SYNTHESIS, PHYSICAL AND CHEMICAL PROPERTIES AND ANXIOLYTIC ACTIVITY OF 2-(4-(R-ARYLIDENAMINO)-5-METHYL-1H-1,2,4-TRIAZOLE-3-YL)THIO)ACETIC ACIDS AND THEIR SALTS

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1. Introduction

Solubility data is used to make the most important decisions from the earliest stages of drug design and throughout the process of their development [1].

In many cases, the physical properties of the pharmaceutical substances need to be modified to achieve the optimal technological characteristics that are suitable for the development of the dosage form. Different strategies are used to change the physical properties of pharmaceutical substances associated with the creation of medicinal products [2].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

It is estimated that 50% of all molecules of medicinal products used in drug therapy are administered as salts. This fact indicates that the formation of a salt of a medicinal substance is an important stage in the development of a medicinal product. Medicinal substances often have certain suboptimal physico-chemical or biopharmaceutical properties that can be overcome by creating saline versions of the drug that are developed and implemented after a rigorous research and development program [3].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

To date, a number of salts of derivatives of 1,2,4-triazole have been synthesized which exhibit a wide range of biological effects [4, 5], low toxicity [6] and have physicochemical properties that simplify the technological features of the creation of new drugs [7].
4. The field of research considering the general problem, which is described in the article

Therefore, we believe that the combinatorial synthesis of organic and inorganic salts of derivatives of 1,2,4-triazole has not only theoretical but also practical significance.

5. Formulation of goals (tasks) of article

The aim of the work is to synthesize and establish the structure of new 2 - ((4- (R-arylideneamino) -5-methyl-4H-1,2,4-triazol-3-yl) thio) acetate acids and their salts where R: 4-dimethylaminobenzylidene, 2-hydroxybenzylidene, 4-hydroxybenzylidene, 4-nitrobenzylidene and the study of the anxiolytic action of the synthesized compounds.

6. Materials and methods of research.

The physicochemical properties of the compounds obtained were investigated according to the methods presented in the State Pharmacopoeia of Ukraine. The melting temperature was determined on an OptiMelt Stanford Research Systems MPA100 (US production) automatic melting device. The elemental composition of the compounds is installed on the elemental analyzer Elemental Vario EL cube (CHNS) (standard - sulfanilamide) [8]. Chromatographic mass spectral studies were performed on a gas-liquid chromatograph of Agilent 1260 Infinity HPLC equipped with an Agilent 6120 mass spectrometer (ionization in an electrical spray (ESI), 1H NMR spectra were recorded on a Mercury 400 spectrometer, DMSO-D6 solvent, internal standard - tetramethylsilane.

The anxiolytic and anxiogenic activity of the compounds were studied in the S. Pellow test [9, 10]. The comparison drug gidazepam was administered at a dose of 7 mg / kg [11, 12].

7. Discussion

There are many methods of synthesizing 5-substituted 4-amino-1,2,4-triazole. To achieve this goal, a method for the synthesis of 5-methyl-4-amino-1,2,4-triazole-3-thiol (1a) by H. Beyer and C.-F. Kröger [13], which offers the synthesis of compound 1a by the interaction of thiocarboxy hydrazone with acetic acid, and the method of E. Hoggarth, which obtained compound 1a by reaction of methyl 2-acetate dithiocarbasinate with hydrazine hydrate [14]. Thus, 5-methyl-4-amino-1,2,4-triazole-3-thiol was obtained according to the method described by E. Hoggarth by reaction of the interaction of potassium 2-acetadithiocarbasinate with hydrazine hydrate.

As starting materials, 4- (R-arylideneamino) -5-methyl-4H-1,2,4-triazole-3-thiols (3a-d) [15, 16], where R-arylideneamino: 4-dimethylaminobenzylidene (3a), 2-hydroxybenzylid amino (3b), 4-hydroxybenzylid amino (3e), 4-nitrobenzylidene (3d).

Synthesis of 4- (R-arylidinamo) -5-methyl-4H-1,2,4-triazole-3-thiols (3a-d), in contrast to those described by the authors [15, 16], was carried out by the addition of aromatic aldehyde (4- 4-nitrobenzaldehyde (2d) to 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol (1a) in an acetic acid medium and heated to dissolve the precipitate. When cooled, substances of red (3a) and yellow (3b-d) colours were formed (Fig. 1).

After analyzing the data of 2 - ((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) acetate acid (4a), no literature was found, but the presence of the CAS identifier indicates its mention in the literature (CAS: 332898-05-2). Compound 4a is synthesized by the addition of 2-chloroacetic acid to an equivalent amount of 4-amino -5-methyl-4H-1,2,4-triazole-3-thiol (1a) pre-dissolved in a solution of isopropyl alcohol and sodium hydroxide (Fig. 2).

Preparation of 2 - ((4- (R-arylidenenamo) -5-methyl-4H-1,2,4-triazol-3-yl) thio) acetate acid (4b-e) was carried out by adding aromatic aldehyde (2a-d) to equivalent amount of 2 - ((4- (amino) -5-methyl-4H-1,2,4-triazole-3-yl) thio) acetic acid (4a) in an acetic acid medium under heating. When cooled, yellow precipitates (4b-e) were obtained (Fig. 3).

![Fig. 1. Synthesis scheme for 4-(R-arylideneamino) -5-methyl-4H-1,2,4-triazole-3-thiols (3a-d)](image-url)
Fig. 2. Scheme of synthesis of 2-((4- (amino) -5-methyl-4H-1,2,4-triazol-3-yl) thio) acetic acid (4a)

Fig. 3. Scheme of synthesis of 2-((4- (R-arylideneamino) -5-methyl-4H-1,2,4-triazol-3-yl) thio) acetate acids (4b-e)

Compound (4c) was obtained by counter-synthesis (Fig. 4). To 0.01 mole of 4- (2-hydroxybenzylideneamino) -5-methyl-4H-1,2,4-triazole-3-thiol solution (3b) pre-dissolved in 40 ml of i-propanol with the addition of an equivalent amount of sodium hydroxide, add 0.01 mol of 2-chloroacetic acid dissolved in 5 ml of purified water. Boil for 5 hours, after which a precipitate forms, which is filtered off. The compound obtained in various ways does not depress the melting point.

Thus, the acids 4a, 4b and 4d obtained under the action of ammonia hydroxide, sodium and potassium hydroxide in aqueous media were obtained the corresponding salts (5a, 5c-f) (Table 1, Fig. 5).

The salts of heavy metals were prepared by the interaction of sodium salt of 2 - ((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) acetate acid with copper, zinc, calcium and iron (5g-j) (Fig. 5).

Fig. 4. Scheme of synthesis of 2-((4- (2-hydroxybenzylideneamino) -5-methyl-4H-1,2,4-triazol-3-yl) thio) acetic acid (4c)
Physico-chemical constants of 2-((4-(R-arylideneamino)-5-(methyl)-4H-1,2,4-triazol-3-yl) thio) acetate acids and their salts

| No. | Compound | R | X | Gross formula | Melt | Yield, % |
|-----|----------|---|---|--------------|------|----------|
| 1.  | 4a       | NH₂ | H⁺ | C₅H₇N₂O₂S   | 176–178 | 71.35    |
| 2.  | 4b       | N=CH-C₆H₄N(CH₃)₂-4 | H⁺ | C₁₄H₁₀N₂O₂S | 140–142 | 65.21    |
| 3.  | 4c       | N=CH-C₆H₄OH-2 | H⁺ | C₁₄H₁₀N₂O₂S | 184–186 | 69.35    |
| 4.  | 4d       | N=CH-C₆H₄OH-4 | H⁺ | C₁₄H₁₀N₂O₂S | 134–136 | 72.31    |
| 5.  | 4e       | N=CH-C₆H₄NO₂-4 | H⁺ | C₁₄H₁₀N₂O₂S | 200–202 | 65.48    |
| 6.  | 5a       | NH₂ | NH₄⁺ | C₅H₇N₂O₂S | 204–206 | 78.56    |
| 7.  | 5b       | NH₂ | C₃H₆N₂H₂⁺ | C₁₀H₁₆N₂O₂S | 168–170 | 61.42    |
| 8.  | 5c       | NH₂ | K⁺ | C₅H₇N₂KO₂S | <240 | 69.93    |
| 9.  | 5d       | NH₂ | Na⁺ | C₅H₇Na₂O₂S | 223–225 | 71.84    |
| 10. | 5e       | N=CH-C₆H₄N(CH₃)₂-4 | Na⁺ | C₁₄H₁₀Na₂O₂S | >240 | 71.15    |
| 11. | 5f       | N=CH-C₆H₄OH-4 | Na⁺ | C₁₄H₁₀Na₂O₂S | >240 | 74.35    |
| 12. | 5g       | NH₂ | 1/2Cu⁺² | C₁₀H₁₄Cu₂O₄S₂ | 238–240 | 74.31    |
| 13. | 5h       | NH₂ | 1/2Zn⁺² | C₁₀H₁₄Zn₂O₄S₂ | <240 | 60.04    |
| 14. | 5i       | NH₂ | 1/2Ca⁺² | C₁₀H₁₄Ca₂O₄S₂ | 212–214 | 61.87    |
| 15. | 5j       | NH₂ | 1/3Fe⁺³ | C₁₅H₂₁Fe₂O₆S₃ | 183–185 | 59.84    |

Fig. 5. Scheme for the synthesis of 2-((4-(R-arylideneamino)-5-methyl-4H-1,2,4-triazol-3-yl) thio) acetate acids salts (5a-j)
8. Results of the research

The composition and structure of all compounds synthesized by us are determined using elemental analysis and physico-chemical methods of analysis: 1H-NMR spectroscopy, the HPLC-MS method.

Elemental analysis of compounds was conducted at the Department of Toxicological and Inorganic Chemistry of the Zaporizhzhya State Medical University in the laboratory of elemental analysis of organic compounds. Determination of the elemental composition of compounds was carried out using the elementar analyzer ELEMENTAR vario EL cube.

Previously, it was shown that 2-(4-amino-5-methyl-1,2,4-triazol-3-ylthio) acetic acid showed high anxiolytic activity, and the synthesis of 2-((2-hydroxybenzylidene) amino) -5 methyl-1,2,4-triazol-3-ylthio) acetic acid should lead to the creation of highly effective anxiolytics [17, 18].

In this way, the anxiolytic properties of acids 4c, 4e and salts 5e, 5f (Table 2) were studied.

Table 2

| Compound/group | The latent period of entry to the sleeves, s | Staying | Number of sleeves visits |
|---------------|----------------------------------------|---------|-------------------------|
| Control       | 16.14±1.03                             | 120.71±11.94* | 183.24±8.72, 49.86±4.85 | 1.71±0.55, 2.43±0.65 |
| Gidazepam     | 24.57±3.70*                            | 120.71±11.94* | 62.71±4.78*               | 0.29±0.18*   |
| Control       | 16.14±1.03                             | 120.71±11.94* | 183.24±8.72, 49.86±4.85 | 1.71±0.55, 2.43±0.65 |
| 4c            | 2.43±0.78*                             | 13.86±6.16   | 268.14±6.23*              | 0.29±0.18*   |
| 4e            | 3.29±0.47*                             | 9.57±2.49*   | 260.00±5.10*              | 0.29±0.18*   |
| 5f            | 3.86±0.91                              | 37.29±9.28*  | 255.29±11.19*             | 0.29±0.18*   |
| 5e            | 4.43±0.30                              | 124.71±13.26*| 94.86±11.86*              | 0.29±0.18*   |

According to the results of the research, it was found that in the conditions of the S. Pellow test after the introduction of the studied compounds there were no substances with anxiolytic action, which would be significantly higher than the reference drug gidazepam. However, sodium salt 5e in its action is approaching to gidazepam. And the rest of the studied substances have a pronounced anxiogenic effect.

Experimental part.

2-((4-amino-5-methyl-1,2,4-triazol-3-ylthio)acetic acid (4a).

To the 0.01 mol of 2-((4-amino-5-methyl-1,2,4-triazole-3-thiol, an equivalent amount of sodium hydroxide and 40 ml of i-propyl alcohol are added, dissolved under heating, 0.01 mol of 2-chloroacetic acid pre-dissolved in a minimum amount of water, boiled for 5 hours to an acid medium, the solution is evaporated, and the dry residue is recrystallized from water.

Compound 4a.

1H-NMR (400 MHz, DMSO-d6, δ=ppm): 2.45 (3H, s), 3.74 (2H, s), 6.29 (2H, s). CHNS elemental analysis calculated for (C10H12N2O2S): found C% 31.72, H% 4.27, N% 29.89, S% 17.02; calculated C% 31.91, H% 4.28, N% 29.77, S% 17.04. The peak of a quasi-molecular ion [MH]+ 189

2-((R-arylideneamino)-5-methyl-1H-1,2,4-triazol-3-yl) thio)acetic acid (4b-e).

To the equivalent of 2 - ((R-amino) -5-methyl-1H-1,2,4-triazol-3-yl) thio) acetic acid (4a) (0.01 mol) in an acetic acid medium under heating added aromatic aldehyde (2a-d) (0.01 mol). When cooled, yellow precipitates (4b-e) were isolated, filtered, washed with ethanol and dried.

Compound 4b.

1H-NMR (400 MHz, DMSO-d6, δ=ppm): 2.37 (3H, s), 2.93 (6H, s), 4.06 (2H, s), 6.68 (2H, m), 7.35 (2H, m), 9.15 (1H, s). CHNS elemental analysis calculated for (C10H12N2O2S): found C% 52.49, H% 5.40, N% 21.86, S% 10.00; calculated C% 52.65, H% 5.37, N% 21.93, S% 10.04. The peak of a quasi-molecular ion [MH]+ 320

Compound 4c.

1H-NMR (400 MHz, DMSO-d6, δ=ppm): 2.35 (3H, s), 3.95 (2H, s), 7.09 (1H, m), 7.19-7.37 (2H, m), 7.56 (1H, m), 9.49 (1H, s), 10.45 (1H, s). CHNS elemental analysis calculated for (C12H16N2O2S): found C% 49.01, H% 4.13, N% 19.27, S% 10.93; calculated C% 49.31, H% 4.14, N% 19.17, S% 10.97. The peak of a quasi-molecular ion [MH]+ 293

Compound 4d.

1H-NMR (400 MHz, DMSO-d6, δ=ppm): 2.25 (3H, s), 3.89 (2H, s), 7.17 (2H, m), 7.42 (2H, m), 9.48 (1H, s), 10.42(1H, s). CHNS elemental analysis calculated for (C12H16N2O2S): found C% 49.11, H% 4.11, N% 19.09, S% 10.96; calculated C% 49.31, H% 4.14, N% 19.17, S% 10.97. The peak of a quasi-molecular ion [MH]+ 293
2-((4- (2-hydroxybenzylidene) -5-methyl-4H-1,2,4-triazol-3-yl) thio) -acetic acid (4c)

To 0.01 mol of 4- (2-hydroxybenzylideneamino) -5-methyl-4H-1,2,4-triazole-3-thiol (2b), pre-dissolved in 40 ml of i-propanol with the addition of an equivalent amount of sodium hydroxide, 0.01 mol of 2-chloro-acetate acid, dissolved in 5 ml of purified water. Boil for 5 hours, after which a precipitate forms, which is filtered off.

Compound 4c.

¹H NMR (400 MHz, DMSO-d₆, δ=ppm): 2.39 (3H, s), 3.94 (2H, s), 7.10 (1H, m), 7.22-7.42 (2H, m), 7.59 (1H, m), 9.52 (1H, s), 10.39 (1H, s). CHNS elemental analysis calculated for (C₅H₃N₂O₂S): found C% 49.01, H% 4.13, N% 19.27, S% 10.93; calculated C% 49.31, H% 4.14, N% 19.17, S% 10.97. The peak of a quasi-molecular ion [MH]+ 293

Ammonium salt of 2-((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) -acetic acid (5a)

To a solution of 0.01 mol of 2-((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) acetic acid (4a), add 50 ml of 25% ammonia solution and mix to dissolve. The solution is filtered, the filtrate is evaporated. Obtain crystalline compounds, white, easily soluble in water, difficult to dissolve in n-butanol and chloroform. For analysis, the compounds are recrystallized from i-propanol.

Compound 5a.

CHNS elemental analysis calculated for (C₅H₃N₂O₂S): found C% 49.46, H% 5.38, N% 34.39, S% 15.70; calculated C% 29.26, H% 5.40, N% 34.12, S% 15.62.

Sodium and potassium salts of 2-((4-R-5-methyl-4H-1,2,4-triazol-3-yl) thio) -acetic acid (5c, 5d-f).

To 0.01 mol of the corresponding 2-((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) acetate acid (4a) in 30 ml of distilled water add 0.01 mol sodium hydroxide or potassium hydroxide and stir to dissolve. The solution is filtered, the filtrate is evaporated. Obtain crystalline compounds, white, easily soluble in water, difficult to dissolve in chloroform.

Compound 5b.

0.01 mol of piperidine is added to 0.01 mol of 2-((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) acetic acid (4a) in 30 ml of i-propanol and heat to dissolve. The solution is filtered, the filtrate is left at room temperature until the solvent evaporates. Obtain crystalline compounds of white colour, readily soluble in water, difficult to dissolve in chloroform.

Compound 5b.

CHNS elemental analysis calculated for (C₅H₃N₂O₂S): found C% 43.76, H% 6.98, N% 25.49, S% 11.65; calculated C% 43.94, H% 7.01, N% 25.62, S% 11.73.

Cu(II), Zn(II), Ca(II) and Fe(III) salts of 2-((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) -acetic acid (5g-j)

To the 0.01 mol of water solution of sodium salt of 2- ((4-amino-5-methyl-4H-1,2,4-triazol-3-yl) thio) acetic acid (5d) was added an equivalent amount of aqueous potassium (II ), zinc (II), calcium (II) and iron (III) chloride in 5 ml of distilled water, and stirred for 2 hours, the precipitate was filtered and washed with distilled water.

9. Conclusions

1. A series of new 2- ((4- (R-arylidene) -5-methyl-4H-1,2,4-triazol-3-yl) thio) acetic acids were synthesized.

2. The structure of synthesized compounds is established using modern physico-chemical methods of analysis.

3. Some physical and chemical properties of the obtained substances are investigated.

4. Under the conditions of the S. Pellow test after the introduction of the studied compounds, no substances with anxiolytic action were detected, which would significantly exceed the reference drug gidazepam.

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