Review Article

Quinoxaline Derivatives As Anticancer Agents: Molecular Targets And SAR

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Abstract

Quinoxaline is a versatile nitrogen-containing heteroaromatic scaffold with considerable potential in anticancer drug discovery because structural modifications of its fused benzene–pyrazine framework can produce compounds with diverse pharmacological activities. This review highlights recent advances in the anticancer potential of quinoxaline derivatives, emphasizing their broad molecular targets and structure–activity relationships (SAR). Quinoxaline-based compounds have demonstrated activity against topoisomerases, tubulin, DNA repair pathways, PARP, histone deacetylases, folate metabolism, reactive oxygen species, VEGFR-2, EGFR, HER2, c-Met, PI3K/Akt/mTOR, PIM kinases, BRD9, BET proteins, PFKFB3, and apoptosis- and metastasis-associated pathways. SAR studies demonstrate that substitution pattern, aromaticity, hydrogen-bonding capacity, electronic properties, linker configuration, and physicochemical characteristics strongly influence anticancer potency and selectivity. Emerging approaches include selective targeting of BRD9 and BD1, inhibition of PFKFB3, VEGFR-2 blockade in treatment-resistant tumors, and modulation of HIF-1α, VEGF, and p21. Despite these advances, most quinoxaline-based anticancer candidates remain at the preclinical stage, with limitations involving inconsistent experimental conditions, inadequate pharmacokinetic characterization, poor aqueous solubility, metabolic instability, and potential off-target toxicity. Future development should therefore emphasize target validation, structure-based optimization, advanced drug-delivery approaches, pharmacokinetic improvement, physiologically relevant disease models, and rational combination strategies. Overall, quinoxaline represents a flexible platform for developing multifunctional and target-directed anticancer agents with potential applications across diverse cancer-associated pathways.

Keywords: Quinoxaline; anticancer agents; apoptosis; topoisomerase; tubulin; VEGFR-2; EGFR; BRD9; BET; PFKFB3; structure–activity relationship; targeted therapy.

1. Introduction

Cancer is characterized by uncontrolled cellular proliferation, resistance to programmed cell death, metabolic adaptation, angiogenesis, invasion, and progressive treatment resistance. These characteristics create a complex therapeutic environment in which conventional cytotoxic agents may be limited by their insufficient selectivity and systemic toxicity. The ongoing development of molecularly targeted therapies has underscored the significance of heterocyclic scaffolds that can interact with specific cancer-associated proteins and pathways [1, 2].

Quinoxaline, also referred to as benzopyrazine, is an aromatic bicyclic heterocycle containing fused benzene and pyrazine rings. This scaffold has been extensively investigated because its nitrogen atoms and planar aromatic architecture provide opportunities for hydrogen bonding, π–π interactions, hydrophobic contacts, and modification at multiple positions [3]. Such chemical flexibility has permitted the development of derivatives with antibacterial, antiviral, antimalarial, neurological, and anticancer properties. In oncology, quinoxaline-containing compounds have been investigated against multiple tumor types and molecular targets [4].

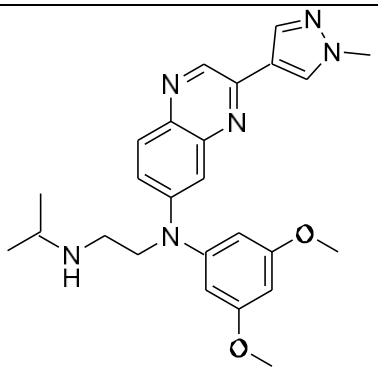
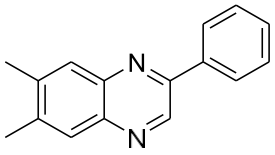
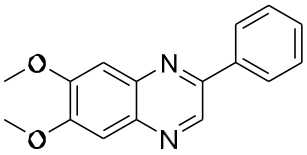
Earlier investigations emphasized DNA intercalation, topoisomerase inhibition, tubulin disruption, and related cytotoxic mechanisms, whereas more recent studies have broadened the target spectrum to include receptor tyrosine kinases, epigenetic readers, metabolic regulators, and signaling proteins [5, 6]. This evolution is particularly important because cancer resistance frequently arises through pathway redundancy or compensatory signaling. A scaffold capable of being optimized toward distinct targets may therefore provide opportunities for overcoming the limitations associated with single-mechanism therapies.

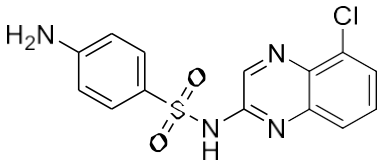
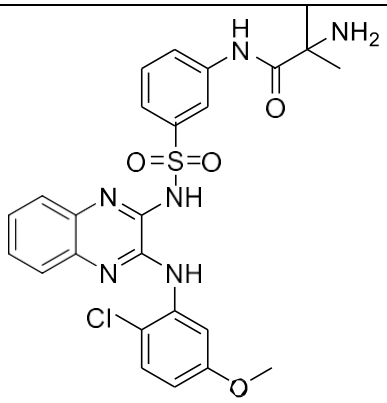
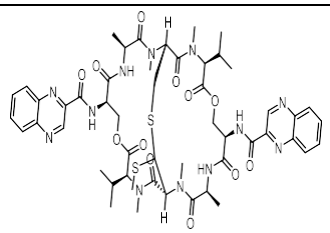
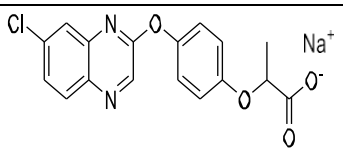
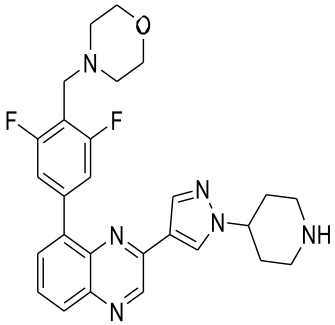
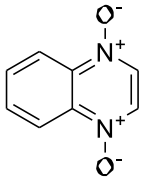
2. Chemical Basis of Quinoxaline-Mediated Anticancer Activity

The pharmacological versatility of quinoxaline derivatives is closely related to the adaptability of their heteroaromatic nuclei. Structural modifications can be achieved through substitution on the pyrazine portion, functionalization of the fused benzene ring, ring fusion, incorporation of additional heterocycles, and attachment

of aromatic or aliphatic substituents. These modifications can alter the target affinity, cellular permeability, aqueous solubility, metabolic stability, and selectivity [7, 8]. Compounds bearing quinoxaline core exhibit various biological activities. They are now recognized as a novel class of anticancer medications demonstrating promising therapeutic potential, particularly against solid tumor types [5]. Several of these compounds have either been approved by the FDA for clinical application or are in various stages of development (see table 1). The literature review demonstrate that quinoxaline derivatives can be engineered into planar DNA-interacting molecules, kinase inhibitors, tubulin-targeting agents, apoptosis inducers, epigenetic modulators, and metabolic inhibitors (see figure 1 and 2). Consequently, the biological behavior of quinoxaline derivatives cannot be predicted solely from their parent scaffolds. Rather, the nature and position of the substituents determine how the molecule interacts with its intended biological environment. Recent SAR analyses suggest that electron-withdrawing substituents on peripheral aromatic rings can enhance the antiproliferative activity of selected chemical series. Substitution at specific positions of the quinoxaline or fused triazoloquinoxaline framework can also substantially affect the activity. In particular, aromatic groups capable of hydrogen bonding and methylamino functionalities have been associated with increased activity in some series [9, 11]. The importance of substitution is target-dependent. For DNA-intercalating compounds, planarity and aromatic surface area can facilitate nucleic acid interactions. In contrast, kinase inhibitors require complementary hydrogen-bonding and hydrophobic interactions within ATP-binding or allosteric pockets. Therefore, SAR interpretation should be linked to the biological target rather than generalized across all quinoxaline derivatives.

Table 1. FDA-approved quinoxaline derivatives exhibiting anticancer properties

S.No.	Name	Structure	Uses	References
1.	Erdafitinib		✓ EGFR inhibitor ✓ Treatment of bile duct, stomach, esophagel, and lung cancer	5
2.	Tyrphostin	 AG 1295  AG 1296	✓ AG 1296 and AG 1295 are selective tyrosine kinase inhibitors, acts by preventing PDGF receptror kinase ✓ Treament of brain tumor	5

3.	Chloroquinoxaline sulfonamide (CQS)		✓ Topoisomerase (Topo) IIβ inhibitor prevents DNA duplication ✓ Potent against human and murine tumor cells ✓ Treatment of lung and colorectal cancer ✓ Phase-II clinical trials	5
4.	Pilaralisib		✓ Phosphoinositide-3 kinase (PI3K) inhibitor ✓ Prevents the tumor from being phosphorylated and treatment of glioblastoma, breast cancer, and lymphoma	5
5.	Echinomycin (Quinomycin A)		✓ DNA Bis-intercalator & HIF-1α Inhibitor ✓ Natural Product / Clinical Evaluation	12
6.	XK469 (NSC 698252)		✓ Selective Topoisomerase IIβ Inhibitor ✓ Phase I Clinical Trials	13
7.	NVP-BSK805		✓ ATP-Competitive JAK2 Kinase Inhibitor ✓ Preclinical / Translational Studies	14
8.	Quinoxaline-1,4-di-N-oxides (QdNOs)		✓ Bioreductive DNA Cleaving Agents (Hypoxia-Selective) ✓ Preclinical / Investigational	15

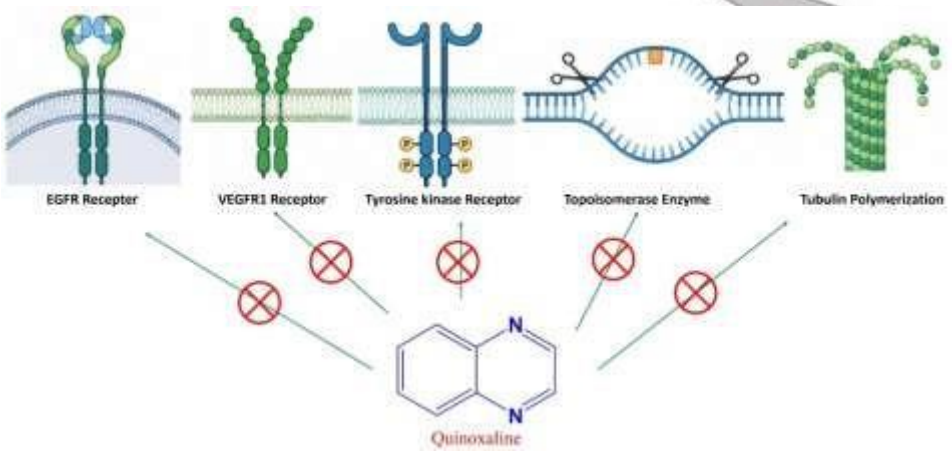


Figure 1. A diagrammatic representation illustrating the classification of quinoxaline-based compounds in relation to their distinct biological targets.

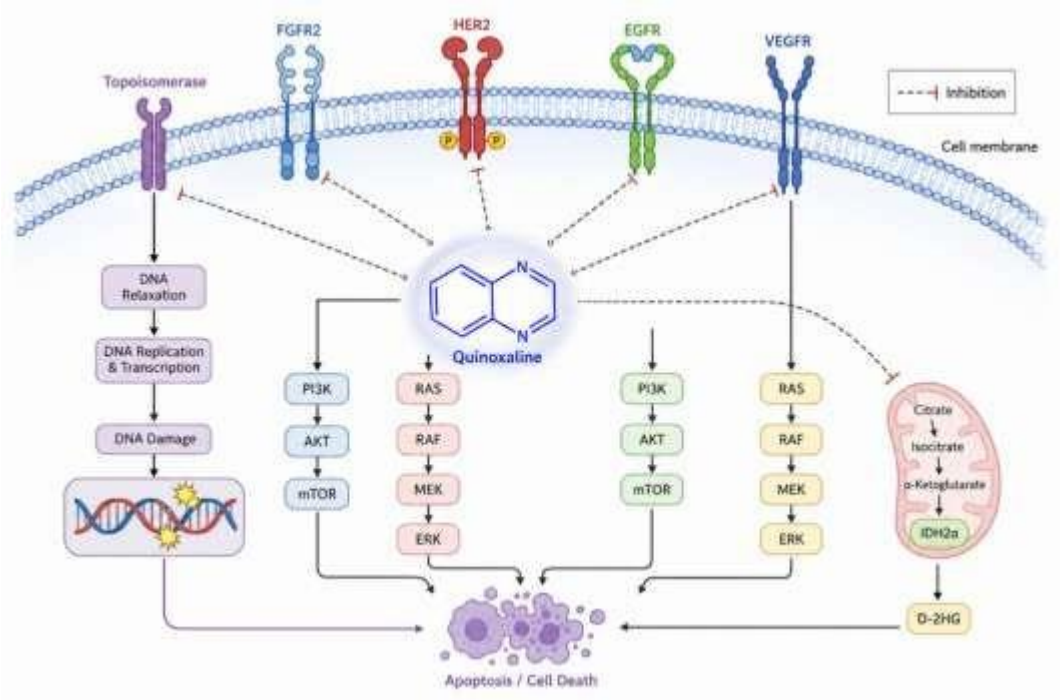


Figure 2. A schematic diagram depicting the mechanism of action of quinoxaline-based compounds on diverse biological targets.

3. Microtubule Targeting and Mitotic Disruption

Microtubules are dynamic cytoskeletal structures essential for intracellular transport and chromosome segregation. Their disruption can produce mitotic arrest, followed by programmed cell death. Conventional microtubule-targeting agents include polymerization inhibitors, such as colchicine-related compounds and vinca alkaloids, as well as polymerization-stabilizing agents, such as taxanes [3]. Quinoxaline derivatives have been investigated, particularly as colchicine-site tubulin inhibitors. Several series have been designed around the structural characteristics of microtubule-disrupting agents, such as combretastatin A4 phosphate, indibulin, and BNC-105. In several quinoxaline derivatives, two aromatic regions connected by a linker were important structural elements, while a 3,4,5-trimethoxybenzyl group repeatedly appeared among the active analogs [16-18].

Experimental investigations support the proposed mechanism. Selected compounds produced G2/M cell-cycle arrest, inhibited tubulin polymerization, competed for the colchicine-binding site, and disrupted microtubule

organization. These effects are consistent with the ability of quinoxaline derivatives to interfere with mitotic progression [4]. Structure-based optimization has also provided a route to improved metabolic stability. Quinoxaline-containing analogs inspired by verubulin have demonstrated activity at the colchicine-binding site, and selected derivatives have shown improved stability and antitumor activity in experimental models, including paclitaxel-resistant melanoma xenografts [19, 20]. Recent work further indicates that imidazoquinoxaline and quinoxaline-benzimidazole systems may retain antitubulin properties [3, 21]. These observations support the continued exploration of the scaffold as a source of microtubule-disrupting agents, although selectivity and systemic toxicity remain important development considerations.

4. DNA Damage, Intercalation and Topoisomerase Inhibition

DNA-directed mechanisms are among the most established areas of quinoxaline anticancer research. The planar aromatic nature of appropriately substituted quinoxaline derivatives facilitates DNA intercalation, whereas other analogs interact with enzymes responsible for maintaining DNA topology.

4.1 DNA intercalation

DNA intercalators insert between adjacent base pairs and can interfere with replication, transcription, and DNA-processing enzymes. Therefore, a number of triazoloquinoxaline and benzo[g]quinoxaline derivatives have been developed as potential DNA-interacting anticancer agents [22–26]. The nature of the substituent strongly affects the antiproliferative activity. In several [1,2,4]triazolo[4,3-a]quinoxaline series [11], changes in the R1 substituent substantially altered the activity against hepatocellular, laryngeal, colorectal, and breast cancer cell lines. Some derivatives demonstrated sub micromolar activity, whereas structurally related analogs were considerably weaker [23–26]. These findings indicate that increased structural complexity does not necessarily translate to improved biological activities. Instead, optimal DNA interaction requires an appropriate combination of planarity, aromatic surface, electronic characteristics and substituent orientation.

4.2 Topoisomerase I

Topoisomerase I regulates DNA topology by producing transient single-strand breaks. Because DNA replication and transcription depend on controlled topological changes, inhibition of topoisomerase I can interfere with cancer cell proliferation. Quinoxaline derivatives containing benzazole substituents have demonstrated topoisomerase I-directed antiproliferative activity. Mechanistic analysis suggests that selected derivatives inhibit topoisomerase I without requiring strong interaction with intact DNA, indicating that DNA intercalation and topoisomerase inhibition may be separable mechanisms within quinoxaline chemistry [27]. A particularly interesting strategy involved dibenzoquinoxaline derivatives designed to simultaneously target topoisomerase I and c-MYC G-quadruplexes. One optimized compound exhibited sub micromolar activity against triple-negative breast cancer cells, illustrating how quinoxaline chemistry can be used to generate compounds with complementary molecular targets [28].

4.3 Topoisomerase II

Topoisomerase II produces transient double-strand DNA breaks and subsequently ligates DNA. Drugs that stabilize the topoisomerase II–DNA cleavage complex can induce persistent DNA damage and apoptosis. Etoposide and anthracyclines are established examples of therapeutic strategies. Quinoxaline derivatives have been explored as selective topoisomerase II inhibitors and dual DNA intercalator/topoisomerase II inhibitors. Triazoloquinoxaline derivatives containing sulfonamide groups have demonstrated antiproliferative effects in neuroblastoma, breast, cervical, and lung cancer models [29]. Other derivatives based on oxiranyl-quinoxaline structures have also been investigated. These studies illustrate how stereochemistry and substituent configuration can affect anticancer activities [30]. A recent systematic review confirmed that topoisomerase inhibition and DNA intercalation remain the major mechanisms of action of quinoxaline derivatives. However, these mechanisms should be evaluated using rigorous target-engagement experiments rather than relying primarily on molecular docking and cytotoxicity measurements.

5. DNA Repair, PARP and Alkylation-Associated Strategies

Quinoxaline-based anticancer drugs represent another opportunity for cancer therapy. Cancer cells frequently experience elevated endogenous DNA damage and become dependent on DNA repair mechanisms to maintain viability. Therefore, inhibiting repair can enhance the effects of DNA-damaging treatments [31]. One innovative approach involves aminoquinoxaline and nitroquinoxaline systems capable of targeting abasic DNA sites. The nitro

derivative can undergo intracellular reduction in the presence of glutathione, generating an activated species capable of interacting with damaged DNA. Combination with chlorambucil increased DNA damage and cytotoxicity, suggesting a strategy for exploiting DNA-repair vulnerabilities in resistant cancer cells [32]. PARP1 is another important DNA repair target. PARP proteins participate in DNA repair and maintenance of genomic integrity, and pharmacological inhibition can increase the susceptibility of cancer cells to DNA damage. Quinoxaline derivatives designed using pharmacophoric features characteristic of PARP inhibitors have demonstrated PARP1 inhibitory and antiproliferative activity [33]. One quinoxaline-based series was designed around a heteroaromatic bicyclic ring, carboxamide group, and auxiliary side chain. A representative derivative showed promising PARP1 and cell growth inhibition compared with olaparib in the reported experimental system [33]. These findings suggest that quinoxaline may be incorporated into DNA-repair inhibitor pharmacophores, although further in-vivo validation is required.

6. Epigenetic Regulation and Chromatin-Associated Targets

The role of epigenetic regulation in cancer has stimulated interest in compounds that target histone-modifying enzymes and chromatin readers. Quinoxaline derivatives have been investigated as histone deacetylase inhibitors and, more recently, as inhibitors of bromodomain-containing proteins [3].

6.1 Histone deacetylases

Histone acetylation influences chromatin structures and gene expression. HDACs remove acetyl groups from histones and other proteins, whereas HDAC inhibition can promote hyperacetylation and alter transcriptional programs. Quinoxaline derivatives designed according to HDAC inhibitor pharmacophores demonstrated anticancer activity against hepatocellular carcinoma models. Substitution at the 2-position influenced activity, with a chlorine-containing derivative performing better than its methoxy analog. Mechanistic evaluation indicated pan-HDAC inhibition, G0/G1 cell cycle arrest, and apoptosis [34].

6.2 BRD9

A major emerging direction identified in the newer literature is bromodomain containing protein 9 (BRD9). Functionalized triazoloquinoxaline derivatives have been investigated as BRD9-targeting compounds, with structural optimization focused on substitution patterns around the triazoloquinoxaline core [35]. This mechanism represents a conceptual expansion beyond direct DNA damage or kinase inhibition, as BRD9 is involved in chromatin-associated regulatory processes. The incorporation of quinoxaline into bromodomain-targeting molecules demonstrates the adaptability of the scaffold toward epigenetic protein recognition.

6.3 BET bromodomains

Another emerging direction involves BD1-selective inhibition of BET proteins. The quinoxaline-based compound DW71177 was reported as a potent and selective BD1 inhibitor, with activity in leukemia and other cancer models. Its biological effects include modulation of c-MYC, ERK1/2 phosphorylation, p21 expression, cell-cycle progression, and apoptosis [36]. The development of BD1-selective quinoxaline compounds is significant because it demonstrates that scaffold optimization can be directed toward domain-level selectivity rather than broad protein inhibition.

7. Kinase-Directed Anticancer Activity

Protein kinases are one of the largest target classes for quinoxaline-based anticancer agents. Their importance arises from the central role of phosphorylation networks in proliferation, survival, metabolism, angiogenesis, invasion, and therapeutic resistance [3].

7.1 VEGFR-2

VEGFR-2 is a particularly important target in anticancer drug discovery. Angiogenesis enables tumor growth and dissemination, and VEGF-mediated activation of VEGFR-2 contributes substantially to tumor vascularization. Numerous quinoxaline, triazoloquinoxaline, and quinoxalinone derivatives have been designed as VEGFR-2 inhibitors. Their structures commonly contain a heteroaromatic region capable of occupying the ATP-binding region, a linker incorporating hydrogen-bonding functionality, and a substituted aromatic region that contributes to hydrophobic interactions [41–49]. Several studies have reported simultaneous VEGFR-2 inhibition and cancer-cell growth suppression. Apoptosis and G2/M cell-cycle arrest are frequently associated with the activity of potent derivatives [37–45]. Recent studies have extended this strategy to resistant cancer models. Alsaif et al. described quinoxaline derivatives with VEGFR-2 inhibition and antiproliferative effects, while Alanazi et al. reported highly

potent derivatives within a broader VEGFR-2-focused series [37, 38]. These findings raise the possibility that quinoxaline-based VEGFR-2 inhibitors may contribute to strategies designed to overcome resistance to established kinase inhibitors.

7.2 EGFR and HER2

EGFR signaling is frequently dysregulated in solid tumors, and resistance to established EGFR inhibitors remains a challenge. Therefore, quinoxaline derivatives have been investigated as bioisosteric replacements for quinazoline-based EGFR inhibitors [1]. Monosubstituted quinoxalines, quinoxalinones, and fused azoloquinoxalines have demonstrated EGFR-directed activity. Some derivatives showed activity against both wild-type and mutant EGFR forms, while others displayed antiproliferative activity comparable to the that of reference compounds [46–42]. An imidazoquinoxaline derivative was evaluated in gefitinib-resistant lung cancer xenografts, and reduced tumor growth, providing in-vivo evidence supporting the continued development of quinoxaline-based EGFR inhibitors [52]. Quinoxaline derivatives have also been explored as dual EGFR/COX-2 inhibitors, illustrating another strategy in which a single scaffold can be optimized for multiple disease-associated targets [43].

7.3 c-Met

c-Met/HGF signaling regulates proliferation, survival, motility, and morphogenesis and is dysregulated in several cancers. Quinoxaline-containing compounds have been incorporated into c-Met type II inhibitors. A series of quinoxaline-containing derivatives demonstrated potent c-Met inhibition, along with activity against lung and colon cancer models. Some compounds showed enzymatic inhibition comparable to or better than that of the reference inhibitor, foretinib [53–55]. This study highlights the value of integrating quinoxaline chemistry with established kinase pharmacophores to access alternative type II inhibitor architectures.

7.4 PI3K/Akt/mTOR and PIM kinases

The PI3K/Akt/mTOR network is a major regulator of cell survival, metabolism, and proliferation. Quinoxaline derivatives have been explored as PI3Kα inhibitors, including compounds that are active against the H1047R mutant form of PI3Kα [56]. Selected difuran-substituted quinoxalines demonstrated activity against both wild-type and mutant PI3Kα and produced G0/G1 arrest followed by apoptosis [56]. Pyrroloquinoxaline derivatives have also been investigated for their effects on downstream Akt signaling. PIM kinases represent another kinase family of interest because they contribute to cell survival, proliferation, metabolism, and therapeutic resistance. Quinoxaline-2-carboxylic acid derivatives have been developed as PIM-1 inhibitors, and subsequent optimization has generated compounds with activity against both PIM-1 and PIM-2 [57, 58].

8. Metabolic and Redox Vulnerabilities

Cancer cells frequently undergo metabolic reprogramming, creating opportunities to target metabolic enzymes and redox homeostasis. Quinoxaline derivatives have exhibited activity in both areas.

8.1 Folate-associated metabolism

Antimetabolites interfere with nucleotide biosynthesis, impairing DNA replication and transcription. Quinoxaline peptidomimetics have been developed as potential inhibitors of thymidylate synthase (TS) and other folate-associated enzymes. More than 100 quinoxaline peptidomimetics have been investigated in related series. Sulfur-containing analogs generally demonstrate stronger antiproliferative effects than their corresponding oxygen-regioisomers, with selected compounds producing low-micromolar activity in breast and colorectal cancer models [59–62]. A recent review emphasized that this area remains relatively underdeveloped and that molecular modeling alone is insufficient to confirm thymidylate synthase inhibition. Therefore, direct enzymatic and in vivo validation is necessary.

8.2 PFKFB3

PFKFB3 is an emerging metabolic target that has been highlighted specifically in the recent systematic literature. The enzyme regulates glycolytic flux, and its dysregulation can support the metabolic demands of cancer cells [63]. A triazolequinoxaline derivative was investigated using structural, computational, and PFKFB3-targeting approaches, illustrating the increasing focus of quinoxaline chemistry on metabolic regulators rather than exclusively classical cytotoxic targets [64].

8.3 Reactive oxygen species and hypoxia

ROS can act as signaling molecules at controlled concentrations but can cause extensive oxidative damage when intracellular levels exceed the cellular buffering capacity. Some quinoxaline derivatives promote ROS accumulation, thereby contributing to apoptosis [65]. Quinoxaline 1,4-di-N-oxide derivatives represent a

particularly interesting approach because they can function as hypoxia-activated prodrugs. Under hypoxic conditions, these compounds undergo bio-reduction and generate reactive species capable of damaging tumor cells. Some derivatives have additionally been associated with inhibition of HIF-1α and VEGF signaling [66–70]. This mechanism is potentially important because hypoxia is a characteristic feature of solid tumors and contributes to angiogenesis, invasion, metastasis, and resistance to treatment.

9. Apoptosis and Other Regulated Cell-Death Mechanisms

Although quinoxaline derivatives act on diverse molecular targets, apoptosis is a recurrent downstream response. The reported mechanisms include activation of caspases, modulation of BAX and Bcl-2, mitochondrial dysfunction, ROS accumulation, and cell cycle arrest. Quinoxaline derivatives containing thiazole-indenoquinoxaline and related fused systems exhibit antiproliferative activity, accompanied by apoptotic responses [71]. Other indenoquinoxaline derivatives have been associated with increased BAX and caspase-3 expression and decreased Bcl-2 expression [72]. Bcl-2 itself has also emerged as a direct target. Quinoxaline-oxadiazole hybrids were designed using structural information from Bcl-2 inhibitor complexes, and the selected compounds displayed significant cytotoxicity accompanied by Bcl-2 downregulation [73]. These findings demonstrate the possibility of designing quinoxalines to act directly on proteins controlling mitochondrial apoptosis. The evidence also extends beyond apoptosis. The source literature discusses regulated cell death pathways, including ferroptosis and pyroptosis, highlighting the increasing recognition of the interconnections among different forms of cellular death. However, compared with apoptosis, mechanistic evidence for non-apoptotic death pathways remains comparatively limited.

10. Metastasis-Associated Targets

Cancer mortality is strongly influenced by metastatic dissemination. MMP-9 participates in the degradation and remodeling of the extracellular matrix and is associated with invasive behavior in several tumor types. Quinoxaline derivatives have been developed as dual MMP-9/monoamine oxidase inhibitors. Several compounds demonstrated nanomolar-level activity against colorectal cancer cells while retaining lower activity against normal colonocytes [74]. Enzyme assays supported the inhibition of MMP-9 and MAO-A, while HIF-1α downregulation was also observed. The dual-target strategy is conceptually important because it moves quinoxaline research beyond simply inhibiting tumor cell proliferation and toward simultaneous interference with processes involved in invasion and metastatic progression.

11. Structure–Activity Relationships and Design Principles

A comprehensive structure–activity relationship (SAR) analysis indicates that the biological activity of quinoxaline derivatives is substantially influenced by the type, electronic characteristics, and spatial arrangement of substituents on the core scaffold. Across various studies, these structural factors collectively determine antiproliferative potency, target selectivity, and overall anticancer efficacy. Position-specific modifications at the C2 and C3 sites of the quinoxaline nucleus primarily affect target binding and intrinsic biological activity. Incorporation of bulky aryl or heteroaryl substituents at these positions can enhance antiproliferative and kinase-inhibitory effects by facilitating favorable interactions within enzyme-binding pockets. Conversely, modifications at the N1 and N4 positions are more closely associated with pharmacokinetic characteristics, such as aqueous solubility, cellular permeability, and molecular selectivity. The incorporation of polar or sterically demanding groups at N1/N4 may improve cellular penetration and, in certain structural contexts, contribute to enhanced kinase selectivity. This trend is exemplified by the study of [37], in which a series of quinoxaline derivatives (15a–d and 17a-d) were evaluated against two human cancer cell lines, MCF-7, HepG-2 and for VEGFR-2 inhibitory activity. The IC50 values obtained for all synthesized compounds are summarized in Table 1 of the study. Lower IC50 values indicate greater antiproliferative or VEGFR-2 inhibitory potency. A clear SAR difference was observed between the two major structural series. Compounds 15a–d and 16, incorporating the 3-methylquinoxaline-2-thiol moiety, were generally less potent than the corresponding 17a–d and 18 derivatives containing the 3-methylquinoxalin-2(1H)-one moiety. Thus, replacement of the quinoxaline-2-thiol functionality with the quinoxalin-2(1H)-one group was favorable for biological activity. The authors consequently identified the quinoxalin-2(1H)-one moiety as a more advantageous pharmacophoric group. This improvement is particularly evident for the corresponding 15a/17a and 15b/17b pairs. Compound 15a showed a VEGFR-2 IC50 of 23.1 nM, whereas 17a showed 11.2 nM. Similarly, 15b

exhibited 3.4 nM, while 17b exhibited only 2.7 nM, demonstrating the superior activity of the quinoxalin-2-one series. The nature of the terminal hydrophobic group had a substantial influence on VEGFR-2 inhibition. Compounds 15a and 17a, bearing an aliphatic N-butyl substituent, showed VEGFR-2 IC50 values of 23.1 and 11.2 nM, respectively. In contrast, replacement of the aliphatic group by a 3-chlorophenyl group in 15b and 17b markedly improved activity, giving IC50 values of 3.4 and 2.7 nM, respectively. Therefore, incorporation of an aromatic hydrophobic group bearing an electron-withdrawing substituent was strongly favored over the aliphatic hydrophobic group. The authors specifically concluded that the 3-chlorophenyl-containing derivatives were biologically preferable to their aliphatic counterparts. The comparison between 15b/17b and 15c/17c further demonstrated the importance of electronic effects at the terminal aromatic region. Compounds 15b and 17b, containing the 3-chlorophenyl electron-withdrawing substituent, were considerably more potent than 15c and 17c, containing the 4-hydroxyphenyl electron-donating substituent. For VEGFR-2 inhibition, 15b showed an IC50 of 3.4 nM, whereas 15c showed 27.8 nM. In the quinoxalin-2-one series, 17b displayed an IC50 of 2.7 nM, compared with 13.9 nM for 17c, which was slightly better than the reference drug sorafenib (3.12 nM). The same trend was evident in the antiproliferative assays: 17b exhibited MCF-7 and HepG-2 IC50 values of 2.8 and 2.3 µM, respectively, whereas 17c showed 17.9 and 14.3 µM. These findings support a preference for an electron-withdrawing substituent over an electron-donating substituent in this region. Compound 15d, containing a 2-hydroxy-4-nitrophenyl terminal group, showed relatively weak VEGFR-2 inhibitory activity with an IC50 of 31.5 nM. Its corresponding quinoxalin-2-one analogue 17d showed improved activity with an IC50 of 11.2 nM, again supporting the beneficial effect of the quinoxalin-2-one pharmacophore. However, 17d remained considerably less potent than 17b (2.7 nM). Thus, although the nitro group provides an electron-withdrawing character, the combined 2-hydroxy-4-nitrophenyl substitution did not produce the same potency as the 3-chlorophenyl group. The data therefore indicate that the overall electronic, steric, and hydrophobic properties of the terminal aromatic substituent, rather than electron-withdrawing character alone, influence VEGFR-2 inhibition. Compounds 16 and 18 incorporated the additional 2-hydroxybenzoyl hydrazide-containing pharmacophoric system. Compound 16, containing the quinoxaline-2-thiol moiety, showed a VEGFR-2 IC50 of 18.5 nM, whereas its quinoxalin-2-one analogue 18 exhibited improved activity with an IC50 of 11.2 nM. Thus, this structural modification again followed the general trend that the quinoxalin-2-one scaffold was more favorable than the quinoxaline-2-thiol scaffold. Nevertheless, compound 18 was less potent than 17b, indicating that the hydrazide-containing terminal group did not provide the same optimal interaction profile as the 3-chlorophenyl substituent.

Molecular docking studies further support the superior activity of compound 17b, as evidenced by its favorable binding free energy toward cytochrome P450 (PDB ID: 4D7D). The amide pharmacophore established hydrogen-bonding interactions with Glu883 and Asp1044, whereas the 3-chlorophenyl substituent engaged in hydrophobic interactions with Leu887, Ile886, and Ile890, along with an electrostatic interaction involving Asp1044. The quinoxaline ring occupied the hinge region and contributed several hydrophobic contacts, while the central phenyl moiety provided additional hydrophobic interactions. Collectively, these favorable binding interactions were proposed to contribute to the enhanced biological activity observed for compound 17b. Overall, the SAR trends observed across these studies highlight that optimal anticancer activity of quinoxaline deriva tives arises from a synergistic combination of electronic modulation and position-specific substitution. Electron-withdrawing groups on peripheral aromatic rings enhance antiproliferative potency, while strategic substitution at the N1 position of the quinoxaline scaffold, particularly the incorporation of amide moiety in the pharmacophore region is critical for achieving high activity. These insights provide a rational framework for the future design and optimization of quinoxaline-based anticancer agents with improved potency and selectivity. These SAR trends are summarized in a generalized SAR map in figure 3.

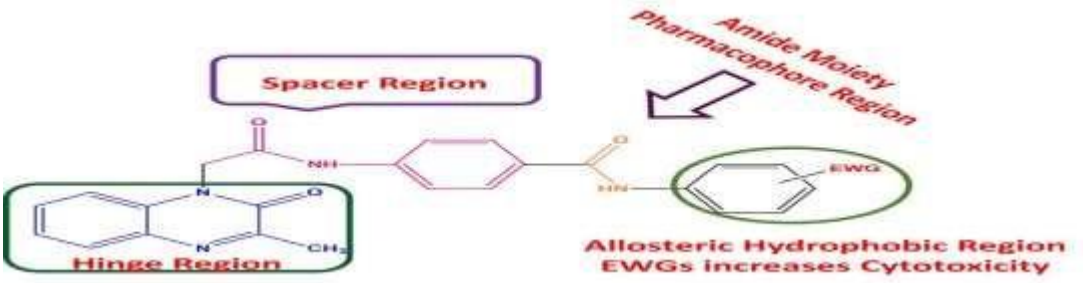


Figure 3. SAR map highlighting core positions critical for the anticancer potency and selectivity of quinoxalines.

Conclusion

Quinoxaline derivatives constitute a chemically adaptable platform for anticancer drug discovery, with demonstrated activity across DNA-directed, cytoskeletal, kinase, epigenetic, metabolic, apoptotic, and metastasis-associated mechanisms. The combined evidence from the demonstrates a clear transition from traditional mechanisms such as DNA intercalation, topoisomerase inhibition, and tubulin disruption toward increasingly diverse targets, including VEGFR-2, EGFR, c-Met, PIM kinases, BRD9, BET proteins, PFKFB3, and other cancer-associated pathways. The scaffold's major strength is its capacity to accommodate target-specific structural modifications. Aromatic substitution, electron-withdrawing groups, hydrogen-bonding functionalities, methylamino groups, linker architecture, and fused heterocycles can substantially alter biological activity. However, these structural features may generate liabilities involving solubility, lipophilicity, metabolism, toxicity, and pharmacokinetics. Therefore, future research should move beyond the discovery of compounds with low cellular IC50 values. A more clinically oriented development paradigm should integrate target validation, rational SAR, biochemical potency, cellular selectivity, resistance profiling, ADME characterization, in vivo efficacy, advanced delivery, and clinically relevant tumor models. Overall, the evidence supports quinoxaline as a multifunctional medicinal chemistry platform with substantial potential for anticancer drug discovery, while emphasizing that rigorous translational validation remains essential before many promising experimental derivatives can be converted into clinically useful therapies.

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