and bromine in acetic acid under The reaction conditions described earlier by Immediata and Day [12] in a good yield. Several N-alkylation methods were used for the synthesis of ethanone derivatives. Dioxolane derivatives were prepared by the reaction with appropriate ethanone, glycol and p-toluensulphonic acid in toluene under reflux through a Dean-Stark trap Scheme 1). Some characteristics of the compounds are given in Table 1. The structures of the compounds were elucidated by IR, 1H-NMR and elemental analysis and all spectral data were in accordance with the assigned structures (Table 2). Their anticonvulsant activities of the compounds were examined by maximal electroshock (MES), subcutaneous metrazol (scMet) tests and also neurotoxicity was determined by the rotarod toxicity test according to the phase I tests of the ADD programme. The compounds were suspended in 30 % aqueous solution of PEG 400 and administered intraperitoneally in a volume of 0.01 ml/g body weight to the mice. The results are shown in Table 3.

4. Discussion
The anticonvulsant activities of the compounds were initially evaluated against MES and ScMet induced seizures using Swiss albino male mice according to the NIH-ADD programme. The results are shown in Table 3. Although it has been reported that the activities of nafimidone and denzimol as well as the other (arylal-

Table 1; Some characteristics of the compounds.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>R’</th>
<th>A</th>
<th>M.p. (°C)</th>
<th>Yild (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>-N</td>
<td></td>
<td>HCl</td>
<td>265-6</td>
<td>60.43</td>
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<tr>
<td>2</td>
<td>-N</td>
<td></td>
<td>HCl</td>
<td>192-3</td>
<td>56.65</td>
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<tr>
<td>3</td>
<td>-N</td>
<td></td>
<td>HCl</td>
<td>214-5</td>
<td>61.12</td>
</tr>
<tr>
<td>4</td>
<td>-N</td>
<td></td>
<td>HCl</td>
<td>243-4</td>
<td>43.36</td>
</tr>
<tr>
<td>5</td>
<td>-N</td>
<td></td>
<td>-</td>
<td>52-3</td>
<td>75.47</td>
</tr>
<tr>
<td>6</td>
<td>-N</td>
<td>CH3</td>
<td>HCl</td>
<td>244-5</td>
<td>82.45</td>
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<tr>
<td>7</td>
<td>-N</td>
<td>CH3</td>
<td>HCl</td>
<td>154-5</td>
<td>62.50</td>
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<tr>
<td>8</td>
<td>-N</td>
<td>CH3</td>
<td>HCl</td>
<td>203-4</td>
<td>77.0</td>
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<tr>
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<td>-N</td>
<td>CH3</td>
<td>HCl</td>
<td>216-7</td>
<td>60.15</td>
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<tr>
<td>10</td>
<td>-N</td>
<td>CH3</td>
<td>-</td>
<td>49-50</td>
<td>72.85</td>
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Table 2: Phase I anticonvulsant screening of the compounds.

<table>
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<tr>
<th>Comp. No.</th>
<th>Comp.</th>
<th>0.5 h</th>
<th>4 h</th>
<th>0.5 h</th>
<th>4 h</th>
<th>0.5 h</th>
<th>4 h</th>
<th>0.5 h</th>
<th>4 h</th>
<th>0.5 h</th>
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<td>3100-3000 (Ar-C-H), 2900 (C-H), 1325 (C-N), 1200 (C-O), 860, 825 (C-H deformation naphthalene B ring) and 745 (C-H deformation naphthalene A ring)</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
</tr>
<tr>
<td>2</td>
<td>3040 (Ar-C-H), 2990 (C-H), 1300 (C-N), 1200 (C-O), 860, 825 (C-H deformation naphthalene B ring) and 745 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
</tr>
<tr>
<td>3</td>
<td>3040 (Ar-C-H), 2900 (C-H), 1350 (C-N), 1200 (C-O), 830 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
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<tr>
<td>4</td>
<td>3100-3000 (Ar-C-H), 2850 (C-H), 1200 (C-N), 1050 (C-O), 880, 830 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
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<tr>
<td>5</td>
<td>3100-3000 (Ar-C-H), 3000-2800 (C-H), 1350 (C-N), 1050 (C-O), 875, 825 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
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<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
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<tr>
<td>6</td>
<td>3100 (Ar-C-H), 3000-2850 (C-H), 1200 (C-N), 1050 (C-O), 860, 825 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
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<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
</tr>
<tr>
<td>7</td>
<td>3100-3000 (Ar-C-H), 3000-2850 (C-H), 1200 (C-N), 1050 (C-O), 870, 830 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
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<tr>
<td>8</td>
<td>3100-3000 (Ar-C-H), 3000-2800 (C-H), 1200 (C-N), 1050 (C-O), 840 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
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<tr>
<td>9</td>
<td>3100-3000 (Ar-C-H), 3000-2800 (C-H), 1200 (C-N), 1040 (C-O), 875, 825 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
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<td>10</td>
<td>3100 (Ar-C-H), 2900 (C-H), 1200 (C-N), 1050 (C-O), 840 (C-H deformation naphthalene B ring) and 750 (C-H deformation naphthalene A ring)</td>
<td>1/1</td>
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<td>1/1</td>
</tr>
</tbody>
</table>

M5: maximal electroshock seizure test, scMet: subcutaneous pentylentetrazole (metrazol) seizure test, Toxicity: rotarod test. 0/1: noactivity at dose level. 1/1: noticeable activity at dose level.

a) Death 10 min after the injection.
5. References


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762 Güney et al. – Dioxolone derivatives