Synthesis, structure and properties of 7'-((4-amino-5-thio-1,2,4-triazole-3-yl)methyl)theophylline derivatives

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The combination of derivatives of 1,2,4-triazole and theophylline creates fertile soil for biologically active substances. The use of these heterocyclic systems allows the use of simple chemical modification methods and available reagents. This determines the relevance of the chosen direction of scientific research.

The aim of the work was to study synthesis methods and study the properties of heterocyclic systems containing theophylline and 1,2,4-triazole fragment in their structure, create a chemical variety that was interesting from a scientific point of view and was promising in the search for biologically active substances.

Materials and methods. Theophylline was used as the starting material. Using alkylation reactions, hydrazinolysis, interaction with a carbon disulfide followed by heterocyclization with an excess of hydrazine hydrate, 7'-((4-amino-5-thio-1,2,4-triazole-3-yl)methyl) theophylline was obtained. The following stages of the chemical conversion included alkylation reactions with haloalkanes, the formation of azomethine compounds by reaction with aromatic aldehydes, and the reaction with aromatic carboxylic acid chlorides. The structure of the obtained compounds was confirmed by data of elemental analysis, ^{1}H NMR spectroscopy and IR-spectrophotometry. The individuality of substances was established by using high performance liquid chromatography with diode-array and mass spectrometric detection.

Results. *S*-alkylderivatives of 7'-((4-amino-5-thio-1,2,4-triazole-3-yl)methyl)-theophylline, Schiff bases and carboxamides were synthesized, their structure was proved, and physical properties were investigated.

The synthesized compounds have been subjected to the *in silico* molecular docking study against the kinases of anaplastic lymphoma by using the 2XP2 ligand, lanosterol 14-α-demethylase by using the 3LD6 ligand, cyclooxygenase-2 by using the ligand 4Z0L which were downloaded from the protein data bank (PDB).

Conclusions. Molecular docking has shown the ability of the synthesized compounds to influence the kinase activity of anaplastic lymphoma, cyclooxygenase-2 and lanosterol-14-α-demethylase.

Синтез, будова та властивості похідних 7'-((4-аміно-5-тіо-1,2,4-тріазол-3-іл)метил)теофіліну

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Поєднання похідних 1,2,4-тріазолу й теофіліну створює підґрунтя для одержання біологічно активних речовин. Застосування цих гетероциклічних систем дає змогу використовувати нескладні методи хімічної модифікації та доступні реагенти. Це зумовлює актуальність обраного напряму наукових пошуків.

Мета роботи – дослідження методів синтезу та вивчення властивостей гетероциклічних систем, що містять у своїй структурі теофілін і 1,2,4-тріазольний фрагмент, створюють цікаве з наукового погляду хімічне різноманіття та є перспективними в галузі пошуку біологічно активних субстанцій.

Матеріали та методи. Як вихідну речовину використали теофілін. За допомогою реакцій алкілування, гідразинолізу, взаємодією з карбон дисульфідом із наступною гетероциклізацією за участю надлишку гідразин гідрату отримали 7'-((4-аміно-5-тіо-1,2,4-тріазол-3-іл)метил)теофілін. Наступні стадії хімічного перетворення включали реакції алкілування галогеналканами, утворення азометинових сполук шляхом взаємодії з ароматичними альдегідами та реакції взаємодії з хлорангідридами ароматичних карбонових кислот. Структура одержаних сполук підтверджена даними елементного аналізу, ^{1}Н ЯМР-спектроскопії та ІЧ-спектрофотометрії. Індивідуальність речовин встановлена за допомогою високоефективної рідинної хроматографії з діодно-матричною та мас-спектрометричною детекцією.

Результати. Синтезували *S*-алкілпохідні 7'-((4-аміно-5-тіо-1,2,4-тріазол-3-іл)метил)теофіліну, основи Шиффа та карбоксаміди, довели їхню будову та дослідили фізичні властивості. Синтезовані сполуки піддали докінговим дослідженням *in silico* для визначення

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можливого впливу на кіназу анапластичної лімфоми з використанням ліганда 2XP2, ланостерол 14-α-деметилазу з використанням ліганда 3LD6, циклооксигеназу-2 з використанням ліганда 4Z0L, які отримали з Банку даних білків (PDB).

Висновки. Молекулярний докінг показав можливість синтезованих сполук впливати на активність кінази анапластичної лімфоми, ланостерол 14-α-деметилази та циклооксигенази-2.

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

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Синтез, строение и свойства производных 7'-((4-амино-5-тио-1,2,4-триазол-3-ил)метил)теофиллина

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Сочетание производных 1,2,4-триазола и теофиллина создает благодатную почву для получения биологически активных веществ. Применение этих гетероциклических систем позволяет использовать несложные методы химической модификации и доступные реагенты. Это обусловливает актуальность выбранного направления научных поисков.

Цель работы – исследование методов синтеза и изучение свойств гетероциклических систем, содержащих в своей структуре теофиллин и 1,2,4-триазольный фрагмент, создают интересное с научной точки зрения химическое разнообразие и являются перспективными в области поиска биологически активных субстанций.

Материалы и методы. Как исходное вещество использовали теофиллин. С помощью реакций алкилирования, гидразинолиза, взаимодействием с карбон дисульфидом с последующей гетероциклизацией с участием избытка гидразин гидрата получен 7-((4-амино-5-тио-1,2,4-триазол-3-ил)метил)теофиллин. Следующие стадии химического превращения включали реакции алкилирования галогеналканами, образования азометиновых соединений путем взаимодействия с ароматическими альдегидами и реакции взаимодействия с хлорангидридами ароматических карбоновых кислот. Структура полученных соединений подтверждена данными элементного анализа, ^{1}H ЯМР-спектроскопии и ИК-спетрофотометрии. Индивидуальность веществ установлена с помощью высокоэффективной жидкостной хроматографии с диодно-матричной и масс-спектрометрической детекцией.

Результаты. Синтезированы *S*-алкилпроизводные 7'-((4-амино-5-тио-1,2,4-триазол-3-ил)метил)теофиллина, основания Шиффа и карбоксамиды, доказано их строение и исследованы физические свойства. Синтезированные соединения подвергнуты докинговым исследованиям *in silico* для определения возможного влияния на киназу анапластической лимфомы с использованием лиганда 2XP2, ланостерол 14-α-деметилазу с использованием лиганда 3LD6, циклооксигеназу-2 с использованием лиганда 4Z0L, которые получены из Банка данных белков (PDB).

Выводы. Молекулярный докинг продемонстрировал возможность синтезированных соединений влиять на активность киназы анапластической лимфомы, ланостерол 14-α-деметилазы и циклооксигеназы-2.

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

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The combination of xanthine and 1,2,4-triazole fragments provides a promising direction in the search for biologically active substances. There are many examples to support this [7]. Thus, substances with analgesic, bronchodilatory and antituberculosis activity were found in this class of compounds.

Methods of combining these compounds involve the formation of a 1,2,4-triazole moiety using xanthine as the starting compound. The literature describes various approaches to the conditions of this transformation [7]. But determining the optimal conditions for this process remains relevant despite the advances in research in this direction.

Aim

The aim of our work was to search for promising compounds from the point of biological activity in a series of derivatives that combine heterocyclic fragments of theophylline and 1,2,4-triazole.

Materials and methods

The implementation of the experimental part of the work has been accompanied by the use of traditional methods of organic synthesis [2,4,8]. Melting points were determined in open capillary tubes in a "MPA 100". The elemental analysis (C, H, N) were performed through the "Elementar vario EL cube" analyzer. IR spectra (4000–400 cm^{-1}) were taken using "ALPHA FT-IR spectrometer". ^{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)).

Chemistry

In the primary stage, the synthesis of theophylline ester was performed using 2-chloroacetic acid, followed by hydrazinolysis and heterocyclization in excess of hydrazine. The formed thiols were used in the reactions of alkylation, synthesis of Schiff bases and carboxamides. The influence of the nature of the solvent and the duration of heating on the yield of the reaction products were investigated. Sodium salt, ester and hydrazide were prepared according to known methods [7]. Hydrazinolysis and subsequent heterocyclization carried out using traditional methods of organic synthesis. The resulting 7'-((4-amino-5-thio-1,2,4-triazole-3-yl)methyl)theophylline

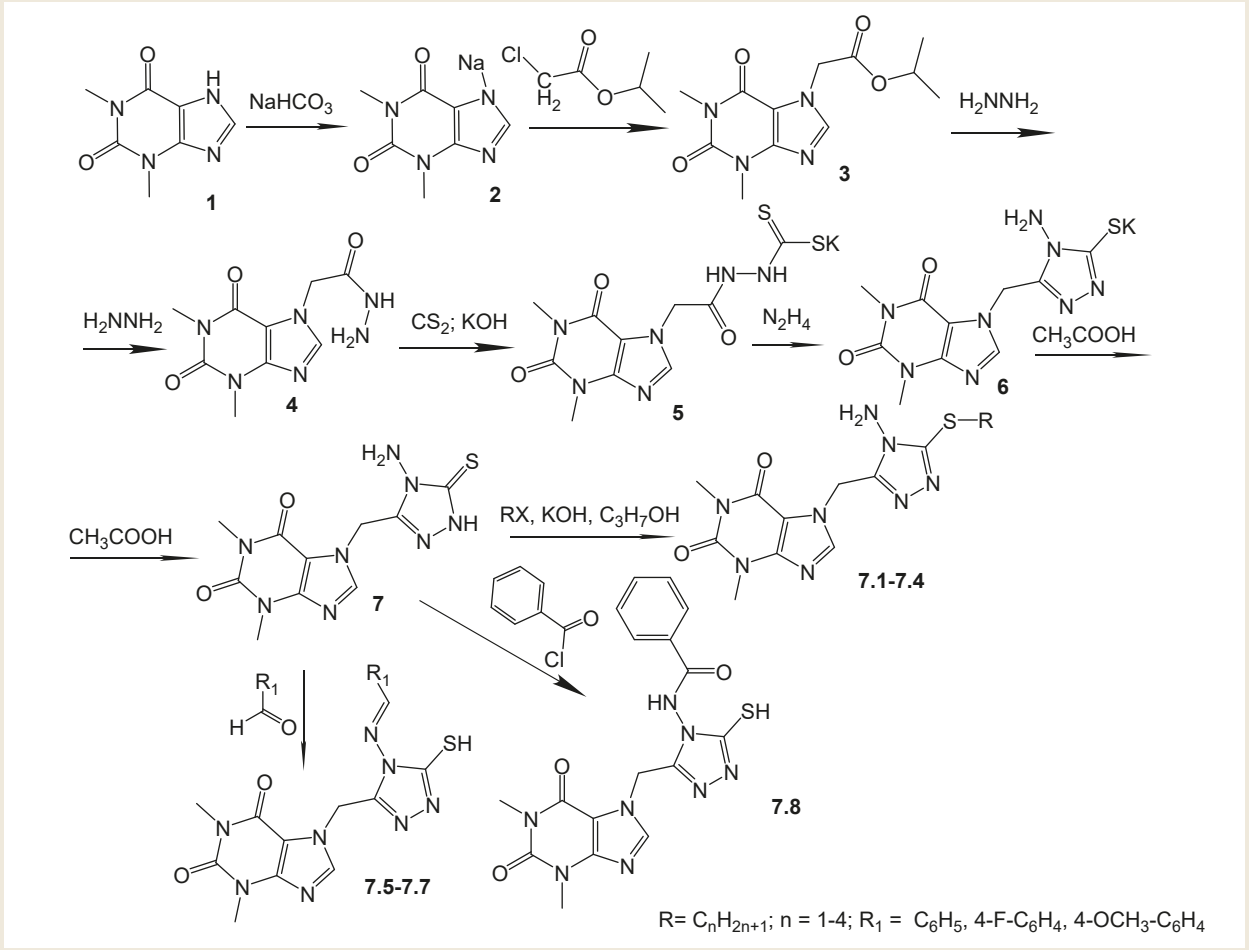

Fig. 1. The synthetic route of title compounds.

was used in *S*-alkylation and derivative reactions involving the amino group (*Fig. 1*).

7'-((4-Amino-3-thio-1,2,4-triazole-5-yl)methyl)theophylline (7). 1 g (0.02 mol) $N_2H_4 \cdot H_2O$ was added to a solution of 3.66 g (0.01 mol) of the potassium 2-(2-(theophylline-7-yl) acetyl)hydrazine-1-carbodithioate dissolved in 3 ml of water. The mixture was refluxed for 2 h, cooled, diluted with water and acidified with CH_3COOH. The product was crystallized from ethanol and isolated as a white solid.

Alkylderivatives of 7'-((4-amino-3-thio-1,2,4-triazole-5-yl)methyl)theophylline (7.1–7.4). To dissolved in 30 ml of propan-1-ol mixture of 0.005 mol of the thiol (7) and an equivalent amount of NaOH add also an equivalent amount of halogenalkane (iodomethane, iodoethane, 1-bromopropane, 1-bromobutane). Heat for 2 h, cooled, the precipitate is filtered, washed with water and crystallized from methanol.

7'-((4-Arylideneamino-3-thio-1,2,4-triazole-5-yl)methyl)theophylline (7.5–7.7). The corresponding aldehyde (0.005 mol) and 4 drops of H_2SO_4 concentrated were added to the compound 7 (0.005 mol) in 1,4-dioxane (50 ml). The reaction mixture was refluxed for 8 h and then diluted with 50 ml of H_2O. The product was crystallized from ethanol.

N-(5-((theophylline-7'-yl)methyl)-3-thioxo-1,2,4-triazole-4-yl)benzamide (7.8). Benzoyl chloride (0.005 mol) was added to a mixture of compound 7 (0.005 mol) and triethylamine (0.7 ml, 0.005 mol) in tetrahydrofuran (50 ml). The reaction mixture was stirred for 10 h. The product was crystallized from ethanol.

Molecular docking

Molecular docking was performed to obtain structural information on the interaction of the synthesized compounds and the corresponding biological structure [5]. The X-ray crystal structures of the corresponding biological targets from the protein database (PDB-ID) in complex with the standard ligand were previously downloaded: kinases of anaplastic lymphoma in the complex of crizotinib (2XP2), lanosterol 14-α-demethylase with ketoconazole (3LD6), cyclooxygenase-2 with diclofenac (4Z0L). The ligands (crizotinib, ketoconazole, diclofenac) were previously removed from the primary structures. Carried out the joining of different ligands to the protein using AUTODOCK. The conformations of the ligand were analyzed in terms of energy, hydrogen bonding and hydrophobic interaction between the ligand and

the receptor protein. A detailed analysis of the ligand-receptor interactions was performed and the final coordinates of the ligand and receptor were saved as pdb files. The binding energy (FEB) of all compounds was calculated.

Results

Optimal conditions were determined and 7'-((4-amino-3-thio-1,2,4-triazole-5-yl)-methyl)theophylline was synthesized and it new derivatives. The alkylation reactions, synthesis of Schiff bases and carboxamides were carried out with the synthesized thiols (*Fig. 1*) [2,4]. The structure of the obtained compounds was confirmed by ^{1}H NMR spectroscopy, chromatographic mass spectrometry and elemental analysis.

In obedience to the IR spectroscopic data of the compounds **7, 7.5–7.8** the observation of C=S stretching bands at 1203–1217 cm^{-1}. Valence vibrations of bonds of C-H alkyl groups form bands in area 2935–2850 cm^{-1}. The synthesized compounds are also characterized by valence vibrations of the C=C bond of the aromatic rings at 1468–1453 cm^{-1}.

In the ^{1}H NMR spectra of compounds (**7.1–7.4**) protons of the S-alkyl fragments resonate in a strong field as a singlet, a triplet or a multiplet in area 3.17–0.97 ppm. Proton of the N=CH fragment forms a signal in the form of the singlet at 8.82–8.71 ppm. The signal in the spectrum of compound **7.8** at 8.09 ppm corresponds to the proton of the CONH fragment and resonates in the form of a singlet.

In the chromatic mass spectra, individual peaks of the molecular ion and peaks of the fragment ions are recorded, which have a high intensity, which confirms the structure and identity of the compounds **7**, **7.1–7.8**.

7'-((4-Amino-3-thioxo-1,2,4-triazole-5-yl)methyl)theophylline (7). Yield: 86 %, m. p. 243-245 °C; IR (cm^{-1}): 3437, 3282 (N-H); 2873 (C-H aliphatic); 1692, 1650 (C=O); 1539 (N-H), 1468, 1455 (C=C, C=N), 1217 (C=S); ^{1}H NMR, δ (ppm): 13.52 (s, 1H, N^2-H, triazole), 8.01 (d, J = 10.6 Hz, 2H, NH_2), 7.93 (s, 1H, CH), 5.15 (s, 2H, N^7-CH_2), 3.56 (s, 3H, N^3-CH_3), 3.39 (s, 3H, N^1-CH_3). Anal. calcd. for $C_{10}H_{12}N_8O_2S$: C, 38.96; H, 3.92; N, 36.34; S, 10.40. Found: C, 38.86; H, 3.93; N, 36.43; S, 10.37.

7'-((4-Amino-3-methylthio-1,2,4-triazole-5-yl)methyl) theophylline (7.1). Yield: 68 %, m. p. 214-216 °C; IR (cm^{-1}): 3312, 3183 (N-H); 2865 (C-H aliphatic); 1694, 1653 (C=O); 1472, 1455 (C=C, C=N). ^{1}H NMR, δ (ppm): 7.96 (s, 1H, C^{8}H theophylline), 5.02 (s, 2H, N^7CH_2), 5.34 (s, 2H, NH_2), 3.54 (s, 3H, N^3-CH_3), 3.45 (s, 3H, N^1-CH_3), 2.68 (s, 3H, CH_3). Anal. calcd. for $C_{11}H_{14}N_8O_2S$: C, 40.99; H, 4.38; N, 34.76; S, 9.95. Found: C, 40.88; H, 4.37; N, 34.85; S, 9.98.

7'-((4-Amino-3-ethylthio-1,2,4-triazole-5-yl)methyl)theophylline (7.2). Yield: 81 %, m. p. 214-216 °C; IR (cm^{-1}): 3317, 3177 (N-H); 2865 (C-H aliphatic); 1697, 1648 (C=O); 1461, 1453 (C=C, C=N); ^{1}H NMR, δ (ppm): 7.98 (s, 1H, C^{8}H theophylline), 5.27 (s, 2H, NH_2), 5.03 (s, 2H, N^7CH_2), 3.52 (s, 3H, N^3-CH_3), 3.47 (s, 3H, N^1-CH_3), 3.17 (m, 2H, S-CH_2-CH_3), 1.34 (t, J = 5.3 Hz, 3H, S-CH_2-CH_3). Anal. calcd. for $C_{12}H_{16}N_8O_2S$: C, 42.85; H, 4.79; N, 33.31; S, 9.53. Found: C, 42.97; H, 4.78; N, 33.39; S, 9.50.

7'-((4-Amino-3-propylthio-1,2,4-triazole-5-yl)methyl) theophylline (7.3). Yield: 73 %, m. p. 201-203 °C; IR (cm^{-1}): 3319, 3173 (N-H); 1699, 1646 (C=O); 1468, 1455 (C=C, C=N); ^{1}H NMR, δ (ppm): 7.99 (s, 1H, C^{8}H theophylline), 5.35 (s, 2H, NH_2), 5.00 (s, 2H, N^7CH_2), 3.55 (s, 3H, N^3-CH_3), 3.42 (s, 3H, N^1-CH_3), 3.14 (t, J = 8.1 Hz,2H, S-CH_2- CH_2-CH_3), 1.77-1.74 (m, 2H, S-CH_2-CH_2-CH_3), 1.06 (t, J = 5.4 Hz, 3H, S-$(CH_2)_2$-CH_3). Anal. calcd. for $C_{13}H_{18}N_8O_2S$: C, 44.56; H, 5.18; N, 31.98; S, 9.15. Found: C, 44.67; H, 5.17; N, 31.98; S, 9.23.

7'-((4-Amino-3-butylthio-1,2,4-triazole-5-yl)methyl)theophylline (7.4). Yield: 69 %, m. p. 214-216 °C ; IR (cm^{-1}): 3318, 3175 (N-H); 1711, 1638 (C=O); 1459, 1451 (C=C, C=N); ^{1}H NMR, δ (ppm): 8.01 (s, 1H, C^{8}H theophylline), 5.39 (s, 2H, NH_2), 4.98 (s, 2H, N^7CH_2), 3.51 (s, 3H, N^3-CH_3), 3.44 (s, 3H, N^1-CH_3), 3.11 (t, J = 8.3 Hz, 2H, S-CH_2-$(CH_2)_2$-CH_3), 1.69 (m, 2H, S-CH_2-CH_2-CH_2-CH_3), 1.43-1.39 (m, 2H, S-$(CH_2)_2$-CH_2-CH_3), 0.97 (t, J = 5.3 Hz, 3H, S-$(CH_2)_3$-CH_3). Anal. calcd. for $C_{14}H_{20}N_8O_2S$: C, 46.14; H, 5.53; N, 30.88; S, 8.80. Found: C, 46.03; H, 5.52; N, 30.82; S, 8.82.

7'-((4-(Benzylideneamino)-3-thio-1,2,4-triazole-5-yl) methyl)theophylline (7.5). Yield: 79%, m. p. 224-226 °C; IR (cm^{-1}): 3097 (C-H Ar); 1683, 1646 (C=O); 1468, 1453 (C=C, C=N), 1208 (C=S), 685 (C-H Ar); ^{1}H NMR, δ (ppm): 13.54 (s, 1H, N^2-H, triazole), 9.83 (s, 1H, SH), 8.71 (s, 1H, N=CH), 8.06 (s, 1H, C^{8}H theophylline), 7.42 – 7.33 (m, 5H, C_6H_5), 5.11 (s, 2H, N^7CH_2), 4.65 (s, 2H, CH_2), 3.50 (s, 3H, N^3-CH_3), 3.42 (s, 3H, N^1-CH_3). Anal. calcd. for $C_{17}H_{16}N_8O_2S$: C, 51.51; H, 4.07; N, 28.27; S, 8.09. Found: C, 51.64; H, 4.06; N, 28.34; S, 8.07.

7'-((3-Thio-4-((4-methoxybenzylidene)amino)-1,2,4-triazole-5-yl)methyl)-theophylline (7.6). Yield: 71 %, m. p. 235-237 °C; IR (cm^{-1}): 3092 (C-H Ar); 1699, 1641 (C=O); 1595, 1474, 1453 (C=C, C=N), 1203 (C=S), 790 (C-H Ar); ^{1}H NMR, δ (ppm): 13.57 (s, 1H, N^2-H, triazole), 8.82 (s, 1H, N=CH), 8.03 (s, 1H, C^{8}H theophylline), 7.61 – 7.53 (d, J = 8.5 Hz, 2H, H-2,6, $C_6H_4OCH_4$), 6.98 (d, J = 8.3 Hz, 2H, H-3,5, $C_6H_4OCH_3$), 4.88 (s, 2H, N^7CH_2), 3.82 (s, 3H, $C_6H_4OCH_3$), 3.41 (s, 3H, N^3-CH_3), 3.22 (s, 3H, N^1-CH_3). Anal. calcd. for $C_{18}H_{18}N_8O_3S$: C, 50.70; H, 4.25; N, 26.28; S, 7.52. Found: C, 50.58; H, 4.26; N, 26.22; S, 7.54.

7'-((4-(4-Fluorobenzylideneamino)-5-thio-1,2,4-triazole-3-yl)methyl)theophylline (7.7). Yield: 68 %, m. p. 222-224 °C; IR (cm^{-1}): 3097 (C-H Ar); 1683, 1646 (C=O); 1591, 1468, 1453 (C=C, C=N), 1208 (C=S), 695 (C-H Ar); ^{1}H NMR, δ (ppm): 13.53 (s, 1H, N^2-H, triazole), 8.75 (s, 1H, N=CH), 8.04 (s, 2H, C^{8}H theophylline), 7.62 (t, 2H, H-2,6, C_6H_4F), 7.07 (t, 2H, H-3,5, C_6H_4F), 4.93 (s, 2H, N^7CH_2), 3.52 (s, 3H, N^3-CH_3), 3.43 (s, 3H, N^1-CH_3). Anal. calcd. for $C_{17}H_{15}FN_8O_2S$: C, 49.27; H, 3.65; N, 27.04; S, 7.74. Found: C, 49.41; H, 3.66; N, 26.96; S, 7.72.

N-(5-((theophylline-7'-yl)methyl)-3-thioxo-1,2,4-triazole-4-yl)benzamide (7.8). Yield: 63 %, m. p. 214-216 °C; IR (cm^{-1}): 3097 (C-H Ar); 1687, 1642 (C=O); 1465, 1448 (C=C, C=N), 1209 (C=S), 713, 689 (C-H Ar); ^{1}H NMR, δ (ppm): 13.56 (s, 1H, N^2-H, triazole), 8.09 (s, 1H, NH), 7.97 (s, 1H, C^{8}H theophylline), 7.91 (d, J = 7.1 Hz, 2H, H-2,6, C_6H_5), 7.56

(t, J = 7.5 Hz, 1H, H-4, C_6H_5), 7.45 (t, J = 7.4 Hz, 2H, H-3,5, C_6H_5), 5.01 (s, 2H, N^7-CH_2), 3.41 (s, 3H, N^3-CH_3), 3.22 (s, 3H, N^1-CH_3). Anal. calcd. for $C_{17}H_{16}N_8O_3S$: C, 49.51; H, 3.91; N, 27.17; S, 7.77. Found: C, 49.37; H, 3.92; N, 27.09; S, 7.79.

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 (ALK tyrosine kinase receptor) receptor revealed that compound **7.8** is the most active with a calculated binding energy of 8.1 kcal/mol (*Table 1*) [3,6,8–10].

Analysis of complexes of synthesized compounds with anaplastic lymphoma kinase showed the participation of the following amino acid residues: A: ASP 1203, A: ALA 1148, A: ARG 1253, A: VAL 1130, A: LEU 1122, A: LEU 1198, A: LEU 1256 (*Fig. 2*).

The next stage is reaching at the base of the specified disparity of synthesizing compounds to the site of the enzyme's link cyclooxygenase-2 (COX-2) (*Table 2*) [9]. Visualization of the interaction of the most active compound (7) with the center of COX-2 allowed to establish that it has a hydrogen bond with the amino acid residue D: TYR 3355, in addition, three pi-alkylhydrophobic interactions with D: LEU 3531, D: 3523, D: 3352.

Docking of 1,2,4-triazole-3-thiol derivatives and reference compound (ketoconazole) against the generated homology model for lanosterol-14α-demethylase was carried out (*Table 3*) [9].

Analysis of the complex of the most active compound with lanosterol-14α-demethylase showed interactions with the following amino acid residues: B: His 447, B: TYR 131, B: ILE 377, B: ILE 379, B: PRO 376, B: MET 487.

Table 1. Energy values of the intermolecular interactions of the studied compounds with anaplastic lymphoma kinase (2XP2)

N	$*E_{min}$, kcal/mol	N	$*E_{min}$, kcal/mol	N	$*E_{min}$, kcal/mol
7	-6.8	7.3	-7,1	7.6	-8,0
7.1	-6,7	7.4	-7,8	7.7	-7,9
7.2	-7,0	7.5	-7,9	**7.8**	**-8,1**
Crizotinib	-9,4				

$*E_{min}$: The minimum energy of complex formation, kcal/mol.

Table 2. Energy values of the intermolecular interactions of the studied compounds with COX-2 (4Z0L)

N	E_{min}, kcal/mol	N	E_{min}, kcal/mol	N	E_{min}, kcal/mol
7	-7,3	7.3	-3,6	7.6	-1,6
7.1	-5,1	7.4	-6.0	7.7	-2,7
7.2	-4,9	7.5	-2,3	7.8	-0,4
Diclofenac	-6,6				

Table 3. Energy values of the intermolecular interactions of the studied compounds with lanosterol-14α-demethylase (3LD6)

N	E_{min}, kcal/mol	N	E_{min}, kcal/mol	N	E_{min}, kcal/mol
7	-7.4	7.3	-8.5	7.6	-9.8
7.1	-7.5	7.4	-8.7	7.7	-9.5
7.2	-8.0	7.5	-9.4	7.8	-9.6
Ketoconazole	-10.1				

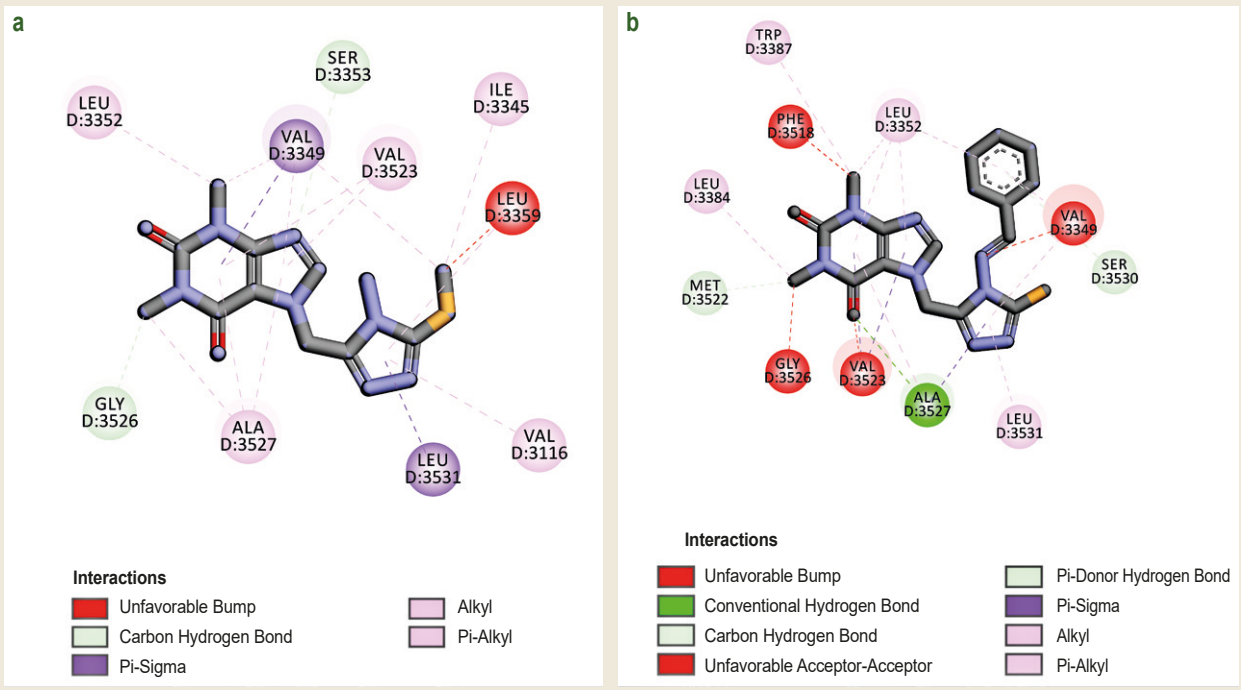

Fig. 2. Visualization of affinity according to the docking: a – compound 7.1 with COX-2 (4Z0L); b – compound 7.5 with COX-2 (4Z0L) [1].

Discussion

The results of molecular docking using three classes of substances demonstrate the different nature of the interactions of synthesized substances with amino acid residues anaplastic lymphoma kinase (2XP2), COX-2 (4Z0L) and lanosterol-14α-demethylase (3LD6).

Amino acid modification of the starting molecule led to an increase in the number of hydrogen chemical bonds and hydrophobic interactions with anaplastic lymphoma kinase (2XP2) and lanosterol-14α-demethylase (3LD6).

The appearance of an alkyl substituent for Sulfur of synthesized substances may be justified in planning further studies related to the search for inhibitors COX-2.

Conclusions

1. An universal method for the preparation of *S*-alkylderivatives of 7'-((4-amino-5-thio-1,2,4-triazole-3-yl)methyl) theophylline was developed. It was found that the highest yield of the products of this chemical transformation was observed in propan-1-ol medium and heated for two hours.

2. The synthesis was substantiated and the peculiarities of the formation of reactions were established of the Schiff bases and carboxamides based on 7'-((4-amino-5-thio-1,2,4-triazole-3-yl)methyl)theophylline. The most suitable solvent for synthesis of the Schiff bases was 1,4-dioxane, for carboxamides – tetrahydrofuran.

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

4. The prospect of studying the antifungal activity of the synthesized compounds based on the use of molecular docking has been shown.

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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