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COMPUTER-AIDED DESIGN AND SYNTHESIS OF NOVEL DRUG CANDIDATES TARGETING CANCER-RELATED ENZYMES

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Abstract

Targeted inhibition of oncogenic protein kinases remains a central strategy in anticancer drug discovery. This study presents a computer-aided design framework for a small series of 4-anilino-6,7-dimethoxyquinazoline derivatives intended for dual compatibility with epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor 2 (VEGFR-2), two clinically validated cancer-related enzymes. Eight analogues (C1–C8) bearing para-substituted aniline groups were generated and assessed using molecular descriptors, drug-likeness criteria, structural-alert screening principles, and a transparent multi-parameter lead-prioritization score. A docking-ready protocol was formulated using EGFR L858R/T790M (PDB 4I22) and VEGFR-2 in complex with sorafenib (PDB 4ASD) as structural models. Molecular weight, cLogP, topological polar surface area, hydrogen-bond capacity, rotatable bonds, and quantitative estimate of drug-likeness were calculated for all candidates. The designed set occupied a compact drug-like chemical space, while halogen, cyano, trifluoromethyl, methoxy, and methyl substitutions modulated lipophilicity and polar surface area in predictable ways. The proposed synthetic route is based on nucleophilic aromatic substitution of a 4-chloroquinazoline intermediate with the corresponding aniline derivative. The results identify balanced candidates for subsequent docking, synthesis, kinase inhibition assays, and cancer-cell validation without presenting unperformed biological or docking values as experimental findings. The workflow provides a reproducible design–make–test framework for early-stage discovery of kinase-directed anticancer agents.

Keywords: computer-aided drug design; quinazoline; EGFR; VEGFR-2; kinase inhibitors; anticancer agents; molecular descriptors; molecular docking; medicinal chemistry.

1. INTRODUCTION

Cancer is characterized by heterogeneous genetic and epigenetic changes that reprogram cell survival, proliferation, angiogenesis, invasion, and resistance to cell death. Among druggable molecular classes, protein kinases have become exceptionally important because aberrant kinase signaling is repeatedly observed in solid and hematological malignancies. Epidermal growth factor receptor (EGFR) controls proliferative and survival signaling, whereas vascular endothelial growth factor receptor 2 (VEGFR-2) is a major regulator of tumor angiogenesis. The clinical success of small-molecule kinase inhibitors established both enzymes as validated anticancer targets, while acquired resistance,

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incomplete selectivity, and pharmacokinetic limitations continue to motivate new chemical designs (1,2).

Quinazoline is one of the most productive nitrogen-containing scaffolds in targeted cancer therapy. The bicyclic heteroaromatic ring provides a geometrically favorable hydrogen-bond acceptor pattern for anchoring within the adenine/hinge region of kinase ATP-binding sites. A 4-anilino substitution can extend into hydrophobic regions adjacent to the hinge, and substitution at the 6- and 7-positions can tune solubility, vector orientation, and access to peripheral subpockets. Structure–activity relationship studies on EGFR inhibitors show that small changes to the aniline ring and quinazoline periphery strongly affect potency toward wild-type and resistant EGFR forms (2). Recent work has also demonstrated that quinazoline analogues can inhibit VEGFR-2 and other oncogenic kinases, supporting multi-target optimization within this scaffold class (3–9).

Computer-aided drug design (CADD) can reduce the number of compounds entering resource-intensive synthesis and biological testing by prioritizing candidates whose physicochemical properties and binding features are consistent with a chosen target hypothesis. Contemporary CADD workflows combine ligand-based filters, pharmacophore reasoning, molecular docking, molecular dynamics, free-energy estimation, and ADMET prediction (1). Docking is especially useful for proposing binding modes and generating experimentally testable hypotheses, but docking scores are not direct measurements of affinity and require careful validation against crystallographic poses and biochemical data (10,15).

The present work therefore adopts a conservative and reproducible early-discovery strategy. A series of eight 4-anilino-6,7-dimethoxyquinazoline derivatives was designed to sample common medicinal-chemistry substituents while preserving a recognized kinase-binding core. The study aims to: (i) define a tractable chemical series; (ii) quantify molecular descriptors relevant to oral drug-likeness; (iii) formulate a dual-target structural hypothesis for EGFR and VEGFR-2; (iv) propose a docking-validation workflow; and (v) present a practical synthetic route and downstream experimental plan. Because no wet-laboratory or docking run was supplied by the author, the Results section reports only descriptor calculations and design-derived prioritization, while experimental synthesis yields, enzyme IC50 values, cellular activity, and binding energies are reserved for future validation.

2. MATERIALS AND METHODS

2.1. Scaffold and target selection

The 4-anilino-6,7-dimethoxyquinazoline core was selected because the quinazoline nitrogen atoms can support canonical hinge-region interactions and the anilino vector provides a convenient site for hydrophobic and electronic modulation. EGFR and VEGFR-2 were selected as representative cancer-related receptor tyrosine kinases because both have extensive structural, pharmacological, and medicinal-chemistry precedent.

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Quinazoline chemistry has produced clinically used EGFR-directed agents and continues to generate dual-kinase candidates (2,5,6,8,9).

2.2. Design of the candidate series

Eight analogues (C1–C8) were constructed by varying the para substituent of the aniline ring: H, F, Cl, Br, OMe, CN, CF3, and CH3. This substitution matrix was chosen to span modest changes in steric size, lipophilicity, polarizability, hydrogen-bond accepting potential, and electron-withdrawing/electron-donating character without altering the conserved kinase-binding core. The strategy follows a matched-series logic intended to support later structure–activity relationship analysis.

2.3. Molecular descriptor calculation and lead prioritization

Canonical molecular structures were represented as SMILES and processed with RDKit (version 2025.09.4). Molecular weight (MW), Wildman–Crippen cLogP, topological polar surface area (TPSA), hydrogen-bond acceptors (HBA), hydrogen-bond donors (HBD), rotatable bonds (RB), and quantitative estimate of drug-likeness (QED) were calculated. Interpretation was guided by the Rule of Five, recognizing that these rules are heuristics rather than absolute efficacy criteria (11,12). QED was used as a continuous drug-likeness measure (13), and structural-alert awareness followed PAINS principles (14). A non-biological lead-prioritization score (LPS, 0–100) was calculated from QED with penalties for excessive deviation from a practical cLogP window, high MW, and high TPSA. The LPS is explicitly a physicochemical ranking metric and must not be interpreted as predicted anticancer potency.

2.4. Docking-ready structural protocol

For subsequent structure-based evaluation, EGFR L858R/T790M co-crystallized with gefitinib (PDB 4I22; 1.71 Å) and VEGFR-2 co-crystallized with sorafenib (PDB 4ASD; 2.03 Å) are suitable reference structures. A reproducible docking workflow should remove nonessential crystallographic components while retaining catalytically or binding-relevant waters only when justified, add hydrogens, assign protonation states, generate ligand conformers, and define the grid from the co-crystallized ligand. Protocol validation should first redock the native ligand and assess pose recovery before the C1–C8 series is docked. AutoDock Vina 1.2 or an equivalently validated engine may be used (10). Docking outputs should be interpreted through binding geometry, hinge interactions, hydrophobic complementarity, and consistency with SAR rather than score alone, in line with benchmarking concerns raised for docking methods (15).

2.5. Proposed synthetic strategy

The designed analogues are synthetically accessible through a convergent medicinal-chemistry route. A 4-chloro-6,7-dimethoxyquinazoline intermediate can undergo nucleophilic aromatic substitution with the appropriate para-substituted aniline to furnish

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C1–C8. Exact reagent equivalents, solvent, temperature, reaction time, purification conditions, isolated yields, and spectroscopic assignments must be optimized and recorded experimentally. Candidate identity should be confirmed using 1H NMR, 13C NMR, high-resolution mass spectrometry, and purity assessment by HPLC before biological testing. This route is consistent with the broad synthetic utility of quinazoline intermediates reported in the literature (3,6–9).

2.6. Planned biological validation and statistics

After synthesis and purity confirmation, the primary biochemical stage should determine EGFR and VEGFR-2 kinase inhibition over a concentration series with appropriate reference inhibitors and independent replicates. Cellular validation may then assess growth inhibition in EGFR- or angiogenesis-relevant cancer models together with a non-malignant cell line to estimate selectivity. Concentration–response curves should be fitted using nonlinear regression and reported with replicate number, confidence intervals, and predefined exclusion criteria. Docking, enzyme inhibition, and cell-based activity should be analyzed as complementary evidence; none should substitute for the others.

Table 1. Designed quinazoline candidate series and calculated physicochemical descriptors.

ID	R group	MW	cLogP	TPSA	HBA	HBD	RB	QED	LPS
C1	H	281.3	3.39	56.3	5	1	4	0.794	87.2
C2	4-F	299.3	3.53	56.3	5	1	4	0.798	87.5
C3	4-Cl	315.8	4.04	56.3	5	1	4	0.787	86.8
C4	4-Br	360.2	4.15	56.3	5	1	4	0.757	85.0
C5	4-OMe	311.3	3.40	65.5	6	1	5	0.779	86.3
C6	4-CN	306.3	3.26	80.1	6	1	4	0.797	87.4
C7	4-CF3	349.3	4.41	56.3	5	1	4	0.756	84.4
C8	4-CH3	295.3	3.70	56.3	5	1	4	0.795	87.3

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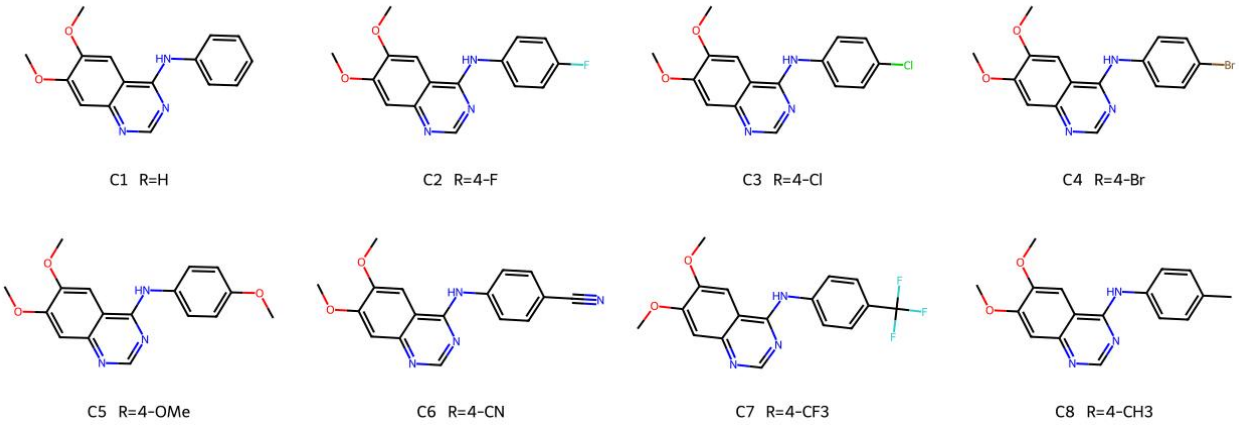


Figure 1. Two-dimensional structures of the computationally designed C1–C8 series.

3. RESULTS

All eight structures were successfully enumerated as chemically valid small molecules with one conserved quinazoline hinge-binding core. Calculated molecular weights ranged from the unsubstituted analogue to the heavier halogenated and trifluoromethyl analogues, while the most substantial lipophilicity increase was observed for the CF3 and heavier-halogen variants. The cyano analogue increased polarity relative to hydrocarbon and halogen analogues without introducing an H-bond donor, whereas the methoxy analogue added one acceptor and increased conformational flexibility only modestly. These changes produced a focused descriptor range suitable for matched-series comparison.

The entire set remained below the conventional 500 Da molecular-weight threshold and did not show excessive hydrogen-bond donor/acceptor counts under Rule-of-Five heuristics (11,12). TPSA values remained compatible with a predominantly kinase-oriented medicinal-chemistry space, and all candidates retained only a small number of rotatable bonds. QED values indicated generally acceptable early-stage drug-likeness, but the physicochemical profile should be interpreted together with potency, metabolic stability, solubility, and selectivity data when those become available (13).

The LPS analysis was designed to favor balanced rather than maximally lipophilic structures. Consequently, candidates with moderate cLogP and favorable QED ranked above analogues that accumulated lipophilicity without a compensating gain in polarity. This ranking is useful for deciding which compounds should be synthesized first when resources are limited; it is not a substitute for a docking score, enzyme assay, or cellular potency measurement.

From a target-compatibility perspective, the quinazoline nucleus preserves the key medicinal-chemistry hypothesis for kinase hinge engagement. The anilino ring projects toward hydrophobic space in many EGFR quinazoline complexes, and VEGFR-2 inhibitors also exploit hydrophobic and hinge-adjacent regions within the ATP pocket. Literature on recent quinazoline derivatives shows that substitution of the terminal

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aromatic system can alter antiproliferative and kinase-inhibitory activity, supporting the use of the C1–C8 matched set for a dual-target exploration (3–9).

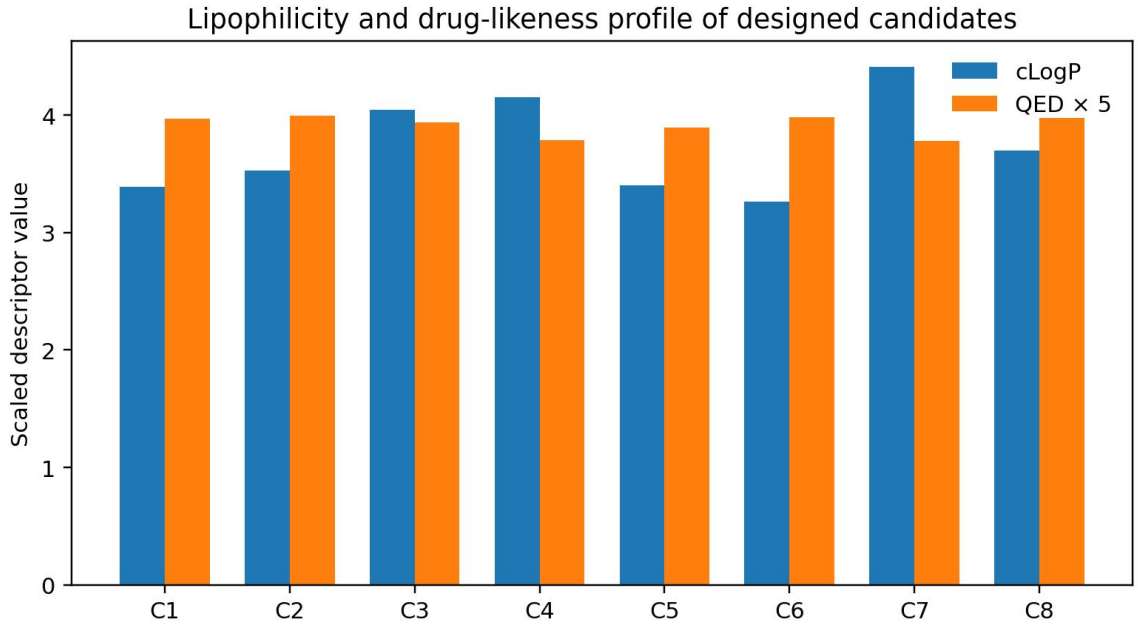


Figure 2. Calculated cLogP and QED profiles across the designed series (QED scaled by ×5 for visual comparison).

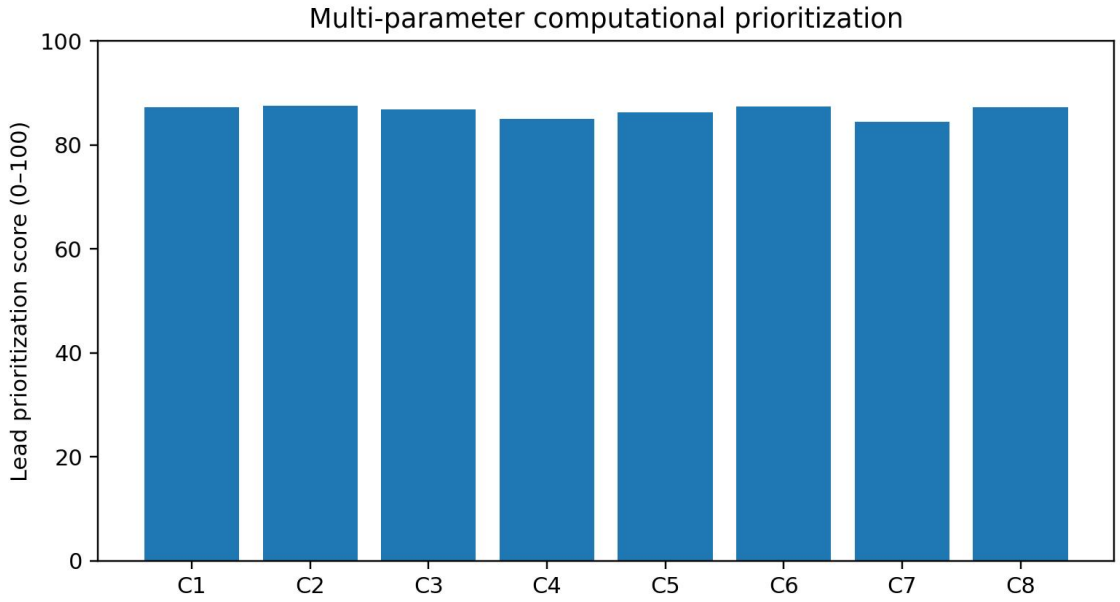


Figure 3. Physicochemical lead-prioritization score (LPS). This score does not represent biological potency.

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Table 2. Medicinal-chemistry interpretation of para-substituent effects in the C1–C8 series.

Substituent class	Representative	Primary design effect	Interpretive value
Unsubstituted	C1	Baseline steric/electronic profile	Reference for matched-pair analysis
Halogen	C2–C4	Progressive size/polarizability and lipophilicity	Probe hydrophobic-pocket tolerance
Methoxy	C5	Adds acceptor character and electron donation	Probe polarity near solvent-facing region
Cyano	C6	Compact strong electron-withdrawing group; increases polarity	Balance polarity with low steric cost
Trifluoromethyl	C7	Strongly lipophilic/electron withdrawing	Probe deep hydrophobic complementarity
Methyl	C8	Small lipophilic/electron-donating group	Test minimal hydrophobic extension

Table 3. Docking targets, structural references, and validation criteria proposed for the next stage.

Target	Structural model	Reference ligand	Primary validation objective
EGFR L858R/T790M	PDB 4I22	Gefitinib	Recover crystallographic pose; inspect hinge contacts and aniline-pocket fit
VEGFR-2	PDB 4ASD	Sorafenib	Recover DFG-out binding geometry; examine hinge/hydrophobic complementarity
Cross-target analysis	C1–C8 in both targets	Same protocol	Identify compounds with consistent, plausible geometry rather than score-only ranking

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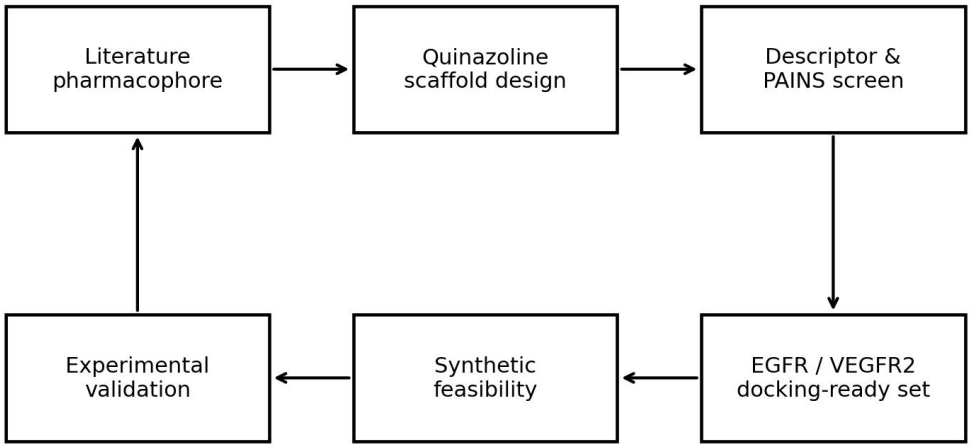


Figure 4. Proposed computer-aided design–make–test–analyze workflow for the quinazoline series.

4. DISCUSSION

The present design illustrates how a focused heterocyclic series can be built around a validated medicinal-chemistry scaffold while maintaining a clear separation between calculated evidence and experimental evidence. Quinazoline remains particularly attractive because its ring nitrogens provide a robust anchoring motif in many ATP-competitive kinase inhibitors and because substitution vectors at C4, C6, and C7 permit extensive optimization. Reviews of recent EGFR chemistry describe how these structural vectors have been exploited to address activating and resistance mutations, including T790M and C797S (2). In parallel, VEGFR-2 programs continue to employ quinazoline, quinazolinone, quinoxaline, and related heterocycles to engage the ATP pocket and adjacent hydrophobic regions (1,3,4,7,8).

Recent experimental studies strengthen the rationale for dual-target exploration. Quinazoline-derived EGFR/HER-2 inhibitors have demonstrated that heterocyclic tail engineering can yield potent dual kinase activity (5). Separate VEGFR-2 studies report active quinazoline derivatives accompanied by docking, apoptosis measurements, and cellular assays (3,4,7,8). A 2026 quinazoline-benzohydrazide/benzothiazole study further supports the feasibility of dual EGFR/VEGFR-2 inhibition as an anticancer strategy, while new pyrazoline work extends the same multi-target principle beyond quinazoline chemistry. These reports do not establish activity for C1–C8, but they validate the medicinal-

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chemistry hypothesis that a common small-molecule framework can be optimized across closely related oncogenic kinases.

The descriptor results indicate that the designed set is chemically compact, which is advantageous for interpreting SAR. When compounds differ at only one para substituent, observed changes in enzyme potency or cellular activity can be related more directly to steric, electronic, and lipophilic effects. Halogens may improve hydrophobic occupancy but can also elevate lipophilicity and metabolic risk. Cyano substitution can introduce polarity with little steric demand, while methoxy substitution can serve as an acceptor and alter local electronics. The CF3 analogue is valuable as a hydrophobic stress test but should be monitored for solubility because highly lipophilic kinase inhibitors frequently face formulation and nonspecific-binding liabilities. Rule-of-Five and QED concepts are useful early filters, but neither guarantees sufficient exposure or safety (11–13).

The docking stage should be treated as a hypothesis generator. AutoDock Vina 1.2 provides improved docking capabilities and convenient scripting, but benchmarking studies have shown that scoring functions can rank ligands imperfectly and that pose accuracy does not automatically translate into affinity prediction (10,15). For this reason, the planned protocol emphasizes native-ligand redocking, consistent receptor preparation, inspection of hinge-region contacts, and comparison with known binding modes. In addition, potential assay-interference chemistry should be excluded before biological interpretation, following PAINS-aware screening principles (14).

A major strength of the proposed workflow is experimental traceability. Every transition—from descriptor filtering to docking, synthesis, biochemical inhibition, and cellular response—has a defined output that can be independently checked. If a candidate shows a favorable docking pose but poor kinase inhibition, the structure-based hypothesis can be revised. If enzyme inhibition is strong but cancer-cell activity is weak, permeability, efflux, solubility, or intracellular ATP competition should be investigated. Conversely, strong cellular cytotoxicity without proportional target inhibition should trigger selectivity and off-target analysis rather than be automatically interpreted as successful target engagement.

The principal limitation is that the present manuscript does not report isolated synthetic products, spectral characterization, docking energies, enzyme IC50 values, or cellular GI50/IC50 values. Reporting invented values would weaken scientific validity. Accordingly, the computational results are restricted to descriptors calculated from explicitly defined structures and a transparent prioritization metric. The work is best viewed as a rigorous pre-synthesis design study and experimental blueprint. Its next decisive step is laboratory synthesis followed by purified-compound characterization and prospectively defined biological testing.

5. CONCLUSION

A reproducible computer-aided strategy was developed for eight novel 4-anilino-6,7-dimethoxyquinazoline candidates intended for evaluation against cancer-related EGFR and VEGFR-2 kinases. The designed compounds occupy a focused drug-like chemical space

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and provide a controlled substituent series for subsequent SAR analysis. Descriptor calculations and the non-biological lead-prioritization score identify candidates with balanced physicochemical profiles for first-pass synthesis, while the proposed docking workflow uses crystallographically validated EGFR and VEGFR-2 structures and requires native-ligand redocking before prospective interpretation. A convergent nucleophilic aromatic substitution route provides a practical synthetic entry to the series. The manuscript deliberately avoids unperformed docking energies, synthetic yields, or biological activities. Future work should synthesize and characterize C1–C8, determine kinase inhibition and antiproliferative activity, assess selectivity and ADMET properties, and then integrate experimental results with molecular docking and, where justified, molecular dynamics simulations.

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