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AI-GUIDED DESIGN AND DEVELOPMENT OF HYBRID MULTI-TARGET TYROSINE KINASE INHIBITORS: EMERGING STRATEGIES FOR DUAL EGFR/VEGFR BLOCKADE WITH PI3K/MTOR/JAK MODULATION

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ABSTRACT

The growing complexity of cancer signalling networks has revealed the limitations of single-target tyrosine kinase inhibitors, particularly against tumours driven by epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR). Crosstalk with downstream pathways such as PI3K/AKT, mTOR, and JAK/STAT frequently enables escape from therapy and promotes drug resistance. Recent medicinal chemistry efforts focus on hybrid or multi-target ligands capable of simultaneously modulating EGFR, VEGFR, and key signalling partners within a single molecular framework. This strategy aims to enhance therapeutic efficacy, mitigate combination-drug toxicity, and delay the onset of resistance by inhibiting compensatory mechanisms. Advances in structure-guided design, scaffold hybridization, and computational modelling have accelerated the discovery of potent dual and triple inhibitors with favourable pharmacokinetic profiles. This review highlights emerging design principles, chemical scaffolds, and preclinical progress in hybrid tyrosine kinase inhibitors as an evolving approach for durable cancer treatment.

KEYWORDS: Cancer; Chemical Scaffolds; Ligands; Scaffold Hybridization; Structure-Guided Design; Tyrosine Kinase.

1. INTRODUCTION

Therapeutic inhibition of epidermal growth factor receptor (EGFR) produces strong initial responses in several cancers, but durable benefit is limited by acquired resistance; for example, progression after third-generation EGFR inhibitors is often associated with the C797S substitution that abolishes covalent inhibitor binding [1]. EGFR signalling interacts with vascular endothelial growth factor (VEGF) pathways in tumours: tumour-cell EGFR activity can up-regulate VEGF and establish autocrine/paracrine loops that reinforce proliferation and survival, providing a biological rationale to consider VEGF/VEGFR co-targeting in EGFR-driven cancers [2]. VEGFR2 activation couples to PLCγ and downstream effectors to control vascular permeability, immune infiltration and the tumour microenvironment mechanisms that influence therapy response and support VEGFR2 as a complementary target to tumour-intrinsic kinases [3]. Medicinal chemistry has produced bona fide small-molecule series that inhibit both EGFR and VEGFR-2 in vitro; for example, thiazolyl-pyrazoline derivatives have been reported with low-nanomolar activity against both kinases and antiproliferative activity in lung cancer cell lines [4]. Privileged heterocyclic scaffolds such as thieno[2,3-d] pyrimidines remain tractable starting points for EGFR-directed design and can be adapted by scaffold hybridisation to engage additional kinases, making them attractive cores for multi-target optimisation [5]. Inhibition of downstream nodes (for example, PI3K/AKT/mTOR) can produce compensatory feedback, including activation of JAK/STAT3 that limits the efficacy of single-node blockade, arguing that multi-target strategies should anticipate and suppress such feedback circuits [6]. Collectively, these studies justify medicinal-chemistry efforts to design single molecules or tightly rationalised combinations that simultaneously blunt EGFR-driven tumour growth, angiogenic VEGFR2 signalling, and key downstream escape routes (e.g., PI3K/STAT3) [7]. This review synthesizes current strategies in hybrid tyrosine kinase inhibitor development, emphasising how simultaneous modulation of EGFR, VEGFR, and allied pathways may overcome resistance.

2. DESIGN STRATEGIES FOR HYBRID EGFR/VEGFR-TARGETED MOLECULES

2.1 Quinazolinone Scaffold Hybridization

Recent medicinal-chemistry efforts reported S-alkylated quinazolin-4(3H)-ones as potent dual EGFR/VEGFR-2 inhibitors. Key analogues (e.g., compound 4) demonstrated micromolar-level inhibition and superior antiproliferative effects compared to sorafenib.

Molecular docking studies confirmed plausible binding modes across both kinase ATP sites, making this scaffold an attractive starting point for hybrid design.[8]

2.2 Fused Pyrazole Derivatives with Dual Kinase Activity

A series of fused pyrazole derivatives was synthesized and assessed for anticancer potential. Among these, compound 3 exhibited strong EGFR inhibition ($IC_{50} \approx 0.06$ μM), while compound 9 was highly potent against VEGFR-2 ($IC_{50} \approx 0.22$ μM). Docking confirmed dual binding capability. These results illustrate how a single fused heterocycle can modulate both targets effectively.[9]

2.3 2-Thioxoimidazolidin-4-one Dual Inhibitors with Apoptotic Function

Researchers developed 2-thioxoimidazolidin-4-one derivatives that simultaneously inhibit EGFR and VEGFR-2 and induce apoptosis. Compounds 6 and 8a outperformed both sorafenib and erlotinib across MCF-7, HepG2, and A549 cell lines, triggering caspase-mediated apoptotic signalling and cell cycle arrest. These multifunctional profiles are promising for multi-pathway targeting.[10]

2.4 Structural Motifs: Diaryl Pyrimidines with Apoptosis Induction

A novel series of 4,6-diaryl pyrimidines was designed to inhibit both EGFR and VEGFR-2. In A-549 cells, compounds 22 and 29 significantly increased Bax levels (~35-37-fold vs. staurosporine) and suppressed migration in wound-healing assays exhibiting both kinase inhibition and functional anti-invasion activity.[11]

3. SAR TRENDS & BINDING-MODE INSIGHTS

3.1 Thienopyrimidine Derivatives (Cyclohepta[4,5] thieno[2,3-d] pyrimidines)

Aml E-S Mghwary et al. reported a series of thienopyrimidine derivatives targeting both EGFR and VEGFR-2. Compound 5f exhibited highly potent EGFR inhibition, 1.18-fold more active than erlotinib and micromolar VEGFR-2 inhibition ($IC_{50} \approx 1.23$ μM). It induced G_2/M cell cycle arrest and apoptosis in MCF-7 cells.[12]

3.2 Dual SAR & Docking: Fused Pyrazoles

Saleh et al. synthesized fused pyrazole derivatives, with compounds 9 and 12 demonstrating excellent dual inhibition. Docking analyses revealed direct hydrogen bonding: compound 9 formed H-bonds with EGFR (Met769, Leu694) and VEGFR-2 (Asp1046, Glu885);

compound 12 exhibited deeper binding in EGFR with stronger docking scores (~-12.90 kcal/mol vs. -12.01 kcal/mol).[13]

3.3 4,6-Diaryl Pyrimidines with Functional Effects

Mostafa et al. designed 4,6-diaryl pyrimidines compounds 22 and 29 stood out with low nanomolar GI_{50} values (22-24 nM) in a 60-cell-line panel. These dual inhibitors elevated pro-apoptotic Bax, reduced Bcl-2, and strongly inhibited cell migration; docking scores were comparable to erlotinib and sorafenib in EGFR and VEGFR-2 sites.[14]

3.4 Pyrazolopyridine Dual Inhibitor

Shimaa M Alhamaky et al. evaluated pyrazole/pyrazolopyridine derivatives: compound 3f displayed dual EGFR and VEGFR-2 inhibition with IC_{50}s around 0.066-0.184 µM and 0.102-0.418 µM, respectively. It induced G1/S arrest, sharply elevated Bax and caspase-3, reduced Bcl-2, and showed strong selectivity toward HCT-116 cancer cells (selectivity index ≈ 20.8).[15]

4. DISTINCT STRATEGIES FOR MULTI-TARGET KINASE MODULATION

4.1 Rational Polypharmacology & Designed Selective Non-Selectivity

Focuses on deliberately designing molecules that perturb multiple relevant targets with a desirable selectivity profile, which balances efficacy and safety by avoiding undesired off-target activity.[16] Employs systems biology to map disease-relevant target networks to guide molecule design.

4.2 Dual-Family Inhibitors via Shared Pocket Features

The kinase inhibitor PP121 exemplifies small molecules rationally designed to selectively inhibit both tyrosine kinases and PI3-kinases. Structural analysis revealed that conserved hydrophobic pockets across these families enabled dual binding.[17]

4.3 Resistance-Busting Covalent and Reversible Covalent Inhibitors

- ***Targeted covalent inhibitors (TCIs):*** Utilize electrophile warheads to form covalent bonds with unique nucleophiles (e.g., cysteine) near the binding site, yielding high potency and durable inhibition. EGFR was among the first kinases targeted by this approach.[18]

- ***Reversible covalent kinase inhibitors (RCKIs):*** Combine selectivity of covalent binding with controlled reversibility to mitigate long-term toxicity risks [19]. These strategies enable targeting of both wild-type and resistant mutants in a single scaffold.

4.4 PROTAC-Mediated Kinase Degradation

PROTACs (Proteolysis Targeting Chimeras) are heterobifunctional molecules that induce ubiquitination and proteasomal degradation of target proteins rather than inhibiting them enzymatically [20]. PROTACs can potentially degrade both EGFR and VEGFR when linked to appropriate ligands, reducing the need for simultaneous binding affinity across both targets.

4.5 Chemogenomics & Fragment-Based Multi-Target Screening

- ***Chemogenomics:*** Systematic testing of chemical libraries against broad target families to identify multi-target active scaffolds and new lead compounds.[21]
- ***Fragment-based approaches:*** While underutilized, this strategy allows the discovery of small fragments that bind multiple targets, which can then be elaborated into multi-target ligands.[16]

4.6 Dynamic Combinatorial Chemistry (DCC)

Protein-templated DCC leverages reversible chemistry (e.g., hydrazone, disulfide exchanges) within a dynamic library to select ligands that best bind the target(s) under biological conditions.[22] This can enable the evolution of molecules that adaptively fit multiple binding sites perfect for designing EGFR/VEGFR hybrids.

5. THERAPEUTIC POTENTIAL OF DUAL EGFR/VEGFR AND MULTI-TARGET STRATEGIES

5.1 Preclinical Efficacy in Tumour Models

Combined inhibition of EGFR and VEGFR pathways has shown strong antitumor activity in preclinical models. In NSCLC xenografts representing primary and acquired resistance, dual blockade (e.g., using vandetanib or bevacizumab plus erlotinib) achieved superior tumour regressions compared to EGFR-targeted therapy alone, likely due to synergistic effects on both tumour cells and tumour vasculature.[23]

5.2 Clinical Evidence in NSCLC

Clinical studies combining EGFR TKIs with anti-VEGF/VEGFR agents (e.g., bevacizumab or ramucirumab) have indicated improved outcomes in EGFR-mutant NSCLC patients: notably, progression-free survival (PFS) increased to approximately 18-19 months compared to ~11-12 months with monotherapy. These combination regimens are now considered promising first-line strategies.[24]

5.3 Meta-Analysis Insights

A systematic review and meta-analysis of randomized trials revealed that dual inhibition significantly improved PFS by about 20% compared with single-target therapy, although benefits in overall survival (OS) were modest. Subgroup analyses suggest that combination regimens (e.g., erlotinib + bevacizumab) yield more consistent PFS gains.[25]

5.4 Broader Rationale Beyond Lung Cancer

Multi-target VEGFR-2 inhibitors targeting EGFR, c-Met, BRAF, HDAC, and others in addition to VEGFR2, have garnered attention for broader anticancer applicability. These dual or multi-target agents may offer enhanced efficacy, better pharmacokinetic profiles, and reduced toxicity compared to traditional single-target VEGFR inhibitors.[26]

5.5 Emerging Monotherapy Dual-Target Agents

Medicinal chemistry efforts have produced dual EGFR/VEGFR inhibitors (e.g., S-alkylated quinazolinones and 2-thioxoimidazolidin-4-ones) that show potent anticancer activity in cell models, matching or exceeding standard therapies in inducing apoptosis, disrupting the cell cycle, and suppressing proliferation.[27,28]

6. PHARMACOLOGICAL ACTIVITIES OF DUAL EGFR/VEGFR AND MULTI-TARGET INHIBITORS

6.1 PP121-Dual Tyrosine Kinase and PI3K Inhibitor

PP121, designed to target both receptor tyrosine kinases (RTKs) and PI3 kinase family members, suppresses proliferation, induces apoptosis, and inhibits migration in anaplastic thyroid carcinoma (ATC) cell lines. It also demonstrated significant tumor growth inhibition in ATC xenograft models, confirming strong anticancer potential.[29]

6.2 Dihydropyrimidine Dual EGFR/VEGFR-2 Inhibitors

Compounds 12 and 15 among a dihydropyrimidine series displayed potent cytotoxicity across cancer cell lines (GI_{50} ≈ 35-37 nM), comparable to erlotinib. Biochemical assays revealed compound 15 inhibited EGFR and VEGFR-2 with IC_{50} values of ~84 nM and ~3.5 nM, respectively, while also inducing apoptosis and confirming binding via molecular docking.[30]

6.3 4,6-Diaryl Pyrimidine Series

Compounds 22 and 29 exhibited GI_{50} values of 22 and 24 nM across a 60-cell-line panel. They elevated apoptotic marker Bax (~35–37-fold) and suppressed Bcl-2 in A-549 cells, and strongly inhibited migration (100% wound closure inhibition at 72 h with compound 22), illustrating functional advantages beyond biochemical inhibition.[31]

Table 1: Approved and Investigational EGFR/VEGFR or Multi-Targeted Agents.

Drug Name	Status	Targets (Key)	Indications / Trials	Reference
Vandetanib	Approved	EGFR, VEGFR-2, RET	Medullary thyroid carcinoma, NSCLC	[32]
Lenvatinib	Approved	VEGFR-1-3, FGFR1-4, PDGFR, RET	Thyroid cancer, RCC, HCC	[33]
Sunitinib	Approved	VEGFR-1-3, PDGFR, KIT, FLT3, RET	RCC, GIST, pancreatic NETs	[34]
Sorafenib	Approved	VEGFR-1-3, RAF kinases, PDGFR, RET	HCC, RCC, thyroid carcinoma	[35]
Cabozantinib	Approved	VEGFRs, MET, RET, AXL	Medullary thyroid cancer, RCC, HCC	[36]
Regorafenib	Approved	VEGFRs, PDGFR, KIT, FGFR, BRAF	mCRC, GIST, HCC	[37]
Linifanib (ABT-869)	Investigational	VEGFR-1-3, PDGFR, KIT, FLT3	Phase II trials in NSCLC, HCC	[38]
XL647	Investigational	EGFR, HER2, VEGFR-2, EphB4	Phase II NSCLC	[39]
Tinengotinib (TT-00420)	Investigational	FGFR1-3, JAK1/2, VEGFRs, Aurora A/B	TNBC and solid tumor trials	[40]
Ibcasertib (CS-2164)	Investigational	VEGFR1-3, PDGFRα, KIT, Aurora B, CSF-1R	Hematological & solid tumors	[41]

7. CONCLUSION

Dual inhibition of EGFR and VEGFR offers a promising way to curb both tumor cell growth and angiogenesis. Advances in scaffold design and multi-target strategies are producing compounds with stronger efficacy and fewer resistance issues. Evidence from recent studies shows that well-engineered dual inhibitors can improve therapeutic outcomes while maintaining tolerable safety profiles, positioning them as valuable candidates for next-generation cancer treatment.

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9. DISCLOSURE OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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