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ILMIY AXBOROTNOMA

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DESIGN AND SYNTHESIS OF 4,6-DISUBSTITUTED QUINAZOLINE DERIVATIVES AS JANUS KINASE INHIBITORS

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Abstract. Janus kinases (JAKs) are recognized as important molecular targets in targeted therapy, and their inhibitors are widely used for the treatment of various autoimmune and inflammatory diseases. Although several JAK inhibitors have been approved by the U.S. Food and Drug Administration (FDA), the development of new compounds with improved selectivity and reduced toxicity remains highly relevant. In this study, a series of novel 4,6-disubstituted quinazoline derivatives were designed using a scaffold-hopping approach, and their targeted synthesis was successfully accomplished, providing a promising basis for the development of more effective JAK inhibitors.

Keywords: Janus kinase, autoimmune diseases, molecular docking, quinazoline, nucleophilic substitution, reduction.

Janus kinaza ingibitorlari sifatida 4,6-dialmashgan xinazolin hosilalarini dizayni va sintezi

Annotatsiya. Janus kinazalar (JAK) targeted terapiyada muhim molekulyar nishonlar hisoblanib, ularga qarshi ingibitorlar turli autoimmun va yallig‘lanish bilan bog‘liq kasalliklarni davolashda qo‘llanilmoqda. Hozirgi kunda bir qator JAK ingibitorlari FDA tomonidan tasdiqlangan bo‘lsa-da, yuqori selektivlik va past toksiklikka ega yangi birikmalarni ishlab chiqish dolzarb bo‘lib qolmoqda. Ushbu tadqiqotda yangi 4,6-dialmashgan xinazolin hosilalari “scaffold-hopping” yondashuvi asosida dizayn qilinib, ularning maqsadli sintezi amalga oshirildi, bu esa kelgusida samarali JAK ingibitorlarini yaratish uchun istiqbolli asos bo‘lib xizmat qiladi.

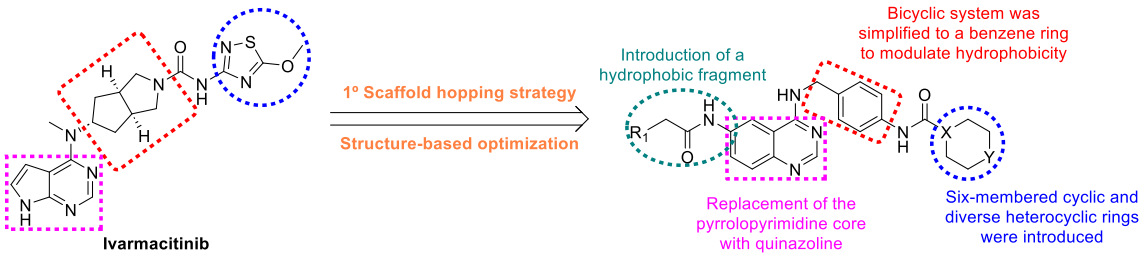
Kalit so‘zlar: Janus kinaza, autoimmun kasalliklar, molekulyar doking, xinazolin, nukleofil almashinish, qaytarilish.

Дизайн и синтез 4,6-дизамещённых производных хиназолина в качестве ингибиторов Янус-киназ

Аннотация. Янус-киназы (JAK) являются важными молекулярными мишенями в таргетной терапии, а их ингибиторы широко применяются для лечения различных аутоиммунных и воспалительных заболеваний. Несмотря на то что ряд ингибиторов JAK одобрен Управлением по контролю за продуктами и лекарствами США (FDA), разработка новых соединений с повышенной селективностью и сниженной токсичностью остаётся актуальной задачей. В настоящем исследовании серия новых 4,6-дизамещённых производных хиназолина была спроектирована с использованием подхода

“scaffold hopping”, и осуществлён их направленный синтез, что создаёт перспективную основу для разработки более эффективных ингибиторов JAK.

Ключевые слова: Янус-киназа, аутоиммунные заболевания, молекулярный докинг, хиназолин, нуклеофильное замещение, восстановление.



Introduction. Contemporary drug discovery faces several significant challenges, including high attrition rates, long development timelines, and escalating costs. In this context, target-based drug design (TBDD) has emerged as a powerful and widely adopted strategy, enabling the rational identification and optimization of bioactive molecules through well-defined molecular targets. To date, more than 1300 therapeutic agents have been approved by the U.S. Food and Drug Administration (FDA), of which approximately 1144 are small-molecule drugs, and notably, over 120 have been discovered using target-based drug design approaches [1, 2]. Importantly, the proportion of newly approved drugs originating from TBDD strategies has steadily increased in recent years.

Among these, small-molecule kinase inhibitors constitute a major class of therapeutics, largely owing to advances in computational modeling, structure-based drug design, and molecular docking techniques [3, 4]. The majority of such small molecules are built upon heterocyclic scaffolds, which serve as privileged structures in medicinal chemistry. In particular, quinazoline-based derivatives, regarded as bioisosteric analogues of purines, have attracted considerable attention due to their strong affinity for ATP-binding sites of kinases and their proven clinical relevance [5].

Within the framework of target-based drug discovery, the Janus kinase (JAK) family, comprising JAK1, JAK2, JAK3, and TYK2 (tyrosine kinase), represents a critical class of non-receptor tyrosine kinases involved in cytokine-mediated signaling pathways. Pharmacological inhibition of JAKs has demonstrated remarkable therapeutic efficacy in the treatment of inflammatory, autoimmune, and hematological disorders [6, 7]. To date, several heterocyclic JAK inhibitors have been approved by major regulatory agencies, including the FDA, EMA (European Medicinal Agency), PMDA (Pharmaceuticals and Medicinal Devices Agency, Japan), and NMPA (National Medical Products Administration, China) (Figure 1), and are currently used in clinical practice. Notable examples include tofacitinib (rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, alopecia areata), baricitinib (rheumatoid arthritis), ruxolitinib (myelofibrosis, graft-versus-host disease, polycythemia vera, acute myeloid leukemia, vitiligo), filgotinib (rheumatoid arthritis), upadacitinib (rheumatoid arthritis, atopic dermatitis, psoriatic arthritis), abrocitinib (atopic dermatitis), and pacritinib (myelofibrosis) [8, 9]:

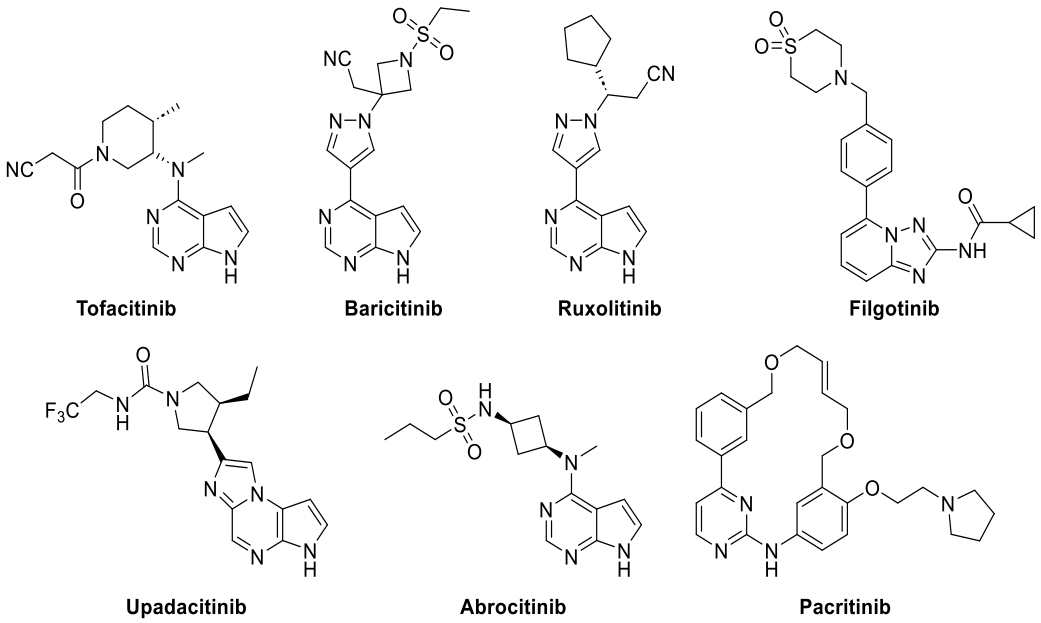


Figure 1. Approved Janus kinase (JAK) inhibitors used in clinical practice

Despite significant progress in JAK-targeted therapy, the development of novel JAK inhibitors with improved selectivity and reduced off-target toxicity remains an important challenge. In this regard, 4,6-disubstituted quinazoline scaffolds represent a privileged framework, as rational substitution at these positions enables scaffold hopping and structural optimization while maintaining key interactions within the ATP-binding site of JAK kinases. Based on this rationale, the present study focuses on the design and synthesis of novel 4,6-disubstituted quinazoline derivatives as potential JAK inhibitors. A structure-based design strategy supported by molecular docking studies was employed to identify favorable substitution patterns, followed by an efficient synthetic route that provides access to key intermediates suitable for further optimization and biological evaluation.

Research methodology. To carry out the targeted synthesis of quinazoline derivatives, a series of 4-aminoquinazolines substituted at the 6-position were rationally designed, and the novelty of the designed compounds was verified using the Reaxys database (https://www.reaxys.com/). Subsequently, molecular docking studies were performed using the Maestro program against the Janus kinase (JAK) protein (PDB ID: 4AQC) retrieved from the Protein Data Bank (PDB) (https://www.rcsb.org/). According to the docking results, 6-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 a high binding affinity of the ligands toward the kinase active site, as exemplified by compounds (Figure 2):

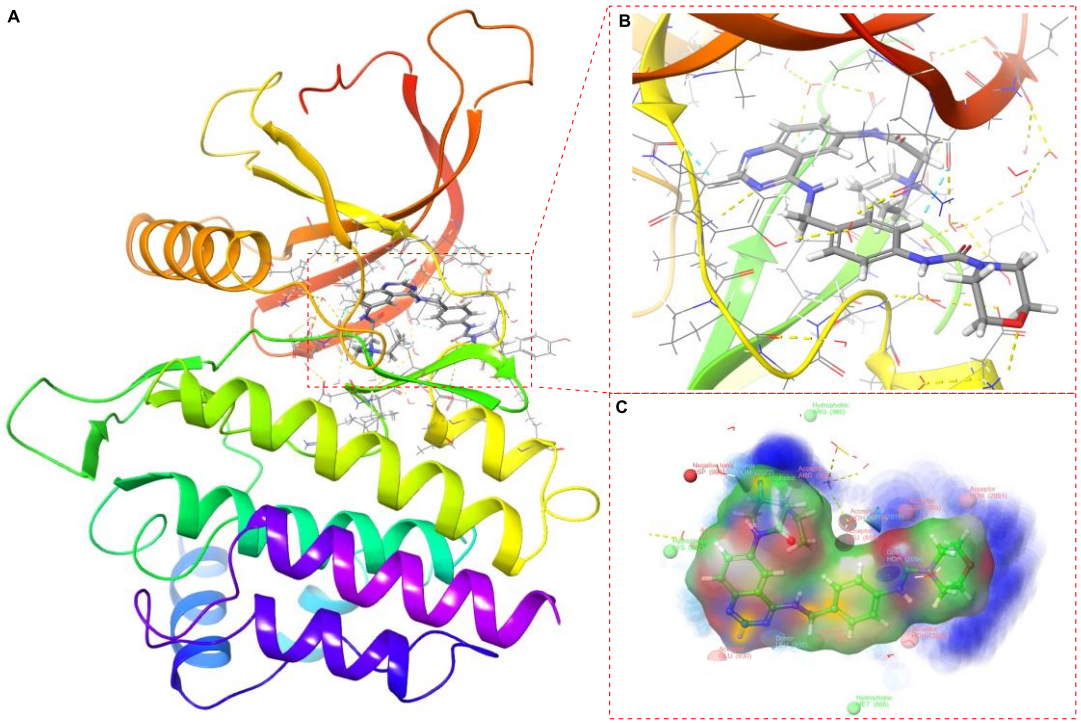
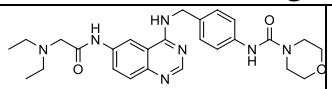
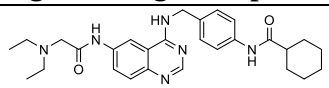
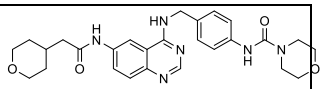
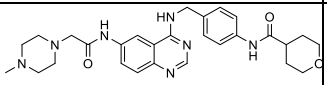
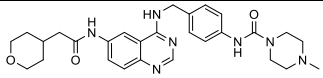
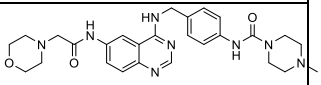
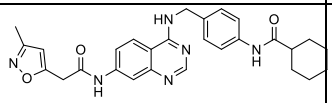
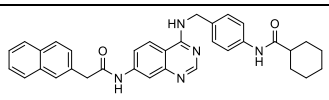
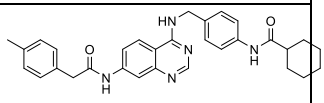


Figure 2. Molecular docking of 4,6-disubstituted quinazoline derivatives with JAK2 (PDB ID: 4AQC)

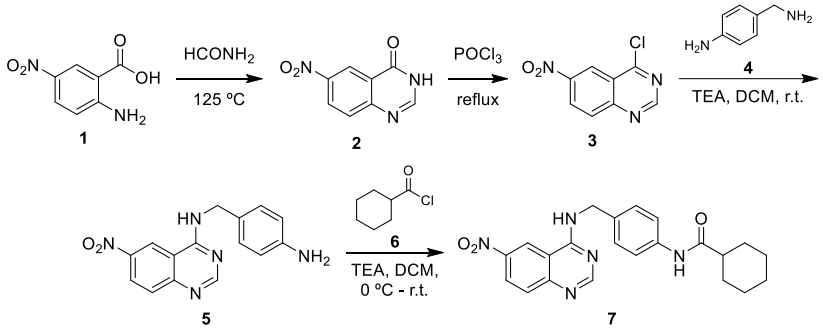
According to the molecular docking results, the compounds exhibiting the lowest binding energies were selected as the most promising candidates, and their corresponding docking scores are presented in Table 1:

Table 1. Binding energies of target compounds

Compounds Structures			
Binding energy, kcal/mol	–8.698	-6.799	-6.671
Compounds Structures			
Binding energy, kcal/mol	-6.564	-6.437	6.345
Compounds Structures			
Binding energy, kcal/mol	-6.218	-6.182	-6.093

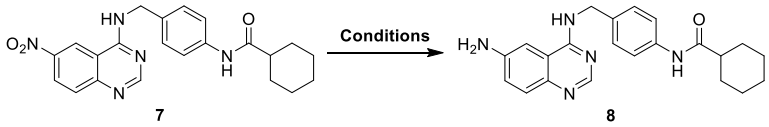
Based on the results of molecular docking studies, a series of promising quinazoline derivatives were identified and selected as priority candidates for synthesis. Guided by literature precedents, a targeted synthetic route for these compounds was subsequently developed, providing an efficient and reliable approach to obtain key intermediates.

The synthesis commenced from commercially available 5-nitroanthranilic acid (**1**). In the first step, compound **1** underwent Niementowski cyclization with formamide under solvent-free conditions at 125 °C, affording 6-nitroquinazolin-4(3*H*)-one (**2**). Subsequently, compound **2** was subjected to chlorination using $POCl_3$ under solvent-free conditions to yield 4-chloro-6-nitroquinazoline (**3**). Intermediate 3 then underwent selective nucleophilic substitution with 4-aminobenzylamine (**4**) in the presence of triethylamine (TEA) as a base in dichloromethane (DCM) at room temperature, furnishing intermediate **5**. In the final step, *N*-(4-aminobenzyl)-6-nitroquinazolin-4-amine (**5**) was acylated by the slow addition of cyclohexanecarbonyl chloride (**6**) under basic conditions (TEA) in DCM at 0 °C (ice bath), affording the nitro intermediate *N*-(4-(((6-nitroquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide (**7**) (Scheme 1).



SCHEME 1. Synthesis of nitro intermediate (**7**)

In the subsequent step, the reduction of the nitro group was investigated. To identify the most efficient and practical reduction protocol, three different methods were evaluated under varied reaction conditions. First, catalytic hydrogenation was carried out using 10% Pd/C under a hydrogen atmosphere in ethyl acetate at room temperature for 3 h. Second, chemical reduction was performed using $SnCl_2 \cdot 2H_2O$ in ethyl acetate under reflux conditions with overnight stirring. Third, a mild reduction system employing tetrahydroxydiboron in the presence of 4,4′-bipyridine in DMF was conducted from 0 °C to room temperature, completing within 10 min (Scheme 2):



SCHEME 2. Synthesis of key intermediate (**8**)

Among the evaluated conditions, the third condition was selected for subsequent studies, as it provided rapid reaction completion, higher yields, and operational simplicity compared to the other methods. Consequently, this approach was considered the most suitable for the efficient reduction of the nitro group in the present synthetic sequence.

Following the successful reduction of the nitro group, the resulting key amino intermediate was subjected to reactions with a diverse set of carboxylic acid derivatives, including acyclic, cyclic, heterocyclic, aromatic, and heteroaromatic acids. These transformations were carried out with the dual aim of obtaining target quinazoline derivatives and systematically investigating their structure–activity relationships (SAR). Reaction conditions were carefully optimized to maximize yields, selectivity, and operational efficiency, thereby enabling the synthesis of a focused library of structurally varied compounds suitable for subsequent biological evaluation.

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.

6-Nitroquinazolin-4(3*H*)-one (2). Yield 85%, light brown solid, Mp 133–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 2.7 Hz, 1H), 8.53 (dd, J = 9.0, 2.7 Hz, 1H), 8.32 (s, 1H), 7.85 (d, J = 9.0 Hz, 1H).

4-Chloro-6-nitroquinazoline (3). Yield 73%, light yellow solid, Mp 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 2.7 Hz, 1H), 8.56 (dd, J = 8.9, 2.7 Hz, 1H), 8.36 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H).

***N*-(4-Aminobenzyl)-6-nitroquinazolin-4-amine (5).** Yield 91%, light yellow solid, Mp 145–146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, J = 2.5 Hz, 1H), 9.38 (t, J = 5.8 Hz, 1H), 8.59 (s, 1H), 8.46 (dd, J = 9.2, 2.5 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H), 6.52 (d, J = 8.3 Hz, 2H), 5.01 (s, 2H), 4.62 (d, J = 5.6 Hz, 2H).

***N*-(4-(((6-Nitroquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide (7).** Yield 68%, off-white solid, Mp 145–146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 9.46 (t, J = 5.8 Hz, 1H), 9.41 (d, J = 2.5 Hz, 1H), 8.59 (s, 1H), 8.48 (dd, J = 9.2, 2.4 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 4.74 (d, J = 5.7 Hz, 2H), 2.30 (t, J = 11.5 Hz, 1H), 1.83 – 1.59 (m, 5H), 1.46 – 1.13 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.17, 160.15, 158.26, 152.86, 144.05, 138.45, 132.92, 129.14, 127.86, 126.33, 120.65, 119.04, 114.08, 44.79, 43.56, 29.12, 25.38, 25.22. HRMS (ESI) calcd for $C_{22}H_{23}N_5O_3$ [M+H]+ 405.1801, found 405.1809.

Three reduction methods for the synthesis of compound 8.

Method A (Catalytic hydrogenation). To a solution of intermediate **7** (0.405 g, 1.0 mmol) in ethyl acetate, 10% Pd/C (0.23 g) was added. The reaction mixture was placed under a hydrogen atmosphere and stirred at room temperature for 3 h. Upon completion of the reaction (monitored by TLC), the mixture was filtered through a pad of Celite to remove the catalyst. The filtrate was concentrated under reduced pressure to afford the crude product, which was subsequently purified by silica gel column chromatography (DCM/MeOH) to yield compound **8**.

Method B ($SnCl_2$-mediated reduction). Intermediate **7** (0.405 g, 1.0 mmol) and $SnCl_2{\cdot}2H_2O$ (1.356 g, 6.0 mmol) were dissolved in ethyl acetate. The resulting mixture was heated under reflux overnight with continuous stirring. After cooling to room temperature, the reaction mixture was filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (DCM/MeOH) to obtain compound **8**.

Method C ($B_2H_4O_4$-mediated reduction). 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**.

N-(4-(((6-aminoquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide (**8**). Yield 75%, light yellow solid, Mp 135–136 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.81 (s, 1H), 8.59 (s, 1H), 7.60 – 7.52 (m, 3H), 7.37 (d, J = 8.6 Hz, 1H), 7.33 (dd, J = 8.9, 2.3 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 6.01 (s, 1H), 4.80 (d, J = 5.8 Hz, 2H), 2.35 – 2.25 (m, 1H), 1.79 – 1.61 (m, 5H), 1.45 – 1.13 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.24, 158.91, 149.05, 147.21, 138.58, 132.33, 128.01, 127.75, 124.64, 119.07, 114.91, 101.62, 44.78, 44.00, 29.13, 25.39, 25.22. HRMS (ESI) calcd for $C_{22}H_{25}N_5O$ [M+H]+ 375.2059 found 375.2056.

Molecular docking. Molecular docking simulations were performed using Maestro Schrodinger. The X-ray crystal structure of JAK2 (PDB ID: 4AQC) was retrieved from the RCSB Protein Data Bank. The protein was prepared by adding hydrogens, assigning protonation states, and removing water molecules beyond 5 Å from heteroatoms. Ligands were constructed and energy-minimized using OPLS4. Docking grids were centered on the ATP-binding site, and the protocol was

validated by re-docking the co-crystallized ligand. All designed quinazoline derivatives were docked into JAK2 to evaluate binding interactions.

Conclusion. Janus kinases (JAKs) represent critical therapeutic targets for various immunological and hematological disorders, and quinazoline-based scaffolds have emerged as highly relevant chemical entities in this context. In the current study, the key amino intermediate was synthesized via multiple approaches, and the reaction conditions were systematically optimized to ensure high yield and operational simplicity. Molecular docking studies identified the most promising compounds, demonstrating high affinity toward the active site of JAK2 (PDB code 4AQC) and forming hydrogen bonds, aromatic hydrogen bonds, and multiple other interactions with the protein. The selected quinazoline derivatives were designed using scaffold-hopping and structural optimization strategies, making them highly prospective as targeted JAK inhibitors. Collectively, these results provide a robust foundation for the targeted synthesis of quinazoline derivatives and their further evaluation in structure–activity relationship studies and biological investigations.

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