Synthesis, structure and properties of some 5-R-4-phenyl-1,2,4-triazole-3-thiol derivatives

A. S. Hotsulia*

Zaporizhzhia State Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
E – critical revision of the article; F – final approval of the article

Pyrrole, 1,2,4-triazole and indole derivatives belong to the group of aza-heterocyclic compounds, which have been associated with significant advances in the development of new drugs. Combining these heterocycles in one molecule increases the likelihood of detecting among these compounds substances with a certain kind of biological activity.

The aim of the work was to optimize the conditions of synthesis and study the properties of S-alkylderivatives of 5-R-4-phenyl-1,2,4-triazole-3-thiol containing pyrrole and indolpropane fragments in their structure.

Materials and methods. Pyrrole and indole-3-butanoic acid were used as key starting reagents. 4-Phenyl-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol was obtained by acylation, hydrazinolysis, nucleophilic addition of phenylisothiocyanate followed by intramolecular heterocyclization. For the synthesis of 5-(3-(indol-3-yl)propyl)-4-phenyl-1,2,4-triazole-3-thiol, the reaction of the interaction of the potassium salt of indole-3-butanoic acid with bromethane was carried out to obtain the appropriate ester. Subsequent stages of chemical conversion included hydrazinolysis reactions, the addition of phenylisothiocyanate, and alkaline cyclization. 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 5-(3-(indol-3-yl)propyl)-4-phenyl-1,2,4-triazole-3-thiol and 4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol has been synthesized and their structure was established and studied physical properties. 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 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 деяких похідних 5-R-4-феніл-1,2,4-тріазол-3-тіолу

А. С. Гоцуля

Похідні піролу, 1,2,4-тріазолу та індолу належать до групи азагетероциклічних сполук, з використанням яких пов'язані значущі успіхи у сфері створення нових лікарських засобів. Поєднання цих гетероциклів в одній молекулі дає змогу підвищити ймовірність виявлення серед відзначених сполук речовин із певним видом біологічної активності.

Мета роботи – оптимізація умов синтезу та дослідження властивостей S-алкілпохідних 5-R-4-феніл-1,2,4-тріазол-3-тіолу, які містять у своїй структурі пірольний та індолпропановий фрагменти.

Матеріали та методи. Як ключові вихідні реагенти використали пірол та індол-3-бутанову кислоту. За допомогою реакцій ацилювання, гідразинолізу, нуклеофільного приєднання фенілізотіоціанату з наступною внутрішньомолекулярною гетероциклізацією одержали 4-феніл-5-(пірол-2-іл)-1,2,4-тріазол-3-тіол. Для синтезу 5-(3-(індол-3-іл)пропіл)-4-феніл-1,2,4-тріазол-3-тіолу попередньо провели реакцію взаємодії калієвої солі індол-3-бутанової кислоти з брометаном, що дало змогу одержати відповідний естер. Наступні стадії хімічного перетворення включали реакції гідразинолізу, приєднання фенілізотіоціанату та лужної циклізації. Структура отриманих 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 5-(3-(індол-3-іл)пропіл)-4-феніл-1,2,4-тріазол-3-тіолу та 4-феніл-5-(пірол-2-іл)-1,2,4-тріазол-3-тіолу, довели їхню будову та дослідили фізичні властивості. Синтезовані сполуки піддані докінґовим дослідженням *in silico* для визначення можливого впливу на кіназу анапластичної лімфоми з використанням ліганду 2XP2, ланостерол 14-α-деметилазу з використанням ліганду 3LD6, циклооксигеназу-2 з використанням ліганду 4Z0L, які одержані з Банку даних білків (PDB).

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***E-mail:** andrey.goculya@gmail.com

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

Ключові слова: 1,2,4-тріазол, пірол, індол, фізико-хімічні властивості, молекулярний докінґ.

Актуальні питання фармацевтичної і медичної науки та практики. – 2019. – Т. 12, № 3(31). – С. 238–244

Синтез, строение и свойства некоторых производных 5-R-4-фенил-1,2,4-триазол-3-тиола

А. С. Гоцуля

Производные пиррола, 1,2,4-триазола и индола относятся к группе азагетероцикличных соединений, с использованием которых связаны значительные успехи в области создания новых лекарственных средств. Сочетание данных гетероциклов в одной молекуле позволяет повысить вероятность установления среди указанных соединений веществ с определенным видом биологической активности.

Цель работы – оптимизация условий синтеза и исследования свойств S-алкилпроизводных 5-R-4-фенил-1,2,4-триазол-3-тиола, содержащих в своей структуре пиррольный и индолпропановый фрагменты.

Материалы и методы. В качестве ключевых исходных реагентов использованы пиррол и индол-3-бутановая кислота. С помощью реакций ацилирования, гидразинолиза, нуклеофильного присоединения фенилизотиоцианата с последующей внутримолекулярной гетероциклизацией получен 4-фенил-5-(пиррол-2-ил)-1,2,4-триазол-3-тиол. Для синтеза 5-(3-(индол-3-ил)пропил)-4-фенил-1,2,4-триазол-3-тиола предварительно проведена реакция взаимодействия калиевой соли индол-3-бутановой кислоты с бромэтаном, что позволило получить соответствующий эфир. Следующие стадии химического превращения включали реакции гидразинолиза, присоединение фенилизотиоцианата и щелочной циклизации. 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. Синтезированны S-алкилпроизводные 5-(3-(индол-3-ил)пропил)-4-фенил-1,2,4-триазол-3-тиола и 4-фенил-5-(пиррол-2-ил)-1,2,4-триазол-3-тиола, 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-деметилазы с использованием лиганда 3LD6, ЦОГ-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: пиррол, 1,2,4-триазол, индол, физико-химические свойства, молекулярный докинг.

Актуальные вопросы фармацевтической и медицинской науки и практики. – 2019. – Т. 12, № 3(31). – С. 238–244

Research in the field of indole compounds has been and remains relevant in the chemistry of heterocycles [1–3]. The reason for this interest is the participation of indole derivatives in the metabolic processes of living systems as biologically active compounds [6]. Derivatives of 1,2,4-triazole and pyrrole, which are structural fragments of a number of known drugs, are of no less interest [4,5]. A variety of chemical modification methods that can be used with respect to these heterocyclic systems, high biological potential with low toxicity give these objects of research all the signs of relevance and practical significance. During the last few years derivatives of indole have attracted much attention because of their special biological activity in medicine and agriculture.

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 pyrrole, 1,2,4-triazole, and indole.

Materials and methods

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) were 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)).

Chemistry

Sodium 4-(indol-3-yl)butanoate. To a mixture of 0.01 mol of 4-(indol-3-yl)butyric acid and 0.01 mol of sodium bicarbonate was added 15 ml of water. This mixture was boiled for 7 hours and evaporated.

Ethyl 4-(indol-3-yl)butanoate. A mixture of 0.01 mol of sodium 4-(indol-3-yl)butanoate was dissolved in 15.0 ml of DMSO at 80 °C and the equivalent of ethyl bromide was added. It was heated at 80 °C for 12 hours. Cooled down. The resulting solution was slowly poured into 60 ml of water. Orange oil was immediately formed and crystallized into orange crystals. This compound had a characteristic unpleasant odor. The crystalline precipitate formed was filtered off and dried.

4-(Indol-3-yl)butanhydrazide. To a solution of 0.01 mol of ethyl 4-(indol-3-yl)butanoate in 20 ml of ethanol was added 0.022 mol of hydrazine monohydrate. It was heated to boiling for 6 hours. The resulting solution was slowly poured into 60 ml of water. Yellow crystals were formed immediately. The crystalline precipitate formed was filtered off and dried.

2-(4-(Indol-3-yl)butanoyl)-N-phenylhydrazinocarbothioamide. 4-(Indol-3-yl)-butanhydrazide was dissolved in a minimal amount of propan-2-ol and the equivalent of phenylisothiocyanate was added. It was heated for 6 hours. It was evaporated to form light yellow oil which gradually crystallized.

5-(3-(Indol-3-yl)propyl)-4-phenyl-1,2,4-triazole-3-thiol. To 0.01 mol of synthesized 2-(4-(indol-3-yl)butanoyl)-*N*-phenylhydrazinocarbothioamide was added 0.011 mol of NaOH as a 7% solution, heated to dissolution and 1 hour afterwards. Then 10 ml of water was added and neutralized with ethane acid. A white crystalline precipitate is formed. This compound was crystallized from propan-2-ol.

Alkylderivatives of 5-R-4-phenyl-1,2,4-triazole-3-thiol. To dissolved in 30 ml of propan-1-ol mixture of 0.005 mol of the corresponding thiol and an equivalent amount of sodium hydroxide was added an equivalent amount of halogenalkane (iodomethane, iodoethane, 1-bromopropane, 1-bromobutane, 1-bromopentane, 1-bromohexane, 1-bromoheptane, 1-bromooctane, 1-bromononane, 1-bromodecane). This mixture was heated for 2 hours, cooled, the precipitate was filtered, washed with water and crystallized from methanol.

Molecular docking

Molecular docking was performed to obtain structural information on the interaction of the synthesized compounds and the corresponding biological structure. For this purpose, 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 indomethacin (4Z0L). The ligands (crizotinib, ketoconazole, indomethacin) were previously removed from the primary structures. It was 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 and discussion

Optimal conditions were determined and 5-(3-(indol-3-yl) propyl)-4-phenyl-1,2,4-triazole-3-thiol, 4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol with their new derivatives were synthesized. Acetylation reactions in diethyl ether, nucleophilic substitution, addition in an alcoholic medium, and intermolecular alkaline heterocyclization were used to obtain the starting thiol. The preparation of the original 4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol and its physical-chemical properties were described in previous work [7]. The alkylation reactions were carried out with the synthesized thiols. The structure of the obtained compounds was confirmed by ^{1}H NMR spectroscopy, chromatographic mass spectrometry and elemental analysis.

According to the IR spectroscopic data of the compounds 2.7, 2.8 which have triazole-3-thione structure, the observation of C=S stretching bands at 1380–1365 cm^{-1} and the absence of an absorption at about 2595–2550 cm^{-1} region cited for SH group have proved that these compounds were in the thionic form. In the IR-spectrum of synthesized alkyl derivatives observe deformation vibrations of alkyl groups in ranges from 630 to 1400 cm^{-1} and H-C-H fragment in a narrow area of frequency 1475–1370 cm^{-1}. For example, for CH_3-group δ-vibrations occupied area at 1373–1380 cm^{-1}. Valence vibrations of bonds of C-H alkyl groups form bands in area 3100–2850 cm^{-1}. 840–780 cm^{-1} occupies a band of average intensity with a complex circuit that has several peaks (skeletal vibrations of C-C bonds). The synthesized compounds are also characterized by valence vibrations of the C=C bond of the aromatic rings at 1563–1515 cm^{-1}.

In the ^{1}H NMR spectra of compounds (*2.2, 2.6, 2.8, 2.19-2.28*) NH proton of the indole ring was seen as singlet at about 10.88–10.14 ppm. The integral intensity of the multiplet signals of the phenyl substituent protons, which are in the range 7.58–6.96 ppm, corresponds to their number in the proposed structures. The signal due to indol-CH_2- methylene protons, present in all compounds, appeared at 3.03–2.09 ppm, as triplet or multiplet. Protons of the S-alkyl fragments (2.9–2.28) resonate in a strong field as a triplet or multiplet in area 3.21–0.84 ppm.

In the chromatic mass spectra, individual peaks of quasimolecular ions [M+1] are recorded, which have a high intensity, which confirms the structure and identity of the compounds 2.7, 2.8-2.28.

2-(4-(Indol-3-yl)propyl)-N-pheylhydrazine-1-carbothioamide (2.4). Yield 89%, m. p. 132-133 °C; ^{1}H NMR, *δ* (ppm): 1.09 (t, 3H, CH_3), 1.98 (q, 2H, CH_2), 2.36 (t, 2H, CH_2), 3.12 (m, 2H, CH_2), 3.42 (q, 2H, CH_2), 3.55 (s, 2H, Ar–CH_2) , 6.96 (m, 1H, H-5), 7.05 (m, 1H, H-6), 7.21 (d, 1H, CH), 7.32 (d, 1H, H-7), 7.55 (d, 1H, H-4), 7.78 (t, 1H, NH–NH–CS–N*H*), 9.08 (d, 1H, N*H*–NH–CS–NH), 9.62 (d, 1H, NH–N*H*–CS–NH), 10.88 (s, 1H, NH indole). Anal. calcd. (%) for $C_{13}H_{16}N_4OS$: C, 59.18; H, 6.62; N, 18.41. Found: C, 59.04; H, 6.63; N, 18.45.

5-(3-(Indol-3-yl)propyl)-4-phenyl-1,2,4-triazole-3-thiol (2.8). Yield 91%, m. p. 191-192 °C ; ^{1}H NMR, *δ* (ppm): 2.11-2.14 (m, 2H, CH_2–C*H*$_2$–CH_2), 2.39 (t, 2H, CH_2–CH_2–C*H*$_2$), 2.94-2.97 (m, 2H, C*H*$_2$–CH_2–CH_2), 6.98 (t, 1H, H-5 indole), 7.06 (t, 1H, CH indole), 7.09 (t, 1H, H-6), 7.24-7.29 (m, 2H, H-7 CH indole), 7.41-7.45 (dd, 2H, C_6H_5), 9.44 (s, 1H, NH–NH–CS–N*H*), 9.61 (d, 1H, NH–N*H*–CS–NH), 9.65 (d, 1H, N*H*–NH–CS–NH), 10.55 (s, 1H, NH indole), 13.45 (s, 1H, SH). Anal. calcd. (%) for $C_{19}H_{18}N_4S$: C 68.24; H 5.43; N 16.75; 9.59. Found: C 68.08; H 5.42; N 16.71; 9.61.

3-(Methylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.9). Yield: 71 %; m. p.: 168-171 °C; ^{1}H NMR, δ (ppm): 7.87 (dd, J = 6.6, 1.6 Hz, 1H, CH pyrrol), 7.56 – 7.51 (m, 3H, C_6H_5), 7.45 (d, 2H, C_6H_5), 7.41 – 7.35 (m, 2H, C_6H_5), 7.20 (dd, J = 6.7, 3.6 Hz, 1H, CH pyrrol), 6.94 (d, 1H, CH pyrrol), 2.75 (s, 3H, CH_3). Anal. calcd. (%) for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86; S, 12.51. Found: C, 61.07; H, 4.71; N, 21.92; S, 12.48.

3-(Ethylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.10). Yield: 74 %; m. p.: 189-191 °C; ^{1}H NMR, δ (ppm): 7.92 (dd, J = 6.6, 1.6 Hz, 1H, CH pyrrol), 7.56 – 7.46 (m, 3H, C_6H_5), 7.40 (d, 2H, C_6H_5), 7.20 (dd, J = 6.7, 3.6 Hz, 1H, CH pyrrol), 6.94 (d, 1H, CH pyrrol), 3.20 (q, J = 5.1 Hz, 2H, CH_2), 1.41 (t, J = 5.1 Hz, 3H, CH_3). Anal. calcd. (%) for $C_{14}H_{14}N_4S$: C, 62.20; H, 5.22; N, 20.72; S, 11.86. Found: C, 62.05; H, 5.21; N, 20.77; S, 11.89.

4-Phenyl-3-(propylthio)-5-(pyrrol-2-yl)-1,2,4-triazole (2.11). Yield: 83 %; m. p.: 177-179 °C; ^{1}H NMR, δ (ppm): 7.92 (dd, J = 6.6, 1.6 Hz, 1H, CH pyrrol), 7.54 – 7.49 (m, 3H, C_6H_5), 7.41 (d, 2H, C_6H_5), 7.24 (dd, J = 6.7, 3.6 Hz, 1H, CH pyrrol), 6.93 (d, 1H, CH pyrrol), 3.07 (t, J = 8.1 Hz, 2H, S-CH_2-CH_2-CH_3), 1.73-1.70 (m, 2H, S-CH_2-CH_2-CH_3), 1.04 (t, J = 5.3 Hz, 3H, S-$(CH_2)_2$-CH_3). Anal. calcd. (%) for $C_{15}H_{16}N_4S$: C, 63.35; H, 5.67; N, 19.70; S, 11.27. Found: C, 63.19; H, 5.68; N, 19.65; S, 11.30.

3-(Butylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.12). Yield: 76 %; m. p.: 193-195 °C; ^{1}H NMR, δ (ppm): 7.92 (dd, J = 6.6, 1.7 Hz, 1H, CH pyrrol), 7.55 – 7.44 (m, 5H, C_6H_5), 7.25 (dd, J = 6.6, 3.7 Hz, 1H, CH pyrrol), 6.93 (d, 1H, CH pyrrol), 3.15 (t, J = 8.3 Hz, 2H, S-CH_2-$(CH_2)_2$-CH_3), 1.71-1.68 (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), 0.95 (t, J = 5.3 Hz, 3H, S-$(CH_2)_3$-CH_3). Anal. calcd. (%) for $C_{16}H_{18}N_4S$: C, 64.40; H, 6.08; N, 18.78; S, 10.74. Found: C, 64.56; H, 6.09; N, 18.73; S, 10.71.

3-(Pentylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.13). Yield: 71 %; m. p.: 217-219 °C; ^{1}H NMR, δ (ppm): 7.98 (dd, J = 6.7, 1.7 Hz, 1H, CH pyrrol), 7.57 – 7.53 (m, 3H, C_6H_5), 7.47 (d, 2H, C_6H_5), 7.25 (dd, J = 6.6, 3.7 Hz, 1H, CH pyrrol), 6.91 (d, 1H, CH pyrrol), 3.16 (t, J = 7.4 Hz, 2H, S-CH_2-$(CH_2)_3$-CH_3), 1.71-1.68 (m, 2H, S-CH_2-CH_2-$(CH_2)_2$-CH_3), 1.42 – 1.37 (m, 4H, S-$(CH_2)_2$-$(CH_2)_2$-CH_3), 0.90 (t, J = 5.4 Hz, 2H, S-$(CH_2)_4$-CH_3). Anal. calcd. (%) for $C_{17}H_{20}N_4S$: C, 65.35; H, 6.45; N, 17.93; S, 10.26. Found: C, 65.17; H, 6.46; N, 17.88; S, 10.29.

3-(Hexylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.14). Yield: 75 %; m. p.: 265-268 °C; ^{1}H NMR, δ (ppm): 7.95 (dd, J = 6.6, 1.7 Hz, 1H, CH pyrrol), 7.58 – 7.53 (m, 3H, C_6H_5), 7.46 (d, 2H, C_6H_5), 7.26 (dd, J = 6.7, 3.6 Hz, 1H, CH pyrrol), 6.93 (d, 1H, CH pyrrol), 3.17 (t, J = 7.9 Hz, 2H, S-CH_2-$(CH_2)_4$-CH_3), 1.70-1.67 (m, 2H, S-CH_2-CH_2-$(CH_2)_3$-CH_3), 1.35 – 1.28 (m, 6H, S-$(CH_2)_2$-$(CH_2)_3$-CH_3), 0.93 – 0.87 (m, 3H, S-$(CH_2)_5$-CH_3). Anal. calcd. (%) for $C_{18}H_{22}N_4S$: C, 66.22; H, 6.79; N, 17.16; S, 9.82. Found: C, 66.07; H, 6.78; N, 17.20; S, 9.84.

3-(Heptylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.15). Yield: 71 %; m. p.: 170-172 °C; ^{1}H NMR, δ (ppm): 7.99 (dd, J = 6.7, 1.7 Hz, 1H, CH pyrrol), 7.57 – 7.53 (m, 3H, C_6H_5), 7.49 (d, 2H, C_6H_5), 7.25 (dd, J = 6.6, 3.7 Hz, 1H, CH pyrrol), 6.94 (d, 1H, CH pyrrol), 3.18 (t, 2H, S-CH_2-$(CH_2)_5$-CH_3), 1.73-1.69 (m, 2H, S-CH_2-CH_2-$(CH_2)_4$-CH_3), 1.37 – 1.29 (m, 8H, S-$(CH_2)_2$-$(CH_2)_4$-CH_3), 0.94 – 0.89 (m, 3H, S-$(CH_2)_6$-CH_3). Anal. calcd. (%) for $C_{19}H_{24}N_4S$: C, 67.02; H, 7.11; N, 16.46; S, 9.42. Found: C, 67.19; H, 7.12; N, 16.42; S, 9.39.

3-(Octylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.16). Yield: 71 %; m. p.: 143-145 °C; ^{1}H NMR, δ (ppm): 8.02 (dd, J = 6.6, 1.6 Hz, 1H, CH pyrrol), 7.58 – 7.53 (m, 3H, C_6H_5), 7.43 (d, 2H, C_6H_5), 7.24 (dd, J = 6.6, 3.7 Hz, 1H, CH pyrrol), 6.88 (d, 1H, CH pyrrol), 3.16 (t, J = 7.9 Hz, 2H, S-CH_2-$(CH_2)_6$-CH_3), 1.74 -1.69 (m, 2H, S-CH_2-CH_2-$(CH_2)_5$-CH_3), 1.32 – 1.24 (m, 10H, S-$(CH_2)_2$-$(CH_2)_5$-CH_3), 0.94 – 0.89 (m, 3H, S-$(CH_2)_7$-CH_3). Anal. calcd. (%) for $C_{20}H_{26}N_4S$: C, 67.76; H, 7.39; N, 15.80; S, 9.04. Found: C, 67.61; H, 7.40; N, 15.76; S, 9.06.

3-(Nonylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.17). Yield: 71 %; m. p.: 138-140 °C; ^{1}H NMR, δ (ppm): 8.00 (dd, J = 6.8, 1.7 Hz, 1H), 7.57 – 7.53 (m, 3H, C_6H_5), 7.44 (d, 2H, C_6H_5), 7.25 (dd, J = 6.7, 3.6 Hz, 1H, CH pyrrol), 6.87 (d, 1H, CH pyrrol), 3.15 (t, J = 7.9 Hz, 2H, S-CH_2-$(CH_2)_7$-CH_3), 1.72-1.68 (m, 2H, S-CH_2-CH_2-$(CH_2)_6$-CH_3), 1.31 – 1.22 (m, 12H, S-$(CH_2)_2$-$(CH_2)_6$-CH_3), 0.92 – 0.85 (m, 3H, S-$(CH_2)_8$-CH_3). Anal. calcd. (%) for $C_{21}H_{28}N_4S$ C, 68.44; H, 7.66; N, 15.20; S, 8.70. Found: C, 68.61; H, 7.65; N, 15.24; S, 8.68.

3-(Decylthio)-4-phenyl-5-(pyrrol-2-yl)-1,2,4-triazole (2.18). Yield: 71 %; m. p.: 168-171 °C; ^{1}H NMR, δ (ppm): 8.02 (dd, J = 6.6, 1.8 Hz, 1H, CH pyrrol), 7.61 – 7.54 (m, 3H, C_6H_5), 7.40 (d, 2H, C_6H_5), 7.24 (dd, J = 6.7, 3.6 Hz, 1H, CH pyrrol), 6.85 (d, 1H, CH pyrrol), 3.15 (t, J = 7.9 Hz, 2H, S-CH_2-$(CH_2)_8$-CH_3), 1.74 – 1.72 (m, 2H, S-CH_2-CH_2-$(CH_2)_7$-CH_3), 1.29 (m, 2H, S-$(CH_2)_2$-CH_2-$(CH_2)_6$-CH_3), 1.27 – 1.21 (m, 12H, S-$(CH_2)_3$-$(CH_2)_6$-CH_3), 0.93 – 0.85 (m, 3H, S-$(CH_2)_9$-CH_3). Anal. calcd. (%) for $C_{22}H_{30}N_4S$: C, 69.07; H, 7.90; N, 14.65; S, 8.38. Found: C, 68.93; H, 7.92; N, 14.68; S, 8.36.

3-(3-(5-(Methylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl)indole (2.19). Yield: 82 %, m. p.: 226-228 °C ; ^{1}H NMR, δ (ppm): 10.16 (s, 1H, NH indole), 7.45-7.38 (dd, 2H, C_6H_5), 7.37 (d, 1H, H-7 CH indole), 7.18 (d, 1H, H-2 indole), 7.13 (t, 1H, H-6 indole), 7.01 (t, 1H, H-5 indole), 2.97 (t, 2H, CH_2-CH_2-CH_2), 2.75 (s, 3H, CH_3), 2.34 (t, 2H, CH_2-CH_2-CH_2), 2.09 (m, 2H, CH_2-CH_2-CH_2). Anal. calcd. for $C_{20}H_{20}N_4S$: C, 68.94; H, 5.79; N, 16.08; S, 9.20. Found: C, 68.77; H, 5.80; N, 16.04; S, 9.22.

3-(3-(5-(Ethylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.20). Yield: 76 %, m. p.: 231-233 °C ; ^{1}H NMR, δ (ppm): 10.17 (s, 1H, NH indole), 7.57-7.51 (m, 3H, C^{4}H indole, C_6H_5), 7.48-7.45 (t, 1H, C_6H_5), 7.38-7.33 (m, 3H, C^{7}H indole, C_6H_5); 7.17 (d, 1H, C^{2}H indole), 7.13 (t, 1H, C^{6}H indole); 7.04 (t, 1H, C^{5}H indole); 3.21-3.19 (m, 2H, S-CH_2-CH_3), 3.01 (t, 2H, CH_2-CH_2-CH_2), 2.89 (t, 2H, CH_2-CH_2-CH_2), 2.19-2.17 (m, 2H, CH_2-CH_2-CH_2), 1.41 (t, 3H, S-CH_2-CH_3). Anal. calcd. for $C_{21}H_{22}N_4S$ C, 69.58; H, 6.12; N, 15.46; S, 8.84. Found: C, 69.73; H, 6.11; N, 15.49; S, 8.82.

3-(3-(4-Phenyl-5-(propylthio)-1,2,4-triazole-3-yl)propyl) indole (2.21). Yield: 69 %, m. p.: 202-204 °C ; ^{1}H NMR, δ (ppm): 10.15 (s, 1H, NH indole), 7.59-7.52 (m, 3H, C^{4}H indole, C_6H_5), 7.48 (t, 1H, C_6H_5), 7.37-7.32 (m, 3H, C^{7}H indole, C_6H_5);

7.20 (d, 1H, C²H indole), 7.14 (t, 1H, C⁶H indole), 7.06 (t, 1H, C⁵H indole), 3.17 (t, 2H, S-CH_2- CH_2-CH_3), 3.03 (t, 2H, CH_2-CH_2-CH_2), 2.87 (t, 2H, CH_2-CH_2-CH_2), 2.29-2.25 (m, 2H, CH_2-CH_2-CH_2), 1.76-1.73 (m, 2H, S-CH_2-CH_2-CH_3), 1.07 (t, 3H, S-$(CH_2)_2$-CH_3). Anal. calcd. for $C_{22}H_{24}N_4S$ C, 70.18; H, 6.43; N, 14.88; S, 8.51. Found: C, 70.02; H, 6.42; N, 14.85; S, 8.53.

3-(3-(5-(Butylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.22). Yield: 75 %, m. p.: 286-288 °C ; ¹H NMR, *δ* (ppm): 10.19 (s, 1H, NH indole), 7.55-7.49 (m, 3H, C⁴H indole, C_6H_5), 7.48 (t, 1H, C_6H_5), 7.36-7.31 (m, 3H, C⁷H indole, C_6H_5), 7.19 (d, 1H, C²H indole), 7.12 (t, 1H, C⁶H indole), 7.05 (t, 1H, C⁵H indole), 3.19 (t, 2H, S-CH_2-$(CH_2)_2$-CH_3), 3.01 (2H, t, CH_2-CH_2-CH_2), 2.88 (t, 2H, CH_2-CH_2-CH_2), 2.19-2.17 (m, 2H, CH_2-CH_2-CH_2), 1.70-1.67 (m, 2H, S-CH_2-CH_2-CH_2-CH_3), 1.39-1.36 (m, 2H, S-$(CH_2)_2$-CH_2-CH_3), 1.06 (t, 3H, S-$(CH_2)_3$-CH_3). Anal. calcd. for $C_{23}H_{26}N_4S$ C, 70.73; H, 6.71; N, 14.35; S, 8.21. Found: C, 70.55; H, 6.69; N, 14.39; S, 8.23.

3-(3-(5-(Pentylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.23). Yield: 78 %, m. p.: 217-219 °C ; ¹H NMR, *δ* (ppm): 10.18 (s, 1H, NH indole), 7.55-7.49 (m, 3H, C⁴H indole, C_6H_5), 7.46 (t, 1H, C_6H_5), 7.34-7.29 (m, 3H, C⁷H indole, C_6H_5); 7.19 (d, 1H, C²H indole), 7.13 (t, 1H, C⁶H indole), 7.06 (t, 1H, C⁵H indole); 3.13 (t, 2H, S-CH_2-$(CH_2)_3$-CH_3), 3.02 (2H, t, CH_2-CH_2-CH_2), 2.89 (t, 2H, CH_2-CH_2-CH_2), 2.19-2.17 (m, 2H, CH_2-CH_2-CH_2), 1.69-1.66 (m, 2H, S-CH_2-CH_2-$(CH_2)_2$-CH_3), 1.41-1.36 (m, 4H, S-$(CH_2)_2$-$(CH_2)_2$-CH_3), 0.92 (t, 3H, S-$(CH_2)_4$-CH_3). Anal. calcd. for $C_{24}H_{28}N_4S$ C, 71.25; H, 6.98; N, 13.85; S, 7.92. Found: C, 71.42; H, 7.00; N, 13.82; S, 7.90.

3-(3-(5-(Hexylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.24). Yield: 81 %, m. p.: 265-268 °C ; ¹H NMR, *δ* (ppm): 10.19 (s, 1H, NH indole); 7.51-7.57 (m, 3H, C⁴H indole, C_6H_5), 7.45 (t, 1H, C_6H_5), 7.34-7.29 (m, 3H, C⁷H indole, C_6H_5); 7.18 (d, 1H, C²H indole), 7.13 (t, 1H, C⁶H indole); 7.08 (t, 1H, C⁵H indole); 3.22 (t, 2H, S-CH_2-$(CH_2)_4$-CH_3), 2.99 (t, 2H, CH_2-CH_2-CH_2), 2.88 (t, 2H, CH_2-CH_2-CH_2), 2.19-2.17 (m, 2H, CH_2-CH_2-CH_2), 1.76-1.73 (m, 2H, S-CH_2-CH_2-$(CH_2)_3$-CH_3), 1.40-1.36 (m, 2H, S-$(CH_2)_2$-CH_2-$(CH_2)_2$-CH_3), 1.33-1.27 (m, 4H, S-$(CH_2)_3$-$(CH_2)_2$-CH_3), 0.94 (t, 3H, S-$(CH_2)_5$-CH_3). Anal. calcd. for $C_{25}H_{30}N_4S$ C, 71.73; H, 7.22; N, 13.38; S, 7.66. Found: 71.57; H, 7.20; N, 13.41; S, 7.68.

3-(3-(5-(Heptylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.25). Yield: 64 %, m. p.: 197-199 °C ; ¹H NMR, *δ* (ppm): 10.18 (s, 1H, NH indole); 7.57-7.52 (m, 3H, C⁴H indole, C_6H_5), 7.48 (t, 1H, C_6H_5), 7.37-7.35 (m, 3H, C⁷H indole, C_6H_5); 7.18 (d, 1H, C²H indole), 7.12 (t, 1H, C⁶H indole), 7.06 (t, 1H, C⁵H indole); 3.17-3.14 (m, 2H, S-CH_2-$(CH_2)_5$-CH_3), 3.00 (t, 2H, CH_2-CH_2-CH_2), 2.89 (t, 2H, CH_2-CH_2-CH_2), 2.20-2.17 (m, 2H, CH_2-CH_2-CH_2), 1.76-1.72 (m, 2H, S-CH_2-CH_2-$(CH_2)_4$-CH_3), 1.48-1.45 (m, 2H, S-$(CH_2)_2$-CH_2-$(CH_2)_3$-CH_3), 1.41-1.39 (m, 6H, S-$(CH_2)_3$-$(CH_2)_3$-CH_3), 0.91 (t, 3H, S-$(CH_2)_6$-CH_3). Anal. calcd. for $C_{26}H_{32}N_4S$ C, 72.18; H, 7.46; N, 12.95; S, 7.41. Found: C, 72.36; H, 7.48; N, 12.92; S, 7.39.

3-(3-(5-(Octylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.26). Yield: 76 %, m. p.: 241-243 °C ; ¹H NMR, *δ* (ppm): 10.17 (s, 1H, NH indole), 7.59-7.54 (m, 3H, C⁴H indole, C_6H_5), 7.48 (t, 1H, C_6H_5), 7.39-7.35 (m, 3H, C⁷H indole, C_6H_5), 7.21 (d, 1H, C²H indole), 7.14 (t, 1H, C⁶H indole); 7.07 (t, 1H, C⁵H indole); 3.22 (t, 2H, S-CH_2-$(CH_2)_6$-CH_3), 2.99 (t, 2H, CH_2-CH_2-CH_2), 2.87 (t, 2H, CH_2-CH_2-CH_2), 2.19-2.17 (m, 2H, CH_2-CH_2-CH_2), 1.68-1.71 (m, 2H, S-CH_2-CH_2-$(CH_2)_5$-CH_3), 1.28-1.45 (m, 10H, S-$(CH_2)_2$-$(CH_2)_5$-CH_3), 0.84-0.88 (t, 3H, S-$(CH_2)_7$-CH_3). Anal. calcd. for $C_{27}H_{34}N_4S$ C, 72.61; H, 7.67; N, 12.54; S, 7.18. Found: C, 72.44; H, 7.65; N, 12.57; S, 7.20.

3-(3-(5-(Nonylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.27). Yield: 77 %, m. p.: 229-231 °C ; ¹H NMR, *δ* (ppm): 10.13 (s, 1H, NH indole), 7.56-7.52 (m, 3H, C⁴H indole, C_6H_5), 7.45 (t, 1H, C_6H_5), 7.32-7.29 (m, 3H, C⁷H indole, C_6H_5); 7.18 (d, 1H, C²H indole), 7.12 (t, 1H, C⁶H indole); 7.07 (t, 1H, C⁵H indole); 3.19-3.16 (m, 2H, S-CH_2-CH_2-$(CH_2)_6$-CH_3), 2.99 (t, 2H, CH_2-CH_2-CH_2), 2.88 (t, 2H, CH_2-CH_2-CH_2), 2.19-2.16 (m, 2H, CH_2-CH_2-CH_2), 1.70-1.66 (m, 2H, S-CH_2-CH_2-$(CH_2)_6$-CH_3), 1.48-1.42 (m, 2H, S-$(CH_2)_2$-CH_2-$(CH_2)_5$-CH_3), 1.38-1.25 (m, 10H, S-$(CH_2)_3$-$(CH_2)_5$-CH_3), 0.88 (t, 3H, S-$(CH_2)_8$-CH_3). Anal. calcd. for $C_{28}H_{36}N_4S$ C, 73.00; H, 7.88; N, 12.16; S, 6.96. Found: C, 72.83; H, 7.86; N, 12.19; S, 6.98.

3-(3-(5-(Decylthio)-4-phenyl-1,2,4-triazole-3-yl)propyl) indole (2.28). Yield: 68 %, m. p. 214-216 °C ; ¹H NMR, *δ* (ppm): 10.16 (s, 1H, NH indole), 7.56-7.51 (m, 3H, C⁴H indole, C_6H_5), 7.48 (t, 1H, C_6H_5), 7.38-7.34 (m, 3H, C⁷H indole, C_6H_5); 7.17 (d, 1H, C²H indole), 7.11-7.09 (t, 1H, C⁶H indole); 7.07-7.04 (t, 1H, C⁵H indole); 3.16-3.12 (m, 2H, S-CH_2-CH_2-$(CH_2)_6$-CH_3), 3.01 (2H, t, CH_2-CH_2-CH_2), 2.89-2.87 (t, 2H, CH_2-CH_2-CH_2), 2.15-2.12 (m, 2H, CH_2-CH_2-CH_2), 1.67-1.63 (m, 2H, S-CH_2-CH_2-$(CH_2)_6$-CH_3), 1.48-1.44 (m, 2H, S-$(CH_2)_2$-CH_2-$(CH_2)_6$-CH_3), 1.39-1.31 (m, 12H, S-$(CH_2)_3$-$(CH_2)_6$-CH_3), 0.92 (t, 3H, S-$(CH_2)_9$-CH_3). Anal. calcd. for $C_{29}H_{38}N_4S$ C, 73.37; H, 8.07; N, 11.80; S, 6.75. Found: C, 73.52; H, 8.09; N, 11.77; S, 6.73.

Molecular modeling was performed to evaluate in advance the prospects of further biological testing *in vitro* for the presence of antagonistic activity. A series of test compounds showed binding levels, at the average and below average, according to scoring functions. Docking experiments of synthesized compounds (2.8, 2.19–2.28) with the 2XP2 (ALK tyrosine kinase receptor) receptor revealed that compounds 2.8, 2.19 and 2.20 are the most active with a calculated binding energy of 7.6 kcal/mol (*Table 1*).

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
2.8	-7,6	2.24	-7,2
2.19	-7,6	2.25	-7,3
2.20	-7,6	2.26	-7,1
2.21	-7,4	2.27	-7,1
2.22	-7,4	2.28	-7,2
2.23	-7,3	*Crizotinib*	-9,4

***Emin:** the minimum energy of complex formation, kcal/mol.

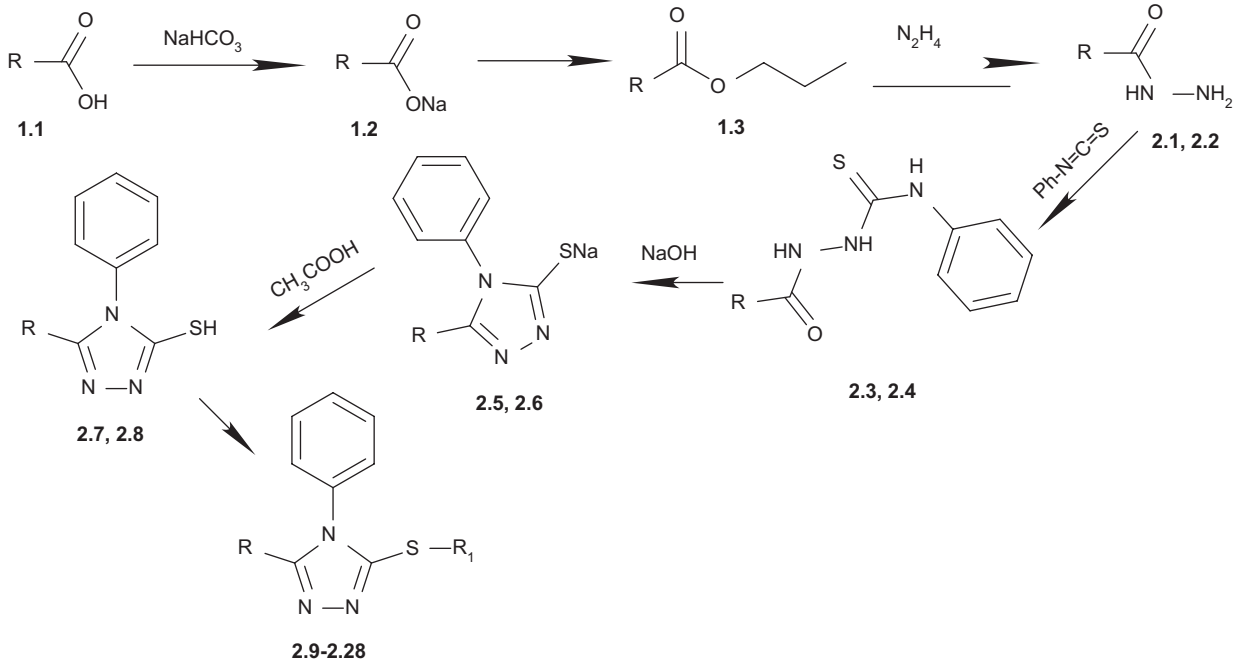

Fig. 1. The synthetic route of title compounds.

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
3.6	-8,9	3.22	-9,8
3.17	-9,4	3.23	-9,6
3.18	-9,5	3.24	-9,7
3.19	-9,7	3.25	-9,9
3.20	-8.5	3.26	-9,8
3.21	-9,8	*nido-dicarbaborate indomethacin*	-19,9

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

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
3.6	-8.7	3.22	-8.5
3.17	-8.5	3.23	-8.5
3.18	-8.5	3.24	-8.5
3.19	-8.5	3.25	-7.7
3.20	-7.9	3.26	-8,8
3.21	-8.5	Ketoconazole	-10.1

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

In order to investigate the probability of detection of molecules with anti-inflammatory activity, the interaction parameters with the active center of cyclooxygenase-2 (COX-2) were studied (*Table 2*).

According to the forecast, the strongest complex with COX-2 forms compounds 3.21, 3.22, 3.25 and 3.26. Tyr 385 and Ser 530 have been shown to be the most significant amino acid residues of the ligand binding site. Most ligands interact with the following aminoacid fragments of the active center of COX-2: Arg 120, His 90, Glu 524, Phe 518, Pro 528, Ser 353, Tyr 355, Tyr 385 and Val 349.

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*).

The molecular docking experiment was established that the synthesized compounds 3.6, 3.17–3.26 exhibit free energy of binding values from -7.7 to -8.8 kcal/mol. Molecular docking analysis also has shown that the complexes of the synthesized compounds interact with the 3LD6 protein with the best rates of change in Gibbs free energy in the Trp 213 region.

Conclusions

1. A universal method for the preparation of alkylderivatives of 5-(3-(indol-3-yl)propyl)-4-phenyl-1,2,4-triazole-3-thiol and 5-(pyrrol-2-yl)-4-phenyl-1,2,4-triazole-3-thiol was developed.

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

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

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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Information about author:

Hotsulia A. S., PhD, Associate Professor of the Department of Natural Sciences for Foreign Students and Toxicological Chemistry, Zaporizhzhia State Medical University, Ukraine.

Відомості про автора:

Гоцуля А. С., канд. фарм. наук, доцент каф. природничих дисциплін для іноземних студентів та токсикологічної хімії, Запорізький державний медичний університет, Україна.

Сведения об авторе:

Гоцуля А. С., канд. фарм. наук, доцент каф. естественных дисциплин для иностранных студентов и токсикологической химии, Запорожский государственный медицинский университет, Украина.

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