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

N. Chalenko, A. Demchenko, G. Syrova

Мета. *Провести цілеспрямований синтез нових потенційних біологічно-активних речовин похідних 2-((4-аміно-5-(фуран-2-іл)-1,2,4-тріазол(4Н)-3-іл)-сульфаніл)-N-ацетамідів та оцінити їх антиексудативну активність на моделі формалінового набряку у щурів.*

Матеріали та методи. *У роботі використовували стандартні методи органічного синтезу, фізико-хімічні методи доведення будови синтезованих сполук, елементний аналіз, ^{1}Н ЯМР-спектроскопію, хромато-мас-спектрометрію, антиексудативну активність вивчено на моделі формалінового набряку у щурів за допомогою цифрового плетизмометра.*

Результати. *Шляхом алкілування 2-((4-аміно-5-(фуран-2-іл))-4Н-1,2,4-тріазол-3-тіона N-арилзаміщеними α-хлорацетамідами в етанолі у лужному середовищі одержані відповідні 2-((4-аміно-5-(фуран-2-іл)-1,2,4-тріазол(4Н)-3-іл)-сульфаніл)-N-ацетаміди. Після кристалізації отримували білі або світло-жовті кристалічні речовини з чіткими температурами плавлення. На моделі формалінового набряку у щурів вивчили антиексудативну активність нових, синтезованих нами 2-((4-аміно-5-(фуран-2-іл)-1,2,4-тріазол(4Н)-3-іл)-сульфаніл)-N-ацетамідів. За результатами проведених досліджень встановлено залежність «хімічна структура – антиексудативна активність» вперше синтезованих сполук. Результати експериментальних досліджень показали, що п'ятнадцять із двадцять однієї сполуки виявили антиексудативну активність, вісім із них перевищували цю активність, або були на рівні референс-препарату – диклофенаку натрію.*

Висновки. *Здійснено синтез двадцяти однієї сполуки похідних 2-((4-аміно-5-(фуран-2-іл)-1,2,4-тріазол(4Н)-3-іл)-сульфаніл)-N-ацетамідів та проведено оцінку антиексудативної активності, встановлено залежність «хімічна структура – антиексудативна активність». Виявлено сполуки-лідери за антиексудативною активністю*

Ключові слова: *синтез, 4-аміно-3-тіо-5-(фуран-2-іл)-1,2,4-тріазол, ацетаміди, алкілування, антиексудативна активність, формаліновий набряк*

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 pharmacophorial 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 lipoxygenase-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 heterocycle 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.

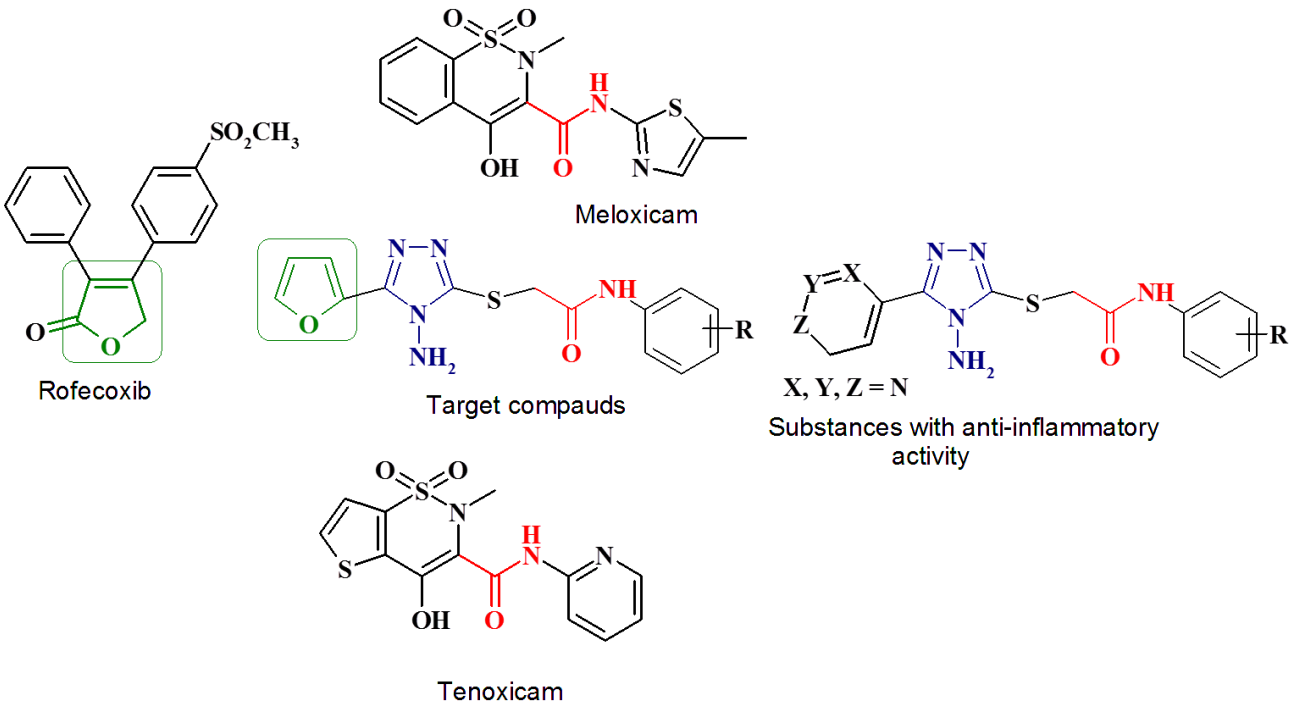

Fig. 1. Structural similarity of the synthesized compounds with known NSAIDs

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 arylacetamide derivatives (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 antiexudative 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 ^{1}H 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)-sulfonyl)-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-triazol-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:

$$\%\ of\ \ inhibition\ of\ \ inflammation = \frac{V_k - V_0}{V_k} \cdot 100\ \%,$$

where V_k – volume of foot in control minus the output volume of this foot before swelling, ml;

V_o – 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 Exel 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 Animal Experiments" (Kyiv, 2001), the Law of Ukraine "On the Protection of Animals from Cruel Treatment" No. 3477-IV 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.

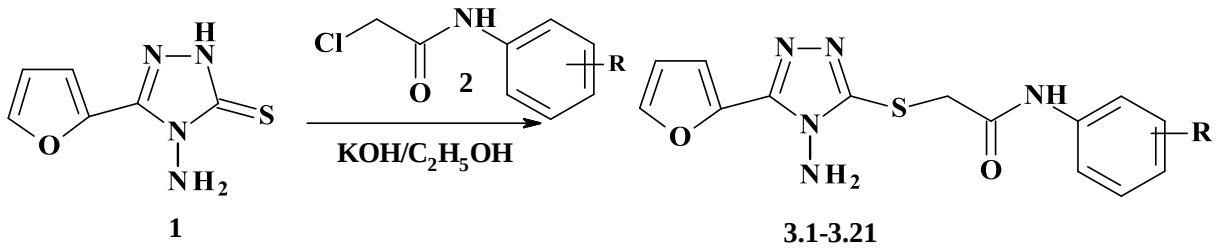

Fig. 2. Synthesis of 2-((4-amino-5-(furan-2-yl)-1,2,4-triazole(4H)-3-yl) -sulfanyl)-N-acetamides (**3.1-3.21**)

Table 1

Physicochemical characteristics of synthesized 2-((4-amino-5-(furan-2-yl)-1,2,4-triazolo (4H) -3-yl) -sulfanyl)-N-acetamides (**3.1–3.21**)

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	$C_{14}H_{13}N_5O_2S$	315.35	53.32 / 53.11	22.21 / 22.25	10.17 / 10.12	316.2
3.2	4-Et	76	212-4	$C_{16}H_{17}N_5O_2S$	343.40	55.96 / 55.56	20.39 / 20.42	9.34 / 9.30	344.4
3.3	4-Bu	83	145-8	$C_{18}H_{21}N_5O_2S$	371.45	58.20 / 58.05	18.85 / 18.92	8.63 / 8.60	372.2
3.4	3-OMe	84	145-7	$C_{15}H_{15}N_5O_3S$	345.37	52.16 / 52.01	20.28 / 20.32	9.28 / 9.22	346.2
3.5	4-OMe	84	211-3	$C_{15}H_{15}N_5O_3S$	345.37	52.16 / 52.03	20.28 / 20.30	9.28 / 9.24	–
3.6	4-OEt	76	135-7	$C_{16}H_{17}N_5O_3S$	359.40	53.47 / 53.35	19.49 / 19.53	8.92 / 8.88	360.2

Continuation of the Table 1

1	2	3	4	5	6	7	8	9	10
3.7	3-CF_3	78	179-81	$C_{15}H_{12}F_3N_5O_2S$	383.34	47.00 / 46.83	18.27 / 18.34	8.36 / 8.39	–
3.8	3-Cl	88	218-20	$C_{14}H_{12}ClN_5O_2S$	349.80	48.07 / 47.94	20.02 / 20.00	9.17 / 9.13	–
3.9	4-Cl	85	188-90	$C_{14}H_{12}ClN_5O_2S$	349.80	48.07 / 47.88	20.02 / 20.09	9.17 / 9.09	–
3.10	3-F	78	200-2	$C_{14}H_{12}FN_5O_2S$	333.34	50.44 / 50.34	21.01 / 21.04	9.62 / 9.58	–
3.11	4-F	83	123-5	$C_{14}H_{12}FN_5O_2S$	333.34	50.44 / 50.32	21.01 / 21.05	9.62 / 9.60	–
3.12	4-NO_2	85	118-9	$C_{14}H_{12}N_6O_4S$	360.35	46.66 / 46.55	23.32 / 23.35	8.90 / 8.87	361.2
3.13	3,4-diMe	84	184-6	$C_{16}H_{17}N_5O_4S$	343.40	55.96 / 55.86	20.39 / 20.33	9.34 / 9.31	–
3.14	2-Me, 3-Cl	85	206-8	$C_{15}H_{14}ClN_5O_2S$	363.82	49.52 / 49.46	19.25 / 19.22	8.81 / 8.79	–
3.15	3-Cl, 4- Me	76	116-8	$C_{15}H_{14}ClN_5O_2S$	363.82	49.52 / 49.39	19.25 / 19.30	8.81 / 8.78	–
3.16	2,4-diCl	86	146-3	$C_{14}H_{11}Cl_2N_5O_2S$	384.24	43.76 / 43.68	18.23 / 18.26	8.35 / 8.32	–
3.17	3,4-diCl	80	248-50	$C_{14}H_{11}Cl_2N_5O_2S$	384.24	43.76 / 43.62	18.23 / 18.25	8.35 / 8.32	–
3.18	2-Cl, 5-CF_3	88	170-2	$C_{15}H_{11}ClF_3N_5O_2S$	417.79	43.12 / 43.00	16.76 / 16.80	7.67 / 7.68	–
3.19	3-COMe	76	175-4	$C_{16}H_{15}N_5O_3S$	357.39	53.77 / 53.68	19.60 / 19.64	8.97 / 8.95	358.2
3.20	2-COO Et	78	146-8	$C_{17}H_{16}N_5O_4S$	387.41	52.70 / 52.61	18.08 / 18.13	8.28 / 8.26	388.2
3.21	4-COO Et	78	172-3	$C_{17}H_{16}N_5O_4S$	387.41	52.70 / 52.59	18.08 / 18.11	8.28 / 8.26	388.2

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 triazolal cycles, 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].

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		NH_2 s, 2H	SCH_2 s, 2H	Other protons
				d, H-3	t, H-4			
3.1	9.21	7.90	7.59-7.27 m, 4H, H-2',3',5',6' 7.05 t, 1H, H-4'	7.22	6.70	6.21	4.15	–
3.2	10.19	7.91	7.33 d, 2H, *J*=8,4, H-3',5' 7.29, d, 2H, *J*=8,4, H-2',6'	7.22	6.72	6.22	4.13	3.05 q, 2H, CH_2 0.98 t, 3H, CH_3
3.3	10.12	7.90	7.51 d, 2H, H-3`,5` 7.12 d, 2H, H-2`,6`	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_2 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` 7.64 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` 7.64 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

Table 3

Antiexudative 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 modelling	Suppression of edema, %
Control pathology		0.58±0.012	0.76±0.032$^{\#,\ddagger\ddagger}$	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$^{\#,\ddagger\ddagger\ddagger}$	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±0.051$^{**,\ddagger,\#\#}$	0
3.7	3-CF_3	0.78±0.015***,‡‡	0.94±0.024$^{***,\#,\ddagger\ddagger\ddagger}$	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-NO_2	0.51±0.02*	0.58±0.04***	62.9
3.13	3,4-diMe	0.58±0.03	0.79±0.025$^{\#,\ddagger}$	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-CF_3	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<0,001; 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 trifluoromethyl- (**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-ethoxy (**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) sulfanil)-N-acetanilides in the fourth position of the phenyl residue of the fluorine, chlorine, methoxy, ethyl, nitro and in the third position of the acetyl radicals is expedient and increases the anti-exudative activity.

Prospects: To stude 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.

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Ganna Syrova, Doctor of Pharmacy, Professor, Head of Department, Department of Medical and Bioorganic Chemistry, Kharkiv National Medical University, Nauky ave., 4, Kharkiv, Ukraine, 61022
E-mail: annasirova@ukr.net

Natalia Chalenko, Assistant, Department of Medical and Bioorganic Chemistry, Kharkiv National Medical University, Nauky ave., 4, Kharkiv, Ukraine, 61022
E-mail: medchem1@ukr.net

Anatoly Demchenko, Doctor of Pharmacy, Professor, Head of Department, Department of Medical Chemistry Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine, Antona Tsedyka str., 14, Kyiv, Ukraine, 03057
E-mail: chem.synthesis.ift@gmail.com