



J. Serb. Chem. Soc. 91 (9) 843–857 (2026)
JSCS–5530

Design of novel quinazoline–chalcone hybrids as potent epidermal growth factor receptor inhibitors

YINGNUO WANG¹, JURANG LI¹, CHUNMENG LI¹, YANG LIU¹, ZHIQIANG CAI^{1*}
and SHUAI LI^{2**}

¹Liaoning Province Professional and Technical Innovation Center for Fine Chemical Engineering of Aromatics Downstream, School of Petrochemical Engineering, Shenyang University of Technology, Liaoning, Liaoyang 111003, P. R. China and ²Shandong Engineering Research Center of Pharmaceutical Green Intelligent Technology, Shandong Academy of Pharmaceutical Sciences, Shandong, Jinan 250101, P. R. China

(Received 13 October 2025, revised 4 June, accepted 13 August 2026)

Abstract: This study successfully designed and synthesized a novel series of quinazoline–chalcone hybrids. The key innovation lies in the molecular hybridization of the pharmacophoric quinazoline scaffold with a chalcone moiety, creating new chemical entities to exploit potential synergistic antitumor effects. A concise multi-step synthetic route was efficiently implemented. Preliminary evaluation demonstrated that a majority of these hybrids exhibited potent anti-proliferative activity against non-small cell lung cancer (NSCLC) cell lines (A549 and H1975) *in vitro*. Molecular docking studies suggested against epidermal growth factor receptor (EGFR) inhibition as a potential mechanism, with the compounds forming stable interactions with the kinase domain. Furthermore, *in silico* absorption, distribution, metabolism and excretion (ADME) and toxicity predictions by SwissADME and ProTox 3.0, respectively, indicated promising drug-like properties and safety profiles. However, the cytotoxicity was assessed only on cancer cell lines, and the selectivity against normal cells remains to be determined. Despite this limitation, the compelling initial results position these novel hybrids as promising leads for future optimization and development.

Keywords: synthesis; EGFR inhibition; molecular docking; antitumor activity; ADME prediction; structure–activity relationship.

INTRODUCTION

Targeted therapies achieve precision treatment by specifically inhibiting key signaling pathways in cancer cells.^{1–5} The 4-aminoquinazoline scaffold serves as a privileged pharmacophore that forms the structural basis of multiple clinically approved EGFR tyrosine kinase inhibitors (EGFR-TKIs),^{6–9} such as zorifertinib.¹⁰

*,** Corresponding authors. E-mail: (*)kahongzqc@163.com; (**)627174596@qq.com
<https://doi.org/10.2298/JSC251013048W>



Its high structural versatility enables rational optimization of inhibitory activity against specific mutations. Meanwhile, natural chalcone derivatives exhibit broad-spectrum antitumor effects through their unsaturated ketone moiety,^{11–14} which modulates diverse oncogenic processes via multiple mechanisms. The present study innovatively integrates the quinazoline core with chalcone structures using flexible linkers.^{15–17} It preserves the critical hydrogen-bonding network between the quinazoline scaffold and EGFR's adenosine triphosphate (ATP)-binding pocket while leveraging chalcone's covalent binding capability to enhance target engagement.¹⁸ The systematic molecular optimization through bioisosteric replacement and pharmacophore refinement generated novel small-molecule inhibitors with improved selectivity and pharmacokinetic profiles.^{19–21}

The molecular design strategy is illustrated in Fig. 1. The third-generation EGFR inhibitor zorifertinib demonstrates a characteristic binding mode wherein the N3 nitrogen atom of the quinazoline core establishes a hydrogen-bonding interaction with the catalytic residue ASP-855 of the target protein. The molecular scaffold occupies the ATP-binding pocket delineated by ARG748, GLY857, ASP855, LYS875 and GLY874 residues, with 6- and 7-position substituents projecting into the solvent-accessible region. This binding conformation exemplifies the conserved structural motif of quinazoline-derived EGFR inhibitors. Accordingly, a rational design strategy was implemented by introducing flexible linkers containing chalcone structures at the 6-position. The unsaturated ketone moiety serves as a Michael acceptor to form selective covalent bonds with target protein residues while the aromatic system enhances binding affinity through hydrophobic inter-

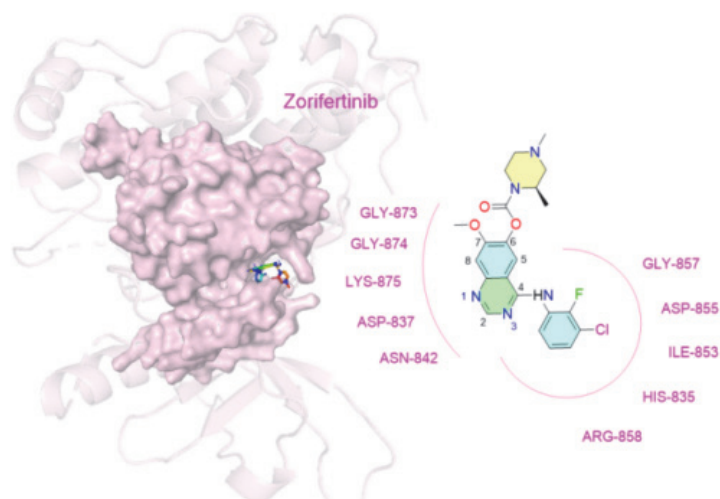


Fig. 1. Zorifertinib molecular docking interaction diagram.

actions.^{22–26} Additionally, the methoxy group at this position is retained to synergistically improve antitumor activity and mutation selectivity.²⁷ Based on the structure–activity relationship analysis, the present study adopted highly selective pharmacophores as the molecular design framework and innovatively constructed a hybrid quinazoline-chalcone molecular system. By integrating the protein-binding patterns and structure–activity relationship data of zorifertinib, this study precisely preserved the quinazoline core structure of EGFR inhibitors using the bioisosterism principle,^{28,29} while systematically optimizing the pharmacokinetic properties of candidate compounds through pharmacophore refinement and isosteric replacement strategies. Through rational design, a series of novel small-molecule EGFR inhibitors, featuring combined quinazoline and chalcone structural motifs, were successfully developed.

Based on the aforementioned research background, the present study synthesized and characterized a series of novel quinazoline–chalcone hybrids using IR, ¹H-NMR, ¹³C-NMR and mass spectrometry. Their antitumor activities were evaluated against A549 and H1975 cell lines. In addition, *in silico* ADME prediction, toxicity prediction, and molecular docking with the EGFR kinase domain (PDB ID:7OXB) were performed to assess drug-like properties and explore the binding mode of representative compound **9h**, providing mechanistic insights into its action.

EXPERIMENTAL

Chemistry

General. All reagents and solvents were commercially available and used as received unless otherwise specified. Reaction progress was monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates (Qingdao Haiyang Chemical Co., Ltd.).

Instrumentation and Characterization. Melting points were determined on an X-4 micro-melting point apparatus and are uncorrected. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker ARX-400 spectrometer (400 MHz for ¹H-NMR, 101 MHz for ¹³C-NMR) in the indicated deuterated solvents (CDCl₃ or DMSO-*d*₆) using tetramethylsilane (TMS) as an internal standard; chemical shifts are reported in ppm and coupling constants (*J*) are given in Hz. FT-IR spectra were acquired on a Bruker Tensor II spectrometer using KBr pellets and wavenumbers are reported in cm^{–1}. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a Finnigan Trace MS spectrometer. Samples were dissolved in a mixed solvent of methanol and acetonitrile and introduced *via* direct infusion in positive ion mode. All observed *m/z* values corresponded to the expected [M]⁺ or [M+H]⁺ of the target compounds.

General procedure for the synthesis of intermediates **2**

At room temperature, the mixed solution of 7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate **1** (1.20 g, 5.12 mmol), toluene (15 mL) and triethylamine (0.88 g, 8.71 mmol) were heated to 80 °C. Then, phosphorus oxychloride (1.96 g, 12.81 mmol) was added to the mixture. After completion, the reaction proceeds directly to the next step.

*General procedure for the synthesis of intermediates 3a–h*³⁰

Substituted aniline (0.48 g, 4.35 mmol) was added to intermediate **2**, and the mixture was stirred for 5 h. After completion, the solvent was concentrated under vacuum and mixed with isopropanol (15 mL) for 12 h. The product was filtered to afford intermediate **3**.

*General procedure for the synthesis of intermediates 4a–h*³⁰

Intermediate **3** (1.00 g, 3.06 mmol), methanol (15 mL) and ammonia solution (1 mL) were stirred at room temperature. After completion, the solvent was concentrated under vacuum, followed by addition of water (8 mL). It was filtered to afford intermediate **4**.

General procedure for the synthesis of intermediates 7a–c

Referred to reference,³¹ taking (2*E*)-1-(4-aminophenyl)-3-(3-methylphenyl)prop-2-en-1-one (**6a**) as an example: 4-aminoacetophenone (1.00 g, 3.70 mmol), 3-methylbenzaldehyde (0.88 g, 3.70 mmol) and ethanol (15 mL) were added sequentially; the reaction vessel was transferred to a cooling bath maintained at 5 °C. Add a 20 % aqueous sodium hydroxide (0.29 g, 7.40 mmol) solution dropwise over 0.25 h. After completion, the solvent was concentrated under vacuum to afford intermediates **7a**. The reaction proceeds directly to the next step.

*General procedure for the synthesis of intermediates 8a–c*³²

Taking *N*-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide (**7a**) as an example: intermediate **7a** (1.00 g, 4.21 mmol), dichloromethane (15 mL), chloroacetyl chloride (1.43 g, 12.64 mmol) and triethylamine (0.51 g, 5.06 mmol) were stirred at 0 °C under nitrogen in a cooling bath. After completion, the mixture was warmed to 25 °C and stirred for 6 h. The solvent was concentrated under vacuum to afford intermediate **8a**.

General procedure for the synthesis of compounds 9a–k

Taking *N*-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[[7-methoxy-4-(phenylamino)quinazolin-6-yl]oxy]acetamide (**9a**) as an example: a mixture of intermediate **4a** (0.50 g, 1.69 mmol), intermediate **8a** (0.58 g, 1.86 mmol), potassium carbonate (0.47 g, 3.39 mmol) and *N,N*-dimethylformamide (10 mL) was heated to 80 °C. After completion, water (20 mL) was added to the mixture, followed by filtration. The filter cake was collected and dried at 50 °C, then purified by column chromatography to afford the final product.

Pharmacological experiments of target compounds

Cell culture. The human NSCLC cell lines A549 and H1975 were obtained from the Shanghai Institute of Life Sciences, Chinese Academy of Sciences. Cells were cultured in RPMI 1640 medium (Invitrogen) supplemented with 10 % fetal bovine serum (FBS, Invitrogen) in a humidified incubator at 37 °C under an atmosphere of 5 % CO₂. The cells were passaged using 0.25 % trypsin (Amresco) upon reaching approximately 90 % confluence.

Cell viability assay (CCK-8). The antiproliferative activity of the synthesized compounds was assessed using the CCK-8 (Wuhan Heyan Biotechnology). Briefly, cells in the logarithmic growth phase were digested, centrifuged, and resuspended in complete medium. Cell density was adjusted to 3 × 10⁴ cells/mL using a hemocytometer. Subsequently, 100 µL of the cell suspension was seeded into each well of a 96-well plate (NEST Biotechnology) and incubated for 24 h to allow attachment. After incubation, the medium was removed and replaced with 100 µL of fresh medium containing various concentrations of the test compounds or the positive control (zorifertinib). Cells treated with medium containing an equivalent volume of DMSO served as the negative control. The plates were then incubated for 72 h. Following the treatment period, 10 µL of CCK-8 reagent was added to each well, and the plates were incubated for an

additional 2 h. The absorbance at 450 nm was measured using a multifunctional microplate reader (Shanghan Hanfei Medical Instrument Co., Ltd.). The inhibition rate (*IR*%) was calculated using the following formula:

$$IR\% = 100 \frac{OD_{\text{sample}} - OD_{\text{negative control}}}{OD_{\text{STSP}} - OD_{\text{negative control}}} \quad (1)$$

The half-maximal inhibitory concentration (IC_{50}) values were determined from concentration–response curves using GraphPad Prism software via nonlinear regression analysis (Bliss method). All experiments were performed in triplicate wells and repeated independently at least three times.

Molecular docking protocol

Molecular docking of target derivatives with EGFR (PDB ID: 7OXB) was performed using AutoDock Vina. Small molecule ligands were prepared in ChemDraw/Chem3D and converted to PDBQT format alongside the pretreated protein. Following binding pocket configuration, 20 docking runs were conducted. Results were selected based on binding energy and conformation, with PyMOL used for interaction visualization.

The selection of the EGFR kinase domain (PDB ID: 7OXB) for molecular docking studies is based on its established relevance in elucidating the structural basis of quinazoline-based inhibitor binding. Although the anticancer activity was evaluated in whole-cell systems, docking simulations against the isolated kinase domain provide mechanistic insights into potential direct interactions with the EGFR target. The 7OXB structure represents a well-characterized model of the ATP-binding pocket and has been widely employed in structural studies of EGFR inhibitors. This approach allows for the prediction of key intermolecular interactions, such as hydrogen bonding and hydrophobic contacts, between the synthesized hybrids and critical residues (*e.g.*, ASP-855, LYS-875), thereby supporting the interpretation of the observed structure–activity relationships and guiding future design strategies.

ADME prediction introduction

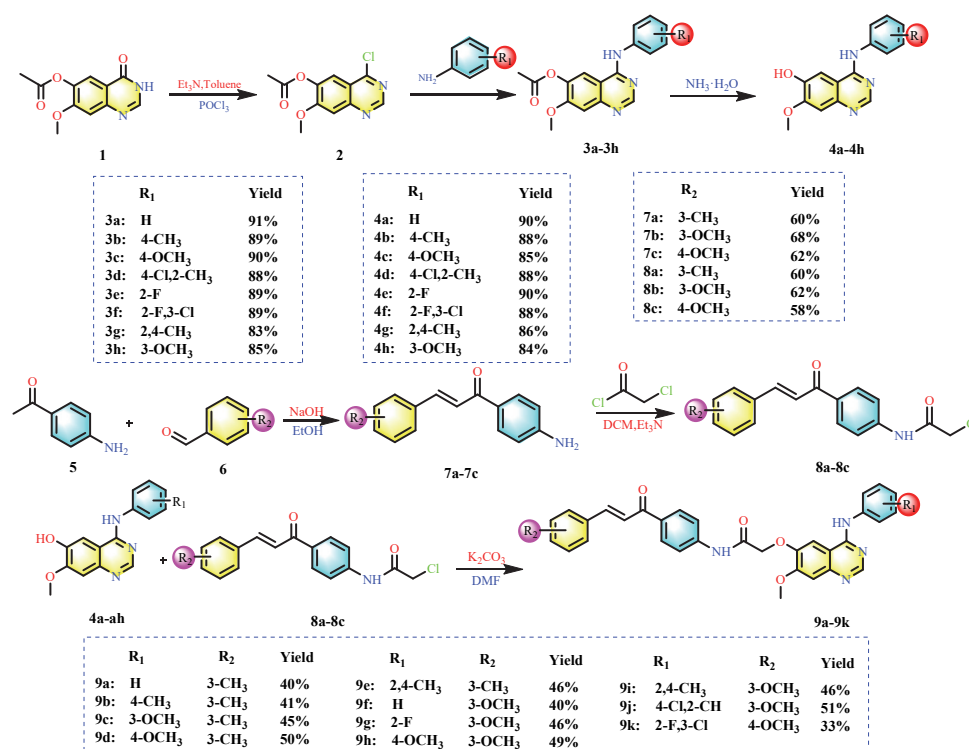
ADME prediction is vital in drug development, using computational models to evaluate a compound's absorption, distribution, metabolism and excretion. Researchers simply input the molecular structure into a prediction platform and run the analysis. The system quickly generates key parameters like partition coefficients and permeability in standardized reports, enabling efficient lead compound optimization. This computer-aided approach significantly accelerates early-stage drug screening.

Toxicity prediction introduction

Toxicity prediction is essential in drug development, using computational models to evaluate the safety profile of a compound. Researchers simply input the molecular structure into a prediction platform and run the analysis. The system quickly generates key parameters such as LD_{50} values and toxicity classes in standardized reports, enabling efficient identification of compounds with favorable safety margins. This computer-aided approach significantly reduces the risk of late-stage drug failure.

RESULTS AND DISCUSSION

Based on the synthesis methods of the references,^{31–35} we systematically optimized the synthetic route for target compounds **9a–k**, as illustrated in Scheme 1. Using 3,4-dihydro-7-methoxy-4-oxoquinazolin-6-yl acetate **1** as the starting mat-



Scheme 1. The synthesis route of target derivatives.

erial in toluene with triethylamine as the acid scavenger, we investigated the effect of reaction temperature on the chlorination with phosphorus oxychloride. As demonstrated in Table S-I of the Supplementary material to this paper, optimal yields of 85–95 % were achieved at 70 °C for 2 h, whereas higher temperatures or prolonged reaction times led to increased byproduct formation. As shown in Table S-II of the Supplementary material, intermediate **2** reacted with substituted anilines for 5 h to give intermediate **3** in high yield exceeding 90 %, with both insufficient and excessive reaction times negatively impacting the yield. Subsequent alkaline hydrolysis of **3** with aqueous ammonia yielded intermediate **4**. In the synthesis of intermediates **7a–c**, the influence of various basic conditions was systematically investigated. Using 4-aminoacetophenone and substituted benzaldehydes as starting materials, the reactions were conducted for 4 h under different basic conditions. As evidenced in Table S-III of the Supplementary material, the results demonstrated that sodium hydroxide afforded the highest product yield, while sodium carbonate showed reduced efficiency due to its weaker alkalinity and poor solubility. When triethylamine was employed as the base, the reaction yield was approximately, only 50 %. The results demonstrate that strong inorganic bases are more

effective than weaker or organic bases in promoting the condensation. For intermediates **8a–c**, optimization showed that a molar ratio of **7a–c** to chloroacetyl chloride of 1.0:2.5 (Table S-IV of the Supplementary material) and addition at 0 °C (Table S-V of the Supplementary material) afforded the best yield, avoiding incomplete conversion or bis-acylation. For the final etherification of **9a–d**, 80 °C proved optimal (Table S-VI of the Supplementary material), balancing conversion and byproduct formation. Screening of bases (Table S-VII of the Supplementary material) indicated that potassium carbonate, owing to its moderate basicity, effectively promoted alkoxide formation without triggering elimination side reactions, unlike sodium hydroxide which reduced yield through competitive elimination.

Through systematic optimization as described, we have established an efficient six-step synthetic route starting from 3,4-dihydro-7-methoxy-4-oxoquinazolin-6-yl acetate **1**, involving sequential chlorination, amination, hydrolysis, condensation, acylation and etherification reactions. Each reaction condition was thoroughly investigated and optimized, with all key steps achieving satisfactory yields to provide sufficient compound samples for subsequent structure-activity relationship studies. This synthetic route demonstrates several advantageous characteristics including readily available starting materials, mild reaction conditions, and straightforward operational procedures.

Antitumor activity

The antitumor activity of the target compounds was evaluated using the CCK-8 assay *in vitro*. Zorifertinib was employed as the positive control drug. The inhibitory effects on A549 and H1975 cell lines are summarized in Table I.

TABLE I. The inhibition rate of target compounds on tumor cells; compounds concentration: 50 μ M

Compound	R ₁	R ₂	Inhibition rate, %	
			A549	H1975
9a	H	3-CH ₃	–4.16	36.77
9b	4-CH ₃	3-CH ₃	0.12	36.17
9c	3-OCH ₃	3-CH ₃	23.80	20.06
9d	4-OCH ₃	3-CH ₃	54.27	62.22
9e	2,4-CH ₃	3-CH ₃	49.82	54.97
9f	H	3-OCH ₃	36.55	58.99
9g	2-F	3-OCH ₃	43.99	62.63
9h	4-OCH ₃	3-OCH ₃	47.80	58.17
9i	2,4-CH ₃	3-OCH ₃	14.96	35.25
9j	4-Cl,2-CH ₃	3-OCH ₃	41.63	34.45
9k	2-F,3-Cl	4-OCH ₃	47.56	61.92
Zorifertinib	–	–	62.14	49.60

The data in Table I demonstrate that the activity of target compounds is closely related to the type and position of R₁ and R₂ substituents in their structures. When R₂ was meta-methyl substituted, compounds **9d** and **9e** exhibited inhibitory rates of 49.82 and 54.27 % against A549 cells, respectively, approaching the efficacy of the positive control zorifertinib (62.14 %). Notably, these compounds demonstrated more pronounced inhibitory effects against H1975 cells, with rates reaching 54.97 and 62.22 % (compared to zorifertinib's 49.60 % in this cell line). These results indicate that meta-methyl substitution can significantly enhance the inhibitory activity of compounds against H1975 cells. This enhancement effect may originate from the steric hindrance effect of meta-methyl optimizing the binding conformation between molecules and target proteins, while its hydrophobicity strengthens interactions with active sites. Additionally, meta-substitution may reduce molecular conformational freedom, maintaining pharmacophores in a more favorable orientation, thereby improving inhibitory efficiency.

Further investigation of the meta-methoxy substituted compounds at the R₂ position revealed that **9j** (R₁: 4-chloro-2-methyl), **9g** (R₁: 2-fluoro) and **9h** (R₁: 4-methoxy) exhibited inhibition rates of 41.63, 43.99 and 47.80 % against A549 cells, respectively, all slightly lower than that of the positive control zorifertinib (62.14 %). In contrast, against H1975 cells, both **9g** (62.63 %) and **9h** (58.17 %) demonstrated significantly enhanced inhibitory activity compared to zorifertinib (49.60 %), whereas **9j** (34.45 %) showed reduced potency. These results clearly indicate that with meta-methoxy substitution, the choice of R₁ substituent significantly impacts biological activity, with the 2-fluoro-substituted compound **9g** demonstrating particularly enhanced inhibition against H1975 cells, achieving an inhibition rate of 62.63 %. The observed activity differences likely stem from the strong electronegativity of the 2-fluoro group facilitating improved hydrogen bonding interactions with the target protein, whereas the steric hindrance introduced by the 4-chloro, 2-methyl disubstitution in **9j** may impair optimal molecular binding to the target site.

Structure–activity relationship analysis demonstrated that the position of R₂ substituents critically influences biological activity. In H1975 cells, meta-substituted compounds **9e** (R₂: 3-methyl) and **9g** (R₂: 3-methoxy) demonstrated significantly superior inhibitory activities of 54.97 and 62.63 %. This marked enhancement suggests that meta-substitution facilitates stronger molecular binding to the target protein. This advantage likely arises from the optimal accommodation within the three-dimensional architecture of the target's active site, improving spatial complementarity and hydrophobic interactions to enhance binding affinity. Furthermore, the structural characteristics of R₁ substituents exert a decisive influence on the antitumor activity of these compounds. Notably, compounds **9d** (R₁: 4-methoxy) and **9e** (R₁: 2,4-dimethyl) exhibited the most prominent inhibitory activities. Specifically, **9d** demonstrated inhibition rates of 54.27 and 62.22 %

against A549 and H1975 cell lines, respectively, while **9e** showed corresponding inhibition rates of 49.82 and 54.97 %. Remarkably, compound **9g** (R₁: 2-fluoro) displayed the strongest inhibitory activity against H1975 cells with an inhibition rate of 62.63 %, although it exhibited relatively weaker activity against A549 cells (43.99 % inhibition), indicating excellent cellular selectivity. Comprehensive analysis reveals that introducing medium-sized electron-donating groups (*e.g.*, methoxy and methyl) at the R₁ position substantially enhances antitumor efficacy, with the 4-methoxy-substituted compounds **9d** and **9h** emerging as particularly promising drug candidates due to their optimal overall performance profile, rendering them promising candidates for further development.

According to the *IC*₅₀ determination results shown in Table II, these compounds exhibited superior inhibitory activity against both A549 (*IC*₅₀: 7.479 μM) and H1975 (*IC*₅₀: 6.652 μM) cell lines compared to zorifertinib (A549: 31.080 μM; H1975: 64.170 μM). Notably, compound **9e** demonstrated the lowest *IC*₅₀ values (A549: 7.479 μM; H1975: 6.652 μM), indicating the most potent inhibitory effect. Furthermore, both **9d** (A549: 8.463 μM; H1975: 7.885 μM) and **9h** (A549: 7.944 μM; H1975: 8.739 μM) displayed *IC*₅₀ values below 10 μM, further confirming their excellent antitumor potential. In conclusion, compounds **9e**, **9d** and **9h** warrant further in-depth investigation due to their remarkable inhibitory activity and structural advantages.

TABLE II. *IC*₅₀ value of preferred compounds

Compound	<i>IC</i> ₅₀ / μM	
	A549	H1975
9d	8.463	7.885
9e	7.479	6.652
9g	20.960	23.500
9h	7.944	8.739
9k	8.113	18.080
Zorifertinib	31.08	54.71

Preliminary structure–activity relationship analysis revealed several key patterns. First, the position of the R₂ substituent on the chalcone moiety had a decisive influence on activity with meta-substitution significantly outperforming para-substitution, likely due to its greater potential to form stable interactions with the target protein. Second, methoxy-substituted compounds generally exhibited stronger activity than their methyl-substituted counterparts, suggesting the importance of hydrogen bonding in target recognition. Additionally, the number of R₁ substituents on the quinazoline moiety also affected activity with mono-substituted derivatives typically outperforming di-substituted analogs, possibly due to steric hindrance effects. These findings provide important guidance for the rational design of future

antitumor drugs. In particular, the lead compound **9h** shows promising development potential and warrants further investigation into its pharmacological mechanisms and preclinical evaluation.

Molecular docking

Molecular docking of the positive control drug zorifertinib and selected target derivatives with EGFR kinase (PDB ID: 7OXB) was performed using AutoDock Vina. The binding modes between ligand molecules and receptor proteins were analyzed to further explore their interactions. The selected target derivative **9h** and the positive control drug zorifertinib were individually docked with the target protein EGFR.

The molecular docking analysis (Fig. 2, PDB ID:7OXB) reveals that compound **9h** binds to EGFR primarily through an extensive hydrogen-bonding network. The quinazoline core forms critical hydrogen bonds with residues in the catalytic pocket (GLU-1015, GLN-820), while the side-chain substituents engage additional residues (GLN-812, ASN-816, TYR-813), collectively contributing to a stable and potent inhibition.

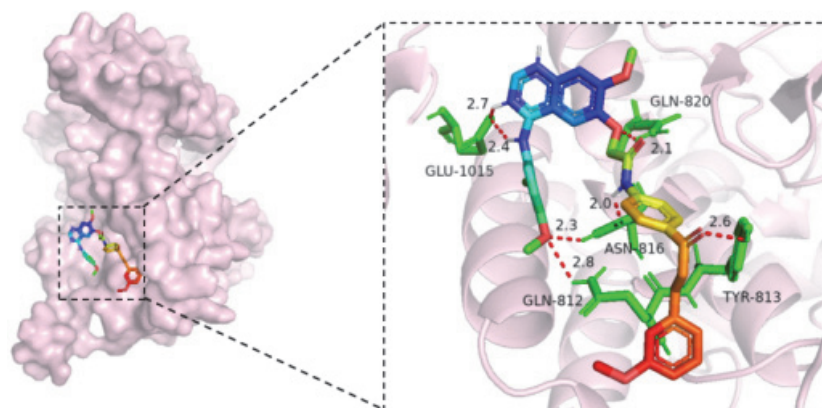


Fig. 2. Molecular docking models of compound **9h** with EGFR (PDB ID code: 7OXB).

Molecular docking of zorifertinib with EGFR (PDB ID: 7OXB, Fig. 3) reveals that its quinazoline core forms three key hydrogen bonds with the kinase domain: the 3-position nitrogen with ASP-855 (1.9 Å), the 4-position amino nitrogen with ASP-837 (2.3 Å), and the 6-position oxygen with LYS-875 (2.3 Å). These interactions, particularly the short, strong bond with ASP-855, are critical for anchoring the inhibitor tightly within the ATP-binding pocket. This binding network enhances stability and specificity, effectively competing with ATP to inhibit EGFR signaling and providing a structural basis for its potent antitumor activity.

While both compound **9h** and zorifertinib share a conserved quinazoline core that targets the ATP-binding pocket of EGFR (PDB ID:7OXB), their distinct side

chains dictate divergent binding modes and inhibitory profiles. Compound **9h**, with its flexible C-6 substituent, engages the solvent-front region (GLN-812, TYR-813), potentially conferring adaptive binding to various mutants like L858R/T790M. In contrast, zorifertinib's rigid structure deeply penetrates the back pocket, forming a strong salt bridge with ASP-855 in the DFG motif and a cation interaction with LYS-875, which may enhance its potency against wild-type EGFR. This analysis suggests that **9h**'s flexibility could be key for a broader mutant spectrum, whereas zorifertinib's pre-organization favors strong wild-type inhibition.

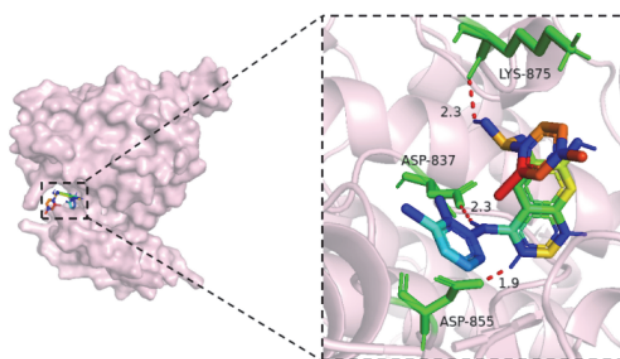


Fig. 3. Molecular docking models of zorifertinib with EGFR (PDB ID code: 7OXB).

Physicochemical properties and ADME prediction

As summarized in Table III, all synthesized compounds (**9a–k**) exhibit molecular weights exceeding 500 Da, constituting a single Lipinski violation, while

TABLE III. Physicochemical properties and ADME properties of target compounds; *RB* – rotatable bonds; *HAcc* – H-bond acceptors; *HDON* – H-bond donors; Lipinski – violation Lipinski Rule of 5; * – *MW* > 500 g/mol, Log *s* – the water solubility of the compound; GI – gastrointestinal absorption; bioavailability score: 0.55

Cmpd.	<i>MW</i> g/mol	<i>RB</i>	<i>HAcc</i> (<10)	<i>HDON</i>	<i>TPSA</i> Å (≤140)	Log <i>P_{o/w}</i>	Log <i>s</i>	GI	Lipinski
9a	544.60	11	6	2	102.44	5.52	– 7.02	Low	1*
9b	558.63	11	6	2	102.44	5.87	– 7.33	Low	1*
9c	574.63	12	7	2	111.67	5.45	– 7.11	Low	1*
9d	574.63	12	7	2	111.67	5.45	– 7.11	Low	1*
9e	572.65	11	6	2	102.44	6.21	– 7.63	Low	1*
9f	560.60	12	7	2	111.67	5.03	– 6.80	Low	1*
9g	578.59	12	8	2	111.67	5.40	– 6.96	Low	1*
9h	590.63	11	6	2	102.44	6.21	– 7.11	Low	1*
9i	588.65	12	7	2	111.67	5.73	– 7.41	Low	1*
9j	609.07	12	7	2	111.67	5.98	– 7.70	Low	1*
9k	613.03	12	8	2	111.67	5.99	– 7.56	Low	1*
Zorifertinib	459.90	6	7	1	79.82	3.65	– 5.50	High	0

other key parameters such as TPSA (102.44–111.67 Å²) and bioavailability scores (0.55) remain within favorable ranges. Despite the predicted low gastrointestinal absorption, the overall physicochemical profiles are typical of beyond-rule-of-5 kinase inhibitors, and the potent *in vitro* antiproliferative activity against NSCLC cells demonstrates that these compounds can effectively reach their intracellular targets. The consistent drug-like parameters across the series, combined with their strong biological activity, highlight the potential of the quinazoline–chalcone hybrids as promising lead compounds for further optimization and development as novel anticancer agents.

Toxicity profile of the designed compound

As shown in Table IV, all designed compounds (**9a–k**) exhibited a predicted *LD*₅₀ of 2000 mg/kg and a toxicity class of 4, whereas zorifertinib showed an *LD*₅₀ of 1150 mg/kg (class 4). The average similarity of the designed compounds ranged from 54.91 to 58.50 %, slightly higher than that of zorifertinib (50.88 %), with prediction accuracies around 67 %. These results indicate that the designed compounds possess toxicity profiles comparable to or slightly better than the reference drug.

TABLE IV. Predicted toxicity properties of target compounds

Compound	Predicted <i>LD</i> ₅₀ mg/kg	Predicted toxicity class (1 to 6)	Average similarity, %	Prediction accuracy, %
9a	2000	4	56.76	67.38
9b	2000	4	56.76	67.38
9c	2000	4	55.25	67.38
9d	2000	4	56.76	67.38
9e	2000	4	55.25	67.38
9f	2000	4	58.50	67.38
9g	2000	4	55.78	67.38
9h	2000	4	58.50	67.38
9i	2000	4	56.40	67.38
9j	2000	4	58.26	67.38
9k	2000	4	54.91	67.38
Zorifertinib	1150	4	50.88	67.38

CONCLUSIONS

Collectively, this study developed novel antitumor agents by designing and synthesizing a series of quinazoline–chalcone hybrids. Their antiproliferative activity was evaluated against A549 and H1975 cell lines, with zorifertinib as the positive control. Molecular docking revealed their stable binding to EGFR, and ADME/toxicity predictions validated their favorable drug-like and safety profiles, particularly for compound **9h**. However, the cytotoxicity was assessed only on cancer cell lines, and the selectivity against normal cells remains to be determined.

Future work will address this limitation to establish their therapeutic selectivity index.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: <https://www.shd-pub.org.rs/index.php/JSCS/article/view/13582>, or from the corresponding author on request.

Acknowledgements. This work was financially supported by the Natural Science Foundation of Liaoning Province (no. 20180550016) and the Scientific Research Foundation of the Education Department of Liaoning Province (no. LJGD2020015).

ИЗВОД

ДИЗАЈН НОВИХ ХИБРИДА ХИНАЗОЛИНА И ХАЛКОНА КАО СНАЖНИХ ИНХИБИТОРА РЕЦЕПТОРА ЕПИДЕРМАЛНОГ ФАКТОРА РАСТА

YINGNUO WANG¹, JURANG LI¹, CHUNMENG LI¹, YANG LIU¹, ZHIQIANG CAI¹ и SHUAI LI²

¹Liaoning Province Professional and Technical Innovation Center for Fine Chemical Engineering of Aromatics Downstream, School of Petrochemical Engineering, Shenyang University of Technology, Liaoning, Liaoyang 111003, P. R. China и ²Shandong Engineering Research Center of Pharmaceutical Green Intelligent Technology, Shandong Academy of Pharmaceutical Sciences, Shandong, Jinan 250101, P. R. China

У оквиру овог истраживања успешно је дизајнирана и синтетисана нова серија хибрида хиназолина и халкона. Најважнија иновација је молекулска хибридизација фармакофорног скелета хиназолина са халконским фрагментом, чиме су створене нове хемијске врсте за испитивање потенцијалног синергистичког антитуморног ефекта. Успешно је спроведена усмерена синтеза у више реакционих корака. Први резултати испитивања показали су да већина синтетисаних хибрида показује снажну антипролиферативну активност *in vitro* према ћелијским линијама неситноћелијског рака плућа (NSCLC) (A549 и H1975). На основу испитивања молекулским докингом предложено је да је инхибиција рецептора епидермалног фактора раста (EGFR) главни механизам деловања и да једињења остварују стабилне интеракције са киназним доменом. Осим тога, *in silico* предвиђање апсорпције, дистрибуције, метаболизма и излучивања (ADME) и предвиђања токсичности добијена на SwissADME и ProTox 3.0 платформама, редом, указују на то да једињења поседују својства слична лековима и одговарајући профил безбедности. Ипак, цитотоксичност је одређена само према ћелијским линијама рака и селективност према нетуморским, здравим, ћелијама тек треба одредити. Без обзира на ова ограничења, почетни резултати су охрабрујући и упућују на наставак оптимизације и развој ових нових хибрида једињења.

(Примљено 13. октобра 2025, ревидирано 4. јуна, прихваћено 13. августа 2026)

REFERENCES

1. E. K. Chung, S. H. Yong, E. H. Lee, E. Y. Kim, Y. S. Chang, S. H. Lee, *Tuber. Respir. Dis.* **86** (2023) 1 (<https://doi.org/10.4046/trd.2022.0066>)
2. K. Li, X. N. Cao, B. Ai, H. Xiao, Q. F. Huang, Z. Zhang, Q. Chu, L. Zhang, X. F. Dai, Y. D. Liao, *Thorac. Cancer* **12** (2021) 2161 (<https://doi.org/10.1111/1759-7714.14044>)
3. X. X. He, H. P. Ren, Y. Li, J. S. Lin, C. Jin, *J. Hepatol.* **19** (2011) 561 (<https://doi.org/10.3760/cma.j.issn.1007-3418.2011.08.001>)

4. J. Z. Lin, L. C. Wu, X. Bai, Y. Xie, A. Q. Wang, H. H. Zhanl, X. B. Yang, X. H. Wan, X. Lu, X. T. Sang, H. T. Zhao, *Oncotarget* **7** (2016) 71036 (<https://doi.org/10.18632/oncotarget.11954>)
5. J. Zou, Y. Zeng, F. Wu, *Curr. Opin. Oncol.* **35** (2023) 22 (<http://doi.org/10.1097/CCO.0000000000000914>)
6. D. Das, J. Hong, *Eur. J. Med. Chem.* **170** (2019) 55 (<https://doi.org/10.1016/j.ejmech.2019.03.004>)
7. S. Wang, Y. Zhang, T. S. Ren, Q. Wu, H. Y. Lu, X. C. Qin, Y. Liu, H. Ding, Q. C. Zhao, *Cell Death Dis.* **16** (2025) 216 (<https://doi.org/10.1038/s41419-025-07539-7>)
8. G. Liu, S. Yang, B. Song, W. Xue, D. Y. Hu, L. H. Jin, P. Lu, *Molecules* **11** (2006) 272 (<https://doi.org/10.3390/11040272>)
9. L. L. Chi, Z. Q. Cai, B. Wang, W. T. Qin, Y. N. Wang, Q. Q. Feng, W. J. Ren, *J. Chem. Soc. Pak.* **45** (2023) 474 (<https://doi.org/10.52568/001391/JCSP/45.06.2023>)
10. M. W. Attwa, N. S. Al-Shakliah, H. AlRabiah, A. A. Kadi, A. S. Abdelhameed, *J. Pharm. Biomed. Anal.* **211** (2022) 114626 (<https://doi.org/10.1016/j.jpba.2022.114626>)
11. H. Ghouila, N. Meksi, W. Haddar, M. F. Mhenni, H. B. Jannet, *Ind. Crops Prod.* **35** (2012) 31 (<https://doi.org/10.1016/j.indcrop.2011.05.026>)
12. C. L. Zhuang, W. Zhang, C. Q. Sheng, W. N. Zhang, C. G. Xing, Z. Y. Miao, *Chem. Rev.* **117** (2017) 7762 (<https://doi.org/10.1021/acs.chemrev.7b00020>)
13. C. K. Wenzel, C. von Montfort, L. Ebbert, N. P. Klahm, A. S. Reichert, W. Stahl, P. Brenneisen, *Toxicol. In Vitro* **91** (2023) 105625 (<https://doi.org/10.1016/j.tiv.2023.105625>)
14. J. D. Zhai, B. X. Sun, F. Sang, *Front. Chem.* **10** (2022) 964089 (<https://doi.org/10.3389/fchem.2022.964089>)
15. E. B. Mass, G. V. Duarte, D. Russowsky, *Mini Rev. Med. Chem.* **21** (2021) 186 (<https://doi.org/10.2174/1389557520666200730160325>)
16. A. Thiriveedhi, R. V. Nadh, N. Srinivasu, K. Kaushal, *Lett. Drug Des. Discovery* **15** (2018) 757 (<https://doi.org/10.2174/1570180814666171013162148>)
17. S. Madhavi, R. Sreenivasulu, R. R. Raju, J. P. Yazala, *Saudi Pharm. J.* **25** (2017) 275 (<https://doi.org/10.1016/j.jsps.2016.06.005>)
18. R. Thomas, W. H. Zhang, *Front. Oncol.* **9** (2019) 800 (<https://doi.org/10.3389/fonc.2019.00800>)
19. A. M. Wasserman, J. Bajorath, *Future Med. Chem.* **3** (2011) 425 (<https://doi.org/10.4155/fmc.10.293>)
20. A. M. Wassermann, J. Bajorath, *Med. Chem. Comm.* **2** (2011) 601 (<https://doi.org/10.1039/c1md00066g>)
21. J. Althaus, T. Hake, M. Lehr, *J. Enzyme Inhib. Med. Chem.* **31** (2016) 131 (<https://doi.org/10.1080/14756366.2016.1178246>)
22. A. Detsi, V. Roussis, A. Tsotinis, C. Roussakis, T. Calgeropoulou, *Synlett* **20** (2005) 3131 (<https://doi.org/10.1055/s-2005-921933>)
23. K. Lu, Y. T. Ma, M. L. Gao, Y. Liu, C. M. Xu, X. Zhao, P. Yu, *Org. Lett.* **18** (2016) 5038 (<https://doi.org/10.1021/acs.orglett.6b02493>)
24. A. Mozo-Villarias, J. Cedano, E. Querol, *Eur. Biophys. J.* **50** (2021) 951 (<https://doi.org/10.1007/s00249-021-01557-x>)
25. L. Xie, D. L. Yang, Q. Y. Lu, H. B. Zeng, *Curr. Opin. Colloid Interface Sci.* **47** (2020) 58 (<https://doi.org/10.1016/j.cocis.2019.12.001>)
26. Q. Sun, Y. F. Fu, W. Q. Wang, *Chem. Phys.* **559** (2022) 111550 (<https://doi.org/10.1016/j.chemphys.2022.111550>)

27. R. L. Yang, J. J. Ma, H. Guo, Q. H. Meng, Y. W. Wang, H. Yan, R. Y. Jin, Z. Li, L. J. Meng, *Nat. Prod. Commun.* **17** (2022) 1934578X211059645 (<https://doi.org/10.1177/1934578X211059645>)
28. A. Dang, S. Dang, B. N. Vallish, *Rev. Recent Clin. Trials* **16** (2021) 193 (<https://doi.org/10.2174/1574887115999201103200248>)
29. J. Cui, Y. F. Hu, Y. H. Guo, J. W. Ma, K. J. Nan, H. Y. Zhang, *Tumor Biol.* **35** (2014) 11701 (<https://doi.org/10.1007/s13277-014-2660-z>)
30. B. Zhang, Z. Liu, S. Xia, Q. Liu, S. Gou, *Eur. J. Med. Chem.* **216** (2021) 113300. (<https://doi.org/10.1016/j.ejmech.2021.113300>)
31. A. H. Abou-Zied, B. G. Youssif, F. M. Mohamed, A. M. Hayallah, M. Abdel-Aziz, *Bioorg. Chem.* **89** (2019) 102997 (<https://doi.org/10.1016/j.bioorg.2019.102997>)
32. Y. Li, Y. Sun, Y. Zhou, X. Li, H. Zhang, G. Zhang, *J. Enzyme Inhib. Med. Chem.* **36** (2020) 207 (<https://doi.org/10.1080/14756366.2020.1852556>)
33. T. Ishida, *Chem. Biodivers.* **2** (2005) 569 (<https://doi.org/10.1002/cbdv.200590038>)
34. X. Wang, Y. Zheng, X. Xu, S. Gao, J. Wang, Q. Gou, *J. Mol. Struct.* **1254** (2022) 132322 (<https://doi.org/10.1016/j.molstruc.2021.132322>)
35. M. Abdel-Aziz, S. E. Park, G. E. D. A. A. Abuo-Rahma, M.H. Sayed, Y. Kwon, *Eur. J. Med. Chem.* **69** (2013) 427 (<https://doi.org/10.1016/j.ejmech.2013.08.040>).