

Synthesis, Characterization, and Examination of Possible Anticancer Effects of a Novel Bis-1,2,3-triazole derivative via Molecular Docking Studies

Ayşe Tan^{1,a,*}¹ Vocational School of Technical Sciences, Mus Alparslan University, Mus, Türkiye

*Corresponding author e-mail address: a.tan@alparslan.edu.tr

Research Article

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ABSTRACT

A new bis-1,2,3-triazole compound (6) was synthesized by utilizing Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) method and characterized by ¹H, ¹³C NMR, and HR-(ESI)-MS analysis. Molecular docking studies against EGFR, mTOR, and p70S6K1 receptor proteins were performed to examine the potential anticancer effects of 6. The inhibition of these receptors has been considered an important therapeutic strategy in anticancer studies. The docking results were compared with those of anastrozole, which is an anticancer drug, and co-crystallized ligands of EGFR, mTOR, and p70S6K1 receptors, which are FMM for EGFR, P2X for mTOR, and 5FI for p70S6K1. The co-crystallized ligands are highly effective inhibitors for the receptors. According to the docking studies, compound 6 has quite good binding affinities with the three receptors. The best binding energy values with mTOR, p70S6K1, and EGFR of 6 are calculated as -10.38 kcal/mol, -9.93 kcal/mol, and -10.02 kcal/mol, respectively. Conversely, anastrozole's best binding values are -8.42 kcal/mol, -8.08 kcal/mol, and -7.55 kcal/mol, respectively. On the other hand, when compared to the binding energies of FMM (-13.16 kcal/mol), P2X (-8.81 kcal/mol), and 5FI (-7.6 kcal/mol), it is seen that compound 6 has better binding energy than them, except for FMM. The EIC (Estimated Inhibition Constant) Ki values with mTOR, p70S6K1, and EGFR of 6 are found as 24.81 nM, 52.21 nM, and 45.28 nM, respectively, while anastrozole's Ki values are 671.53 nM, 1190 nM, and 2950 nM. On the other hand, the Ki values of P2X, 5FI, and FMM are 347 nM, 2700 nM, and 25.5 nM, respectively. These results show that compound 6 has much better binding energy than anastrozole, P2X, and 5FI. Therefore, the compound may show considerable inhibitory effects against these receptor proteins and could be considered a potential candidate drug for anticancer studies.

Keywords: Anticancer, EGFR, mTOR, p70S6K, 1,2,3-triazole



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^a  0000-0003-2692-7923

1. Introduction

Cancer is one of the most common causes of death in the world [1]. Cancer is characterized by the uncontrolled proliferation, division, and accumulation of abnormal cells[2]. There are many methods, such as chemotherapy, radiotherapy, surgery, hormone therapy, and immunotherapy, to treat cancer[2]. It is well known that chemotherapy is very beneficial in cancer treatment. However, chemotherapy has been significantly restricted because of the toxic side effects of available anticancer drugs[3]. Due to the inadequacy of existing treatments and the side effects of anticancer drugs, the discovery of new anticancer drugs and methods remains necessary. There are many therapeutic targets in anticancer drug discovery and design, such as epidermal growth factor receptor (EGFR)[4], mammalian target of rapamycin (mTOR)[5], and human ribosomal S6 kinase domain (p70S6K1)[6] receptors. EGFR is a protein belonging to a family of receptor tyrosine kinases that is found on the cell surface and regulates processes such as cell growth, division, and survival[7]. EGFR is frequently overexpressed, mutated, or aberrantly activated in many tumor types[8, 9]. This can lead to uncontrolled growth of

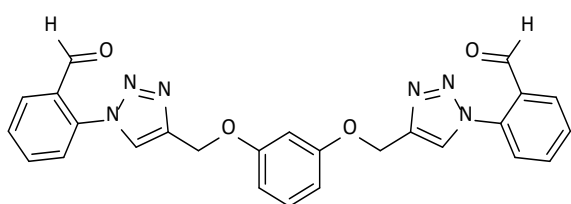
cells, metastasis, and the development of resistance to treatment[8]. mTOR is a serine/threonine kinase that controls many essential cellular processes, including cell growth, metabolism, protein synthesis, and survival. mTOR is also overactive in many types of cancer, promoting tumor development[10, 11]. Regarding p70S6K1, it is a serine/threonine kinase and one of the targets of the mTOR pathway. But mTORC1, which is a complex of mTOR, activates p70S6K1 by phosphorylating it. Thus, in cancer cells, protein synthesis increases, the cell grows, and multiplies[12]. Therefore, the inhibition of these receptors has been considered a significant therapeutic target for new anticancer drug design and discovery[4-6, 8].

The 1,2,3-triazole ring, which occupies a prominent position among *N*-heterocyclic compounds, has attracted considerable attention in medicinal chemistry and drug discovery due to its remarkable chemical stability, metabolic resistance, and ability to engage in hydrogen bonding and π - π interactions with biological targets[13]. The 1,2,3-triazole scaffold often directly contributes to biological activity by enhancing binding affinity and

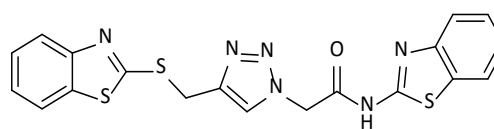
selectivity. For instance, several reported 1,2,3-triazole derivatives have demonstrated potent anticancer activity through apoptosis induction and cell cycle arrest mechanisms, while others have shown significant xanthine oxidase (XO) inhibitory activity comparable to standard inhibitors[13]. In addition, some hybrid molecules incorporating this ring have exhibited promising anti-HIV and antiviral activities by targeting viral enzymes[14, 15], as well as notable antimicrobial and antifungal effects against clinically relevant strains[16, 17]. Anti-inflammatory and anticholinesterase activities have also been documented, highlighting the broad pharmacological versatility of this scaffold[18, 19]. Additionally, the triazole ring can readily bind to many enzymes and receptors via various noncovalent interactions. Therefore, it is also used in various molecular docking studies[13]. The triazole is often used as a linker in the synthesis of various hybrid molecules, such as 1,2,3-

triazole-1,2,3-triazole hybrids, 1,2,3-triazole-imidazopyridine hybrids, 1,2,3-triazole-benzoxazole hybrids, 1,2,3-triazole-1,3-disubstituted pyrazole hybrids, and 1,2,3-triazole-benzothiazole hybrids in the discovery of anticancer pharmacophores (Figure 1), and these compounds have been reported to exhibit significant anticancer activity[20-24]

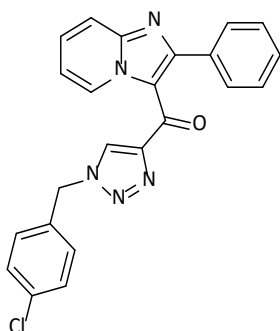
Given the above information, a new bis-1,2,3-triazole compound (6) containing two triazole rings in the same structure, based on the various biological activities of the triazole ring, was synthesized to contribute to anticancer drug discovery as a novel anticancer drug candidate with potential inhibitory activity against EGFR, mTOR, and p70S6K1 receptor enzymes. The compound was characterized using various spectroscopic techniques. Finally, the potential inhibitory activity of the compound against these enzymes was investigated using molecular docking studies.



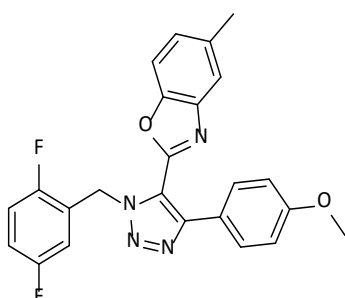
1,2,3-triazole-1,2,3-triazole



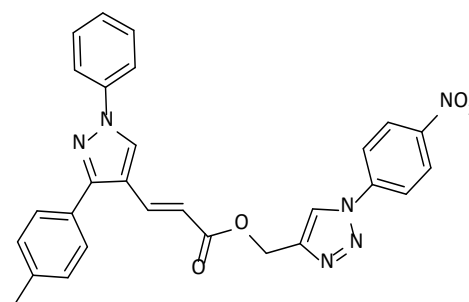
1,2,3-triazole-benzothiazole



1,2,3-triazole-imidazopyridine



1,2,3-triazole-benzoxazole



1,2,3-triazole-1,3-disubstituted pyrazole

Figure 1. Some hybrids 1,2,3-triazole derivatives possessing anticancer activity

2. Materials and Methods

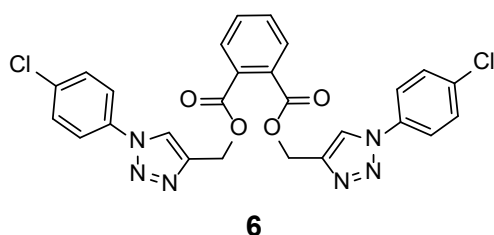
All chemical compounds in this study were purchased from *Sigma-Aldrich* and used without further purification. The ^1H NMR and ^{13}C NMR spectra were recorded on a *Bruker* (Avance III) 400 MHz NMR spectrometer. The mass spectrum was recorded on *Agilent Technologies* 6530 Accurate-Mass Q-TOF LC/MS.

2.1. Synthesis

Phthalic acid (2), di(prop-2-yn-1-yl) phthalate (3), and azidobenzene (5) were synthesized as mentioned in previous studies [13, 25, 26].

The synthesis of bis((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl) phthalate (6)

To a stirred solution, compound 3 (1 mmol) in 15 mL of MeOH was added 5 (1 mmol), and then, solutions of sodium *L*-ascorbate (0.1 mmol) in 2,5 mL of H_2O and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.1 mmol) in 2,5 mL of H_2O , respectively, were added to the medium at room temperature. The reaction mixture was stirred at room temperature overnight until compound 3 was completely consumed. Then, to the mixture was added 10 mL of ethyl acetate, and extraction was performed with H_2O (3×15 mL). The organic layer was dried over sodium sulfate. The crude product was purified by washing with diethyl ether.



Yield: 80%, white solid, ^1H NMR (400 MHz, DMSO- d_6 , ppm) δ 8.92 (s, 2H), 7.93 (d, $J = 8$ Hz, 4H), 7.81 – 7.79 (m, 2H), 7.72 – 7.69 (m, 2H), 7.66 (d, $J = 8$ Hz, 4H), 5.44 (s, 4H). ^{13}C NMR (100 MHz, DMSO- d_6 , ppm) δ 166.95, 143.14, 135.66, 133.55, 132.32, 131.55, 130.23, 129.38, 123.64, 122.20, 58.88, HR-(ESI)-MS ($\text{C}_{26}\text{H}_{18}\text{Cl}_2\text{N}_6\text{O}_4$): m/z 550.08832 $[M+H]^+$ (calc. 550.37 $[M+H]^+$).

2.2. Molecular Docking Studies

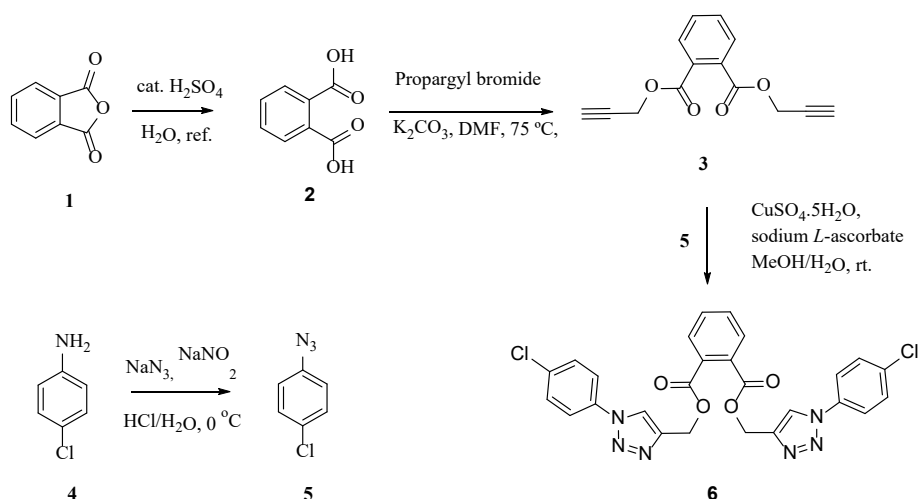
3D crystallographic structures of mTOR (PDB ID: 4JT5), p70S6K1 (PDB ID: 4L3J), and EGFR (PDB ID: 1XKK) were downloaded from the Protein Data Bank (www.rcsb.org) [27]. 2D structures of compound 6 and anastrozole were drawn on ChemDraw Professional 16.0. Autodock 4.2 [28] was used to perform molecular docking studies, and the

docking procedures were applied as in our previous work [6]. The results of docking were visualized via Discovery Studio Visualizer 2021 [29].

3. Results and Discussion

3.1. Chemistry

The target compound (6) was synthesized by the reaction steps given in Scheme 1. First, the phthalic acid (2) was obtained from the phthalate anhydride (1) in an aqueous medium with a catalytic amount of H_2SO_4 [25]. The di-alkyne compound (3) was synthesized with the reaction of phthalic acid (2) with propargyl bromide in DMF [26]. On the other hand, 4-chloroaniline (4) was treated with NaN_3 and NaNO_2 in an aqueous HCl solvent system to obtain an azidobenzene compound (5) [13]. In the last step, Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) method [30] was utilized to synthesize the target compound (6). Di-alkyne (3) and azidobenzene (5) compounds were reacted in the presence of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and sodium *L*-ascorbate in a MeOH/ H_2O solvent system, and compound 6 was obtained.



Scheme 1. Synthesis of compound 6.

3.2. Characterization

The characterization of compound 6 was performed with ^1H , ^{13}C NMR, and HR-(ESI)-MS analysis (Figures 2-4). The ^1H NMR and ^{13}C NMR spectra of 6 were recorded in DMSO- d_6 . Compound 6 has a symmetrical structure; therefore, the same protons of 6 were observed at the same chemical shift values. According to the literature, the characteristic aromatic proton of a 1,4-disubstituted 1,2,3-triazole ring appears as a singlet in the downfield region of the ^1H NMR spectrum, typically around $\delta \approx 7.5$ – 9 ppm [31-33]. In a study previously reported by our group, the signal corresponding to the aromatic proton of the 1,2,3-triazole ring attached to the chlorobenzene ring was characterized at 9.06 ppm [18]. In the ^1H NMR spectrum of 6 (Figure 2), the aromatic protons of the two triazole rings, which are attached to a chlorobenzene ring, were observed at δ 8.92 ppm (s, 2H). This value is in good

agreement with previously reported work [18]. The aromatic protons of the chlorobenzene rings to which the triazole rings are attached were observed at δ 7.93 ppm (d, $J = 8$ Hz, 4H) and 7.66 ppm (d, $J = 8$ Hz, 4H). Similarly, these aromatic protons are consistent with the literature [18]. The aromatic protons of the benzene ring to which the ester carbonyl groups are attached were characterized at δ 7.81-7.79 (m, 2H) and 7.72 – 7.69 ppm (m, 2H). The 1,4-disubstituted methylene protons of 6 were observed at δ 5.44 (s, 4H) [18]. The integration and chemical shift values of the protons observed in the spectrum support the proposed structural characterization. Regarding the ^{13}C NMR spectrum (Figure 3), because of the symmetrical structure of 6, 11 different carbon signals were observed in the spectrum. The signals of the carbonyl carbons of the ester groups were observed

at δ 166.95 ppm, and the signals in the 143.14-122.20 ppm range were characterized as aromatic carbons, including the triazole rings. Finally, the 1,4-disubstituted methylene carbons of **6** were observed at δ 58.88 ppm. In the HR-

(ESI)-MS analysis (Figure 4), the peak of the $[M + H]^+$ ion in the mass spectrum of **6** was determined at 550.08832 m/z (for $C_{26}H_{18}Cl_2N_6O_4$).

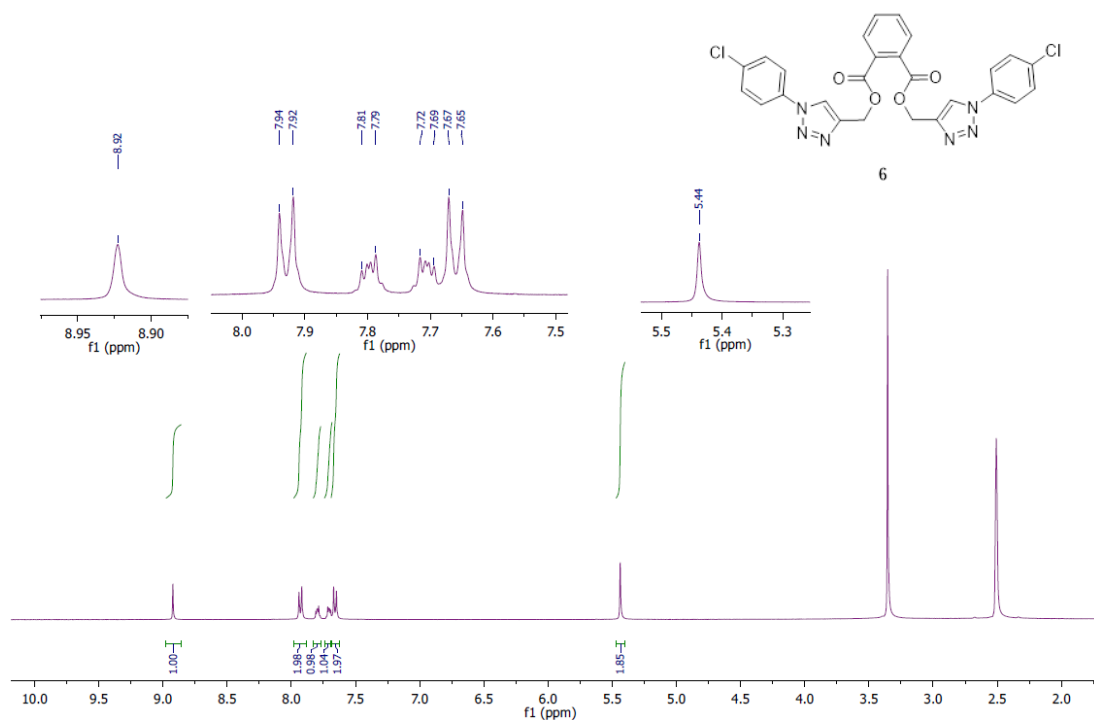


Figure 2. 1H NMR spectrum of compound **6**.

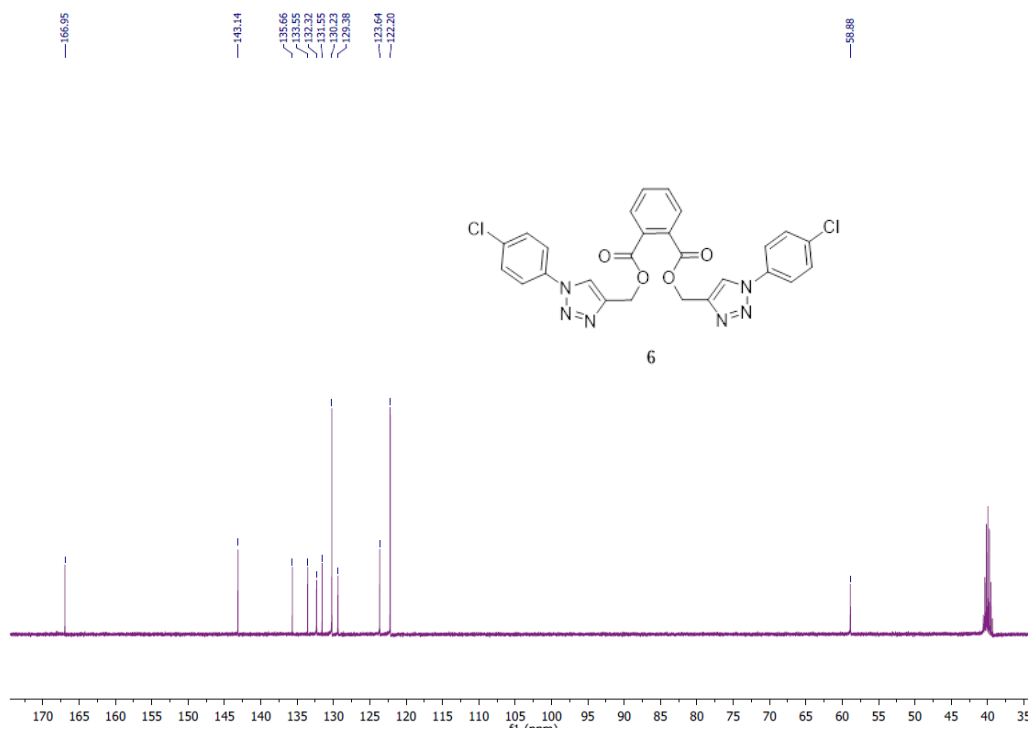


Figure 3. ^{13}C NMR spectrum of compound **6**.

Spectra

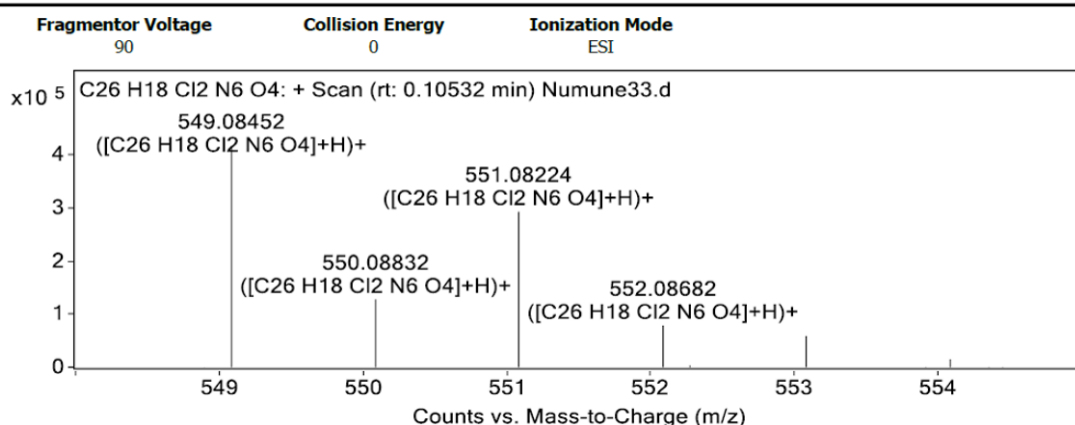


Figure 4. HR-(ESI)-MS spectrum of compound 6.

3.3. Molecular Docking Studies

In this study, the interactions of the bis-1,2,3-triazole compound (6) with mTOR, EGFR, and p70S6K1 have been investigated via molecular docking studies. The docking studies were carried out on the 3D crystallographic structures of 4JT5 for mTOR, 4L3J for p70S6K1, and 1XKK for EGFR. The crystal structure of the EGFR tyrosine kinase domain in complex with lapatinib (FMM) represents a well-characterized model for investigating type I kinase inhibitors and ATP-competitive binding modes[34]. Lapatinib is a small-molecule tyrosine kinase inhibitor (TKI) that inhibits the EGFR[35]. It is an important model inhibitor in cancer therapy and is widely used in studies investigating the EGFR signaling pathway. In our previous study, the binding energy for FMM was calculated as -13.16 kcal/mol, and the EIC (Estimated Inhibition Constant) K_i was determined to be 25.5 nM[6]. Similarly, the mTOR kinase domain structure has enabled detailed analysis of the catalytic cleft and facilitated structure-guided optimization of ATP-competitive mTOR inhibitors[36]. The 4JT5 has a co-crystallized ligand: PP242 (or TORKinib or P2X). It is an important inhibitor for mTOR[36]. In our previous study, the binding energy for P2X was calculated as -8.81 kcal/mol, and the EIC, K_i value was determined to be 347 nM[7]. The p70S6K1 crystal structure provides a robust structural framework for elucidating ligand interactions within the active site of this key downstream effector[37]. The 4L3J has a co-crystallized ligand, which is 5FI (or PF-4708671). It is an important inhibitor for p70S6K1[37]. In our previous study, the binding energy for 5FI was calculated as -7.6 kcal/mol, and the EIC, K_i value was determined to be 2700 nM[6].

Some studies have reported that anastrozole plays a significant role in the inhibition of EGFR and mTOR with some inhibitors together[38, 39]. Additionally, anastrozole is an important anticancer drug for breast cancer. In this study, the docking results were compared with anastrozole and the other inhibitors, which are FMM, P2X, and 5FI. All docking parameters are summarized in Table 1. According to the docking studies, compound 6 has quite good binding affinities against three receptors. In

molecular docking studies, the best binding energy is an important parameter for predicting ligand-protein interactions. Compounds exhibiting lower binding energy values are generally considered to have stronger binding affinity with the target protein. Therefore, they may display higher biological activity. When investigated, compound 6 may exhibit considerable activity against these receptor proteins. While the best binding energies with mTOR, p70S6K1, and EGFR of 6 are -10.38 kcal/mol, -9.93 kcal/mol, and -10.02 kcal/mol, respectively, anastrozole's best binding values are -8.42 kcal/mol, -8.08 kcal/mol, and -7.55 kcal/mol, respectively. According to the results, compound 6 may show more potent activity than anastrozole against these three enzymes. On the other hand, when compared to the binding energies of FMM, P2X, and 5FI, it is seen that compound 6 has better binding energy than them except for FMM. The EIC, K_i values with mTOR, p70S6K1, and EGFR of 6 are found as 24.81 nM, 52.21 nM, and 45.28 nM, respectively. On the other hand, anastrozole's K_i values are 671.53 nM, 1190 nM, and 2950 nM, respectively.

These results show that compound 6 has much better binding energies than anastrozole, P2X, and 5FI suggest that the compound may have better anticancer effects on these receptors (mTOR, p70S6K1, and EGFR) than anastrozole, P2X, and 5FI. In the interaction of 6 with EGFR, the ester carbonyl group formed a conventional hydrogen bond with Lys745 residue. On the other hand, the triazole rings formed π -sigma, π -sulfur, and π -alkyl interactions with some residues (Table 2, Figures 5 and 8). In the interaction of 6 with mTOR, while the ester carbonyl group formed a conventional hydrogen bond with Val2240, the triazole rings formed π -cation, π -sigma, π - π T-shaped, and π - π Stacked π -alkyl interactions with some residues (Table 2, Figures 6 and 8). Regarding the interactions of 6 with p70S6K1, the benzene ring to which the diester group is attached formed π -alkyl interactions with Leu149, Leu152, Ala98, and Val133 residues. The triazole rings formed π -cation, π -anion, and π -alkyl interactions with some residues (Table 2, Figures 7 and 8).

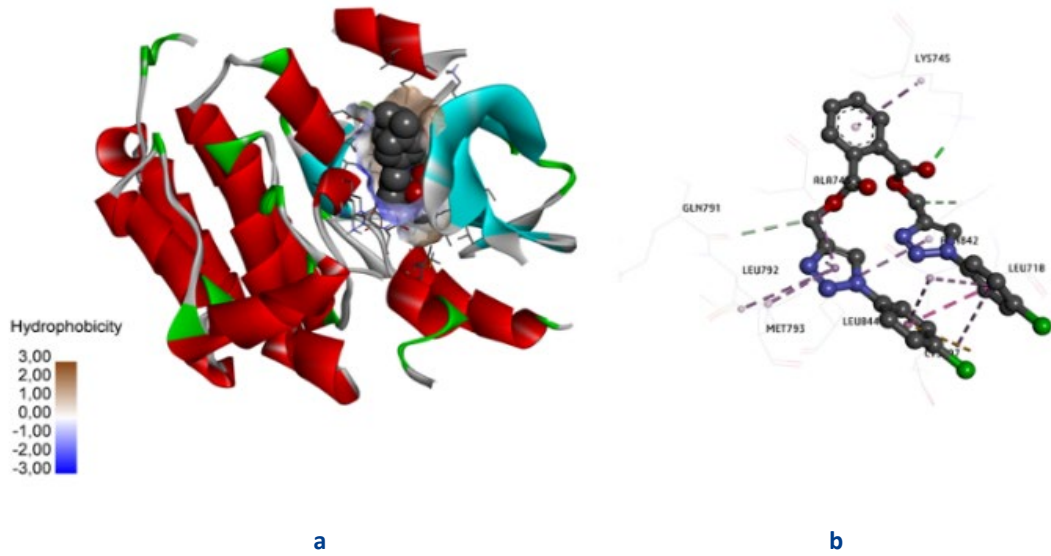


Figure 5. The best binding pose (a) and three-dimensional interactions (b) of 6 with EGFR.

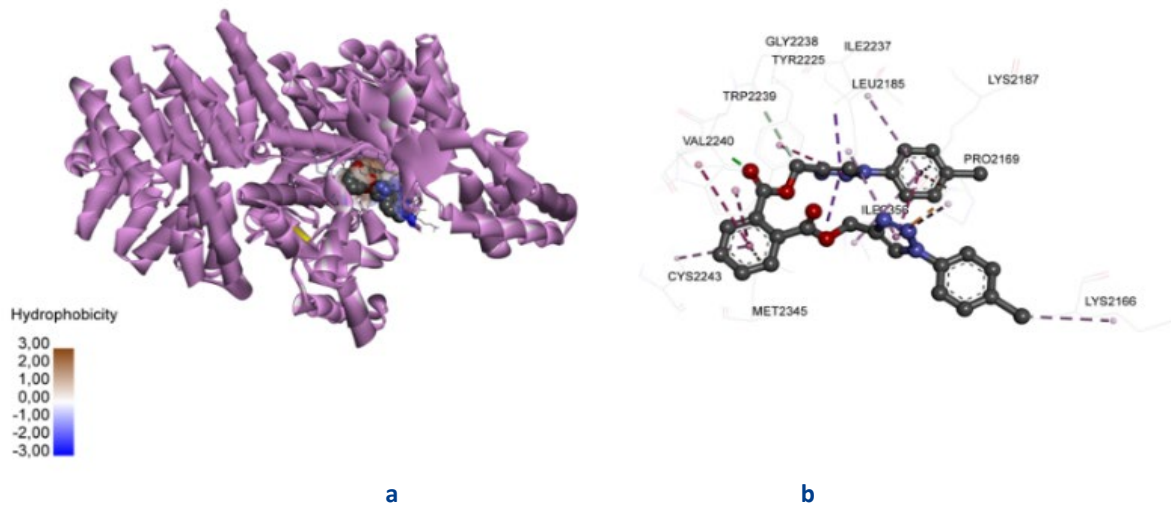


Figure 6. The best binding pose (a) and three-dimensional interactions (b) of 6 with mTOR.

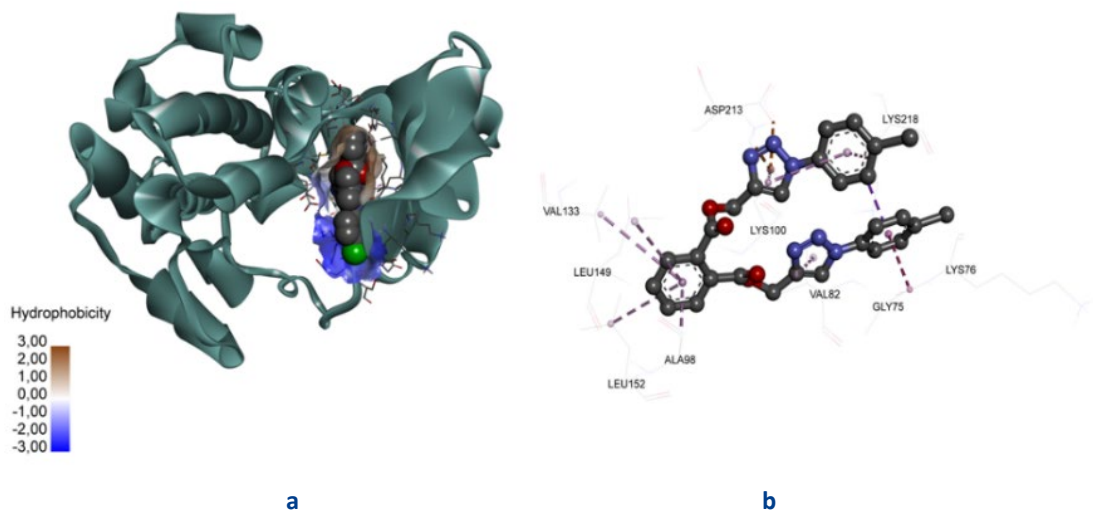


Figure 7. The best binding pose (a) and three-dimensional interactions (b) of 6 with p70S6K1.

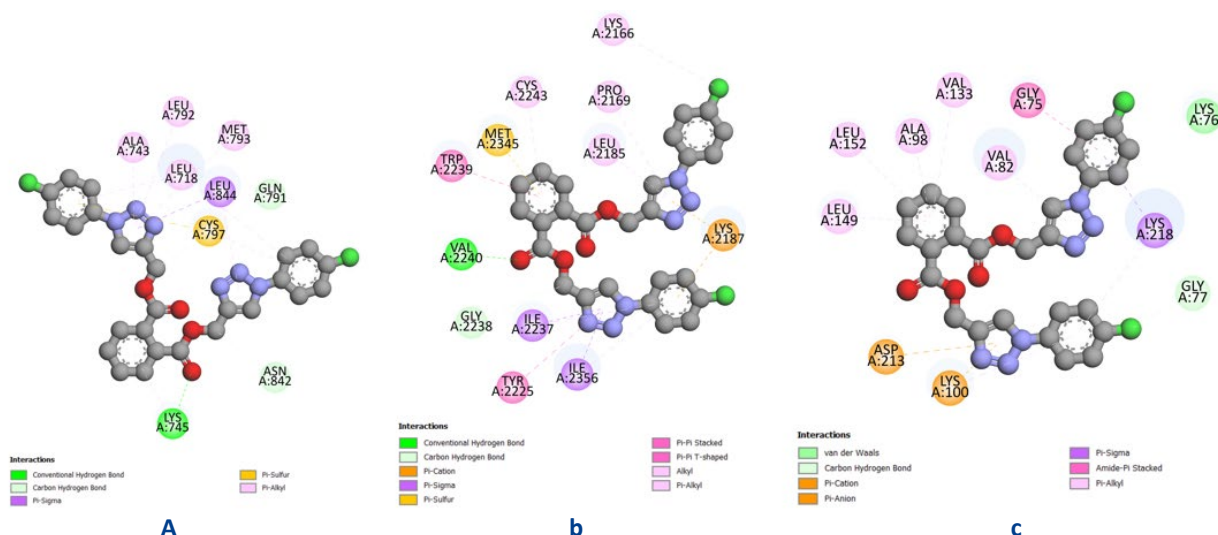


Figure 8. 2D interaction diagrams of 6 with EGFR (a), mTOR (b), and p70S6K1 (c).

Table 1. Some docking parameters of 6 and anastrozole with mTOR, p70S6K1, and EGFR.

Docking Parameters	mTOR		p70S6K1		EGFR	
	6	Anastrozole	6	Anastrozole	6	Anastrozole
EFEB (kcal/mol)	-10.38	-8.42	-9.93	-8.08	-10.02	-7.55
EIC, Ki (nM)	24.81	671.53	52.21	1190	45.28	2950
FIE (kcal/mol)	-13.36	-9.61	-12.92	-9.28	-13.00	-8.74
VHDE (kcal/mol)	-13.24	-9.53	-12.78	-9.23	-12.80	-8.69
EE (kcal/mol)	-0.12	-0.08	-0.14	-0.05	-0.20	-0.05
FTIE (kcal/mol)	-2.44	-1.21	-2.71	-1.23	-3.66	-1.24

*EFEB: Estimated Free Energy of Binding, EIC: Estimated Inhibition Constant, FIE: Final Intermolecular Energy, VHDE: VdW+Hbond+Desolv Energy, EE: Electrostatic Energy, FTIE: Final Total Internal Energy

Table 2. Interacting residues and types of 6 with mTOR, p70S6K1, and EGFR.

Receptor	Interacting residues (Distance, Å)	Interaction Types
EGFR	Ala743 (3.74 Å), Leu792 (4.97 Å), Met793(5.19 Å), Leu718 (5.37 Å and 4.37 Å), Leu844 (4.93 Å), Lys745 (4.08 Å)	π -alkyl
	Lys745 (3.00 Å)	Conventional hydrogen
	Asn842 (3.32 Å), Gln791(3.71 Å)	C-H
	Cys797(5.68 Å)	π -sulfur
	Leu844 (3.75 Å)	π -sigma
	Lys2187 (4.49 Å)	π -cation
	Met2345 (3.64 Å)	π -sulfur
	Trp2239 (4.23 Å and 5.22 Å)	π - π Stacked
	Tyr2225 (4.75 Å)	π - π T-shaped
	Ile2237 (3.61 Å), Ile2356 (3.61 Å)	π -sigma
mTOR	Pro2169 (5.46 Å), Leu2185 (5.16 Å), Cys2243 (4.85 Å), Ile2237 (3.11 Å), Ile2356 (5.04 Å), Lys2166 (4.61 Å)	π -alkyl
	Val2240 (1.89 Å)	alkyl
	Gly2238 (3.77 Å)	Conventional hydrogen
	Asp213 (4.30 Å)	C-H
	Lys100(2.25 Å)	π -anion
	Val133(5.09 Å), Ala98 (3.85 Å), Leu152(5.12 Å), Leu149(4.98 Å), Lys100 (5.36 Å), Lys218 (4.80 Å)	π -cation; π -donor
	Gly75 (4.64 Å)	π -alkyl
	Lys218 (3.43 Å)	Amide- π -Stacked
		π -sigma

In summary, first, a new bis-1,2,3-triazole compound (6) was synthesized via CuAAC in a good yield and characterized by ^1H , ^{13}C -NMR, and HR-(ESI)-MS spectroscopic methods. All analyses confirmed that compound 6 has a symmetric structure with two 1,4-disubstituted 1,2,3-triazole rings. Secondly, molecular

docking studies were carried out to examine the possible interactions of compound 6 with mTOR, p70S6K1, and EGFR enzymes, which are known to be important therapeutic targets in anticancer studies for the discovery and design of new anticancer agents, and the docking results were compared with anastrozole and co-

crystallized ligands, which are FMM for EGFR, P2X for mTOR, and 5FI for p70S6K1. According to these results, compound 6 has much better binding energy than anastrozole, P2X, and 5FI. The lower the binding energy, the better the possible interactions. Based on these results, compound 6 may effectively interact with and inhibit these receptors and may be tested as a potential inhibitor *in vitro* anticancer study.

Conflict of Interest

There are no conflicts of interest in this work.

Acknowledgments

The author is thankful to Mus Alparslan University.

Declaration of Generative AI

The author used Grammarly and ChatGPT for language editing during the preparation of this manuscript. Each AI-generated output was carefully reviewed and verified by the author to ensure scientific integrity and accuracy. Consequently, the author takes full responsibility for the final content and conclusions of the study.

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