SYNTHESIS OF POTENTIAL ANTIEXUDATIVE PREPARATIONS FOR 2-((4-AMINO-5-(FURAN-2-IL)-1,2,4-TRIAZOLE-(4H)-3-YL)-SULFANYL)-N-ACETAMIDE SERIES

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1. Introduction
The value of nonsteroidal anti-inflammatory drugs (NSAIDs) in modern therapies of various diseases cannot be overestimated. Non-treatment of inflammatory processes often leads to prolonged incapacity to work and even to the disability of the population [1, 2]. At the same time, a significant spectrum of existing side effects of NSAIDs can impair the quality of life of patients [3]. Therefore, today there is an active search for new "small" molecules with a clear anti-inflammatory action, suitable for creating on their basis more effective NSAIDs with a higher safety profile and selectivity of action [4, 5].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues
Thanks to the fundamental research in the field of organic synthesis and pharmaceutical chemistry, there is a modern concept for the creation of new pharmaceutical products. One of the basic principles of which is the synthesis of structures containing pharmacoplatinic fragments, which allows to predict the pharmacological properties of substances at the stage of planning their synthesis. Therefore, the design of the presented study consisted in the implementation of the concept of structural modification of the "triazol" matrix in order to achieve the required pharmacological profile, namely anti-inflammatory action [6, 7].

3. Analysis of recent studies and publications in which a solution of the problem and which draws on the author
Derivatives of 1,2,4-triazole-3-thione have a significant pharmacological potential, which is primarily due to the low toxicity of this class of compounds, as well as the ability to influence various biological targets [8, 9]. A significant number of studies [10, 11] is devoted to the search for derivatives of 1,2,4-triazole-3-thione substances with analgesic and anti-inflammatory activity, in some cases selectivity of inhibitory activity on cyclooxygenase-2 and also on lipooxygenase-5 [12, 13].

Previously, we carried out the synthesis of acetamide derivatives of 5-(pyridine-2(3)(4)-yl)-4-amino-3-thio-4H-1,2,4-triazole (Fig. 1) with anti-inflammatory activity [14, 15]. One of the main pharmacofore fragments of the modern COX-2 highly selective inhibitor - rofecoxib is the hetercycle furan. In addition, the positive influence of the furan ring on anti-inflammatory activity was established by Ukrainian scientists [16]. Therefore, in the presented study, we decided to synthesize 5-furanyl-substituted 4-amino-3-thio-1,2,4-trisole as the starting reagent in order to increase the anti-inflammatory activity.
Drugs tenoxicam and meloxicam contain carboxamide residue in their structure [17], and compounds with significant anti-inflammatory action were found among acetamide derivatives [18, 19]. Therefore, the next direction of modification is the synthesis of 4-amino-3-thio-5-(furan-2-yl)-1,2,4-triazole arylacetamides (Fig. 1).

4. Formulation of goals (tasks) of Article

The aim of the study was to synthesize new potential biologically active substances of derivatives of 2-((4-amino-5-(furan-2-yl)-1,2,4-triazole(4H)-3-yl)) -sulfanyl)-N-acetamides, determination of their structure and physico-chemical properties, evaluation of their anti-exudative activity (AEA) and discussion of the relationship between structure activity.

5. Statement of the basic material of the study (methods and objects) with the justification of the results

To establish the prospects of synthesis and optimization of further pharmacological screening, we made a preliminary forecast of the biological activity of the compounds planned for synthesis using the computer program PASS [20]. 4-amino-3-thio-5-(pyridine-2(3- yl)-4H-1,2,4-triazole acetamides were selected for synthesis for which an analgesic and anti-inflammatory effect was predicted (Ra ≥ 0.50).

All solvents and reagents were obtained from commercial sources. The melting points (°C) were determined using the Kofler device. The 1H NMR spectrum was recorded on a Bruker Varian Mercury (400 MHz) device in DMSO-d6, an internal TMS standard. The chromatographic mass spectrometry analysis was performed on a PE SCIEX API 150EX chromatograph. Elemental analysis was performed on a micro-analyzer Euro Vector EA-3000 (Eurovector SPA, Redavalle, Italy). The content of the elements was within ± 0.4 % of the theoretical values.

4-amino-5-(furan-2-yl)-4H-1,2,4-triazole-3-thione (1) synthesis was carried out according to the method described in the literature [21]

General method of synthesis of 2-((4-amino-5-(furan-2-yl)-1,2,4-triazole(4H)-3-yl))-sulfanyl)-N-acetamides (3.1-21). To a solution of 0.002 mol of 2-(4-amino-5-(furan-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (1) in 20 ml of ethanol, 20 ml of 0.002 M aqueous KOH solution was added. A 0.002 mol solution of the corresponding chloroacetamide (2) was added with stirring to the resulting solution. The reaction mixture was heated to reflux for 1 hour, then poured into 200 ml of distilled water. The isolated precipitate is filtered off, washed with water, dried, recrystallized from ethanol.

Antiexudative activity was studied on models of formalin swelling of the paws in rats. The studies were conducted on 138 white male rats weighing 180–200 g. Edema was modeled using subplanetary administration in the posterior right paw of 0.1 ml of 2 % formalin solution. The volume of the paw was measured using a digital plethysmometer prior to the administration of the drugs and on the background of maximal edema 4 hours after the formalin injection simulation [22, 23]. The studied compounds 2-((4-amino-5-(furan-2-yl)-4H-1,2,4-triazole-3-yl) sulfanyl)-N-acetamide were administered to test animals at a dose of 10 mg / kg, reference diclofenac sodium at a dose of 8 mg / kg (D-Na) [24].

An increase in edema was expressed in milliliters. Percent inhibition of inflammation was calculated by the formula:

\[
\text{% of inhibition of inflammation} = \frac{V_c - V_e}{V_c} \cdot 100 \%
\]

where \(V_c\) – volume of foot in control minus the output volume of this foot before swelling, ml;
\( V_r \) – volume of the foot that is swollen in the experiment minus the output volume of this foot, ml.

Statistical processing of the obtained results was carried out using the methods of variation statistics using the t-criterion of the Student using computer programs STATISTIS 7.0, StatPlus 2009 and MS Excel 2007.

The rats were kept under vivarium in accordance with the rules of humane treatment of laboratory animals. The research was conducted in compliance with the principles of Directive 210/63 / EU of the European Parliament and the Council of the European Union “On the Protection of Animals Used for Scientific Purposes” (Brussels, 2010) and “General Ethical Principles of Animals Protection from Cruel Treatment” No. 3477 of February 21, 2006, as amended, and the Order of the Ministry of Youth and Sport of Ukraine “On Approval of the Procedure for the Conduct by Scientific Institutes of Experiments on Animals” No. 249 dated March 1, 2012.

6. Results and their discussion

Synthesis of the starting 4-amino-3-thio-5-(furan-2-yl)-4H-1,2,4-triazole-3-thiol (1) was carried out using the one-pot method described earlier [21]. Reactions were started with furan-2-carboxylic acid hydrazide with carbon disulfide in ethyl alcohol in the presence of potassium hydroxide to form potassium dithiocarbazinate intermediate, followed by cyclical condensation with excess hydrazine, yielding tiotriazole (1) as a white solid with a good yield. Hydrazide of furan-2-carboxylic acid, in turn, was synthesized from the corresponding ether of furan-2-carboxylic acid by reaction with hydrazine hydrate.

The alkylation of 2-((4-amino-5-((furan-2-yl)-4H-1,2,4-triazole-3-thione) (1) was carried out by boiling with N-aryl-substituted α-chloroacetamides (2) in ethanol in the presence of KOH (Fig. 2).

Acetamides (3.1-3.21) were obtained with satisfactory yields (Tab. 1). Purification of the synthesized compounds was carried out by crystallization from ethanol, resulting in white crystalline substances with clear melting temperatures. According to chromatomass spectrometry, products synthesized are individual substances.

![Fig. 2. Synthesis of 2-((4-amino-5-((furan-2-yl)-1,2,4-triazole(4H)-3-yl) -sulfanyl)-N-acetamides (3.1-3.21)](image)

Table 1

| No. | R         | Yield, % | Melt, °C | Gross formula | M.m.   | Calculated, % | Found, % | [M+H]+ |
|-----|-----------|----------|----------|---------------|--------|---------------|----------|--------|
|     |           |          |          |               |        | C             | N        | S      |        |
| 1   | 2         | 3        | 4        | 5             | 6      | 7             | 8        | 9      | 10     |
| 3.1 | H         | 80       | 156-8    | C_{13}H_{18}N_{2}O_{7}S | 315.35 | 53.32         | 53.11    | 22.25  | 10.17  | 10.12  | 316.2 |
| 3.2 | 4-Et      | 76       | 212-4    | C_{13}H_{18}N_{2}O_{7}S | 343.40 | 55.96         | 55.56    | 20.39  | 9.34   | 9.30   | 344.4 |
| 3.3 | 4-Bu      | 83       | 145-8    | C_{13}H_{21}N_{2}O_{7}S | 371.45 | 58.20         | 58.05    | 18.85  | 8.63   | 8.60   | 372.2 |
| 3.4 | 3-OMe     | 84       | 145-7    | C_{13}H_{19}N_{2}O_{7}S | 345.37 | 52.16         | 52.01    | 20.28  | 9.28   | 9.22   | 346.2 |
| 3.5 | 4-OMe     | 84       | 211-3    | C_{13}H_{19}N_{2}O_{7}S | 345.37 | 52.16         | 52.03    | 20.28  | 9.28   | 9.24   | -      |
| 3.6 | 4-OEt     | 76       | 135-7    | C_{13}H_{19}N_{2}O_{7}S | 359.40 | 53.47         | 53.35    | 19.49  | 8.92   | 8.88   | 360.2 |
The structure of synthesized acetamides 3.1-3.21 was confirmed by data from elemental analysis, $^1$H NMR spectroscopy and chromatographic mass spectrometry (Tab. 1, 2). $^1$H NMR spectra of compounds 3.1-3.21 are characterized by the presence of: signals of the phosphorus residue protons in the position of 5 triazolacycles, which resonate in the form of two doublets in the sites 8.00–7.90 and 7.25–7.15 (H-5, H-3, respectively), as well as the triplet H-4 at 6.72–6.70 ppm; the singlet signal of the proton group SCH2 at 4.28–4.12 ppm; a singlet of NH-acetamide residue in a weak field (11.00–9.21 ppm). Signals of protons of aryl radicals in terms of intensity, multiplicity, and location on the spectrum correspond to the placement of substituents.

The results of the study of anti-exudative activity of substances of synthesized acetamides 3.1-3.21 are presented in Tab. 3. To study the AEA, studies were carried out to compare the effects of 2-((4-amino-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl) sulfanyl derivatives-N-acetamide in a dose of 10 mg / kg with a reference diclofenac sodium in a dose of 8 mg / kg (D-Na) [24].

|   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| 3.7 | 3-CF$_3$ | 78 | 179-81 | C$_{15}$H$_{12}$F$_3$N$_5$O$_2$S | 383.34 | 47.00 | 18.27 | 8.36 |   |   |
| 3.8 | 3-Cl | 88 | 218-20 | C$_{14}$H$_{12}$ClN$_4$O$_2$S | 349.80 | 48.07 | 19.64 | 9.17 |   |   |
| 3.9 | 4-Cl | 85 | 188-90 | C$_{14}$H$_{12}$ClN$_4$O$_2$S | 349.80 | 48.07 | 19.64 | 9.17 |   |   |
| 3.10 | 3-F | 78 | 200-2 | C$_{14}$H$_{12}$FN$_3$O$_2$S | 333.34 | 50.44 | 21.01 | 9.62 |   |   |
| 3.11 | 4-F | 83 | 123-5 | C$_{14}$H$_{12}$FN$_3$O$_2$S | 333.34 | 50.44 | 21.01 | 9.62 |   |   |
| 3.12 | 4-NO$_2$ | 85 | 118-9 | C$_{14}$H$_{12}$NO$_2$S | 360.35 | 46.66 | 23.32 | 8.90 | 361.2 |
| 3.13 | 3,4-diMe | 84 | 184-6 | C$_{14}$H$_{12}$N$_3$O$_2$ | 343.40 | 55.96 | 20.39 | 9.34 |   |   |
| 3.14 | 2-Me, 3-Cl | 85 | 206-8 | C$_{14}$H$_{12}$ClN$_2$O$_2$ | 363.82 | 49.52 | 19.25 | 8.81 |   |   |
| 3.15 | 3-Cl, 4- Me | 76 | 116-8 | C$_{14}$H$_{12}$ClN$_2$O$_2$ | 363.82 | 49.52 | 19.25 | 8.81 |   |   |
| 3.16 | 2,4-diCl | 86 | 146-3 | C$_{14}$H$_{12}$ClN$_2$O$_2$ | 384.24 | 43.76 | 18.23 | 8.35 |   |   |
| 3.17 | 3,4-diCl | 80 | 248-50 | C$_{14}$H$_{12}$ClN$_2$O$_2$ | 384.24 | 43.76 | 18.23 | 8.35 |   |   |
| 3.18 | 2-Cl, 5-CF$_3$ | 88 | 170-2 | C$_{15}$H$_{12}$ClF$_3$N$_2$O$_2$S | 417.79 | 43.12 | 16.76 | 7.67 |   |   |
| 3.19 | 3-COMe | 76 | 175-4 | C$_{16}$H$_{15}$N$_2$O$_2$S | 357.39 | 53.77 | 19.60 | 8.97 | 358.2 |
| 3.20 | 2-COO Et | 78 | 146-8 | C$_{17}$H$_{16}$N$_2$O$_2$S | 387.41 | 52.70 | 18.08 | 8.28 | 388.2 |
| 3.21 | 4-COO Et | 78 | 172-3 | C$_{17}$H$_{16}$N$_2$O$_2$S | 387.41 | 52.70 | 18.08 | 8.28 | 388.2 |
Table 2
Data of $^1$H NMR spectra of synthesized 2-((4-amino-5-(furan-2-yl)-1,2,4-triazol (4H)-3-yl)-sulfanyl)-N-acetamides (3.1-3.21) chemical shift, δ, ppm

| Compound | NH, s, 1H | Furan 1H, H-5 | Ar-H | Furan 2H, s, 2H | SCH$_3$, s, 2H | Other protons |
|----------|-----------|---------------|------|----------------|----------------|---------------|
| 3.1      | 9.21      | 7.90          | 7.59–7.27 m, 4H, H-2’,3’-5’,6’ | 7.22 | 6.70 | 6.21 | 4.15 | – |
| 3.2      | 10.19     | 7.91          | 7.33 d, 2H, J=8.4, H-3’,5’ | 7.22 | 6.72 | 6.22 | 4.13 | 3.05 q, 2H, CH$_3$ 0.98 t, 3H, CH$_3$ |
| 3.3      | 10.12     | 7.90          | 7.51 d, 2H, H-3’,5’ | 7.22 | 6.70 | 6.22 | 4.16 | 2.50 t, 2H, CH$_2$ 1.54–1.50 q, 2H, CH$_2$ 1.31–1.25-m, 2H, CH$_2$ 0.8 t, 3H, CH$_3$ |
| 3.4      | 10.21     | 7.90          | 6.90 s, 1H, H-2’ | 7.61–7.51 m, 3H, H-4’,5’,6’ | 7.25 | 6.70 | 6.20 | 4.19 | 3.75 s, 3H, OCH$_3$ |
| 3.5      | 10.21     | 7.90          | 7.48 d, 2H, H-3’,5’ | 6.99 d, 2H, H-2’,6’ | 7.25 | 6.71 | 6.22 | 4.12 | 3.72 s, 3H, OCH$_3$ |
| 3.6      | 10.22     | 7.90          | 7.58 d, 2H, H-3’,5’ | 7.05 d, 2H, H-2’,6’ | 7.25 | 6.71 | 6.22 | 4.13 | 4.02 q,2H, OCH$_3$ 1.15 t, 3H, SH$_3$ |
| 3.7      | 10.69     | 7.90          | 8.08 s, 1H, H-2’ | 7.77 d, 1H, H-4’ | 7.59 t, 1H, H-5’ | 7.42 d, 1H, H-6’ | 7.25 | 6.70 | 6.20 | 4.19 | – |
| 3.8      | 10.55     | 7.90          | 7.80 t, 1H, H-5’ | 7.45 d, 1H, H-4’ | 7.35 s, 1H, H-2’ | 7.14 d, 1H, H-6’ | 7.25 | 6.71 | 6.22 | 4.17 | – |
| 3.9      | 10.48     | 7.90          | 7.62 d, 2H, H-3’,5’ | 7.38 d, 2H, H-2’,6’ | 7.25 | 6.71 | 6.21 | 4.16 | – |
| 3.10     | 10.56     | 7.90          | 7.37–7.22 m, 3H, H-4’,5’,6’ | 6.98–6.82 m, 1H, H-2’ | 7.59 | 6.71 | 6.25 | 4.17 | – |
| 3.11     | 10.39     | 7.90          | 7.61–7.58 m, 2H H-3’,5’ | 7.18–7.13 m, 2H, H-2’,6’ | 7.25 | 6.71 | 6.19 | 4.15 | – |
| 3.12     | 11.00     | 7.90          | 7.59–7.29 m, 4H | 7.25 | 6.71 | 6.19 | 4.27 | – |
| 3.13     | 10.16     | 7.90          | 7.35–7.24 m, 3H | 7.15 | 6.72 | 6.19 | 4.17 | 2.18 s, 6H, 2×CH$_3$ |
| 3.14     | 9.96      | 7.91          | 7.37–7.18 m, 4H, H-4’,5’,6’, furan H-3 | 6.72 | 6.21 | 4.17 | 2.23 s, 3H, SH$_3$ |
| 3.15     | 10.44     | 7.90          | 7.78 s, 1H, H-2 | 7.35–7.28 m, 2H, H-5’,6’ | 7.25 | 6.71 | 6.19 | 4.15 | 2.27 s, 3H, SH$_3$ |
| 3.16     | 10.65     | 7.62          | 7.97 d, 2H, H-5’,6’ | 7.56 s, 1H, H-3’ | 7.24 | 6.71 | 6.21 | 4.16 | – |
| 3.17     | 10.65     | 7.97          | 7.90 s, 1H, H-5’ | 7.48 d, 1P, H-6’ | 7.24 | 6.71 | 6.21 | 4.17 | – |
| 3.18     | 10.22     | 7.91          | 8.29 d, 1H, H-6’ | 7.77 d, 1H, H-3’ | 7.55 d, 1H, H-4’ | 7.25 | 6.71 | 6.22 | 4.26 | – |
| 3.19     | 10.56     | 7.92          | 7.61–7.51 m, 3H, H-4’,5’,6’ | 6.90 s, 1H, H-2’ | 7.25 | 6.71 | 6.21 | 4.12 | 3.79 s, 3H, SOCH$_3$ |
| 3.20     | 11.00     |               | 8.30 d, 1H, H-3’ | 7.93–7.90 m, 2H, furan H-5, H-6’ | 6.74 t, 1H, H-4’ | 7.33–7.17 m, 2H, furan H-3, H-5’ | 6.71 | 6.22 | 4.28 | 4.06, q., 2H, OCH$_2$ 1.15 t, 3H, CH$_3$ |
| 3.21     | 10.72     |               | 8.30 d, 1H, H-3’ | 7.99–7.90 m, 2H, furan H-5, H-6’ | 6.74 t, 1H, H-4’ | 7.33–7.17 m, 2H, furan H-3, H-5’ | 6.70 | 6.21 | 4.28 | 4.01, q., 2H, OCH$_2$ 1.14 t, 3H, CH$_3$ |
Antixedudative activity of 2-((4-amino-5-(furan-2-yl))-1,2,4-triazolo(4H)-3-yl)-sulfanyl)-N-acetamides (3.1-3.21) (n=6)

| Compound | R | Initial paw volume | Volume of the paw 4 hours after the edema modeling | Suppression of edema, % |
|----------|---|--------------------|-----------------------------------------------|--------------------------|
| Control path|  | 0.58±0.012 | 0.76±0.032* | 0 |
| 3.1 | H | 0.75±0.04 | 0.78±0.016 | 81.5 |
| 3.2 | 4-Et | 0.47±0.05 | 0.54±0.07 | 61.1 |
| 3.3 | 4-Bu | 0.57±0.03 | 0.81±0.02 | 0 |
| 3.4 | 3-OMe | 0.64±0.04 | 0.75±0.03 | 37.0 |
| 3.5 | 4-OMe | 0.76±0.03 | 0.81±0.015 | 70.3 |
| 3.6 | 4-OEt | 0.61±0.03 | 0.83±0.05 | 0 |
| 3.7 | 3-CF3 | 0.78±0.015 | 0.94±0.024 | 9.1 |
| 3.8 | 3-Cl | 0.53±0.08 | 0.76±0.05 | 0 |
| 3.9 | 4-Cl | 0.54±0.02 | 0.62±0.01 | 55.5 |
| 3.10 | 3-F | 0.53±0.03 | 0.68±0.027 | 16.7 |
| 3.11 | 4-F | 0.55±0.01 | 0.64±0.02 | 50.0 |
| 3.12 | 4-NO2 | 0.51±0.02 | 0.58±0.04 | 62.9 |
| 3.13 | 3,4-diMe | 0.58±0.03 | 0.79±0.025 | 0 |
| 3.14 | 2-Me, 3-Cl | 0.56±0.05 | 0.66±0.027 | 44.0 |
| 3.15 | 3-Cl, 4-Me | 0.53±0.015 | 0.73±0.03 | 0 |
| 3.16 | 2,4-diCl | 0.51±0.03 | 0.62±0.01 | 38.8 |
| 3.17 | 3,4-diCl | 0.54±0.02 | 0.7±0.023 | 11.0 |
| 3.18 | 2-Cl, 5-CF3 | 0.52±0.02 | 0.64±0.01 | 33.3 |
| 3.19 | 3-COMe | 0.50±0.016 | 0.58±0.02 | 53.0 |
| 3.20 | 2-COOEt | 0.69±0.02 | 0.88±0.015 | 0 |
| 3.21 | 4-COOEt | 0.56±0.014 | 0.67±0.03 | 38.9 |
| D-Na | 0.57±0.03 | 0.67±0.051 | 44 |

Note: * – reliability deviation regarding control pathology, p<0.01; ** – reliability deviation regarding control pathology, p<0.05; *** – reliability deviation regarding control pathology, p<0.001; — reliability deviation regarding D-Na, p<0.01; — reliability deviation regarding D-Na, p<0.05; — reliability deviation regarding D-Na, p<0.001; # – reliability deviation regarding the initial volume of the paw, p<0.01; ## – reliability deviation regarding the initial volume of the paw, p<0.05; ### – reliability deviation regarding the initial volume of the paw, p<0.01; n – number of animals in the group

Among twenty one compounds synthesized by us, 3.1–3.21, fifteen found anti-exudative activity. Location of compounds 3.1–3.21 by AEA could be:

3.1>5.12>2.9>19>11>14>D-Na>21>16>4>18>10>17>7>8=13=15=3=6=20, that percentage (%) regarding AEA:

81.5>70.3>62.9>61.1>55.5>53.0>50>44>44>38.9>38.8>37>33.3>16.7>11>9.1>0=0=0=0=0=0.

Compound 3.1 with an uncharged phenyl radical was the leader of the study: it significantly reduced swelling by 81.5 %, which is almost twice the effect of the reference sodium diclofenac (44 %).

Sufficiently high rates of edema suppression showed compounds with methoxy radicals in 3 (3.4) and 4 (3.5) positions of the phenyl cycle: 37 % and 70.3 %, respectively. While the 4-ethoxy derivative (3.6) did not demonstrate any anti-exudative activity at all. The 3-acetyl substituent helps to suppress the strain to 53 % (3.19), which exceeds the sodium diclofenac score by 9 % (Table 3). Also, high AEA ratios in compounds with ethyl radicals (3.2) – 61.1 % and nitro group (3.12) – 62.9 %.

Differently, the anti-exudative activity of fluorinated derivatives was found: compounds with trifluoroethyl- (3.7) and 3-fluorophenyl (3.10) radicals had a slight suppression of edema – 9.1 % and 16.3 %, respectively. At the same time, the presence of 4-fluorophenyl radical (3.11) led to suppression of edema by 50 %, which even exceeds the value of the reference drug.

It was not possible to find clear regularities in the case of chlorinated derivatives: only the compound with 4-chlorophenyl (3.9) radical reduced the swelling by 55.5 %, while the 3-Cl-substituted derivative (3.8) did not completely reduce it (0 %). Dichloro-substituted compounds (3.16) and (3.17) have mean values of anti-exudative activity (38.8 and 11.0 %, respectively).

There was no inhibition by the compound with the following substituents in the phenyl ring: 4-butyl (3.3), 4-ethox (3.6), 3-chloro (3.8), 3,4-dimethyl (3.13), 3-chloro, 4-methyl (3.15), 2-ethylacetyl (3.20).

Consequently, eight of the twenty-one derivatives of 2-((4-amino-5-(furan-2-yl))-1,2,4-triazole(4H)-3-yl)-sulfanyl)-N-acetamide derivatives have anti-exudative activity greater (3.1, 3.2, 3.5, 3.9, 3.11, 3.12, 3.19) or at the reference (3.14) level.

7. Conclusions from the conducted research and prospects for further development of this field

1. Twenty-one new compounds were synthesized in the series of derivatives of 2-((4-amino-5-(furan-2-yl))-
4H-1,2,4-triazol-3-yl) sulfanyl)-N-acetamides, their physical and chemical characteristics have been established. The structure of the synthesized compounds is confirmed by data from elemental analysis, $^1$H NMR spectra and chromatographic mass spectrometry.

2. All synthesized compounds were investigated for anti-exudative activity on the model of formalin swelling of the paw in rats. Fifteen compounds have shown anti-exudative activity. Among the leaders were identified seven compounds: 3,1, 3,2, 3,5, 3,9, 3,11, 3,12, 3,19, which significantly suppressed swelling by 81.5%; 61.1%; 70.3%; 55.5%; 62.9%; 53.0%, respectively, and significantly exceeded the activity of sodium diclofenac (44%).

3. After analyzing of the relationship between "structure-anti-inflammatory activity" we consider the introduction into the molecule of 2- ((4-amino-5- (furan-2-yl) -4H-1,2,4-triazol-3-yl) sulfanyl)-N-acetanilides in the fourth position of the phenyl residue of the fluorene, chlorine, methoxy, ethyl, nitro and in the third position of the acetyl radicals is expedient and increases the anti-exudative activity.

Prospects: To study new synthesized compounds of 2-((4-amino-5- (furan-2-yl) -4H-1,2,4-triazol-3-yl) sulfanyl)-N-acetamide 3,1-3,21 considering their potential analgesic activity.

References

1. Ignatov Yu. D., Kukov G. V., Mazurov V. I. Klinicheskaia farmakologiia nesteroidnykh protivovospalitelnykh sredstv. Moscow: GEOTAR, 2010. 258 p.
2. Karateev A. E. Primenenie NPVP: skhematicheskii podkhod // Russkii meditsinskii zhurnal. 2012. Issue 25. P. 1558.
3. Demetskaia A. Nezheletelnye lekarstvennye reaktii: NPVP // Farmasevt praktik. 2017. Issue 2. P. 28–29.
4. Küçükgüzel Ş. G., Çika-Sızgın P. Recent advances bioactive 1,2,4-triazole-3-thiones // European Journal of Medicinal Chemistry. 2015. Vol. 97. P. 830–870. doi: http://doi.org/10.1016/j.ejmech.2014.11.033
5. Novel 1H-1,2,3-; 2H-1,2,3-; 1H-1,2,4- and 4H-1,2,4-triazole derivatives: a patent review (2008 – 2011) / Ferreira V. F., da Rocha D. R., da Silva F. C., Ferreira P. G., Boechat N. A., Magalhães J. L. // Expert Opinion on Therapeutic Patents. 2013. Vol. 23. Issue 3. P. 319–331. doi: http://doi.org/10.1517/13543776.2013.749862
6. Kharb R., Sharma P. C., Yar M. S. Pharmacological significance of triazole scaffold // Journal of Enzyme Inhibition and Medicinal Chemistry. 2010. Vol. 26, Issue 1, P. 1–21. doi: http://doi.org/10.3109/14756360903524304
7. 1,2,4-Triazole-based benzothiazole/benzoxazole derivatives: Design, synthesis, p38a MAP kinase inhibition, anti-inflammatory activity and molecular docking studies / Tariq S., Kamboj P., Alam O., Amir M. // Bioorganic & Medicinal Chemistry. 2018. Vol. 81. P. 630–641. doi: http://doi.org/10.1016/j.bmc.2018.09.015
8. Moussa T. H., Elia A. N. Design, synthesis and preliminary pharmacological evaluation of new possible non-steroidal anti-inflammatory agents having the 5-(methylsulfonyl)-1,2,4-triazole-3-amine phosphor // Der Pharma Chemica. 2015. Vol. 7. Issue 9. P. 279–293.
9. Novel synthesis of 4H-1,2,4-triazole-3-thiol derivatives with 2-(2,6-dichlorophenylamino)benzyl fragment in molecules and their anti-inflammatory activity / Shemeta Y. L., Lelyukh M. I., Zimenkovsky B. S., Lesyk R. B. // Current Issues in Pharmacy and Medicine: Science and Practice. 2016. Vol. 1, Issue 20. P. 18–25. doi: http://doi.org/10.14739/2409-2932.2016.161103
10. Synthesis, Molecular Docking and Anticancer Activity of Difluorinated Derivatives as Cyclooxygenase Enzyme Inhibitors / Coşkun G., Djikic T., Hayal T., Türkel N., Yelekçi K., Şahin F., Küçükgüzel Ş. // Molecules. 2018. Vol. 23, Issue 8. P. 1969. doi: http://doi.org/10.3390/molecules23081969
11. Design, synthesis, and biological evaluation of 3-alkylthio-4,5-diaryl-1H-1,2,4-triazoles as selective COX-2 inhibitors / Navidpour L., Shafaroodi H., Abdi K., Amini M., Ghahremani M. H., Dehpour A. R., Shafiee A. // Bioorganic & Medicinal Chemistry. 2006. Vol. 14, Issue 8. P. 2507–2517. doi: http://doi.org/10.1016/j.bmc.2005.11.029
12. Discovery of novel hybrids of diaryl-1,2,4-triazoles and caffeic acid as dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase for cancer therapy / Cai H., Huang X., Xu S., Shen H., Zhang P., Huang Y. et. al. // European Journal of Medicinal Chemistry. 2016. Vol. 108. P. 89–103. doi: http://doi.org/10.1016/j.ejmech.2015.11.013
13. Discovery of potential anti-inflammatory drugs: diaryl-1,2,4-triazoles bearing N-hydroxyurea moiety as dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase / Jiang B., Huang X., Yao H., Jiang J., Wu X., Jiang S. et. al. // Organic & Biomolecular Chemistry. 2014. Vol. 12, Issue 13. P. 2114–2127. doi: http://doi.org/10.1039/c3ob41936c
14. Syrovaya A. O., Chalenko N. N., Demchenko A. M. The Synthesis of potential anti-inflammatory substances among 4-amino-5-(pyridin-4-yl)-1,2,4-triazole(4H)-3-yl-thioacetamides and their chemical modification // Der Pharma Chemica. 2016. Vol. 8. Issue 21. P. 17–21.
15. The Synthesis of 4-amino -5-(pyridin-2(3)-Yl) -1,2,4-triazole (4H)-3-ylthio acetamide derivatives as potential anti-inflammatory substances / Syrovaya A., Chalenko N., Bezuglyi P., Demchenko A. // ScienceRise: Pharmaceutical Science. 2017. Vol. 1, Issue 5. P. 40–44. doi: http://doi.org/10.15587/2519-4852.2017.93332
16. Syntez, peretorevienia, fizyko-kinichni vlastivosti 4-alkil- ary1-4aminopokhidnykh 1,2,4-triazol-3-tioliv iz zalyskhami frahmentiv furanu / Parchenko V. V., Yerokhin V. Ye., Panasenko O. I., Knysz Ye. H. // Zaporozhsky medetsynskyi zhurnal. 2010. Vol. 12. Issue 4. P. 83–87.
17. Xu S., Rouzer C. A., Marnett L. J. Oxicams, a class of nonsteroidal anti-inflammatory drugs and beyond // IUBMB Life. 2014. Vol. 66, Issue 12. P. 803–811. doi: http://doi.org/10.1002/iub.1334
18. Anticancer, Anti-Inflammatory, and Analgesic Activities of Synthesized 2-Substituted phenox) Acetamide Derivatives / Rani P., Pal D., Hegde R. R., Hashim S. R. // BioMed Research International. 2014. Vol. 2014. P. 1–9. doi: http://doi.org/10.1155/2014/386473
19. Planning, Synthesis, and Pharmacological Activity of Alkyl Derivatives of 3-Mercapto-4-Phenyl-5-Arylaminoethyl-1,2,4-Triazole-(4H) / Saidov N. B., Kadamov I. M., Georgiyants V. A., Taran A. V. // Pharmaceutical Chemistry Journal. 2014. Vol. 47, Issue 11. P. 581–585. doi: http://doi.org/10.1007/s11094-014-1011-0

20. Way2Drug – main. (Prediction of Activity Spectra for Substances) PASS. URL: http://www.way2drug.com/PASSonline/

21. Nadkarni B., Kamat V., Khadse B. Synthesis and Anthelmintic Activity of 3,6-Disubstituted-7H-s-triazolo(3,4-b) (1,3,4) thiadiazones // Arzneimittel-Forschung. 2011. Vol. 51, Issue 7. P. 569–573. doi: http://doi.org/10.1055/s-0031-1300811

22. Drohovoz S. M., Zupanets I. A., Mokhort M. A. Eksperimentalne (doklinichne) vyvchennia farmakolohichnykh rechovin, yaki proponuetsia yak nesteroidni protyzapalni zasoby // Doklinichni doslidzhennia likarskykh zasobiv: handbook. Kyiv: Avitsenna, 2001. P. 242–306.

23. Rybolovlev Iu. R., Rybolovlev R. S. Dozirovanie veshchestv dla mlekopitaushchikh po konstantam biologicheskoi aktivnosti // Doklady AN SSSR. 1979. Issue 6. P. 1513–1516

24. Doklinichni doslidzhennia likarskykh zasobiv: textbook / ed. by Stefanov O. V. Kyiv: Avitsenna, 2001. 527 p.

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