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SYNTHESIS OF NEW 4,4'-(1H-1,2,3-TRIAZOLE)-BIS(1H-PYRAZOL-5-OLS) AND PROSPECTS FOR THEIR STUDY AS POTENTIAL ANTITUMOR AGENTS

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The aim *of our work is to develop an efficient synthesis of a series of novel 4,4'-(1H-1,2,3-triazol)bis(1H-pyrazol-5-ols), synthesize the target substances, and perform molecular docking focusing on the interaction of the synthesized compounds with the active sites of known cytostatics targeting various stages of oncogenesis.*

Materials and methods. *The structure and purity of the obtained substances were confirmed by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and LC/MS. Docking studies were performed for the substances synthesized using Autodock 4.2 software.*

Results and discussion. *A series of novel 4,4'-(1H-1,2,3-triazol)bis(1H-pyrazol-5-ols) were synthesized via a tandem Knoevenagel–Michael reaction from two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one with various 1,2,3-triazole aldehydes catalyzed by ammonium acetate in ethanol in high yields. As a result of the analysis of the array of docking computations and a detailed analysis of the geometric arrangement in the active sites of tumour targets (C-abl kinase, deoxycytidine kinase (dCK), CSF1 receptor, EGFRK receptor, FOLR2 receptor, it was found that the synthesized derivatives may have antitumor effects through the mechanism of inhibition of the EGFRK receptor.*

Conclusions. *According to the molecular docking data, the newly synthesized derivatives 4,4'-((1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) may have an antitumor effect through the mechanism of EGFRK receptor inhibition*

Keywords: *1,2,3-triazole, pyrazole, synthesis, anticancer activity, docking studies*

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1. Introduction

Pyrazole and 1,2,3-triazole are well-established pharmacophoric scaffolds found in numerous drugs exhibiting diverse biological activities, including anticancer properties. For instance, pyrazole is a structural component of known anti-inflammatory and anticancer agents such as celecoxib [1], lonazolac [2], and crizotinib [3] (Fig. 1).

The five-membered 1,2,3-triazole ring system is extensively explored in various drug development studies. The triazole derivatives were reported to possess plethora of biological activities, including anticancer, antimalarial, antiviral, antimicrobial, antifungal, analgesic, antidiabetic, anti-obesity, antihypertensive, as well as other activities (Fig. 1), due to their ability to bind and modulate the activity of a diverse range of enzymes and receptors in the biological systems *via* non-covalent interactions [4–6]. 1,2,3-Triazole is a privileged building block in the discovery of new anticancer agents, and some of its derivatives have already been applied in clinics or under clinical trials for fighting against cancers. Hybrid molecules occupy an important position in cancer control, and hybridization of 1,2,3-triazole framework with other anticancer pharmacophores may provide valuable therapeutic intervention for the treatment of cancer, especially drug-resistant cancer [7].

Furthermore, 1,2,3-triazoles are stable and easily accessible through efficient synthesis. These motifs with three nitrogen heteroatoms can be easily prepared using 'Click Chemistry' via azide-alkyne cycloaddition reactions catalyzed by copper, ruthenium and various other catalysts [4].

Therefore, we hypothesized that a molecule incorporating both pharmacophoric moieties, pyrazole and 1,2,3-triazole, might exhibit anticancer properties due to a synergistic effect. To optimize the potential spatial arrangement of pyrazole and triazole moieties within the active site of the target protein, we selected a short and flexible methylene linker.

The literature describes various bis-pyrazole molecules with diverse biological activities [8–10]. [8] synthesized bis-pyrazoles **1** and evaluated their antiviral activity, while [9] reported on the antimicrobial activity of N-phenylpyrazoles **2**. [10] described the anticancer activity of certain bis-pyrazoles **3** (Fig. 2). However, bis-pyrazole-1,2,3-triazole conjugates linked by a methylene bridge represent a relatively novel class of compounds, and their anticancer properties remain largely unexplored.

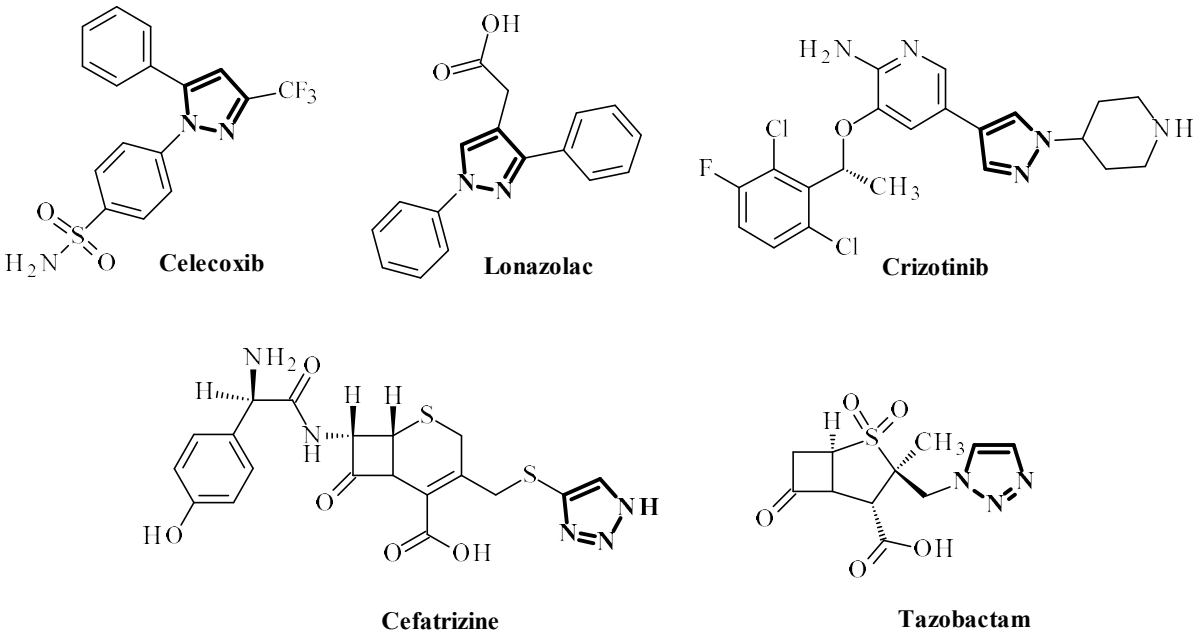


Fig. 1. 1,2,3-Triazole and pyrazole containing molecules with different biological activities

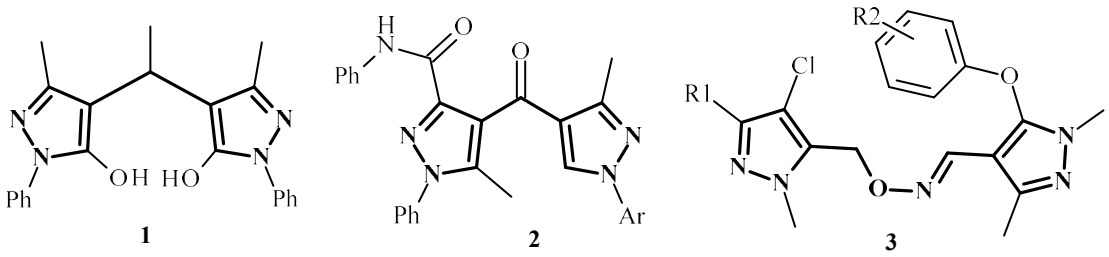


Fig. 2. Structures of the bioactive bis-pyrazole-based molecules

The aim of our work is to develop an efficient method for the synthesis of a series of novel 4,4'-(1H-1,2,3-triazol)bis(1H-pyrazol-5-ols), synthesize the target substances, and perform a detailed analysis of the interaction of the synthesized compounds with the active sites of known cytostatics targeting various stages of oncogenesis.

2. Planning (methodology) of research

The methodology of our research was as follows: new 4,4'-(1H-1,2,3-triazol)bis(1H-pyrazol-5-ols) combine a pyrazole and 1,2,3-triazole fragments as pharmacophoric moieties. It is worth noting that compounds containing these scaffolds have a characteristic wide range of activities, including anticancer [10, 11]. That is why the combination of these pharmacophores can lead to a promising synthetic matrix, which can be used to obtain a number of derivatives with potential anticancer activity.

To obtain the target 4,4'-(1H-1,2,3-triazol)bis(1H-pyrazol-5-ols), a tandem Knoevenagel–Michael reaction from two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one with various 1,2,3-triazole aldehydes was proposed that enabled the production of 24 new compounds.

To confirm our hypothesis, molecular docking was performed on the targets of known cytostatics: active centres of macromolecules from the Protein Data Bank of C-abl kinase, deoxycytidine kinase (dCK), and CSF1 receptor, EGFRK receptor, FOLR2 receptor. The binding affinity and the interaction potential of non-binding interactions between the investigated complexes were calculated. The selected targets represent important proteins involved in cancer progression; namely, they participate in various signalling pathways that regulate cell growth and apoptosis [12, 13], limit the rate of nucleotide excision repair [14], are crucial for the survival and differentiation of macrophages [15], etc. The structural features of the newly synthesized compounds with available aromatic systems and hydrogen bond donors/acceptors will allow for various interactions with kinase domains and receptor binding pockets, making them promising candidates for docking studies with selected peptides. Thus, the above targets have the potential to discover new inhibitors or targeting agents.

3. Materials and methods

3. 1. Chemistry

Reagents manufactured by Sigma-Aldrich, USA, were used in this work. The required reagents were purified using standard techniques. Control of the reactions was carried out using thin-layer chromatography (eluent – ethyl acetate-hexane 1:2) on the plates "Sorbfil UV-254". NMR spectra were acquired on two spectrometers: 1H NMR spectra were measured on Agilent 400 MHz and Jeol-ECZL 400 MHz, and 13C NMR spectra were measured on a Jeol-ECZL instrument at 100 MHz. The solvent

was dimethyl sulfoxide (DMSOd_6). Chemical shifts are shown on a scale (m.ch.). LC/MS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a Luna-C18 column, Phenomenex (100×4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) using a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min.

General Experimental Procedure for the Synthesis of 4,4'-(1H-1,2,3-triazol)bis(1H-pyrazol-5-ols) (6a-x).

The mixture of 1H-1,2,3-triazole-4-carbaldehyde **4a-x** (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **5** (2 mmol), sodium acetate (0.2 mmol) was dissolved in ethanol (10 mL). The solution was refluxed for 2 h at 100 °C. After completion of the reaction, according to TLC data, the reaction mixture was cooled to room temperature. The precipitate was filtered off, washed with ethanol, and crystallized from ethanol, giving a yield of 95–98 %.

4,4'-((1-(3-fluorophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6a, 95 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: δ 13.76 (*s*, 1H, OH), 12.45 (*s*, 1H, OH), 8.55 (*s*, 1H, CH-triazol), 7.89–7.76 (*m*, 2H, Ar), 7.69 (*d*, *J*=8.0 Hz, 4H, Ar), 7.58 (*td*, *J*=8.3, 6.3 Hz, 1H, Ar), 7.42 (*t*, *J*=7.7 Hz, 4H, Ar), 7.32–7.18 (*m*, 3H, Ar), 5.10 (*s*, 1H, CH), 2.33 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 164.20, 161.77, 149.84, 146.25, 138.56, 138.45, 132.33, 132.24, 129.44, 126.13, 121.32, 121.19, 116.36, 116.33, 115.70, 115.49, 108.02, 107.76, 26.71.

LC/MC *m/z*: 522,2 [(M+H)$^+$].

4,4'-((1-benzyl-1H-1,2,3-triazol-4-yl)methylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6b, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: δ 13.86 (*s*, 1H, OH), 12.38 (*s*, 1H, OH), 7.93 (*s*, 1H, CH-triazol), 7.69 (*d*, *J*=8.0 Hz, 4H, Ar), 7.44 (*s*, 4H), 7.37–7.18 (*m*, 7H, Ar), 5.54 (*s*, 2H, CH_2), 5.02 (*s*, 1H, CH), 2.29 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 148.54, 146.22, 136.93, 129.47, 129.20, 128.52, 128.38, 126.14, 123.20, 121.09, 53.08, 26.77, 12.13.

LC/MC *m/z*: 518,2 [(M+H)$^+$].

4,4'-((1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6c, 98 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.85 (*s*, 1H, OH), 12.41 (*s*, 1H, OH), 7.98 (*s*, 1H, CH-triazol), 7.69 (*d*, *J*=8.0 Hz, 4H, Ar), 7.51–7.33 (*m*, 5H, Ar), 7.24 (*s*, 2H, Ar), 7.12 (*dtd*, *J*=17.9, 9.4, 2.4 Hz, 3H, Ar), 5.58 (*s*, 2H, Ar), 5.03 (*s*, 1H, CH), 2.30 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 163.85, 161.42, 148.58, 139.73, 139.66, 131.31, 131.23, 129.46, 124.39, 124.36, 123.46, 121.08, 115.45, 115.25, 115.21, 114.99, 52.34, 26.71.

LC/MC *m/z*: 536,2 [(M+H)$^+$].

4,4'-((1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6d, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.90 (*s*, 1H, OH), 12.49 (*s*, 1H, OH), 8.28 (*s*, 1H, CH-triazol), 7.78 (*s*, 1H, Ar), 7.72–7.64 (*m*, 4H, Ar), 7.58–7.51 (*m*, 1H, Ar), 7.51–7.46 (*m*, 1H, Ar), 7.46–7.34 (*m*, 5H, Ar), 7.23 (*t*, *J*=7.4 Hz, 2H, Ar), 5.14 (*s*, 1H, CH), 2.34 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 156.96, 155.50, 153.01, 149.12, 131.57, 131.50, 129.46, 126.34, 126.04, 126.01, 125.46, 125.35, 121.22, 117.74, 117.55, 116.40, 26.69.

LC/MC *m/z*: 522,2 [(M+H)$^+$].

4,4'-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6e, 98 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.43 (*s*, 1H, OH), 12.46 (*s*, 1H, OH), 8.40 (*s*, 1H, CH-triazol), 8.13 (*dd*, *J*=8.1, 1.4 Hz, 1H, Ar), 7.89–7.80 (*m*, 1H, Ar), 7.80–7.71 (*m*, 2H, Ar), 7.71–7.62 (*m*, 4H, Ar), 7.40 (*t*, *J*=7.7 Hz, 4H, Ar), 7.20 (*t*, *J*=7.3 Hz, 2H, Ar), 5.11 (*s*, 1H, CH), 2.31 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 149.23, 146.27, 144.51, 134.70, 131.29, 129.67, 129.44, 127.91, 126.15, 125.89, 124.16, 121.17, 56.59, 26.73, 19.11, 12.18.

LC/MC *m/z*: 549,2 [(M+H)$^+$].

4,4'-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6f, 95 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.88 (*s*, 1H, OH), 12.41 (*s*, 1H, OH), 7.93 (*s*, 1H, CH-triazol), 7.74–7.64 (*m*, 4H, Ar), 7.44 (*t*, *J*=7.8 Hz, 4H, Ar), 7.41–7.34 (*m*, 1H, Ar), 7.29–7.16 (*m*, 5H, Ar), 5.62 (*s*, 2H, Ar), 5.03 (*s*, 1H, CH), 2.30 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 161.74, 159.29, 148.50, 146.20, 130.97, 129.47, 126.15, 125.29, 123.83, 123.68, 123.32, 121.08, 116.18, 115.97, 47.17, 47.13, 26.79, 26.73, 12.13.

LC/MC *m/z*: 536,2 [(M+H)$^+$].

4,4'-((1-(3,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6g, 97 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.82 (s, 1H, OH), 12.45 (*s*, 1H, OH), 8.38 (*d*, *J*=0.9 Hz, 1H, CH-triazol), 7.77–7.66 (*m*, 5H, Ar), 7.59 (*dd*, *J*=8.2, 2.4 Hz, 1H, Ar), 7.44 (*s*, 4H, Ar), 7.32–7.19 (*m*, 3H, Ar), 5.11 (*d*, *J*=0.9 Hz, 1H, CH), 2.35 (*d*, *J*=9.5 Hz, 6H, 2CH_3), 2.29 (*s*, 3H, Ar-CH_3), 2.26 (*s*, 3H, Ar-CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 149.44, 137.21, 135.21, 131.01, 129.43, 121.21, 120.75, 117.72, 26.73, 19.88, 19.49.

LC/MC *m/z*: 532,2 [(M+H)$^+$].

4,4'-((1-(2,3-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6h, 95 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.83 (*s*, 1H, OH), 12.43 (*s*, 1H, OH),8.28 (*d*, *J*=0.9 Hz, 1H, CH-triazol), 7.83 (*dd*, *J*=8.0, 1.7 Hz, 1H, Ar), 7.66 (*dt*, *J*=7.2, 1.2 Hz, 4H, Ar), 7.59 (*dd*, *J*=8.0, 1.7 Hz, 1H, Ar), 7.52 (*t*, *J*=8.0 Hz, 1H, Ar), 7.40 (*t*, *J*=7.7 Hz, 4H, Ar), 7.20 (*t*, *J*=7.4 Hz, 2H, Ar), 5.12 (*d*, *J*=1.0 Hz, 1H, CH), 2.31 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 148.55, 136.91, 133.37, 132.34, 129.44, 128.26, 127.78, 125.27, 121.21, 26.69.

LC/MC *m/z*: 573,1 [(M+H)$^+$].

4,4'-((1-methyl-1H-1,2,3-triazol-4-yl)methylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6i, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.97 (*s*, 1H, OH), 12.39 (*s*, 1H, OH), 7.82 (*s*, 1H, CH-triazol), 7.69 (*d*,

J=8.2 Hz, 4H, Ar), 7.54–7.16 (*m*, 6H, Ar), 5.00 (*s*, 1H, CH), 3.97 (*s*, 3H, CH_3-triazol), 2.31 (*s*, 6H, $2CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 202.60, 148.48, 146.19, 129.46, 123.72, 121.14, 36.64, 26.73.

LC/MC *m/z*: 442,2 [$(M+H)^+$].

4,4'-((1-cyclohexyl-1H-1,2,3-triazol-4-yl)methylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6j, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.88 (*s*, 1H, OH), 12.35 (*s*, 1H, OH), 7.84 (*s*, 1H, CH-triazol), 7.70 (*d*, *J*=8.1 Hz, 3H, Ar), 7.44 (*s*, 4H), 7.24 (*s*, 2H, Ar), 5.01 (*s*, 1H, CH), 4.48–4.32 (*m*, 1H), 2.30 (s, 6H, $2CH_3$), 1.99 (*d*, *J*=11.9 Hz, 2H), 1.71 (*ddt*, *J*=29.7, 25.7, 12.5 Hz, 5H), 1.46–1.16 (*m*, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 147.94, 129.45, 121.11, 120.82, 59.43, 33.41, 26.79, 25.22, 25.12.

LC/MC *m/z*: 510,2 [$(M+H)^+$].

4,4'-((1-(cyclopropylmethyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6k, 97 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.92 (*s*, 1H, OH), 12.37 (*s*, 1H, OH), 7.87 (*s*, 1H, CH-triazol), 7.70 (*d*, *J*=8.0 Hz, 4H, Ar), 7.51–7.35 (*m*, 4H, Ar), 7.25 (*s*, 2H, Ar), 5.03 (*s*, 1H, CH), 4.17 (*d*, *J*=7.3 Hz, 2H), 2.39–2.19 (*m*, 6H, 2CH3), 1.23 (*tt*, *J*=8.0, 4.7 Hz, 1H), 0.59–0.43 (*m*, 2H), 0.40–0.25 (*m*, 2H).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 148.23, 146.21, 129.46, 122.47, 121.10, 54.03, 26.76, 12.02, 4.22.

LC/MC *m/z*: 482,2 [$(M+H)^+$].

4,4'-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6l, 98 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.95 (*s*, 1H, OH), 12.56 (*s*, 1H, OH), 8.69 (*d*, *J*=1.0 Hz, 1H, CH-triazol), 8.40–8.32 (*m*, 2H, Ar), 8.26–8.17 (*m*, 2H, Ar), 7.74–7.62 (*m*, 4H, Ar), 7.40 (*t*, *J*=7.8 Hz, 4H, Ar), 7.21 (*t*, *J*=7.4 Hz, 2H, Ar), 5.11 (*d*, *J*=1.1 Hz, 1H, CH), 2.32 (*s*, 6H, $2CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 150.38, 146.98, 141.49, 129.44, 126.06, 121.55, 121.18, 120.93, 56.56, 26.70, 19.11.

LC/MC *m/z*: 549.2.

4,4'-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6m, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.89 (*s*, 1H, OH), 12.44 (*s*, 1H, OH), 8.50 (*s*, 1H, CH-triazol), 7.91–7.81 (*m*, 2H, Ar), 7.76–7.62 (*m*, 6H, Ar), 7.40 (*t*, *J*=7.8 Hz, 4H, Ar), 7.20 (*t*, *J*=7.4 Hz, 2H, Ar), 5.08 (*d*, *J*=1.0 Hz, 1H, CH), 2.31 (*s*, 6H, $2CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 149.86, 133.21, 129.43, 122.37, 121.48, 121.18, 121.09, 26.71, 19.11.

LC/MC *m/z*: 583.1.

4,4'-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6n, 95 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.89 (*s*, 1H, OH), 12.44 (*s*, 1H, OH), 8.49 (*s*, 1H, CH-triazol), 7.96–7.89 (*m*, 2H, Ar), 7.71–7.65 (*m*, 4H, Ar), 7.62–7.56 (*m*, 2H, Ar), 7.40 (*t*, *J*=7.9 Hz, 4H, Ar), 7.26–7.14 (*m*, 2H, Ar), 5.08 (*d*, *J*=1.0 Hz, 1H, CH), 2.31 (*s*, 6H, $2CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 149.85, 136.04, 133.10, 130.29, 129.43, 122.13, 121.19, 121.14, 26.71.

LC/MC *m/z*: 539.1.

4,4'-((1-(p-tolyl)-1H-1,2,3-triazol-4-yl)methylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6o, 95 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.87 (*s*, 1H, OH), 12.42 (*s*, 1H, OH), 8.38 (*d*, *J*=2.0 Hz, 1H, CH-triazol), 7.70 (*ddd*, *J*=22.6, 8.3, 2.2 Hz, 7H, Ar), 7.40 (*t*, *J*=8.1 Hz, 5H, Ar), 7.35–7.11 (*m*, 4H, Ar), 5.08 (*d*, *J*=2.3 Hz, 1H, CH), 2.31 (*s*, 9H, $3CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 149.51, 146.22, 138.46, 135.03, 130.68, 129.43, 121.19, 120.83, 120.34, 26.73, 21.08.

LC/MC *m/z*: 518.2.

4,4'-((1-(3,5-difluorophenyl)-1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6p, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.89 (*s*, 1H, OH), 12.44 (*s*, 1H, OH), 8.59 (*d*, *J*=1.0 Hz, 1H, CH-triazol), 7.84–7.75 (*m*, 2H, Ar), 7.73–7.62 (*m*, 4H, Ar), 7.49–7.30 (*m*, 5H, Ar), 7.20 (*t*, *J*=7.4 Hz, 2H, Ar), 5.09 (*d*, *J*=1.1 Hz, 1H, CH), 2.31 (*s*, 6H, $2CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 164.66, 164.52, 162.21, 162.06, 150.06, 139.17, 139.04, 129.43, 121.54, 121.16, 104.34, 104.13, 104.04, 103.87, 26.67.

LC/MC *m/z*: 540.2.

4,4'-((1-(2-(methylthio)phenyl)-1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6q, 98 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.87 (*s*, 1H, OH), 12.42 (*s*, 1H, OH), 8.10 (*s*, 1H, CH-triazol), 7.75–7.62 (*m*, 4H, Ar), 7.54–7.44 (*m*, 2H, Ar), 7.43–7.35 (*m*, 5H, Ar), 7.28 (*td*, *J*=7.4, 1.6 Hz, 1H, Ar), 7.20 (*t*, *J*=7.5 Hz, 2H, Ar), 5.11 (*s*, 1H, CH), 2.34 (*d*, *J*=16.5 Hz, 9H, $3CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 148.50, 135.77, 135.08, 130.80, 129.45, 127.14, 127.06, 125.94, 124.32, 121.19, 26.76, 15.36.

LC/MC *m/z*: 550.2.

4,4'-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6r, 98 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.87 (*s*, 1H, OH), 12.42 (*s*, 1H, OH), 8.44 (*s*, 1H, CH-triazol), 7.97–7.86 (*m*, 2H, Ar), 7.67 (*d*, *J*=8.0 Hz, 4H, Ar), 7.48–7.31 (*m*, 6H, Ar), 7.20 (*t*, *J*=7.3 Hz, 2H, Ar), 5.08 (*d*, *J*=0.9 Hz, 1H, CH), 2.31 (*s*, 6H, $2CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 163.20, 160.76, 149.68, 133.83, 133.80, 129.43, 122.85, 122.76, 121.29, 121.19, 117.26, 117.03, 57.42, 26.71.

LC/MC *m/z*: 550.2.

4,4'-((1-(3,4-difluorophenyl)-1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6s, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.89 (*s*, 1H, OH), 12.44 (*s*, 1H, OH), 8.51 (*s*, 1H, CH-triazol), 8.10 (*ddd*, *J*=11.6, 7.1, 2.7 Hz, 1H, Ar), 7.84–7.75 (*m*, 1H, Ar), 7.74–7.55 (*m*, 5H, Ar), 7.40 (*t*, *J*=7.8 Hz, 4H, Ar), 7.20 (*t*, *J*=7.4 Hz, 2H, Ar), 5.08 (*s*, 1H, CH), 2.31 (*s*, 6H, $2CH_3$).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 149.90, 148.17, 146.24, 129.43, 121.48, 121.17, 119.29, 119.10, 117.35, 117.31, 117.28, 110.68, 110.46, 26.70.

LC/MC *m/z*: 540.2.

4,4'-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6t, 97 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.91 (*s*, 1H, OH), 12.46 (*s*, 1H, OH), 8.74 (*d*, *J*=1.0 Hz, 1H, CH-triazol), 8.70 (*t*, *J*=2.2 Hz, 1H, Ar), 8.38 (*ddd*, *J*=8.2, 2.2, 1.0 Hz, 1H, Ar), 8.24 (*ddd*, *J*=8.3, 2.2, 0.9 Hz, 1H, Ar), 7.80 (*t*, *J*=8.2 Hz, 1H, Ar), 7.75–7.64 (*m*, 4H, Ar), 7.40 (*t*, *J*=7.8 Hz, 4H, Ar), 7.20 (*t*, *J*=7.4 Hz, 2H, Ar), 5.12 (*s*, 1H, CH), 2.33 (*s*, 6H, 2CH_3).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 150.15, 149.07, 146.27, 137.84, 131.96, 129.43, 126.52, 126.13, 123.35, 121.68, 121.15, 115.10, 56.56, 26.74, 19.10, 12.16.

LC/MC *m/z*: 549.2.

4,4'-((1-(tetrahydro-2H-thiopyran-4-yl)-1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6u, 98 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.82 (*s*, 1H, OH), 12.36 (*s*, 1H, OH), 7.87 (*s*, 1H, CH-triazol), 7.75–7.59 (*m*, 4H, Ar), 7.40 (*t*, *J*=7.8 Hz, 4H, Ar), 7.20 (*t*, *J*=7.7 Hz, 2H, Ar), 4.98 (*d*, *J*=0.8 Hz, 1H, CH), 4.48 (*tt*, *J*=11.7, 3.5 Hz, 1H, CH), 2.86–2.58 (*m*, 4H, 2CH_2), 2.32–2.14 (*m*, 8H, 2CH_3, CH_2), 2.10–1.90 (*m*, 2H, CH_2).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 129.45, 121.12, 58.66, 34.80, 27.58, 26.76.

LC/MC *m/z*: 528.2.

4,4'-((1-(cyclobutylmethyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6v, 97 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.83 (*s*, 1H, OH), 12.35 (*s*, 1H, OH), 7.77 (*d*, *J*=0.8 Hz, 1H, CH), 7.72–7.59 (*m*, 4H, Ar), 7.40 (*t*, *J*=7.8 Hz, 4H, Ar), 7.20 (t, *J*=7.4 Hz, 2H, Ar), 5.04–4.91 (*m*, 1H, CH), 4.28 (*d*, *J*=7.3 Hz, 2H, CH_2), 2.66 (*hept*, *J*=7.4 Hz, 1H, CH), 2.27 (*s*, 6H, 2CH_3), 1.96–1.82 (*m*, 2H, CH_2), 1.82–1.61 (*m*, 4H, 2CH_2).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 148.02, 129.46, 122.87, 121.09, 54.32, 35.72, 26.71, 25.52, 18.06.

LC/MC *m/z*: 496.2.

4,4'-((1-((tetrahydrofuran-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6w, 96 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.84 (*s*, 1H, OH), 12.36 (*s*, 1H, OH), 7.86 (*s*, 1H, CH-triazol), 7.66 (*dt*, *J*=8.5, 1.4 Hz, 4H, Ar), 7.40 (*t*, *J*=7.9 Hz, 4H, Ar), 7.20 (*t*, *J*=7.4 Hz, 2H, Ar), 4.99 (*s*, 1H, CH), 4.27 (*d, J*=7.5 Hz, 2H), 3.69 (*td*, *J*=8.1, 5.6 Hz, 1H, CH), 3.58 (*ddd*, *J*=9.0, 7.3, 1.8 Hz, 2H, CH2), 3.38 (*dd*, *J*=8.7, 5.5 Hz, 1H, CH), 2.64 (*dtd*, *J*=15.0, 7.5, 1.8 Hz, 1H, CH), 2.27 (*s*, 6H, 2CH3), 1.83 (*dtd*, *J*=12.4, 8.0, 5.6 Hz, 1H, CH), 1.53 (*ddt*, *J*=12.4, 7.8, 6.3 Hz, 1H, CH).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 148.21, 146.18, 129.46, 126.14, 123.24, 121.09, 70.44, 67.26, 51.98, 40.11, 29.73, 26.71, 12.15.

LC/MC *m/z*: 512.2.

4,4'-((1-(cyclohexylmethyl)-1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) 6x, 95 % yield.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 13.82 (*s*, 1H, OH), 12.37 (*s*, 1H, OH), 7.78 (*s*, 1H, CH-triazol), 7.69 (*d*, *J*=8.0 Hz, 4H, Ar), 7.44 (*t*, *J*=7.9 Hz, 4H, Ar), 7.24 (*s*, 2H. Ar), 5.02 (*s*, 1H, CH), 4.14 (*d*, *J*=7.1 Hz, 2H, CH2), 2.31 (*s*, 6H, 2CH3), 1.74 (*d*, *J*=7.8 Hz, 1H, CH), 1.66–1.53 (*m*, 3H, CH_2, CH), 1.53–1.39 (*m*, 2H, CH_2), 1.23–1.01 (*m*, 3H, CH_2, CH), 0.92 (*q*, *J*=11.4 Hz, 2H, CH_2).

^{13}C NMR (100 MHz, DMSO-D_6) δ: 147.93, 146.18, 129.45, 123.35, 121.05, 55.47, 38.75, 30.25, 26.70, 26.29, 25.56.

LC/MC *m/z*: 524.2.

3. 2. Molecular docking studies

For receptor-oriented flexible docking, the Autodock 4.2 software package was used. Ligands were prepared using the MGL Tools 1.5.6 program. The Ligand optimization was performed using the Avogadro program. To perform calculations in the Autodock 4.2 program, the output formats of the receptor and ligand data were converted to a special PDBQT format. The receptor maps were made using MGL Tools and AutoGrid programs. Our previous studies [16] provided a similar software package with docking parameters.

In the selection of targets, attention was focused on known cytostatics that affect various parts of oncogenesis and the analyzed targets with which they bind. Therefore, active centres of macromolecules from the Protein Data Bank of C-abl kinase (PDB ID: 6NPE) [17–19], deoxycytidine kinase (dCK) (PDB ID: 5MQT) [20], and CSF1 receptor (PDB ID: 4R7I) [20–22], EGFRK receptor (PDB 1M17) [23], FOLR2 receptor (PDB ID: 4KN2) [24, 25], were used as docking targets:

– 6NPE **A**: coordinates *x*=18.099, *y*=–6.311, *z*=–10.037, size *x*=24, *y*=28, *z*=24;

– 5MQT A: coordinates *x*=–5.56, *y*=130.393, *z*=26.966, size *x*=24, *y*=22, *z*=22;

– 4R7I **A**: coordinates *x*=38.187, *y*=13.996, *z*=77.422, size *x*=26, *y*= 16, *z*=22;

– 1M17 A: coordinates *x*=24.337, *y*=0.983, *z*=53.545, size *x*=28, *y*=16, *z*=22;

– 4KN2 **A**: coordinates *x*=40.191, *y*=6.332, *z*=40.934, size *x*=24, *y*=26, *z*=22.

Water molecules, ions, and ligands were removed from the PDB file. Visual analysis of the complexes of the tested molecules in the active sites of the peptides, visualization of redocking, and calculation of RMSD values were performed using the Discovery Studio Visualizer program.

4. Results

The 1*H*-1,2,3-triazole-4-carbaldehyde derivatives were prepared by the 1,3-dipolar Huisgen cycloaddition reaction between azides and 3,3-diethoxyprop-1-yne catalyzed by Cu(I) in THF:H_2O, yielding only 1,4-regioisomers in 63-82 % yields as described [26] (Fig. 3). The structures of the desired 1*H*-1,2,3-triazole-4-carbaldehydes were confirmed by ^{1}H NMR and LC/MS spectral analysis. The ^{1}H NMR spectrum revealed a singlet at

δ 10.05–9.95 ppm corresponding to aldehyde hydrogen. A singlet signal at δ 8.06–8.19 ppm was observed for triazole hydrogen.

The synthesis of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **5** was carried out by the interaction of phenylhydrazine with ethylacetoacetate in an equimolar ratio under heating for 2 h to give a solid product in 89 % yield.

The developed **6a-x** triazole-pyrazole conjugates were synthesized from the corresponding 1,2,3-triazole aldehydes **4a-x** and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **5** in 60 % ethanol at 85 °C for 3 h in an 95-98 % yield (Fig. 3). The structures of all **6a-x** triazole-pyrazole conjugates were confirmed by physical data and spectral analysis.

In our previous studies [27] monosubstituted product of this reaction (4-((1-(3-fluorophenyl)-1H-1,2,3-triazol-4-yl)methylene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one) was also obtained and characterized by X-ray structural analysis.

As a result of the molecular docking, it was established that the activity of the studied molecules in relation to tumour targets can be realized by creating complexes between them, the stability of which is ensured mainly due to the energetically favourable geometric arrangement of the ligands in the active centre of the corresponding target, the formation of hydrogen bonds between them, intermolecular electrostatic and donor-acceptor interactions. As a consequence, the thermodynamic probability of such binding is confirmed by the calculated scoring functions (Affinity DG, kcal/mol), free energy (EDoc (kcal/mol) and binding constants Ki (uM). For comparative evaluation, estimated values were calculated for known cytostatics (Table 1 and Appendix 1).

Redocking of the reference compounds relative to the selected targets revealed that they are located in well-documented binding sites, where they form a range of interactions with amino acid residues of the corresponding sites, which is in good agreement with the results of crystallographic studies [17–25]. The redocked native ligand structures showed similar orientations and binding positions in the active site region in relation to the crystallized native ligand structures with RMSD values ≤2 Å (Imatinib (6NPE) – 0.779 Å; Imatinib (5MQT) 1.937 Å; Imatinib (4R7I) 0.370 Å; Erlotinib (1M17) 1.813 Å; Pemetrexed (4KN2) 1.012 Å). The ligand poses, and binding site areas were determined correctly, as shown by the example of redocking of imatinib and erlotinib against C-abl kinase (6NPE), FOL2 (4KN2) and EGFRK (1M17) receptor targets, respectively (Fig. 4, *a–c*).

Table 1

Scoring function (Affinity DG) value for the best conformational positions of potential anticancer agents in complex with biotargets

Molecules	Affinity DG, kcal/mol				
	C-abl kinase	Deoxycytidine kinase	CSF1 receptor	Receptor EGFRK	FOLR2 receptor
6a	–9.2	–8.9	–8.5	–10.4	–9.9
6b	–8.4	–9.2	–8.2	–10.1	–10.1
6c	–8.8	–9.2	–8.6	–10.3	–10.3
6d	–9.2	–8.9	–8 .6	–10.1	–9.8
6e	–9.0	–9.1	–8.0	–10.4	–9.0
6f	–8.7	–8.8	–8.7	–10.2	–10.0
6g	–9.3	–9.1	–9.2	–9.9	–10.7
6h	–9.2	–9.1	–8.9	–10.2	–9.3
6i	–8.3	–7.7	–8.0	–9.0	–8.6
6j	–8.6	–7.8	–8.2	–9.6	–9.0
6k	–8.6	–9.8	–7.8	–9.7	–9.0
6l	–9.6	–8.5	–8.8	–9.5	–10.0
6m	–9.0	–8.5	–8.7	–10.5	–9.8
6n	–9.2	–8.6	–7.7	–9.1	–9.8
6o	–9.2	–8.8	–8.8	–10.6	–10.0
6p	–9.2	–9.1	–8.8	–10.2	–10.1
6q	–8.7	–8.7	–8.1	–10.0	–8.9
6r	–9.2	–8.2	–8.6	–10.0	–9.7
6s	–9.1	–8.6	–8.9	–10.3	–10.0
6t	–9.0	–9.3	–8.9	–9.8	–10.2
6u	–8.5	–7.8	–8.1	–9.2	–9.0
6y	–8.4	–9.3	–7.9	–9.4	–9.3
6w	–8.7	–8.3	–7.7	–9.7	–8.5
6x	–8.5	–8.8	–7.8	–10.6	–10.1
Imatinib	–12.7	–9.6	–12.3	–	–
Erlotinib	–	–	–	–7.4	–
Pemetrexed	–	–	–	–	–11.3

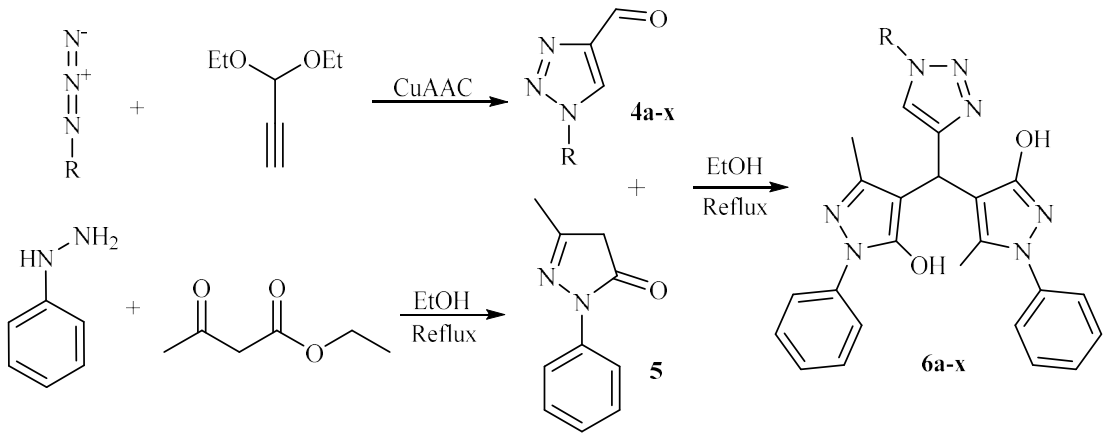
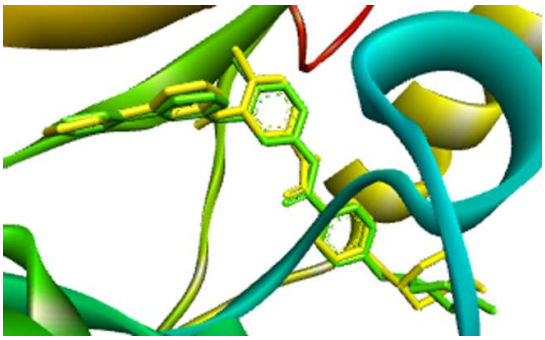
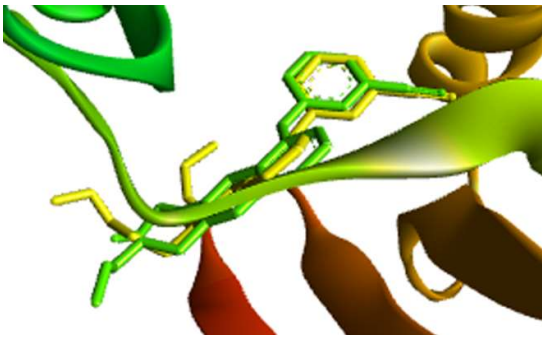


Fig. 3. Synthesis of target triazole-pyrazole conjugates



a



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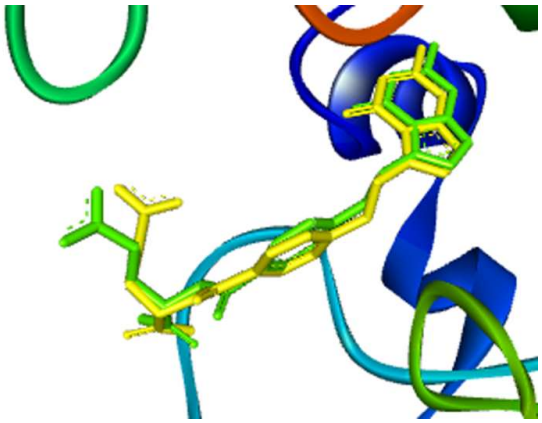


c

Fig. 4. Superimposed co-crystalized (green) and re-docking native ligand (yellow) in the active site of biotarget:
a – Imatinib against C-abl kinase;
b – Erlotinib against EGFRK receptor;
c – Pemetrexed against FOL2 receptors

According to the values obtained, the tested molecules will have a moderate inhibitory effect on C-abl kinase, deoxycytidine kinase, CSF1 receptor, FOLR2 receptor since the calculated estimated values for them do not exceed the effect of the declared reference drugs or are at the level or have average values. The best activity of the tested molecules will be observed in relation to the EGFRK receptor (Table 1 and Appendix 1), since the values of the scoring function and free energy exceeded the absolute values of Erlotinib, and the binding constants were several times lower. Among the molecules being studied, 6b, 11g, 6h, and 6n stand out as the most effective in terms of their activity on the EGFRK receptor. Additionally, these compounds are expected to have some activity against the FOLR2 receptor, as indicated by the calculated free energy and binding constants shown in Appendix 1. However, it's important to note that their results do not surpass those of Pemetrexed.

To evaluate the binding modes of the selected molecules to the active sites of EGFRK and FOLR2 receptors, a detailed analysis of the geometric arrangement of energetically favourable positions was performed, and the resulting complexes with the studied targets were analyzed. Table 2 shows the types of interaction with the amino acid residues of the active sites of EGFRK and FOLR2 receptors for the most promising molecules in comparison with the reference ligands.

Table 2

Types of interactions with amino acid residues of the active sites of EGFRK and FOLR2 receptors for promising molecules

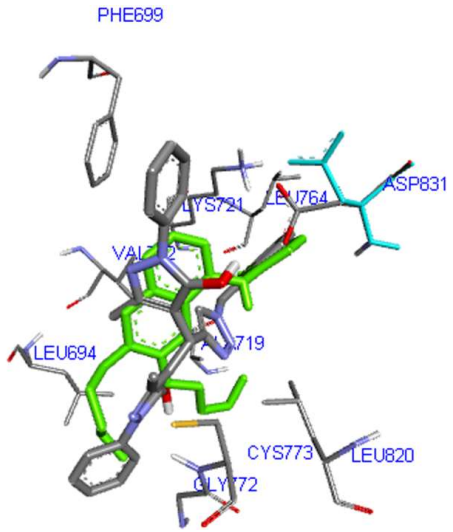
Molecule	Amino acid residues (types of interactions)
EGFRK receptor	
6b	Asp831 (H-bond, **π**-anion), Phe699 (**π-π**), Gly772 (H-bond), Leu694 (**π-σ**, **π**-Alk), Lys721 (**π**-cation), Val702 (2×Alk), Cys773 (Alk), Ala719 (**π**-Alk), Leu820 (2×**π**-Alk), Leu764 (**π**-Alk)
6g	Asp831 (acceptor-acceptor), Phe699 (2×**π-π**), Leu694 (**π**-Alk), Lys721 (**π**-Alk, Alk), Val702 (Alk, **π**-Alk), Cys773 (H-bond, Alk), Ala719 (**π**-Alk), Leu820 (**π**-Alk), Met742 (Alk), Leu764 (2×Alk)
6h	Asp831 (H-bond, **π**-anion), Phe699 (**π-π**), Met742 (**π**-Sulfur, Alk), Leu694 (**π-σ**), Lys721 (**π**-Alk Alk), Val702 (**π**-Alk Alk), Cys773 (donor-donor), Ala719 (**π**-Alk), Leu820 (2× Alk), Leu764 (Alk)
6n	Asp831 (**π**-anion), Phe699 (**π-π**), Leu694 (2×**π**-Alk), Lys721 (**π**-cation), Val702 (**π-σ**, Alk), Ala719 (**π**-Alk, Alk), Leu820 (**π**-Alk)
Erlotinib	Met769 (2×H-bond), Lys721 (**π**-cation, Alk), Val702 (2× **π-σ**), Met742 (**π**-Sulfur), Ala719 (H-bond), Leu764 (H-bond)
FOLR2 receptor	
6g	Lys35 (donor-donor, π-cation), Trp156 (3×**π-π,** 2×**π-σ**), **Trp118 (π-H, π-Alk), Tyr76 (π-H,** 2×Alk, π-π), Tyr101(π-Alk), Trp187(π-Alk)
6m	Lys35 (donor-donor, π-cation), Trp156 (3×**π-π,** 2×**π-σ**), **Tyr76 (**2×H-bond, π-π), Trp187(π-π, π-Alk)
6n	Lys35 (donor-donor, π-cation), Trp156 (3×**π-π,** 2×**π-σ**), **Tyr76 (H**-bond, π-π, π-Alk), Trp187(π-Alk)
6t	His151 (2×H-bond), Arg119 (H-bond), Trp156 (H-bond, π-π), Arg152 (π-Alk), Trp118 (π-π, π-**σ**), **Tyr76 (π-π), Trp187(π-π), Gly153 (π-H)**
Pemetrexed	Gly153 (H-bond), Gln116 (H-bond), Arg152 (H-bond), Trp156 (donor-donor, π-π), Trp118 (π-π), Tyr76 (π-σ), Thr98 (H-bond), Tyr101(**π-π**), Trp187(2×**π-π**), Asp97 (2×H-bond), His151 (H-bond), Arg119 (H-bond)

This analysis revealed that the formation of complexes of molecules 6b and 6n with the EGFRK receptor (Table 2) was facilitated by favourable intermolecular

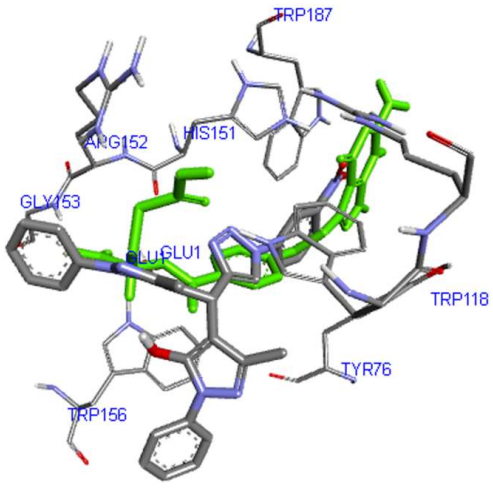
interactions, but in the complexes with molecules 6g and 6h, unfavourable donor-donor and acceptor-acceptor interactions with amino acid residues of Asp831 and Cys773 (Table 2), respectively, were involved, which may lead to a decrease in the predicted activity.

In the case of complex formation with amino acid residues of the FOLR2 receptor active site, molecules 6g, 6m, 6n (Table 2) also had an unfavorable donor-donor binding to the Lys35 residue. Among the proposed molecules, only molecule 6t (Table 2) is likely to have the best affinity to this receptor in terms of the binding mode and stability of the complex.

As a result of the detailed geometric arrangement of promising molecules in the active sites of peptides and the obtained docking calculations, the hit molecules 6b against EGFRK receptor and 6t against FOLR2 receptor which may form stable complexes with the corresponding amino acid residues due to favourable intermolecular interactions. Fig. 5 shows the superpositions of molecules 6b and 6t in relation to EGFRK and FOLR2 receptors, respectively.



a



b

Fig. 5. Superpositions of the hit molecules (grey-coloured) and ligand (green-coloured) in the active site of biotargets: *a* – molecule 6b against EGFRK receptor; *b* – molecule 6t against FOLR2 receptor

5. Discussion

The synthesis of derivatives of 1,2,3-triazole-attached bis-pyrazoles with aromatic substituents in the triazole fragment was previously described [28]. Our proposed method allows the synthesis of a wide range of derivatives containing 1-phenyl-substituted 1H-pyrazol-5-ols. In addition, the spectrum of substituents was expanded by including heterocyclic, aliphatic, and other aromatic moieties in the triazole fragment. It gave us hope and reason to expand the spectrum of activity. The results of molecular docking confirmed our expectations about the compounds' possible antitumor activity.

The results of molecular docking for antitumor targets indicate that the newly synthesized derivatives 4,4'-((1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) may have antitumor effects through the mechanism of EGFRK receptor inhibition. It is also important to emphasize that this group of compounds has moderate calculated values relative to other targets (C-abl kinase, deoxycytidine kinase, CSF1 and FOLR2 receptors), which, in our opinion, will give a higher probability of potential effect in experimental screening, since it affects several links in the pathogenesis of cancer.

Practical Relevance. The proposed studies of derivatives 4,4'-((1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) can be used for the synthesis of a wider range of substances of this series and to optimize the molecular docking procedure according to the chosen direction.

Study limitations. The use of molecular docking methodology for activity prediction is advisory, so pharmacological screening should be performed to confirm the docking results.

Prospects for further research. The results of docking studies have shown the prospects of the obtained derivatives as anticancer agents; therefore, they can be recommended for experimental screening.

6. Conclusions

Derivatives of 4,4'-((1H-1,2,3-triazol-4-yl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) were synthesized. The structure and purity of the obtained substances were confirmed ^{1}H NMR, ^{13}C NMR and LC/MS.

According to the molecular docking data, the newly synthesized derivatives 4,4'-((1H-1,2,3-triazol-4-yl) methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) may have an antitumor effect through the mechanism of EGFRK receptor inhibition. It is also important to emphasize that this group of compounds has moderate calculated values relative to other targets (C-abl kinase, deoxycytidine kinase, FOLR2 and CSF1 receptor), which we believe will give a higher probability of potential antitumor effect in experimental screening.

Conflicts of interest

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

Data will be made available on request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

Acknowledgements

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