eISSN: 2564-6524
ISSN: 1015-3918 (1971-2010)

ANKARA ÜNİVERSİTESİ

ECZACILIK FAKÜLTESİ DERGİSİ

JOURNAL OF FACULTY OF PHARMACY OF ANKARA UNIVERSITY

Cilt / Vol : 47
Sayı / No : 3
Yıl / Year : 2023

eISSN: 2564-6524
ISSN: 1015-3918 (1971-2010)

ANKARA ÜNİVERSİTESİ

ECZACILIK FAKÜLTESİ DERGİSİ

JOURNAL OF FACULTY OF PHARMACY OF ANKARA UNIVERSITY

Cilt / Vol: 47
Sayı / No: 3
Yıl / Year: 2023

ANKARA ÜNİVERSİTESİ ECZACILIK FAKÜLTESİ DERGİSİ

(*Ankara Ecz. Fak. Derg.*) **eISSN: 2564-6524**
ISSN: 1015-3918 (1971-2010)

Sahibi:

Prof. Dr. Asuman BOZKIR

J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 47(3): 1020-1032, 2023
Doi: 10.33483/jfpau.1280492

ORIGINAL ARTICLE / ÖZGÜN MAKALE

SYNTHESIS AND PROPERTIES OF *S*-ALKYL 4-(4-CHLOROPHENYL)-5-(PYRROLE-2-YL)-1,2,4-TRIAZOLE-3-THIOL DERIVATIVES

S-ALKİL 4-(4-KLOROFENİL)-5-(PİROL-2-İL)-1,2,4-TRİAZOL-3-TİYOL TÜREVLERİNİN SENTEZİ VE ÖZELLİKLERİ

Andrey GOTSULYA[1]*, Sergey FEDOTOV[1], Olena ZINYCH[2], Tetiana TROFIMOVA[3], Tetiana BRYTANOVA[4]

[1]Zaporizhzhia State Medical and Pharmaceutical University, Faculty of Pharmacy, Department of Natural Sciences for Foreign Students and Toxicological Chemistry, Zaporizhzhia, Ukraine

[2]Zaporizhzhia State Medical and Pharmaceutical University, Department of Human Anatomy, Operative Surgery and Topographic Anatomy, Zaporizhzhia, Ukraine

[3]Bogomolets National Medical University, Department of Clinical Pharmacology and Clinical Pharmacy, Kyiv, Ukraine

[4]Zaporizhzhia State Medical and Pharmaceutical University, Department of Pharmaceutical, Organic and Bioorganic Chemistry, Zaporizhzhia, Ukraine

ABSTRACT

Objective: *The aim of the work was to develop effective methods for the synthesis of promising heterocyclic systems based on pyrrole and 1,2,4-triazole. In the process of realizing of this aim, 10 new S-alkyl 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol derivatives were synthesized.*
Material and Method: *Chemical structures of synthesized compounds were characterized with elemental analysis, ^{1}H-NMR, LC-MS techniques. The biological potential of the synthesized substances was estimated by the molecular docking method and ADME analysis.*
Result and Discussion: *An optimum method for the synthesis of S-alkyl 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol has been developed. In molecular modeling studies, the compounds were found to be similar to known drugs in some respects. The interaction of each*

* **Corresponding Author / Sorumlu Yazar:** Andrey Gotsulya
e-mail / e-posta: andrey.goculya@gmail.com, **Phone / Tel.:** +380990425382

Submitted / Gönderilme : 12.04.2023
Accepted / Kabul : 01.09.2023
Published / Yayınlanma : 20.09.2023

molecule with the crystal structures of cyclooxygenase-2, lanosterol-14α-demethylase in the active site was considered in silico. Pharmacokinetic parameters for a number of the synthesized compounds have been predicted by ADME analysis.
Keywords: *1,2,4-triazole, ADME analysis, docking, synthesis*

ÖZ

Amaç: *Çalışmanın amacı, pirol ve 1,2,4-triazole dayalı gelecek vaat eden heterosiklik sistemlerin sentezi için etkili yöntemler geliştirmektir. Belirtilen hedefin gerçekleştirilmesi sürecinde 10 yeni S-alkil 4-(4-klorofenil)-5-(pirol-2-il)-1,2,4-triazol-3-tiyol türevi sentezlenmiştir..*
Gereç ve Yöntem: *Sentezlenen bileşiklerin kimyasal yapıları element analiz, ^{1}H NMR, LC-MS teknikleri ile karakterize edildi. Sentezlenen maddelerin biyolojik potansiyeli moleküler yerleştirme yöntemi ve ADME analizi ile tahmin edildi.*
Sonuç ve Tartışma: *S-alkil 4-(4-klorofenil)-5-(pirol-2-il)-1,2,4-triazol-3-tiyol türevlerinin sentezi için optimal bir yöntem geliştirilmiştir. Moleküler modelleme çalışmalarında, bileşiklerin bazı açılardan bilinen ilaçlara benzer olduğu bulunmuştur. Her molekülün kristal yapıdaki siklooksijenaz-2 ve lanosterol-14α-demetilaz aktif bölgesi ile etkileşimi in silico olarak değerlendirildi. Sentezlenen bileşiklerin bir kısmı için farmakokinetik parametreler ADME analizi ile tahmin edildi.*
Anahtar Kelimeler: *1,2,4-triazol, ADME analizi, moleküler modelleme, sentez*

INTRODUCTION

Derivatives of 1,2,4-triazole have a high chemical and pharmacological potential, which makes this class of compounds highly promising in the sense of creating an original drug product [1-8]. The 1,2,4-triazole system has already proven to have significant potential in the development of antifungal drugs (fluconazole, voriconazole, ravuconazole, terconazole, itraconazole and sertaconazole), anticancer drugs (anastrozole, vorozol and letrozole), anti-migraine drugs (rizatriptan), antidotes for metal poisoning (deferasirox), anxiolytic drugs (alprazolam and triazolam), and antiviral drugs (ribavirin). The group of antifungal drugs that were created with the participation of this heterocycle is very significant. For example, such a drug as voriconazole allows you to successfully treat even difficult-to-treat forms of mycosis (Figure 1).

Pyrrole derivatives are represented by a smaller number of medicines. However, there are quite effective drugs among them. For example, amtolmetine guacyl has been used as a non-steroidal anti-inflammatory drug for many years (Figure 1).

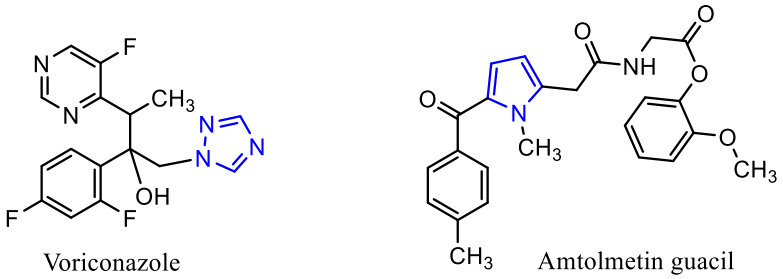

Figure 1. Examples of successful drug design based on 1,2,4-triazole and pyrrole

Among the directions of the first stages of work with this cycle, a special place is occupied by the possibility of its combination with heterocyclic synthons of a different nature [9-12]. The specified approach significantly facilitates the creation of the desired product of chemical transformation, which ultimately has a high probability of formation of a biologically active substance [13]. Of particular interest in the implementation of this strategy is the combination of a triazole fragment with a pyrrole fragment. This interest was also supported by certain achievements of both foreign and Ukrainian scientists [14-16]. In order to obtain new compounds, it was decided to directly combine the cycles of

1,2,4-triazole and pyrrole by a covalent bond and introduce a 4-chlorophenyl substituent into the tandem.

The aim of the work was to synthesize *S*-alkyl derivatives of 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol as potential biologically active compounds. An effective tool that can help model the mechanism of interaction of synthesized substances with biological targets (enzymes, receptors) is molecular docking. The presence in the structure of the synthesized substances of pyrrole and 1,2,4-triazole, which can actively promote the formation of hydrogen, hydrophobic and other bonds, substantiates the need for molecular docking.

An important step in the process of creating a biologically active substance is the preliminary evaluation of pharmacokinetic parameters. ADME (Adsorption, Distribution, Metabolism, Excretion) analysis provides a reasonably accurate assessment of these parameters.

Thus, the combined use of molecular docking and ADME analysis will allow an exact evaluation of the feasibility of further *in vitro* and *in vivo* studies of the synthesized series of substances.

MATERIAL AND METHOD

Chemistry

The intermediate thiol was obtained in several stages. The first step was the synthesis of 2,2,2-trichloro-(pyrrole-2-yl)ethanone. The chemical reaction proceeded easily with the active participation of pyrrole and trichloroacetyl chloride in diethyl ether (Figure 2) [17].

Previously, solutions of pyrrole (**1**) and freshly distilled trichloroacetyl chloride (**2**) in diethyl ether were prepared separately. The resulting pyrrole solution was slowly added dropwise to the trichloroacetyl chloride solution while stirring without heating. After 1 hour, a solution of potassium carbonate in water was added. After that, the organic solvent layer was separated and evaporated. The reaction product in the form of 2,2,2-trichloro-1-(pyrrole-2-yl)ethan-1-one (**3**) was washed three times with *n*-hexane. This stage is more thoroughly described in an earlier work [17].

The next stage was the preparation of pyrrole-2-carbohydrazide (**4**). To implement this stage, the starting substance (**3**) was involved in the process of hydrazinolysis in an alcoholic medium. As a reagent, hydrazine hydrate was used in a fivefold excess. The reaction was carried out in a medium of propan-2-ol with heating for 2 hours.

These chemical transformation products have been synthesized in accordance with the described methods and have physical constants that correspond to the literature data [17].

The obtained pyrrole-2-carbohydrazide (**4**) has been used in the reaction with 4-chlorophenylisothiocyanate. The isolated *N*-(4-chlorophenyl)-2-(pyrrole-2-carbonyl)hydrazine-1-carbothioamide (**5**) was then subjected to intramolecular heterocyclization in an alkaline medium.

The synthesized 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol (**6**) was used in alkylation reactions with halogenated alkanes to further determine the biological potential of the synthesized series of substances (**6.1-6.10**).

The structure of the synthesized substances was confirmed using modern physical and chemical methods of analysis.

All substances used in the experiments were given with accompanying documents confirming their quality and purity.

The structure of synthesized substances, their purity, as well as their individuality of chemical conversion products were confirmed using modern physical and chemical methods of analysis. The melting temperature of all synthesized substances was determined on SRS Inc MPA 100 equipment using the open capillary method. A VarioELcube analyzer (CHNS) was used to establish the nature of the elements that form the studied substances, as well as to determine the quantitative ratio of the elements. ^{1}H NMR spectroscopy spectra were recorded using a Varian Mercury-400 spectrometer. Tetramethylsilane was used as an internal standard. Dimethylsulfoxide-d_6 was used as a solvent. An Agilent "1260 Infinity" high performance liquid chromatography system, supplemented with an Agilent "6120" spectrometer, was used to perform chromatography-mass spectrometry. Spraying in an electric field was used as a method of ionization.

***N*-(4-chlorophenyl)-2-(pyrrole-2-carbonyl)hydrazinecarbothioamide (5) [17]**

To a solution of 2.5 g (0.02 mol) of pyrrole-2-carbohydrazide in 80 ml of ethanol cooled with ice was added an equivalent amount of 3.39 g (0.02 mol) of 4-chlorophenylisothiocyanate. The resulting mixture is heated at 110°C for 2 hours. On cooling, a yellow-white crystalline precipitate, insoluble in water and soluble in organic solvents, is formed.

It is purified by crystallisation from propan-2-ol and treatment of the hot saturated solution with activated carbon followed by filtration. The yield is 83%. Melting point = 162 - 164ºC.

4-(4-Chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol (6)

5.89 g (0.02 mol) of *N*-chlorophenyl-2-(pyrrole-2-carbonyl)hydrazinecarbothioamide is added to an equivalent amount of sodium hydroxide that has been previously dissolved in a small amount of water. The resulting mixture is heated for one hour. Cool it down. Add dilute acetic acid until the solution is completely neutralized, accompanied by the formation of a white precipitate, which is separated by filtration. The reaction product is insoluble in water, soluble in organic solvents and in an aqueous alkali solution.

S-alkyl derivatives of 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol (6.1-6.10).

To a mixture of 0.005 mol of 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol and 0.005 mol of sodium hydroxide dissolved in 40 ml of ethanol, 0.005 mole of haloalkane (iodomethane, bromoethane, 1-bromopropane, 1-bromobutane, 1-bromopentane, 1-bromohexane, 1-bromoheptane, 1-bromooctane, 1-bromononane, 1-bromodecane). Heat for 2 hours, cool, filter the sediment, wash with purified water. For analysis, crystallize from methanol. White substances, insoluble in water, soluble in organic solvents.

4-(4-Chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol (6). Yield (%): 69, m. p. (°C): 267 – 269. ^{1}H-NMR (400 MHz), δ (ppm): 13.93 (s, 1H, SH), 11.74 (s, 1H, pyrrole NH), 7.71-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.50-7.43 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.89 (d, J = 3.0 Hz, H-3, pyrrole), 5.97 (t, J = 3.1 Hz, H-5, pyrrole), 5.35-5.29 (m, H-4, pyrrole). ESI MS (m/z): $[M+H]^+$ at 277.5. Elemental analysis (EA) ($C_{12}H_9ClN_4S$), calculated, %: C - 52.08, H - 3.28, N - 20.25, S - 11.58; obtained, %: C - 51.94, H - 3.29, N - 20.20, S - 11.61.

4-(4-Chlorophenyl)-3-(methylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.1). Yield (%): 74, m. p. (°C): 194 – 195. ^{1}H-NMR (400 MHz), δ (ppm): 11.74 (s, 1H, pyrrole NH), 7.71-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.50-7.43 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.89 (d, J = 3.0 Hz, H-3, pyrrole), 5.97 (t, J = 3.1 Hz, H-5, pyrrole), 5.33-5.28 (m, H-4, pyrrole), 2.74 (s, 2H, CH_3). ESI MS (m/z): $[M+H]^+$ at 291,5. Elemental analysis (EA) ($C_{13}H_{11}ClN_4S$), calculated, %: C - 53.70, H - 3.81, N - 19.27, S - 11.03; obtained, %: C - 53.57, H - 3.82, N - 19.22, S - 11.06.

4-(4-Chlorophenyl)-3-(ethylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.2). Yield (%): 69%, m. p. (°C): 163 – 164. ^{1}H-NMR (400 MHz), δ (ppm): 11.74 (s, 1H, pyrrole NH), 7.71-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.51-7.44 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.88 (d, J = 3.0 Hz, H-3, pyrrole), 5.98 (t, J = 3.2 Hz, H-5, pyrrole), 5.34-5.29 (m, H-4, pyrrole), 3.21 (q, J=6.2 Hz, 2H, S-C$\underline{H}_2$-CH_3), 1.35 (t, J=6.0 Hz, 3H, S-CH_2-C$\underline{H}_3$). ESI MS (m/z): $[M+H]^+$ at 305,5. Elemental analysis (EA) ($C_{14}H_{13}ClN_4S$), calculated, %: C - 55.17, H - 4.30, N - 18.38, S - 10.52; obtained, %: C - 55.02, H - 4.29, N - 18.43, S - 10.55.

4-(4-Chlorophenyl)-3-(propylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.3). Yield (%): 77, m. p. (°C): 158 – 159. ^{1}H-NMR (400 MHz), δ (ppm): 11.73 (s, 1H, pyrrole NH), 7.71-7.65 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.50-7.43 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.90 (d, J = 3.0 Hz, H-3, pyrrole), 5.98 (t, J = 3.1 Hz, H-5, pyrrole), 5.32-5.26 (m, H-4, pyrrole), 3.15 (t, J=5.2 Hz, 2H, S-C$\underline{H}_2$-C_2H_5), 1.79 (q, J=5.4 Hz, 2H, S-CH_2-C$\underline{H}_2$-CH_3), 1.05 (t, J=7.0 Hz, 3H, S-$(CH_2)_2$-C$\underline{H}_3$). ESI MS (m/z): $[M+H]^+$ at 319.5. Elemental analysis (EA) ($C_{15}H_{15}ClN_4S$), calculated, %: C - 56.51, H - 4.74, N - 17.57, S - 10.06; obtained, %: C - 56.65, H - 4.73 , N - 17.61, S - 10.04.

4-(4-Chlorophenyl)-3-(butylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.4). Yield (%): 81, m. p. (°C): 163 – 164. ^{1}H-NMR (400 MHz), δ (ppm): 11.74 (s, 1H, pyrrole NH), 7.71-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.50-7.43 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.90 (d, J = 3.1 Hz, H-3, pyrrole), 5.96 (t, J = 3.2 Hz, H-5, pyrrole), 5.33-5.27 (m, H-4, pyrrole), 3.17 (t, J=6.6 Hz, 2H, S-C$\underline{H}_2$-C_3H_7), 1.82 – 1.77 (m, 2H, S-

CH_2-C<u>*H*</u>$_2$-C_2H_5), 1.39-1.34 (m, 2H, S-$(CH_2)_2$-C<u>*H*</u>$_2$-CH_3), 0.93 (t, *J*=6.9 Hz, 3H, S-$(CH_2)_3$-C<u>*H*</u>$_3$). ESI MS (m/z): $[M+H]^+$ at 333,5. Elemental analysis (EA) ($C_{16}H_{17}ClN_4S$), calculated, %: C - 57.74, H - 5.15, N - 16.83, S - 9.63; obtained, %: C - 57.59, H - 5.16, N - 16.79, S - 9.66.

4-(4-Chlorophenyl)-3-(pentylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.5). Yield (%): 74, m. p. (°C): 166 – 167. ^{1}H-NMR (400 MHz), δ (ppm): 11.73 (s, 1H, pyrrole NH), 7.70-7.65 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.50-7.43 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.89 (d, *J* = 3.0 Hz, H-3, pyrrole), 5.97 (t, *J* = 3.1 Hz, H-5, pyrrole), 5.35-5.30 (m, H-4, pyrrole), 3.25 (t, *J*=6.0 Hz, 2H, S-C<u>*H*</u>$_2$-C_4H_9), 1.76 – 1.69 (m, 2H, S-CH_2-C<u>*H*</u>$_2$-C_3H_7), 1.42 – 1.34 (m, 4H, S-$(CH_2)_2$-(C<u>*H*</u>$_2$)$_2$-CH_3), 0.96 – 0.88 (m, 3H, S-$(CH_2)_4$-C<u>*H*</u>$_3$). ESI MS (m/z): $[M+H]^+$ at 347.5. Elemental analysis (EA) ($C_{17}H_{19}ClN_4S$), calculated, %: C - 58.86, H - 5.52, N - 16.15, S - 9.24; obtained, %: C - 59.01, H - 5.53, N - 16.11, S - 9.22.

4-(4-Chlorophenyl)-3-(hexylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.6). Yield (%): 69, m. p. (°C): 168 – 169. ^{1}H-NMR (400 MHz), δ (ppm): 11.74 (s, 1H, pyrrole NH), 7.70-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.50-7.43 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.89 (d, *J* = 3.0 Hz, H-3, pyrrole), 5.97 (t, *J* = 3.1 Hz, H-5, pyrrole), 5.34-5.29 (m, H-4, pyrrole), 3.24 (t, *J*=6.4 Hz, 2H, S-C<u>*H*</u>$_2$-C_5H_{11}), 1.71 – 1.65 (m, 2H, S-CH_2-C<u>*H*</u>$_2$-C_4H_9), 1.41 – 1.34 (m, 2H, S-$(CH_2)_2$-C<u>*H*</u>$_2$-C_3H_7), 1.34 – 1.26 (m, 4H, S-$(CH_2)_3$-(C<u>*H*</u>$_2$)$_2$-CH_3), 0.92 – 0.85 (m, 3H, S-$(CH_2)_5$-C<u>*H*</u>$_3$). ESI MS (m/z): $[M+H]^+$ at 361.5. Elemental analysis (EA) ($C_{18}H_{21}ClN_4S$), calculated, %: C - 59.90, H - 5.87, N - 15.52, S - 8.88; obtained, %: C - 60.07, H - 5.86, N - 15.48, S - 8.90.

4-(4-Chlorophenyl)-3-(heptylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.7). Yield (%): 76, m. p. (°C): 174-175 ºC. ^{1}H-NMR (400 MHz), δ (ppm): 11.73 (s, 1H, pyrrole NH), 7.71-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.50-7.43 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.88 (d, *J* = 3.0 Hz, H-3, pyrrole), 5.99 (t, *J* = 3.1 Hz, H-5, pyrrole), 5.34-5.28 (m, H-4, pyrrole), 3.23 (t, *J*=6.2 Hz, 2H, S-C<u>*H*</u>$_2$-$(CH_2)_5$-CH_3), 1.72 – 1.65 (m, 2H, S-CH_2-C<u>*H*</u>$_2$-C_5H_{11}), 1.42 – 1.36 (m, 2H, S-$(CH_2)_2$-C<u>*H*</u>$_2$-C_4H_9), 1.32 – 1.21 (m, 6H, S-$(CH_2)_3$-(C<u>*H*</u>$_2$)$_3$-CH_3), 0.92 – 0.85 (m, 3H, S-$(CH_2)_6$-C<u>*H*</u>$_3$). ESI MS (m/z): $[M+H]^+$ at 375.5. Elemental analysis (EA) ($C_{19}H_{23}ClN_4S$), calculated, %: C - 60.87, H - 6.18, N - 14.94, S - 8.55; obtained, %: C - 60.73, H - 6.17, N - 14.97, S - 8.57.

4-(4-Chlorophenyl)-3-(octylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.8). Yield (%): 73, m. p. (°C): 182-183 ºC. ^{1}H-NMR (400 MHz), δ (ppm): 11.73 (s, 1H, pyrrole NH), 7.71-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.51-7.44 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.88 (d, *J* = 3.1 Hz, H-3, pyrrole), 5.98 (t, *J* = 3.2 Hz, H-5, pyrrole), 5.33-5.27 (m, H-4, pyrrole), 3.21 (t, *J*=6.3 Hz, 2H, S-C<u>*H*</u>$_2$-C_7H_{15}), 1.71 – 1.65 (m, 2H, S-CH_2-C<u>*H*</u>$_2$-C_6H_{13}), 1.38 – 1.22 (m, 10H, m, 2H, S-$(CH_2)_2$-(C<u>*H*</u>$_2$)$_5$-CH_3), 0.93 – 0.86 (m, 3H, S-$(CH_2)_7$-C<u>*H*</u>$_3$). ESI MS (m/z): $[M+H]^+$ at 389.5. Elemental analysis (EA) ($C_{20}H_{25}ClN_4S$), calculated, %: C - 61.76, H - 6.48, N - 14.40, S - 8.24; obtained, %: C - 61.93, H - 6.49, N - 14.36, S - 8.22.

4-(4-Chlorophenyl)-3-(nonylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.9). Yield (%): 82, m. p. (°C): 161-162 ºC. ^{1}H-NMR (400 MHz), δ (ppm): 11.74 (s, 1H, pyrrole NH), 7.71-7.65 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.51-7.42 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.90 (d, *J* = 3.0 Hz, H-3, pyrrole), 5.97 (t, *J* = 3.1 Hz, H-5, pyrrole), 5.33-5.28 (m, H-4, pyrrole), 3.25 (t, *J* = 6.5 Hz, 2H, S-C<u>*H*</u>$_2$-$(CH_2)_7$-CH_3), 1.73 – 1.64 (m, 2H, S-CH_2-C<u>*H*</u>$_2$-C_7H_{15}), 1.37 – 1.31 (m, 2H, S-$(CH_2)_2$-C<u>*H*</u>$_2$-C_6H_{13}), 1.28 – 1.19 (m, 10H, S-$(CH_2)_3$-(C<u>*H*</u>$_2$)$_5$-CH_3), 0.90 – 0.84 (m, 3H, S-$(CH_2)_8$-C<u>*H*</u>$_3$). ESI MS (m/z): $[M+H]^+$ at 403.5. Elemental analysis (EA) ($C_{21}H_{27}ClN_4S$), calculated, %: C - 62.59, H - 6.75, N - 13.90, S - 7.96; obtained, %: C - 62.43, H - 6.76, N - 13.87, S - 7.98.

4-(4-Chlorophenyl)-3-(decylthio)-5-(pyrrole-2-yl)-1,2,4-triazole (6.10). Yield (%): 85, m. p. (°C): 144-145 ºC. ^{1}H-NMR (400 MHz), δ (ppm): 11.74 (s, 1H, pyrrole NH), 7.70-7.64 (m, 2H, H-2,6, 4-Cl-C_6H_4), 7.48-7.42 (m, 2H, H-3,5, 4-Cl-C_6H_4), 6.90 (d, *J* = 3.0 Hz, H-3, pyrrole), 5.98 (t, *J* = 3.1 Hz, H-5, pyrrole), 5.34-5.28 (m, H-4, pyrrole), 3.23 (t, *J*=6.5 Hz, 2H, S-C<u>*H*</u>$_2$-C_9H_{19}), 1.71 – 1.66 (m, 2H, S-CH_2-C<u>*H*</u>$_2$-C_8H_{17}), 1.38 – 1.23 (m, 12H, S-$(CH_2)_3$-(C<u>*H*</u>$_2$)$_6$-CH_3), 0.88 – 0.82 (m, 3H, S-$(CH_2)_9$-C<u>*H*</u>$_3$). ESI MS (m/z): $[M+H]^+$ at 417.5. Elemental analysis (EA) ($C_{22}H_{29}ClN_4S$), calculated, %: C - 63.37, H - 7.01, N - 13.44, S - 7.69; obtained, %: C - 63.53, H - 6.99, N - 13.41, S - 7.71.

Molecular Docking

The next stage of scientific work involved molecular docking. This action is necessary to justify possible further studies of the biological potential of the synthesized substances.

The choice of the direction of *in silico* studies has been defined by the nature of structural

fragments of the synthesized substances. The presence of the pyrrole cycle determined the possibility of testing the presence of anti-inflammatory activity. For this purpose, a model of cyclooxygenase-2 has been chosen, inhibition of which can lead to anti-inflammatory activity. The 1,2,4-triazole cycle and the alkyl fragments represent certain structural elements that may be associated with antifungal activity. To test this hypothesis, it was chosen to test lanosterol 14α-dimethylase, whose inhibition may be associated with antifungal activity.

Standard ligands with the above enzymes were downloaded from Protein Data Bank [18].

The first stage of molecular docking involved the preparation of a ligand. For this purpose, the programs MarvinSketch-6.3.0, Chem 3D and AutoDockTools-1.5.6 were used [19,20].

The second stage provided for the active use of both software products

Discovery Studio 4.0 and AutoDockTools-1.5.6, which made it possible to prepare the enzyme model.

The final stage of molecular docking included the use of the Vina program and AutoDockTools-1.5.6, which made it possible to visualize the location of the studied ligands in the active sites of the enzymes.

ADME Analysis

The graphical interface of the SwissADME website was used to calculate the main pharmacokinetic parameters. The available descriptors and molecular parameters were calculated according to the explanations given in [21].

Among the main descriptors and parameters that were determined were the lipophilicity index (Log P), the topological polar surface area of molecules (TSPA), the Csp^3 fraction, the number of rotating bonds and the molar refraction. They are directly related to the most important properties of molecules, including size, lipophilicity, conformational mobility and the ability to form hydrogen bonds.

In addition, the determination of TSPA allows for predicting adsorption, bioavailability and blood-brain barrier permeability. For the express evaluation of drug-like properties, pellet diagrams were used, which allow for taking into account the parameters of lipophilicity, size, polarity, solubility and flexibility.

RESULT AND DISCUSSION

Chemistry

The general sequence of chemical transformations that allow obtaining the target reaction products (**6.1-6.10**) is shown in Figure 2.

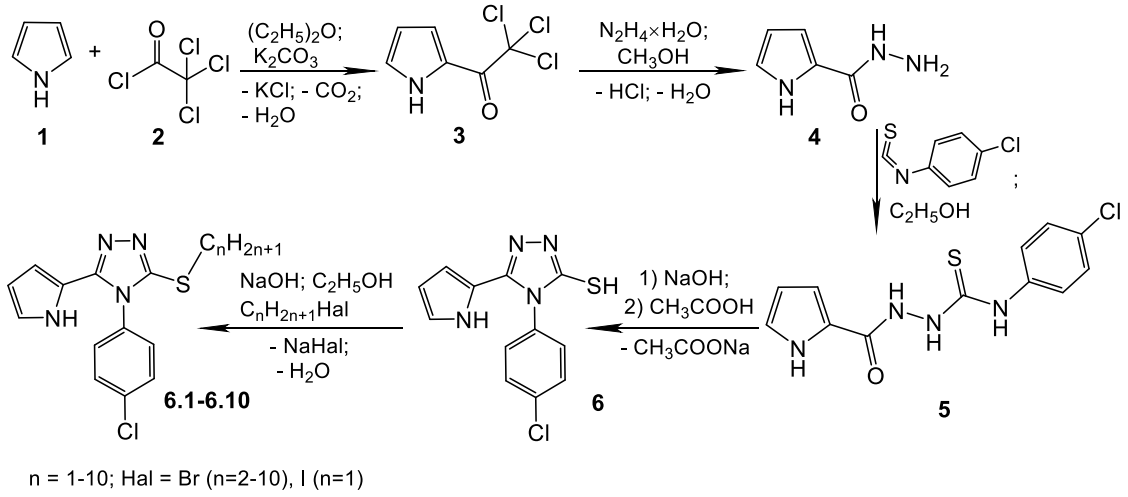

Figure 2. The scheme for the synthesis of target products of chemical transformation

All synthesized S-alkyl derivatives of 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol (**6.1**-**6.10**) are white crystalline substances that are practically insoluble in water, soluble in monoatomic alcohols when heated, well soluble in DMF and DMSO.

^{1}H NMR spectra of the synthesized compounds (**6**, **6.1**-**6.10**) are characterized by signals of NH protons, which are registered as a singlet at 11.74-11.73 ppm. Proton signals of the 4-chlorophenyl substituent are recorded as multiplets: H-2 and H-6 at 7.71-7.64 ppm, H-3 and H-5 at 7.51-7.42 ppm. The signals of the protons of the pyrrole substituent are easily interpreted and are represented by a doublet (H-3) at 6.90-6.88 ppm, a triplet (H-5) at 5.99-5.96 ppm, and a multiplet (H-4) at 5.35-5.26 ppm. Protons of S-alkyl fragments resonate in the strong part of the field in the form of signals with various intensities in the region of 3.25-0.82 ppm. For example, singlet signals of methyl protons of the thiomethyl fragment (-S-CH_3) are present at 2.74 ppm (**6.1**). Multiplet signals from protons of methylene fragments (-S-(C$\underline{H}_2$)$_n$-CH_3) are recorded at a stronger field (1.82-1.65 ppm and 1.42-1.19 ppm).

A gradual increase in the length of the S-alkyl chain leads to the appearance of signals of methyl group protons (-S-$(CH_2)_n$-C$\underline{H}_3$) in the range of 0.93-0.82 ppm.

Molecular Docking

The analysis of docking interactions of the synthesized compounds allows us to conclude that hydrophobic contacts predominate in a number of synthesized compounds with the active site of cyclooxygenase-2, which makes the synthesized substances similar in type of contacts to celecoxib (Figure 3). For example, compound **6.7** with the participation of a hexyl substituent forms alkyl interactions with amino acid residues of Leu A: 93, Tyr A: 116, Tyr A: 356, Val A: 89, Val A: 117. In turn, phenyl, pyrrole and triazole fragments make a significant contribution to the formation of π-alkyl interactions with residues Leu A: 353, Leu A: 532, Phe A: 519, Val A: 524 (Table 1). These contacts are enhanced by the π-σ-interactions of the 1,2,4-triazole fragment with residues Ala A: 528 and Val A: 350. Additionally, the presence of an intermolecular hydrogen bond of π-donor nature involves the pyrrole fragment of the studied compound and residue Ser A: 531 (Figure 3).

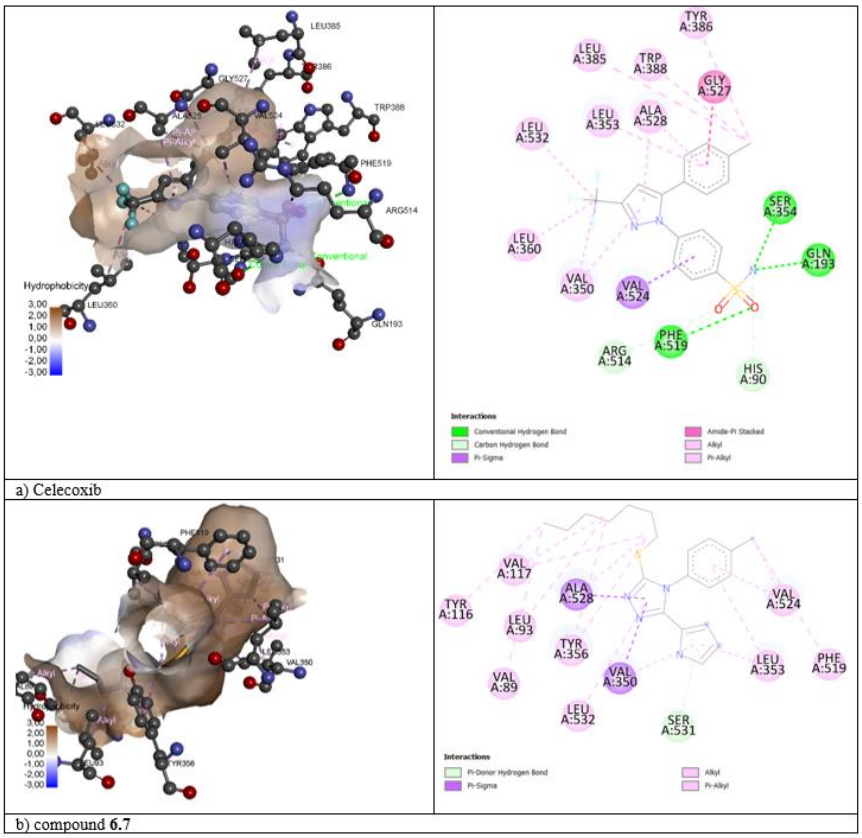

Figure 3. Visualization scheme for binding celecoxib and compound **6.7** to COX-2

Table 1. The result of visualization of the interaction of the synthesized substances with the active site of COX-2

№	Amino acid fragments
6	Ala A: 528, Gly A: 527, Leu A: 385, Ser A: 354, Trp A: 388, Tyr A: 356, Tyr A: 386, Val A: 350, Val A: 524
6.1	Ala A: 528, Leu A: 353, Leu A: 532, Phe A: 519, Ser A: 531, Tyr A: 356, Val A: 350, Val A: 524
6.2	Ala A: 528, Leu A: 353, Leu A: 360, Leu A: 532, Tyr A: 356, Val A: 117, Val A: 350, Val A: 524
6.3	Ala A: 528, Arg A: 121, Glu A: 525, Leu A: 93, Leu A: 532, Pro A: 529, Ser A: 120, Tyr A: 116, Tyr A: 356, Val A: 89, Val A: 117
6.4	Ala A: 528, Arg A: 121, Glu A: 525, Leu A: 93, Leu A: 360, Leu A: 532, Phe A: 358, Pro A: 529, Ser A: 120, Tyr A: 116, Tyr A: 356, Val A: 89, Val A: 117,
6.5	Ala A: 528, Arg A: 121, Leu A: 353, Leu A: 532, Phe A: 519, Pro A: 529, Val A: 117, Val A: 350, Val A: 524,
6.6	Ala A: 517, Arg A: 514, His A: 90, His A: 95, Pro A: 515, Tyr A: 91
6.7	Ala A: 528, Leu A: 93, Leu A: 385, Leu A: 532, Phe A: 519, Ser A: 531, Tyr A: 116, Tyr A: 356, Val A: 89, Val A: 117, Val A: 350, Val A: 524
6.8	Ala A: 528, His A: 90, Leu A: 93, Leu A: 353, Leu A: 532, Tyr A: 116, Tyr A: 356, Val A: 89, Val A: 117
6.9	Ala A: 528, His A: 90, Leu A: 93, Leu A: 353, Leu A: 532, Ser A: 531, Tyr A: 116, Tyr A: 356, Val A: 89, Val A: 117, Val A: 350
6.10	Ala A: 528, Arg A: 121, His A: 90, Leu A: 353, Leu A: 532, Ser A: 120, Tyr A: 356, Val A: 89, Val A: 117, Val A: 350, Val A: 524, Val A: 532

The minimum free binding energy of the synthesized compounds with COX-2 is in the range of -0.4...-8.5 kcal×mol^{-1}, which allows us to indirectly assess the probability of anti-inflammatory activity as low (Table 2).

Table 2. Energy of interaction with COX-2

№	ε_{min}, $\frac{kcal}{mol}$	№	ε_{min}, $\frac{kcal}{mol}$	№	ε_{min}, $\frac{kcal}{mol}$
6	-8.3	6.4	-6.6	6.8	-0.4
6.1	-8.2	6.5	-8.4	6.9	-0.7
6.2	-7.4	6.6	-4.8	6.10	-7.3
6.3	-6.6	6.7	-8.5	*Celecoxib*	-13.4

* ε_{min} - The minimum energy of complex formation.

The nature of the amino acid residues involved in the formation of bonds with fluconazole and the studied compounds in most cases was identical (Figure 4). However, in terms of the number of bonds formed, a number of the synthesized compounds are superior to fluconazole (Table 3). The active role here is played by the S-alkyl substituent of the 1,2,4-triazole cycle, with which most hydrophobic interactions are formed. For example, the heptyl substituent of the most promising compound **6.7** is involved in the formation of alkyl interactions with residues Ala A: 256, Arg A: 96, Leu A: 100, Leu A: 152, Phe A: 399 and Val A: 395 (Figure 4). It is also necessary to note the possibility of π-alkyl interaction involving phenyl, pyrrole and triazole fragments and residues Cys A: 394, Leu A: 324 and Arg A: 96, respectively. This interaction is enhanced by π-π T-stacking contacts, which can occur with the active role of the π-chemical bond of the pyrrole synthon and the residue Tyr A: 76. The presented picture of interactions is qualitatively complemented by intermolecular hydrogen bonds that arise between the Hydrogen atom of the NH group of the pyrrole and the residue Gln A: 72.

The minimum energy of affinity of the synthesized compounds for lanosterol 14α-demethylase is expectedly high, although none of them exceeds fluconazole in this respect (Table 4).

The development of a biologically active substance with high activity and low toxicity is one of the main tasks of modern medicinal chemistry. The level of pharmacological activity, as well as toxicity, is determined by a number of factors, including the speed and completeness of absorption, distribution, metabolism and elimination. It is possible to preliminarily assess these indicators using the SwissADME computer service, which allows calculating physicochemical, pharmacokinetic, drug-like properties and related parameters.

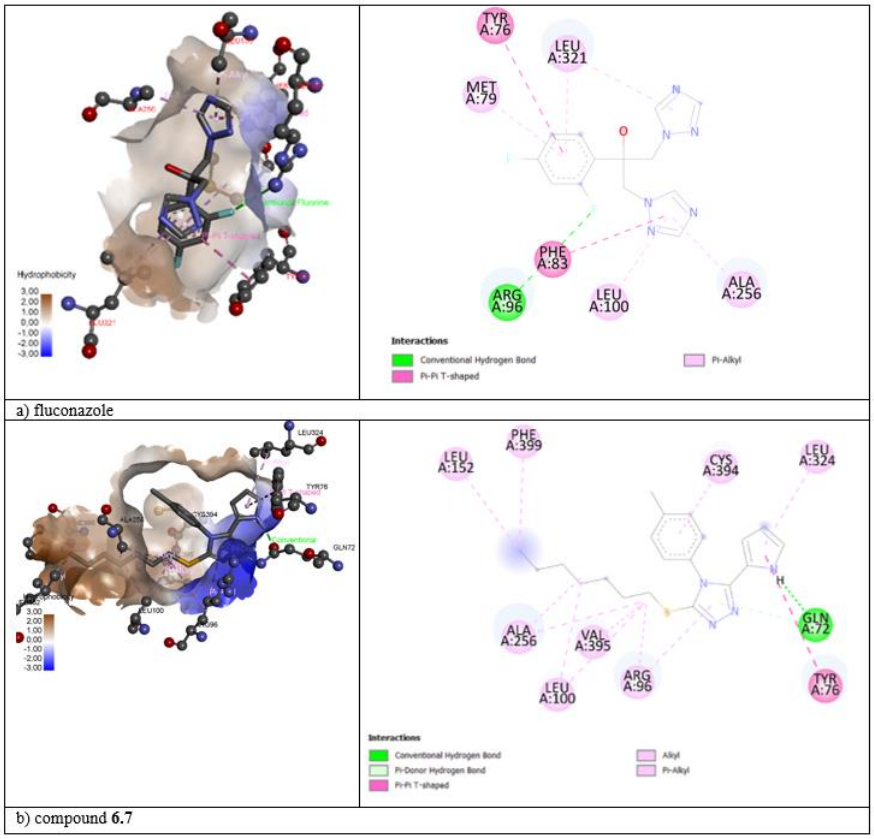

Figure 4. Imaging scheme for binding fluconazole and compound **6.7** to lanosterol 14α-demethylase

Table 3. The result of visualization of the interaction of the synthesized substances with the lanosterol 14α-demethylase active site

№	Amino acid fragments
6	Ala A: 256, Ala A: 400, Cys A: 394, Leu A: 315, Phe A: 387, Pro A: 320, Thr A: 260
6.1	Ala A: 76, Ala A: 88, Lys A: 79, Lys B: 79, Ser A: 80, Phe A: 84, Tyr A: 92, Ile A: 64
6.2	Ala A: 256, Arg A: 96, His A: 259, Leu A: 321, Leu A: 324, Phe A: 78, Tyr A: 76, Val A: 434
6.3	Ala A: 256, Arg A: 96, Cys A: 394, His A: 259, Leu A: 100, Leu A: 321, Met A: 79, Phe A: 78, Phe A: 83, Tyr A: 76, Val A: 434
6.4	Ala A: 76, Ala B: 76, Ala A: 88, Glu A: 83, Leu A: 100, Leu A: 152, Leu A: 321, Ser A: 80, Ser B: 80, Phe A: 84, Tyr A: 92
6.5	Ala A: 256, Arg A: 96, His A: 392, Leu A: 321, Leu A: 324, Met A: 79, Val A: 395
6.6	Ala A: 256, Arg A: 96, His A: 392, Leu A: 321, Leu A: 324, Met A: 79, Val A: 395
6.7	Ala A: 256, Arg A: 96, Cys A: 394, Gln A: 83, Leu A: 100, Leu A: 152, Leu A: 321, Phe A: 399, Tyr A: 76, Val A: 395
6.8	Ala A: 256, Cys A: 394, Leu A: 321, Leu A: 324, Pro A: 320, Phe A: 78, Tyr A: 76
6.9	Ala A: 256, Arg A: 96, Cys A: 394, Leu A: 100, Leu A: 321, Met A: 79, Met A: 99, Phe A: 83, Tyr A: 76
6.10	Ala A: 256, Arg A: 96, Cys A: 394, Leu A: 100, Leu A: 321, Met A: 79, Met A: 99, Phe A: 83, Tyr A: 76

Table 4. Energy of interaction with lanosterol-14α-demethylase

№	ε_{min}, $\frac{kcal}{mol}$	№	ε_{min}, $\frac{kcal}{mol}$	№	ε_{min}, $\frac{kcal}{mol}$
6	-7.4	6.4	-8.0	6.8	-7.3
6.1	-6.7	6.5	-8.2	6.9	-7.4
6.2	-6.8	6.6	-8.3	6.10	-7.6
6.3	-6.8	6.7	-8.7	*Fluconazole*	-10.9

* ε_{min} - The minimum energy of complex formation.

ADME Analysis

The development of a biologically active substance with high activity and low toxicity is one of the main tasks of modern medicinal chemistry. The level of pharmacological activity, as well as toxicity, is determined by a number of factors, including the speed and completeness of absorption, distribution, metabolism and elimination. It is possible to preliminarily assess these indicators using the SwissADME computer service, which allows calculating physicochemical, pharmacokinetic, drug-like properties and related parameters.

Based on the results of this analysis, it was found that the synthesized compounds meet the required criteria in terms of molar mass (the criteria from 150 to 500 g/mol), molecular refraction (the criteria from 40 to 130) and topological polar surface area (the criteria from 20 to 130 Å2) (Table 5). At the same time, three compounds (**6.8, 6.9** and **6.10**) do not meet the required value in terms of the number of rotating bonds (there should be no more than 9 rotating links) (Table 5). Similarly, compounds **6.1, 6.2, 6.3** do not have the required degree of saturation, which is expressed by the presence of a fraction of sp^3-hybridized Cabons not less than 0.25 (Table 5).

The arithmetic mean of the five indicators (iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT) allows to estimate the required level of lipophilicity. For example, according to the Log Po/w (MLOGP) index, compounds **6.7-6.10** do not meet the required value (should be < 4.15), according to the Log Po/w (XLOGP3) index - compounds **6-10** (should be from -0.7 to + 5.0), according to the Log Po/w (WLOGP) index - compounds **6.7-6.10** (must be < 5.88) (Table 5). Thus, in a number of the synthesized compounds, derivatives with the number of carbon atoms in the alkyl substituent not exceeding six have the required lipophilicity (Table 5). Most of the synthesized compounds (**6.1-6.7**) successfully pass the Lipinski, Ghose, Veber, Egan and Muegge filters (Table 5). In addition, given the bioavailability criterion of 0.55 for these seven compounds, *in vivo* bioavailability using rats can be expected to be 10% or higher (Table 5).

The probability of gastrointestinal absorption for most of the synthesized compounds (**6.1-6.8**) is high (Table 5). However, only three of the obtained substances (**6.1-6.3**) have a chance to cross the blood-brain barrier (Table 5). The range of values of the molecular permeability index through the skin (log Kp) is from -5.9 to -3.49 cm/s, which suggests a satisfactory possibility of realizing this property (Table 5). If the log Kp value is > -2.5 cm/s, then it is concluded that the ability to penetrate the skin is relatively low.

According to the prediction results, most of the compounds (**6.1-6.8**) are not substrates of P-glycoprotein, an ATP-binding cassette transporter that removes toxins and xenobiotics from the cell (Table 5). Therefore, the risk of multidrug resistance to these compounds is low.

Synthetic accessibility is estimated in the range from 1 (very easy to synthesize) to 10 (very difficult to synthesize). In the range of synthesized compounds, this indicator forms an interval of 2.67 - 3.82, i.e., the realization of the synthesis of these compounds is quite realistic (Table 5).

Table 5. Results of ADME analysis of synthesized compounds

Molecular descriptor/ constant	**Compound**									
	6.1	**6.2**	**6.3**	**6.4**	**6.5**	**6.6**	**6.7**	**6.8**	**6.9**	**6.10**
Fraction Csp^3	0.08	0.14	0.20	0.25	0.29	0.33	0.37	0.40	0.43	0.45
Number of rotatable bonds	3	4	5	6	7	8	9	10	11	12
Molar refractivity	77.88	82.68	87.49	92.30	97.10	101.91	106.72	111.53	116.33	121.14
TPSA, $Å^2$	71.80	71.80	71.80	71.80	71.80	71.80	71.80	71.80	71.80	71.80
Log Po/w (iLogP)	2.64	2.64	3.15	3.30	3.51	3.66	3.76	4.02	4.33	4.69
Log Po/w (XLogP3)	3.04	3.41	3.94	4.29	4.84	5.38	5.92	6.46	7.00	7.54
Log Po/w (WLogP)	3.64	4.03	4.42	4.81	5.20	5.59	5.98	6.37	6.76	7.15
Log Po/w (MLogP)	2.83	3.08	3.33	3.58	3.81	4.05	4.27	4.50	4.72	4.93
Log Po/w (SILICOS-IT)	3.22	3.57	3.93	4.30	4.68	5.06	5.45	5.84	6.24	6.63
Consensus Log Po/w	3.07	3.35	3.75	4.06	4.41	4.75	5.08	5.44	5.81	6.19
Lipinski filter	+	+	+	+	+	+	+	-	-	-
Ghose filter	+	+	+	+	+	+	+	-	-	-
Veber filter	+	+	+	+	+	+	+	+	-	-

Table 5 (*continue*). Results of ADME analysis of synthesized compounds

Molecular descriptor/ constant	Compound									
	6.1	**6.2**	**6.3**	**6.4**	**6.5**	**6.6**	**6.7**	**6.8**	**6.9**	**6.10**
Egan filter	+	+	+	+	+	+	+	-	-	-
Muegge filter	+	+	+	+	+	+	+	-	-	-
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Gastrointestinal absorption	High	High	High	High	High	High	High	High	Low	Low
Blood-brain barrier is permeable	+	+	+	-	-	-	-	-	-	-
P-glycoprotein substrate	-	-	-	-	-	-	-	-	+	+
Log Kp, cm/s	-5.92	-5.74	-5.45	-5.28	-4.98	-4.68	-4.38	-4.09	-3.79	-3.49
PAINS alert	0	0	0	0	0	0	0	0	0	0
Brenk's alert	0	0	0	0	0	0	0	0	0	0
Leadlikeness	+	+	-	-	-	-	-	-	-	-
Synthetic accessibility	2.67	2.85	3.03	3.14	3.25	3.36	3.48	3.48	3.70	3.82

The SwissADME radar can also be used for rapid bioavailability assessment. According to the results of this method, compounds **6.4** and **6.5** can be considered drug-like. It is for these compounds that the radar plot falls within the required physicochemical range, which is determined by lipophilicity, size, polarity, solubility, saturation and flexibility (pink area in the figure) (Figure 5).

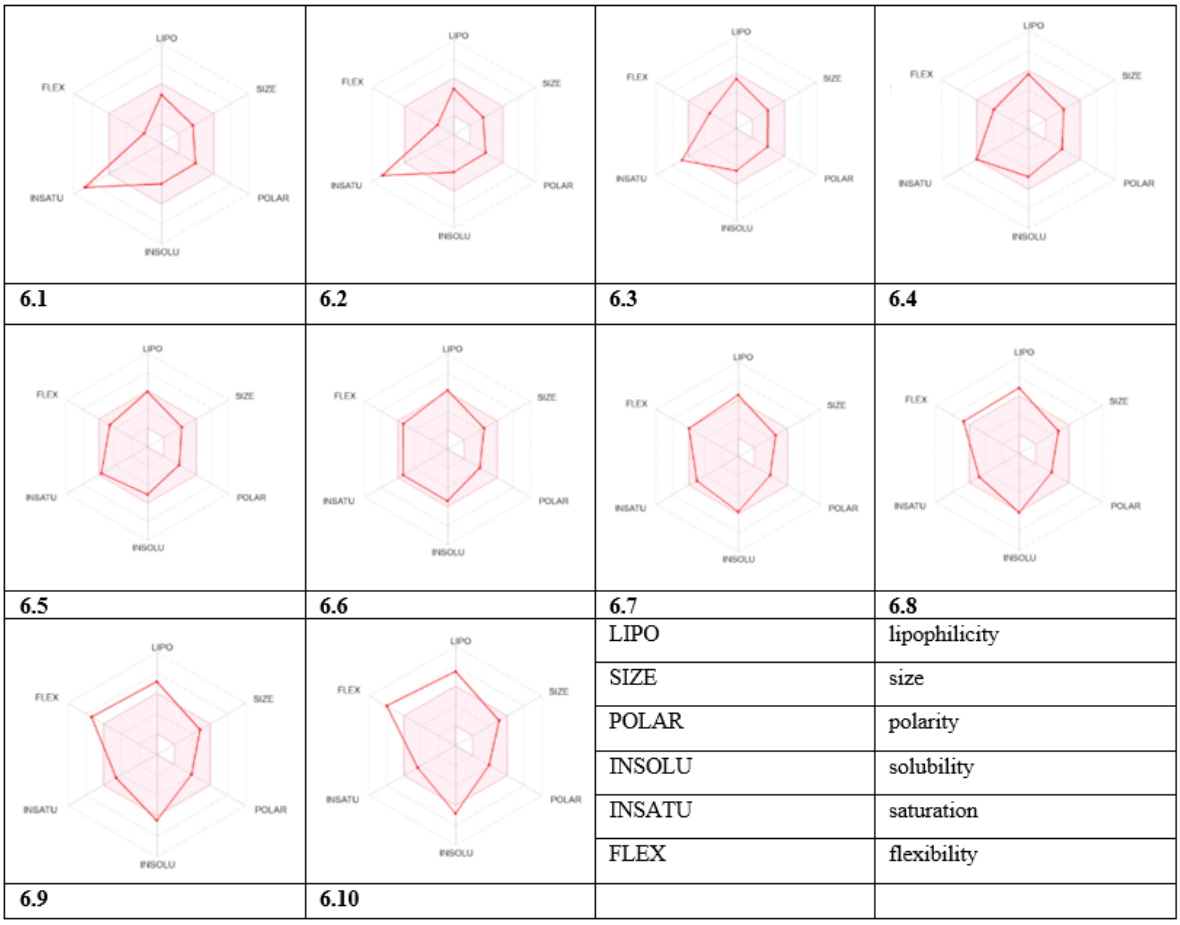

Figure 5. SwissADME bioavailability radar

The synthesis of new derivatives of *S*-alkyl 4-(4-chlorophenyl)-5-(pyrrole-2-yl)-1,2,4-triazole-3-thiol has been successfully carried out. The structure and identity of all substances have been confirmed. The results of the ADME analysis and molecular modelling helped to confirm the prospects for further more in-depth studies of a number of synthesized compounds. The most attractive for further biological studies is the antifungal activity.

AUTHOR CONTRIBUTIONS

Concept: A.G., S.F.; Design: A.G., S.F.; Control: A.G.; Sources: A.G., S.F.; Materials: S.F., O.Z., T.T., T.B.; Data collection and/or Processing: S.F., O.Z., T.T.; Analysis and/or Interpretation: A.G., S.F.; Literature Review: A.G., O.Z., T.B. T.T.; Manuscript Writing: A.G., S.F.; Critical Review: T.B.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

REFERENCES

1. Grytsai, O., Valiashko, O., Penco-Campillo, M., Dufies, M., Hagege, A., Martial, S., Pagès, G., Ronco, C., Benhida, R. (2020). Synthesis and biological evaluation of 3-amino-1,2,4-triazole derivatives as potential anticancer compounds. Bioorganic Chemistry, 104271. [CrossRef]
2. El-Reedy, A.A.M., Soliman, N.K. (2020). Synthesis, biological activity and molecular modeling study of novel 1,2,4-triazolo[4,3-*b*][1,2,4,5]tetrazines and 1,2,4-triazolo[4,3-*b*][1,2,4]triazines. Scientific Reports, 10, 6137. [CrossRef]
3. Abdellatif, K.R.A., Abdelall, E.K.A., Elshemy, H.A.H., Philoppes, J.N., Hassanein, E.H.M., Kahk, N.M. (2021). Optimization of pyrazole-based compounds with 1,2,4-triazole-3-thiol moiety as selective COX-2 inhibitors cardioprotective drug candidates: Design, synthesis, cyclooxygenase inhibition, anti-inflammatory, ulcerogenicity, cardiovascular evaluation, and molecular modeling studies. Bioorganic Chemistry, 114, 105122. [CrossRef]
4. Shcherbyna, R., Panasenko, O., Polonets, O., Nedorezanıuk, N., Duchenko, M. (2021). Synthesis, antimicrobial and antifungal activity of ylidenhydrazides of 2-((4-R-5-R_1-4*H*-1,2,4-triazol-3-yl)thio)acetaldehydes. Journal of Faculty of Pharmacy of Ankara University, 45(3), 504-514. [CrossRef]
5. El Bakri, Y., Marmouzi, I., El Jemli, M., Anouar, E.H., Karthikeyan, S., Harmaoui, A., Faouzi, M.E.A., Mague, J.T., Essassi, E.M. (2019). Synthesis, biological activity and molecular modeling of a new series of condensed 1,2,4-triazoles. Bioorganic Chemistry, 92, 1031932019. [CrossRef]
6. Samelyuk, Y.G., Kaplaushenko, A.G. (2014). Synthesis of 3-alkylthio(sulfo)-1,2,4-triazoles, containing methoxyphenyl substituents at C^5 atoms, their antipyretic activity, propensity to adsorption and acute toxicity. Journal of Chemical and Pharmaceutical Research, 6(5), 1117-1121.
7. Boraei, A.T.A., Sarhan, A.A.M., Yousuf, S., Barakat, A. (2020). Synthesis of a new series of Nitrogen/Sulfur heterocycles by linking four rings: Indole; 1,2,4-triazole; pyridazine; and quinoxaline. Molecules, 25(3), 450. [CrossRef]
8. Mioc, M., Avram, S., Bercean, V., Kurunczi, L., Ghiulai, R.M., Oprean, C., Soica, C. (2018). Design, synthesis and biological activity evaluation of *S*-substituted 1*H*-5-mercapto-1,2,4-triazole derivatives as antiproliferative agents in colorectal cancer. Frontiers in Chemistry, 6, 373. [CrossRef]
9. Frolova, Y., Kaplaushenko, A., Nagornaya, N. (2020). Design, synthesis, antimicrobial and antifungal activities of new 1,2,4-triazole derivatives containing 1*H*-tetrazole moiety. Journal of Faculty of Pharmacy of Ankara University, 44(1), 70-88. [CrossRef]
10. Safonov, A. (2020). Method of synthesis novel *N*'-substituted 2-((5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetohydrazides. Journal of Faculty of Pharmacy of Ankara University, 44(2), 242-252. [CrossRef]
11. Hotsulia, A.S., Fedotov, S.O. (2019). 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. Current Issues in Pharmacy and Medicine: Science and Practice, 12(1), 4-9. [CrossRef]

12. Fedotov, S.O., Hotsulia, A.S. (2021). Synthesis and properties of *S*-derivatives of 4-amino-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-3-thiol. Current Issues in Pharmacy and Medicine: Science and Practice, 14(3), 268-274. [CrossRef]
13. Simurova, N.V., Maiboroda, O.I. (2021) Antiviral activity of 1,2,4-triazole derivatives (microreview). Chemistry of Heterocyclic Compounds, 57, 420-422. [CrossRef]
14. Roman, G., Bostănaru, A.C., Năstasă, V., Mareș, M. (2019). Design, synthesis, and evaluation of the antimycobacterial activity of 3-mercapto-1,2,4-triazole-pyrrole hybrids. Turkish Journal of Chemistry, 43(2), 531-546. [CrossRef]
15. Bijev, A.T., Prodanova, P. (2007). Derivatives of 4-amino-4*H*-1,2,4-triazole-3-thiols linked to the pyrrole cycle and some products of their *S*-alkylation. Chemistry of Heterocyclic Compounds, 43(3), 306-313. [CrossRef]
16. Saidov, N.B., Georgiyants, V.A., Demchenko, A.M. (2014). Directed synthesis of potential antitumor substances among derivatives of 3-mercapto-4-(1*H*-pyrrol-1-yl)-5-cyclohexyl-1,2,4-triazole(4*H*). Journal of Organic and Pharmaceutical Chemistry, 12(1(45)). 43-46. [CrossRef]
17. Gotsulya, A.S., Verba, D.P., Panasenko, O.I., Knysh, Y.G. (2017). Synthesis and study of the properties of derivatives 4-phenyl-5-(1*H*-pyrrole-2-yl)-4*H*-1,2,4-triazole-3-thiols. Farmatsevtychnyi Zhurnal, 1, 59-66. [CrossRef]
18. Protein Data Bank, pdb. Retrieved from http://www.rcsb.org/pdb/home/home.do.
19. MarvinSketch version 17.21.0, ChemAxon. Retrieved from http://www.chemaxon.com.
20. Trott, O., Olson, A.J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, 31, 455-461. [CrossRef]
21. Daina, A., Michielin, O., Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Report, 7(1), 42717. [CrossRef]