



Synthesis and properties of some pyrazole derivatives of 1,2,4-triazole-3-thiol

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A – концепція та дизайн дослідження; B – збір даних; C – аналіз та інтерпретація даних; D – написання статті; E – редагування статті; F – остаточне затвердження статті

Nitrogen-containing heterocyclic compounds play an important role in the modern pharmaceutical industry. This is due to their significant biological potential. 1,2,4-Triazole and pyrazole are known pharmacophores that are responsible for the formation of a wide range of activities. The construction of the target molecule using 1,2,4-triazole and pyrazole is also interesting in terms of the availability of starting reagents and the simplicity of chemical transformations. The combination of these heterocycles in one molecule allows increasing its opportunities of participation in various biological processes.

The aim of the research was to examine the conditions for obtaining S-alkyl derivatives of 5-(5-methylpyrazole)-4-ethyl-1,2,4-triazole-3-thiol and to investigate these compounds' properties.

Materials and methods. The first phase of the research involved the use of diethyl oxalate, acetone and sodium methylate as starting substances for the synthesis of the intermediate. The obtained methyl 2,4-dioxopentanoate in the following step was converted into 5-methylpyrazole-3-carbohydrazide with the double amount of hydrazine hydrate. The subsequent modification of the molecule implied a stepwise use of the reactions of nucleophilic addition of ethyl isothiocyanate and alkaline cyclization. Thus, the obtained 5-(5-methylpyrazole)-4-ethyl-1,2,4-triazole-3-thiol became subject to an alkylation process. To establish the composition and identify the structure of the isolated substances, ¹H NMR and infrared spectra were recorded, as well as qualitative and quantitative indicators of the elemental composition of the synthesized structures were obtained. The individual nature of the presence of substances and the degree of their purity were determined using high performance liquid chromatography with two types of detection: diode-matrix and mass spectrometric.

Results. The synthesis of alkyl derivatives of 5-(5-methylpyrazole)-4-ethyl-1,2,4-triazole-3-thiol was carried out and the optimal conditions for the process of obtaining these substances were determined. The structure of the products of chemical transformation is confirmed and the results of the study of its physical properties are recorded.

The results of docking studies allowed to confirm the prospects of the chosen direction of synthetic transformations, which ultimately allowed to determine the biological potential of the obtained compounds. The model enzymes were kinase of the anaplastic lymphoma (code 2XP2), 14-alpha demethylase of the lanosterol (code 3LD6) and cyclooxygenase-1 (code 3N8Y), information on which was obtained from the Protein Structures Database (PDB).

Conclusions. Molecular docking resulted in obtaining data that form a concept of a certain level of probability of synthesized compounds' influence on the activity of these enzyme structures.

Key words: 5-methylpyrazole, 1,2,4-triazole, physical-chemical properties, molecular docking.

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Синтез і властивості деяких піразолопохідних 1,2,4-тріазол-3-тіолу

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Нітрогеномісні гетероциклічні сполуки відіграють важливу роль у сучасній фармацевтичній галузі. Це пов'язано зі значущим біологічним потенціалом цих сполук. 1,2,4-Тріазол і піразол – відомі фармакофори, що відповідають за формування широкого спектра активностей. Конструювання цільової молекули з використанням 1,2,4-тріазолу та піразолу є також цікавим із погляду доступності вихідних реагентів і простоти хімічних перетворень. Поєднання цих гетероциклів в одній молекулі дає змогу збільшити можливість участі в різноманітних біологічних процесах.

Мета роботи – дослідження умов одержання S-алкілпохідних 5-(5-метилпіразол)-4-етил-1,2,4-тріазол-3-тіолу та вивчення властивостей цих сполук.

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Key words: 5-methylpyrazole, 1,2,4-triazole, physical-chemical properties, molecular docking.

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Матеріали та методи. Початковий етап роботи передбачав використання діетилоксалату, ацетону та натрій метилату як вихідних речовин для синтезу проміжного продукту хімічного перетворення. Одержаний метил 2,4-діоксопентаноат на наступному етапі застосований у процесі перетворення у 5-метилпіразол-3-карбогідрозид за участю подвійної кількості гідразин гідрату. Наступна модифікація молекули полягала в поетапному використанні реакцій нуклеофільного приєднання етилізотиоціанату та лужної гетероциклізації. Сформований так 5-(5-метилпіразол)-4-етил-1,2,4-тріазол-3-тіол піддавали процесу алкілювання. Для встановлення складу та ідентифікації структури виділених речовин записані ^1H ЯМР та інфрачервоні спектри, а також одержані якісні та кількісні показники елементного складу синтезованих структур. Індивідуальний характер наявності речовин і ступінь їхньої чистоти визначені з використанням вискоєфективної рідинної хроматографії з двома видами детекції: діодно-матричної та мас-спектрометричної.

Результати. Здійснили синтез алкілпохідних 5-(5-метилпіразол)-4-етил-1,2,4-тріазол-3-тіолу та визначили оптимальні умови процесу одержання цих речовин. Підтверджена будова продуктів хімічного перетворення та зафіксовані результати дослідження фізичних властивостей. Результати докінгових досліджень дали змогу підтвердити перспективність обраного напрямку синтетичних перетворень, що врешті дало змогу визначитися з біологічним потенціалом одержаних сполук. Модельні ферменти – анапластичної лімфони кінназа (код 2XP2), 14-альфа деметилаза ланостеролу (код 3LD6) та циклооксигеназа-1 (код 3N8Y), інформацію щодо яких використано з бази Банку даних білкових структур (PDB).

Висновки. У результаті молекулярного докінгу отримали відомості, що формують уявлення про певний рівень імовірності впливу синтезованих сполук на активність названих ферментних структур.

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

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Синтез и свойства некоторых пиразолпроизводных 1,2,4-триазол-3-тиола

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Нитрогенсодержащие гетероциклические соединения играют важную роль в современной фармацевтической отрасли. Это связано со значительным биологическим потенциалом указанных соединений. 1,2,4-Триазол и пиразол – известные фармакофоры, которые отвечают за формирование широкого спектра активностей. Конструирование целевой молекулы с использованием 1,2,4-триазола и пиразола интересно с точки зрения доступности исходных реагентов и простоты химических превращений. Совмещение этих гетероциклов в одной молекуле позволяет увеличить возможность участия в разнообразных биологических процессах.

Цель работы – исследование условий получения S-алкилпроизводных 5-(5-метилпиразол)-4-этил-1,2,4-триазол-3-тиола и изучение свойств указанных веществ.

Материалы и методы. Начальный этап работы предусматривал использование диэтилоксалата, ацетона и натрий метилата как исходных веществ для постановки синтеза промежуточного продукта химического преобразования. Полученный метил 2,4-диоксопентаноат на следующем этапе применен в процессе преобразования в 5-метилпиразол-3-карбогидразид при участии двойного количества гидразин гидрата. Последующая модификация молекулы предусматривала использование этилизотиоцианата и щелочную гетероциклізацію. Сформированный таким образом 5-(5-метилпиразол)-4-этил-1,2,4-тріазол-3-тіол подвергали процессу алкілювання. Для установления состава и идентификации структуры выделенных веществ записаны ^1H ЯМР и инфракрасные спектры, а также получены качественные и количественные показатели элементного состава синтезированных структур. Индивидуальный характер присутствия веществ и степень их чистоты определены с использованием высокоэффективной жидкостной хроматографии с двумя видами детекции: диодно-матричной и масс-спектрометрической.

Результаты. Проведен синтез алкілпроизводных 5-(5-метилпіразол)-4-етил-1,2,4-тріазол-3-тіола и определены оптимальные условия процесса получения указанных веществ. Подтверждено строение продуктов химического преобразования, зафиксированы результаты исследования физических свойств. Результаты докингових досліджень позволяют подтвердить перспективность выбранного направления синтетических преобразований, что дало возможность определиться с биологическим потенциалом полученных веществ. Модельные ферменты: анапластической лимфони кінназа (код 2XP2), 14-альфа деметилаза ланостерола (код 3LD6) и циклооксигеназа-1 (код 3N8Y), информация о которых использована из базы Банка данных белковых структур (PDB).

Выводы. В результате молекулярного докинга получены данные, которые формируют представление про определенный уровень вероятности влияния синтезированных соединений на активность указанных ферментных структур.

Ключевые слова: 5-метилпиразол, 1,2,4-тріазол, фізико-хімічні властивості, молекулярний докінг.

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The search for new biologically active substances is a priority of modern pharmaceutical science [1–6].

Among the great variety of pharmacologically active molecules, special attention is drawn to the products of the processes of combining individual synthons into a more complex molecule [7–9]. For example, pyrazole and 1,2,4-triazole derivatives are well studied and demonstrate a wide range of biological activity. Therefore, a combination

of such fragments, which show different mechanisms of interaction with the biological target, within one molecule, is quite interesting and relevant.

Aim

The aim of the research was to study the conditions for obtaining and studying the properties of S-alkyl derivatives of 5-(5-methylpyrazole)-4-ethyl-1,2,4-triazole-3-thiol.

Materials and methods

Chemistry. Pyrazole was selected as an intermediate for chemical transformation. This five-membered heterocycle was formed using diethylxalate, acetone and sodium methanoate. Synthesized 5-methylpyrazole-3-carbohydrazide was used to form a fragment of 1,2,4-triazole. The obtained 5-(5-methylpyrazole)-4-ethyl-1,2,4-triazole-3-thiol was used to carry out S-alkylation reactions using halogenoalkanes.

Properties (physical, chemical) of the produced organic materials have been examined in compliance with articles of the State Pharmacopoeia. The melting temperature has been defined in open capillary tubes ("MP 100 Melting Point Systems" manufactured by Mettler Toledo). Qualitative and quantitative elemental analysis was carried out with the "Vario EL cube" manufactured by Elementar Analysensysteme GmbH. Infrared spectra were obtained with the ALPHA FT-IR Spectrometer manufactured by Bruker. Nuclear magnetic resonance spectra on Hydrogen nuclei 1 (400 MHz) were recorded using the instrument "Varian Mercury 400 MHz" spectrometer. Tetramethylsilane in dimethylsulfoxide- d_6 solution was used as an internal standard for measuring chemical shifts. Chromatography mass spectra were recorded using the instrument "Agilent 1260 Infinity HPLC" in conjunction with a mass spectrometer "Agilent 6120" (technique of the ionization – electrospray (ESI)).

Methyl 5-methylpyrazole-3-carboxylate (4). 20 g $H_2N-NH_2 \times H_2O$ (0.4 mol) in 60 ml ethyl alcohol is added with cooling to a solution containing 0.4 mol of methyl 2,4-dioxopentanoate (**3**) in propan-2-ol. Reaction mixture was heated for 1 hour. Then the alcohol was distilled off under vacuum. The resulting precipitate (99 %) was recrystallized from aqueous ethyl alcohol. Formed solid was dried to generate **4** with a melting point of 82–83 °C (Fig. 1).

5-Methylpyrazole-3-carbohydrazide (5). A mixture of intermediate **4** (58.4 g) and $H_2N-NH_2 \times H_2O$ (25 g) was heated at reflux for 7 hours. After cooling, the precipitate was filtrated and recrystallized from H_2O (Fig. 1). Yield: 88 %; melting point: 153–155 °C; IR (v, cm^{-1}): 3408-3237 (NH, NH_2), 1625 (C=O); 1H NMR (δ , ppm): 2.24 (s, 3H, CH_3), 4.32 (s, 2H, NH_2), 6.37 (s, 1H, pyrazole, =CH-), 9.18 (s, 1H, CONH), 13.52 (s, 1H, pyrazole, NH). Analytically calculated (%): C 42.85, H 5.75, N 39.98. Found: C 42.75, H 4.82, N 40.06.

2-(5-Methylpyrazole-3-carbonyl)-N-ethylhydrazine-1-carbothioamide (6). A mixture of intermediate **5** (0.05 mol), 145 ml of 1,4-dioxane and 65 ml of H_2O was heated to dissolve the starting compound. Then C_2H_5NCS (0.05 mol) was added and the solution was heated to reflux for 1 hour. After cooling, 100 ml of H_2O was added. The resulting substances was filtered and washed with H_2O and ethyl alcohol. Then it was crystallized from dimethylformamide (Fig. 1). Yield: 70 %; melting point: 263–265 °C; IR (v, cm^{-1}): 3230 (NH), 1648 (C=O); 1H NMR (δ , ppm): 2.26 (s, 3H, CH_3), 6.45 (s, 1H, pyrazole, =CH-), 8.54 (s, 1H, CONH), 9.63 (s, 1H, NHCS), 13.28 (s, pyrazole, NH). Analytically calculated (%): C 42.28, H 5.77, N 30.81, S 14.11. Found C 42.19, H 5.78, N 30.85, S 14.07.

5-(5-Methylpyrazole-3-yl)-4-ethyl-1,2,4-triazole-3-thiol (7). A mixture of compound **6** (0.01 mol), NaOH (0.011 mol) and 60 ml of H_2O was heated to reflux for 2 hours. After cooling, 2 ml of CH_3COOH concentrated was added to mixture. The resulting compound **7** was filtered, washed with H_2O and recrystallized from dimethylformamide (Fig. 1). Yield: 85 %; melting point: 310–312 °C; IR (v, cm^{-1}): 2744 (SH). 1H NMR (δ , ppm): 1.27 (t, $J=6.0$ Hz, 3H, CH_2-CH_3), 2.34 (s, 3H, CH_3), 4.33 (q, $J=6.2$ Hz, 2H, CH_2-CH_3), 6.50 (s, 1H, pyrazole, =CH-). Analytically calculated (%): C 45.92, H 5.30, N 33.47, S 15.32. Found C 46.05, H 5.29, N 33.56, S 15.29.

Alkylation. Compound **7** (0.05 mol) was added to a solution of 0.05 mol of NaOH in 35 ml of H_2O , until complete dissolution was reached. Subsequently, a solution of 0.055 mol of the alkylating part in methanol or propan-2-ol was added (Fig. 1). The obtained precipitate was filtered, washed by water and recrystallized with ethyl alcohol to give a white solid (**7.1–7.10**).

Molecular docking was performed to obtain structural information on the interaction of the synthesized compounds and the corresponding biological structure [10,11]. In order to solve the indicated problem, models of the necessary biological target were used. The source of the indicated biological models was the Protein Database. Kinases of anaplastic lymphoma (ALK) in the complex of crizotinib, 14-alpha demethylase of lanosterol with ketoconazole and cyclooxygenase-1 (COX-1) with diclofenac were used from the base. AUTODOCK was used to carry out the process of attaching the studied ligands to the proteins under consideration. The energy interaction between the ligand and protein, hydrogen bonds and hydrophobic interaction were used to analyze the docking interaction [12–14].

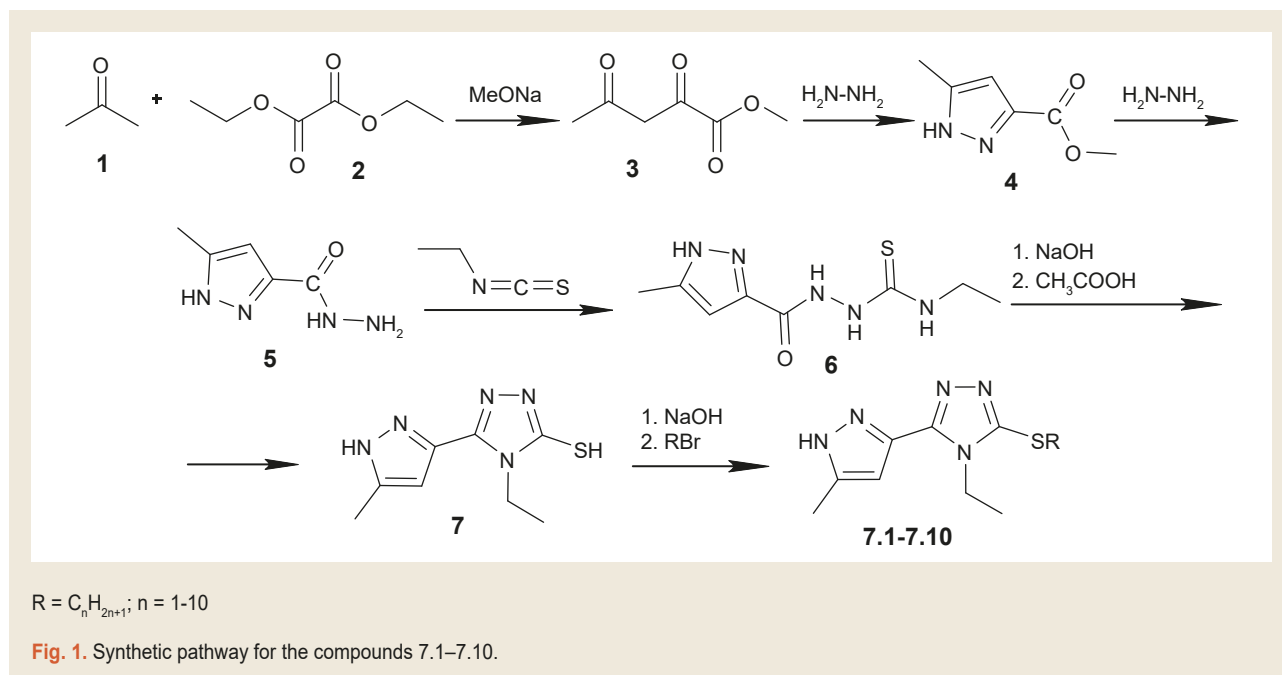
Results

The synthesis of the compounds 7.1–7.10 has been described in Fig. 1.

3-(5-Methylpyrazol-3-yl)-5-methylthio-4-ethyl-1,2,4-triazole (7.1). Yield: 76 %; melting point: 164–165 °C; IR (v, cm^{-1}): 3227 (NH), 1604 (C=N); 1H NMR (δ , ppm): 1.29 (t, $J=6.2$ Hz, 3H, CH_2-CH_3), 2.33 (s, 3H, CH_3), 2.76 (s, 3H, S- CH_3), 4.35 (q, $J=6.1$ Hz, 2H, CH_2-CH_3), 6.47 (s, 1H, pyrazole, =CH-), 11.73 (s, 1H, pyrazole, NH). Analytically calculated (%): C 48.41, H 5.87, N 31.36, S 14.36. Found: C 48.28, H 5.86, N 31.44, S 14.32. ESI-MS: $m/z = 223$ [M+1], 225 [M+3].

3-Ethylthio-5-(5-methylpyrazol-3-yl)-4-ethyl-1,2,4-triazole (7.2). Yield: 77 %; melting point: 83–84 °C; IR (v, cm^{-1}): 3232 (NH), 1599 (C=N); 1H NMR (δ , ppm): 1.30 (t, $J=6.1$ Hz, 3H, CH_2-CH_3), 1.44 (t, $J=5.1$ Hz, 3H, S- CH_2-CH_3), 2.35 (s, 3H, CH_3), 3.19–3.21 (m, $J=4.8$ Hz, 2H, S- CH_2-CH_3), 4.35 (q, $J=6.1$ Hz, 2H, CH_2-CH_3), 6.45 (s, 1H, pyrazole, =CH-), 11.71 (s, 1H, pyrazole, NH). Analytically calculated (%): C 50.61, H 6.37, N 29.51, S 13.51. Found C 50.48, H 6.38, N 29.59, S 13.55. ESI-MS: $m/z = 237$ [M+1], 239 [M+3].

3-(5-Methylpyrazol-3-yl)-4-ethyl-5-propylthio-1,2,4-triazole (7.3). Yield: 78 %; melting point: 80–82 °C; IR (v,



cm^{-1}): 3221 (NH), 1611 (C=N); 1H NMR (δ , ppm): 1.08 (t, $J = 5.4$ Hz, 3H, S-(CH₂)₂-CH₃), 1.32 (t, $J = 6.1$ Hz, 3H, CH₂-CH₃), 1.73–1.76 (m, 2H, S-CH₂-CH₂-CH₃), 2.34 (s, 3H, CH₃), 3.15 (t, 2H, S-CH₂-CH₂-CH₃), 4.35 (q, $J = 6.2$ Hz, 2H, CH₂-CH₃), 6.47 (s, 1H, pyrazole, =CH-), 11.74 (s, 1H, pyrazole, NH). Analytically calculated (%): C 52.56, H 6.82, N 27.86, S 12.76. Found: C 52.71, H 5.70, N 27.93, S 10.71. ESI-MS: $m/z = 251$ [M+1], 253 [M+3].

3-Butylthio-5-(5-methylpyrazol-3-yl)-4-ethyl-1,2,4-triazole (7.4). Yield: 67 %; melting point: 74–76 °C; IR (ν , cm^{-1}): 3230 (NH), 1595 (C=N); 1H NMR (δ , ppm): 0.84 (t, $J = 5.3$ Hz, 3H, S-(CH₂)₃-CH₃), 1.28 (t, $J = 6.1$ Hz, 3H, CH₂-CH₃), 1.37–1.40 (m, 2H, S-(CH₂)₂-CH₂-CH₃), 1.68–1.71 (m, $J = 8.16, 7.27$ Hz, 2H, S-CH₂-CH₂-CH₂-CH₃), 2.33 (s, 3H, CH₃), 3.18 (t, 2H, S-CH₂-(CH₂)₂-CH₃), 4.36 (q, $J = 6.0$ Hz, 2H, CH₂-CH₃), 6.46 (s, 1H, pyrazole, =CH-), 11.75 (s, 1H, pyrazole, NH). Analytically calculated (%): C 54.31, H 7.22, N 26.39, S 12.08. Found: C 54.17, H 7.20, N 26.32, S 12.11. ESI-MS: $m/z = 265$ [M+1], 267 [M+3].

3-(5-Methylpyrazol-3-yl)-5-pentylthio-4-ethyl-1,2,4-triazole (7.5). Yield: 74 %; melting point: 71–73 °C; IR (ν , cm^{-1}): 3221 (NH), 1609 (C=N); 1H NMR (δ , ppm): 0.85 (t, $J = 5.3$ Hz, 3H, S-(CH₂)₄-CH₃), 1.36–1.41 (m, 7H, CH₂-CH₃, S-(CH₂)₂-(CH₂)₂-CH₃), 1.66–1.69 (m, $J = 7.92, 7.25$ Hz, 2H, S-CH₂-CH₂-(CH₂)₂-CH₃), 2.33 (s, 3H, CH₃), 3.15 (t, $J = 5.1$ Hz, 2H, S-CH₂-(CH₂)₃-CH₃), 4.37 (q, $J = 6.2$ Hz, 2H, CH₂-CH₃), 6.47 (s, 1H, pyrazole, =CH-), 11.74 (s, 1H, pyrazole, NH). Analytically calculated (%): C 55.88, H 7.58, N 25.07, S 11.47. Found: C 56.01, H 7.56, N 25.13, S 11.44. ESI-MS: $m/z = 279$ [M+1], 281 [M+3].

3-Hexylthio-5-(5-methylpyrazol-3-yl)-4-ethyl-1,2,4-triazole (7.6). Yield: 82 %; melting point: 70–71 °C; IR (ν , cm^{-1}): 3235 (NH), 1624 (C=N); 1H NMR (δ , ppm): 0.88 (t, $J = 5.4$ Hz, 3H, S-(CH₂)₅-CH₃), 1.37–1.42 (m, $J = 4.8$ Hz, 1.7,

1.3 Hz, 9H, CH₂-CH₃, S-(CH₂)₂-(CH₂)₃-CH₃), 1.72–1.75 (m, $J = 7.8$ Hz, 2H, S-CH₂-CH₂-(CH₂)₃-CH₃), 2.33 (s, 3H, CH₃), 3.18 (t, $J = 7.9$ Hz, 2H, S-CH₂-(CH₂)₄-CH₃), 4.36 (q, $J = 6.1$ Hz, 2H, CH₂-CH₃), 6.47 (s, 1H, pyrazole, =CH-), 11.73 (s, 1H, pyrazole, NH). Analytically calculated (%): C 57.31, H 7.90, N 23.87, S 10.93. Found: C 57.16, H 7.88, N 23.82, S 9.44. ESI-MS: $m/z = 293$ [M+H⁺], 295 [M+3].

3-Heptylthio-5-(5-methylpyrazol-3-yl)-4-ethyl-1,2,4-triazole (7.7). Yield: 66 %; melting point: 69–71 °C; IR (ν , cm^{-1}): 3219 (NH), 1591 (C=N); 1H NMR (δ , ppm): 0.88 (t, 3H, S-(CH₂)₆-CH₃), 1.33–1.40 (m, 11H, CH₂-CH₃, S-(CH₂)₂-(CH₂)₄-CH₃), 1.70–1.73 (m, $J = 8.2$ Hz, 2H, S-CH₂-(CH₂)₅-CH₃), 2.31 (s, 3H, CH₃), 3.18 (t, $J = 7.9$ Hz, 2H, S-CH₂-(CH₂)₅-CH₃), 4.36 (q, $J = 6.1$ Hz, 2H, CH₂-CH₃), 6.47 (s, 1H, pyrazole, =CH-), 11.73 (s, 1H, pyrazole, NH). Analytically calculated (%): C 58.60, H 8.20, N 22.78, S 10.43. Found: C 58.76, H 7.09, N 22.72, S 10.46. ESI-MS: $m/z = 307$ [M+H⁺], 309 [M+3].

3-(5-Methylpyrazol-3-yl)-5-octylthio-4-ethyl-1,2,4-triazole (7.8). Yield: 82 %; melting point: 66–68 °C; IR (ν , cm^{-1}): 3221 (NH), 1607 (C=N); 1H NMR (δ , ppm): 0.89 (t, $J = 5.4$ Hz, 3H, S-(CH₂)₇-CH₃), 1.32–1.38 (m, 13H, CH₂-CH₃, S-(CH₂)₂-(CH₂)₅-CH₃), 1.68–1.71 (m, $J = 8.0$ Hz, 2H, S-CH₂-CH₂-(CH₂)₅-CH₃), 2.31 (s, 3H, CH₃), 3.19 (t, $J = 7.8$ Hz, 2H, S-CH₂-(CH₂)₇-CH₃), 4.37 (q, $J = 6.2$ Hz, 2H, CH₂-CH₃), 6.46 (s, 1H, pyrazole, =CH-), 11.73 (s, 1H, pyrazole, NH). Analytically calculated (%): C 59.78, H 8.47, N 21.78, S 9.97. Found: C 59.61, H 8.49, N 21.73, S 9.99. ESI-MS: $m/z = 321$ [M+H⁺], 323 [M+3].

3-(5-Methylpyrazol-3-yl)-5-nonylthio-4-ethyl-1,2,4-triazole (7.9). Yield: 69 %; melting point: 62–63 °C; IR (ν , cm^{-1}): 3227 (NH), 1584 (C=N); 1H NMR (δ , ppm): 0.89 (t, $J = 5.4$ Hz, 3H, S-(CH₂)₈-CH₃), 1.32–1.38 (m, 15H, CH₂-CH₃, S-(CH₂)₂-(CH₂)₆-CH₃), 1.68–1.71 (m, $J = 8.2$ Hz, 2H, S-CH₂-CH₂-(CH₂)₆-CH₃), 2.32 (s, 3H, CH₃), 3.17 (t, $J = 7.9$ Hz, 2H, S-CH₂-(CH₂)₇-CH₃),

Table 1. Molecular docking calculation with ALK

№	E_{min} , kcal/mol	№	E_{min} , kcal/mol	№	E_{min} , kcal/mol
6	-5.4	7.4	-7.6	7.8	-7.8
7.1	-6.1	7.5	-7.7	7.9	-7.7
7.2	-6.1	7.6	-7.4	7.10	-7.5
7.3	-7.5	7.7	-7.7	Crizotinib	-9.4

E_{min} : the minimum interaction energy, kcal/mol.

Table 2. Molecular docking calculation with COX-1

№	E_{min} , kcal/mol	№	E_{min} , kcal/mol	№	E_{min} , kcal/mol
6	-8.8	7.4	-6.2	7.8	-6.9
7.1	-5.3	7.5	-6.2	7.9	-7.3
7.2	-5.4	7.6	-6.3	7.10	-7.4
7.3	-5.6	7.7	-6.5	Diclofenac	-19,9

E_{min} : the minimum interaction energy, kcal/mol.

Table 3. Molecular docking calculation with lanosterol 14 α -demethylase

N	E_{min} , kcal/mol	N	E_{min} , kcal/mol	N	E_{min} , kcal/mol
6	-6.0	7.4	-8.5	7.8	-9.5
7.1	-6.1	7.5	-8.5	7.9	-9.3
7.2	-6.4	7.6	-8.4	7.10	-9.2
7.3	-8.5	7.7	-8.5	Ketoconazole	-10.1

E_{min} : the minimum interaction energy, kcal/mol.

4.37 (q, $J = 6.0$ Hz, 2H, CH_2-CH_3), 6.46 (s, 1H, pyrazole, =CH-), 11.72 (s, 1H, pyrazole, NH). Analytically calculated (%): C 60.86, H 8.71, N 20.87, S 9.56. Found C 60.71, H 8.69, N 20.82, S 9.58. ESI-MS: $m/z = 335 [M+H^+]$, 337 $[M+3]$.

3-Decylthio-5-(5-methylpyrazol-3-yl)-4-ethyl-1,2,4-triazole (7.10). Yield: 86 %; melting point: 60–61 °C; IR (ν , cm^{-1}): 3233 (NH), 1610 (C = N); 1H NMR (δ , ppm): 0.91 (t, $J = 5.4$ Hz, 3H, S-(CH_2)₉- CH_3), 1.26–1.35 (m, 17H, CH_2-CH_3 , S-(CH_2)₂-(CH_2)₇- CH_3), 1.66–1.70 (m, $J = 8.1$ Hz, 2H, S- CH_2-CH_2 -(CH_2)₇- CH_3), 2.33 (s, 3H, CH_3), 3.09–3.13 (t, $J = 7.6$ Hz, 2H, S- CH_2 -(CH_2)₈- CH_3), 4.38 (q, $J = 6.1$ Hz, 2H, CH_2-CH_3), 6.49 (s, 1H, pyrazole, =CH-), 11.75 (s, 1H, pyrazole, NH). Analytically calculated (%): C 61.85, H 8.94, N 20.04, S 9.17. Found C 61.68, H 8.92, N 20.09, S 9.19. ESI-MS: $m/z = 349 [M+H^+]$, 351 $[M+3]$.

Hydrogen atoms of the thioalkyl fragment generate signals in the strong part of the magnetic field [9]. For example, the Hydrogen signal of the thiomethyl group appears as a singlet at 2.76 ppm (7.1). The lengthening of the alkyl chain first leads to a shift in the signal of the methyl group to a stronger part of the magnetic field (up to S- C_4H_9). Further elongation of the alkyl fragment (S- $C_5 \dots C_{10}$) does not cause significant shifts in the Hydrogen signals of the methyl group. The methylene proton signals are observed in the region of strong fields in the form of a triplet at 3.09–3.19 ppm or multiplets at 1.26–1.42 ppm and at 1.66–1.76 ppm.

In the IR-spectrum of compounds 7.1–7.10 deformation vibrations of alkyl groups in ranges from 655 cm^{-1} to 1270 cm^{-1}

and H-C-H fragment in a narrow area of frequency 1480–1365 cm^{-1} are observed. For example, for CH_3 -group δ -vibrations occupied an area of 1373–1378 cm^{-1} . Valence vibrations of bonds of C-H alkyl groups form bands in the area of 3075–2845 cm^{-1} .

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

The methodology for rational drug development involves the use of molecular docking. Docking experiments of synthesized compounds (7, 7.1–7.8) with the 2XP2 (anaplastic lymphoma receptor tyrosine kinase) receptor revealed that compound 7.8 is the most active with a calculated binding energy of 8.1 kcal/mol (Table 1) [6,8–10].

It is known about the manifestation of anti-inflammatory activity, which is associated with the combination of triazole and pyrazole fragments within one molecule. In addition, it has been established which aminoacid residues of cyclooxygenases are directly responsible for the formation of hydrogen intermolecular bonds with substances that demonstrate biological activity. Thus, this area of research involving S-alkyl derivatives of 5-(5-methylpyrazol-3-yl)-4-ethyl-1,2,4-triazole-3-thiol is quite interesting. Cyclooxygenase-1 was chosen as the model enzyme (Table 2).

The effect of 1,2,4-triazole derivatives on the activity of lanosterol 14- α demethylase is a proven fact. It is established that 1 and 2 Nitrogen atoms of 1,2,4-triazole fragment are responsible for the formation of π - π -interaction with the active center of the specified enzyme. Therefore, a docking

study of the effect of synthesized compounds on this enzyme was considered relevant and was carried out (Table 3).

Discussion

According to the docking results, the synthesized compounds show different levels of binding to the aminoacid residues of anaplastic lymphoma kinase, cyclooxygenase-1 and lanosterol-14 α -demethylase.

The transition from thiol to its alkyl derivatives in a number of synthesized compounds leads to an increase in the level of binding to the active centers of anaplastic lymphoma kinase and lanosterol-14 α -demethylase.

Docking to cyclooxygenase-1 revealed a decrease in the interaction energy with the specified enzyme of the synthesized alkyl derivatives in comparison with the original thiol. The most relevant for further studies was 3-(5-methylpyrazol-3-yl)-5-octylthio-4-ethyl-1,2,4-triazole.

Conclusions

1. The optimal conditions for obtaining S-alkyl derivatives of 5-(5-methylpyrazole)-4-ethyl-1,2,4-triazole-3-thiol were determined. It was found that the highest yield of products of the alkylation reaction of 5-(5-methylpyrazole-3-yl)-4-ethyl-1,2,4-triazole-3-thiol was observed when methanol and propan-2-ol were used as solvents.

2. As a result of the molecular docking of the synthesized compounds, promising structures for further studies of anti-inflammatory and antifungal activity were identified. The most promising object for further research is 3-(5-methylpyrazol-3-yl)-5-octylthio-4-ethyl-1,2,4-triazole.

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

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