UDC 616.831-005.4-08.039.71:615.27

THE SYNTHESIS OF 4-THIAZOLIDINONE DERIVATIVES USING 2-(4-R-2-FORMYLPHENOXY)-N-(R'-PHENYL)ACETAMIDES AND THEIR ANTI-INFLAMMATORY ACTIVITY

S.M.Golota, K.E.Danylyuk*, T.I.Yushchenko*, N.I.Voloshchuk*, O.V.Bilyk*, R.B.Lesyk

Danylo Halytsky Lviv National Medical University
69, PekarskaStr., Lviv, 79010. E-mail: roman.lesyk@gmail.com
* Vinnytsya National Pirogov Memorial Medical University

Key words: 4-thiazolidinones; NSAIDs; 2-(4-R-2-formylphenoxy)-N-(R'-phenyl)acetamides; anti-exudative activity

The research is devoted to the rational design of new non-steroidal anti-inflammatory drugs (NSAIDs) using the 4-thiazolidinone "core". A series of 2-(4-R-2-formylphenoxy)-N-(R'-phenyl)acetamides has been synthesized from salicylic aldehydes for structural modifications of basic heterocycles. The aldehydes obtained are active carbonyl agents and suitable "building blocks" for the focused synthesis of biologically active compounds. Ylidene derivatives of 2-thioxo-4-thiazolidinone and 2-(4-hydroxyphenyl)imino-4-thiazolidone have been synthesized in the Knoevenagel reaction conditions. The one-pot reaction between 3(5)-merkapto-1,2,4-triazoles, chloroacetic acid and the salicylic aldehyde derivatives synthesized have been used for the synthesis of 5-ylidene-thiazolo[3,2-b][1,2,4]triazol-6-one. Parameters of acute toxicity and the anti-exudative activity (carrageenin paw edema test) have been studied for the ylidene derivatives synthesized. It has been found that all compounds synthesized demonstrate the anti-exudative activity, and some "structure – acute toxicity – anti-exudative activity" relationships have been analyzed. Based on the results of in vivo studies the lead compound – 4-{2-[4-chloro-2-(6-oxothiazolo[3,2-b][1,2,4]triazole-5-ylidenemethyl)-phenoxy]-acetylamino}-benzoic acid ethyl ester that demonstrates the anti-exudative activity equivalent to the classic NSAID Diclofenac has been identified, it has a low level of toxicity and can be recommended for the profound study.

СИНТЕЗ ПОХІДНИХ 4-ТІАЗОЛІДИНОНУ З ВИКОРИСТАННЯМ 2-(4-R-2-ФОРМІЛФЕНОКСИ)-N-(R'-ФЕНІЛ) АЦЕТАМІДІВ ТА ЇХ ПРОТИЗАПАЛЬНА АКТИВНІСТЬ

С.М.Голота, К.Є.Данилюк, Т.І.Ющенко, Н.І.Волощук, О.В.Білик, Р.Б.Лесик

Ключові слова: *4-тіазолідинони; НПЗЗ; 2-(4-R-2-формілфенокси)-N-(R'-феніл)ацетаміди; антиексудативна активність*

Дослідження присвячено раціональному дизайну нових нестероїдних протизапальних лікарських засобів (НПЗЗ) з використанням 4-тіазолідинонового «каркасу». Для структурної модифікації цільового гетероциклу синтезовано ряд 2-(4-R-2-формілфенокси)-N-(R'-феніл)ацетамідів, які є активними карбонільними сполуками, зручними «building blocks» для спрямованого синтезу біологічно активних сполук. В умовах реакції Кньовенагеля з 2-тіоксо-4-тіазолідиноном, 2-(4-гідроксифеніл)іміно-4-тіазолідиноном та при однореакторній взаємодії з 3(5)-меркапто-1,2,4-триазолом і монохлороцтовою кислотою та синтезованими похідними саліцилових альдегідів отримано групу відповідних іліденпохідних. Для синтезованих іліденових похідних проведені дослідження параметрів гострої токсичності та антиексудативної активності з використанням карагенінової моделі запального процесу. Встановлено, що всі синтезовані сполуки демонструють антиексудативну активність та проаналізовані деякі закономірності «структура – гостра токсичність – антиексудативна активність». За результатами in vivo досліджень ідентифіковано сполуку – лідер – етиловий естер 4-{2-[4-хлоро-2-(6-оксотіазоло[3,2-b][1,2,4]триазол-5-ілідинметил)-феноксі]-ацетиламіно}-бензоатної кислоти, яка демонструє антиексудативну активність, еквівалентну лікарському засобу «Диклофенак» на фоні низької токсичності та може бути рекомендований для поглиблених досліджень.

СИНТЕЗ ПРОИЗВОДНЫХ 4-ТИАЗОЛИДИНОНА С ИСПОЛЬЗОВАНИЕМ 2-(4-R-2-ФОРМИЛФЕНОКСИ)-N-(R'-ФЕНИЛ)АЦЕТАМИДОВ И ИХ ПРОТИВОВОСПАЛИТЕЛЬНАЯ АКТИВНОСТЬ

С.М.Голота, К.Е.Данилюк, Т.И.Ющенко, Н.И.Волощук, О.В.Билык, Р.Б.Лесик

Ключевые слова: *4-тиазолидиноны; НПВС; 2-(4-R-2-формилфенокси)-N-(R'-фенил)ацетамиды; антиэкссудативная активность*

Исследование посвящено рациональному дизайну новых нестероидных противовоспалительных средств (НПВС) с использованием 4-тиазолидинонового «каркаса». Для структурной модификации целевого гетероцикла исходя из салициловых альдегидов синтезирован ряд 2-(4-R-2-формилфенокси)-N-(R'-фенил)ацетамидов, которые являются активными карбонильными соединениями и удобными «building blocks» для направленного синтеза биологически активных соединений. В условиях реакции Кнёвенагеля с 2-тиоксо-4-тиазолидиноном, 2-(4-гидроксифенил)имино-4-тиазолидиноном, а также при однореакторном взаимодействии 3(5)-меркапто-1,2,4-триазола, монохлоруксусной кислоты и синтезированных производных салициловых альдегидов получено группу соответствующих илиденпроизводных. Для синтезированных соединений проведены исследования параметров острой токсичности и антиэкссудативной активности с использованием каррагениновой модели воспалительного процесса. Установлено, что все синтезированные соединения демонстрируют противовоспалительное действие и проанализированы некоторые закономерности «структура – острая токсичность – антиэкссудативная активность». По результатам in vivo исследований идентифицировано соединение – лидер: этиловый эфир 4-{2-[4-хлор-2-(6-оксотиазоло[3,2-b][1,2,4]триазол-5-илиденметил)-феноксі]-ацетиламино}-бензойной кислоты, которое демонстрирует антиэкссудативную активность, эквивалентную лекарственному средству «Диклофенак» на фоне низкой токсичности и может быть рекомендовано для углубленных исследований.

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the oldest and most widely used groups of drugs today [1]. There are more than 20 original monocomponent NSAIDs, about 200 generics and a significant number of combined drugs and their generic versions at the Ukrainian pharmaceutical market [2]. However, the problem of searching and creating new NSAIDs remains open, primarily to eliminate gastrointestinal, cardiovascular and renovascular risks in their long-term use [3-5]. Drugs affect the cellular metabolism of arachidonic acid, which is a substrate for the synthesis of active intracellular intermediates, eicosanoids, leukotrienes and others, and is the key mechanism for therapeutic and adverse effects of different classes of NSAIDs [6]. Organic compounds from different classes [7-9], including 4-thiazolidinone derivatives [10-13], can change the phospholipase A2 activity blocking the process of arachidonic acid releasing from cell membranes phospholipids; selective and non-selective inhibit cyclooxygenases types 1 and 2 (COX-1 and COX-2) and thus prevent the arachidonic acid transformation to eicosanoids; inhibit 5-lipoxygenase (5-LOX) preventing the arachidonic acid conversion to leukotrienes; demonstrate multiactivity against the enzyme systems (COX-2/5-LOX dual inhibitors), etc. According to the modern concepts PPAR-receptors play an important role in the cellular mechanisms of inflammatory processes [14]. It is known that 4-thiazolidinones are "classic" high affinity ligands for PPARγ-receptors [15].

The systematic research in the field of potential NSAIDs synthesis and screening among 4-thiazolidinone derivatives is the priority direction for the research group of the Department of Pharmaceutical, Organic and Bioorganic Chemistry at Danylo Halytsky Lviv National Medical University [16-21]. The qualitative and quantitative "structure – antiinflammatory activity" databases obtained for 4-thiazolidinones allow to carry out the rational structural design of the 4-thiazolidinone "core" for searching new potential NSAIDs. The aim of this research was the synthesis of 5-ylidene-4-thiazolidinones from 2-(4-R-2-formylphenoxy)-N-(R'-phenyl)acetamides, as well as the study of their anti-exudative activity and acute toxicity.

Target 2-(4-R-2-formylphenoxy)-N-(R'-phenyl)acetamides **1-6** were obtained in the alkylation reaction of 2-hydroxy- and 5-chloro-2-hydroxybenzaldehydes (salicylic aldehydes) with chloroacetamide, N-(R'-phenyl)chloroacetamides and 2-chloro-1-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-ethanone in the ethanol medium in the presence of potassium hydroxide (Fig. 1).

Compounds **1-6** are useful "building blocks" for structural modification of 4-thiazolidinone scaffold in position 5, and they give the corresponding ylidene-derivatives with high yields in the Knoevenagel reaction with 2-thioxo-4-thiazolidinone (**7-9**, **11**, **13**), 2-(4-hydroxyphenyl)imino-4-thiazolidinone (**12**) and the one-pot reaction with 3(5)-mercapto-1,2,4-triazole and chloroacetic acid (**10**) (Fig. 2).

The structure of the compounds synthesized was confirmed by ^{1}H-NMR spectra. Protons of CH_2-CH fragments in the pyrazoline ring of compounds **6** and **13** form a characteristic AMX system due to their diastereoisomerism. This system appears in ^{1}H-NMR spectra as three duplicate doublets at 3.30-3.40, 4.00-4.15 and 5.70-5.90 ppm with constant J_{AM} = 17.8-18.0, J_{Ax} = 10.7-10.9 and J_{Mx} = 3.0-3.8 Hz.

The acute toxicity was studied in order to assess the prospects of the compounds synthesized as biologically active substances. Pastushenko's express – method was used for determination of acute toxicity parameters [22]. White mice of both sexes weighing 20-27 g were used for the experiment. The animals were kept on a standard diet with a free access to food and water during the experiment. The test compounds were dissolved in Tween-80 and purified water and introduced intraperitoneally. The observation of the animals was performed for 14 days. The LD_{50} values determined for the test substances (Fig. 3) were higher or equivalent to the LD_{50} of the reference drug Diclofenac and allowed to refer them to moderately

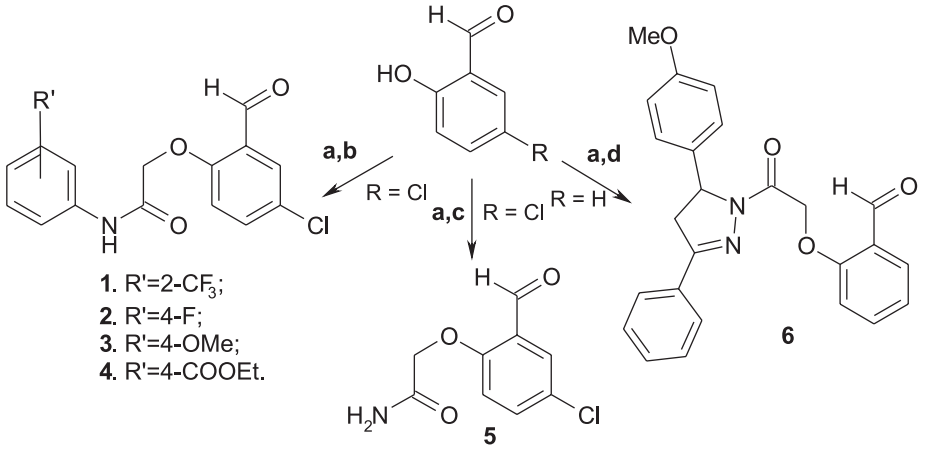

Fig. 1: **a** – KOH; **b** – N-(R'-phenyl)chloroacetamides; **c** – chloroacetamide; **d** – 2-chloro-1-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-ethanone.

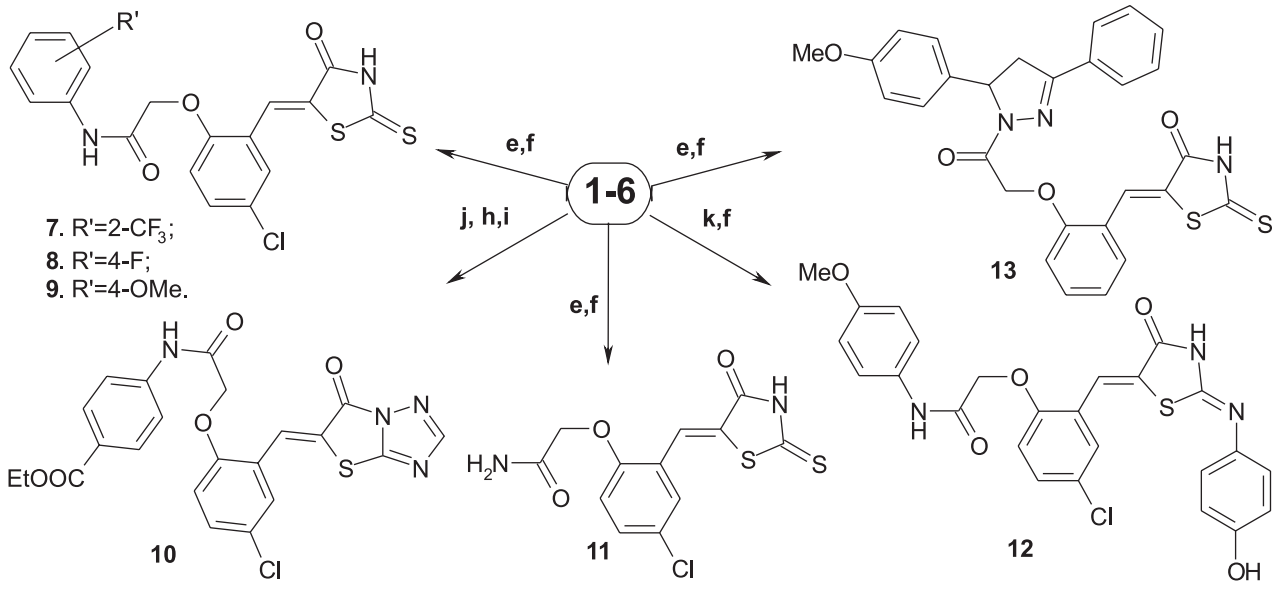

Fig. 2: **e** – 2-Thioxo-4-thiazolidinone; **f** – AcOH, AcONa; **j** – 3(5)-mercapto-1,2,4-triazole; **h** – $ClCH_2COOH$; **i** – Ac_2O, AcOH, AcONa; **k** – 2-(4-hydroxyphenyl)imino-4-thiazolidinone.

toxic (**7**) and low-toxic (**8-13**) compounds according to K. K. Sidorov classification (the III and IV class of toxicity) [23]. In the analysis of the "structure – acute toxicity" relationship it has been found that higher levels of LD_{50} have the following compounds: the annelated derivative of 4-thiazolidinone (**10**) containing the unsubstituted amide function (**11**) or the diphenylpyrazoline moiety (**13**) in the ylidene fragment, while derivatives **7-9**, **12** with N-(R'-phenyl)chloroacetamides substituents in the molecule are more toxic.

The carrageenin paw edema test was used for the anti-exudative activity screening of the compounds synthesized [24]. The inflammatory edema of the paw was generated by injection of 0.05 ml 1% carrageenin solution (Sigma) into the right hind limb of the mice [25]. The compounds and reference drug were administered intraperitoneally one hour before the carrageenin injection in the doses of 0.05 LD_{50}. The control group of animals was administered an equivalent amount of the solvent. Animals were taken out from the experiment by the cervical vertebrae dislocation at 3 hr after injecting carrageenan (at the peak of action) and limbs masses were measured and compared after disarticulation at the hip joints. The anti-exudative activity (AEA) of compounds was calculated using the equation:

$$\text{AEA} = 100\% - \frac{Me.e. - Mh.e.}{Me.c. - Mh.c.} \cdot 100\%,$$

where: *Me.e.(c) and Mh.e.(c)* are edema and healthy limbs weight for experimental and control animals, respectively.

The results of AEA screening (Fig. 3) demonstrate that all compounds synthesized are active. The range

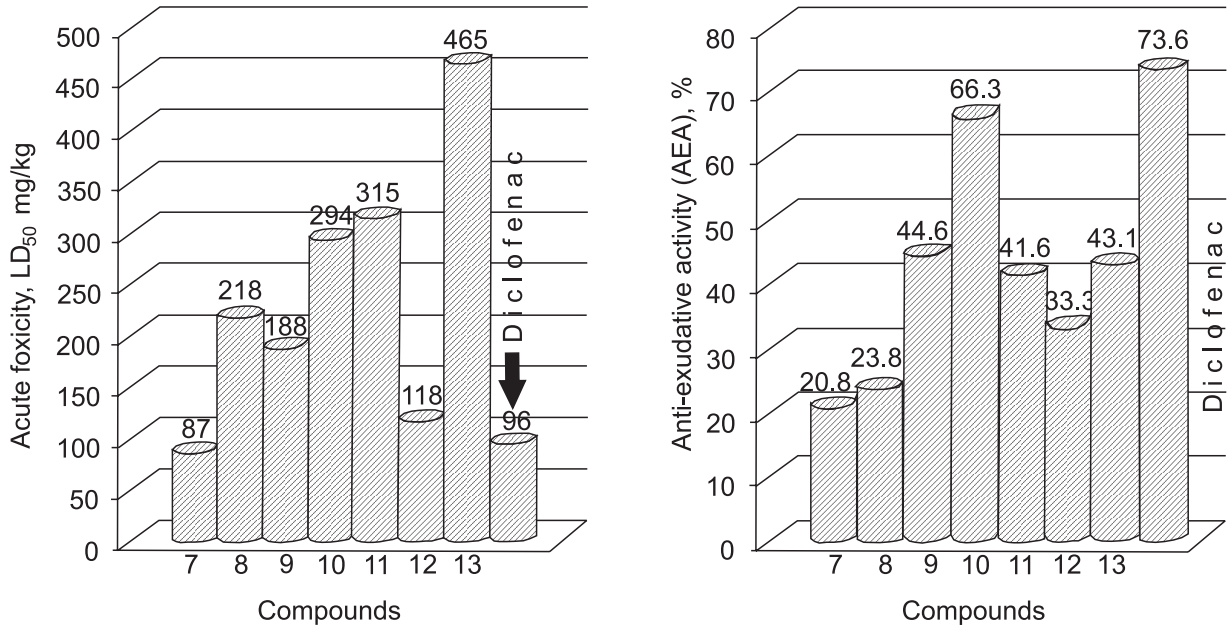

Fig. 3. Acute toxicity and the anti-exudative activity of compounds **7-13**.

of AEA values of the compounds synthesized in relation to the reference drug are from 27.2% (**7**) to 88.3% (**10**). Derivatives with a fluorine atom in the phenylacetamide fragment (**7**, AEA = 20.8%; **8**, AEA = 23.8%) are characterized by the lowest activity level. The change of fluorine to the methoxy group in the *p*-position of compound **8** causes a significant increase of the anti-inflammatory effect – **9**, AEA = 44.6%. The equivalent effect was obtained by simplifying the O-alkylmoiety in the ylidene fragment to the unsubstituted amide group (**11**, AEA = 41.6%), as well as by structural complication of the diphenylpyrazoline substituent (**13**, AEA = 43.1%). The presence of the *p*-hydroxyphenylimine fragment in position 2 of the 4-thiazolidinone core (**12**) causes decrease of AEA in relation to thioxoanalogue **9**, and is 33.3%. The anelated 4-thiazolidinone derivative **10** shows the highest AEA = 66.3% among the compounds synthesized and equivalent to the reference drug.

Experimental Part

Melting points were measured in open capillary tubes on a BŰCHI B-545 melting point apparatus and were uncorrected. The elemental analysis (C, H, N) was performed using a Perkin-Elmer 2400 CHN analyzer and was within ± 0.4% of the theoretical values. The ^{1}H-NMR spectra were recorded on a Varian Gemini spectrometer at 400 MHz using the mixture of DMSO-d_6+CCl_4 as a solvent and TMS as an internal standard. Chemical shift values are reported in ppm units with the use of δ scale.

***The general procedure for the synthesis of 2-(4-R-2-formylphenoxy)-N-(R'-phenyl)acetamides* 1-6**. Reflux the mixture of 5-chloro-2-hydroxy- (**1-5**) or 2-hydroxybenzaldehydes (**6**) (10 mmol), N-(R'-phenyl)chloroacetamides (**1-4**), chloroacetamide (**5**) 2-chloro-1-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-ethanone (**6**) (10 mmol) and potassium hydroxide (10 mmol) for 2 h in the anhydrous ethanol medium. Separate the resulting solution and distill in vacuum. Recrystallize the precipitate from ethanol or isopropanol.

2-(4-Chloro-2-formylphenoxy)-N-(2-trifluoromethylphenyl)-acetamide (**1**). Yield – 82%. M.p. – 154-157°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 4.60s (2H, CH_2), 6.80 d (1H, C_6H_3, *J*=8.1Hz), 7.00 d (1H, C_6H_3, *J*=8.1 Hz), 7.05 d (1H, C_6H_3, *J*=2.7Hz), 7.10-7.30 m (4H, C_6H_4), 10.20s (1H, CHO), 13.90 br.s (1H, NH). Calculated, %: C53.90, H 3.30, N 4.00. $C_{16}H_{11}ClF_3NO_3$. Found, %: C 53.72, H 3.10, N 3.92.

2-(4-Chloro-2-formylphenoxy)-N-(4-fluorophenyl)-acetamide (**2**). Yield – 78%. M.p. – 169-171°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 4.55 s (2H, CH_2), 6.90 d (1H, C_6H_3, *J*=8.0 Hz), 7.00 t (1H, C_6H_4, *J*=7.6 Hz),7.10 d (1H, C_6H_3, *J*=8.0 Hz), 7.20 d (1H, C_6H_3, *J*=2.9 Hz), 7.30 d (1H, C_6H_4, *J*=0.7Hz), 7.50 t (1H, C_6H_4, *J*=7.6 Hz), 7.60 d (1H, C_6H_4, *J*=0.7 Hz), 9.95 s (1H, CHO), 13.50 br.s (1H, NH). Calculated, %: C 58.70, H 3.70, N 4.60. $C_{15}H_{11}ClFNO_3$. Found, %: C 58.55, H 3.60, N 4.55.

2-(4-Chloro-2-formylphenoxy)-N-(4-methoxyphenyl)-acetamide (**3**). Yield – 84%. M.p. – 184-187°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 3.55 s (3H, CH_3), 4.55s (2H, CH_2), 6.85 d (1H, C_6H_3, *J*=7.8 Hz), 6.95 d (1H, C_6H_3, *J*=7.8 Hz), 7.15d (1H, C_6H_3, *J*=2.7 Hz), 7.20 d (2H, C_6H_4, *J*=8.0 Hz), 7.40 d (2H, C_6H_4, *J*=8.0 Hz), 10.20 s (1H, CHO), 13.60 br.s (1H, NH). Calculated, %: C 60.00, H 4.70, N 4.55. $C_{16}H_{14}ClNO_4$. Found, %: C 60.10, H 4.41, N 4.38.

4-[2-(4-Chloro-2-formylphenoxy)-acetylamino]-benzoic acid ethyl ester (**4**). Yield – 81%. M.p. – 173-175°C.^{1}HNMR, δ, ppm, (*J*, Hz): 1.20 t (3H, CH_3), 4.10 q (2H, CH_2), 4.45 s (2H, CH_2), 6.90 d (1H, C_6H_3, *J*=8.0 Hz), 7.20 d (1H, C_6H_3, *J*=8.0 Hz), 7.30 d (1H, C_6H_3, *J*=2.9 Hz), 7.50 d (2H, C_6H_4, *J*=8.2 Hz), 7.70 d (2H, C_6H_4, *J*=8.2 Hz), 10.20 s (1H, CH), 11.50 br.s (1H, NH). Calculated, %: C 59.70, H 4.60, N 4.00. $C_{18}H_{16}ClNO_5$. Found, %: C 59.76, H 4.46, N 3.87.

2-(4-Chloro-2-formylphenoxy)acetamide (**5**). Yield – 75%. M.p. – 179-181°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 4.40 s (2H, CH_2), 6.80 d (1H, C_6H_3, *J*=7.4 Hz), 7.00 d (1H, C_6H_3, *J*=2.3 Hz), 7.10 d (1H, C_6H_3, *J*=7.4 Hz), 7.20 s (2H, NH), 10.10s (1H, CHO), 13.60 br.s (1H, NH). Calculated, %: C 50.70, H 3.70, N 6.60. $C_9H_8ClNO_3$. Found, %: C 50.60, H 3.77, N 6.56.

2-{2-[5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-pyrazol-1-yl]-2-oxoethoxy}-benzaldehyde (**6**). Yield – 84%. M.p. – 168-171°C.^{1}H NMR, δ, ppm, (*J*, Hz): 3.30 dd (1H, CH_2, *J*=18.0; 4.0 Hz), 3.75 s (3H, OCH_3), 4.00 dd (1H, CH_2, *J*=17.9;10.9Hz), 4.60s (2H, CH_2), 5.70 dd (1H, CH_2, *J*=12.6; 3.9 Hz), 6.80 t (1H, C_6H_4, *J*=8.3Hz), 6.85d (2H, C_6H_4, *J*=8.7 Hz), 7.15d (2H, C_6H_4, *J*=8.7 Hz), 7.25 d (1H, C_6H_4, *J*=0.7 Hz), 7.30–7.40 m (3H, C_6H_5), 7.65 t (1H, C_6H_4, *J*=8.3 Hz), 7.75 d (1H, C_6H_4, *J*=0.7 Hz), 7.85 d (2H, C_6H_4, *J*=8.7 Hz), 10.30s (1H, CHO). Calculated, %: C 72.70, H 5.70, N 6.80. $C_{25}H_{22}N_2O_4$. Found, %: C 72.45, H 5.35, N 6.76.

***The general procedure for the synthesis of ylidene derivatives* 7-9 *and* 11-13**. Reflux the mixture of the appropriate oxocompounds **1-3** or **5-6** (10 mmol), 2-thioxo-4-thiazolidinone (**7-9**, **11**, **13**) or 2-(4-hydroxyphenyl)imino-4-thiazolidinone (**12**) (10 mmol) and anhydrous sodium acetate (15mmol) for 2 h in a glacial acetic acid (5 ml). Filter the powders obtained, wash with ethanol and recrystallize with the corresponding solvent.

***The procedure for the synthesis of ylidene derivative* 10.** Reflux the mixture of 1,2,4-triazole-3(5)-thiol (10 mmol), chloroacetic acid (10 mmol), oxocompound **4** (10 mmol) and anhydrous sodium acetate (15 mmol) for 2 h in the mixture of acetic anhydride (5 ml) and glacial acetic acid (5 ml). Filter the powders obtained, wash with ethanol and recrystallize with acetic acid.

2-[4-Chloro-2-(4-oxo-2-thioxo-thiazolidin-5-ylidene)phenoxy]-N-(2-trifluoromethylphenyl)

acetamide (**7**)**.** Yield – 67%. M.p. – 236 (with decomp.) °C. ^{1}H NMR, δ, ppm, (*J*, Hz): 4.90 s (2H, CH_2), 7.10 d (1H, C_6H_3, *J*=8.2 Hz), 7.30 d (1H, C_6H_3, *J*=8.2 Hz), 7.35 s (1H, C_6H_3, *J*=2.9 Hz), 7.40-7.60 m (4H, C_6H_4), 7.90 s (1H, CH), 9.50 s (1H, NH), 13.60 br.s (1H, NH). Calculated, %: C 48.50, H 2.70, N 5.80. $C_{19}H_{12}ClF_3N_2O_3S_2$. Found, %: C 48.26, H 2.56, N 5.92.

2-[4-Chloro-2-(4-oxo-2-thioxo-thiazolidin-5-ylidene)phenoxy]-N-(4-chlorophenyl)acetamide (**8**)**.** Yield – 71%. M.p. – 242-244°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 4.80 s (2H, CH_2), 7.10 d (1H, C_6H_3, *J*=7.8 Hz), 7.30 d (1H, C_6H_3, *J*=7.8 Hz), 7.35 d (1H, C_6H_3, *J*=2.6 Hz), 7.00 t (1H, C_6H_4, *J*=7.6 Hz), 7.40 d (1H, C_6H_4, *J*=0.5 Hz), 7.60 t (1H, C_6H_4, *J*=7.8 Hz), 7.70 d (1H, C_6H_4, *J*=0.5 Hz), 7.90 s (1H, CH),10.00 s (1H, NH). Calculated, %: C 51.30, H 2.80, N 6.70. $C_{18}H_{12}ClFN_2O_3S_2$. Found, %: C 51.12, H 2.86, N 6.62.

2-[4-Chloro-2-(4-oxo-2-thioxo-thiazolidin-5-ylidene)phenoxy]-N-(4-methoxyphenyl)acetamide (**9**)**.** Yield – 74%. M.p. – 248 (with decomp.) °C. ^{1}H NMR, δ, ppm, (*J*, Hz): 3.65 s (3H, OCH_3), 4.60 s (2H, CH_2), 7.10 d (1H, C_6H_3, *J*=7.5 Hz), 7.15 d (1H, C_6H_3, *J*=7.5 Hz), 7.20 d (1H, C_6H_3, *J*=2.4 Hz), 7.30 d (2H, C_6H_4, *J*=7.8 Hz), 7.50 d (2H, C_6H_4, *J*=7.8 Hz), 7.90 s (1H, CH), 10.00 s (1H, NH), 11.30 br.s (1H, NH). Calculated, %: C 52.60, H 3.60, N 6.60. $C_{19}H_{15}ClN_2O_4S_2$. Found, %: C 52.47, H 3.48, N 6.44.

4-{2-[4-Chloro-2-(6-oxothiazolo[3,2-b][1,2,4]triazol-5-ylidenemethyl)-phenoxy]-acetylamino}-benzoic acid ethyl ester (**10**)**.** Yield – 83%. M.p. – 176-178°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 1.30 t (3H, CH_3), 4.30 q (2H, CH_2), 4.90 s (2H, CH_2), 7.10 d (1H, C_6H_3, *J*=7.3 Hz), 7.40 d (1H, C_6H_3, *J*=7.3 Hz), 7.50 d (1H, C_6H_3, *J*=2.2 Hz), 7.70 d (2H, C_6H_4, *J*=7.7 Hz), 7.90 d (2H, C_6H_4, *J*=7.7 Hz), 8.25 s (1H, CH), 8.50s (1H, CH), 10.40 s (1H, NH), 11.60 br.s (1H, NH). Calculated, %: C 54.50, H 3.50, N 11.70. $C_{22}H_{17}ClN_4O_5S$. Found, %: C 54.49, H 3.53, N 11.55.

2-[4-Chloro-2-(4-oxo-2-thioxo-thiazolidin-5-ylidene)phenoxy]-acetamide (**11**). Yield – 63%. M.p. – 240 (with decomp.) °C. ^{1}H NMR, δ, ppm, (*J*, Hz): 4.60s (2H, CH_2), 7.00 d (1H, C_6H_3, *J*=7.9 Hz), 7.40 d (1H, C_6H_3, *J*=7.9 Hz), 7.50 d (1H, C_6H_3, *J*=2.4 Hz), 7.60 s (2H, NH), 7.80s (1H, CH), 13.80 br.s (1H, NH). Calculated, %: C 43.70, H 2.70, N 8.60. $C_{12}H_9ClN_2O_3S_2$. Found, %: C 43.84, H 2.76, N 8.52.

2-{4-Chloro-2-[2-(4-hydroxyphenyl)imino-4-oxo-thiazolidin-5-yliden]-phenoxy}-N-(4-methoxyphenyl)acetamide (**12**)**.** Yield – 81%. M.p. > 250°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 3.75 s (3H, CH_3), 4.75 s (2H, CH_2), 6.80 d (2H, C_6H_4, *J*=7.8 Hz), 6.90 d (2H, C_6H_4, *J*=7.8 Hz), 7.00 d (1H, C_6H_3, *J*=8.2 Hz), 7.10 d (1H, C_6H_3, *J*=8.2 Hz), 7.30 d (1H, C_6H_3, *J*=2.7 Hz), 7.40 d (2H, C_6H_4, *J*=8.1 Hz), 7.60 d (2H, C_6H_4, *J*=8.1 Hz), 8.00s (1H, CH), 9.40 s (1H, OH), 9.75s (1H, NH), 11.20 br.s (1H, NH). Calculated, %: C 59.00, H 3.90, N 8.50. $C_{25}H_{20}ClN_3O_5S$. Found, %: C 58.88, H 3.95, N 8.24.

5-(2-{2-[5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-2-oxoethoxy}-benzeliden)-2-thioxo-thiazolidin-4-one (**13**). Yield – 83%. M.p. – 233-235°C. ^{1}H NMR, δ, ppm, (*J*, Hz): 3.40 dd (1H, CH_2, *J*=17.8, 3.9Hz), 3.80 s (3H, OCH_3), 4.15 dd (1H, CH_2, *J*=18.1, 10.7Hz), 4.70 s (2H, CH_2), 5.90 dd (1H, CH_2, *J*=12.4, 3.8Hz), 7.00 t (1H, C_6H_4, *J*=8.5Hz), 7.05 d (2H, C_6H_4, *J*=8.7 Hz), 7.20 d (2H, C_6H_4, *J*=8.7 Hz), 7.30 d (1H, C_6H_4, *J*=0.9 Hz), 7.35–7.50 m (3H, C_6H_5), 7.70 t (1H, C_6H_4, *J*=8.5 Hz), 7.80 d (1H, C_6H_4, *J*=0.9 Hz), 7.90 d (2H, C_6H_4, *J*=8.7 Hz), 8.50 s (1H, CH), 9.90 s (1H, NH). Calculated, %: C 63.60, H 4.50, N 7.90. $C_{28}H_{23}N_3O_3S_4$. Found, %: C 63.50, H 4.38, N 7.93.

Conclusions

1. The effective synthetic method for 2-(4-R-2-formylphenoxy)-N-(R'-phenyl)acetamides, which are suitable "building blocks" for the structural design of new potential bioactive 4-thiazolidinones has been developed.

2. A series of 5-ylidene-4-thiazolidinones from 2-(4-R-2-formylphenoxy)-N-(R'-phenyl)acetamides has been synthesized and their anti-exudative activity in the carrageenin paw edema test in mice has been studied.

3. It has been found that all compounds synthesized have a significant anti-inflammatory activity, and the "lead-compound" – 5-ylidene derivative of thiazolo[3,2-b][1,2,4]triazole-6-one exhibiting the anti-exudative activity equivalent to the classic NSAID Diclofenac with the low acute toxicity level has been identified.

References

1. *Green G. A. Clinical Cornerstone, 2001, Vol. 3, No.5, pp.50-59.*
2. *http://compendium.com.ua/atc/M01#M01A_B05*
3. *Laine L. J. Cardiovasc. Pharmacol., 2006, Vol. 47, No.1, pp.60-66.*
4. *Graham D. J. JAMA, 2006, Vol. 296, No.13, pp.1653-1656.*
5. *Gambaro G., Perazella M. A. J. Internal Medicine, 2003, Vol. 253, pp. 643-652.*
6. *Brash A. R. J. Clin. Invest., 2001, Vol. 107, No.11, pp. 1339-1345.*
7. *Levin J. I., Laufer S. Royal Society of Chemistry, 2012, 528 p.*
8. *Dennis E. A. et al. Chem. Rev., 2011, Vol. 111, No.10, pp. 6130-6185.*
9. *Praveen Rao P. N., Knaus E. E. J. Pharm. Pharmaceut. Sci., 2008, Vol. 11, No.2, pp. 81s-110s.*
10. *Seno K. et al. J. Med. Chem., 2000, Vol. 43, No.6, pp. 1041-1044.*
11. *Ottana R. et al. Bioorg. Med. Chem., 2005, Vol. 13, pp.4243-4252.*
12. *Charlier C., Mishaux C. Eur. J. Med. Chem., 2003, Vol. 38, pp.645-659.*
13. *Geronikaki A. A. et al. J. Med. Chem., 2008, Vol. 51, No.6, pp.1601-1609.*
14. *Michalik L. et al. Pharm. Rev., 2006, Vol. 58, No.4, pp.726-741.*

15. *Grygiel-Górniak B. Nutrition J., 2014, Vol. 13, pp.17.*
16. *Lesyk R. et al. Boll. Chim. Farm., 1998, Vol. 137, No.6, pp.210-217.*
17. *Zimenkovsky B. et al. Eur. J. of Pharm. Sci., 1998, Vol. 6., Suppl. 1, p.119.*
18. *Lesyk R. et al. Eur. J. of Pharm. Sci., 1999, Vol. 8., Suppl. 2, p.27.*
19. *Zimenkovsky B. et al. J. Pharm. Pharmacol., 1999, Vol. 51. p.264.*
20. *Lesyk R. et al. Boll. Chim. Farm., 2002, Vol. 141, No.3, pp.197-201.*
21. *Lesyk R. B. et al. Farmac. Zhurn. – Pharm. J., 2003, No.5, pp.58-61.*
22. *Pastushenko T. V. et al. Hihiena i Sanitarija – Hygiene&Sanitary, 1985, No.6, pp.46-48.*
23. *Sidorov K. K. Toksikologiya novykh promyshlennykh khimicheskikh veschestv (Toxicology of new industrial chemical substances), M.: Medicina, 1973, Vyp.3, p.47.*
24. *Morris C. J. Inflammation Protocols. Methods in Molecular Biology, 2003, Vol. 225, pp.115-121.*
25. *Stefanov O. V. Doklinichni doslidzhennya likarskyh zasobiv: Metodychni rekomendatsii (Preclinical studies of drugs. Guidelines), Kyiv, 2001, 528 p.*

Надійшла до редакції 19.06.2015 р.