Synthesis, structure and properties of *N*-R-2-(5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetamides

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Heterocyclic compounds remain the most promising group of compounds, through which the new drugs with characteristic list of properties are successfully created. Examples of this systems are 1,2,4-triazole and pyrazole. The presence in one molecule structure of fragments of two different azaheterocycles is synthetically interesting and allows increasing the probability to obtain biologically active substance with a wide spectrum of action.

The aim of the work was to optimize the synthesis conditions and investigate the properties of N-R-2-(5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetamides in case of change of chemical process conditions.

Methods and results. Ethyl 5-methyl-1*H*-pyrazole-3-carboxylate, which was obtained by known techniques using acetone, diethyl oxalate, sodium methoxide, followed by hydrazine hydrate in equivalent amount, was used as the key starting reagent. The resulting ethyl 5-methyl-1*H*-pyrazole-3-carboxylate was used to carry out hydrazinolysis reactions and nucleophilic addition of phenyl isothiocyanate with subsequent alkaline heterocyclicization. The synthesized 5-(5-methyl-1*H*-pyrazol-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiole was used in alkylation reactions with promising reagents for the design of pharmacophoric fragments. The products of such reaction are *N*-R-2-(5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetamides. The structure of the resulting compounds was confirmed by elemental analysis, ^{1}H NMR spectroscopy, IR spectrophotometry. The individuality of the substances was determined by thin-layer chromatography and chromatographic mass spectrometry. For synthesized compounds, preliminary screening was performed using the PASS On-line® software and molecular docking.

Conclusions. *N*-R-2-5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetamides are obtained with high yields and purity, their properties are investigated.

Синтез, будова та властивості *N*-R-2-(5-(5-метил-1*H*-піразол-3-іл)-4-феніл-4*H*-1,2,4-тріазол-3-ілтіо)ацетамідів

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Гетероциклічні сполуки залишаються найбільш перспективною групою, за їхньою допомогою відбувається успішне створення нових лікарських засобів із характерним переліком властивостей. Прикладами таких систем є 1,2,4-тріазол і піразол. Наявність у структурі однієї молекули фрагментів двох різних азагетероциклів є синтетично цікавим і дає змогу збільшити ймовірність одержання біологічно активної субстанції з широким спектром дії.

Мета роботи – оптимізація умов синтезу та дослідження властивостей *N*-R-2-(5-(5-метил-1*H*-піразол-3-іл)-4-феніл-4*H*-1,2,4-тріазол-3-ілтіо)ацетамідів при зміні умов перебігу хімічного процесу.

Методи та результати. Як ключовий вихідний реагент використали етил 5-метил-1*H*-піразол-3-карбоксилат, який одержали за відомими методиками з використанням ацетону, діетилоксалату, натрій метилату та з наступним використанням гідразин гідрату в еквівалентній кількості. Одержаний етил 5-метил-1*H*-піразол-3-карбоксилат використали для реакцій гідразинолізу та нуклеофільного приєднання фенілізотіоціанату з наступною лужною гетероциклізацією. Синтезований 5-(5-метил-1*H*-піразол-3-іл)-4-феніл-4*H*-1,2,4-тріазол-3-тіол використаний у реакціях алкілування перспективними реагентами для конструювання фармакофорних фрагментів. Продуктами такої реакції є *N*-R-2-(5-(5-метил-1*H*-піразол-3-іл)-4-феніл-4*H*-1,2,4-тріазол-3-ілтіо)ацетаміди. Структура одержаних сполук підтверджена за допомогою елементного аналізу, спектроскопії ^{1}Н ЯМР, ІЧ-спектрофотометрії. Індивідуальність речовин встановлена за допомогою тонкошарової хроматографії та хромато-мас-спектрометрії. Для синтезованих сполук здійснили попередній розрахунковий скринінг за допомогою програмного продукту PASS On-line® та молекулярного докінгу.

Висновки. Одержали з високими виходами та чистотою *N*-R-2-(5-(5-метил-1*H*-піразол-3-іл)-4-феніл-4*H*-1,2,4-тріазол-3-ілтіо) ацетаміди, доведели їхню структуру та дослідили властивості.

Ключові слова: 1,2,4-тріазол, піразол, фізико-хімічні властивості, молекулярний докінг.

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Синтез, строение и свойства *N*-R-2-(5-(5-метил-1*H*-пиразол-3-ил)-4-феніл-4*H*-1,2,4-триазол-3-илтио)ацетамидов

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Гетероциклические соединения остаются наиболее перспективной группой, с их помощью происходит успешное создание новых лекарственных средств с характерным перечнем свойств. Примеры таких систем – 1,2,4-триазол и пиразол. Наличие в структуре одной молекулы фрагментов двух разных азагетероциклов синтетически интересно и позволяет увеличить вероятность получения биологически активной субстанции с широким спектром действия.

Цель работы – синтез и исследование свойств *N*-R-2-(5-(5-метил-1*H*-пиразол-3-ил)-4-феніл-4*H*-1,2,4-триазол-3-илтио)ацетамидов при изменении условий протекания химического процесса.

Методы и результаты. В качестве ключевого исходного реагента использован этил 5-метил-1*H*-пиразол-3-карбоксилат, который получен по известным методикам с использованием ацетона, диэтилоксалата, натрий метилата и с последующим использованием гидразин гидрата в эквивалентном количестве. Полученный этил 5-метил-1*H*-пиразол-3-карбоксилат использован для проведения реакций гидразинолиза и нуклеофильного присоединения фенилизотиоцианата с последующей щелочной гетероциклизацией. Синтезированный 5-(5-метил-1*H*-пиразол-3-ил)-4-фенил-4*H*-1,2,4-триазол-3-тиол использован в реакциях алкилирования перспективными реагентами для конструирования фармакофорных фрагментов. Продукты такой реакции – *N*-R-2-(5-(5-метил-1*H*-пиразол-3-ил)-4-фенил-4*H*-1,2,4-триазол-3-илтио)ацетамиды. Структура полученных соединений подтверждена с помощью элементного анализа, спектроскопии ^{1}Н ЯМР, ИК-спектрофотометрии. Индивидуальность веществ установлена с помощью тонкослойной хроматографии и хромато-масс-спектрометрии. Для синтезированных соединений проведен предварительный расчетный скрининг с помощью программного продукта PASS On-line® и молекулярного докинга.

Выводы. Получены с высокими выходами и чистотой *N*-R-2-(5-(5-метил-1*H*-пиразол-3-ил)-4-феніл-4*H*-1,2,4-триазол-3-илтио) ацетамиды, доказана их структура и исследованы свойства.

Ключевые слова: 1,2,4-триазол, пиразол, физико-химические свойства, молекулярный докинг.

Актуальные вопросы фармацевтической и медицинской науки и практики. – 2019. – Т. 12, № 1(29). – С. 4–9

1,2,4-Triazole derivatives have physical-chemical and pharmacological properties that determine their widespread use, including as biologically active substances [1]. The objective reasons for this are the high synthetic potential of this heterocycle and the possibility of introducing various substitutes at the stage of ring formation [2,7]. In the literature there is a lot of data on a wide range of pharmacological activity of pyrazole derivatives (analgesic activity) and 1,2,4-triazole (antifungal, antipsychotic, antioxidant, anti-cancer activity) [1,3–9]. The availability of presence in the single molecule structure of fragments of two different azaheterocycles is synthetically engaging and allows to increase the probability of obtaining biologically active substance with a wide spectrum of activity [10]. This served as a prerequisite for the targeted synthesis of 1,2,4-triazole-3-thiole derivatives, which in the fifth position contain a 5-methylpyrazole fragment [9]. Thus, the modification of 1,2,4-triazole-3-thiole derivatives by the introduction of 5-methylpyrazole and the study of the properties of the obtained compounds are an urgent task.

The aim

The aim of the work was to synthesize of *N*-aryl-(heteryl)-2-(5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetamides and investigate its properties.

Materials and methods

During the study, pyrazole was selected as synthon for the preparation of a new series of compounds. It is important to note that due to the variety and strength of pharmacological effects that appear, this structure is worthy among heterocyclic compounds. 5-(5-Methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiole was obtained from diethyloxalate, acetone and sodium methanoate through a series of successive stages (*Table 1*).

The study of physical-chemical properties of the obtained compounds was carried out using methods listed in the State Pharmacopoeia of Ukraine. Melting points were determined in open capillary tubes in a "Stanford Research Systems Melting Point Apparatus 100" (SRS, USA). The elemental analysis (C, H, N) was performed using the "Elementar vario EL cube" analyzer (Elementar Analysensysteme, Germany). IR spectra (4000–400 cm^{-1}) were taken off the module ALPHA-T of Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). ^{1}H NMR spectra (400 MHz) were recorded at "Varian-Mercury 400" spectrometer with $SiMe_4$ as internal standard in DMSO-d_6 solution. Chromatography-mass spectral studies were conducted on the instrument "Agilent 1260 Infinity HPLC" equipped with a mass spectrometer "Agilent 6120" (method of ionization – electrospray (ESI)).

Molecular docking. Studies were carried out by molecular docking as an approach to the search for molecules with affinity for a specific biological target. As biological targets, we used such macromolecules from Protein Data Bank (PDB): the enzyme COX-2 in combination with indomethacin and celecoxib (PDB ID – 3LN1). The choice of biological targets is due to literary data on the mechanism of anti-inflammatory agents' action. The research methodology consisted of the following stages: *1)* preparation of the ligand: construction of structural formulas of compounds using program MarvinSketch 6.3.0 and their preservation in mol-format; generation of 3D structure of compound formulas – molecular modeling (Hyper Chem 8 program using the method of molecular mechanics MM+

and semi-empirical quantum mechanical method PM3, with the maximum number of cycles and Polak-Ribiere algorithm and preservation of molecules in PDB files); use AutoDockTools-1.5.6 to convert PDB – to PDBQT files; *2)* preparation of enzymes: removal of water molecules and ligand from a file using the software package Discovery Studio 4.0 and preservation of the enzyme in PDB format; use AutoDockTools-1.5.6 to convert PDB- to PDBQT-files ; *3)* actual molecular docking: implementation of doking with the program "Vina" with the following spatial parameters of the active center of the enzyme: center_x = 18.37, center_y = – 52.296, center_z = 53.949, size_x = 18, size_y = 16, size_z = 16 for COX-2 (3LN1); visualization of data using program Discovery Studio 4.0.

Ethyl 5-methylpyrazole-3-carboxylate. Hydrazine hydrate (10 g, 0.2 mol) in ethanol (25 ml) is gradually added with stirring and cooling to a solution of methyl 2,4-dioxopentanoate (0.2 mol) in alcohol. After 1 hour of heating, the alcohol was discarded. The resulting compound (99 %) was recrystallized from aqueous ethanol in the form of a needle crystal with a melting point of 82 °C (*Fig. 1*).

3-Methylpyrazole-5-carbohydrazide. Ethyl 5-methylpyrazole-3-carbo-xylate (58.4 g) and hydrazine hydrate (25 g) were heated for 8 hours. The reaction product was obtained in the form of prismatic crystals, which was recrystallized from water. After drying at 100 °C, the reaction product had a melting point of 153 – 154 °C. Yield – 90 % (*Fig. 1*).

2-(5-Methyl-1H-pyrazole-3-carbonyl)-N-hydrazinocarbothioamide. 0.05 mol of 5-methylpyrazole-3-carbohydrazide, 150 ml of dioxane and 60 ml of water are heated to dissolve the starting material. And an equivalent amount of phenyl isothiocyanate to the obtained solution, boil for 1 hour, cool, add 100 ml of water, the precipitate is filtered off, washed with water, propan-2-ol and crystallized from DMF. Yield – 71 %. Melting point = 263–265 ºC (*Fig. 1*).

5-(5-Methyl-1H-pyrazole-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiole. A mixture of 0.01 mol of 2-(5-methyl-1*H*-pyrazole-3-carbonyl)-*N*-hydrazino-carbothioamide, 0.011 mol of sodium hydroxide and 50 ml of water is heated to reflux for 2 hours, cooled and add 2 ml of concentrated chloride acid. The resulting precipitate is filtered off, washed with water. Recrystallized from DMF. Yield – 84 %. Melting point = 253–256 ºC (*Fig. 1*).

Alkylation. 0.05 mol 5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiole is added to a solution of 0.05 mol of sodium hydroxide in 30-40 ml of water, reaching complete dissolution. Subsequently, a solution of 0.055 mol of the alkylating part in methanol or propan-2-ol is added (*Fig. 1*).

Protons of methyl groups resonate in the strong part of the field at 2.32–2.35 ppm (methylpyrazole and methylisoxazole fragments) and at 3.74 ppm. (4-methoxyphenyl fragment). The protons of the methylene fragments are resonated at 3.61–3.98 (-S-CH_2-) and at 4.52–4.55 ppm. (-HN-CH_2-) in the form of singlets. Chemical displacements of aromatic protons vary widely in ^{1}H NMR spectra: for example, the proton in the *para*-position of the phenyl substituent and in the *ortho*- and *meta*-positions of the 4-methoxyphenyl substituent of compound 15 form multiplets in the range of 7.16–7.24 ppm. Other protons in the *ortho*- and *meta*-positions of the phenyl substituent form the corresponding zones of doublets in the regions at 7.76 ppm. and at 7.49 ppm. Hydrogen at C_4 atom of the pyrazole fragment resonates at 6.62 ppm. in the form of a singlet. Presenting a proton signal of the NH fragment of the pyrazole ring with a chemical shift of 13.44 ppm. in the form of a wider singlet (*Table 2*).

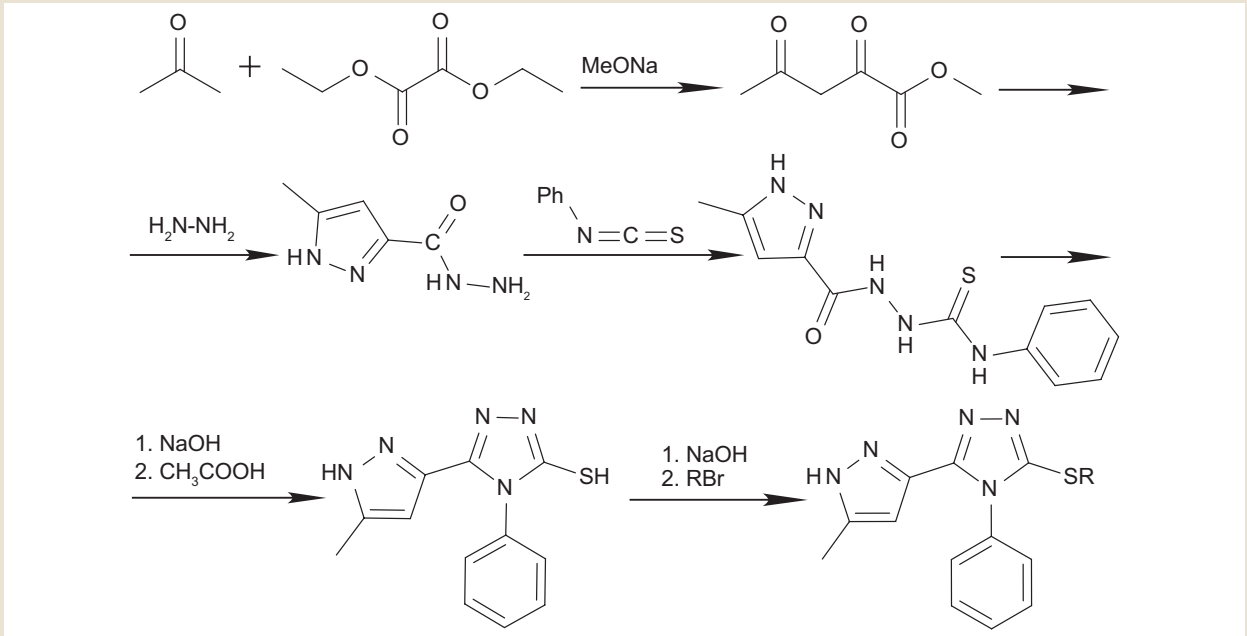
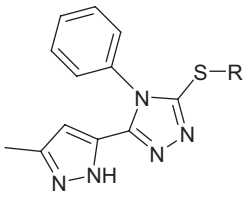


Fig. 1. A scheme for the synthesis of 5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiole.

Table 1. Characterization data of synthesized compounds



N	R	M. p., °C	Molecular formula	Yield, %
1	3-F-C_6H_4-NH-CO-CH_2-	159–160	$C_{21}H_{19}FN_6OS$	69
2	2-*F*-C_6H_4-CH_2-NH-CO-CH_2-	182–184	$C_{22}H_{21}FN_6OS$	82
3	2-*Cl*-C_6H_4-NH-CO-CH_2-	172–174	$C_{21}H_{19}ClN_6OS$	74
4	2-Cl-C_6H_4-CH_2-NH-CO-CH_2-	190	$C_{22}H_{21}ClN_6OS$	68
5	3-Cl-C_6H_4-NH-CO-CH_2-	177–178	$C_{21}H_{19}ClN_6OS$	77
6	3-Cl-C_6H_4-CH_2-NH-CO-CH_2-	162–165	$C_{22}H_{21}ClN_6OS$	79
7	4-Cl-C_6H_4-NH-CO-CH_2-	178–180	$C_{21}H_{19}ClN_6OS$	68
8	4-Cl-C_6H_4-CH_2-NH-CO-CH_2-	167–168	$C_{22}H_{21}ClN_6OS$	76
9	2-Br-C_6H_4-NH-CO-CH_2-	168–171	$C_{21}H_{19}BrN_6OS$	71
10	2-Br-C_6H_4-CH_2-NH-CO-CH_2-	181–183	$C_{22}H_{21}BrN_6OS$	73
11	3-Br-C_6H_4-NH-CO-CH_2-	188–189	$C_{21}H_{19}BrN_6OS$	85
12	4-Br-C_6H_4-NH-CO-CH_2-	192–195	$C_{21}H_{19}BrN_6OS$	82
13	4,4,4-FC-C_6H_4-NH-CO-CH_2-	179–181	$C_{22}H_{19}F_3N_6OS$	85
14	4,4,4-FC-C_6H_4-CH_2-NH-CO-CH_2-	174–176	$C_{23}H_{21}F_3N_6OS$	87
15	4-OCH_3-C_6H_4-CH_2-NH-CO-CH_2-	157–159	$C_{23}H_{24}N_6O_2S$	74
16	2-CH_3- isoxazole-NH-CO-CH_2-	158–162	$C_{19}H_{19}N_7O_2S$	79

Table 2. ^{1}H NMR chemical shifts of synthesized compounds

N	^{1}H NMR (ppm)
1	2.32 (s, 3H, CH_3), 3.62 (s, 2H, -S-C$\underline{H_2}$-), 6.62 (s, 1H, pyrazole, =CH-), 6.95-7.14 (m, 2H, -$C_6\underline{H_4}$-NH-), 7.19-7.25 (m, 3H, -$C_6\underline{H_4}$-NH-, C_6H_5), 7.46 (dd, 2H, C_6H_5), 7.75 (dd, 2H, C_6H_5), 8.32 (d, 2H, C_6H_5), 11.43 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
2	2.33 (s, 3H, CH_3), 3.62 (s, 2H, -S-C$\underline{H_2}$-), 4.56 (s, 2H, -C$\underline{H_2}$-NH-), 6.62 (s, 1H, pyrazole, =CH-), 6.92 (d, 1H, -$C_6\underline{H_4}$-CH_2-NH-), 7.06 (t, 1H, -$C_6\underline{H_4}$-CH_2-), 7.19-7.30 (m, 3H, -$C_6\underline{H_4}$-CH_2-, $C_6\underline{H_5}$), 7.38-7.51 (m, 3H, -$C_6\underline{H_4}$-CH_2-, $C_6\underline{H_5}$), 7.76 (d, 1H, C_6H_5), 11.41 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
3	2.32 (s, 3H, CH_3), 3.62 (s, 2H, -S-C$\underline{H_2}$-), 6.62 (s, 1H, pyrazole, =CH-), 6.95-7.14 (m, 2H, -$C_6\underline{H_4}$-NH-), 7.19-7.25 (m, 2H, -$C_6\underline{H_4}$-NH-, C_6H_5), 7.55 (dd, 2H, C_6H_5), 7.84 (dd, 2H, C_6H_5), 8.35 (d, 2H, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
4	2.32 (s, 3H, CH_3), 3.62 (s, 2H, -S-C$\underline{H_2}$-), 4.50 (s, 2H, -C$\underline{H_2}$-NH-), 6.62 (s, 1H, pyrazole, =CH-), 6.95-7.14 (m, 2H, -$C_6\underline{H_4}$-CH_2-NH-), 7.19-7.27 (m, 2H, -$C_6\underline{H_4}$-CH_2-NH-, C_6H_5), 7.55 (dd, 2H, C_6H_5), 7.84 (dd, 2H, C_6H_5), 8.35 (d, 2H, C_6H_5), 11.45 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
5	2.33 (s, 3H, CH_3), 3.89 (s, 2H, -S-C$\underline{H_2}$-), 6.62 (s, 1H, pyrazole, =CH-), 7.15 (d, 1H, C_6H_5), 7.22 (t, 1H, C_6H_5), 7.35 (d, 1H, C_6H_5), 7.52-7.57 (m, 3H, -$C_6\underline{H_4}$-NH-, C_6H_5), 7.75-7.77 (m, 3H, -$C_6\underline{H_4}$-NH-, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
6	2.33 (s, 3H, CH_3), 3.89 (s, 2H, -S-C$\underline{H_2}$-), 4.58 (s, 2H, -C$\underline{H_2}$-NH-), 6.62 (s, 1H, pyrazole, =CH-), 7.15 (d, 1H, C_6H_5), 7.22 (t, 1H, C_6H_5), 7.35 (d, 1H, C_6H_5), 7.52-7.57 (m, 3H, -$C_6\underline{H_4}$-NH-, C_6H_5), 7.75-7.77 (m, 3H, -$C_6\underline{H_4}$-NH-, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
7	2.33 (s, 3H, CH_3), 3.89 (s, 2H, -S-C$\underline{H_2}$-), 6.62 (s, 1H, pyrazole, =CH-), 7.22 (t, 1H, C_6H_5), 7.44-7.50 (m, 4H, -$C_6\underline{H_4}$-NH-, C_6H_5), 7.75-7.78 (m, 4H, -$C_6\underline{H_4}$-NH-, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
8	2.33 (s, 3H, CH_3), 3.89 (s, 2H, -S-C$\underline{H_2}$-), 4.60 (s, 2H, -C$\underline{H_2}$-NH-), 6.62 (s, 1H, pyrazole, =CH-), 7.22 (t, 1H, C_6H_5), 7.44-7.50 (m, 4H, C_6H_5), 7.75-7.78 (m, 4H, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
9	2.32 (s, 3H, CH_3), 3.64 (s, 2H, -S-C$\underline{H_2}$-), 6.62 (s, 1H, pyrazole, =CH-), 7.09-7.16 (m, 2H, -$C_6\underline{H_4}$-NH-), 7.24-7.31 (m, 2H, -$C_6\underline{H_4}$-NH-, C_6H_5), 7.65 (dd, 2H, C_6H_5), 7.86 (dd, 2H, C_6H_5), 8.37 (d, 2H, C_6H_5), 11.45 (s, 1H, pyrazole, -NH-), 11.82 (s, 1H, -NH-)

Cont. table 2.

N	^{1}H NMR (ppm)
10	2.32 (s, 3H, CH_3), 3.64 (s, 2H, -S-CH_2-), 4.50 (s, 2H, -CH_2-NH-), 6.62 (s, 1H, pyrazole, =CH-), 7.10-7.17 (m, 2H, -C_6H_4-CH_2-NH-), 7.25-7.33 (m, 2H, -C_6H_4-CH_2-NH-, C_6H_5), 7.62 (dd, 2H, C_6H_5), 7.87 (dd, 2H, C_6H_5), 8.35 (d, 2H, C_6H_5), 11.45 (s, 1H, pyrazole, -NH-), 11.82 (s, 1H, -NH-)
11	2.33 (s, 3H, CH_3), 3.84 (s, 2H, -S-CH_2-), 6.62 (s, 1H, pyrazole, =CH-), 7.14 (d, 1H, C_6H_5), 7.20 (t, 1H, C_6H_5), 7.32 (d, 1H, C_6H_5), 7.44-7.51 (m, 3H, -C_6H_4-NH-, C_6H_5), 7.65-7.71 (m, 3H, -C_6H_4-NH-, C_6H_5), 11.46 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
12	2.33 (s, 3H, CH_3), 3.91 (s, 2H, -S-CH_2-), 6.62 (s, 1H, pyrazole, =CH-), 7.33 (t, 1H, C_6H_5), 7.49-7.55 (m, 4H, -C_6H_4-NH-, C_6H_5), 7.76-7.79 (m, 4H, -C_6H_4-NH-, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.81 (s, 1H, -NH-)
13	2.33 (s, 3H, CH_3), 3.91 (s, 2H, -S-CH_2-), 6.60 (s, 1H, pyrazole, =CH-), 7.24-7.30 (m, 3H, -C_6H_4-NH-, C_6H_5), 7.52-7.57 (m, 4H, -C_6H_4-NH-, C_6H_5), 7.78 (dd, 4H, -C_6H_4-NH-, C_6H_5), 11.46 (s, 1H, pyrazole, -NH-), 11.82 (s, 1H, -NH-)
14	*2.33 (s, 3H, CH_3)*, 3.90 (s, 2H, -S-CH_2-), 4.54 (s, 2H, -CH_2-NH-), 6.62 (s, 1H, pyrazole, =CH-), 7.23-7.29 (m, 3H, -C_6H_4-NH-, C_6H_5), 7.54-7.61 (m, 4H, -C_6H_4-NH-, C_6H_5), 7.76 (dd, 2H, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.83 (s, 1H, -NH-)
15	*2.33 (s, 3H, CH_3)*, 3.61 (s, 2H, -S-CH_2-), 3.74 (s, 3H, -C_6H_4-OCH_3), 4.49 (s, 2H, -CH_2-NH-), 6.62 (s, 1H, pyrazole, =CH-), 6.86 (dd, 2H, -C_6H_4-OCH_3), 7.16-7.24 (m, 3H, -C_6H_4-OCH_3, C_6H_5), 7.50 (dd, 2H, C_6H_5), 7.79 (dd, 2H, C_6H_5), 11.44 (s, 1H, pyrazole, -NH-), 11.83 (s, 1H, -NH-)
16	*2.33-2.35 (m, 6H, 2-CH_3*-isoxazole, 3-CH_3-pyrazole), 3.98 (s, 2H, -S-CH_2-), 6.17 (s, 1H, =CH-, isoxazole), 6.62 (s, 1H, pyrazole, =CH-), 7.22 (t, 1H, C_6H_5), 7.50 (dd, 2H, C_6H_5), 7.76 (dd, 2H, C_6H_5), 11.40 (s, 1H, pyrazole, -NH-), 11.83 (s, 1H, -NH-)

Table 3. Affinity (kcal / mol) of investigated compounds to cyclooxygenase-2

Sub.	Affinity, (kcal/mol) to COX-2 (3LN1)	Sub.	Affinity, (kcal/mol) to COX-2 (3LN1)
1	-8.7	7	-8.6
2	-9.3	8	-9.2
3	-9.1	9	-8.5
4	-8.0	10	-9.0
5	-9.2	11	-9.3
6	-9.1	Celecoxib	-14.6

Changing the position of the substituents from the vapor position to the *ortho*-position of the aromatic fragments causes a slight bias of signals towards the weaker field. The same is true of the change in the nature of the halogen at the aryl substituent: the transition from chlorine to bromine and iodine also causes a shift in the chemical bias in a weaker field (*Table 2*).

In the mass spectrum, there is a peak of the molecular ion and peaks of fragment ions, which confirm this structure.

PASS screening demonstrated the possibility of occurrence of compounds of this class with a certain probability of antituberculous (P_a = 36–55 %) and antiatherosclerotic (P_a=37–45 %) activity. Attention is drawn to the ability to reduce the activity of cytidine deaminase substitution (P_a = 59–76 %), which may negatively effect, for example, the ability of the human body to fight some viruses.

Based on molecular docking data, it was found that the compounds which were tested for the study were characterized by a moderate level of affinity for the COX-2 enzyme (*Table 3*).

For one of the compounds with the highest affinity, the complex of the active site of the enzyme COX-2 was visualized and it was established that *N*-(2-fluorobenzyl)-2-(5-(5-methyl-1*H*-pyrazol-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio) acetamide is characterized by the formation of hydrogen bonds of the second Nitrogen atom of the pyrazole fragment and the Oxygen atom of the -S-CH_2-C(O)-fragment with the amino acid residue ARG D:499 respectively.

Conclusions

1. A universal method for the preparation of *N*-aryl-(heteryl)-2-(5-(5-methyl-1*H*-pyrazole-3-yl)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)acetamides was developed.

2. The structure and individuality of the synthesized compounds was confirmed by ^{1}H NMR, IR and LC-MS spectra, elemental analysis.

3. The biological activity forecast for the first-time obtained compounds was carried out using the computer PASS program and molecular docking. The biological potential of new compounds was ascertained.

Prospects for further research. According to the research results it is planned to expand the line of this class of compounds to identify promising biologically active compounds among them.

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