International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

"Multitargeted Approaches in Cancer Therapy Using Nitrogen-Embedded Compounds"

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Abstract:

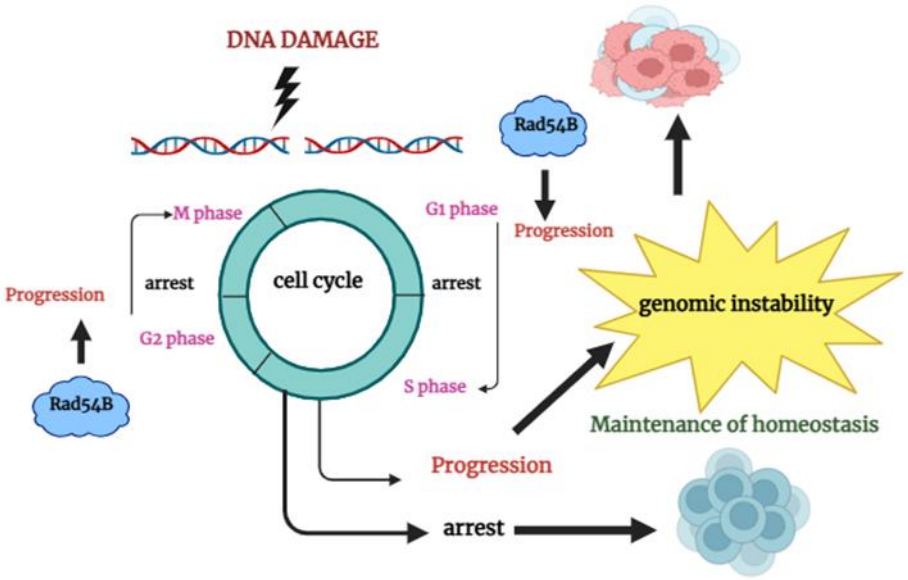
Cancer continues to be one of the most widespread and life-threatening diseases globally, driving the pursuit of more effective and less harmful treatment strategies. Among the promising approaches, nitrogen-containing heterocyclic compounds—such as quinoline, quinazoline, and pyrimidine—have received considerable attention for their diverse anticancer properties. These molecular frameworks play a critical role in targeted cancer therapies due to their capacity to inhibit essential enzymes and pathways like EGFR, PARP, PI3K, and topoisomerases. This overview emphasizes the structure-activity relationships (SAR), therapeutic mechanisms, and recent progress in the design of nitrogen-based anticancer agents. It discusses a range of compounds that exhibit strong activity against cancers such as those affecting the breast, lungs, liver, and colon, supported by molecular docking and in vivo studies that confirm their target-binding potential and therapeutic efficacy. Overall, this document offers valuable insights for researchers involved in the discovery and development of innovative cancer therapies utilizing nitrogen-rich molecular scaffolds.

Keywords:

Nitrogen-containing scaffolds, Quinoline, Quinazoline, Pyrimidine, Cancer therapy, EGFR inhibition, Molecular docking, SAR, Targeted therapy, Anticancer agent

1. Introduction:

Cancer remains a major global health challenge and a leading cause of life-threatening conditions across both developing and developed countries. [1] According to the World Health Organization (WHO) report from 2020, approximately 18.1 million new cancer cases were reported, along with around 9.6 million cancer-related deaths.[2] It is recognized as the second most common cause of death, following cardiovascular diseases. Among women, breast cancer is the most frequently diagnosed form and the second leading cause of cancer-related mortality.[3] Several treatment modalities are available for cancer, including chemotherapy, hormone therapy, radiation therapy, photodynamic therapy, immunotherapy, hyperthermia, stem cell therapy, targeted therapy, and surgical intervention in certain cases. Despite the availability of a wide range of anticancer drugs, treatment efficacy is often hindered by challenges such as multidrug resistance in cancer cells and severe adverse effects associated with chemotherapy, leaving patients physically and emotionally drained.[4]



To overcome these limitations, the development of anticancer agents that act through multiple mechanisms offers a promising approach.[5] Such multitargeted therapies reduce the likelihood of resistance and help mitigate issues related to drug-drug interactions and dose-limiting toxicities often encountered in combination treatments. Notably, some of these multitargeted anticancer agents have already advanced into preclinical and clinical stages of development.[6]

Figure 1: cell cycle of cancer

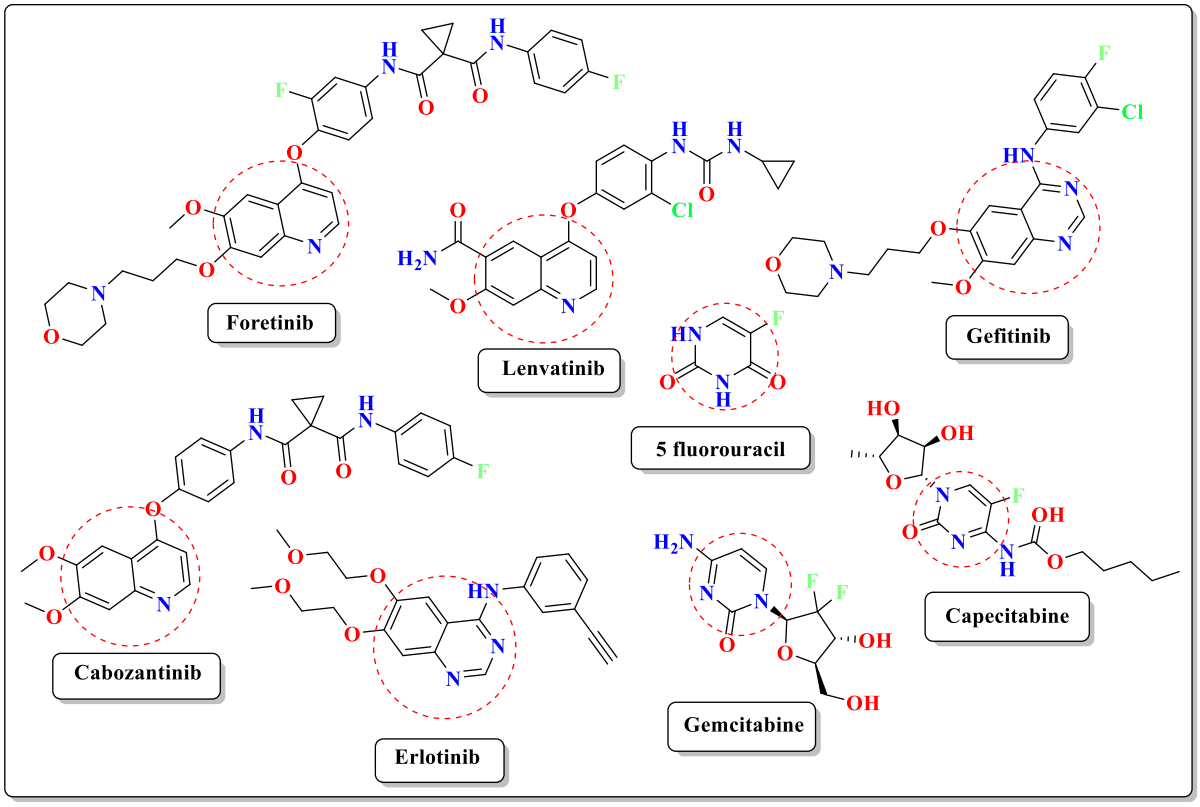


Figure 2: FDA approved marketed drug

SAR of Nitrogen containing anticancer agents:

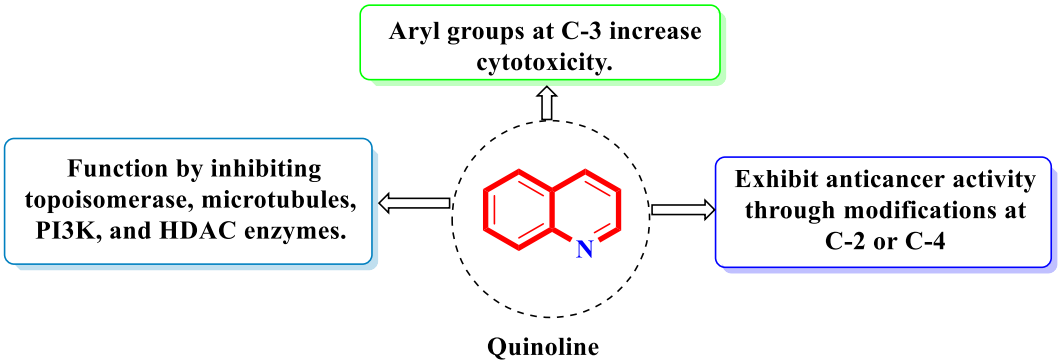


Figure 3: General SAR of Quinoline scaffold

Quinoline derivatives, with a bicyclic structure containing nitrogen at position 1, show significant anticancer activity. Modifications at C-2 or C-4 impact DNA intercalation and topoisomerase inhibition, key mechanisms in cancer therapy. Aryl groups at C-3 enhance hydrophobic interactions, boosting the cytotoxic potential of these compounds. The typical molecular formula for quinoline is C_9H_7N, though it may vary with additional functional groups. These derivatives exert their anticancer effects by inhibiting topoisomerase, microtubules, PI3K, and HDAC, all crucial for tumor cell growth and survival. Structural modifications allow for the fine-tuning of their anticancer properties, enhancing their therapeutic potential. [7-8]

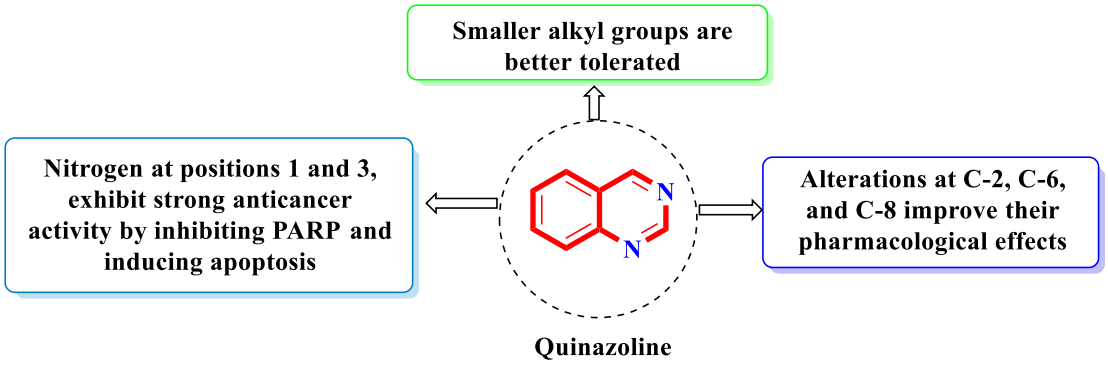


Figure 4: General SAR of Quinazoline scaffold

Quinazoline derivatives, characterized by nitrogen atoms at positions 1 and 3, exhibit strong anticancer properties, primarily through the inhibition of PARP and the induction of apoptosis. Structural modifications at C-2, C-6, and C-8 significantly improve their pharmacological efficacy. These changes contribute to enhanced potency and selectivity against cancer cells. Smaller alkyl groups at certain positions are better tolerated than bulkier ones, making them more suitable for drug development. The molecular alterations enable these compounds to effectively target cancer cell mechanisms, including DNA repair and cell cycle regulation. As a result, quinazoline derivatives hold promise as potent anticancer agents. [9-10]

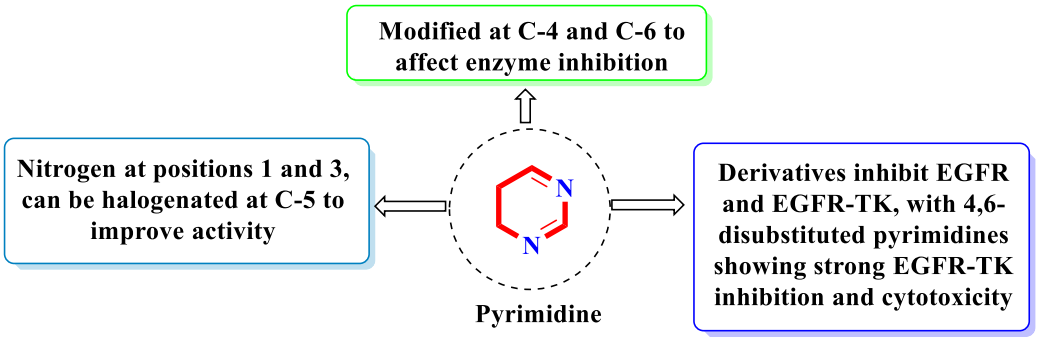


Figure 5: General SAR of Pyrimidine scaffold

Pyrimidine derivatives, featuring nitrogen atoms at positions 1 and 3, demonstrate potent anticancer properties, especially when halogenated at C-5, which boosts their biological activity. Alterations at C-4 and C-6 are critical in modulating enzyme inhibition, thereby enhancing their therapeutic potential. These compounds are primarily recognized for their ability to inhibit EGFR and its tyrosine kinase (EGFR-TK), with 4,6-disubstituted pyrimidines showing strong EGFR-TK inhibition and notable cytotoxic effects. These targeted structural modifications enable the compounds to effectively attack cancer cells, making them promising for use in targeted cancer therapies. The molecular formula typically follows the pyrimidine core ($C_4H_4N_2$), with modifications depending on the additional groups at various positions. [11-12]

Table 1: SAR of Nitrogen containing scaffolds

Derivative	Core Structure	Key Modifications	Mechanism of Action	Example
Quinoline Derivatives	Bicyclic system with nitrogen at position 1 and a carbonyl group at position 2 or 4.	**Substituents at C-2 or C-4:** Affect DNA intercalation and topoisomerase inhibition. **Aryl Groups at C-3:** Enhance hydrophobic interactions and cytotoxicity. **Functional Groups:** Hydroxyl or halogen groups modulate activity and selectivity.	Inhibition of topoisomerase, microtubules, PI3K, and HDAC.	Hybrid quinolone-chalcone derivatives demonstrate potent anticancer activity.
Quinazoline Derivatives	Bicyclic system with nitrogen at positions 1 and 3.	**Substituents at C-2, C-6, and C-8:** Influence pharmacological activity.	PARP inhibition, cell cycle arrest, apoptosis induction.	2,4-Disubstituted quinazoline derivatives exhibit strong PARP inhibition and cytotoxicity.

Derivative	Core Structure	Key Modifications	Mechanism of Action	Example
		Electron-Donating Groups: Enhance potency. **Small Alkyl or Aromatic Groups at N-1:** More tolerated than bulky groups.		
Pyrimidine Derivatives	Six-membered ring with nitrogen at positions 1 and 3.	**Halogenation at C-5:** Improves activity. **Substituents at C-4 and C-6:** Affect enzyme inhibition and cytotoxicity. **Hybridization:** Combining with other heterocycles enhances potency.	Inhibition of EGFR, ARO, and EGFR-TK.	4,6-Disubstituted pyrimidine derivatives show potent EGFR-TK inhibition and cytotoxicity.

Aly RM et al. [13] developed a new series of quinoline derivatives aimed at exhibiting anticancer properties through EGFR inhibition. Among these, **compound (1)** demonstrated notable EGFR inhibition ranging from 70–85%, and showed varying IC_{50} values against MCF-7 breast cancer cells. The IC_{50} value against EGFR was recorded at 0.49 µM, while the IC_{50} against MCF-7 cells stood at 5.069 µM, underlining the compound's effectiveness in targeting breast cancer. Notably, **compound (1)** was the most efficacious in terms of both EGFR inhibition and anticancer activity. Molecular docking studies conducted via Discovery Studio 2.5 revealed that **compound (1)** docked into the EGFR active site and was compared with Lapatinib and Gefitinib. Superimposition studies showed better alignment with Lapatinib than with lead compound III or Gefitinib, suggesting similar binding behaviours at the EGFR site. Key binding interactions included hydrogen bonding with ATP-binding site residues MET 793 and GLN 791, which are vital for strong affinity. Additionally, the meta-substituted phenyl ring and hydrophobic elements of the compound accommodated well in EGFR's hydrophobic region, enhancing its binding stability. Overall, the study points to **compound (1)** as a promising candidate for EGFR-targeted anticancer therapy.

Wang X et al. [14] synthesized a series of 6,7-disubstituted-4-(2-fluorophenoxy) quinoline derivatives as selective inhibitors of the c-Met kinase. Among them, **compound (2)** emerged as the most effective, with a c-Met kinase IC_{50} of 1.1 nM, and demonstrated significant cytotoxicity against cancer cell lines including HT-29, MKN-45, and A549. SAR analysis emphasized the critical role of the 1H-imidazole-4-carboxamido linker in enhancing potency. **Compound (2)** also showed selective inhibition across several kinases, including EGFR, for which it had a much higher IC_{50} of 690 nM, indicating its specificity towards c-Met. This suggests that **compound (2)** could be more suited for targeting c-Met-driven oncogenic pathways. The study thus presents **compound (2)** as a valuable lead for future development of c-Met-

specific anticancer agents. EGFR, while still a key target in oncology—especially in NSCLC and head and neck cancers—continues to drive research toward more potent and selective inhibitors.

Chauhan M et al. [15] designed and synthesized novel anticancer agents based on 4-aryl(alkyl)amino-3-nitroquinoline and 2,4-diaryl(dialkyl)amino-3-nitroquinoline frameworks. These were prepared via regioselective nucleophilic substitution of 2,4-dichloro-3-nitroquinoline in water under microwave-assisted conditions. The antiproliferative potential of the compounds was evaluated against human lung (A-549 and H-460) and colon (HCT-116 wild type and HCT-116-p53 null) cancer cell lines, all known to overexpress EGFR. Among them, **compound (3)** demonstrated strong anticancer efficacy with IC_{50} values ranging from 4.8 µM to 11.2 µM, on par with erlotinib. SAR findings showed that substituting dibenzylamines with dianilines enhanced cytotoxicity. These compounds also exhibited minimal toxicity against normal buccal cavity cells, indicating their selectivity. Molecular docking, using EGFR's co-crystal structure with erlotinib (PDB 1M17), showed the compounds effectively bound within the ATP-binding pocket of EGFR. Notable interactions included π-cation interactions with Phe699 and Lys721, and hydrogen bonding with Asp831. **Compound (3)** exhibited stronger binding due to additional functional groups. The similarity of their binding pattern to erlotinib supports their potential in overcoming resistance to EGFR-targeted therapies. The research supports the utility of these quinoline derivatives in anticancer drug design.

Liu D et al. [16] synthesized twenty-two 7-fluoro or 8-methoxy-substituted 4-anilinoquinolines and assessed their antitumor activity, particularly targeting EGFR. These compounds were tested against HeLa (cervical cancer) and BGC823 (gastric cancer) cell lines. Ten compounds showed potent activity, outperforming gefitinib. Among them, **compound (4)** was the most active, with IC_{50} values of 7.15 µM for HeLa and 4.65 µM for BGC823, significantly surpassing gefitinib (IC_{50} = 17.12 µM for HeLa and 19.27 µM for BGC823). This indicates that **compound (4)** is over 2.4 times more potent against HeLa and more than 4.1 times stronger against BGC823 than gefitinib. Structural optimization at positions C7 or C8 played a key role, with 7-fluoro derivatives being more potent than 8-methoxy ones. Though docking studies were not detailed, such analyses typically assess hydrogen bonding and hydrophobic interactions within EGFR's active site. Evaluating **compound (4)**'s binding behaviour could provide further understanding of its enhanced potency. The results suggest that 4-anilinoquinolines like **compound (4)** merit further investigation as targeted anticancer agents.

Ahsan MJ et al. [17] synthesized novel quinoline analogues and evaluated their anticancer activity against HeLa and MDA-MB-435 cell lines. **Compound (5)** exhibited the most notable activity, with GI_{50} values of 35.1 µM for HeLa and 60.4 µM for MDA-MB-435 cells. At 10^{-4} M concentration, **compound (48)** inhibited HeLa cell growth by 66.9% while showing negligible effects (0.6%) on MDA-MB-435 cells, indicating selective cytotoxicity. SAR analysis revealed that a 4-methoxy group on the phenyl ring enhanced anticancer activity. Molecular docking confirmed strong binding of **compound (5)** to EGFR-TK, involving hydrogen bonding with Met793 and Asp855, along with hydrophobic contacts with residues like Met793, Leu792, and Gly796. These interactions contribute to stable complex formation within the EGFR active site, supporting the compound's potential as a lead anticancer candidate.

El-Gamal MI et al. [18] developed diarylamide derivatives containing 6,7-dimethoxy (or dihydroxy) quinoline groups and evaluated their anticancer activity. Among these, **compound (6)** exhibited the strongest cytotoxic effects at 10 µM, outperforming Imatinib. It showed potent inhibition of C-RAF

kinase, suggesting that its anticancer activity is primarily through C-RAF inhibition rather than EGFR, which it only weakly inhibited (<47%). **Compound (6)** demonstrated superior efficacy against melanoma, colon, and breast cancer lines. Docking studies supported its binding within the C-RAF active site, with stabilizing interactions like hydrogen bonds and hydrophobic contacts. The presence of a 3,5-bis(trifluoromethyl)phenyl moiety contributed to its potency. Although MD simulations were not included, their future use was suggested to validate the compound's binding dynamics. This identifies **compound (6)** as a lead C-RAF-targeted anticancer agent.

Su T et al.[19] synthesized new quinoline derivatives and assessed their anticancer properties. **Compound (7)** emerged as the most effective, exhibiting potent antiproliferative activity with low micromolar IC_{50} values (2.5–3.7 μM) across cell lines such as HCT-116, RKO, A2780, and HeLa. In vivo studies confirmed its efficacy, with an 82.1% tumor reduction in a colorectal cancer model, and no apparent toxicity. Mechanistically, the compound induced autophagy-dependent cell death via ATG5, rather than traditional apoptosis. While previous quinoline compounds are often linked to EGFR inhibition, this study focused on autophagy, without incorporating docking or dynamics studies. The biological assays confirmed its therapeutic potential.

Effendi N et al. [20] developed and synthesized a new series of radioiodinated benzo[d]imidazole-quinoline compounds aimed at targeting PDGFRβ, a receptor frequently overexpressed in several cancers and fibrotic conditions. Among the derivatives, **compound (8)** was identified as the most promising, showing high binding affinity toward PDGFRβ, increased cellular uptake in receptor-positive tumor cells, and favourable in vivo biodistribution. Notably, **compound (8)** achieved superior tumor localization and tumor-to-blood ratios compared to its counterparts, highlighting its suitability as an imaging probe. Structural tweaks on the quinoline framework significantly affected receptor binding and biological performance, as evidenced by molecular docking studies that informed the compound's optimization. While molecular dynamics simulations were not performed, docking data shed light on the structure–activity relationship. Interestingly, beyond its imaging capability, the compound also exhibited marked antiproliferative effects in PDGFRβ-overexpressing cancer cells, suggesting a dual function as both a diagnostic and therapeutic agent. Overall, **compound (8)** represents a leading candidate for further development in targeted cancer imaging and potentially therapeutic interventions via PDGFRβ blockade.

Nan X et al. [21] created a series of 4-phenoxyquinoline compounds bearing sulfonylurea groups to act as selective inhibitors of the c-Met receptor tyrosine kinase. By introducing sulfonylurea moieties into the quinoline backbone, the team aimed to improve potency and specificity. The standout compound, **compound (9)**, exhibited strong c-Met inhibitory activity with an IC_{50} of 1.98 nM, surpassing the performance of the reference drug Foretinib. Additionally, **compound (9)** demonstrated potent cytotoxicity across various human cancer cell lines, notably HT460, MKN-45, HT-29, and MDA-MB-231, indicating broad anticancer potential. SAR studies revealed that electron-withdrawing groups on the quinoline and phenyl rings improved both potency and selectivity. Molecular docking illustrated that **compound (9)** binds effectively within the ATP-binding site of c-Met, establishing key molecular interactions that explain its high affinity. Although no MD simulations were described, the docking insights provided structural rationale for the observed biological results and a foundation for future modelling efforts. In summary, **compound (9)** is a compelling lead for targeted cancer therapy via selective c-Met inhibition.

Lu JX et al. [22] synthesized a novel group of quinoline-based dihydrazone compounds, aiming to explore their selective anticancer effects. Among them, **compounds (10)** and **(11)** showed significant antiproliferative effects against the MCF-7 breast cancer cell line, with IC_{50} values ranging from 7.01–34.32 µM. These compounds displayed minimal cytotoxicity in healthy liver cells, reflecting a promising safety profile. Apoptosis assays and morphological analyses indicated that both compounds induce programmed cell death, supporting their anticancer efficacy. Molecular docking studies revealed strong potential interactions with CDK2 and DNA, pointing to interference with key regulators of the cell cycle. Although molecular dynamics simulations were not employed, the docking data clarified the compounds' mechanisms. Taken together, **compounds (10)** and **(11)** represent promising anticancer candidates due to their selective cytotoxicity, interaction with critical molecular targets, and the absence of nitrosamine impurities—an important safety consideration. Further optimization, mechanistic exploration, and in vivo testing are encouraged to advance their clinical relevance.

Xing A et al. [23] synthesized a novel series of heterocyclic phenolic hydrazone compounds (L1–L4), evaluating their antioxidant and anticancer properties. Of these, **compound (12)** demonstrated the most potent antiproliferative activity against BGC-823, MCF-7, and A549 cancer cell lines, surpassing the efficacy of 5-fluorouracil (5-FU). Importantly, **compound (12)** exhibited no toxicity toward normal liver cells (HL-7702), reflecting a strong safety profile. It also excelled in antioxidant assays (DPPH and ABTS), outperforming BHT. DFT analysis showed that L3 had a lower HOMO-LUMO energy gap, suggesting favourable reactivity and chemical stability—desirable for drug development. Molecular docking confirmed strong binding of **compound (12)** to targets 4AGM and 2CDU, aligning with its observed bioactivity. Structural elements like fluoro-substitution on the pyridine ring enhanced biological interactions. Overall, **compound (12)** is a dual-action agent with promising anticancer and antioxidant capabilities, supported by experimental and computational results. Future research should focus on further optimization, in vivo validation, and pharmacokinetic profiling.

Li S et al. [24] reported the synthesis of quinoline derivatives for their anticancer potential. Among these, **compound (13)** emerged as the most active, showing IC_{50} values below 1.0 µM against several cancer cell lines, especially those from colorectal and liver origins. SAR analysis indicated that large alkoxy groups at the 7-position and optimized amine substitutions significantly contributed to increased efficacy. Mechanistic studies revealed that **compound (13)** activates the p53/Bax apoptosis pathway—a key tumor-suppressive mechanism. This was further validated in vivo, where **compound (13)** markedly inhibited tumor growth in a colorectal xenograft model in mice. While detailed molecular docking or MD simulation results were not provided, SAR and structure-based design indicated a rationale for ligand optimization. Functional groups responsible for binding and pathway modulation suggest the value of in silico modelling to further enhance the compound's efficacy. In conclusion, **compound (13)** stands out as a robust lead for cancer drug development due to its strong in vitro and in vivo performance and its defined apoptotic mechanism.

Vennila KN et al. [25] developed a new set of 2-chloro-N-substituted amino quinolines targeting non-small cell lung cancer (NSCLC). Among these, **compound (14)** showed promising antiproliferative effects against A549 cells, with an IC_{50} of 29.4 µM, making it a viable candidate compared to pemetrexed. Structural validation was performed using various spectroscopic techniques. Mechanistic insights from molecular docking suggested that **compound (14)** binds effectively to PI3K/AKT/mTOR pathway

proteins, which are central to tumor growth and survival. Docking results indicated strong binding energy and structural complementarity within the active sites, supporting the compound's mechanism. Additionally, **compound (14)** exhibited a favourable ADME profile and met Lipinski's criteria, reinforcing its drug-likeness. SAR analysis emphasized the impact of substitution patterns and functional groups on biological efficacy, guiding future design. In summary, **compound (14)** is a noteworthy lead for NSCLC therapy, combining efficacy, target-specific binding, and favourable pharmacokinetics. Further research should include in vivo testing, pharmacokinetic studies, and structural refinements.

Solomon VR et al. [26] synthesized sulfonyl-modified 4-aminoquinoline compounds targeting breast cancer. Among them, **compound (15)** showed the highest cytotoxicity against MDA-MB468 cells with a GI_{50} of 0.7 µM. It caused cell cycle arrest at the prometaphase-metaphase transition, disrupted mitosis by forming abnormal spindles, and elevated lysosomal activity, all contributing to its potent antiproliferative action. Additionally, **compound (15)** showed selectivity, requiring higher doses to affect non-cancerous cells, thus offering a good therapeutic index. When combined with agents like bortezomib or monastrol, it produced synergistic anticancer effects. Molecular docking indicated strong binding to proteins involved in cell proliferation, and MD simulations confirmed the stability of the compound within target binding sites over time. This stability supports consistent biological activity. Therefore, **compound (15)** is a compelling lead for breast cancer treatment, with strong cytotoxic potential, selective activity, and validated molecular interactions, paving the way for further preclinical development.

Li B et al. [27] developed N′-substituted methylene-4-(quinoline-4-amino) benzoylhydrazides as potential treatments for liver cancer. Among these, **compounds (16) and (17)** displayed strong antiproliferative effects on hepatic cancer cells, with IC_{50} values under 10 µM, and lower toxicity toward normal cells. These compounds acted as c-Myc inhibitors, promoting apoptosis by reducing Bcl-2 expression and increasing Bax levels, resulting in cell cycle arrest and inhibited survival in HepG2 cells. **Compound (16)** was especially potent, with IC_{50} values of 9.6 ± 0.7 µM for SMMC-7721 cells and 6.3 ± 0.2 µM for Huh7 cells, inducing dose-dependent apoptosis with low toxicity in normal cells. The compounds also reduced cancer cell migration, further enhancing their anticancer profile. While molecular docking and MD simulations were not described, these tools could provide valuable insight into the compounds' interactions and facilitate further optimization. **Compound (16)**, in particular, stands out for its efficacy and safety, supporting its advancement in cancer therapy development.

Nan X et al. [28] synthesized 4-(2-fluorophenoxy) quinoline derivatives targeting c-Met, with focus on their structure-activity relationships. Derivatives featuring α-acyloxycarboxamide linkers exhibited enhanced potency and selectivity against H460 and HT-29 cell lines. Among these, **compound (18)** was the most effective, outperforming Foretinib with IC_{50} values of 0.14 ± 0.03 µM (H460), 0.20 ± 0.02 µM (HT-29), and 0.42 ± 0.03 µM (MDA-MB-231), showing 1.3 to 1.7 times greater potency. The compound inhibited H460 cell proliferation in a time- and dose-dependent manner. Molecular docking using AutoDock 4.2 revealed that **compound (18)** fits well in the c-Met active site, forming key hydrogen bonds with Met1160 and Asp1222 and a π-π interaction with Phe1223. Its 4-fluorophenyl group lodged within a hydrophobic pocket, indicating a strong and favourable binding conformation. Although MD simulations were not included, they could further confirm binding stability and guide future refinement. Overall, **compound (18)** is a highly potent and selective candidate for c-Met-targeted cancer therapy.

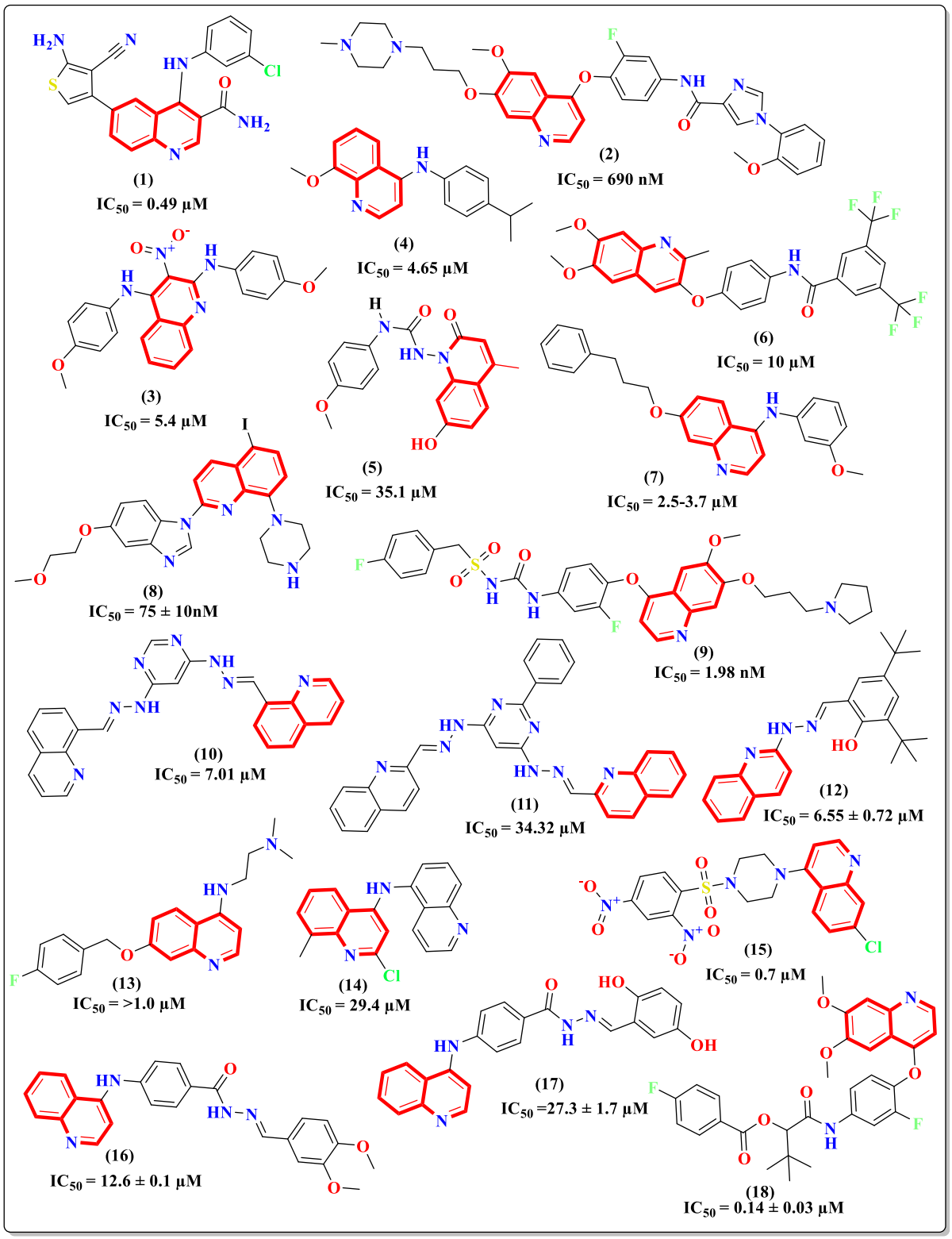


Figure 6: Nitrogen containing anticancer agents with their IC50 values

Pan C et al. [29] synthesized a series of quinazoline derivatives targeting FGFR4, a receptor tyrosine kinase implicated in hepatocellular carcinoma. Among the synthesized compounds, **compound (19)** emerged as the most potent candidate, exhibiting strong inhibitory activity against FGFR1–4 kinases with IC50 values of 5.6 nM (FGFR1), 2.2 nM (FGFR2), 8.5 nM (FGFR3), and 4.6 nM (FGFR4). In vitro, **compound (19)**

demonstrated significant antiproliferative effects against FGFR4-overexpressing Huh7 liver cancer cells, with an IC_{50} of 6.35 nM, and showed favourable pharmacokinetic properties, including 57.5% oral bioavailability. In vivo evaluation using a Huh7 xenograft model confirmed its tumor-suppressive effects with minimal toxicity. Molecular docking studies revealed that **compound (19)** fits stably within the ATP-binding pocket of FGFRs, forming key hydrogen bonds and hydrophobic interactions that rationalize its high potency and selectivity. These findings identify **compound (19)** as a promising FGFR4-targeted anticancer agent for further development.

Zhang B et al. [30] synthesized a series of sulfamoylphenyl-quinazoline derivatives aimed at dual inhibition of EGFR and CAIX, two key targets associated with tumor growth and hypoxic microenvironments. Among the synthesized molecules, **compound (20)** emerged as the most potent, exhibiting strong dual inhibitory activity with IC_{50} values of 0.029 μM against EGFR and 0.087 μM against CAIX. In vitro antiproliferative studies revealed that **compound (20)** significantly inhibited the growth of EGFR-overexpressing A431 cancer cells with an IC_{50} of 0.12 μM, and also displayed selectivity by showing lower toxicity toward normal cells. The dual-target approach was supported by molecular docking studies, which demonstrated that **compound (20)** effectively binds to the ATP-binding pocket of EGFR through hydrogen bonding and hydrophobic interactions, while also fitting well into the active site of CAIX, engaging in coordination with the zinc ion and forming additional stabilizing interactions. These findings highlight **compound (20)** as a promising dual-function anticancer agent, offering both antiproliferative and anti-hypoxic tumor microenvironment effects.

Teng Y et al. [31] synthesized a novel series of quinazoline derivatives targeting PI3Kδ, a lipid kinase implicated in various hematologic malignancies. The design strategy focused on enhancing selectivity for the δ isoform while minimizing off-target effects on other PI3K isoforms. Among the synthesized compounds, **compound (21)** emerged as the most potent and selective inhibitor, exhibiting an impressive IC_{50} value of 27.5 nM against PI3Kδ and showing over 270-fold selectivity over PI3Kα, β, and γ isoforms. In vitro antiproliferative assays demonstrated that **compound (21)** effectively inhibited the proliferation of SU-DHL-6 lymphoma cells with an IC_{50} of 0.11 μM, while maintaining low cytotoxicity in normal human peripheral blood mononuclear cells (PBMCs). Molecular docking studies revealed that **compound (21)** occupies the ATP-binding pocket of PI3Kδ, forming crucial hydrogen bonds with residues Val828 and Lys779 and engaging in hydrophobic interactions that stabilize its conformation, thus supporting its high potency and selectivity. Overall, **compound (21)** stands out as a promising lead compound for selective PI3Kδ inhibition with potential applications in targeted cancer therapies.

Li Z et al. [32] synthesized a series of quinazoline derivatives as potent and selective inhibitors of lysine-specific demethylase 1 (LSD1), an enzyme implicated in various cancers. Among the synthesized compounds, **compound (22)** emerged as the most promising, exhibiting a significantly enhanced LSD1 inhibitory activity with an IC_{50} of 0.69 μM, compared to the parent compound erlotinib (IC_{50} = 35.80 μM). In vitro studies demonstrated that **compound (22)** effectively suppressed LSD1-mediated demethylation in MGC-803 cells, leading to reduced colony formation, inhibited cell migration, and induced apoptosis. In vivo, **compound (22)** achieved a remarkable tumor size reduction of 81.6% and 96.1% at doses of 40 and 80 mg/kg/day, respectively, in a xenograft mouse model. Molecular docking studies revealed that **compound (22)** binds to the active site of LSD1, forming key interactions that contribute to its potent

inhibitory activity. These findings suggest that quinazoline derivatives, particularly **compound (22)**, hold promise as novel LSD1 inhibitors for cancer therapy.

Zhuo LS et al. [33] synthesized a series of quinazoline-based 1,6-naphthyridinone derivatives as selective MET kinase inhibitors, aiming to improve antitumor efficacy. Among these, **compound (23)** exhibited the most potent activity, with an IC_{50} of 9.0 nM against MET, outperforming the reference compound Cabozantinib (IC_{50} = 2.3 nM). In vivo studies demonstrated that **compound (23)** significantly inhibited tumor growth in the U-87 MG xenograft model, achieving a tumor growth inhibition (TGI) of 131% at a dose of 12.5 mg/kg, with 4 out of 6 mice showing partial regression. Molecular docking studies revealed that **compound (23)** effectively binds to the ATP-binding pocket of MET, forming key interactions that contribute to its high potency and selectivity. These findings suggest that **compound (23)** is a promising lead for the development of selective MET inhibitors with enhanced antitumor activity.

Zeinyeh W et al. [34] synthesized a series of pyridoquinazoline-based compounds as selective Haspin kinase inhibitors, aiming to develop new anticancer agents. Among these, compound **(24)** emerged as the most potent, exhibiting an IC_{50} of 50 nM against Haspin. This compound demonstrated excellent selectivity over a broad panel of 486 kinases, highlighting its potential for targeted therapy. In cellular assays, **compound (24)** effectively inhibited Haspin activity in various cancer cell lines, leading to reduced cell proliferation. Molecular docking studies revealed that **compound (24)** binds to the ATP-binding pocket of Haspin, forming key interactions that contribute to its high potency and selectivity. These findings suggest that **compound (24)** is a promising lead for the development of selective Haspin inhibitors with potential anticancer applications.

Badawi WA et al. [35] synthesized a series of pyrimidine-based hydrazones and evaluated their antiproliferative activity against MCF-7 and MDA-MB-231 human breast cancer cell lines. Among these, **compound (25)** emerged as the most potent and selective inhibitor. It exhibited IC_{50} values ranging from 0.87 µM to 12.91 µM in MCF-7 cells and 1.75 µM to 9.46 µM in MDA-MB-231 cells, outperforming the positive control 5-fluorouracil (5-FU), which had IC_{50} values of 17.02 µM and 11.73 µM, respectively. **Compound (25)** demonstrated superior selectivity for cancerous cells over normal MCF-10A breast cells, achieving the highest selectivity index among the tested compounds. Mechanistic studies revealed that **compound (25)** induced a significant increase in caspase-9 levels in MCF-7 cells (27.13 ± 0.54 ng/mL), surpassing that of the positive control Staurosporine (19.011 ± 0.40 ng/mL). Additionally, **compound (25)** induced pre-G1 apoptosis and arrested the cell cycle at the S and G1 phases in MCF-7 cells. Further investigations demonstrated that **compound (25)** inhibited aromatase (ARO) and epidermal growth factor receptor (EGFR) enzymes by 39% and 36%, respectively, relative to the reference drugs letrozole and erlotinib. Molecular docking studies confirmed the binding of **compound (25)** to the active sites of ARO and EGFR, supporting its potential as a dual-target anticancer agent.

Zuo Y et al. [36] designed and synthesized a series of 4-arylamine substituted pyrimidine derivatives as noncovalent EGFR inhibitors to overcome the C797S mutation, a key resistance mechanism against third-generation EGFR inhibitors like osimertinib in non-small cell lung cancer (NSCLC). Among these, **compound (26)** emerged as the most potent and selective inhibitor. It demonstrated exceptional antiproliferative activity with IC_{50} values of 24.6 nM against HCC827 cells, and 16.06 nM and 11.81 nM against EGFR^19del/T790M/C797S and EGFR^L858R/T790M/C797S mutants, respectively, outperforming osimertinib (IC_{50} = 52.28 nM and 157.60 nM). **Compound (26)** effectively inhibited

colony formation, arrested the cell cycle at the G2/M phase, and induced apoptosis in HCC827 cells. In vivo, it significantly suppressed tumor growth in a xenograft mouse model without noticeable toxicity. Molecular docking studies revealed that **compound (26)** binds to the ATP-binding pocket of EGFR, forming interactions with key residues, thereby inhibiting both wild-type and mutant EGFR kinase activity. These findings position **compound (26)** as a promising candidate for the treatment of EGFR-mutant NSCLC resistant to Osimertinib.

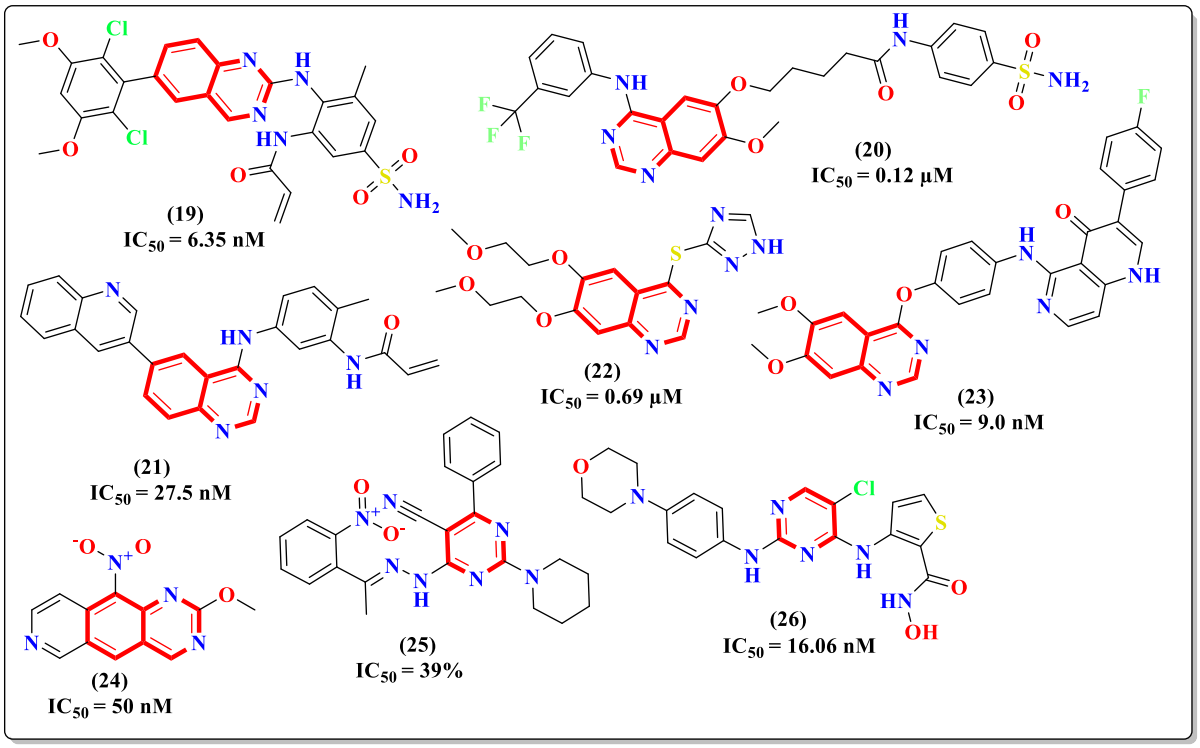


Figure 7: Nitrogen containing anticancer agents with their IC_{50} values

Summary:

Nitrogen-containing heterocyclic scaffolds such as quinoline, quinazoline, and pyrimidine have shown significant potential in the development of targeted anticancer therapies due to their ability to interact with multiple oncogenic proteins. Among the compounds studied, Compound (20) stands out as the most promising candidate. It is a quinoline-based molecule that exhibits potent dual inhibition of EGFR and CAIX, with exceptionally low IC_{50} values of 0.029 µM and 0.087 µM, respectively. This dual-targeting mechanism is particularly advantageous, as it suppresses tumor proliferation and also addresses the hypoxic microenvironment commonly associated with aggressive tumor growth. Additionally, Compound (20) has demonstrated strong antiproliferative effects in EGFR-overexpressing cancer cell lines while exhibiting low toxicity toward normal cells, suggesting an excellent therapeutic index. Compound (19) is a quinazoline-based derivative that selectively inhibits FGFR1–4, with a strong focus on FGFR4, a target linked to hepatocellular carcinoma. It showed an IC_{50} of 4.6 nM against FGFR4 and 6.35 nM in Huh7 liver cancer cells. It also possesses favourable pharmacokinetic properties, including 57.5% oral bioavailability, and demonstrated effective tumor suppression in preclinical models, supporting its potential for liver cancer treatment. Compound (2) is a highly potent and selective c-Met kinase inhibitor with an IC_{50} of 1.1 nM. It shows strong cytotoxicity across a range of cancer cell lines while exhibiting

minimal activity against EGFR, reducing the risk of off-target effects. Similarly, Compound (18), another c-Met inhibitor, demonstrated superior potency compared to Foretinib in H460 lung cancer cells, with an IC_{50} of 0.14 μM. Lastly, Compound (21) selectively inhibits PI3Kδ, with an IC_{50} of 27.5 nM and over 270-fold selectivity over other PI3K isoforms, making it highly effective in suppressing lymphoma cell growth. Together, these compounds illustrate the strong therapeutic promise of nitrogen-based heterocyclic scaffolds in developing selective, multitargeted cancer treatments, with Compound (20) emerging as the lead candidate due to its unique dual-target efficacy and favourable safety profile.

Table 2: summary of potent compounds

Compound	Scaffold Type	Primary Targets	IC_{50} Values	Key Highlights
(20)	Quinoline-based	EGFR, CAIX	EGFR: 0.029 μM CAIX: 0.087 μM	Dual-target inhibition; effective in EGFR+ cancers; low toxicity to normal cells
(19)	Quinazoline-based	FGFR1–4 (esp. FGFR4)	FGFR4: 4.6 nMHuh7 cells: 6.35 nM	Strong selectivity for FGFR4; good oral bioavailability (57.5%); effective in vivo
(2)	Quinazoline-based	c-Met	1.1 nM	Highly specific; strong cytotoxicity; minimal EGFR activity
(18)	Quinoline-based	c-Met	0.14 μM (H460 lung cancer cells)	More potent than Foretinib
(21)	Quinazoline-based	PI3Kδ	27.5 nM	>270-fold selectivity over other PI3K isoforms; active against lymphoma cells

2. Conclusion:

Nitrogen-containing heterocyclic scaffolds like quinoline, quinazoline, and pyrimidine show great promise in cancer therapy due to their ability to target multiple oncogenic proteins such as EGFR, PARP, PI3K, HDAC, and c-Met. Among them, **Compound (20)** is the most potent, with dual inhibition of EGFR and CAIX (IC_{50}: 0.029 μM and 0.087 μM), effectively suppressing tumor growth and addressing cancer-related hypoxia, while showing low toxicity to normal cells. **Compound (19)**, a quinazoline derivative, targets FGFR1–4, especially FGFR4, relevant in liver cancer, with an IC_{50} of 4.6 nM and good oral bioavailability (57.5%), demonstrating strong in vivo efficacy. **Compound (2)** selectively inhibits c-Met (IC_{50}: 1.1 nM) with minimal off-target effects. **Compound (18)**, another c-Met inhibitor, surpasses Foretinib in lung cancer potency. **Compound (21)** is a selective PI3Kδ inhibitor (IC_{50}: 27.5 nM), effective against lymphoma. Overall, these compounds underscore the potential of nitrogen-based scaffolds in

developing selective, multitargeted anticancer therapies, with **Compound (20)** leading due to its potent dual action and high therapeutic index.

Abbreviations:

Abbreviation	Full Form
EGFR	Epidermal Growth Factor Receptor
PARP	Poly ADP-Ribose Polymerase
PI3K	Phosphoinositide 3-Kinase
HDAC	Histone Deacetylase
SAR	Structure-Activity Relationship
TK	Tyrosine Kinase
IC_{50}	Half Maximal Inhibitory Concentration
NSCLC	Non-Small Cell Lung Cancer
ADME	Absorption, Distribution, Metabolism, Excretion
MD	Molecular Dynamics

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