Full Paper

Synthesis and Studies on Antidepressant and Anticonvulsant Activities of Some 3-(2-Thienyl)pyrazoline Derivatives

Zuhal Ozdemir¹, H. Burak Kandilci², Bulent Gumusel², Unsal Calis¹, and A. Altan Bilgin¹

¹ Hacettepe University Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Ankara, Turkey
² Hacettepe University Faculty of Pharmacy, Department of Pharmacology, Ankara, Turkey

In this study, the synthesis of twelve 3-(2-thienyl)pyrazoline derivatives are described. The structures of all compounds were confirmed by UV, IR, ¹H-NMR, mass spectral data, and microanalyses. In the pharmacological studies, antidepressant and anticonvulsant activities of these compounds have been screened. The antidepressant activities of the compounds were investigated by Porsolt’s behavioral despair test (forced swimming) on albino mice and compared with tranylcypromine. Among the compounds examined, the compounds ⁹ and ¹² showed significant antidepressant activity. Anticonvulsant activities of the compounds were determined by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet.) tests, neurotoxicities were determined by rotarod toxicity test on albino mice. Compound ⁸ was found to be protective against MES in the range of 30–300 mg/kg dose levels at four hours. None of the synthesized compounds showed neurotoxicity at 30–300 mg/kg dose levels.

Keywords: Anticonvulsant activity / Antidepressant activity / 3-Pyrazoline derivatives

Received: April 10, 2008; accepted: July 31, 2008

DOI 10.1002/ardp.200800068

Introduction

The chemistry and the synthesis of 2-pyrazoline derivatives have attracted widespread attention in recent years. The present popularity of these derivatives is mainly due to their structural similarity to isocarboxazid (Fig. 1), a monoamine oxidase (MAO) inhibitor, which is well known to show prominent antidepressant activity [1]. In earlier studies, 1,3,5-triphenyl-2-pyrazolines are reported to possess MAO inhibitory activities by Palmar et al., [2] and Soni et al., [3]. In a recent paper, Chimenti et al., [4] reported enantioselective MAO-A and MAO-B inhibiting properties of 1-thiocarbamoyl-2-pyrazolines. MAO inhibitors have been proven to show antidepressant activity both in laboratory animals and man [5, 6].

Correspondence: B. Gumusel, PhD, Professor of Pharmacology, Hacettepe University, Faculty of Pharmacy, Department of Pharmacology, 06100 Ankara, Turkey.
E-mail: gumusel@hacettepe.edu.tr
Fax: +90 312 305-2026

Abbreviations: maximal electroshock seizure (MES); monoamine oxidase (MAO); subcutaneous pentylenetetrazole (metrazol) (scMet.)

© 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Figure 1. Structure of isocarboxazid(4’-benzyl-5-methyl-oxazole-3-carbohydrazide).
Results and Discussion

As shown in Scheme 1, the starting compound, 1-(2-thienyl)-3-phenyl/(2-thienyl)-2-propen-1-one was obtained by the reaction of benzaldehyde and 2-thienylaldehyde with acetylthiophen in a Claisen–Schmidt condensation reaction. The reaction of 1-(2-thienyl)-3-phenyl/(2-thienyl)-2-propen-1-one with phenylhydrazine and thiosemicarbazide in presence of sodium hydroxide in ethanol gave 1-phenyl (1 and 2), and 1-thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines (3 and 4), respectively. Treatment of the starting compound with hydrazine hydrate in ethanol, followed by addition of thiocyanates in the presence of triethylamine in ether provided 1-N-substituted thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines 5–12. Although compounds 1 and 2 have already been reported previously by Ried and Dankert [15], they have been included in our research program to screen their activity. The structures of the isolated compounds were characterized by spectral methods and microanalyses. All spectral data are in accordance with the assumed structures.

In the UV spectra of the compounds, two absorption maxima were observed at 206–244 and 327–353 nm due to C=N and Ar-N-N=C-Ar groups, respectively. In the IR spectra, all compounds displayed pyrazoline C=N stretching (1501–1576 cm–1), C^4-H deformation (1362–1464 cm–1), C-N stretching (1069–1189 cm–1), thiocarbamoyl group N-H stretching (3112–3481 cm–1), and C=S stretching (1315–1357 cm–1) bands.

In the 1H-NMR spectra of the compounds H_A, H_B, and H_X, protons of the pyrazoline ring were observed as doublet of doublet at δ = 2.98–3.30 ppm (J_AB = 17.44–17.69 Hz), 3.45–3.75 ppm (J_AB = 3.43–3.71 Hz), and 5.98–6.97 ppm (J_BX = 11.34–11.66 Hz), respectively. N-H protons of the thiocarbamoyl group were generally seen at 7.23–9.10 ppm as broad bands. All the other protons belonging methyl, ethyl, allyl groups, benzene and thiophene rings were seen accordingly to the expected chemical shift and integral values.

The mass spectroscopic fragmentation of the compounds was studied under electron ionization. Molecular ion peaks [M]^+ were prominent for all the compounds, confirmed the molecular weights of the examined compounds. The fragmentation pattern was essentially identical. Fragments resulting from the loss of the SH ion from the thiocarbamoyl group were observed for all compounds. On the other hand, α-cleavage adjacent to both sides of the C=S group have also been observed causing ejection of NHR or CSNHR type of ions. Microanalyses results were also in accordance with the theoretical amounts.

In-vivo antidepressant activities of the compounds were assessed in mice applying the forced swimming test. The forced swimming test, which is a behavioral test, used to predict the efficacy of antidepressant treatments [16]. It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors [17] and typical antidepressants [18]. It also has a good predictive value for the antidepressant potency in humans [19]. The obtained data on the antidepressant activity of the compounds and reference drug were given in Table 1. The compounds 2, 4, 9, 10, 12 bearing a thienyl group at the 5-position of the pyrazoline ring (except 11) showed marked antidepressant activity. Among the mentioned derivatives, most promising results were obtained with the compounds carrying 1-N-methylthiocarbamoyl (9) and 1-N-phenylthiocarbamoyl- (12) on the pyrazoline ring. The mentioned derivatives significantly reduced the duration of immobility times at the 10 mg/kg dose level when compared to the control (p < 0.05, Table 1).

Anticonvulsant activities of the synthesized compounds were also investigated by maximal electroshock (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet.) tests, and results from these experiments are shown in Table 2. Seizure assays and neurotoxicity were
Pyrazoline Derivatives as Antidepressant—Anticonvulsant

Table 1. Antidepressant activities of the synthesized compounds.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Antidepressant activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration of immobility (sec) (Mean ± S.E.M.)</td>
</tr>
<tr>
<td>1</td>
<td>188 ± 7.7</td>
</tr>
<tr>
<td>2</td>
<td>96 ± 21.2*</td>
</tr>
<tr>
<td>3</td>
<td>158 ± 18.3</td>
</tr>
<tr>
<td>4</td>
<td>84 ± 21.5*</td>
</tr>
<tr>
<td>5</td>
<td>174 ± 14.2</td>
</tr>
<tr>
<td>6</td>
<td>190 ± 10</td>
</tr>
<tr>
<td>7</td>
<td>154 ± 19.9</td>
</tr>
<tr>
<td>8</td>
<td>148 ± 29.1</td>
</tr>
<tr>
<td>9</td>
<td>43 ± 15.3*</td>
</tr>
<tr>
<td>10</td>
<td>88 ± 21.2*</td>
</tr>
<tr>
<td>11</td>
<td>182 ± 14.9</td>
</tr>
<tr>
<td>12</td>
<td>48 ± 18.9*</td>
</tr>
<tr>
<td>Tranylcypromine sulfate (10 mg/kg, ip)</td>
<td>57 ± 11.6</td>
</tr>
<tr>
<td>Control</td>
<td>201 ± 8.6</td>
</tr>
</tbody>
</table>

* Values represents the mean ± S.E.M. (n = 6–9).
* Significantly compared to control (Dunnet’s test; p < 0.05).

determined by rotarod toxicity test according to the phase-I tests of the anti-epileptic drug development (ADD) program which were developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) [20, 21]. According to the results of the in-vivo experiments, it is difficult to extract a definite structure-anticonvulsant activity relationship between of the tested compounds 1–12. As shown in Table 2, the significant difference in activity was observed depending on both aryl group at 5-position and the substituents on the thiocarbamoyl at the first position of the pyrazoline ring. Compound 4, 1-thiocarbamoyl-3,5-di-(2-thienyl)-2-pyrazoline, was found ineffective in the dose range of 30–300 mg/kg, while some remarkable activity were observed with compound 3 having a phenyl at 5-position in the 300 mg/kg-dose level at four hours. Anticonvulsant activity of the compounds bearing a phenyl group at the 5-position are taken into consideration, it could be concluded that the substitution of thiocarbamoyl group always resulted in good activity either at half hour at the 300 mg/kg-dose level (compounds 5 and 7) or at four hours (compounds 6 and 8). Among the compounds with phenyl, compound 8 possessed the most prominent and consistent activity against MES in the range of 30–300 mg/kg-dose levels at four hours. It is worth saying that all compounds which exhibited activity were found to be protective against MES-induces seizures at their high dose level (300 mg/kg). However, only two compounds (compounds 6 and 12) exhibited activity against scMet.-induced seizures at the 300 mg/kg-dose level. Neurotoxicity was observed in none of the synthesized compounds in the dose range of 30–300 mg/kg.

Conclusion

In summary, we have reported the synthesis and biological evaluation of 3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazoline derivatives as novel candidate antidepressant /
anticonvulsant compounds. Generally, the synthesized compounds having a phenyl substituent at the 5’ position of the pyrazoline ring (compounds 3, 5, 6, 7, 8) possess remarkable anticonvulsant activity. Among the mentioned derivatives, most promising results were obtained with the compound 8 carrying 1-N-phenylthiocarbamoyl-phenylthiocarbamoyl against MES in the range of 30–300 mg/kg dose levels at four hours. On the contrary, however, the compounds bearing a thienyl at the 5-position of the ring (compounds 2, 4, 9, 10, 12, except 11) attract attention with their antidepressant activity. Two of them (compounds 9 and 12) showed a larger antidepressant activity than tranylcypromine. It is worth saying that the compounds having a N-phenylthiocarbamoyl at 1-position of pyrazoline ring exhibited a remarkable antidepressant and anticonvulsant activity. Therefore, such compounds would represent a fruitful matrix for the development of a new class of antidepressant and anticonvulsant agents and would deserve further investigation and derivatization as a promising scaffold.

This study was supported by Hacettepe University Scientific Research Foundation (Project no: 0302 30100).

The authors have declared no conflict of interest.

**Experimental**

**Chemistry**

All chemicals used in this study were supplied by E. Merck (Germany), Aldrich Chemical Co. (Munich, Germany) and Fluka AG (Buchs, Switzerland). Melting points were taken in a Thomas Hoover capillary melting point apparatus (Thomas Hoover, Philadelphia, PA, USA) and are uncorrected. UV spectra were obtained on Agilent 8453 UV-Visible spectrophotometer in methanol. IR spectra were recorded in a Bruker Vector 22 IR Opus Spectroscopic Software Version 2.0 (Bruker Bioscience, Billerica, MA, USA) using KBr pellets. 1H-NMR spectra were recorded on a Bruker Avance 200 MHz FT spectrometer (Bruker) in CDCl3 using TMS as internal standard. Mass spectra were recorded on a Bruker Esquire 6000 mass selective electron impact detector (Agilent, Palo Alto, CA, USA) using KBr pellets. 1H-NMR spectra were recorded on a Bruker Avance 400 MHz FT spectrometer (Bruker) in CDCl3 using TMS as internal standard. Mass spectra were recorded on a Bruker Avance 200 MHz FT spectrometer (Bruker) in CDCl3 using TMS as internal standard. Mass spectra were recorded on a Bruker Avance 400 MHz FT spectrometer (Bruker) in CDCl3 using TMS as internal standard. Mass spectra were recorded on a Bruker Avance 400 MHz FT spectrometer (Bruker) in CDCl3 using TMS as internal standard.

**1-(2-Thienyl)-3-phenyl/(2-thienyl)-2-propen-1-ones**

Chalcone derivatives were obtained from 2-acetylthiophene (0.01 mol) and appropriate aldehydes (0.01 mol) by known methods [22–26].

**1-Phenyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

The solution of appropriate chalcone (0.01 mol) and phenylhydrazine (0.02 mol) in ethanolic sodium hydroxide (0.025 mol, 20 ml) was refluxed for four hours. The product was poured into ice water and the crude product, which was separated out, was filtered and crystallized from a proper solvent.

**1,5-Diphenyl-3-(2-thienyl)-2-pyrazoline**

**1-Phenyl-3,5-di-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

**1-Thiocarbamoyl-3-(2-thienyl)-5-phenyl/(2-thienyl)-2-pyrazolines**

© 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

www.archpharm.com
11.27 Hz, 1H, H3), 6.90 (b, 1H, NH), 6.90 – 7.50 (m, 6H, thiophene); MS m/z: 293 [M]+ (89%), 260 [M – SH] (70%), 233 [M – CS(NH)2] (34%), 183 [M – C6H5NS] (75%), 169 [M – C6H5N2S] (100%), 151 [C6H5N3S] (24%), 110 [C6H5NS] (57%). Anal. Calcld. for C14H15N3S3: C, 52.30; H, 4.70; N, 13.07; S, 29.92. Found: C, 52.83; H, 5.18; N, 12.83; S, 19.58. Found: C, 62.72; H, 5.18; N, 12.86; S, 19.91.

1-N-Phenylthiocarbamoyl-3-(2-thienyl)-5-phenyl-2-pyrazoline 8

Yield: 67%; m.p.: 122 – 3°C (Crys. solv.: EtOH); UV \( \lambda_{	ext{Max}} \) [nm]: 202 (log e 4.47), 251 (log e 4.43), 346 (log e 4.22); IR \( \nu \) [KBr] [cm⁻¹]: 3343 (N-H stretching), 1588, 1513 (C=N stretching), 1451 (C=H deformation), 1343 (C=S stretching), 1169 (C=N'- stretching); \( \nu \) [KBr] [cm⁻¹]: 3343 (N-H stretching), 1588, 1513 (C=N stretching), 1451 (C=H deformation), 1343 (C=S stretching), 1169 (C=N'- stretching); \( \nu \) [KBr] [cm⁻¹]: 3343 (N-H stretching), 1588, 1513 (C=N stretching), 1451 (C=H deformation), 1343 (C=S stretching), 1169 (C=N'- stretching); \( \nu \) [KBr] [cm⁻¹]: 3343 (N-H stretching), 1588, 1513 (C=N stretching), 1451 (C=H deformation), 1343 (C=S stretching), 1169 (C=N'- stretching).

Yield: 56%; m.p.: 117 – 118°C (Crys. solv.: MeOH); UV \( \lambda_{	ext{Max}} \) [nm]: 224 (log e 4.30), 244 (log e 4.32), 341 (log e 4.02); IR \( \nu \) [KBr] [cm⁻¹]: 3380 (N-H stretching), 1587, 1506 (C=N stretching), 1441, 1370 (C=H deformation), 1158 (C=N' stretching); \( \nu \) [KBr] [cm⁻¹]: 3380 (N-H stretching), 1587, 1506 (C=N stretching), 1441, 1370 (C=H deformation), 1158 (C=N' stretching); \( \nu \) [KBr] [cm⁻¹]: 3380 (N-H stretching), 1587, 1506 (C=N stretching), 1441, 1370 (C=H deformation), 1158 (C=N' stretching); \( \nu \) [KBr] [cm⁻¹]: 3380 (N-H stretching), 1587, 1506 (C=N stretching), 1441, 1370 (C=H deformation), 1158 (C=N' stretching); \( \nu \) [KBr] [cm⁻¹]: 3380 (N-H stretching), 1587, 1506 (C=N stretching), 1441, 1370 (C=H deformation), 1158 (C=N' stretching); \( \nu \) [KBr] [cm⁻¹]: 3380 (N-H stretching), 1587, 1506 (C=N stretching), 1441, 1370 (C=H deformation), 1158 (C=N' stretching).
The synthesized compounds were screened for their antidepressant activity using Poroselt's behavioral despair (forced swimming) test [16]. Local breed, male albino mice (20–24 g) were used in the forced swimming test under standard conditions with free access to food and water. They were housed in groups of six. On the test day, mice were dropped one at a time into a plexiglass cylinder (height 25 cm, diameter 10 cm) containing 10 cm of water at 23–25°C [14]. On this day, mice were assigned into different groups (n = 6–9 for each group). Tranlycypromine sulfate was supplied by Sigma Chemical Co. The synthesized compounds (10 mg/kg), and tranlycypromine sulfate, as a reference antidepressant drug (10 mg/kg), were suspended in a 1% aqueous solution of Tween 80. The drugs were injected intraperitoneally (ip) to mice (22 g) in a standard volume of 0.5 mL/kg. Control animals received 30% aqueous PEG 400. Pentyleneetetrazole (metrazol) was administered subcutaneously (sc) from the back of the neck. The rotarod toxicity test was performed on a 1-inch diameter knurled wooden rod, rotating at 6 rpm.

**References**


