Depending on the nature of substituents, some derivatives of 1,2,4-triazoline-5-thione show various biological activities, such as antiinflammatory (1), antituberculostatic (2), anticancer (3) and antibacterial (4), as well as they are used as herbicides and fungicides (5). The broad spectrum of biological activity of these compounds was an inspiration for synthesis of new derivatives. In previous paper we described 1-aminomethyl derivatives of 3-R-4-phenyl-∆2-1,2,4-triazoline-5-thione (6). These compounds were screened for their antibacterial activity. One compound appeared to be a promising precursor of compounds with the increased inhibitory activity against Gram-negative bacteria.

This work is a continuation of search for new compounds with promising biological activities. Thus, 3-benzyl-4-ethyl-1,2,4-triazoline-5-thione (1) was subjected to the reaction with piperazine derivatives and the corresponding 1-aminomethyl-3-benzyl-4-ethyl-1,2,4-triazoline-5-thione derivatives (2-5) were obtained.

The reactions carried out in this work are presented on Scheme 1.

**EXPERIMENTAL**

Melting points were determined in a Fisher-Johns block and are listed without corrections. The IR spectra were recorded in KBr using Specord IR-75 spectrophotometer. The 1H NMR spectra were recorded on a Bruker Avance 300 in DMSO-d6 with TMS as an internal standard.

Elemental micro analysis for C, H, N were performed in the Department of Organic Chemistry, Lublin Medical of University and were within ± 0.5% of theoretical values.

Chemicals were purchased from Merck or Lancaster and used without purification.

Synthesis of 1-aminomethyl-3-benzyl-4-ethyl-1,2,4-triazoline-5-thione derivatives (2-5)

*General procedure*

(0.01 mole) of compound (1) was dissolved in 10 mL of anhydrous ethanol. Then 0.8 g (0.01 mole) of 37% formaldehyde aqueous solution and 0.02 mole of appropriate amine were added. The mixture was refluxed for 6 h. After cooling, the precipitate was filtered off, dried and recrystallized from ethanol.

**Scheme 1.**

Figure 1. Fitting of the optimized structure of compound (1). Energy optimization 15.59 kcal/mol. Calculation was performed by the Amber 2 force field using HyperChem 7.5.
RESULTS AND DISCUSSION

3-Benzyl-4-ethyl-1,2,4-triazoline-5-thione (1) was used as the starting material. This compound was synthesized by intermolecular cyclization of 4-ethyl-1-phenylacetyl thiosemicarbazide with 2% NaOH solution. Thiosemicarbazide derivative was obtained according to the method described in (7).

Compound (1) was subjected to the reaction with piperazine derivatives. The reactions were carried out in ethanolic solution, in the presence of a small amount of formalin, by using appropriate: N-phenylpiperazine, 1-(4-methoxyphenyl) piperazine, 1-(4-fluorophenyl)-piperazine and 1-(3-chlorophenyl) piperazine. The conditions of the reactions were established experimentally.

Taking into account the possibility of existing of thiol-thione isomerism, 1,2,4-triazoline-5-thione derivatives in the nucleophilic substitution reactions can give both S- or N- derivatives (8). Our observation suggests that 3-benzyl-4-ethyl-1-2,4-triazoline-5-tione exist mainly in the thione form (Figure 1) and give N-substituted derivatives. The signal of protons characteristic for the –NH–C=S group found in the starting material was not observed in the ‘H NMR spectra of new compounds. The structure of new compounds was confirmed by elemental analysis, as well as the their IR and ‘H NMR spectra. The detailed physico-chemical data of the obtained compounds (2-5) are presented in Table 1.

REFERENCES


Table 1. Physical and analytical data for compounds (2-5).

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>Formula</th>
<th>Yield %</th>
<th>IR (cm⁻¹)</th>
<th>‘H NMR – δ (ppm)</th>
<th>M.W.</th>
<th>M.p.°C</th>
<th>KBr</th>
<th>DMSO – d₆</th>
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<td>2</td>
<td>C₆H₅</td>
<td>C₂₂H₂₇N₅S</td>
<td>80</td>
<td>3060 CH arom. 2938, 1440 CH aliph. 1599 C=N 1440 C-N</td>
<td>0.93 (t, 3H CH₃), 2.73-2.83 (m, 4H, 2CH₂), 3.10- 3.12 (m, 4H, 2CH₂), 3.92 (s, 2H, CH₂), 4.18 (s, 2H,CH₂), 5.08 (s, 2H, CH₂), 6.74-7.37 (m, 10 H, 2 arom. benz.)</td>
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</tr>
<tr>
<td>3</td>
<td>4-OCH₃C₆H₄</td>
<td>C₂₂H₂₉N₅OS</td>
<td>83</td>
<td>3043 CH arom. 2952, 1426 CH aliph. 1569 C=N 1496 C-N</td>
<td>0.97 (s, 3H, CH₃), 3.30-3.44 (m, 8H, 4CH₂), 3.72 (s, 3H, CH₃), 3.87 (t, 2H,CH₂), 4.15 (s, 2H, CH₂), 6.92-7.37 (m, 9H, 2 arom. benz.)</td>
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<td>4</td>
<td>4-FC₆H₄</td>
<td>C₂₂H₂₆N₅SF</td>
<td>78</td>
<td>3045 CH arom. 2968, 1450 CH aliph. 1558 C=N 1484 C-N</td>
<td>0.92 (s, 3H, CH₃), 2.57-2.83 (m, 4H, 2CH₂), 2.97-3.08 (m, 4H, 2CH₂), 3.32 (s, 2H,CH₂), 4.15 (q, 2H, CH₂), 5.08 (s, 2H,CH₂), 6.90-7.00 (m, 4H, arom. benz.)</td>
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<td>5</td>
<td>3-ClC₆H₄</td>
<td>C₂₂H₂₆N₅SCl</td>
<td>81</td>
<td>3058 CH arom. 2971, 1441 CH aliph. 1564 C=N 1478 C-N</td>
<td>0.91 (s, 3H, CH₃), 2.55-2.81 (m, 4H, 2CH₂), 2.06-3.18 (m, 4H, 2CH₂), 3.32 (s, 2H, CH₂), 4.18 (q, 2H,CH₂), 5.08 (s, 2H,CH₂), 6.75-6.94 (m, 4H, arom. benz.)</td>
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</table>

Table 1. Physical and analytical data for compounds (2-5).