

DESIGN AND REGIOSELECTIVE SYNTHESIS OF TRIAZOLE– COUMARIN–CHALCONE HYBRIDS: STRUCTURAL ELUCIDATION AND COMPUTATIONAL ANTICANCER EVALUATION

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A novel series of triazole–coumarin–chalcone hybrid molecules was synthesized via a copper-catalyzed click reaction between various benzyl azide derivatives and coumarin-based alkynes bearing a chalcone moiety. The required alkyne intermediates were prepared through a base-catalyzed O-alkylation of a pre-synthesized coumarin–chalcone precursor. This synthetic strategy enabled the efficient integration of three distinct pharmacophoric units into a single molecular framework. The structures of the resulting hybrids were comprehensively characterized using one- and two-dimensional NMR spectroscopy. In particular, HSQC and HMBC experiments allowed unambiguous assignment of key proton and carbon resonances and confirmed the regioselective formation of the 1,4-disubstituted triazole ring. These spectroscopic analyses enabled precise signal assignments and conclusively confirmed the regioselective formation of the 1,4-disubstituted triazole moiety. Moreover, the observed long-range correlations allowed clear discrimination between the desired hybrid structure and any possible alternative cycloaddition products. The consistency between synthetic outcomes and spectroscopic data validates the successful formation of the intended hybrid molecules. Molecular docking studies revealed specific and favorable binding interactions between the synthesized compounds and the active site of the target protein, providing valuable insight into the possible mode of action as a breast cancer inhibitor. Furthermore, an in-silico evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADMETox) properties indicated a promising pharmacokinetic and safety profile. These findings suggest that the synthesized hybrid molecules represent an attractive lead candidate for the development of novel anticancer therapeutics.

Keywords: triazole, coumarin, chalcone, 2D-NMR, anticancer

1. Introduction

Molecular hybridization (MH) is a well-established and widely applied strategy in contemporary drug design [1]. This approach is extensively employed by medicinal chemists to identify, optimize, and refine novel lead compounds with enhanced biological performance [2]. The fundamental principle of molecular hybridization lies in the rational combination of two or more distinct pharmacophoric units – each characterized by specific and complementary mechanisms of action – into a single molecular framework. By integrating these pharmacophores, it is often possible to achieve synergistic effects that surpass the activity of the parent compounds while simultaneously improving pharmacokinetic and pharmacodynamic properties [2].

In recent years, triazole derivatives have attracted considerable attention in medicinal chemistry due to their remarkable chemical stability and versatile biological activities [3]. Triazole-containing scaffolds are

frequently incorporated into hybrid molecules because of their favorable physicochemical characteristics, including high metabolic stability, strong hydrogen-bonding capability, and resistance to enzymatic degradation [4].

Numerous biologically active compounds, such as anticancer, antibacterial, antiviral, and antifungal agents, exploit triazole moieties as key structural elements [5]. The incorporation of triazole fragments into hybrid molecules has been shown to enhance cellular membrane penetration, reduce systemic toxicity, improve solubility, and prolong stability in biological environments [6]. These advantages make triazole derivatives particularly attractive for the rational design of multifunctional therapeutic agents as illustrated by the example provided in *Figure 1*.

In parallel, coumarin-based compounds have emerged as a highly promising class of bioactive molecules. Coumarins exhibit a wide range of pharmacological activities, including anticancer, anti-

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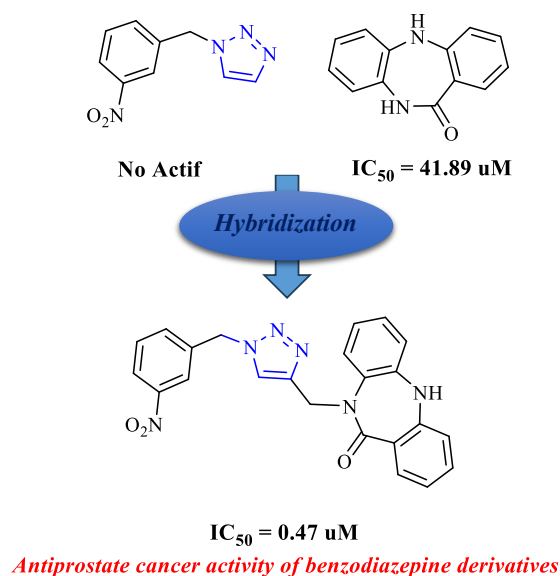


Figure 1: Effect of triazole hybridization [7]

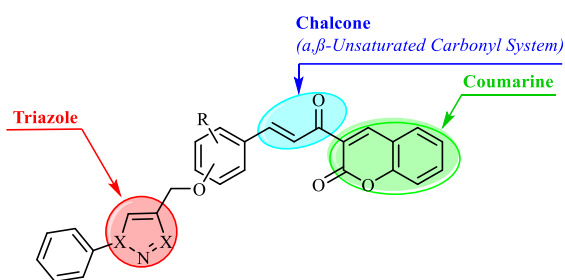


Figure 2: Coumarin–chalcone–triazole hybrid

inflammatory, antimicrobial, anticoagulant, and antioxidant effects [8]. Their structural diversity and favorable safety profile have contributed to growing interest in their application as lead compounds in drug discovery. As a result, coumarin derivatives have become central to numerous research efforts aimed at developing new therapeutic agents for disease prevention and treatment [9].

Considering these observations, and as part of our ongoing research program focused on the development and optimization of thiazole-related derivatives, we propose the rational design and synthesis of novel hybrid molecules combining coumarin and triazole pharmacophores [10],[11]. In addition, the incorporation of an enone moiety is expected to further enhance biological activity and modulate the physicochemical properties of the resulting hybrids. The enone functional group is known for its ability to participate in key molecular interactions, which may contribute to improved binding affinity and biological efficacy [12]. The proposed coumarin–chalcone–triazole hybrid structure is illustrated in Figure 2.

The present work adopts a step-by-step synthetic strategy to construct these coumarin–triazole–enone hybrids in a controlled and systematic manner. Through this rational hybridization approach, we aim to generate new molecular entities with improved activity profiles, enhanced stability, and optimized physicochemical characteristics, thereby contributing to the development of promising candidates for further pharmacological investigation.

2. Experimental

2.1. General remarks

Melting points were measured using a Kofler bench method. All reactions were monitored by TLC (E. Merck Kieselgel 60 F-254), with detection by UV light at 254 nm. ¹H and ¹³CNMR spectra were recorded on a Bruker AC 400 MHz FTNMR spectrometer using DMSO-d₆ as the solvent. Chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane TMS (δ = 0 ppm) used as an internal reference and coupling constants (J) were given in Hz. The following multiplicity abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All chemicals and solvents were purchased from commercial sources and used as received [13].

2.2. General procedure for the synthesis of 3-acetyl-2H-chromen-2-one (3)

A mixture of salicylaldehyde **1** (7.24 mmol) and ethyl acetoacetate **2** (8.64 mmol) was placed in a round-bottom flask, followed by the addition of five drops of piperidine as a base catalyst. The reaction mixture was stirred at room temperature for 15 min, leading to the formation of a yellow precipitate. The crude solid was collected and purified by recrystallization from ethanol to give 3-acetyl-2H-chromen-2-one **3** in excellent yield. Light-yellow solid. Yield: 94%. Melting point: 121–124 °C [14].

2.3. General procedure for the synthesis of (E)-3-(3-(4-hydroxyphenyl)acryloyl)-2H-chromen-2-one derivatives (5a-c)

An ice-cooled solution of 3-acetyl-2H-chromen-2-one **3** (1 mmol) and the appropriate aldehyde **4a-c** (1.2 mmol) in ethanol (15 mL) was prepared. A pre-cooled 50% aqueous sodium hydroxide solution (2 mL) was added dropwise with continuous stirring. The reaction mixture was maintained at 0 °C for 1 h and subsequently stirred at room temperature for 24 h. After completion, the reaction mixture was poured into ice-water and neutralized with acetic acid. The resulting solid was filtered, washed several times with cold water, dried, and recrystallized from acetone to afford the desired products (**5a-c**).

2.4. General procedure for the synthesis of O-propargylated coumarin-chalcone derivatives (**7a-c**)

A mixture of hydroxy-coumarin-chalcone derivatives (**5a-c**) (1 mmol), propargyl bromide **6** (1.2 mmol) and K_2CO_3 (2 mmol) in acetone (15 mL) was stirred at reflux for 3 h. Water (15 mL) was added and the mixture was extracted with dichloromethane (3 x 15 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated. The final residue was recrystallized from ethanol to afford the desired compounds **7a-c**.

2.5. General procedure for the synthesis of 1,2,3-triazole derivatives via 1,3-dipolar cycloaddition (**10a-e**)

Benzyl azide derivatives **9a,b** (1 mmol) and coumarin-chalcone-derived alkynes **7a-c** (1 mmol) were dissolved in a biphasic mixture of CH_2Cl_2/H_2O (10 mL, 1:1) in a 50 mL round-bottom flask. Copper (II) sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$, 0.1 mmol) and sodium ascorbate (0.2 mmol) were then added to the reaction mixture. The reaction was stirred at room temperature for 12 h and monitored by thin-layer chromatography (TLC). Upon completion, the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was recrystallized from ethanol to afford the corresponding pure triazole derivatives **10a-e**.

(E)-3-(3-(4-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)acryloyl)-2H-chromen-2-one

(**10b**): Yellow solid (41%); mp 188-190 °C; 1H NMR (400 MHz, DMSO) δ 8.61 (s, 1H, H-4), 8.31 (s, 1H, H-5'''), 7.93 (d, J = 7.8, 1.5 Hz, 1H, H-2'), 7.79 – 7.66 (m, 2H), 7.63 – 7.46 (m, 3H), 7.44 (td, J = 7.6, 1.2 Hz, 1H), 7.42 – 7.28 (m, 6H), 7.18 (s, 1H), 7.05 (d, J = 8.4, 1.2 Hz, 1H, H-2''), 5.62 (s, 2H, H-6'''), 5.19 (s, 2H, H-6''), 3.79 (s, 3H, H-5'''). ^{13}C NMR (101 MHz, DMSO) δ 188.05, 158.82, 154.77, 152.19, 147.97, 146.58, 145.46, 143.18, 136.47, 134.43, 130.71, 129.23, 128.62, 128.42, 127.59, 126.50, 125.40, 124.32, 123.23, 118.87, 116.67, 113.45, 112.46, 62.15, 56.49, 56.07, 53.29, 19.04.

2.6. Molecular docking

Molecular docking was employed to predict the binding orientation and interactions of the synthesized compounds within the active site of epidermal growth factor receptor (EGFR). The crystal structure of wild-type EGFR co-crystallized with AZD9291 (PDB ID: 4ZAU) was retrieved from the RCSB Protein Data Bank. All docking simulations were carried out using AutoDock Vina version 1.1.2 following a standardized workflow.

2.6.1. Receptor preparation

The protein structure was prepared prior to docking by removing all crystallographic water molecules and non-essential heteroatoms, while biologically relevant cofactors were retained. Polar hydrogen atoms were added, and Gasteiger partial charges were assigned. The prepared receptor was subsequently saved in PDBQT format.

2.6.2. Ligand preparation

Ligand structures were constructed and converted into three-dimensional conformations. All rotatable bonds were defined to allow conformational flexibility. Gasteiger charges were assigned, and the ligands were saved in PDBQT format for docking.

2.6.3. Docking protocol

Docking calculations were performed using a grid box centered at x = 15.390, y = 20.300, and z = 12.455 Å, with grid box dimensions of 33.412 x 26.567 x 20.403 Å³. The exhaustiveness parameter was set to 8, and nine binding poses were generated for each ligand. All other parameters were kept at their default values.

2.6.4. Docking validation

To validate the docking protocol, the co-crystallized ligand AZD9291 (Osimertinib) was re-docked into the EGFR binding site using the same docking parameters applied to the test compounds. The resulting docked pose was superimposed on the experimental crystal structure, and the root mean square deviation (RMSD) was calculated. The low RMSD value obtained (0.0 Å) demonstrates good agreement between the predicted and experimental binding modes, confirming the reliability of the docking procedure. Protein-ligand interactions were visualized and analyzed using BIOVIA Discovery Studio Visualizer [15].

2.7. ADMET and drug-likeness prediction

The physicochemical and biological properties of small molecules play a crucial role in determining their drug-like behavior and therapeutic potential. In this study, the SwissADME and ADMETlab 3.0 web platforms were employed in combination with Lipinski's rule of five to evaluate molecular suitability, predict oral pharmacokinetics, and assess ADMET parameters, including absorption, distribution, metabolism, excretion, and toxicity. Compounds with favorable oral absorption generally exhibit a molecular weight below 500 g/mol, a logP value not exceeding five, no more than five hydrogen-bond donors, ten or fewer hydrogen-bond acceptors, and a topological polar surface area (TPSA) of up to 140 Å². Molecules that satisfy these criteria are commonly regarded as orally bioavailable drug candidates [16].

3. Results and analysis

3.1. Experiments

Our synthetic strategy begins with the preparation of the key O-propargyl-substituted coumarin–chalcone intermediates **5a–c**, obtained through a three-step reaction sequence. First, the condensation of salicylaldehyde **1** with ketoester **2** affords 2-acetylcoumarin **3** in excellent yield (94%). The coumarin–chalcone derivatives **5a–c** were then synthesized via a base-catalyzed (NaOH) aldol condensation between 2-acetylcoumarin **3** and a series of hydroxyaromatic aldehydes at room temperature.

In the final step, O-alkylation of the coumarin–chalcones with propargyl bromide produced the O-propargylated compounds **7a–c** in excellent yields.

Assembly of the target hybrid structures was achieved through a Cu-catalyzed azide–alkyne cycloaddition ("click chemistry"), the key step enabling formation of the 1,2,3-triazole–coumarin–chalcone framework. Accordingly, the reaction of the propargyl derivatives with benzyl azide was carried out in a dichloromethane/water (1:1) solvent system, using $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and sodium ascorbate as catalysts at room temperature. This procedure delivered a diverse set of 1,2,3-triazole–coumarin–chalcone hybrids in good to excellent yields. The complete synthetic routes for preparing the chalcone–azole–coumarin hybrids are illustrated in *Figure 3*.

The interpretation of both ^1H and ^{13}C NMR spectra provides strong evidence that the reaction yields the 1,4-disubstituted 1,2,3-triazole with high regioselectivity. In the Cu(I)-catalyzed click reaction

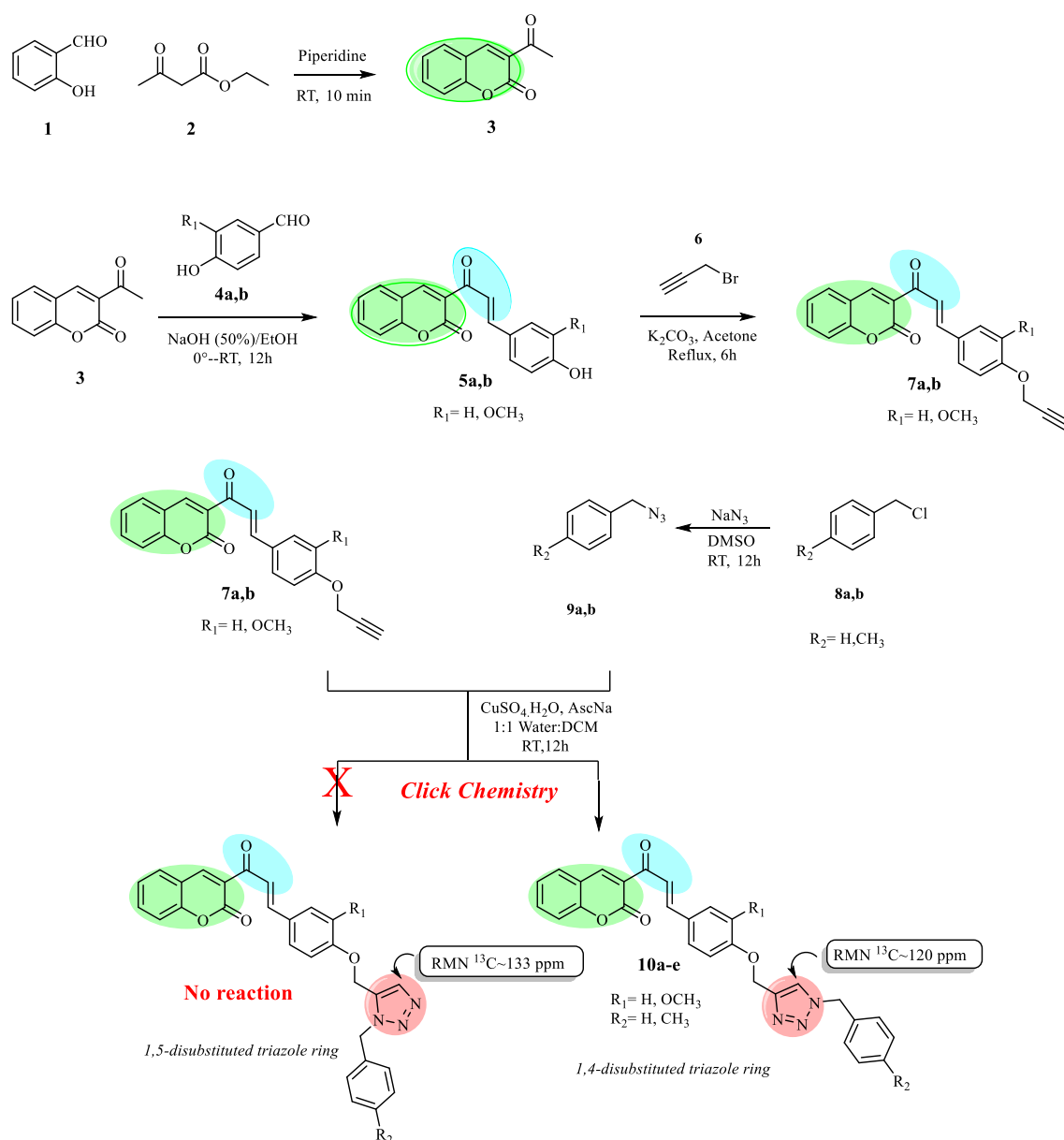


Figure 3: Synthetic route for the preparation of coumarine-chalcone-triazole hybrids **10a–e**

between the terminal alkyne and the aromatic azide, formation of either the 1,4- or the 1,5-disubstituted triazole is theoretically possible. The ^{13}C NMR signals, however, clearly indicates the exclusive formation of the 1,4-regioisomer. The triazole carbon resonating near 120 ppm corresponds to C-4 of a 1,4-substituted triazole, a value widely documented in previous studies [17]. In contrast, a signal around 133 ppm – expected for the 1,5-isomer – is absent, confirming the complete absence of this alternative product.

^1H NMR data further strengthen this assignment. The distinctive chemical shift of the triazole proton, combined with the absence of resonances characteristic of the 1,5-isomer, supports selective cycloaddition at the 1,4-positions. These spectroscopic observations are consistent with the known mechanistic pathway of copper-catalyzed azide-alkyne cycloaddition, which favors formation of the 1,4-disubstituted heterocycle through a copper-acetylide intermediate [18]. Altogether, the NMR evidence demonstrates that the reaction proceeds with excellent regioselectivity toward the 1,4-disubstituted triazole structure.

The newly synthesized triazole-linked coumarin hybrids (**10a-e**) are presented in Table 1.

Table 1: Structures of synthesized molecules

	Compound	Yield (%)
10a		45
10b		41
10c		20
10d		32
10e		27

1D and 2D NMR analysis are used to unequivocally establish the exact structure of the triazole-coumarin-chalcone hybrid compound. Taking as a representative example, compound **10b** (Figure 4), where it was apparently possible to distinguish between the two methylene groups $6''\text{-CH}_2$ and $6'''\text{-CH}_2$ appearing as singlets at δ_{H} 5.19 and 5.62 ppm, respectively.

The $6''\text{-CH}_2$ represents the linking bridge between the triazole and coumarin heterocycles. These protons showed important HMBC cross-peak correlations with the surrounding carbons. Therefore, $6''\text{-CH}_2$ could be assigned through $3J_{\text{H/C}}$ HMBC correlations with C-5''' (δ_{C} 125.4 ppm) and C-4''' (δ_{C} 148.1 ppm) as well as a $2J_{\text{H/C}}$ HMBC correlation with C-4''' (δ_{C} 143.2 ppm). However, the $6'''\text{-CH}_2$ showed interesting $3J_{\text{H/C}}$ HMBC correlation with the protonated triazole carbon C-5''' (δ_{C} 125.4 ppm) and the phenyl protons C-2''' (δ_{C} 128.4 ppm) and C-1''' (δ_{C} 136.5 ppm). The main HMBC correlations supporting these assignments are presented in Figure 5.

Furthermore, the chalcone moiety can also be observed through the presence of signals corresponding to the protons of the ketone α,β -unsaturated system, represented by two doublets at δ_{H} 7.05 and 7.93 ppm, respectively, with a coupling constant of $J=16$ Hz, evidencing the (E)-configuration. The neighboring carbon resonances of H-2' and H-3' were assigned from

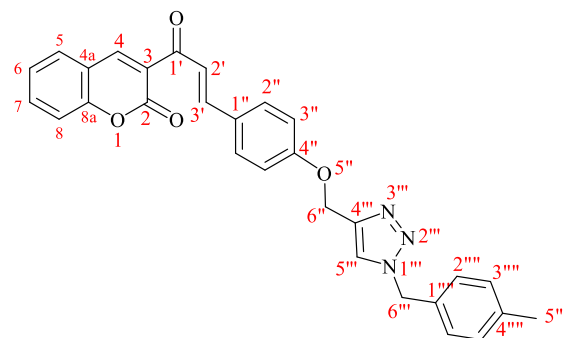


Figure 4: Compound **10b**

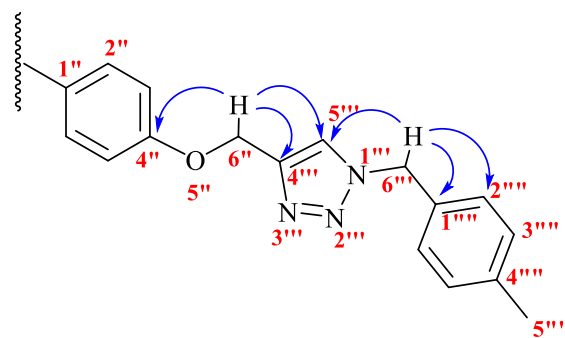


Figure 5: HMBC correlation of $6''\text{-CH}_2$ and $6'''\text{-CH}_2$

the main HMBC correlations as shown in [Figure 6](#). H-2' correlates through $3J_{H/C}$ HMBC with two quaternary carbons, C-3 (126.52 ppm) and C-1'' (127.99 ppm) and through $2J_{H/C}$ HMBC correlations with C-1' (188.14 ppm) and C-3' (113.45 ppm). Meanwhile, the H-3' proton shows clear connections with C-2'' (146.58 ppm) and C-1' (188.14 ppm) through $3J_{H/C}$ HMBC, and with C-2' (145.46 ppm), C-1'' (127.99 ppm) through $2J_{H/C}$ HMBC correlations.

The coumarin vinyl carbon is located in the ^{13}C NMR spectrum at $\delta_{\text{C}} = 146.7$ ppm, which was confirmed through HMBC correlations. This proton further shows important $3J_{H/C}$ HMBC connectivities with the carbonyl groups C-1' (δ_{C} 188.14 ppm) and C-2 (δ_{C} 158.82 ppm) and the C-5 (δ_{C} 130.71 ppm) and C-8a (δ_{C} 154.77 ppm) of the connected phenyl group. The $2J_{H/C}$ HMBC correlations of the same proton show important connections with C-4a (δ_{C} 118.87 ppm) and C-3 (δ_{C} 126.52 ppm) as presented in [Figure 7](#).

3.2. Simulations

3.2.1. Molecular docking study

Molecular docking of ligands 10a–e was performed within the ATP-binding site of wild-type EGFR (PDB ID: 4ZAU) to elucidate their binding modes and key stabilizing interactions. All ligands adopted comparable orientations within the active pocket and exhibited favorable binding affinities ranging from -7.7 to -8.7 kcal/mol. The complete docking results, including 3D and 2D interaction views, are summarized in [Table 2](#).

Ligands 10a and 10b formed a classical hinge hydrogen bond with Met793, confirming an ATP-competitive binding mode. Among them, ligand 10b additionally interacted with Asp800 through hydrogen bonding, which may contribute to enhanced complex stability. Ligand 10e displayed the highest binding affinity (-8.7 kcal/mol), supported by a hydrogen bond with Gln791 and a carbon hydrogen bond involving Met793. Furthermore, multiple π - π stacking interactions and hydrophobic π -alkyl contacts with Val726, Ala743, and Lys745 significantly contributed to binding stabilization, indicating efficient pocket occupancy and optimal aromatic alignment.

Ligand 10c showed moderate binding affinity (-8.1 kcal/mol), characterized by hydrogen bonding with Leu718, extensive aromatic π - π stacking, and π -sulfur interactions with Cys797. In contrast, ligand 10d exhibited the weakest affinity (-7.7 kcal/mol), forming predominantly hydrophobic interactions and lacking both hinge hydrogen bonding and aromatic stacking interactions.

To validate the docking protocol, the co-crystallized ligand of EGFR was redocked into the active site. The top-ranked pose reproduced the experimental binding conformation with an RMSD of $0.0 \text{ \AA}$ and a binding affinity of -8.2 kcal/mol. Visual superposition revealed excellent overlap between the redocked and crystallographic poses, particularly within the hinge region and ATP-binding pocket, confirming the reliability and accuracy of the applied docking protocol.

The superposition of the co-crystallized and redocked ligand is shown in [Figure 8](#).

Overall, ligands combining hinge hydrogen bonding with aromatic and sulfur-mediated interactions demonstrated superior binding performance within the EGFR active site.

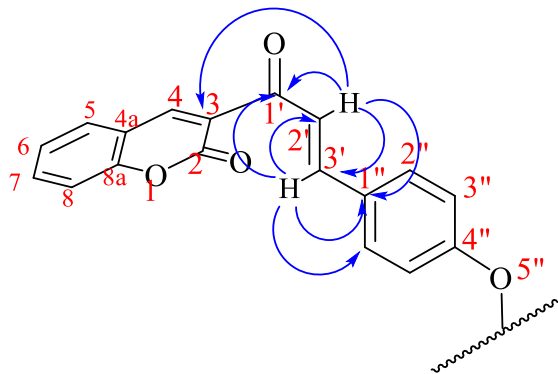


Figure 6: HMBC correlation of 2'-CH and 3'-CH

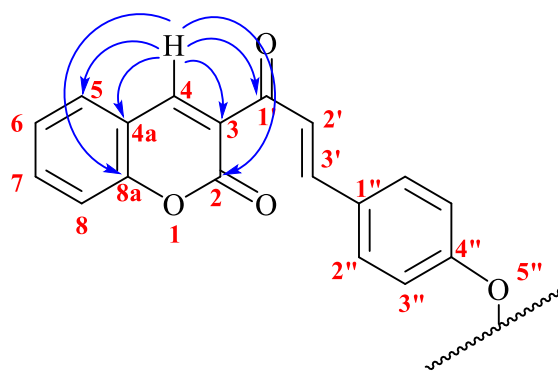


Figure 7: HMBC correlation of 4-CH₂

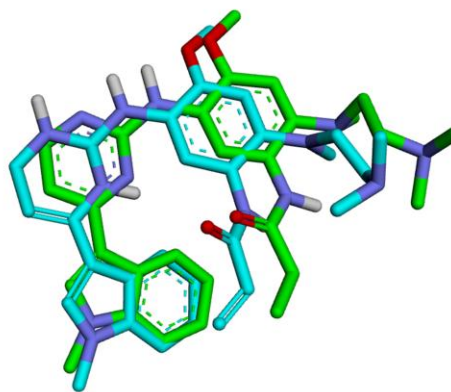


Figure 8: Superposition of the co-crystallized and the redocked ligand (blue: re-docked ligand; green: co-crystallized ligand)

Table 2: Molecular docking results: 3D view of binding site interactions and 2D view of the binding conformation

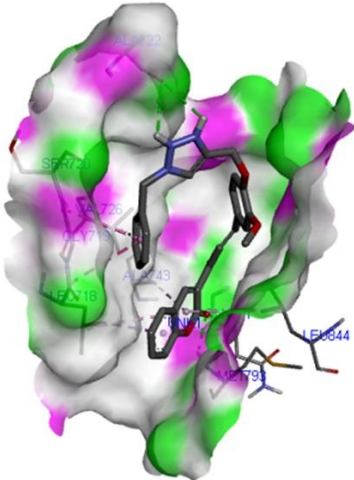
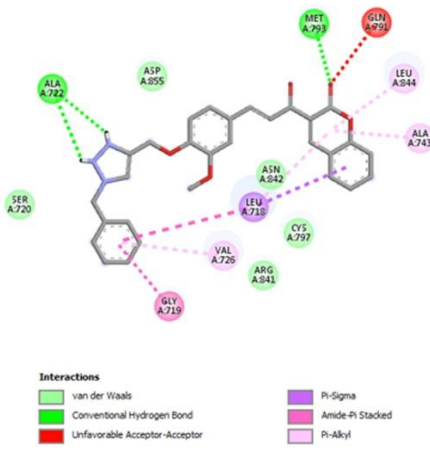
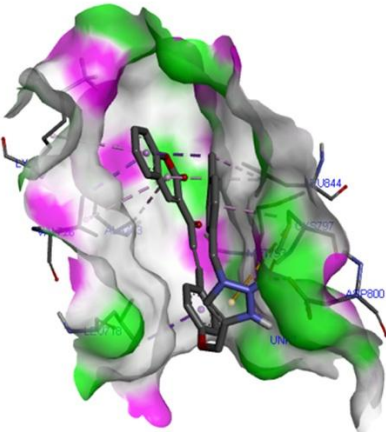
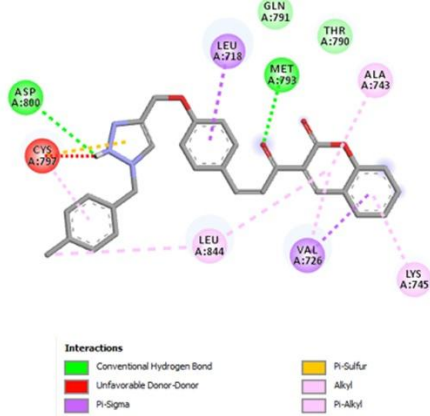
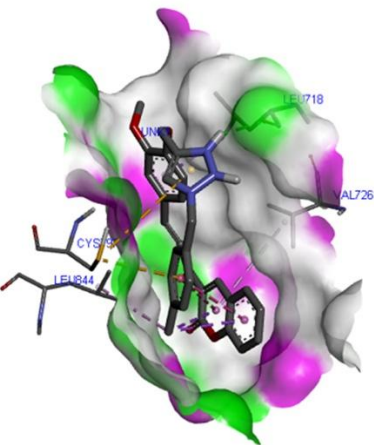
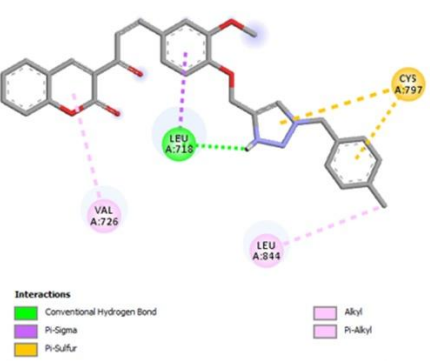
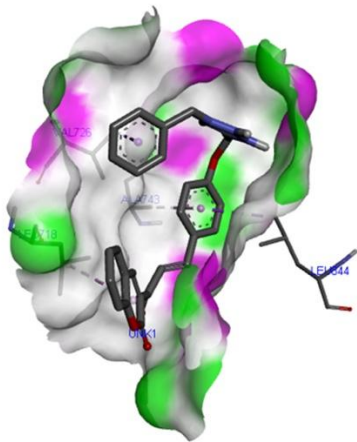
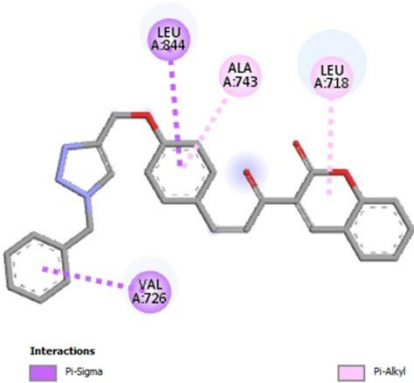
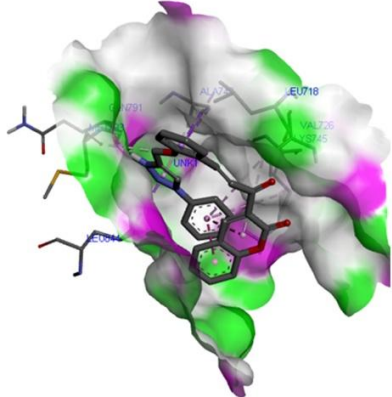
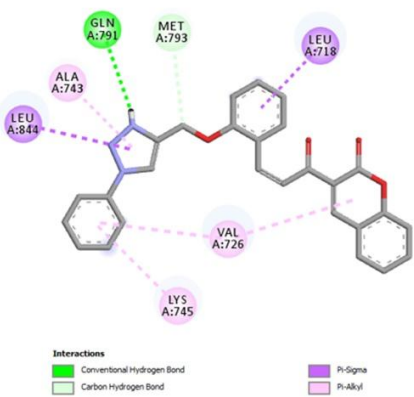
Ligand	3D-interactions	2D-interactions	Binding energy (kcal/mol)
10a			-8.5
10b			-8.5
10c			-8.1

Table 2 (continued): Molecular docking results: 3D view of binding site interactions and 2D view of the binding conformation

Ligand	3D-interactions	2D-interactions	Binding energy (kcal/mol)
10d			-7.7
10e			-8.7

3.2.2. ADMET analysis

In silico ADMET evaluation of the designed triazole–coumarin–chalcone derivatives (10a–e) indicated a generally favorable pharmacokinetic profile (Table 3). All compounds were predicted to exhibit high gastrointestinal absorption, which is supported by their moderate topological polar surface area (TPSA) values ranging from 87.22 to 96.45 Å², together with suitable lipophilicity and hydrogen-bonding characteristics that favor passive intestinal diffusion.

Regarding distribution, none of the compounds were predicted to cross the blood–brain barrier, which is consistent with their TPSA values exceeding the commonly accepted threshold (~70 Å²) for BBB penetration. This profile suggests a potential safety advantage for non-CNS therapeutic applications. In addition, all molecules were predicted to be non-substrates of P-glycoprotein, indicating limited

susceptibility to efflux mechanisms and potentially improved cellular retention.

Metabolic liability was observed across the series, as all compounds were predicted to inhibit CYP2C9 and CYP2C19, indicating a moderate risk of drug–drug interactions. Compound 10a was additionally predicted to inhibit CYP3A4, suggesting a higher interaction potential relative to the remaining analogues. No inhibition of CYP1A2 or CYP2D6 was predicted for any compound.

From a safety perspective, the absence of PAINS alerts supports the reliability of the predicted bioactivity. Overall, compounds 10d and 10e, which combine favorable TPSA values, high GI absorption, lack of BBB penetration, and a reduced CYP inhibition profile, displayed the most balanced ADMET characteristics and appear to be suitable candidates for further optimization.

Table 3: ADMET prediction of newly designed compounds

Molecule	TPSA (Å ²)	Absorption		Distribution		Metabolism	Toxicity	
		HIA	C2P	BBB	P-GpI	CYP2C9	hERG	AOT
10a	96.45	● +(High)	● +(High)	● -(No)	● NI	● I	● NA	● III
10b	87.22	● +(High)	● +(High)	● -(No)	● NI	● I	● NA	● III
10c	87.22	● +(High)	● +(High)	● -(No)	● NI	● I	● NA	● III
10d	87.22	● +(High)	● +(High)	● -(No)	● NI	● I	● NA	● III
10e	87.22	● +(High)	● +(High)	● -(No)	● NI	● I	● NA	● III

TPSA= Topological Polar Surface Area, HIA = Human intestinal absorption, C2P = CACO-2 permeability, BBB = Blood brain barrier, P-GpI = P-glycoprotein inhibitor, CYP450 2C9 = Cytochrome P450 2C9, hERG = human Ether-a-go-go Related Gene, AOT = Acute oral toxicity, I = inhibitor, NI = non-inhibitor

3.2.3. Lipinski's rule of five evaluation

Lipinski's rule of five was applied to evaluate the oral drug-likeness of the designed triazole–coumarin–chalcone derivatives (**10a–e**). The assessment considered molecular weight (MW < 500), lipophilicity (LogP < 5), hydrogen bond acceptors (HBA ≤ 10), hydrogen bond donors (HBD ≤ 5), and rotatable bonds (RB ≤ 10). The corresponding Lipinski parameters and validation are presented in Table 4.

Lipinski's rule of five analysis indicates that the majority of the designed compounds possess favorable physicochemical properties for oral administration. Four out of five molecules (Molecules **10a**, **10b**, **10d**, and **10e**) fully comply with all Lipinski criteria, suggesting good potential for oral bioavailability. Their molecular weights remain below the 500 g/mol threshold, their lipophilicity values are within the acceptable range, and their

hydrogen bonding capacity is well balanced, with no hydrogen bond donors and a moderate number of acceptors.

Molecule **10c** shows a single Lipinski violation due to a molecular weight slightly above 500 g/mol. However, this marginal violation does not necessarily exclude oral activity, as several approved drugs exceed this limit [19]. Importantly, Molecule **10c** still maintains acceptable lipophilicity and hydrogen bonding properties.

Overall, the Lipinski evaluation supports the drug-likeness of this compound series, particularly for oral delivery. These results indicate that the compounds are suitable candidates for further optimization, although additional improvements in solubility and metabolic liability may be required during lead optimization.

Table 4: Lipinski validation of the newly designed drug-candidates

Compounds	Molecular weight (g/mol)	Log P	H-bond acceptors	H-bond donors	Rotatable bonds	Lipinski rule validation
Rule	< 500	< 5	≤ 10	≤ 5	≤ 10	
10a	493.51	4.33	7	0	9	Accepted
10b	477.51	4.57	6	0	8	Accepted
10c	507.54	4.61	7	0	9	Accepted*
10d	463.48	4.34	6	0	8	Accepted
10e	449.46	4.16	6	0	7	Accepted

*: **10c** slightly exceeds the molecular weight threshold (500 g·mol⁻¹) but remains acceptable due to compliance with other Lipinski parameters

4. Conclusion

In this work, a new series of triazole–coumarin–chalcone hybrid molecules were rationally designed and synthesized using a copper-catalyzed azide–alkyne cycloaddition strategy. The synthetic route enabled the efficient integration of three pharmacologically relevant scaffolds into a single framework. Structural elucidation by comprehensive 1D and 2D NMR analyses, including HSQC and HMBC experiments, confirmed the regioselective formation of the 1,4-disubstituted triazole ring and validated the proposed molecular structures. Molecular docking studies demonstrated favorable binding affinities and key stabilizing interactions between the synthesized hybrids and the active site of a breast cancer–related target protein, supporting a plausible inhibitory mechanism. Furthermore, *in silico* ADMET and drug-likeness assessments revealed acceptable physicochemical properties, promising oral bioavailability, and low predicted toxicity. Overall, these integrated findings highlight triazole–coumarin–chalcone hybrids as promising lead candidates and provide a solid foundation for further optimization and biological evaluation in anticancer drug discovery.

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