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DESIGN, SYNTHESIS, AND MOLECULAR DOCKING STUDIES OF 4,7-DISUBSTITUTED QUINAZOLINE DERIVATIVES

Abstract*: Currently, targeted drug design is advancing rapidly, enabling the rational discovery of new biologically active compounds. Various approaches are employed in the design of novel drug candidates, among which molecular docking is a key tool. In this study, we utilized scaffold hopping and structural optimization strategies to design a series of novel 4,7-disubstituted quinazoline derivatives. Subsequently, molecular docking studies were performed to identify the most promising target compounds, which are currently being synthesized.*

***Keywords**: molecular docking, drug design, scaffold hopping, heterocyclic compounds, quinazoline, condensation, nucleophilic substitution, reduction.*

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4,7-DIALMASHGANGAN XINAZOLIN HOSILALARINING DIZAYNI, SINTEZI VA MOLEKULYAR DOKING TADQIQOTLARI

***Annotatsiya**: Hozirgi kunda maqsadli dori preparatlari dizayni (targeted drug design) rivojlanib bormoqda va yangi biologik faol moddalarni izlash maqsadli tarzda olib borilmoqda. Yangi dori vositalarini dizayn qilish jarayonida turli metodlardan foydalanilmoqda, ulardan biri molekulyar doking hisoblanadi. Ushbu tadqiqotda biz “asosiy strukturani almashtirish” (“scaffold hopping”) va “strukturaviy takomillashtirish” (“structural optimization”) strategiyalaridan foydalangan holda bir qator yangi 4,7-dialmashgan xinazolin hosilalarini dizayn qildik. Keyinchalik molekulyar doking tadqiqotlari yordamida eng istiqbolli maqsadli birikmalar tanlab olindi va ularning sintezi amalga oshirilmoqda.*

***Kalit so‘zlar**: molekulyar doking, dori dizayni, “asosiy strukturani almashtirish” (“scaffold hopping”), geterosiklik birikmalar, xinazolin, kondensatsiya, nukleofil almashinish, qaytarilish.*

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ДИЗАЙН, СИНТЕЗ И ИССЛЕДОВАНИЯ МОЛЕКУЛЯРНОГО ДОКИНГА 4,7-ДИЗАМЕЩЁННЫХ ПРОИЗВОДНЫХ ХИНАЗОЛИНА

***Аннотация**: В настоящее время целевой дизайн лекарственных препаратов (targeted drug design) быстро развивается, что позволяет рационально открывать новые биологически активные соединения. При дизайне новых потенциальных лекарственных препаратов используются различные подходы, среди которых ключевым инструментом является молекулярный докинг. В данном исследовании мы использовали стратегии скаффолд-хоппинга и структурной оптимизации для дизайна серии новых 4,7-дизамещенных производных хиназолина. Затем были проведены исследования молекулярного докинга для выявления наиболее перспективных целевых соединений, которые в настоящее время синтезируются.*

***Ключевые слова**: молекулярный докинг, дизайн лекарств, скаффолд-хоппинг, гетероциклические соединения, хиназолин, конденсации, нуклеофильное замещение, восстановление.*

Introduction

Heterocyclic compounds occupy a prominent position in organic chemistry and are widely distributed in biological systems. Many essential biomolecules present in the human body, including the nitrogenous bases of DNA and RNA, possess heterocyclic structures that are primarily based on purine and pyrimidine frameworks. Consequently, heterocyclic compounds, particularly analogues of purine and pyrimidine bases, have attracted significant attention due to their pronounced biological activity, high selectivity, and pharmacological relevance. In recent years, research focused on heterocyclic systems has intensified considerably, with increasing emphasis on elucidating structure–activity relationships and developing novel bioactive scaffolds [1].

At present, a substantial proportion of drugs approved by the U.S. Food and Drug Administration (FDA) contain heterocyclic cores, underscoring their crucial role in modern drug design [2]. Among these, bicyclic quinazoline derivatives are of particular importance, as they exhibit potent activity against key biological targets, including kinases such as Janus kinases (JAKs). In parallel, the significance of computer-aided drug design (CADD) methodologies has steadily increased in contemporary drug discovery [3]. Techniques such as molecular docking, virtual screening, and structure-based optimization enable the efficient identification and prioritization of promising candidates, facilitate the evaluation of ligand–target interactions, and streamline synthetic efforts [4]. From this perspective, the computational design of heterocyclic compounds, especially quinazoline-based derivatives, represents a powerful and widely adopted strategy in modern medicinal chemistry [5].

Literature review

Janus kinase (JAK) inhibitors represent an important class of therapeutic agents for the treatment of a wide range of immunological and hematological disorders [6, 7]. To date, several small-molecule JAK inhibitors have been approved by the U.S. Food and Drug Administration (FDA), while numerous additional candidates are currently undergoing clinical evaluation across different phases of development [8, 9]. These advances highlight the clinical relevance of JAK signaling pathways and continue to stimulate the discovery of novel JAK-targeted therapeutic strategies.

In recent years, diverse and innovative approaches have been explored to enhance the therapeutic potential of JAK modulation. Wang et al. reported a series of novel PROTAC-based JAK2 degraders identified as promising therapeutic agents for the treatment of myeloproliferative neoplasms [10]. Shen and co-workers demonstrated that dual CTSL/JAK inhibitors based on 2-aminopyrimidine scaffolds exhibit significant potential for the treatment of acute lung injury [11]. Hu et al. investigated JAK/HDAC dual inhibitors as a novel and promising strategy for the treatment of psoriasis [12], while Park and colleagues reported the use of selective JAK1 inhibitors derived from pyrrolopyridine scaffolds for the treatment of pulmonary fibrosis [13]. In addition, Bu and co-workers described gastrointestinal locally activated pyrimidine derivatives as an effective and innovative approach for the treatment of ulcerative colitis [14]. Gordhan et al. further demonstrated the therapeutic efficacy of JAK inhibitors in the treatment of dry eye disease [15], whereas Thoma and his team reported that the development of “soft drug” JAK inhibitors may reduce adverse effects in the treatment of atopic dermatitis [16]. Moreover, emerging studies indicate that JAK1 PROTACs and JAK/HDAC dual inhibitors also exhibit notable antitumor activities, further expanding the therapeutic scope of JAK-targeted compounds [17, 18]. Taken together, these findings underscore the versatility of JAK inhibition strategies and highlight the importance of rational scaffold selection and structural optimization in the development of next-generation

JAK-targeted agents. Guided by these literature precedents, the present study employs structure-based design and computational methodologies to identify and optimize novel quinazoline-based JAK inhibitors, followed by targeted synthesis and evaluation.

Research methodology

Based on previously reported studies, including several FDA-approved Janus kinase (JAK) inhibitors [8, 9] and other compounds demonstrating high inhibitory activity [13, 19], a rational design strategy was implemented for the development of novel quinazoline derivatives. Key structural features responsible for JAK inhibition were carefully analyzed and incorporated into the design process. By applying scaffold hopping and systematic structural modification approaches, the quinazoline core was selected as a versatile framework for further optimization, enabling the generation of structurally diverse derivatives with the potential to enhance binding interactions and inhibitory potency.

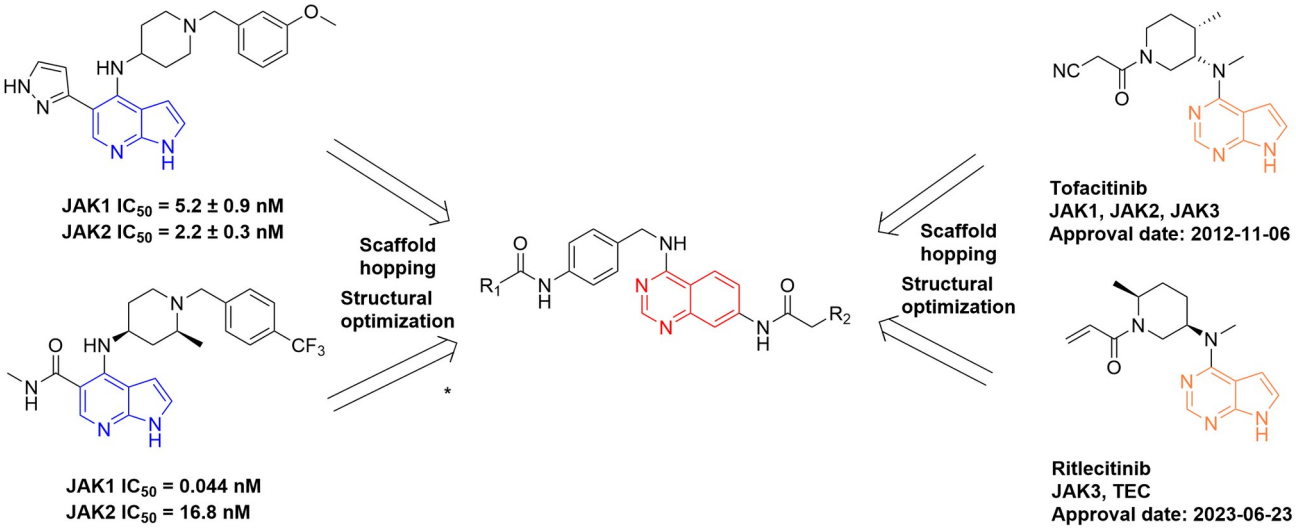


Figure 1. Design strategy of novel 4,7-disubstituted quinazoline derivatives

To enable the targeted synthesis of quinazoline derivatives, a series of 4-aminoquinazolines substituted at the 7-position were rationally designed, and the novelty of the proposed structures was confirmed using the Reaxys database. Following the design stage, molecular docking studies were employed as a structure-based screening tool to evaluate the binding potential of the designed compounds

prior to synthesis. Docking simulations were performed using the Maestro program against the Janus kinase (JAK2) protein (PDB ID: 4AQC) obtained from the Protein Data Bank. The docking results revealed that 7-substituted 4-aminoquinazoline derivatives exhibited superior binding modes, characterized by the formation of key hydrogen bonds and favorable intermolecular interactions with active-site residues of the JAK protein. These interactions indicated strong binding affinity toward the kinase active site, as exemplified by representative compounds (Figure 2):

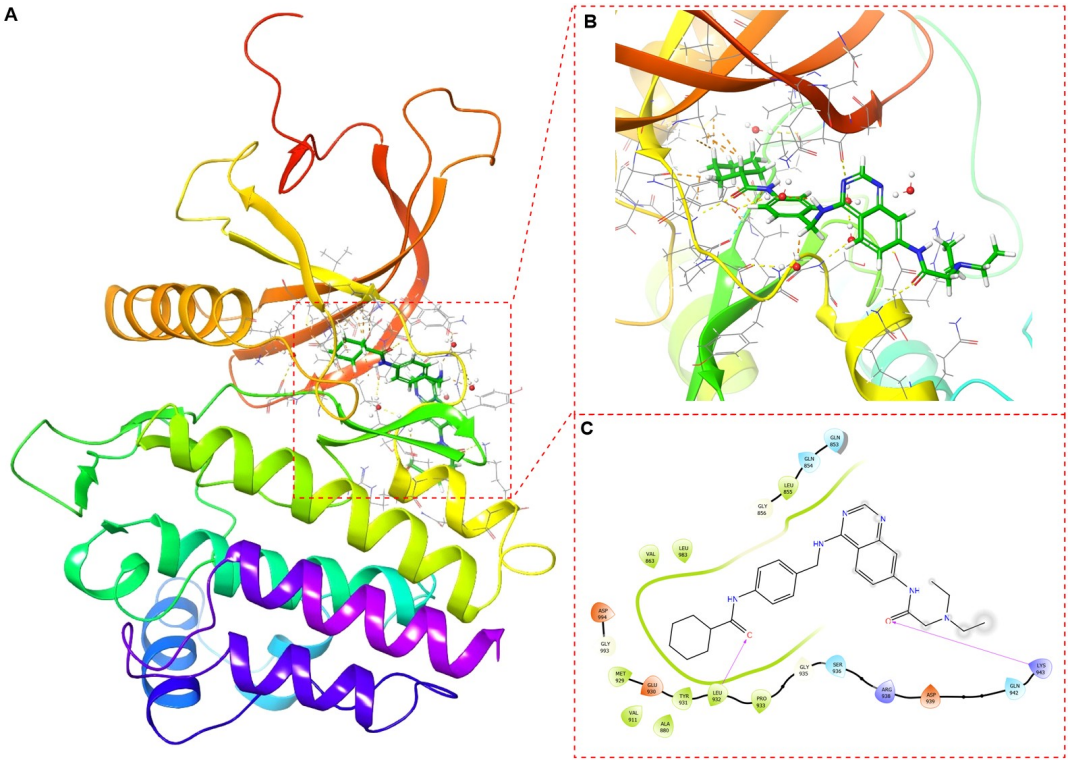
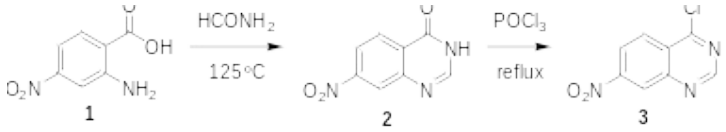


Figure 2. Molecular docking of 4,7-disubstituted quinazoline derivatives with JAK2

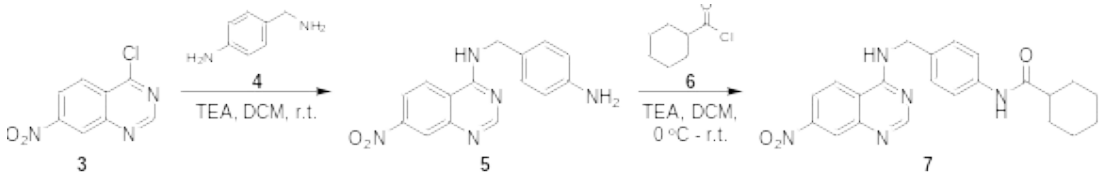
Molecular docking analysis revealed the formation of key ligand–protein interactions within the active site, enabling the identification of quinazoline derivatives with favorable binding profiles. Based on the molecular docking results, several quinazoline derivatives exhibiting favorable binding profiles were selected as priority candidates for synthesis. On the basis of reported literature methodologies, a rational and targeted synthetic strategy was subsequently designed to efficiently access the desired compounds and their key intermediates.

The synthesis started from commercially available 4-nitroanthranilic acid (**1**). This compound was cyclized with formamide under solvent-free conditions via the Niementowski reaction at 125 °C to obtain 7-nitroquinazolin-4(3*H*)-one (**2**). Subsequently, compound **2** was chlorinated using $POCl_3$ under solvent-free conditions, yielding 4-chloro-7-nitroquinazoline (**3**) (Scheme 1):



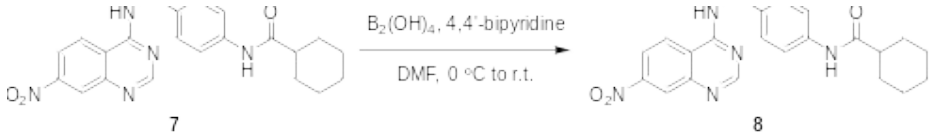
Scheme 1. Synthesis of 4-chloro-7-nitroquinazoline (**3**)

Intermediate **3** was subjected to nucleophilic substitution with 4-aminobenzylamine (**4**) in the presence of triethylamine (TEA) in dichloromethane (DCM) at room temperature, affording intermediate **5**. Compound **5** was acylated with cyclohexanecarbonyl chloride (**6**) under basic conditions (TEA) in DCM at low temperature, yielding the nitro intermediate **7** (Scheme 2):



Scheme 2. Synthesis of nitro intermediate (**7**)

In the subsequent step, the reduction of the nitro group was carried out using a mild reduction system consisting of tetrahydroxydiboron in the presence of 4,4′-bipyridine in DMF. The reaction was performed from 0 °C to room temperature and was completed within 10 min (Scheme 3):



Scheme 3. Synthesis of key intermediate (**8**)

After successful reduction of the nitro group, the obtained key amino intermediate was further functionalized through reactions with a broad range of carboxylic acid derivatives, including acyclic, cyclic, heterocyclic, aromatic, and

heteroaromatic acids. These reactions were performed to generate the target quinazoline derivatives and to enable a systematic evaluation of their structure–activity relationships (SAR). The reaction conditions were optimized to ensure high yields, good selectivity, and practical efficiency, allowing the preparation of a structurally diverse compound library suitable for subsequent biological studies.

Analysis results

The starting materials were obtained from commercial suppliers and used without further purification. All solvents, including ethanol, petroleum ether, toluene, ethyl acetate, and 1,2-dichloroethane, were anhydrous to avoid moisture interference. Reaction progress was monitored by thin-layer chromatography (TLC) on $HSGF_{254}$ silica plates (2.5 × 5 cm), with samples applied using 0.3 × 100 mm glass microcapillaries. Chromatograms were visualized under UV light at 254 and 365 nm or by iodine staining. Tetramethylsilane (TMS) was used as an internal standard in NMR analysis. Structural characterization was carried out using ^{1}H and ^{13}C NMR spectra recorded on a VARIAN 400 MHz spectrometer at room temperature. HRMS was performed on a QTRAP® 6500+ LC-MS system to confirm molecular composition and structure.

Preparation of 7-Nitroquinazolin-4(3H)-one **(2).** Yield 82%, light brown solid, Mp 127–129 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.34 (d, J = 2.2 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H), 8.22 (dd, J = 8.7, 2.3 Hz, 1H).

Preparation of 4-Chloro-7-nitroquinazoline **(3).** Yield 71%, light yellow solid, Mp 137–139 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 8.7 Hz, 1H), 8.31 (s, 1H), 8.24 (dd, J = 8.7, 2.3 Hz, 1H).

Preparation of N-(4-Aminobenzyl)-7-nitroquinazolin-4-amine **(5).** Yield 90%, yellow solid, Mp 150–151 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (t, J = 5.9 Hz, 1H), 8.60 (s, 1H), 8.56 (d, J = 9.1 Hz, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 9.0, 2.4 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H), 6.52 (d, J = 8.3 Hz, 2H), 5.07 (s, 2H), 4.63 (d, J = 5.8 Hz, 2H).

Preparation of N-(4-(((7-Nitroquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide **(7)**. Yield 70%, light yellow solid, Mp 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.22 (t, J = 5.7 Hz, 1H), 8.60 – 8.53 (m, 2H), 8.41 (d, J = 2.4 Hz, 1H), 8.26 (dd, J = 9.0, 2.4 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 4.74 (d, J = 5.6 Hz, 2H), 2.35 – 2.23 (m, 1H), 1.85 – 1.58 (m, 5H), 1.44 – 1.13 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.18, 159.08, 159.00, 157.02, 149.90, 149.20, 138.41, 133.02, 127.71, 125.35, 122.66, 119.05, 118.55, 44.79, 43.50, 29.13, 25.39, 25.23.

Preparation of N-(4-(((7-aminoquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide (**8**)

Intermediate **7** (0.405 g, 1.0 mmol) and a catalytic amount of 4,4′-bipyridine were dissolved in DMF at 0 °C under an ice bath. Tetrahydroxydiboron ($B_2H_4O_4$) (0.27 g, 3.0 mmol) was added portionwise with stirring, and the reaction was allowed to proceed for 10 min, gradually warming to room temperature. Upon completion, the reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (DCM/MeOH) to afford compound **8**. Yield 77%, light yellow solid, Mp 130–131 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.24 (t, J = 6.0 Hz, 1H), 8.19 (s, 1H), 7.92 (d, J = 8.9 Hz, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.78 (dd, J = 8.9, 2.3 Hz, 1H), 6.62 (d, J = 2.2 Hz, 1H), 5.86 (s, 2H), 4.65 (d, J = 5.7 Hz, 2H), 2.34 – 2.24 (m, 1H), 1.82 – 1.58 (m, 5H), 1.44 – 1.12 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.14, 158.79, 154.68, 152.75, 150.38, 138.13, 134.31, 127.47, 123.76, 118.97, 115.87, 105.39, 105.05, 44.79, 42.96, 29.15, 25.40, 25.24.

Molecular docking. Molecular docking studies were carried out using the Maestro (Schrödinger) software package. The X-ray crystal structure of JAK2 (PDB ID: 4AQC) was obtained from the RCSB Protein Data Bank. Protein preparation

included the addition of hydrogen atoms, assignment of appropriate protonation states, and removal of water molecules located more than 5 Å from heteroatoms. Ligand structures were generated and energy-minimized using the OPLS4 force field. Docking grids were defined around the ATP-binding site, and the docking protocol was validated through re-docking of the co-crystallized ligand. Subsequently, all designed quinazoline derivatives were docked into the JAK2 active site to assess their binding interactions.

Conclusion

In this study, a rational design strategy combined with molecular docking was successfully applied to the development of novel quinazoline derivatives as potential Janus kinase inhibitors. Structure-based virtual screening enabled the identification of key ligand–protein interactions and the selection of promising candidates exhibiting favorable binding affinities. Guided by these results, an efficient and reliable synthetic route was established, allowing the preparation of structurally diverse 4,7-disubstituted quinazoline derivatives. The obtained compounds represent a focused molecular library suitable for further biological evaluation and structure–activity relationship studies, highlighting the effectiveness of integrating computational design with targeted synthesis in early-stage drug discovery.

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