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Synthesis and *in vivo* evaluation of pyrazoline-thiazolidin-4-one hybrid Les-5581 as a potential non-steroidal anti-inflammatory agent

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Aim. Synthesis and *in vivo* study of acute toxicity, anti-inflammatory (anti-exudative) activity and side effects of pyrazoline-thiazolidin-4-one hybrid Les-5581 under conditions of therapeutic use in experimental animals. **Methods.** Traditional organic synthesis. The Litchfield-Wilcoxon method. Carrageenin- and formaldehyde-induced inflammatory paw edema models of white rats. Clinical laboratory tests: study of general blood parameters and biochemical profile of liver function (ALT, AST, LF and γ-GGT levels). Evaluation of ulcerogenic action. **Results.** The target hybrid Les-5581 has been synthesized in a convenient and efficient aminolysis of 5-etoxymethylidenerhodanine by 3,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole. The LD50 value for Les-5581 was determined with intraperitoneal use and it was 510 mg/kg. Les-5581 exhibits significant anti-inflammatory activity at a dose of 50 mg/kg (intraperitoneal use) in an experiment on carrageenin- and formaldehyde-induced inflammatory models in white rats. The use of Les-5581 does not provoke a negative impact on the blood pattern, the liver enzymes function and has no ulcerogenic effect. **Conclusions.** The pyrazoline-thiazolidine-4-one hybrid Les-5581 is a good molecular platform for development of new potential low-toxicity anti-inflammatory drugs without ulcerogenic action.

K e y w o r d s: pyrazoline, thiazolidin-4-one, NSAIDs, molecular hybrid

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs in modern medicine and represent diverse classes of chemical compounds [1]. Usually NSAIDs are taken systematically, for a long time and in the large doses. NSAIDs are characterized by different types of undesirable effects such as gastrointestinal (GI) and cardiovascular risks, hepato- and nephrotoxicity, negative impact on central nervous and blood systems *etc* [2]. The molecular mechanisms underlying this toxicity have not yet been fully elucidated but it is known that the oxidative stress (OS) and reactive oxygen species (ROS) are key factors which play an important role in the pathogenesis of "NSAIDs-gastropathy" [3], "NSAID-induced hepatotoxicity" [4, 5], *etc.* Thus, presence antioxidant properties are a desirable and useful characteristic for potential NSAIDs to overcome side effects [6].

New small molecules as modern anti-inflammatory agents with synergic action and minimizing toxicity were developed using molecular hybridization and multiple-ligand drugs techniques [7, 8]. The combination of anti-oxidative and anti-inflammatory scaffolds in one molecule was shown to be a promising strategy for the search, further optimization and development of new hits/leads/candidates as potent and safe NSAIDs [8, 9]. The study of hybridization of potential scaffolds with both antioxidant and anti-inflammatory properties is of particular interest.

The structurally diverse thiazolidin-4-ones and 3,5-disubstituted-2-pyrazolines demonstrate good anti-inflammatory properties. These heterocycles generally realize their anti-iflammatory action through dual COX-2/LOX-5 inhibition, selective COX-2 inhibition or phospholipase A2 activity modulation [10-12]. Moreover, above-mentioned scaffolds possess potentital antioxidant properties. 4-Thiazolidone derivative rosiglitazone, with peroxisome proliferator activated receptor (PPAR-γ) agonism properties, can modulate NADPH-oxidase 4 (NOX4) and decrease the ROS generation induced by hypoxia in the mouse lung as well as human pulmonary artery smooth muscle cells. This effect is probably mediated by NF-kB [13, 14]. Other PPAR-γ agonist pioglitazone reduces brain superoxide in stroke-prone spontaneously hypertensive rats by NOX inhibition [15]. A lot of modified 2-pyrazolines demonstrate excellent antioxidant activity compared with the reference standard molecules in *in vitro* tests such as DPPH assay, NO scavenging, superoxide scavenging, H_2O_2-scavenging activity assay [12, 16, 17] *etc.*

Our experience in the search for potential pharmacological agents confirms the feasibility of synthesis and study of the properties of hybrid molecules with thiazlodin-4-one and pyrazoline moieties [18,19].

In the present work we describe synthesis and study of pyrazoline-thiazolidin-4-one hybrid Les-5581 - its acute toxicity, anti-inflammatory activity on the carragenin- and formaline-induced models, as well as influence on blood pattern, liver function and ulcerogenic impact under the treatment conditions. This work is a part of our research devoted to the search for anti-inflammatory agents and study on the inflammatory processes of different genesis [20-23].

Materials and Methods

Synthesis. All organic chemicals and solvents were procured from Sigma-Aldrich, Merck and used without doing any further purification. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F254) [were] used and spots visualized under UV light. The 5-ethoxymethylene-2-thioxo-thiazolidin-4-one (**1**) was synthesized using method [24]. 3,5-Bis-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole (**2**) was synthesized using method [19].

The synthesis of *5-[3,5-bis-(4-chloro-phenyl)-4,5-dihydro-pyrazol-1-ylmethylene]-2-thioxo-thiazolidin-4-one* (**3**): in a round bottom flask is placed by 0.01 mole of **1** and **2**, add 10 ml of ethanol. The mixture was heated at reflux for 2 hours. After cooling, the precipitate formed is filtered off and recrystallized from DMF-ethanol. Yield: 74 %, M.p. – >250 °C. ^{1}H NMR, δ, ppm: 3.56 dd, 4.07 dd, 5.19 m (3H, CH-CH_2, pyrazoline), 6.90–7.50 m (8H, 2*C_6H_4), 8.00 s (1H, -CH=), 13.00 bs (1H, NH). ESI-MS: *m/z*435 $[M+H]^+$ (100 %). Calculated, %: C, 52.54, H, 3.02, N, 9.67. $C_{19}H_{13}Cl_2N_3OS_2$. Found, %: C, 52.60, H, 3.10, N, 9.80.

Animals. The experiment was performed on white male rats weighing 180-220 g and white mice of both sexes weighing 20-27 g. All the animals used for this study were kept in standard cages and maintained under controlled laboratory conditions of temperature (22±3°C), humidity and 12 hour day-12 hour night and had free access to food (standard pellet diet) and water ad libitum. The animals were treated humanely throughout the study period adhering to the guideline for use and care of animals in declaration of Helsinki (National Research Council, 2011). The experiment design and study protocol were approved by the Animal Ethics Committee of the Danylo Halytsky Lviv National Medical University, protocol No. 19, September 17, 2018.

Acute toxicity. The acute toxicity studying was performed to assess the prospects of the synthesized compounds as biologically active substances. The LD_{50} value was determined by the method of Litchfield and Wilcoxon [25]. Test compounds were dissolved in tween-80 and purified water and administered intraperitoneally. The observation of the animals was performed for 14 days.

Anti-inflammatory (antiexudative) assay. The 54 male albino rats weighing 180-220 g were used for studying antiexudative activity. The selected animals were randomly divided into groups of six in each. The carrageenan-induced hind paw oedema was produced by the method of Winter *et al.* [26]. Carrageenan solution (1.0 % in sterile 0.9 % NaCl) was injected subcutaneosly into the subplanar region of the hind paw (0.1 mL to each paw) 1h after administration of the test compound. The synthesized compound was intraperitoneally injected in a dose 50 mg/kg (in saline solution with one drop of Tween-80™). Diclofenac (tablets "Diclofenac sodium", "Zdorovja narodu", Ukraine) in dose 8 mg/kg; Acetylsalicylic acid (tablets "Acetylsalicylic acid-Darnitsa", "Darnitsa", Ukraine) in dose 100 mg/kg, Ibuprofen (tablets "Ibuprofen-Darnitsa", "Darnitsa", Ukraine) in dose 50 mg/kg; Ketorolac (tablets "Ketanov", "Terapia SA", Romania) in dose 10 mg/kg were used as reference drug. Control rats received only saline solution with one drop of Tween-80™. The hind paw volume was measured with an elec-

tronic onkograph immediately before and 4h after carrageenan injection. The formaldehyde-induced paw edema in rats was produced by the injecting of 0.1 ml 2 % formaldehyde solution into sub-plantar aponeurosis of the left hind limb one hour after the drug administration [27]. Paw volumes were measured 4h, 24 h, 72 h and 120 h after formaldehyde injection as described earlier. Diclofenac in dose of 8 mg/kg was used as a reference drug. The effect of test compounds on a decrease of paw oedema was compared with that in intact control. The antiexudative activity (AEA) was expressed as a decrease of rats paw oedema, calculated using the equation and given in percentage:

$$AEA,\% = \frac{\Delta Vcontrol - \Delta Vexperiment}{\Delta Vcontrol} * 100\ \%$$

where $\Delta V_{control}$ and $\Delta V_{experiment}$ – the mean values of the volume difference for control and experimental animals hinds respectively.

Hematological Assays. Sampling blood [from the lateral tail vein of the rats] into vacuum tubes with solution Na_2EDTA was carried out for hematological studies in the appropriate experiment [28]. Level of hemoglobin and blood cells (erythrocytes, plates, leukocytes) was counted by automatic cell counter ABS-Micros 60-OT (Horiba Medical, Montpellier, France) in certified clinical laboratory of Danylo Halytsky Lviv National Medical University. White blood cell morphology was done (after staining by Romanowsky-Giemsa) by an experienced clinical laboratory specialist.

Assessment of liver function. The serum collected from the albino rats was used for estimation of biochemical parameters to determine the functional state of the liver. The levels of total alkaline phosphatase (ALP), gamma glutamyltransferase (γ-GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were estimated photometrically according to the reported methods using CORMAY ACCENT-200 automatic analyzer (PZ Cormay, Poland).

Ulcerogenic activity estimation. The estimation of ulcerogenic activity was performed according to the recommendations **[**29**].** All animals were sacrificed under deep anesthesia 6 hours after drug treatment, then their stomachs were removed, opened along the great curvature and rinsed with saline solution 0.9 %. The gastric mucosa was examined by means of a magnifying glass (2X) to assess the incidence of redness and spot ulcers. The mucosal damage was evaluated according to the following score: 0 - no visible damage; 1 - presence of edema or hemorrhages, 1-3 small ulcers; 2 - several (more than 3) small ulcers or 1 ulcer of considerable size; 3 - ulcer of considerable size (diameter up to 4 mm); 4 - several large ulcers; 5 - breakthrough ulcer. The gastric mucosal ulceration score was calculated by the difference between the mean score of each treated group and the mean score of control group.

Statistical Analysis. All data were processed using the statistical package Statistica 10.0 (Statsoft/Dell, Tulsa, OK, USA). The descriptive statistics of the data in tables include mean ± standard error of the mean (SEM) or mean ± standard deviation. Significance was assessed by using the one-way ANOVA followed by *t*-test. Values were considered statistically significant when *P* value is less than 0.05.

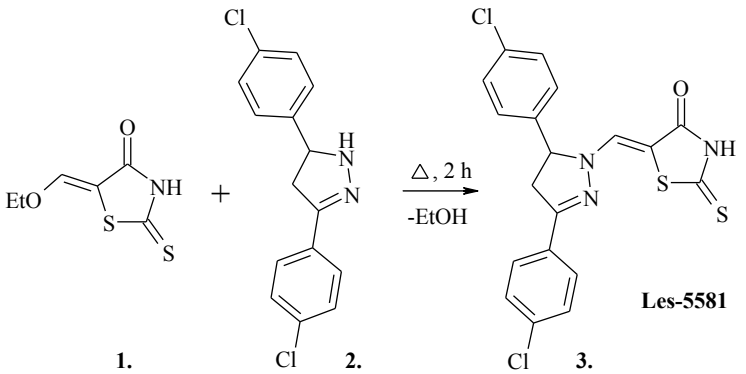

Fig. 1. Scheme of Les-5581 synthesis.

Results and discussion

The target hybrid Les-5581 has been synthesized in convenient and efficient aminolysis of 5-etoxymethylidenerhodanine (**1**) by 3,5-disubstituted-2-pyrazoline with satisfactory yield (74 %) and purity according to the scheme (Fig. 1):

The acute toxicity (LD_{50} value) of Les-5581 was studied by intraperitoneally administration in white mice. The approximate doses range from 300 mg/kg to 800 mg/kg was established based on series experiments. The LD_{50} value for Les-5581 was determined to be 510 mg/kg. During the experiment with dose 510 mg/kg the animals were clean, active, had satisfactory appetite, responded to sound and light stimuli, the urinary and defecation processes and general behavioral parameters were normal, breathing disorder was noted. The animals deaths during the first day were observed in animal groups that received Les-5581 in a dose of more than 510 mg/kg.

Anti-inflammatory activity of Les-5581 was studied with dose 50 mg/kg, i.e. 0.1 LD_{50} dose. The carrageenan-induced hind paw oedema as the acute process model was used for anti-inflammatory activity estimation at the first stage of experiment. The peak of pathology process was observed 4 hours after the inflammation induction. At this moment, the tested Les-5581 demonstrated a good level of the anti-inflammatory activity (40.2 % of inflammation inhibition), which was the same as with Ibuprofen, a little bit higher than with acetylsalicylic acid and ketanov, and only by 13.5 % less than the diclofenac sodium activity (Table 1).

The formaldehyde test was used for the modeling of chronic inflammatory process. Les-5581 at dose of 50 mg/kg demonstrated good level of activity growing in dynamics over 5 days of experiment (Table 2). Noteworthy, a better anti-inflammatory activity (45.1 %) was observed on the 5th day (120 h) compared to diclofenac sodium in these conditions. During the period from 4 h to 72 h the antiexudative activity of Les-5581 was a slightly lower than the diclofenac sodium effect.

So, Les-5581 displays promising anti-inflammatory activity in both acute and chronic inflammatory process models.

Hematological profile and impact on blood system of Les-5581 have been estimated in the

Table 1. In vivo **anti-inflammatory activity of Les-5581 on carrageenan-induced paw oedema in rats (intraperitoneally use, M±m, n=6 in each group)**

Groups/Parameters	Doses	Rat hind limb volume increase, 4 hours, %	Inflammation inhibition, % (AEA)
Carragenan (Pathology model)	1 %. 0.1 ml	131.2±5.1	-
Diclofenac sodium	8.0 mg/kg	70.1±3.2	46.5
Acetylsalicylic acid	100 mg/kg	80.4±3.5	38.4
Ibuprofen	50.0 mg/kg	78.5±4.4	40.1
Ketanov	10.0 mg/kg	79.2±4.2	39.6
Les-5581	50.0 mg/kg	78.4±3.8	40.2

Table 2. In vivo **anti-inflammatory activity of Les-5581 on formaldehyde-induced paw oedema in rats (intraperitoneally use, M±m, n=6 in each group)**

Compounds, doses / Time points	Growth of oedema (%) compared to intact animals			
	4 hours	24 hours	72 hours	120 hours
Formaldehyde 2 %, 0.1 ml (Pathology model)	121.6±8.0	110.3±7.1	91.1±6.2	73.1±6.3
Les-5581, 50 mg/kg	85.0±7.1	74.6±6.4	54.3±4.8	40.1±3.2
	Inhibition of oedema (%) compared to pathology model			
	30.1	32.4	40.4	45.1
Diclofenac sodium, 8 mg/kg	68.7±5.3	63.7±5.4	45.4±2.5	35.8±2.9
	Inhibition of oedema (%) compared to pathology model			
	43.5	42.2	50.1	38.3

end of experiment for both inflammation models in the blood test (Tables 3-5). No influence on blood pattern was observed.

An insignificant increase in the plate level, moderate an increase in the erythrocyte sedimentation rate and strong neutrophilia and

Table 3. **Hematological profile of rats with carrageenan-induced paw oedema and treated with Les-5581 and diclofenac sodium (intraperitoneally use, M±m, n=6 in each group)**

Groups/Blood parameters	Intact control	Carragenan, 0,1 ml, 1,0 %	Les-5581, 50 mg/kg	Diclofenac sodium, 8 mg/kg
ESR, mm/h	0.9±0.2	2.1±0.3$^{\#}$	1.5±0.1*	1.6±0.2*
Hemoglobin, g/l	148±14	146±23	148±19	148±21
Red blood cells,10^{12}/l	7.9±0.6	8.1±0.8	8.2±0.7	8.0±0.9
Plates,10^{9}/l	705±51	823±71	773±64	761±58
White blood cells,10^{9}/l	8.2±1.2	9.5±1.1	9.0±1.2	9.1±1.5
Stab leukocytes, %	2.1±0.3	3.2±0.3*	2.4±0.3	2.7±0.3
Segmental leukocytes, %	22.5±2.4	33.9±3.9*	28.5±2.5	30.1±2.3*
Lymphocytes, %	71.4±2.4	56.8±2.3*	63.7±2.4*	61.8±2.0*
Eosinophils, %	1.2±0.3	1.7±0.3	1.5±0.3	1.6±0.3
Basophils, %	0.8±0.2	0.9±0.3	0.9±0.3	0.9±0.3
Monocytes, %	2.0±0.4	3.5±0.4*	3.0±0.4	2.9±0.4

ESR — Erythrocyte sedimentation rate, * — $p < 0.05$; $^{\#}$ — $p < 0.001$ compared with intact control group

Table 4. **Hematological profile (red blood) of rats with formaldehyde-induced paw oedema and treated with Les-5581 and diclofenac sodium (intraperitoneally use, M±m, n=6 in each group)**

Parameters/ Time points	ESR, mm/h	Hemoglobin, g/l	Red blood cells, 10^{12}/l	Plates, 10^9/l
Intact control				
	0.8±0.1	156±12	8.4±0.7	635±54
Formaldehyde, 2 %, 0,1 ml				
24 h	2.7±0.3#	152±14	7.9±0.6	709±63
72 h	1.9±0.3*	156±20	8.2±0.7	756±55
120 h	1.5±0.1	153±18	8.8±0.7	732±59
Les-5581, 50 mg/kg				
24 h	1.9±0.3*	149±15	8.4±0.8	733±47
72 h	1.5±0.2*	153±17	8.6±0.6	698±62
120 h	1.3±0.3	155±18	7.9±0.7	701±68
Diclofenac sodium, 8 mg/kg				
24 h	1.7±0.3*	150±19	8.0±0.5	707±59
72 h	1.4±0.2*	152±20	8.3±0.7	686±70
120 h	1.2±0.2	154±14	8.1±0.7	735±81

ESR — Erythrocyte sedimentation rate, * — $p < 0.05$; # — $p < 0.001$ compared with intact control group

lymphocytopenia were observed in experimental animals 4 hours after administration of phlogogenic agents. The application of Les-5581 and diclofenac sodium had a positive effect on the blood parameters normalization. The values of the parameters in the groups with treatment by Les-5581 and diclofenac sodium on the 5th day of the experiment reached the level of intact animals on the formaldehyde-induced paw oedema model. At the same time, in the "pathology model" group, the corresponding indicators on the 5th day reached only the 4-hour level in the treated animals.

A significant increase of liver enzymes levels was observed in the formaldehyde-induced paw oedema conditions for untreated animals (Table 6). If compared with the intact control, in this group the enzymes levels were higher as follows: ALT 1.8-fold, AST 1.9-fold, ALP 1.7-fold, γ-GGT 1.5-fold.

Table 5. **Hematological profile (white blood) of rats with formaldehyde-induced paw oedema and treated with Les-5581 and diclofenac sodium (intraperitoneally use, M±m, n=6 in each group)**

Parameters / Time points	White blood cells, 10^9/l	Stab leukocytes, %	Segmental leukocytes, %	Lymphocytes, %	Eosinophils, %	Basophils, %	Monocytes, %
Intact control							
-	7.3±1.3	1.4±0.3	26.2±1.8	68.5±1.9	1.2±0.3	0.9±0.2	1.8±0.4
Formaldehyde, 2 %, 0.1 ml							
24 h	9.6±1.2*	2.3±0.4*	34.8±3.3*	56.9±2.0	1.7±0.3	0.8±0.2	3.5±0.4
72 h	9.0±2.4	2.2±0.3	35.4±2.9*	56.6±1.7	1.6±0.3	0.9±0.3	3.3±0.4
120 h	8.5±2.0	2.0±0.3	30.3±2.2	62.7±2.2	1.4±0.3	0.9±0.3	2.7±0.4
Les-5581, 50 mg/kg							
24 h	8.7±2.1	2.2±0.4	31.3±2.7	61.6±1.8	1.7±0.4	0.8±0.2	2.9±0.3
72 h	8.3±2.3	1.7±0.2	28.7±2.1	64.9±2.0	1.4±0.3	0.8±0.2	2.5±0.3
120 h	8.0±1.6	1.6±0.3	27.2±2.3	66.5±2.1	1.3±0.2	0.9±0.3	2.5±0.3
Diclofenac sodium, 8 mg/kg							
24 h	8.9±1.8	2.1±0.3	32.8±3.0	59.5±2.1	1.6±0.3	0.9±0.2	3.1±0.4
72 h	8.2±1.9	1.8±0.2	27.5±2.5	65.8±2.4	1.4±0.2	0.8±0.2	2.7±0.3
120 h	8.1±1.9	1.5±0.4	26.1±2.4	67.3±2.2	1.5±0.2	0.9±0.3	2.7±0.3

*$p<0.05$; #$p<0.001$ compared with intact control group

Table 6. **The liver enzymes activity in rats with formaldehyde-induced paw oedema and treated with Les-5581 and diclofenac sodium (intraperitoneally use, M±m, n=6 in each group)**

Parameters/Time points	ALT, U/l	AST, U/l	ALP, U/l	γ-GGT, IU/l
Intact control				
	63.2±7.1	179.1±21.8	257.5±15.9	3.4±0.9
Formaldehyde, 2 %, 0.1 ml				
24 h	119.3±9.4#	357.0±16.5#	453.8±39.2#	5.2±0.8*
72 h	95.0±8.2*	275.5±19.8#	378.2±24.7*	5.3±1.0*
120 h	79.6±6.3	223.7±18.2	305.2±29.4	4.4±0.6
Les-5581, 50 mg/kg				
24 h	92.5±8.5	223.2±21.0	312.2±31.6	5.0±0.7
72 h	88.2±7.7	209.8±18.9	296.9±28.7	5.4±1.0*
120 h	77.6±6.8	197.6±19.0	279.7±24.5	5.0±1.1
Diclofenac sodium, 8 mg/kg				
24 h	95.9±6.2*	236.4±29.4*	293.8±28.4	5.1±0.6
72 h	81.2±7.0	193.2±20.3	274.1±22.8	5.2±0.9*
120 h	69.7±5.3	180.2±16.8	263.7±21.4	4.9±0.8

* — $p < 0.05$; # — $p < 0.001$ compared with intact control group

At the same time, the administration of tested Les-5581 and reference drug does not show any negative impact and results in return from the biochemical changes to a normal level.

Les-5581 was evaluated for the ulcerogenic activity after repeated apllication in dose 50 mg/kg in rats in the formaldehyde-induced paw oedema test. The results were compared with the intact control group and diclofenac sodium group (Table 7). The second group showed significant ulcerogenic risk with a high ulceration score. The tested compound did not show any ulcerogenic activity.

Table 7. **Ulcerogenic pattern of rats with formaldehyde-induced paw oedema and treated with Les-5581 and diclofenac sodium (intraperitoneally use, M±m, n=6 in each group)**

Parameters/Groups	Animals with ulcers, n'	Ulcer degree, points
Intact control, 120 h	0	0±0.00
Formaldehyde, 2 %, 0.1 ml, 120 h	0	0±0.00
Les-5581, 50 mg/kg, 120 h	0	0±0.00
Diclofenac sodium, 8 mg/kg, 120 h	6	1.6±0.2

So, the analysis of results suggests that Les-5581 is [a] good molecular platform for designing new potential anti-inflammatory agents with a low toxicity. The absence of ulcerogenic action and no influence on general blood parameters allow assumption that in the realization of anti-inflammatory effect of Les-5581 the inhibition of COX-2 or LOX-5 plays a key role rather than the COX-1 inhibition. Probably, the presence of half-saturated pyrazoline ring in the Les-5581 structure might have important impact on the compound redox properties. Therefore, the hybrid Les-5581 can reduce the "oxidative stress pathways", which occur under the inflammation process and are responsible for both anti-inflammatory effect realization and ulcerogenic action.

Conclusions

In the present study we report the anti-inflammatory activity evaluation and toxicity characterization of pyrazoline-thiazolidin-4-one hybrid (Les-5581) *in vivo*. Les-5581 demonstrated a good level of anti-inflammatory activity in the models of carrageenan- (acute pro-

cess) and formaldehyde-induced (chronic process) rat paw oedema; it was shown to be moderately toxic by intraperitoneally administration (LD_{50} =510 mg/kg). The study of side effects indicates that use of Les-5581 does not provoke negative changes in blood test, liver enzymes function and does not manifest the ulcerogenic action. The studied pyrazoline-thiazolidin-4-one hybrid is a good candidate for further investigations regarding its potential use in therapy of the inflammatory diseases.

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Синтез та оцінка *in vivo* піразолін-тіазолідин-4-онового гібриду Les-5581 як потенційного нестероїдного протизапального агента

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Мета. Синтез, *in vivo* дослідження гострої токсичності, протизапальної (антиексудативної) активності та оцінка побічних ефектів в умовах терапевтичного застосування на експериментальних тваринах піразолін-тіазолідин-4-онового гібриду Les-5581. **Методи.** Традиційний органічний синтез. Метод Літчфілда і Уілкоксона. Моделі каррагенін- та формальдегід-індукованого запального набряку лапи білих щурів. Клінічні лабораторні тести: дослідження загальних параметрів крові та біохімічного профілю функції печінки (рівні АЛТ, АСТ, ЛФ та γ-ГГТ). Оцінка ульцерогенної дії. **Результати.** Здійснено синтез цільового гібриду Les-5581 за допомогою зручного та ефективного амінолізу 5-етоксиметиліденроданіну при дії 3,5-біс-(4-хлорфеніл)-4,5-дигідро-1*H*-піразолу. Визначено показник LD_{50} для Les-5581 при внутрішньоочеревинному введенні, який становить 510 мг/кг. Встанолено, що Les-5581 проявляє значну протизапальну активність в дозі 50 мг/кг (внутрішньоочеревинне введення) на каррагенін- та формальдегід-індукованих моделях запального процесу у білих щурів. В той же час застосування Les-5581 не спричиняє ульцерогенної дії та негативного впливу на загальні показники крові, функцію ензимів печінки. **Висновки.** Піразолін-тіазолідин-4-оновий гібрид Les-5581 є хорошою молекулярною платформою для розробки нових потенційних протизапальних засобів з низькою токсичністю та відсутністю ульцерогенної дії.

Ключові слова: піразолін, тіазолідин-4-он, НПЗЗ, молекулярний гібрид

Синтез и оценка *in vivo* пиразолин-тиазолидин-4-онового гибрида Les-5581 как потенциального нестероидного противовоспалительное агента

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Цель. Синтез, *in vivo* исследования острой токсичности, противовоспалительной (антиэкссудативной) активности и оценка побочных эффектов в условиях терапевтического применения на экспериментальних животных пиразолин-тиазолидин-4-онового гибрида Les-5581. **Методы.** Традиционный органический синтез. Метод Литчфилда и Уилкоксона. Модели каррагенин- и формальдегид-индуцированного воспалительного отека лапы белых крыс. Клинические лабораторные тесты: исследование общих параметров крови и биохимического профиля функции печени (уровни АЛТ, АСТ, ЩФ и γ-ГГТ). Оценка ульцерогенного действия. **Результаты.** Осуществлён синтез целевого гибрида Les-5581 с помощью удобного и эффективного аминолиза 5-етоксиметилиденроданина при действии 3,5-бис-(4-хлорфенил)-4,5-дигидро-1Н-пиразола. Определено значение LD50 для Les-5581 при внутрибрюшинном введении, которое составляет 510 мг/кг. Установлено, что Les-5581 проявляет значительную противовоспалительную активность в дозе 50 мг/кг (внутрибрюшинное введение) на каррагенин- и формальдегид-индуцированных моделях воспалительного процесса у белых крыс. В то же время применение Les-5581 не вызывает негативного влияния на общие показатели крови, функцию энзимов печени и не оказывает ульцерогенного действия. **Выводы.** Пиразолин-тиазолидин-4-оновый гибрид Les-5581 является хорошей молекулярной платформой для разработки новых потенциальных противовоспалительных средств с низкой токсичностью и отсутствием ульцерогенного действия.

Ключевые слова: пиразолин, тиазолидин-4-он, НПВП, молекулярный гибрид

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