Investigation of physical and chemical properties of new derivatives of 5- (thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiols

A. V. Khilkovets*

Zaporizhzhia State Medical University, Ukraine

Heterocyclic compounds are one of the most important branches of modern organic chemistry and are widely used in medicine, pharmacy, agriculture, and in the production of new materials. One of these compounds is 1,2,4-triazole, which has attracted the attention of scientists around the world for many years.

The aim of the work is to synthesize new derivatives of 5- (thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiols and study their physical-chemical properties, conducting primary pharmacological screening.

Materials and methods. Organic synthesis classical methods were used in the study, as well as a complex of physical-chemical analysis methods (1H NMR spectroscopy, elemental analysis, Elisa and chromato-mass spectral studies) were done. Prediction of pharmacological activity was carried out by using the PASS online computer program.

Results. Two initial compounds were obtained: 5-(thiophene-3-ylmethyl)-4phenyl-1,2,4-triazole-3-thiol and 5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-thiol. During their further chemical transformation, a number of new corresponding alkyl derivatives were obtained. The structure of the synthesized compounds was confirmed using modern physical-chemical methods of analysis. Based on the results of pharmacological screening, the high activity of the obtained compounds can be predicted.

Conclusions. 5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-thiol, 5-(thiophene-3-ylmethyl)-4-phenyl-1,2,4-triazole-3-thiol and a number of their alkyl derivatives were synthesized. The structure and individuality were proved thanks to modern physical and chemical methods of analysis. Having analyzed the results of primary pharmacological screening of a number of obtained compounds, some of them were selected for further study.

Key words: 5-(thiophene-3-ylmethyl)-4-R-1,2,4-triazole-3-thiol, synthesis, physical and chemical properties.
Investigation of physical and chemical properties of new derivatives of 5-(thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiols

A. V. Hylkovets

Heterocyclic compounds are one of the most important branches of modern organic chemistry and are widely used in medicine, pharmacy, agriculture, and in the production of new materials [1–3]. One of these compounds is 1,2,4-triazole, which has attracted the attention of scientists around the world for many years.

Despite a large amount of existing information on the study of 1,2,4-triazole derivatives, this topic still remains relevant, since these derivatives are potentially biologically active substances. Currently, there is a growing tendency in the scientific world to combine 1,2,4-triazole with various substituents, functional groups, as well as aromatic and heterocyclic fragments [4–6]. Such studies are undoubtedly promising and original. The new molecules obtained in this way exhibit a wide range of biological activity, and most of them are low-toxic, which is undoubtedly of great importance [7,8]. It is also interesting that the introduction of various pharmacophores into the molecule leads to the formation of new properties, which certainly opens opportunities for creating a new “ideal” compound.

According to the literature, we were convinced that the combination of 1,2,4-triazole and a five-membered heterocycle-thiophene is insufficiently studied. In our opinion, this combination is very promising, since the thiophene molecule is aromatic and has high reactivity. Existing data on the obtained thiophene-containing compounds have shown the presence of high biological activity and low toxicity.

**Aim**

The aim of the work is to synthesize new derivatives of 5-(thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiols and study their physical-chemical properties, conducting primary pharmacological screening.

**Materials and methods of research**

Chemical names of compounds are given according to the IUPAC nomenclature (1979) and the IUPAC recommendations (1993). The study of the physical and chemical properties of the obtained substances was carried out by using the methods listed in the state Pharmacopoeia of Ukraine. The melting points were determined by the open capillary method on an OptiMelt MPA 100 instrument with a platinum RTD sensor. Element analysis was carried out by using the elementary vario EL cube analyzer (system Elementar Analy-sen, Germany). IR spectra (4000–400 cm \(^{-1}\)) were obtained by using the ALPHA-t module of the Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). \(^{1}H\) NMR spectra (400 MHz) were recorded on a Varian-MR 400 spectrometer with an internal SiMe\(_4\) standard in a DMSO-d\(_6\) solution. Chromato-mass-spectral studies were carried out on the Agilent 1260 Infinity HPLC device, which is equipped with an Agilent 6120 mass spectrometer (electrospray ionization method (ESI)). The prediction of pharmacological activity was performed using the online computer program PASS.

To obtain new compounds, we used the generally accepted synthesis method [9], according to which 3-thiophenecarboxylic acid was used as the starting substance. During further chemical transformations, the corresponding N-R-2-(2-(thio- phene-3-yl)acetyl)hydrazine carbothioamides were obtained. The cycle was closed in an alkaline medium, and acetate acid was added to the neutral medium to further isolate the initial thiols. Thus, two starting substances were obtained: 5-(thiophene-3-ylmethyl)-4phenyl-1,2,4-triazole-3-thiol (1) and 5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-thiol (2) (Fig. 1).

The next step was to obtain a number of alkyl derivatives [3–9].

The reaction was carried out in an alcoholic medium by...
Fig. 1. The synthesis of 5-(thiophene-3-ylmethyl)-4-phenyl-1,2,4-triazole-3-thiol (1) and 5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-thiol (2).

Fig. 2. The synthesis of haloalkanes.

Fig. 3. The synthesis of dihaloalkanes.
adding an equivalent amount of alkali to the initial thiols and corresponding haloalkanes (Fig. 2). In the case of dihaloalkanes, double the amount of Alkali was added (Fig. 3). The synthesized compounds were recrystallized from a mixture of methanol and water in various ratios.

Results
The IR spectra of the obtained compounds were characterized by the presence of clear bands of valence and other vibrations of strong and medium intensity of the main fragments of molecules. In the initial compounds, we observed valence vibrations C = C in the region of 1620–1680 cm⁻¹, C = N in the cycle – 1480–1500 cm⁻¹, as well as a high intensity of thiophene valence vibrations in the region of 690–750 cm⁻¹. There were valence vibrations in the range of 2550–2590 cm⁻¹, which indicated the presence of the S-H group. Valence vibrations of the CH₂ group were in the range of 2870–2940 cm⁻¹, CH₃ – 2950–2975 cm⁻¹, and deformation vibrations of the S-C group in the region of 1325 cm⁻¹ are clearly observed in the alkyl derivatives which we obtained.

4-phenyl-5-(thiophen-3-ylmethyl)-1,2,4-triazole-3-thiol (1) Yield.: 75 %; Mp.: 188–190 °C; ¹H NMR (400 MHz, DMSO-d₆) δ: 7.46–7.52 (m, 3H-14,15,16 C₆H₅), 7.22–7.29 (m, 2H-13,17 C₆H₅), 6.96 (s, 1H-2 thiophen), 6.75 (d, J = 4.58 Hz, 2H-3,4 thiophen), 3.85 (s, 2H, CH₂); Anal. Calcd. (%): C 57.12, H 4.06, N 15.32. Found: C 57.29, H 4.05, N 15.33.

5-(thiophen-3-ylmethyl)-1,2,4-triazole-3-thiol (2) Yield.: 56 %; Mp.: 178–180 °C; ¹H NMR (400 MHz, DMSO-d₆) δ: 7.49 (dd, J = 4.73, 2.90 Hz, 1H-2 thiophen), 7.30 (s, 1H-5 thiophen), 7.03 (d, J = 4.88 Hz, 1H-4 thiophen), 3.89 (s, 2H, CH₂); Anal. Calcd. (%): C 42.62, H 3.58, N 21.30. Found: C 42.58, H 3.58, N 21.29.

Discussion
The structure and individuality of the obtained compounds were proved thanks to modern physical-chemical methods of analysis. Careful analysis of the ¹H NMR spectra indicates the production of new alkyl derivatives. On the spectrums, in the region typical for aromatic compounds, there were characteristic signals of the phenyl radical in the form of multiplets. Thiophene cycle signals in the form of singlet and doublet.
were also observed in the same region. A clear methylene linker signal between the thiophene and 1,2,4-triazole heterocycle was present as a singlet. Successful alkylation was indicated by the presence of a series of duplets, singlets, and multiplets, which indicated the addition of an alkyl radical along the sulfur atom, for example in compound 3-(pentylthio)-4-phenyl-5-(thiophen-3-ylmethyl)-1,2,4-triazole (3): 3.29 (s, 2H, CH$_2$), 2.97–3.06 (m, 2H, CH$_2$), 1.52 – 1.63 (m, 2H, CH$_2$), 1.23 (s, 2H, CH$_2$), 0.80 (d, J = 6.71 Hz, 3H, CH$_3$).

Conclusions

1. A number of new S-alkyl derivatives of 5-((thiophene-3-ylmethyl)-4phenyl-1,2,4-triazole-3-thiols and 5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-thiols were synthesized.

2. The individuality and the structure of the obtained compounds were proved by using a complex of modern physical-chemical methods of analysis.

Prospects for further researches. Having analyzed the results of primary pharmacological screening, some promising compounds were selected for further, more in-depth study.

Conflicts of interest: author has no conflict of interest to declare.