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New Hybrid Molecules Based on Sulfur-Containing Nicotinonitriles: Synthesis, Analgesic Activity in Acetic Acid-Induced Writhing Test, and Molecular Docking Studies

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Abstract—New hybrid molecules bearing furyl and 1,4-dihydronicotinonitrile (or 1,4,5,6-tetrahydronicotinonitrile) fragments have been prepared. The analgesic activity was studied in vivo (rats) in acetic acid-induced writhing test. Some compounds showed activity exceeding that of the reference compound (metamizole). Molecular docking was performed with all the compounds against COX-1 and COX-2. Also, we performed the docking studies in order to find new possible protein targets.

Keywords: nicotinonitriles, 1,4-dihydropyridines, 1,4,5,6-tetrahydropyridines, analgesics, molecular docking

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INTRODUCTION

In the modern world, special attention is paid to chronic pain syndrome, which often occurs as a result of various pathological processes. Thus, pain is an integral companion in more than 60% of cancer patients, especially in the presence of a widespread tumor process [1–3]. Among currently existing drugs of nonsteroidal origin, indomethacin, ketorolac, ibuprofen, and diclofenac have the most powerful anti-inflammatory activity [4–6]. However, the gastropathy they cause in some cases limits the long-term use of these drugs (see, for example, Varrassi et al. [7]). For this reason, today the issue of development, research and introduction into clinical practice of new highly effective, safe and affordable low-molecular-weight analgesics of a new generation is acute [8–10]. Of particular interest from this point of view are partially saturated derivatives of nicotinonitrile (3-cyanopyridine), synthetically available compounds, for which high activity against viruses of the genus *Flavivirus* (tick-borne encephalitis virus, Powassan virus [11]), pronounced anti-inflammatory [12] and analeptic effects [13], adaptogenic [14] and analgesic effects [15]. Despite the rather good study of nicotinonitriles (reviews [16–19]), partially hydrogenated analogs have not been adequately studied, especially in terms of their biological activity.

In recent years, a very popular direction in drug design is the synthesis of so-called hybrid or multimodal molecules [20–25]. This concept is based on the combination in one molecule of fragments with different pharmacotherapeutic profiles, connected directly or through a flexible spacer. The consequence of such "conjugation" may be an increase in the effect of the drug due to more efficient binding to the protein target, the emergence of new types of activity, the elimination of side effects, or a decrease in drug resistance.

The purpose of this work is to create hybrid molecules that bind pharmacophore subunits – fragments of a partially hydrogenated pyridine ring and a 2-furyl residue, and to study the analgesic activity of the obtained compounds in vivo in the acetic acid writhing test. Partially saturated pyridine subunits belong to the group of privileged scaffolds [26, 27]. The choice of the furan fragment was due to the biological significance of furan derivatives [28–31] and the preparative convenience of introducing the 2-furyl substituent.

RESULTS AND DISCUSSION

Compound screening. Using the OSIRIS Property Explorer [32], SwissADME [33], admetSAR [34], and

Abbreviations: NSAID, non-steroidal anti-iflammatory drugs; ADMET, absorption, distribution, metabolism, excretion, toxicity pharmacokinetics parameters; COX-1, cyclooxigenase 1; COX-2, cyclooxygenase 2.

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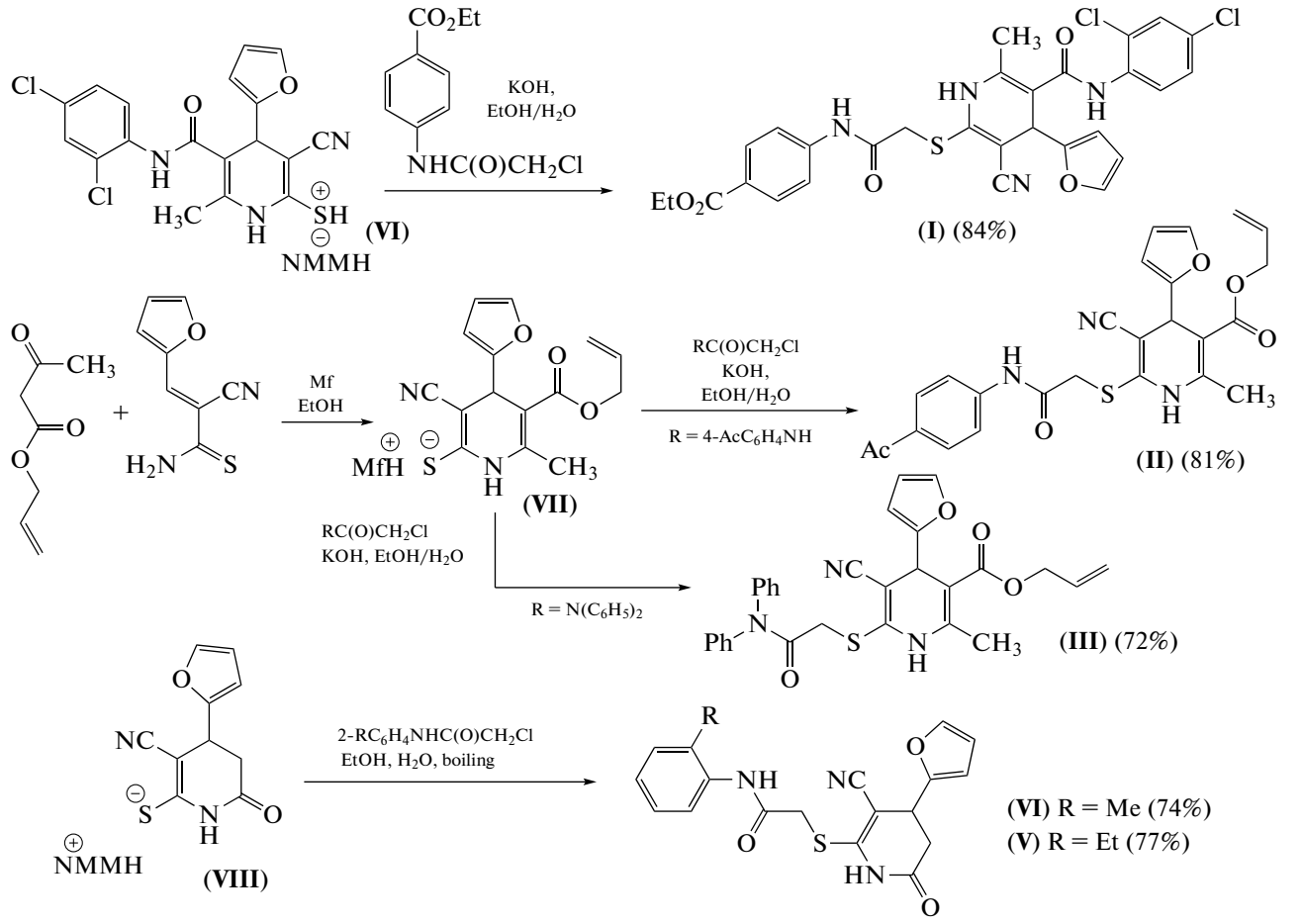
GUSAR [35] software services, the ADMET parameters were estimated. (Absorption, Distribution, Metabolism, Excretion, Toxicity) and compliance with the bioavailability criteria for the base of compounds from 170 previously synthesized new sulfur-containing derivatives of 1,4-di- and 1,4,5,6-tetrahydropyridines containing a 2-furyl substituent in position 4 of the pyridine ring. The following parameters were evaluated: molecular weight of the compound, lipophilicity as *c*log*P* is the logarithm of the distribution coefficient between *n*-octanol and water $\log(c_{octanol}/c_{water})$, TPSA (topological polar surface area), number of hydrogen bond acceptors and donors, solubility (log*S*), a number of toxicological characteristics (calculated mutagenic potential according to Ames, acute toxicity, etc.), the possibility of gastrointestinal absorption and penetration through the blood-brain barrier, an overall assessment of the pharmacological potential of the compound (drug score) (see Supplementary Information, Tables S1 and S2). Based on the results of the analysis, five compounds were selected from the library (**I–V**) (Scheme 1), which for the most part meets the criteria for oral bioavailability, does not reveal the predicted risk of toxic effects and has rather high predicted values of the pharmacological potential of the compound (drug score). Estimated assessment of acute toxicity allows attributing compounds (**I–V**) to **IV** and **V** hazard classes according to OECD criteria [36]. Using the online service Swiss Target Prediction [37, 38], a preliminary assessment of biotargets was also carried out.



Scheme 1. Synthesis of 4-(2-furyl)-1,4-dihydropyridine-3-carbonitriles (**I**-**III**) and 4-(2-furyl)-1,4,5,6-tetrahydropyridine-3-carbonitriles (**IV**) and (**V**). NMM, *N*-methylmorpholine, Mf, morpholine.

Five samples of sulfur-containing di- and tetrahydropyridines selected using virtual bioscreening programs are the most promising, taking into account the proposed biotargets for the pharmacological correction of pain. Possible targets for compounds (**I–V**), according to preliminary estimates, there may be COX-1 and COX-2 cyclooxygenases.

Synthesis of compounds (I–V). The initial 6-methyl-4-(2-furyl)-5-[(2,4-dichlorophenyl)carbamoyl]-3-cyano-1,4-dihydropyridine-2-thiolate *N*-meth-

Table 1. Analysis of variance of the analgesic activity of the compounds (**I**–**V**) in vivo on rats in the acetic acid writhing test

Group of animals	Dose, mg/kg	Average, *a*	Dispersion, σ^2	Standard deviation, σ	The coefficient of variation, *V*
Control	–	23.0	2.22	1.49	6.48
Analgin	7	21.0	1.78	1.33	6.35
(I)	5	18.8	0.84	0.91	4.89
(II)	5	14.9	0.99	0.99	6.70
(III)	5	17.6	1.15	1.07	6.11
(IV)	5	15.3	0.9	0.95	6.20
(V)	5	10.3	1.34	1.16	11.26

Animals of the control group were injected with 1 ml of a 7% solution of acetic acid intraperitoneally.

ylmorpholine (**VI**) required to obtain a connection (**I**), was synthesized according to the general procedure described in [39–41] (Scheme 1). Connection (**I**) was synthesized by the subsequent *S*-alkylation of the starting thiolate (**VI**) *N*-chloroacetyl derivative of benzocaine in a water–alcohol medium in the presence of a 10% KOH solution. Morpholinium 5-[(allyloxy)carbonyl]-6-methyl-4-(2-furyl)-3-cyano-1,4-dihydropyridine-2-thiolate (**VII**), necessary for obtaining 1,4-dihydronicotinonitriles (**II**) and (**III**), was obtained according to the procedures described in the literature [42, 43]. Sulfur-containing dihydropyridines (**II**) and (**III**) were obtained by alkylation of thiolate (**VII**) with the corresponding α-chloroacetamides. On heating 1,4,5,6-tetrahydropyridine-2-thiolate (**VIII**) [44–46] in aqueous alcohol with *ortho*-*R*-substituted chloroacetanilide gave the target compounds (**IV**) and (**V**) (Scheme 1).

The structure of the compounds (**I–V**) confirmed by the data of IR and NMR spectroscopy on nuclei ^{1}H and ^{13}C. The spectral data are given in Supplementary Information.

Analgesic activity of compounds (I–V) in vivo in the acetic acid writhing test. Determination of the analgesic activity of the compounds was carried out on the model of acetic writhing, based on the contraction of the abdominal muscles due to irritation of the serous membrane injected intraperitoneally with a solution of acetic acid. The criterion of analgesic activity in this test is considered to be a significant decrease in the amount of writhing in the group of animals treated with the drug relative to the control group, provided that the compound does not have a myorelexant effect [47, 48].

Experiments were carried out on mature male rats ($n = 70$) in the autumn–winter period according to the recommendations [49–51]. The rats were divided into seven groups ($n = 10$): control (with simulated peritovisceral pain without pharmacological correction), reference (comparison group, analgin) and five experimental groups according to the number of studied compounds (**I**–**V**). Rats of the reference group were injected with analgin (7 mg/kg), animals of the experimental groups with compounds (**I**–**V**) (intragastrically, 5 mg/kg) 1.5 hours before the administration of the algogen. Algogen (acetic acid) was injected intraperitoneally in a volume of 1.0 mL of a 7% solution once [47–49], after 20 min, the number of acetic writhings was counted over a 15-minute interval.

The experimental data obtained, recorded during the observation of the experimental animals of the control group, are given in numerical terms in terms of the number of acetic writhings in Table 1. Thus, the results of the analysis of the data array obtained showed that 20 min after intraperitoneal injection of 1 mL of 7% acetic acid, the rats began to pull their hind limbs backwards, and they pressed the anterior abdominal wall to the bottom of the cage. All rats in this group were thirsty. During 15 min of observation, the number of acetic writhings was 23.0. The use of the non-steroidal anti-inflammatory drug (NSAID) metamizole sodium (analgin) (reference group) 1.5 hours before the injection of the algogen (acetic acid solution) contributed to a decrease in the number of writhings by 8.7% (up to 21.0).

As can be seen from the Table 1 data, all tested compounds (**I**–**V**), administered intragastrically, are able to reduce the number of acetic writhings in rats of the experimental groups after an intraperitoneal injection of 1 mL of a 7% solution of acetic acid to a greater extent than the reference drug. Thus, in laboratory animals treated with the compound (**I**) 90 min before the administration of the algogen, a decrease in acetic acid writhing was found in comparison with the control group of rats by 18.3%. In the experimental group of animals receiving 1,4-dihydropyridine (**III**), a decrease in acetic acid writhing by 23.5% was revealed in comparison with rats in the control group. Tetrahydropyridine (**IV**) was even more effective as an analgesic; in this group, a decrease in the studied quantitative indicator by 33.5% was registered in comparison with rats in the control group without pharmacological correction (more effective than analgin by 27.1%).

The most significant results in the experiment were recorded in the experimental groups of rats treated with 1,4-dihydronicotinonitrile (**II**) and tetrahydron-

Table 2. Values of scoring functions for compounds (**I**–**V**) and comparators

Compound	Calculated value of the scoring function, kcal/mol	
	COX-1 (PDB ID 1HT5)	COX-2 (PDB ID 1CX2)
(I)	−10.1	−7.3
(II)	−8.2	−6.6
(III)	−9.4	−7.0
(IV)	−8.9	−6.8
(V)	−9.0	−7.2
Analgin	−7.7	−6.3
Ibuprofen	−6.4	−5.9
diclofenac	−7.1	−6.1
Indomethacin	−9.2	−7.4
Ketorolac	−7.2	−6.5
Aspirin	−5.7	−6.1
Meloxicam	−9.6	−9.7
Nimesulide	−8.2	−9.0
Valdecoxib	−8.5	−8.5

icotinonitrile (**V**). Compound (**II**) containing in its structure a fragment *para*-aminobenzoic acid is able to reduce the number of acetic writhings by 35.2% when compared with the indicators in the control group. Comparison with reference group rats showed that the compound (**II**) was 1.4 times more effective than analgin in eliminating acute pain.

The introduction (**V**) compound resulted in a 55.2% reduction in the number of acetic writhings compared to the control group. At the same time, its analgesic activity exceeds that of analgin by 2.04 times.

Molecular docking. Molecular docking of compounds (**I**–**V**) was performed using the Webina 1.0.3 web service (https://durrantlab.pitt.edu/webina/), an online application for launching AutoDock Vina in a browser [52]. Crystallographic models of target proteins, cyclooxygenases COX-1 (PDB ID 1HT5) and COX-2 (PDB ID 1CX2), were taken from the Protein Data Bank (www.rcsb.org) and prepared using Autodock Tools (https://autodock.scripps.edu/). NSAIDs from the group of nonselective COX-1 inhibitors (ibuprofen, diclofenac, indomethacin, ketorolac, aspirin) and selective COX-2 inhibitors (meloxicam, nimesulide, valdecoxib) were used as reference compounds. The 3D structures of the reference drugs were taken from the Drugbank database (https://go.drugbank.com/). Table 2 shows the values of the calculated scoring functions of compound binding (**I**–**V**) and reference preparations with active sites of COX-1 and COX-2 cyclooxygenases.

Based on the results given in Table 2, the compounds (**I**), (**III**) and (**V**) show a greater affinity for COX-1 and COX-2 cyclooxygenases. However, all compounds (**I**–**V**) show a greater affinity for COX-1 and COX-2 in comparison with NSAIDs from among the nonselective inhibitors of COX-1. Selective inhibitors from among the reference compounds (especially meloxicam) show a higher affinity for COX-2 than the studied compounds, while for COX-1 the results can be considered comparable.

In order to identify other possible protein targets for compounds (**I**–**V**), a search was carried out using the new protein ligand docking protocol GalaxySagittarius [53] based on the GalaxyWeb web server [54, 55]. The 3D structures of the compounds were preliminarily optimized by means of molecular mechanics in the MM2 force field in order to select the geometry corresponding to the energy minimum. Molecular docking using the GalaxySagittarius protocol was performed in the Binding compatibility prediction and Re-ranking using docking modes. Table 3 S3 (see Supplementary Information) presents docking results for each of the compounds (**I**–**V**) for 20 protein–ligand complexes with the minimum binding free energy ΔG_{bind} and the best overall score for protein–ligand interaction. Predicted protein targets are identified by ID in the Protein Data Bank (PDB) and in the UniProt database. In general, it can be noted that common targets for compounds (**I**–**V**) is blood coagulation factor Xa (PDB ID 2P95), epidermal growth factor receptor (EGFR, PDB ID 3BEL), peroxisome proliferator-activated receptor-gamma (hPPARgamma, PDB ID 2VV0), free fatty acid receptor-1 (GPR40, PDB ID 5TZR), liver X-receptor (LXRβ, PDB ID 5JY3) and a number of others. Tetrahydropyridines (**IV**) and (**V**) are probable ligands for protein kinase A (PDB ID 4UJA), the first bromodomain of bromodomain-containing protein 4 (BRD4, PDB ID 5D3S), mutant Bcr-Abl^{T315I} tyrosine kinase (PDB ID 4TWP), which plays a key role in the pathogenesis of chronic myeloid leukemia, as well as for tyrosine protein kinase ITK (PDB ID 4PQN). It should be noted a higher affinity for protein targets of 1,4-dihydropyridine derivatives (**I**–**III**) compared to 1,4,5,6-tetrahydropyridines (**IV**) and (**V**). Figures 1 and 2 show 3D visualizations of individual ligand–receptor complexes for compounds (**I**) and (**V**).

In general, according to the results of docking compounds (**I**–**V**) are of interest for further screening in order to search for antithrombotic, antitumor agents, and agents for the treatment of autoimmune diseases.

EXPERIMENTAL

Equipment and general conditions for identification of compounds. NMR spectra ^{1}H and ^{13}C were recorded on a spectrometer 400/MR (Agilent, United States;

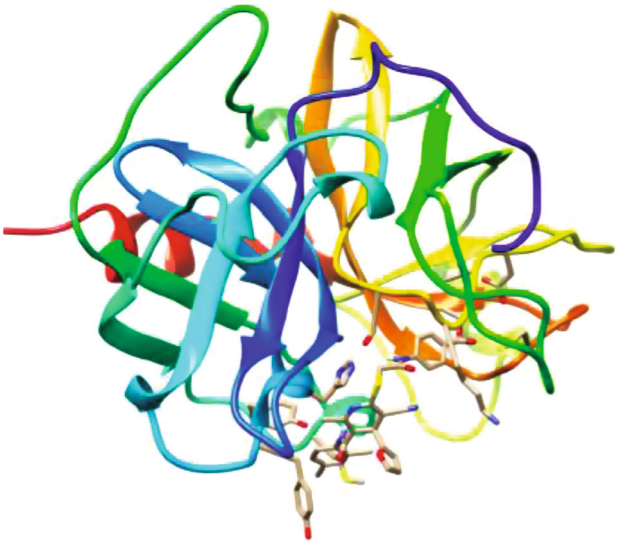


Fig. 1. The predicted structure of the protein–ligand complex of dihydropyridine (**I**) and coagulation factor XIa (PDB ID 4X6O).

400 and 100 MHz, respectively) in a solution of DMSO-d_6, residual solvent signals (δ 2.49, 39.50 ppm, DMSO) were used as a standard. IR spectra were obtained on a Vertex 70 spectrophotometer (Bruker, Germany) with an ATR attachment on a diamond crystal, error ±4 cm^{-1}. Elemental analysis was performed on an Elementar Vario Microcube instrument (Elementar, Germany). The individuality of the samples obtained was controlled by TLC on Sorbfil-A plates (OOO Imid, Krasnodar, Russia), eluent acetone–hexane, 1 : 1, developer iodine vapor, UV detector.

Ethyl 4-(2-((6-methyl-4-(2-furyl)-5-((2,4-dichlorophenyl)carbamoyl)-3-cyano-1,4-dihydropyridin-2-yl)-thio) acetamido)benzoic acid (I). 1,4-Dihydropyridine-2-thiolate *N*-methylmorpholine (**VI**) [41] (0.6 g, 1.18 mmol) was suspended in 5 mL of EtOH, 0.65 mL (1.25 mmol) of 10% aqueous KOH was added with stirring. The resulting solution was added through a paper filter to a warm (40–50°C) solution of 4-(2-chloroacetamido)benzoic acid ethyl ester (0.29 g, 1.18 mmol) in 3 mL of EtOH. The mixture was stirred and heated (40–50°C), a precipitate formed within 5 min, which, after 12 h, was filtered off, washed with aqueous EtOH, and dried at 60°C. White powder, yield 0.61 g (84%).

Allyl esters 6-[(2-(*R*-amino-2-oxoethyl)thio]-2-methyl-4-(2-furyl)-5-cyano-1,4-dihydropyridine-3-carboxylic acid (II), (III); general methodology. Morpholinium 1,4-dihydropyridine-2-thiolate (**VII**) [42, 43] (0.75 g, 1.93 mmol) was suspended in 8 mL of EtOH, 1.0 mL (1.93 mmol) of 10% aqueous KOH was added with stirring, and stirred until dissolved. The resulting solution was slowly added through a paper filter to a solution of the corresponding α-chloroacetamide (1.95 mmol) in EtOH (5–6 mL). The mixture was stirred for 3 h, the precipitate was filtered off, washed with aqueous EtOH and dried at 60°C.

6-{[2-(4-Acetylphenyl)amino-2-oxoethyl]thio}-2-methyl-4-(2-furyl)-5-cyano-1,4-dihydropyridine-3-carboxylic acid allyl ester (II). White powder, 81% yield.

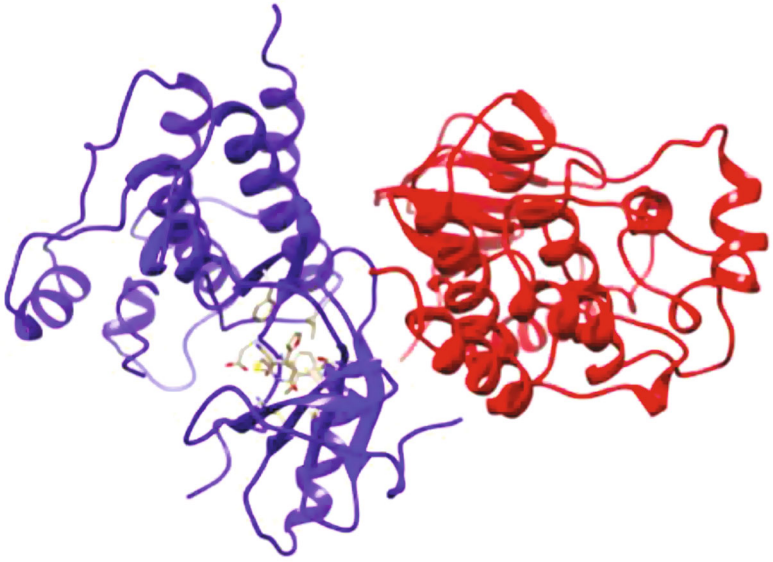


Fig. 2. The predicted structure of the protein–ligand complex of tetrahydropyridine (**V**) and proto-oncogenic serine-threonine protein kinase B-raf (PDB ID 4MBJ).

2-Methyl-6-{[2-(diphenylamino)-2-oxoethyl]thio}-4-(2-furyl)-5-cyano-1,4-dihydropyridine-3-carboxylic acid allyl ester (III). Beige powder, 72% yield.

2-{[6-Oxo-4-(2-furyl)-3-cyano-1,4,5,6-tetrahydropyridin-2-yl]thio}-*N*-(2-*R*-phenyl)acetamides (IV), (V); general methodology. Tetrahydropyridine-2-thiolate *N*-methylmorpholine (**VIII**) [44–46] (0.5 g, 1.6 mmol) was dissolved on heating in 60% EtOH (7 mL). The resulting solution was added through a paper filter to a warm (40–50°C) solution of the corresponding *ortho*-R-substituted chloroacetanilide (1.6 mmol) in EtOH (3–4 mL) with stirring. The precipitate formed after 48 h was filtered off, washed with 60% EtOH and petroleum ether, and dried at 60°C.

N-(2-Methylphenyl)-2-{[6-oxo-4-(2-furyl)-3-cyano-1,4,5,6-tetrahydropyridin-2-yl]thio}acetamide (IV). Beige powder, 74% yield.

2-{[6-Oxo-4-(2-furyl)-3-cyano-1,4,5,6-tetrahydropyridin-2-yl]thio}-N-(2-ethylphenyl)acetamide (V). Beige powder, 77% yield.

Spectral and elemental analysis data for compounds (**I**–**V**) are given in Supplementary Information.

Analgesic effect of compounds (I–V) in vivo on rats in the acetic acid writhing test. The experiments were carried out on outbred male rats (n = 70) weighing 220–250 g of sexually mature age (6 months) from the vivarium of the State Institution of the St. Luke Lugansk State Medical University, LPR, in the autumn–winter period according to the recommendations [49–51]. Before the start of the experiment, a thorough examination of all rats was carried out, their weight, age, physical activity and condition of the coat were taken into account. Experimental groups consisting of 10 rats were formed by random selection. Rats were divided into seven groups: control (with simulated peritovisceral pain without pharmacological correction), reference (comparison group, analgin) and five experimental groups according to the number of compounds studied (**I**–**V**). Algogen (acetic acid) was administered in a volume of 1.0 mL of a 7% solution once, according to classical pharmacological procedures [47–49]. Analgin (sodium metamizole, JSC Pharmstandard, Russia) at a dose of 7 mg/kg was used as a reference drug for the reference group of rats. Compounds (**I**–**V**) were administered intragastrically at a dose of 5 mg/kg 1.5 hours before the administration of the algogen. The quantitative experimental characteristic in the work is the number of acetic acid writhings in a 15-minute interval 20 minutes after the administration of the algogen (1.0 mL of a 7% solution of acetic acid intraperitoneally).

Statistical processing of the results was carried out on the basis of recommendations [49–51] and according to known formulas and methods of mathematical statistics characterizing quantitative variability. When processing the experimental data, the following indicators were determined: the arithmetic mean of the number of scratching movements a, dispersion of values σ^2 around the arithmetic mean, standard deviation σ, the coefficient of variation V. The significance of differences between the reference and experimental groups was assessed in comparison with the control group by Student's t-test.

Molecular docking. Molecular docking to COX-1 and COX-2 cyclooxygenases was performed using the Webina 1.0.3 service (https://durrantlab.pitt.edu/webina/), molecular docking to search for new probable protein targets was performed using the Galaxy-Sagittarius service [53] based on the GalaxyWeb web server [54, 55]. Molecular graphics were processed and visualized using the UCSF Chimera software package [56, 57].

CONCLUSIONS

In accordance with the criteria for bioavailability and evaluation of ADMET parameters, five compounds synthesized by us in the Himex laboratory were selected from a library of 170 pyridine derivatives: derivatives of 4-(2-furyl)-1,4-dihydronicotinonitrile and 4-(2-furyl)-1,4,5,6-tetrahydronicotinonitrile. The in vivo analgesic effect of these compounds in the acetic acid writhing test on rats was studied. All the studied compounds showed analgesic activity of various degrees of severity, exceeding that of metamizole sodium. The analgesic effect of tetrahydropyridine (**V**) is more than two times higher than that for the reference drug (analgin). Molecular docking of compounds with respect to COX-1 and COX-2 was carried out, as well as docking in order to search for other possible targets. The docking results show that compounds (**I**), (**III**) and (**V**) have the highest affinity for COX-1 and COX-2 active sites.

New compounds are of interest for further research in the search for anti-inflammatory drugs and the pharmacotherapy of pain syndrome.

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COMPLIANCE WITH ETHICAL STANDARDS

The studies were carried out in accordance with the rules of good laboratory practice when conducting preclin-

ical studies in Russia (Order of the Ministry of Health of the Russian Federation No. 199n dated April 1, 2016), as well as in accordance with the norms and principles of the EU Council Directive on the protection of vertebrate animals used for experimental and other scientific purposes.

Conflict of Interests

The authors declare they have no conflicts of interest.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1134/S1068162022030104.

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