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An insight into the therapeutic impact of quinoxaline derivatives: Recent advances in biological activities (2020–2024)☆

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ABSTRACT

Quinoxaline derivatives have garnered significant attention due to their wide-ranging therapeutic applications. Research from 2020 to 2024 has demonstrated their potent bioactivity across various domains, including anticancer, antimicrobial, antiviral, anti-inflammatory, and antidiabetic activities. Structural modifications guided by structure–activity relationship (SAR) studies have enabled the development of targeted quinoxaline-based compounds with enhanced efficacy. These derivatives interact with critical biological targets such as enzymes, receptors, and signaling pathways, offering promising avenues for treating complex diseases like cancer and infectious diseases. Advanced studies, including molecular docking and ADMET analyses, have further clarified their pharmacological profiles, optimizing their drug-like properties and bioavailability. This review provides a comprehensive overview of the recent advancements in quinoxaline-based therapies, underscoring their potential impact on modern drug discovery and therapeutic applications.

Introduction

Heterocyclic compounds play a crucial role in medicinal chemistry due to their versatile structures and ability to interact with biological targets, making them integral to drug design. Their unique ring systems, often incorporating atoms like nitrogen, oxygen, or sulfur, enhance molecular stability and reactivity. Nitrogen-containing heterocycles are particularly significant, as nitrogen contributes to key interactions with enzymes and receptors, improving drug-likeness and pharmacokinetic properties [1,2]. These N-heterocyclic compounds are widely found in drugs for treating various conditions, such as antibiotics and anticancer agents, underscoring their broad therapeutic relevance.

Quinoxaline, a nitrogen-containing heterocyclic compound, is recognized for its chemical stability and versatile framework, making it a valuable scaffold in medicinal chemistry. Structurally, quinoxaline consists of a fused benzene and pyrazine ring, providing a rigid planar core (Fig. 1) that facilitates interaction with various biological targets, including enzymes and receptors. Its importance stems from the ease with which it can be functionalized, allowing for the incorporation of various substituents at different positions on the ring [3]. This functionalization enables fine-tuning its physicochemical properties, such as solubility, lipophilicity, and binding affinity, which can be optimized for specific therapeutic applications. Common modifications include halogenation, alkylation, and introducing electron-donating or electron-

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withdrawing groups, significantly expanding its pharmacological potential. As a result, quinoxaline derivatives have shown activity in diverse therapeutic areas, including anticancer [4], antimicrobial [5], antidiabetic [6], and antiviral [7] treatments, further underscoring the compound's importance in drug discovery.

A recent bibliometric analysis of quinoxaline-related research, conducted using the Scopus database, yielded a total of 841 documents, indicating a strong research focus on this scaffold over the last five years. The data highlights a steady increase in publications from 2020 to 2022, followed by a slight decrease in 2023, and stabilization in 2024, suggesting sustained interest in this chemical scaffold (Fig. 2A). Geographically, China and India dominate the research output, reflecting significant scientific activity in these regions, particularly in chemical and pharmaceutical sciences. This is followed by contributions from countries such as Saudi Arabia, the United States, and Egypt (Fig. 2B). In terms of publication types, the majority are original research articles (92.9 %), with reviews accounting for 4.5 % (Fig. 2C), indicating a focus on novel discoveries and ongoing explorations of quinoxaline's therapeutic potential. The subject areas most represented include Chemistry (37.3 %), Materials Science (13.7 %), Biochemistry (11.1 %), and Chemical Engineering (10.1 %) (Fig. 2D), underlining the multidisciplinary applications of quinoxaline derivatives in various fields, especially in medicinal chemistry and materials development.

Unique physicochemical characteristics of quinoxalines

Quinoxaline derivatives are heterocyclic compounds characterized by the fusion of benzene and pyrazine rings. Their unique combination of electronic, structural, physicochemical, and reactive properties makes them a pivotal scaffold in drug discovery, influencing a wide array of biological activities such as anticancer, antiviral, and antimicrobial effects.

The nitrogen atoms in the pyrazine ring impart strong electron-withdrawing properties to quinoxalines, enhancing π-conjugation and stabilizing charge distribution. This facilitates robust π-π interactions with biological macromolecules, including nucleic acids and proteins. For example, quinoxalines exhibit higher electron affinity compared to bioisosteric analogs like quinoline, enabling stronger interactions with DNA and RNA targets. These attributes are particularly relevant in the design of DNA-intercalating agents for anticancer therapies [8].

The nitrogen atoms and functionalizable positions on the quinoxaline ring enhance their hydrogen bonding potential, allowing for specific interactions with biological targets. Their weakly basic nature enables the formation of salts under acidic conditions, which facilitates interactions within biological systems at physiological pH. This property is advantageous in designing drugs targeting proton-rich environments, such as tumor microenvironments or acidic cellular compartments [9].

Quinoxalines exhibit notable thermal stability and solubility characteristics, making them versatile in synthetic methodologies. They are sparingly soluble in water but display significant solubility in organic solvents like ethanol and acetonitrile. Their dipole moment, influenced by the electron-withdrawing nature of the pyrazine ring, contributes to their polar interactions with biological targets. Additionally, their partition coefficient (logP) can be modulated through substitutions at specific positions, optimizing lipophilicity for enhanced cellular uptake and bioavailability [10].

The 2- and 3-positions on the quinoxaline ring are highly amenable to chemical modifications, allowing for the development of derivatives with tailored biological activities. Substitutions at these positions influence the electronic properties of the scaffold, enabling fine-tuning of binding affinities to specific targets. For instance, 2,3-bis-substituted quinoxalines have been optimized for anticancer activity by enhancing interactions with topoisomerases and tubulin polymerization sites. Green chemistry approaches, such as microwave-assisted synthesis and recyclable catalysts, have also streamlined their production [11].

Quinoxalines exhibit redox behavior due to their electron-rich aromatic system, a property exploited in designing compounds with photochemical and electrochemical applications. Their ability to undergo reduction (n-doping) or oxidation (p-doping) has been utilized in polymer chemistry and biological redox reactions. These redox properties also contribute to modulating oxidative stress pathways, a key mechanism in cancer and infectious disease treatment [12].

As bioisosteres of quinoline and naphthalene, quinoxalines offer enhanced hydrogen bonding and π-stacking potential due to their additional nitrogen atoms. Their structure supports multimodal interactions, combining π-stacking, hydrogen bonding, acid-base interactions, and polar contacts. These binding mechanisms have been validated in molecular docking studies, where quinoxalines effectively inhibit multiple enzymes involved in cancer progression and immune evasion [13].

Natural and commercially-available quinoxaline derivatives

In addition to their synthetic versatility, quinoxaline compounds are found in nature, though in limited occurrences. Certain microorganisms, such as bacteria and fungi, produce natural quinoxaline derivatives with notable biological activities. For example, echinomycin, a quinoxaline-based antibiotic produced by *Streptomyces* species, exhibits potent antitumor and antibacterial properties through DNA intercalation [14]. Other naturally occurring quinoxaline alkaloids from marine organisms have also demonstrated promising antimicrobial and anticancer activities, further emphasizing the compound's biological relevance.

Commercially available quinoxaline derivatives have significantly impacted various therapeutic areas, with several notable examples being widely used in medicine and industry. **Carbadox**, a quinoxaline-based compound, is extensively used in veterinary medicine as a growth promoter and antimicrobial agent in swine feed due to its effectiveness against bacterial infections, particularly in treating and preventing dysentery [15]. In human medicine, quinoxaline derivatives like **Erdafitinib**, a fibroblast growth factor receptor (FGFR) inhibitor [16], have gained approval for treating advanced urothelial carcinoma, a type of bladder cancer. Erdafitinib targets FGFR mutations, commonly

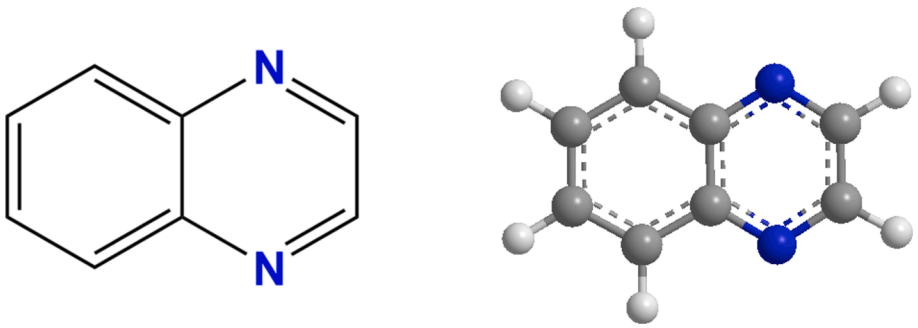


Fig. 1. 2D and 3D representations of the quinoxaline ring.

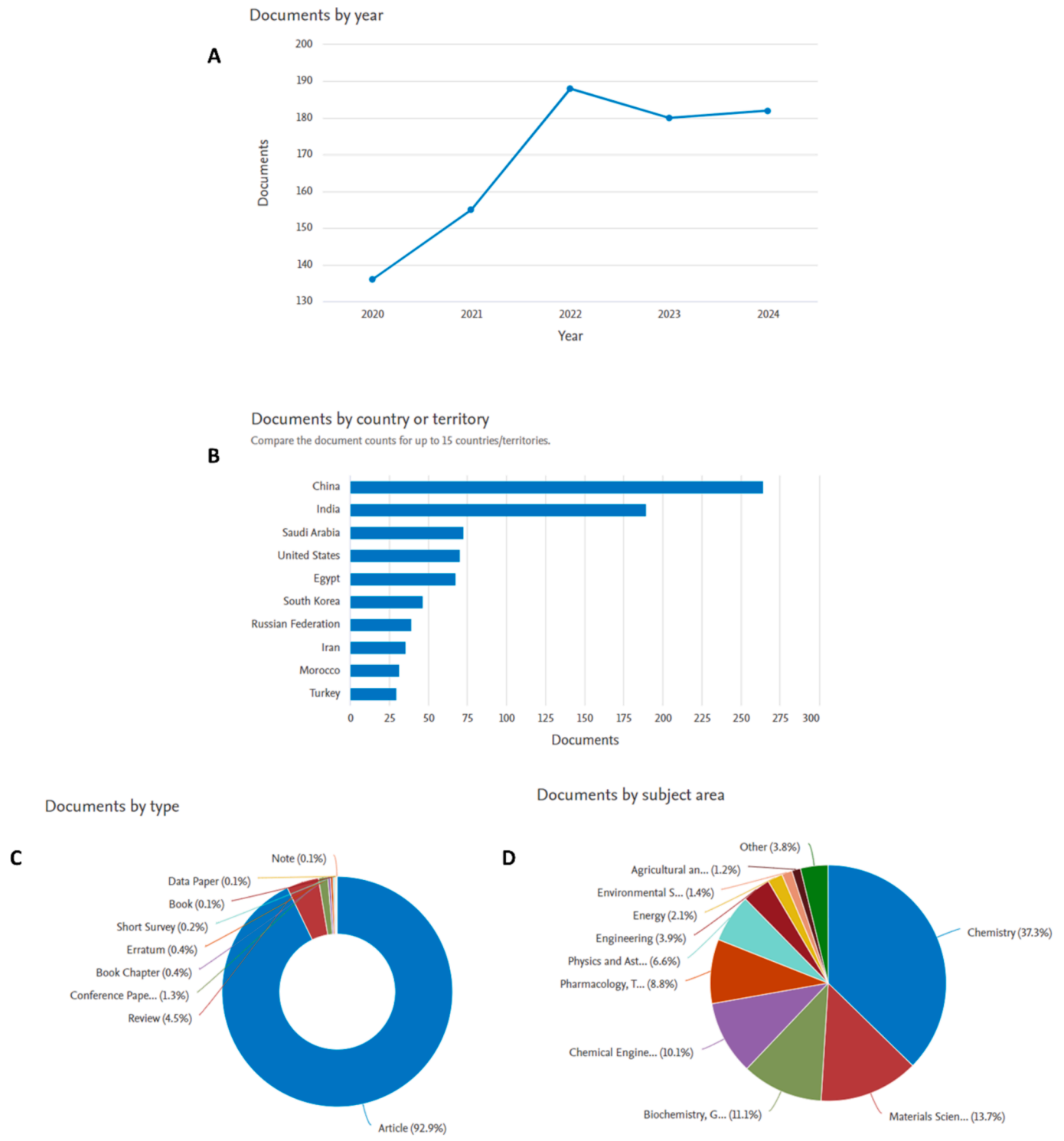
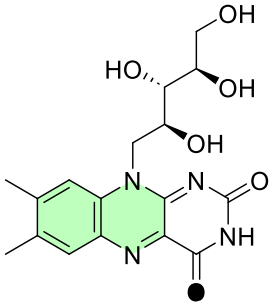
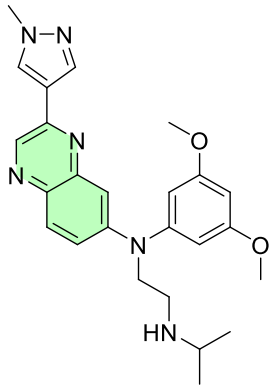
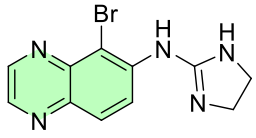
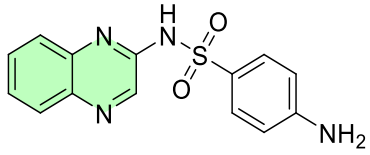
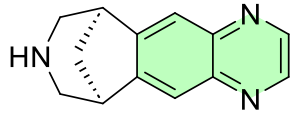


Fig. 2. A. Analysis of yearly publication trends retrieved from Scopus using the keyword 'quinoxaline,' accessed on October 23, 2024; B. Breakdown of publications by country based on Scopus search with the keyword 'quinoxaline,' accessed on October 23, 2024; C. Overview of document types from a Scopus search using the keyword 'quinoxaline,' accessed on October 23, 2024; D. Examination of research areas related to 'quinoxaline' from a Scopus search, accessed on October 23, 2024.

associated with tumor growth and progression, demonstrating the potential of quinoxaline derivatives in precision cancer therapies. Another notable example is **Glecaprevir**, a protease inhibitor combined with pibrentasvir, a highly effective treatment for chronic hepatitis C (HCV) infections [17]. Examples of commercially available quinoxaline derivatives are summarized in Table 1. These examples highlight the versatility and effectiveness of quinoxaline derivatives in both veterinary and human medicine, further underscoring their broad therapeutic relevance and ongoing development across various medical fields.

This review highlights the pharmacological activities, structure–activity relationship (SAR), and mechanistic studies of quinoxaline derivatives, focusing on recent studies from the last five years. By exploring their diverse biological activities, including anticancer, antimicrobial, antiviral, antidiabetic, and anti-inflammatory effects, as well as their ADMET profiles, this review provides a comprehensive understanding of their therapeutic potential. The versatility of quinoxaline

Table 1
Examples of quinoxaline derivatives with therapeutic uses in both veterinary and human medicine.

Drug name	Chemical structure	Indication	Mechanism of action
Riboflavin		Vitamin B2 deficiency, migraine prevention	Serves as a cofactor in enzyme reactions, important for energy production and cellular function.
Erdafitinib		Urothelial carcinoma	Inhibits fibroblast growth factor receptors (FGFR), blocking signaling pathways involved in cancer cell growth.
Brimonidine		Glaucoma, ocular hypertension	Alpha-2 adrenergic receptor agonist, decreases aqueous humor production and increases uveoscleral outflow.
Sulfaquinoxaline		Coccidiosis in poultry and livestock	Inhibits folic acid synthesis in bacteria and protozoa, interfering with DNA synthesis.
Varenicline		Smoking cessation	Partial agonist of nicotinic acetylcholine receptors, reduces cravings and withdrawal symptoms.

(*continued on next page*)

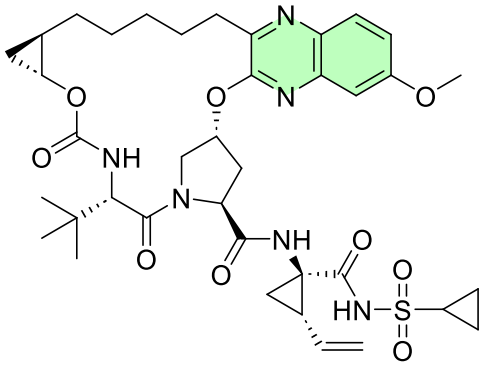
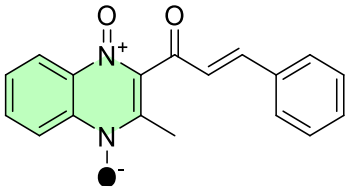
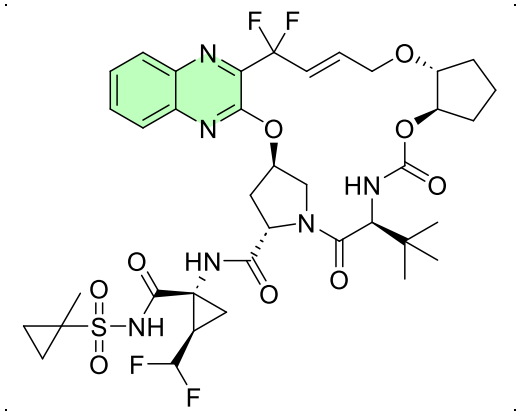
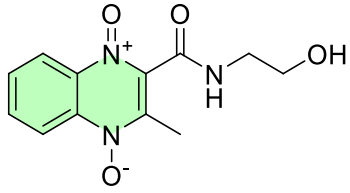
derivatives and their fine-tuning ability through structural modifications make them promising candidates for ongoing drug development across various medical fields.

Biological activities of quinoxaline derivatives

Anticancer activity

Cancer is a leading global health challenge, characterized by uncontrolled cell growth and the ability to invade surrounding tissues and spread to distant organs [18,19]. It remains one of the primary causes of

Table 1 (*continued*)

Drug name	Chemical structure	Indication	Mechanism of action
Grazoprevir		Hepatitis C (chronic infection)	Inhibits NS3/4A protease, preventing viral replication of the hepatitis C virus.
quinocetone		Growth promotion in animals	Inhibits bacterial DNA synthesis by binding to bacterial DNA gyrase.
Glecaprevir		Hepatitis C (chronic infection)	Inhibits NS3/4A protease, preventing viral replication of the hepatitis C virus.
Olaquindox		Growth promotion in livestock	Inhibits bacterial DNA synthesis, particularly targeting gram-negative bacteria.

death worldwide, with millions of new cases diagnosed each year [20–22]. Despite advances in treatments such as surgery, chemotherapy, radiotherapy, and immunotherapy, cancer continues to pose significant therapeutic challenges due to its complexity, genetic diversity, and the development of drug resistance [23–25]. Additionally, conventional treatments often come with severe side effects, highlighting the need for more effective and targeted therapies. The search for novel anticancer agents is a critical area of research, focusing on compounds that selectively target cancer cells while minimizing harm to normal tissues. In this context, small-molecule drugs have emerged as promising candidates for improving cancer treatment outcomes, particularly those capable of modulating key pathways involved in tumor growth and survival [26,27]. Quinoxaline derivatives have demonstrated considerable potential as anticancer agents through various mechanisms. These compounds target several critical biological processes in cancer cells, including kinase inhibition, DNA intercalation, topoisomerase inhibition, and the disruption of tubulin polymerization [28]. By interacting with these pathways, quinoxaline-based derivatives can induce apoptosis, inhibit cell proliferation, and block angiogenesis. In particular, they have shown efficacy against multiple cancer types, such as breast, liver, and colon cancers. This section presents recent developments and notable examples of quinoxaline derivatives exhibiting significant anticancer properties, as summarized in Fig. 3.

Kinase inhibitors

VEGFR-2 inhibitors. VEGFR-2 (vascular endothelial growth factor receptor 2) plays a pivotal role in angiogenesis, the process by which new

blood vessels form from existing ones, which is essential for tumor growth and metastasis [29]. Inhibition of VEGFR-2 has become a crucial therapeutic strategy in cancer treatment, as it can effectively cut off the blood supply to tumors, limiting their growth and ability to spread [30]. Quinoxaline derivatives have emerged as potent VEGFR-2 inhibitors, demonstrating significant antiproliferative and pro-apoptotic activities in various cancer models. These compounds inhibit tumor angiogenesis and directly induce cancer cell death by disrupting key signaling pathways mediated by VEGFR-2. For example, Alsaif et al. synthesized new quinoxaline derivatives targeting VEGFR-2 and evaluated their anticancer and pro-apoptotic activities against MCF-7 and HepG2 cell lines [31]. The compounds, particularly **1**, **2**, **3**, and **6** (Fig. 4), displayed significant anti-proliferative activities with IC_{50} values ranging from 4.1 μM to 11.7 μM for both cell lines, comparable to the reference drug sorafenib. The VEGFR-2 inhibitory assays showed that these compounds exhibited IC_{50} values between 3.4 nM and 6.8 nM, with compound **1** being the most effective (IC_{50} = 3.4 nM). Further analysis revealed compound **1** induced apoptosis in HepG2 cells by increasing the Bax/Bcl-2 ratio by 3.8-fold and elevating caspase-3 and caspase-9 levels by 1.8-fold and 1.9-fold, respectively. Molecular docking studies confirmed that compound **1** binds efficiently within the VEGFR-2 active site, interacting with crucial residues such as Glu883 and Asp1044. These results highlight compound **1** as a promising candidate for further development as a VEGFR-2 inhibitor with anticancer potential.

Continuing their investigation, Alsaif et al. identified and synthesized a series of [1,2,4]triazolo[4,3-a]quinoxalines as potent VEGFR-2 tyrosine kinase inhibitors, focusing on their anticancer potential [32]. The most active compound, **7** (Fig. 4), demonstrated significant antiproliferative activity, with IC_{50} values of 8.2 μM and 5.4 μM against MCF-7 and HepG2 cell lines, respectively, compared to the reference drug sorafenib (IC_{50} = 3.51 and 2.17 μM). Moreover, **7** showed potent VEGFR-2 inhibition, with an IC_{50} of 3.4 nM, close to that of sorafenib (IC_{50} = 3.12 nM). This compound induced cell cycle arrest at the G2/M phase in HepG2 cells and significantly increased apoptotic markers. Specifically, **7** elevated Bax expression by 2.33-fold and reduced Bcl-2 expression by 1.88-fold, leading to a 4.87-fold increase in the Bax/Bcl-2 ratio. Additionally, it upregulated cleaved caspase-3 and caspase-9 by 2.44- and 2.69-fold, indicating its strong pro-apoptotic effects. Molecular docking studies confirmed that **7** effectively binds within the VEGFR-2 active site, forming stable hydrogen bonds with key residues like Glu883 and Asp1044. This supports its potential as a lead candidate for further anticancer development.

In a subsequent study, the same group synthesized two series of [1,2,4] triazolo[4,3-a]quinoxaline derivatives as VEGFR-2 inhibitors to target angiogenesis in cancer [33]. Among these, compound **4** (Fig. 4) demonstrated the highest cytotoxicity with IC_{50} values of 6.2 μM against MCF-7 and 4.9 μM against HepG2 cell lines, close to sorafenib's values (3.53 and 2.18 μM, respectively). Enzymatic assays confirmed that **4** also exhibited potent VEGFR-2 inhibition, with an IC_{50} of 3.9 nM, nearly matching sorafenib (IC_{50} = 3.13 nM). Other compounds like **5**, **8**, and **9** (Fig. 4) also showed notable cytotoxic and VEGFR-2 inhibitory effects with IC_{50} values ranging from 11.7 to 15.3 μM and 4.2 to 5.7 nM, respectively. Molecular docking and ADMET studies supported these findings, showing favorable interactions with VEGFR-2's active site and

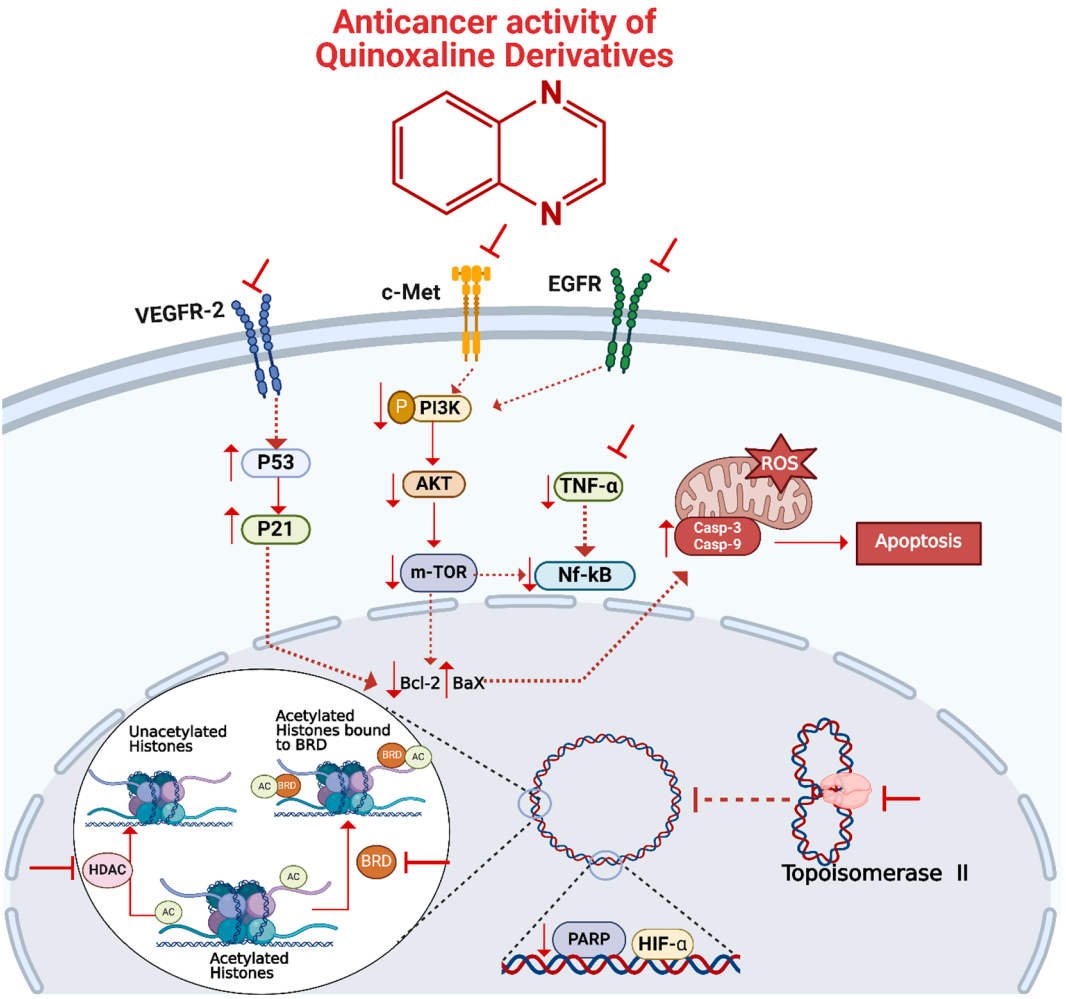


Fig. 3. Different mechanisms of quinoxaline derivatives as anticancer agents.

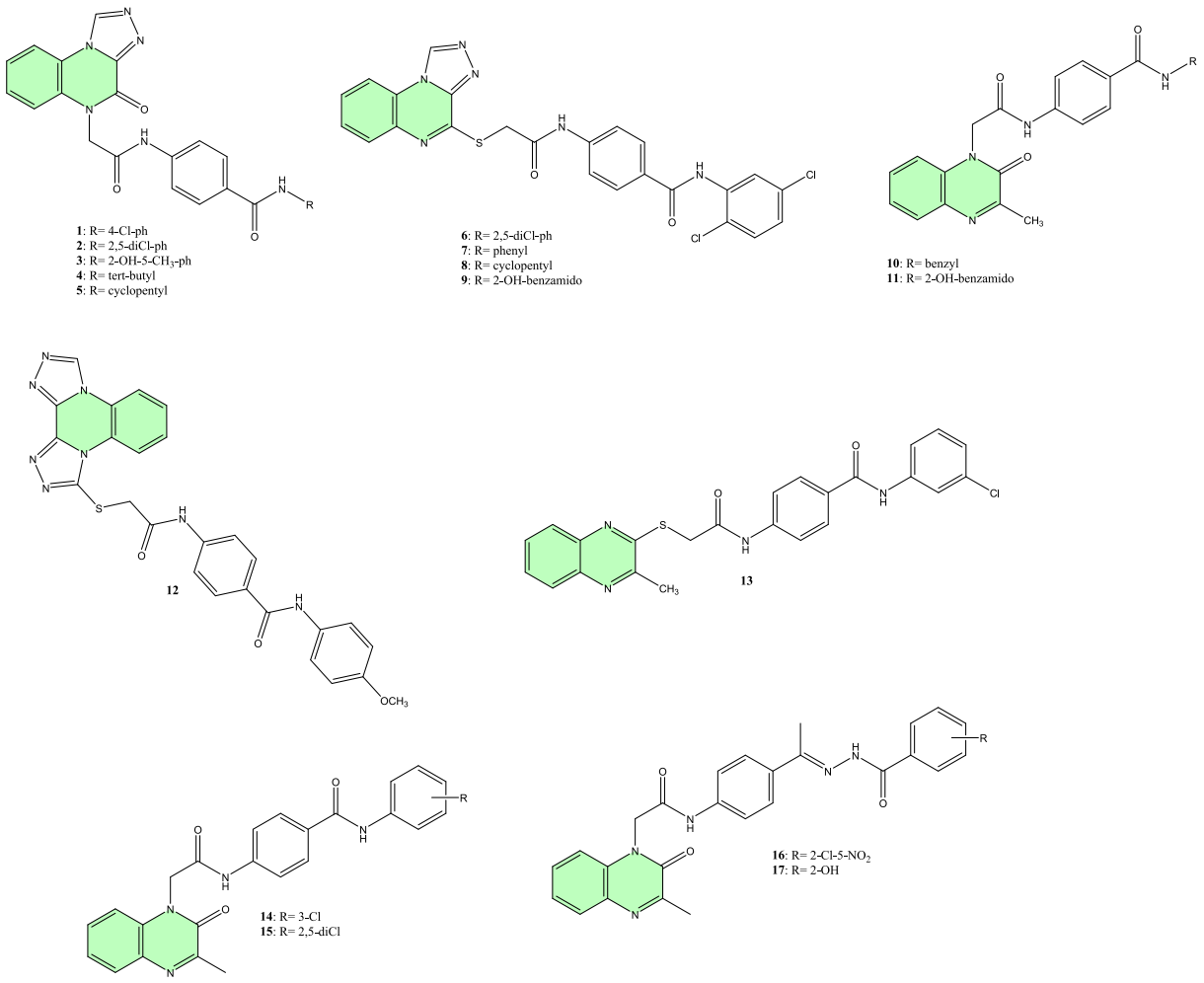


Fig. 4. Structures of compounds **1–17** as VEGFR-2 inhibitors.

promising drug-likeness. Compound **4**'s superior activity suggests it is a strong candidate for further development as an anticancer agent.

Expanding on this research, El-Adl et al. developed a new series of quinoxaline-2(1H)-one derivative targeting VEGFR-2- to inhibit tumor angiogenesis and demonstrate anticancer activity [34]. The study evaluated these compounds against HepG-2, MCF-7, and HCT-116 cell lines, using sorafenib as a control. Compound **10** (Fig. 4) emerged as the most potent, showing IC_{50} values of 5.30 μM, 2.20 μM, and 5.50 μM against HepG-2, MCF-7, and HCT-116, respectively, outperforming both doxorubicin and sorafenib. Furthermore, compounds **10** and **11** (Fig. 4) showed superior VEGFR-2 inhibition with IC_{50} values of 1.09 μM and 1.19 μM, respectively, compared to sorafenib's 1.27 μM. Molecular docking studies supported these findings, demonstrating that compounds **10** and **11** formed stable hydrogen bonds with key residues like Glu883 and Asp1044 within the VEGFR-2 active site, mimicking the binding pattern of sorafenib. This study highlights compound **10** as a promising VEGFR-2 inhibitor for further development in cancer therapy.

In a separate study, Alanazi et al. synthesized a series of bis([1,2,4] triazolo)[4,3-a:3′,4′-c]quinoxaline derivatives designed as VEGFR-2 inhibitors, assessing their antiproliferative and pro-apoptotic activities against HepG2 and MCF-7 cell lines [35]. The most potent compound, **12** (Fig. 4), displayed IC_{50} values of 3.2 μM and 3.3 μM for VEGFR-2 inhibition and HepG2 cytotoxicity, respectively, outperforming sorafenib (IC_{50} = 3.1 μM). Compound **12** induced G2/M cell cycle arrest and a 3.5-fold increase in apoptosis relative to controls, elevating caspase-3 and caspase-9 levels by 2.07- and 1.72-fold and increasing the BAX/Bcl-2 ratio to 3.45. Molecular docking confirmed that **12** forms stable interactions with key VEGFR-2 residues (Glu883 and Asp1044), supporting its potential as a lead compound for further anticancer development.

Building on their earlier work, Alanazi et al. designed and synthesized a new series of quinoxaline-based VEGFR-2 inhibitors [36], evaluating their antiproliferative activity against MCF-7 and HepG-2 cancer cell lines. Compounds **13** and **14** (Fig. 4) were identified as the most potent, with IC_{50} values of 2.3 μM and 2.8 μM for MCF-7 and 4.2 μM and 2.8 μM for HepG-2, respectively, outperforming sorafenib. In particular, compound **14** showed potent VEGFR-2 inhibition with an IC_{50} of 2.7 nM. Mechanistic studies revealed that **14** induces G2/M cell cycle arrest and promotes apoptosis in HepG-2 cells, evidenced by the upregulation of caspase-3 and caspase-9 and a 10-fold increase in the Bax/Bcl-2 ratio. Molecular docking studies confirmed compound **14** effectively binds to the VEGFR-2 active site, forming hydrogen bonds with key residues like Glu883 and Asp1044. Additionally, ADMET and DFT analyses suggested favorable pharmacokinetic properties, highlighting compound **14** as a promising candidate for further anticancer development.

Following this, Alanazi et al. continued their work by developing another series of quinoxaline-based derivatives as VEGFR-2 inhibitors to explore their anticancer properties [37]. The most potent compound, **15** (Fig. 4), demonstrated significant antiproliferative activity against MCF-7 and HepG2 cell lines with IC_{50} values of 12.9 μM and 7.5 μM, respectively. Furthermore, it exhibited exceptional VEGFR-2 inhibitory activity, with an IC_{50} of 3.8 nM, nearly comparable to the standard drug sorafenib (IC_{50} = 3.12 nM). Molecular docking studies confirmed compound **15** effectively binds within the active site of VEGFR-2, forming

stable interactions with key residues such as Glu883 and Asp1044, crucial for its inhibitory function. The ADMET profiling showed favorable drug-likeness and bioavailability, supporting its potential as a lead candidate for further development as an anticancer agent.

In related research, Yousef et al. synthesized a series of new quinoxaline-2(1H)-one derivative as potential VEGFR-2 inhibitors and evaluated their antiproliferative effects against HepG-2, HCT-116, and MCF-7 cell lines [38]. The most active compound, **16** (Fig. 4), exhibited IC_{50} values of 4.50 μM for HepG-2, 2.40 μM for HCT-116, and 5.90 μM for MCF-7, significantly outperforming the reference drugs doxorubicin and sorafenib. Compound **16** also showed potent VEGFR-2 inhibition with an IC_{50} of 0.75 μM, better than sorafenib's 1.29 μM. Other derivatives like **17** (Fig. 4) also displayed strong antiproliferative activity, with IC_{50} values of 5.34, 4.19, and 6.06 μM for HepG-2, HCT-116, and MCF-7, respectively. Molecular docking studies revealed that these compounds effectively interacted with key residues in the VEGFR-2 active site, including Glu883 and Asp1044, demonstrating stable binding patterns. Additionally, in silico ADMET analysis confirmed favorable pharmacokinetic properties for the most active compounds.

Additionally, Ismail et al. developed a series of novel quinoxaline-based VEGFR-2 inhibitors to halt angiogenesis, exploring their antiproliferative activity against HCT-116 and MCF-7 cancer cell lines [39]. Among the compounds, **18** (Fig. 5) demonstrated the most potent activity with IC_{50} values of 8.26 μM for HCT-116 and 7.57 μM for MCF-7, surpassing the standard drug sunitinib in potency. The compound also showed a VEGFR-2 inhibitory IC_{50} of 0.063 μM, making it 2.2 times more potent than sunitinib (IC_{50} = 0.139 μM) and 1.2 times more potent than sorafenib (IC_{50} = 0.076 μM). Further studies revealed that **18** induced cell cycle arrest at the G2/M phase and increased the expression of p53 and caspase-3 in MCF-7 cells, leading to apoptosis. Its anti-angiogenic potential was confirmed by the suppression of VEGF-A levels and inhibition of cell migration in MCF-7 cells, as evidenced by a lower scratch closure percentage than the control. Molecular docking studies supported these findings, showing that **18** binds effectively within the VEGFR-2 active site. Additionally, in silico ADME analysis indicated favorable pharmacokinetic properties, suggesting compound **18** is a promising candidate for further anticancer development targeting angiogenesis.

Ismail et al. further advanced their research by developing a series of novel quinoxaline-3-propanamides targeting VEGFR-2, focusing on their antiproliferative and apoptotic activities against HCT-116 and MCF-7 cancer cell lines [40]. The most potent compounds, particularly **19**, **20**, and **21** (Fig. 5), showed higher cytotoxicity than standard drugs like doxorubicin and sorafenib. Compound **21** exhibited significant selectivity, with selectivity indices (SI) of 19.97 for HCT-116 and 23.87 for MCF-7, surpassing those of doxorubicin (SI 0.72 for HCT-116). The IC_{50} values for compound **21** were 5.81 μM for HCT-116 and 4.61 μM for MCF-7, aligning with its potent VEGFR-2 inhibitory activity (IC_{50} = 0.076 μM), comparable to sorafenib. Mechanistic studies revealed that compound **21** effectively reduced VEGF-A levels, induced G2/M cell cycle arrest by 3.59-fold, and promoted apoptosis through both necrotic and programmed cell death pathways, as evidenced by increased expression levels of caspase-3 (8.84-fold), p53 (15.59-fold), and BAX (4.3-fold), while lowering BCL2 expression. Docking studies confirmed strong binding interactions within the VEGFR-2 active site, supporting its potential for further therapeutic development.

In another line of research, Ayoup et al. developed a novel series of triazole-tethered quinoxalines as dual VEGFR-2/MAO-B inhibitors,

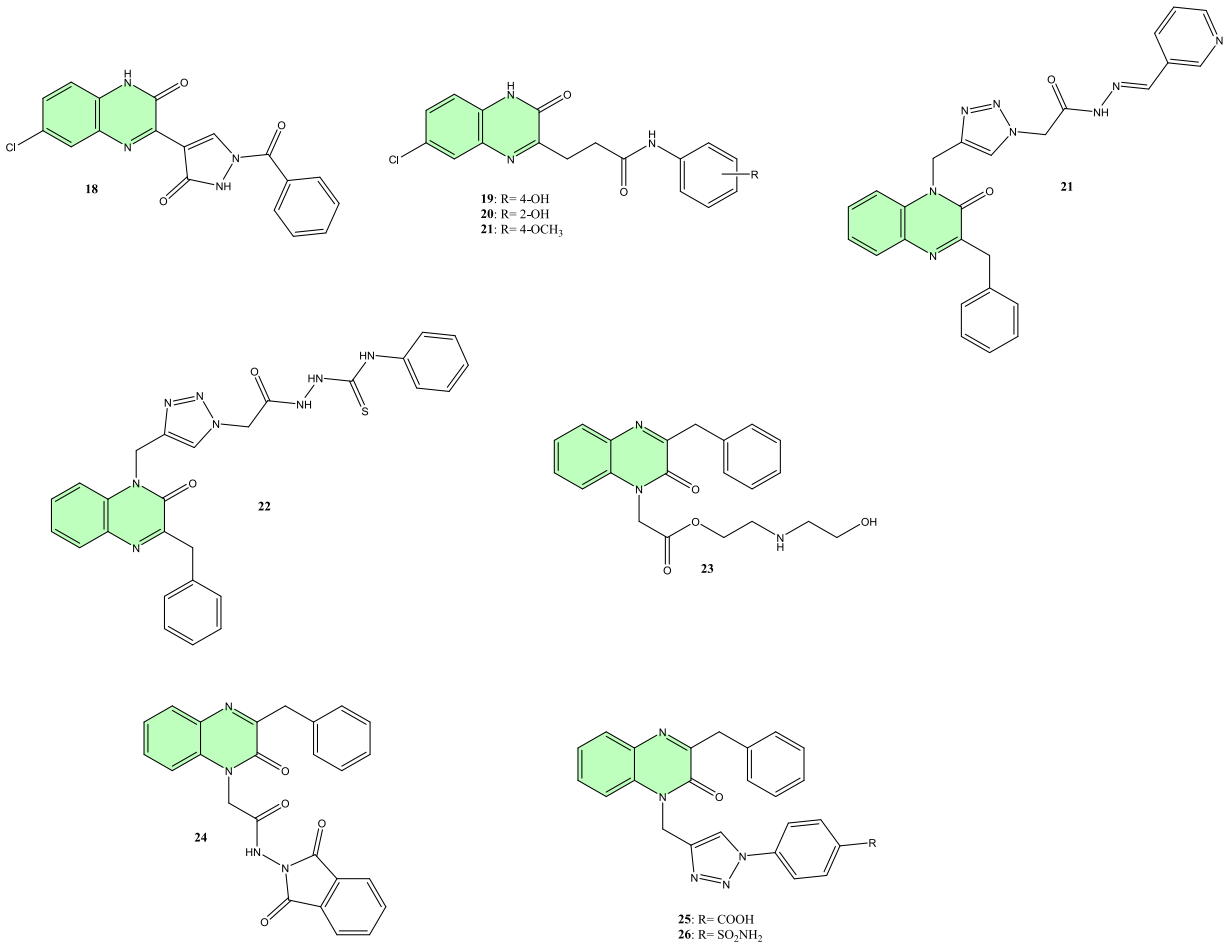


Fig. 5. Structures of compounds **18–26** as VEGFR-2 inhibitors.

aiming to inhibit colorectal cancer (CRC) progression by targeting hypoxia and epithelial-mesenchymal transition (EMT) pathways [41]. The most potent compounds, **21** and **22** (Fig. 5), exhibited IC_{50} values of 18.04 μM and 7.85 μM, respectively, against HCT-116 CRC cells. Compound **22**, in particular, showed remarkable VEGFR-2 inhibition with an IC_{50} of 9.91 nM and selective inhibition of MAO-B over MAO-A (IC_{50} of 209.6 nM for MAO-B vs. 629.1 nM for MAO-A). Compound **22** downregulated Hypoxia-inducible factor 1-α (HIF-1α) expression by 16.96-fold and significantly inhibited HCT-116 cell migration by over 90 %. Docking studies confirmed the binding of these compounds within the VEGFR-2 and MAO-B active sites, highlighting their potential as dual inhibitors to halt CRC progression and metastasis.

Moreover, the same group designed a library of quinoxaline hybrids targeting key colorectal cancer markers like HIF-1α, VEGF, and p21 [42]. Compounds **23**, **24**, **25**, and **26** (Fig. 5) demonstrated potent cytotoxicity against HCT-116 cells, with IC_{50} values ranging from 0.05 to 0.07 μM while maintaining high selectivity (SI values up to 29.40). Compound **25** exhibited the highest pro-apoptotic activity, significantly downregulating HIF-1α and VEGF by 0.3-fold and 0.4-fold, respectively, and enhancing the expression of p21, p53, and BAX by 3.83-, 4.96-, and 4.32-fold. These compounds also showed no cytotoxicity against normal colonocytes, proving their safety. Docking studies confirmed strong binding within VEGFR-2's active site, supporting their potential as dual-targeted therapies.

EGFR inhibitors. Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that plays a critical role in cell proliferation, survival, and differentiation [43]. Aberrant activation of EGFR signaling has been linked to the progression and metastasis of various cancers, making it an important therapeutic target in oncology. Inhibiting EGFR has become a key strategy in cancer therapy, especially for conditions like non-small cell lung cancer (NSCLC), colorectal cancer, and breast cancer [44]. Over the years, quinoxaline derivatives have emerged as promising EGFR inhibitors, demonstrating potent anticancer activity by blocking the EGFR signaling pathway. These inhibitors not only interfere with tumor growth but also address issues related to drug resistance, enhancing the effectiveness of treatment. This section highlights recent advancements in developing quinoxaline-based EGFR inhibitors, focusing on their mechanisms of action and potential applications in cancer therapy.

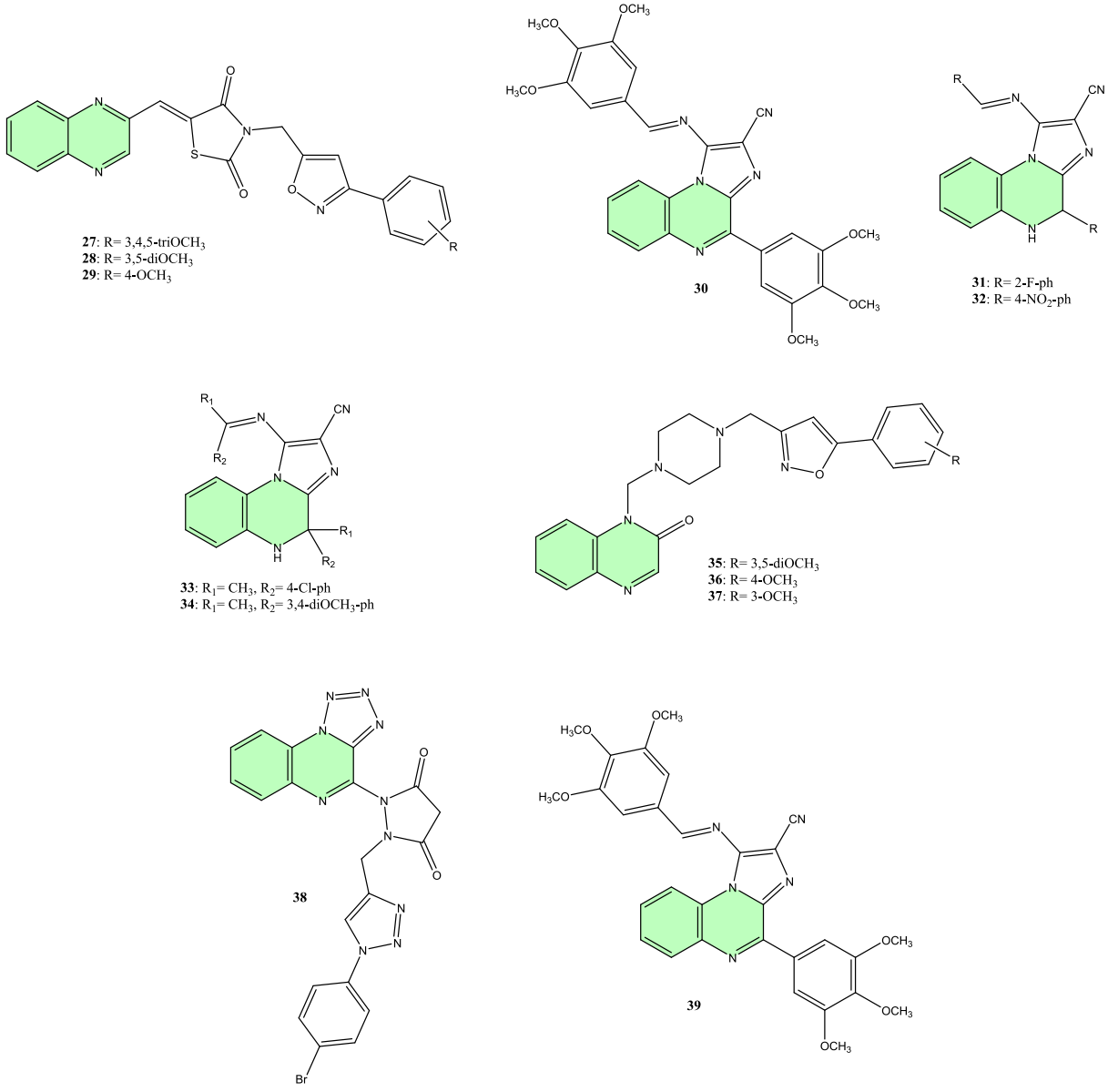


Fig. 6. Structures of compounds **27–39** as EGFR inhibitors.

Building on this, Srimath et al. synthesized a series of quinoxaline-thiazolidine-2,4-dione-isoxazole conjugates targeting EGFR and evaluated their anticancer activity against MCF-7, HepG2, and HCT-116 cancer cell lines [45]. Among the compounds, **27**, **28**, and **29** (Fig. 6) demonstrated the highest potency. Specifically, compound **27** showed IC_{50} values of 0.80 μM, 1.05 μM, and 1.12 μM against MCF-7, HepG2, and HCT-116, respectively, outperforming the reference drug erlotinib (IC_{50} values ranging from 1.20 to 1.45 μM). Compound **27** also exhibited superior EGFR tyrosine kinase inhibition with an IC_{50} of 0.62 μM, compared to erlotinib's 1.23 μM. SAR analysis indicated that the presence of electron-donating methoxy groups on the phenyl ring enhanced activity, positioning **27** as a promising lead compound for further development as an EGFR-targeted anticancer agent.

In a related study, Kumar et al. synthesized a non-covalent imidazo [1,2-a]quinoxaline-based inhibitors targeting EGFR [46]. The study highlighted five compounds—**30**, **31**, **32**, **33**, and **34**—(Fig. 6) as the most potent EGFR wild-type (EGFRWT) inhibitors, with IC_{50} values of 211.22 nM, 222.21 nM, 193.18 nM, 223.32 nM, and 221.53 nM, respectively, comparable to the positive control, erlotinib (IC_{50} = 221.03 nM). Among these, compound **30** emerged as the most promising, particularly against the gefitinib-resistant H1975 NSCLC cell line harboring the EGFRL858R/T790M mutation, showing an IC_{50} of 3.65 μM, while gefitinib's IC_{50} was >20 μM. Molecular docking revealed that compound **30** occupied the ATP binding pocket of both wild-type and mutant EGFR, similarly to erlotinib, forming hydrogen bonds with key residues like Met793. Additionally, **30** exhibited significant anti-proliferative effects on A549, HCT-116, and MDA-MB-231 cell lines, with IC_{50} values ranging from 2.7 μM to 5.1 μM. Further mechanistic studies demonstrated its ability to modulate redox potential, alter mitochondrial membrane permeability, and induce apoptosis, emphasizing its potential as a lead candidate for treating resistant forms of lung cancer.

Furthermore, Ravula et al. synthesized a series of quinoxaline-piperazine-linked isoxazole conjugates, targeting EGFR as a potential therapeutic strategy for cancer treatment [47]. The compounds were evaluated for their anticancer activity against MCF-7 and A549 cell lines. The most potent compounds, **35**, **36**, and **37** (Fig. 6), demonstrated IC_{50} values of 2.10 μM, 2.26 μM, and 2.42 μM against MCF-7, respectively, and 2.92 μM, 3.12 μM, and 3.18 μM against A549 showing greater potency than the standard drug erlotinib, which had IC_{50} values of 2.56 μM and 3.24 μM, respectively. In EGFR tyrosine kinase inhibition assays, compounds **35** and **36** exhibited IC_{50} values of 0.85 μM and 1.10 μM, outperforming erlotinib's IC_{50} of 1.24 μM. Molecular docking studies indicated that these compounds formed stable complexes with EGFR, with compound **35** showing the strongest binding affinity. Additionally, in silico ADMET analysis confirmed favorable pharmacokinetic profiles for these compounds, highlighting their potential for further development as effective anticancer agents targeting EGFR.

In another investigation, Badithapuram et al. designed and synthesized a series of quinoxaline derivatives targeting the EGFR pathway, evaluating their anticancer potential against human cancer cell lines, including HeLa (cervical cancer), MCF-7 (breast cancer), HEK 293T (embryonic kidney), and A549 (lung cancer) [48]. Among these, compound **38** (Fig. 6), which contains a bromine substituent, exhibited the most potent anticancer activity. Specifically, it achieved IC_{50} values of 3.20 μM for HeLa, 4.19 μM for MCF-7, 3.59 μM for HEK 293T, and 5.29 μM for A549, outperforming the standard drug doxorubicin. Molecular docking studies indicated that **38** strongly binds to the EGFR receptor, forming two hydrogen bonds with LYS721 and MET769 residues, with bond lengths of 1.88 Å and 2.50 Å, respectively. The study concludes that the electron-withdrawing bromine substituent at the phenyl ring's fourth position is critical for enhancing the compound's binding affinity and cytotoxicity, establishing **38** as a promising candidate for further anticancer development.

Likewise, Bhat et al. conducted an in-depth evaluation of the non-covalent imidazo[1,2-a]quinoxaline-based EGFR inhibitor, compound **39** (Fig. 6) focusing on its antitumor activity in vivo using an A549 xenograft model in nude mice [49]. The study demonstrated that **39**, administered at a high dose (30 mg/kg), significantly reduced tumor size compared to a low dose (10 mg/kg) and the tumor control group. The high-dose treatment resulted in a tumor growth inhibition rate of 33 %, outperforming gefitinib, which achieved 27 % under similar conditions. Kaplan–Meier survival analysis indicated that mice treated with high-dose **39** showed improved survival rates, aligning with tumor volume reduction and confirming the compound's efficacy. Histological analysis and immunoblotting revealed cytotoxic effects characterized by cytoplasmic damage in tumor cells and decreased levels of key proteins such as AKT and PI3K. At the same time, PTEN expression was upregulated, highlighting the mechanism of action targeting the EGFR pathway. Furthermore, microsomal stability assays confirmed **39**'s favorable pharmacokinetic profile in both human and mouse liver microsomes, supporting its potential for further development as a therapeutic agent for EGFR-dependent cancers.

Similarly, El Saeed et al. synthesized novel triazoloquinoxaline-pyrazole hybrids and assessed their antiproliferative activity against MCF-7, HepG-2, and HCT-116 cancer cell lines using the Sulforhodamine-B assay [50]. Among the synthesized compounds, **40** (Fig. 7) exhibited the highest cytotoxicity, showing IC_{50} values of 2.79 μM, 3.07 μM, and 3.64 μM for MCF-7, HepG-2, and HCT-116 cell lines, respectively, making it twice as potent as the reference drug Doxorubicin. Compound **40** also demonstrated significant EGFR inhibitory activity, with an IC_{50} of 0.98 μM against wild-type EGFR, far superior to Gefitinib's IC_{50} of 18.07 μM, and an IC_{50} of 27.45 μM against mutant EGFR (L858R). Additionally, **40** induced G2/M cell cycle arrest and apoptosis in MCF-7 cells, elevating active Caspase-3 levels and increasing the BAX/Bcl-2 ratio, indicative of mitochondrial apoptosis pathway activation. In silico ADME analysis confirmed its oral bioavailability, positioning **40** as a promising lead for further development as an anticancer agent.

Fayed et al. expanded the scope of EGFR inhibitors by evaluating a series of new quinoxaline derivatives for their antiproliferative and apoptotic activities, specifically targeting EGFR in both wild-type and mutant forms (EGFRL858R) [51]. Seven compounds, particularly **41**, **42**, **43**, **44**, **45**, **46**, and **47** (Fig. 7), showed strong activity with IC_{50} values ranging from 7.57 to 28.44 μM against HepG-2, HCT-116, and MCF-7 cancer cell lines. Among them, compound **41** was the most potent, showing an IC_{50} of 7.57 μM in MCF-7 cells. Mechanistic studies revealed that these compounds significantly increased the BAX/Bcl-2 ratio by up to 10.6-fold and elevated active Caspase-3 levels by as much as 10.69-fold, indicating their strong pro-apoptotic effect—these derivatives also induced cell cycle arrest at the G2/M and pre-G1 phases, enhancing their apoptotic activity. Additionally, EGFR inhibition assays demonstrated IC_{50} values of 75 nM to 1.547 μM for wild-type and 63.70 to 87.34 nM for mutant EGFR, confirming their dual-inhibitory potential. Molecular docking studies revealed effective binding with EGFR's active site, with binding energies ranging from −15.86 to −16.97 kcal/mol, comparable to erlotinib's −17.84 kcal/mol, suggesting these compounds as promising candidates for further anticancer development.

Fu et al. added to this body of work by synthesizing a series of aminopyrimidine derivatives bearing dihydroquinoxalinone, aiming to create third-generation EGFR inhibitors that target the L858R/T790M mutation in non-small-cell lung cancer (NSCLC) [52]. Among the derivatives, compound **48** (Fig. 7) showed remarkable inhibitory activity against EGFRL858R/T790M, with an IC_{50} of 15 nM. It also exhibited significant anti-proliferative effects in H1975 cells expressing the EGFRL858R/T790M mutation, with an IC_{50} of 166.43 nM. Mechanistic studies demonstrated that compound **48** effectively downregulated EGFR-mediated signaling pathways, including phosphorylation of EGFR and AKT, promoting apoptosis in these cells. Flow cytometric analysis confirmed that treatment with compound **48** induced apoptosis in a concentration-dependent manner, showing rates of 10.93 %, 15.83 %,

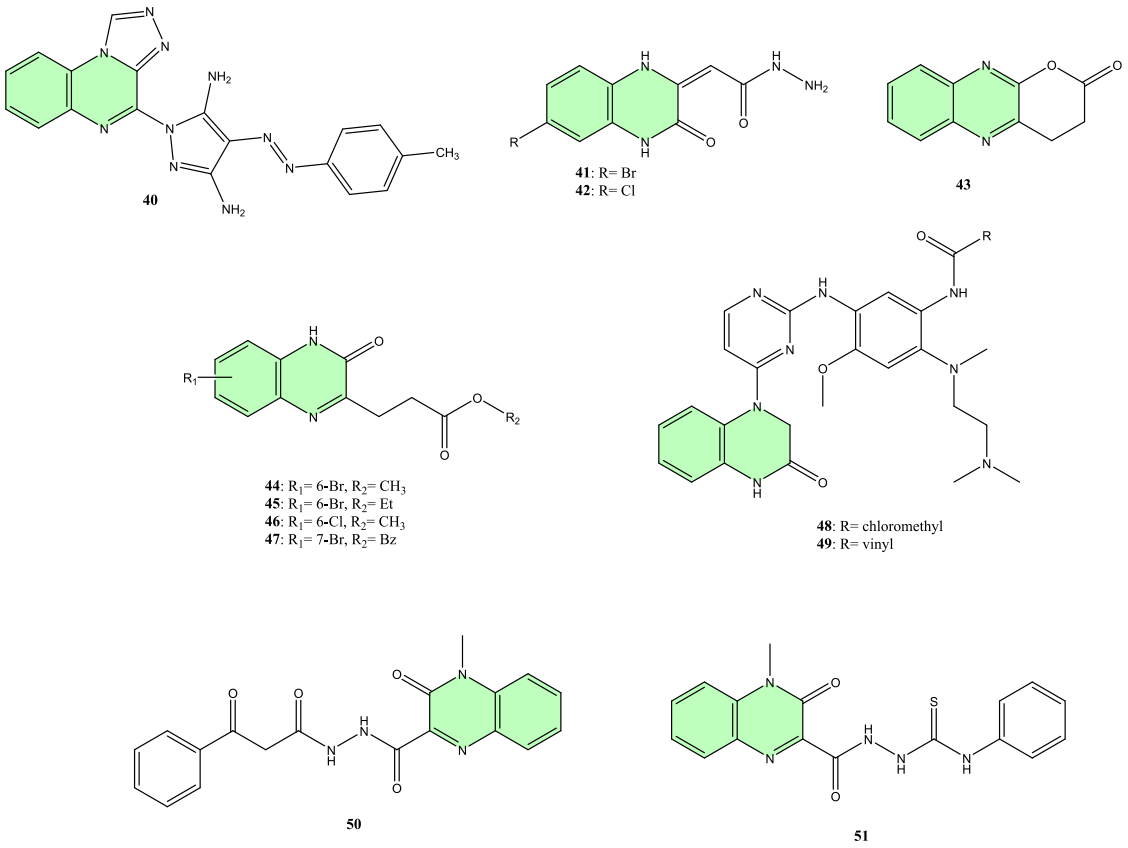


Fig. 7. Structures of compounds **40–51** as EGFR inhibitors.

and 28.10 % at 50, 150, and 450 nM concentrations, respectively. The docking studies revealed that compound **48** formed stable hydrogen bonds with key residues such as Asn842 and Met793, similar to known inhibitors like Osimertinib. These findings highlight compound **48**'s potential as a highly selective and potent EGFR inhibitor, making it a promising candidate for further development in overcoming drug resistance in NSCLC.

Cao et al. explored a series of dihydroquinoxalinone derivatives as EGFRL858R/T790M inhibitors for treating NSCLC [53]. The most potent compound, **49** (Fig. 7), exhibited exceptional kinase inhibitory activity with an IC50 of 0.55 nM against the double mutant EGFRL858R/T790M and an anti-proliferative IC_{50} of 5.88 nM in H1975 cells, which harbor the mutation. Compound **49** also demonstrated a high selectivity index, showing minimal cytotoxicity against normal MRC-5 cells (IC_{50} >10,000 nM) compared to Osimertinib's IC_{50} of 2,674.0 nM. The compound effectively downregulated EGFR-mediated signaling pathways and promoted apoptosis dose-dependently. Furthermore, in vivo studies confirmed compound **49** significantly suppressed xenograft tumor growth without causing significant weight loss or toxicity in treated mice. These results suggest that compound **49** holds promise as a lead candidate for targeting drug-resistant EGFR mutations in NSCLC.

In a distinct approach, Ahmed et al. aimed to address both cancer and inflammation by synthesizing quinoxaline derivatives that target EGFR and COX-2 simultaneously [54]. The most potent compounds, **50** and **51** (Fig. 7), exhibited strong anticancer activity with IC_{50} values ranging from 0.81 μM to 2.91 μM across three cancer cell lines (MCF-7, HepG2, and HCT-116). Specifically, compound **51** showed superior inhibition of COX-2 (IC_{50} = 0.46 μM) while demonstrating high selectivity compared to COX-1 (IC_{50} = 30.41 μM), resulting in a selectivity index (SI) of 66.11. Compound **50** also performed well, inhibiting EGFR with an IC_{50} of 0.6 μM. Molecular docking studies supported these findings, showing that these compounds are effectively bound to the active sites of EGFR and COX-2, aligning with the observed biological activities. The results suggest that compounds **50** and **51** are promising for further development as dual-function anticancer and anti-inflammatory agents.

c-Met inhibitors. c-Met, a receptor tyrosine kinase involved in various oncogenic processes, plays a critical role in tumor growth, angiogenesis, and metastasis [55]. Inhibiting c-Met signaling has emerged as a promising therapeutic strategy for several cancers, particularly those resistant to conventional treatments. Quinoxaline derivatives have shown potential in targeting c-Met, demonstrating significant inhibitory activity and antitumor effects across various cancer cell lines. This section discusses the latest advancements in developing quinoxaline-based c-Met inhibitors and their implications for cancer therapy.

A notable study by Wang et al. highlights the design of 4-phenoxy-pyridine-based quinoxaline derivatives aimed at c-Met kinase inhibition [56]. Their findings revealed several compounds with potent inhibitory effects, with IC_{50} values below 10 nM. Notably, compound **52** (Fig. 8) showed the highest potency with an IC_{50} of 1.91 nM, surpassing foretinib, the reference drug. In cytotoxicity assays, **52** demonstrated strong activity against A549, H460, and HT-29 cancer cell lines, with IC_{50} values of 1.57 μM, 0.94 μM, and 0.65 μM, respectively. Additional assays confirmed that **52** induced apoptosis in HT-29 and A549 cells and significantly inhibited A549 cell migration, suggesting its antimetastatic potential. Molecular docking studies supported its strong binding affinity to the c-Met kinase, highlighting its potential as a lead compound for further development.

Similarly, Kim et al. developed a series of novel quinoxaline derivatives as selective c-Met kinase inhibitors [57]. The team synthesized several analogs and assessed their inhibitory activity against c-Met kinase and their effects on the MKN-45 human gastric cancer cell line, which overexpresses c-Met. Compound **53** (Fig. 8) was identified as the most potent inhibitor, demonstrating an IC_{50} of 6 nM against c-Met

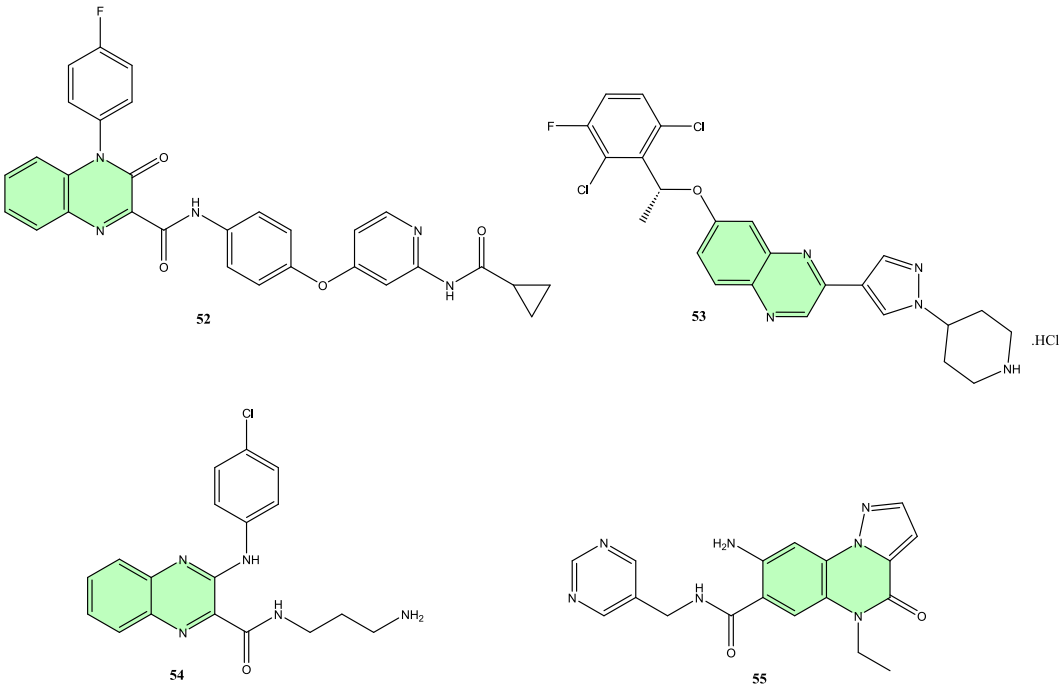


Fig. 8. Structures of compounds **52–55** as c-Met and PI3K inhibitors.

kinase and 175 nM against the MKN-45 cell line, indicating strong selectivity and potency. In vivo studies using MKN-45 xenograft models in mice showed that compound **53** effectively suppressed tumor growth, achieving a 48 % tumor growth inhibition (TGI) at a dose of 20 mg/kg, which was notably higher than the TGI observed with crizotinib (29 % TGI at the same dose). The compound also exhibited favorable pharmacokinetic properties, including high metabolic stability and minimal CYP enzyme inhibition, making it a suitable candidate for further development. Molecular docking studies supported the compound's mode of action, showing that it formed crucial interactions within the c-Met kinase active site, further validating its potential as a targeted anticancer therapy.

PI3K inhibitors. The PI3K-Akt-mTOR pathway is a crucial cellular proliferation, survival, and metabolism regulator. Dysregulation of this pathway, commonly observed in various cancers, promotes tumor growth and therapeutic resistance [58]. Targeting PI3K with specific inhibitors has emerged as a promising strategy to combat these malignancies. Quinoxaline-based PI3K inhibitors offer the potential for selective pathway inhibition, contributing to novel anticancer therapies.

In line with this, Chen et al. synthesized 3-arylaminoquinoxaline-2-carboxamide derivatives and evaluated their anticancer potential by targeting the PI3K-Akt-mTOR signaling pathway [59]. The most potent compound, **54** (Fig. 8), exhibited significant cytotoxicity across five cancer cell lines, with IC_{50} values ranging from 3.3 to 6.6 μM, outperforming the control LY294002, a known PI3K inhibitor. Compound **54** effectively inhibited the phosphorylation of Akt at Thr308 and Ser473, indicating dual inhibition of the PI3K and mTOR pathways. This inhibition led to cell cycle arrest at the G2/M phase and induction of apoptosis in MGC-803 cells, with a marked increase in pro-apoptotic proteins (Bax, Bim) and a decrease in anti-apoptotic proteins (Bcl-2). The compound also increased intracellular ROS levels and disrupted mitochondrial membrane potential (ΔΨm), further confirming its pro-apoptotic effects. In vivo studies using the MGC-803 xenograft model showed that **54** reduced tumor growth by 28 % at a dose of 20 mg/kg, with minimal toxicity. These results suggest compound **54** is a promising candidate for developing new anticancer therapies targeting the PI3K-Akt-mTOR pathway.

To further enhance isoform selectivity within the PI3K family, Gu et al. synthesized a series of 4-oxo-4,5-dihydropyrazolo[1,5-a]quinoxaline-7-carboxamide derivatives as selective PI3Kα inhibitors using a virtual screening and structure optimization approach [60]. The most potent derivative, **55** (Fig. 8), displayed an IC_{50} of 0.24 μM for PI3Kα and demonstrated substantial selectivity over other PI3K isoforms, including 17-fold selectivity over PI3Kδ and 41-fold over PI3Kβ. In cell proliferation assays, compound **55** inhibited the growth of Kasumi-1 and T47D cells, with IC_{50} values of 1.64 μM and 1.82 μM, respectively. Further pharmacokinetic studies showed that **55** had favorable oral bioavailability (91.8 %) and a plasma AUC0-t of 3294.05 ng·h/mL at 5 mg/kg. These findings suggest that **55** is a promising candidate for further development as a PI3Kα-targeted anticancer agent due to its potent inhibitory activity, selectivity, and favorable pharmacokinetic properties.

Other kinases. Given the critical role of BTK (Bruton's tyrosine kinase) in the B cell receptor signaling pathway, its inhibition has emerged as a promising therapeutic strategy in cancer therapy [61]. By targeting BTK, particularly in B cell malignancies, the proliferation and survival of malignant B cells can be effectively curtailed, offering significant potential for improved patient outcomes.

Focused on this promising therapeutic target, Su et al. synthesized a series of pyrrolo[1,2-a]quinoxalin-4(5H)-one derivative as non-covalent BTK inhibitors aimed at treating B cell malignancies and autoimmune disorders [62]. Among these, compounds **56** and **57** (Fig. 9) demonstrated high potency with IC_{50} values of 7.41 nM and 11.4 nM, respectively, against BTK. Compound **56** showed equivalent or better potency in cell-based assays with U937 and Ramos cells, displaying IC_{50} values of 8.0 μM and 8.8 μM, respectively, comparable to the reference inhibitor BMS-986142. In a U937 xenograft mouse model, compound **56** achieved a tumor growth inhibition (TGI) of 65.61 % at a dose of 50 mg/kg, outperforming ibrutinib, which achieved a TGI of 43.06 %. Molecular docking studies confirmed that compound **56** binds effectively to BTK's ATP-binding pocket, forming stable hydrogen bonds with Met477 and Ala478, crucial for its inhibitory action. The selectivity profiling of compound **56** across a panel of 468 kinases further demonstrated its high specificity, making it a promising candidate for further

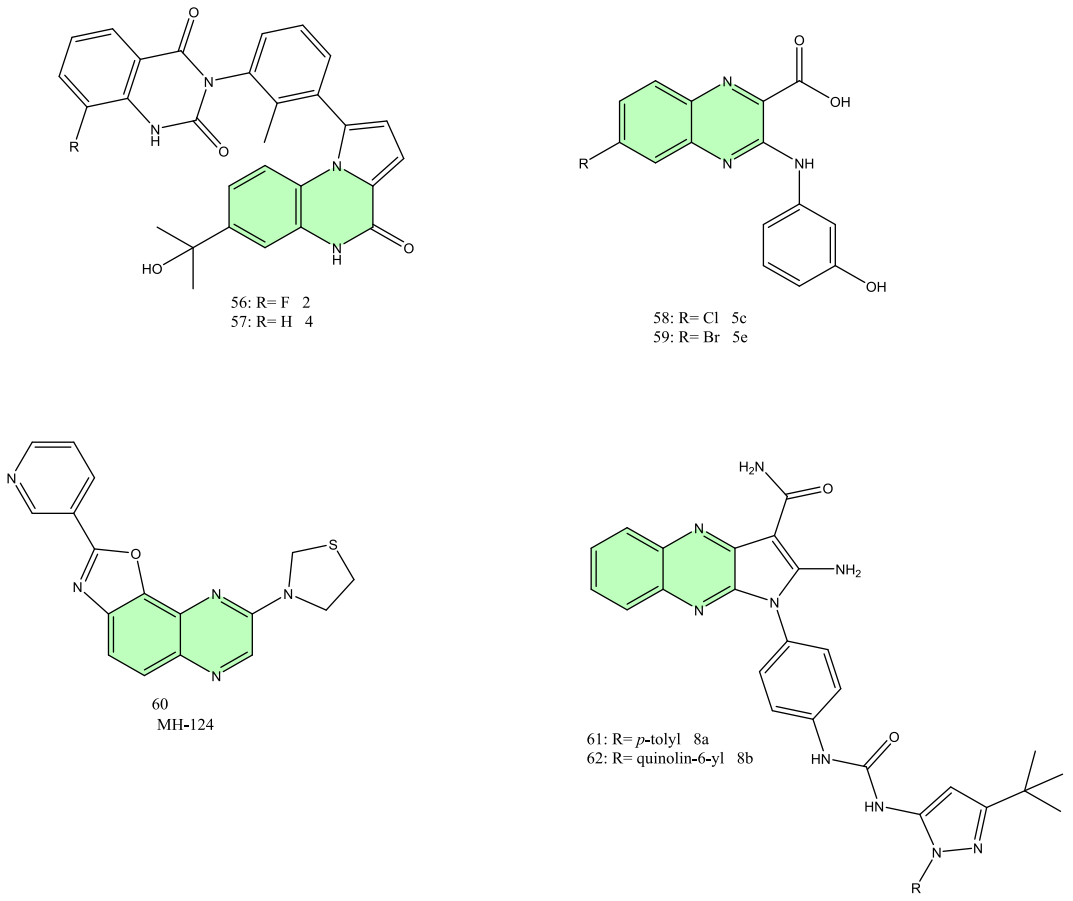


Fig. 9. Structures of compounds **56–62** as c-Met and PI3K inhibitors.

development as a selective BTK inhibitor.

Similarly, targeting Pim kinases, particularly Pim-1 and Pim-2, has gained significant attention in cancer therapy due to their critical role in regulating cell survival, proliferation, and resistance to chemotherapy in several malignancies [63]. Inhibiting these kinases is a promising therapeutic approach for hematologic cancers and solid tumors. In this context, Oyallon et al. synthesized quinoxaline derivatives as dual Pim-1/2 kinase inhibitors, targeting hematologic malignancies such as acute myeloid leukemia (AML) and solid tumors like colorectal carcinoma. The most potent compounds, **58** and **59** (Fig. 9), exhibited submicromolar inhibitory activity with IC50 values of 0.13 μM and 0.16 μM for Pim-1 and 0.17 μM and 0.58 μM for Pim-2, respectively. These compounds also showed significant antiproliferative effects against MV4-11 (AML) and HCT-116 (colorectal carcinoma) cell lines, with compound **59** demonstrating selective inhibition of myeloid leukemia cells while sparing normal bone marrow stromal cells. Further, compound **58** induced cell cycle arrest at the G1 phase and increased apoptosis by upregulating pro-apoptotic proteins like Bax while downregulating anti-apoptotic proteins like Bcl-2. Docking studies revealed that these derivatives formed stable interactions within the ATP-binding pocket of Pim-1 and Pim-2, showing promise as selective Pim kinase inhibitors for cancer therapy.

Another important kinase is Glycogen synthase kinase-3α (GSK-3α), which is increasingly recognized as a pivotal target in cancer treatment due to its role in regulating cell growth and survival pathways. Its inhibition, particularly in glioblastoma, can potentially enhance the effectiveness of existing therapies like temozolomide (TMZ), especially in resistant cases [64]. Building on this, Hasyeoui et al. designed and synthesized a series of oxazolo[5,4-f]quinoxaline derivatives as selective inhibitors of glycogen synthase kinase-3α (GSK-3α), aiming to enhance the efficacy of temozolomide (TMZ) in glioblastoma treatment [65]. The lead compound, **60** (Fig. 9), exhibited strong selectivity for GSK-3α with an IC_{50} of 17 nM, compared to 239 nM for GSK-3β. This compound showed no significant toxicity in non-cancerous neurons or NSC-34 cells at concentrations up to 10 μM. In combination with TMZ, MH-124 significantly reduced the TMZ IC_{50} values in glioblastoma cell lines N15-0385 and 4339. In particular, MH-124 at 0.5 μM lowered the TMZ IC_{50} for the TMZ-resistant N15-0385 cells from over 1000 μM to 573.5 μM, demonstrating synergistic effects. These results suggest that MH-124 is a promising GSK-3α inhibitor that may potentiate TMZ's efficacy in resistant glioblastoma cases.

Further expanding the repertoire of kinase inhibitors, receptor tyrosine kinases such as EphA3 and EphB4 play pivotal roles in cancer progression, particularly in regulating cell proliferation and metastatic pathways [66]. Modulating these kinases has opened new avenues for targeted therapies, especially in hematological malignancies and solid tumors. To explore this potential, Unzue et al. synthesized two novel pyrrolo[3,2-b]quinoxaline derivatives (**61** and **62**) (Fig. 9) as kinase inhibitors, specifically targeting EphA3 and EphB4 tyrosine kinases, aiming for application in hematological malignancies [67]. Compound **61** demonstrated a higher potency with a cellular EC_{50} of 360 nM against EphB4, outperforming **62** with an EC_{50} of 1100 nM. Both compounds displayed antiproliferative activity across the NCI-60 cancer cell line panel, showing particular efficacy in leukemia cell lines like K562, with GI_{50} values as low as 31 nM. In vivo efficacy of **61** was confirmed in a mouse lymphoma xenograft model, reducing tumor size significantly at 100 mg/kg. Molecular docking and chemical proteomics revealed the compounds' ability to engage key kinases, including BTK, LYN, and mTOR, which are relevant in lymphomas. These compounds also inhibited cellular angiogenesis, with **61** reducing tube formation by 90 % in HUVEC cells, highlighting its potential in inhibiting tumor growth and metastasis. The results suggest that **61** is a promising candidate for

further development as a multitargeted anticancer agent.

DNA intercalators and topoisomerase II (Topo II) inhibitors

Quinoxaline-based derivatives have emerged as versatile candidates for anticancer therapy, demonstrating strong intercalative properties and Topo II inhibition potential [68]. These properties, combined with the established potency of DNA intercalators and Topoisomerase II (Topo II) inhibitors as anticancer agents, underscore the potential of quinoxaline derivatives in disrupting DNA processes critical for cancer cell proliferation and survival [54].

Building on this strategy, El-Adl et al. designed and synthesized a series of [1,2,4]triazolo[4,3-a]quinoxaline derivatives as DNA intercalators and Topoisomerase II (Topo II) inhibitors [69]. Compounds were evaluated for anticancer activity against HepG2, HCT-116, and MCF-7 cancer cell lines. The most potent compounds, **63**, **64**, and **65** (Fig. 10), exhibited IC_{50} values of 4.55 μM, 6.18 μM, and 3.93 μM in HepG2, respectively, outperforming doxorubicin (IC_{50} = 7.94 μM). Compound **63** showed the highest DNA intercalation capacity, with an IC_{50} of 25.27 μM, better than doxorubicin (31.27 μM). Molecular docking confirmed these compounds bind effectively to the DNA-Topo II complex, forming multiple hydrogen bonds and stabilizing the cleavable complex. These results support their potential as dual-function anticancer agents targeting DNA and Topo II.

Following this work, El-Adl et al. further synthesized 17 [1,2,4] triazolo[4,3-a]quinoxaline derivatives and evaluated them against HepG2, HCT-116, and MCF-7 cancer cell lines to assess their anticancer potential [70]. The most effective compound, **66** (Fig. 10), showed IC_{50} values of 22.08 μM for HepG2, 27.13 μM for HCT-116, and 17.12 μM for MCF-7, demonstrating about one-third of the potency of doxorubicin in the same assays. Molecular docking studies revealed that **66** had a binding affinity of −105.42 kcal/mol and formed twelve hydrogen bonds within the DNA structure, indicating a strong interactive potential comparable to doxorubicin. DNA-binding assays supported this, showing an IC_{50} of 35.33 μM. The structure–activity relationship analysis highlighted those dual substitutions at positions 1 and 5 on the quinoxaline core significantly enhanced DNA binding and cytotoxicity. In silico ADMET profiling, they suggested favorable drug-like properties, including good oral absorption and CNS penetration, making **66** a promising candidate for further development as an anticancer agent.

Expanding the scope of quinoxaline-based Topo II inhibitors, Abbass et al. designed and synthesized a series of quinoxaline derivatives as potential Topo II inhibitors and apoptosis inducers, targeting multiple cancer cell lines, including HCT-116, HepG2, and MCF-7 [71]. Among these, compounds **67**, **68**, **69**, **70**, and **71** (Fig. 10) exhibited significant antiproliferative activity, with IC_{50} values ranging from 2.81 to 10.23 μM. Compound **71** demonstrated the most potent activity, especially against HepG2 cells, with an IC_{50} value of 2.81 μM, outperforming the reference drug doxorubicin (IC_{50} = 4.17 μM). Further studies confirmed compound **71** inhibited Topo II activity with an IC_{50} of 0.52 μM and exhibited strong DNA intercalating properties, with a DNA-binding affinity of 42.15 μM. In apoptosis assays, compound **71** increased caspase-3 and caspase-9 levels by 10- and 7-fold compared to control, indicating its effectiveness in inducing programmed cell death. Molecular docking revealed that compound **71** interacts efficiently with the DNA-Topo II complex, supporting its mechanism as an intercalative Topo II poison.

In a novel approach, Mandi et al. introduced the concept of targeting abasic DNA sites using an aminoquinoxaline derivative (**72**) (Fig. 11) in combination with chlorambucil [72]. Compound **72**, derived from its nitro precursor (**73**) (Fig. 11) through reduction by glutathione (GSH), selectively cleaved abasic DNA sites at nanomolar concentrations. This activity was enhanced under hypoxic conditions in HCT-116 cells exhibiting high GSH levels. When combined with chlorambucil, **72** significantly increased DNA damage and apoptosis. The combination treatment caused extensive double-stranded DNA breaks, as shown by

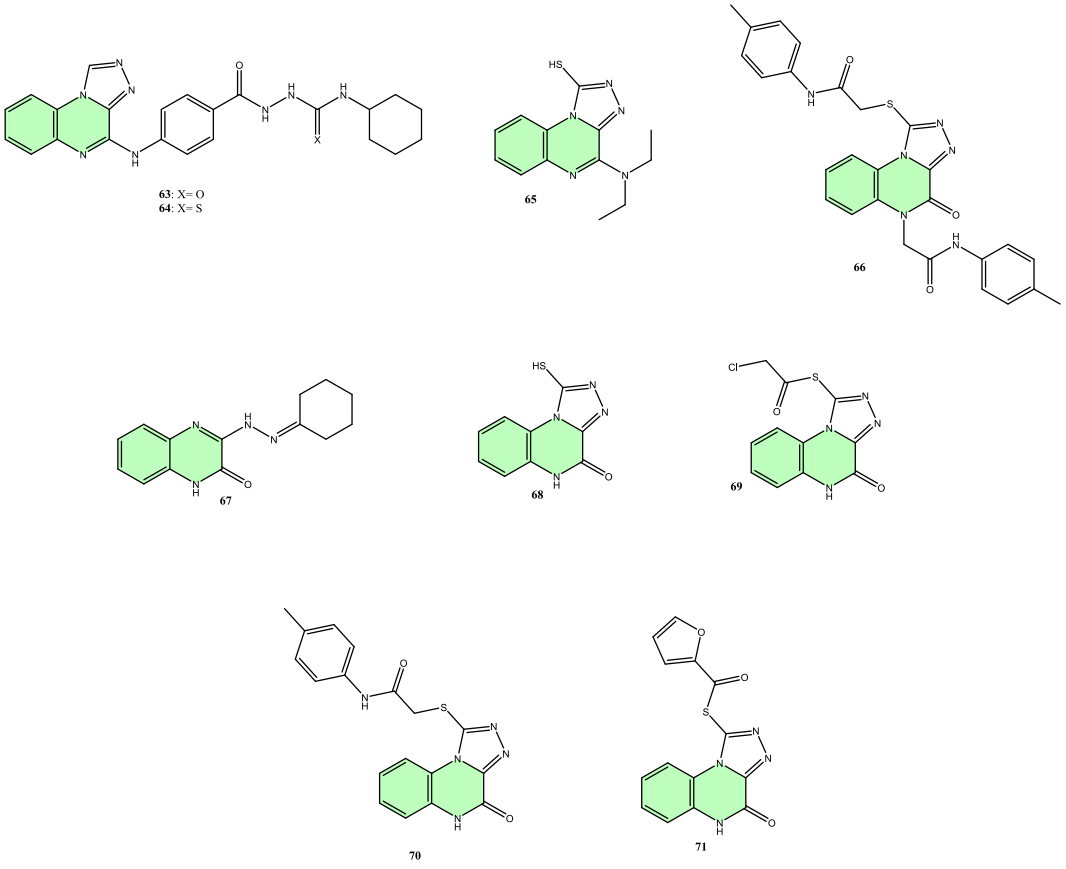


Fig. 10. Structures of compounds **63–71** as DNA intercalators and Topo II inhibitors.

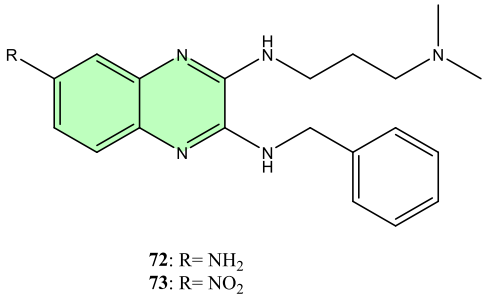
γ-H2AX foci formation, leading to G2/M cell-cycle arrest and triggering apoptosis. The combination therapy was more effective than either treatment alone, demonstrating a synergistic effect that enhanced cytotoxicity. This study suggests that targeting abasic sites with **72**, especially in conjunction with DNA-alkylating agents like chlorambucil, could be an effective strategy for colorectal cancer therapy.

Further expanding the utility of quinoxaline-based compounds, Varma et al. synthesized quinoxaline-based organometallic Re(I) carbonyl complexes and evaluated their DNA interaction, anticancer, antibacterial, and oxidative stress-inducing properties [73]. The complexes exhibited groove binding with DNA, confirmed through UV–visible spectroscopy and viscosity measurements, showing strong intrinsic binding constants. The most potent complex, **74** (Fig. 11), displayed an IC_{50} value of 12.3 μM against HCT116 colon cancer cells, surpassing standard drugs like cisplatin (IC_{50} = 18.9 μM). Antibacterial studies revealed that all complexes had significant activity, particularly against *S. aureus* and *E. coli*, with minimum inhibitory concentrations (MIC) as low as 1.6 μM. Additionally, complex **74** induced high reactive oxygen species (ROS) and lipid peroxidation levels, correlating with its cytotoxic effects. Molecular docking supported the DNA-binding affinity, suggesting these complexes' potential as multi-target therapeutic agents.

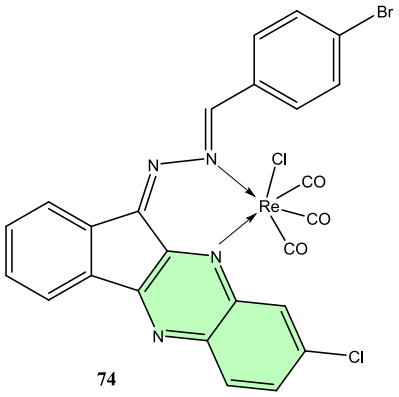
In another study, Majhi et al. developed a metal-free, domino synthesis of fused quinoxaline [1,4]-diazepine hybrids via an SNAr reaction [74]. The synthesized compounds were evaluated for DNA binding, revealing that compound **75** (Fig. 11), with an N-1 benzyl group, showed the strongest interaction. Compound **75** exhibited a high binding constant (KBH ~ 2.15 × 10^4 M^{-1}) and a significant Stern-Volmer quenching constant (Ksv ~ 12.6 × 10^3 M^{-1}). Molecular docking studies confirmed its intercalation into the GC-rich major groove of DNA, comparable to ethidium bromide. Antiproliferative assays showed that **75** was most potent in HeLa cells, with an IC_{50} of 13.3 μM, inducing apoptosis primarily through early apoptosis pathways. This study highlights the potential of these hybrids as DNA-targeted anticancer agents.

Saha et al. synthesized a series of mono-quinoxaline derivatives designed to intercalate DNA and induce necroptosis in apoptosis-resistant cancer cells [75]. Compound **76** (Fig. 11) emerged as the most potent, showing significant DNA intercalation capabilities and causing structural alterations that led to necroptosis via the ZBP1-RIP3-MLKL pathway in RIP3-expressing HT-29 colon cancer cells. The compound effectively increased ZBP1 expression, promoting programmed cell death even when apoptosis was blocked by a pan-caspase inhibitor (Z-VAD). In RIP3-silenced cell lines (HCT116 and HeLa), co-administration of a DNA hypomethylating agent, 5-aza-2′-deoxycytidine (5-AD), restored RIP3 expression, enabling compound **76** to induce necroptosis. These findings highlight **76**'s potential as a therapeutic candidate for cancers that resist conventional apoptosis-driven therapies by activating alternative cell death pathways.

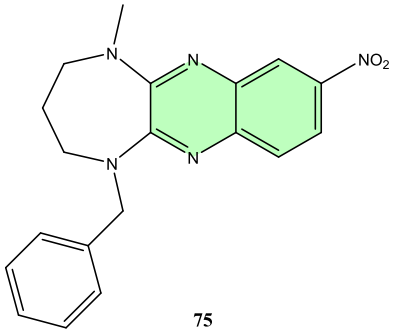
Pal et al. investigated the substituent effects of benzyl moieties in nitroquinoxaline derivatives on DNA binding and their ability to destabilize DNA structure, leading to histone eviction [76]. They found that hydrophobic *para*-substituents, such as *para*-todo (compound **77**) (Fig. 11), maximized DNA base destacking and induced significant DNA condensation and nucleosome disassembly at lower micromolar concentrations. Compound **77** demonstrated the highest anticancer activity, with an IC_{50} of 0.44 μM in HCT116 colon carcinoma cells. The DNA structural alteration was entropically driven, primarily by hydrophobic



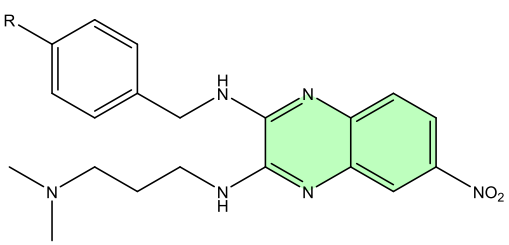
72: R= NH_2
73: R= NO_2



74



75



76: R= phenyl
77: R= iodo

Fig. 11. Structures of compounds **72–77** as DNA intercalators and Topo II inhibitors.

interactions, facilitating chromatin disruption and cellular cytotoxicity. Compounds with polar or hydrophilic substituents showed minimal effects, underscoring the importance of hydrophobicity in DNA interaction and histone eviction.

HDAC inhibitors

Histone deacetylases (HDACs) regulate gene expression by deacetylating histones, leading to chromatin compaction and transcriptional repression [77]. In cancer, HDAC inhibition reactivates tumor suppressor genes, inducing apoptosis and cell cycle arrest. HDAC inhibitors, like vorinostat, are used in cancer therapy to reduce tumor growth and enhance other treatments [78]. Quinoxaline derivatives have been investigated as HDAC inhibitors, contributing to the development of novel anticancer therapies. A noteworthy example is the work of Ma et al., who synthesized a series of quinoxaline derivatives as histone deacetylase inhibitors (HDACIs) targeting hepatocellular carcinoma (HCC) [79]. Among the synthesized compounds, **78** (Fig. 12) exhibited the most potent cytotoxic activity with IC_{50} values of 1.53 μM and 3.06 μM against HepG-2 and HuH-7 cell lines, respectively. It also showed strong inhibitory activity against HDAC1, HDAC4, and HDAC6, with IC_{50} values of 1.76, 1.39, and 3.46 μM, respectively, outperforming the reference drug suberoylanilide hydroxamic acid (SAHA). Compound **78** induced significant cell cycle arrest at the G0/G1 and S phases and enhanced apoptosis, increasing the apoptotic cell percentage by 9.98- and 10.81-fold in early and late phases, respectively. Molecular docking studies supported these findings by confirming that compound **78** fits well within the HDAC binding pocket, interacting effectively with key residues. The results suggest that **78** is a promising HDACI candidate for further development against liver cancer.

Expanding on this, Yang et al. developed a series of novel HDAC inhibitors based on a 3-(benzazol-2-yl)quinoxaline framework using a pharmacophore fusion strategy [80]. Among the synthesized compounds, **79** (Fig. 12) demonstrated the most potent antiproliferative activity, particularly against HCT-116 colon cancer cells, with an IC_{50} of 0.91 μM, significantly outperforming the standard drug Vorinostat (IC_{50} = 5.66 μM). Compound **79** also induced apoptosis, arrested the cell cycle at the G2/M phase, and promoted ROS generation, further inhibiting cell invasion and migration. It significantly upregulated histone H3 and α-tubulin acetylation levels and strongly inhibited Topoisomerase I (Topo I), confirming its dual-targeting mechanism. Molecular docking revealed that **79** effectively binds to HDAC and Topo I active sites, supporting its potential as a promising multifunctional HDAC inhibitor.

Expanding beyond HDAC inhibition, Sirtuins (SIRTs), another class of histone deacetylases, also play a critical role in cancer progression, with SIRT1 being a key regulator of cellular aging, metabolism, and tumor resistance to apoptosis [81]. Baldha et al. explored the quinoxaline framework further by developing SIRT1 inhibitors through a sonochemical thiocyanation approach on pyrrolo[1,2-a]quinoxalines [82]. They synthesized several derivatives, identifying compounds **80**, **81**, and **82** (Fig. 12) as the most potent based on in vitro and silico studies. Compound **80** exhibited the highest activity with an IC_{50} of 2.67 μM against SIRT1, outperforming nicotinamide (IC_{50} = 106.5 μM). The structure–activity relationship (SAR) analysis indicated that compounds with 4-cyano, 2,4-dichloro, or 2-hydroxy substitutions on the C-4 aryl group enhanced SIRT1 inhibition. Molecular docking studies revealed that **80** formed a hydrogen bond with ILE347, and its thiocyanate group played a crucial role in its interaction through hydrogen and pi-sulfur interactions. The ADME predictions for **80** indicated high GI absorption and favorable drug-like properties. This compound and 81 and 82 showed promising selectivity for SIRT1 over SIRT2, making them strong candidates for further pharmacological development.

Bromodomain (BRD) inhibitors

BRD inhibitors target BET proteins, which recognize acetylated histones and regulate the transcription of oncogenes like MYC. By disrupting this interaction, BRD inhibitors [83], including quinoxaline derivatives, reduce cancer cell proliferation and induce apoptosis. For example, Ali et al. designed and synthesized **83** (Fig. 13), a [1,2,4] triazolo[4,3-a]quinoxaline-based compound, as a potent and selective BD1 inhibitor for treating acute myeloid leukemia (AML) [84]. Eighty-three demonstrated high affinity for BD1 with KD values between 5.5 and 13.6 nM while showing much lower affinity for BD2 (86–163 nM). In MV4-11 AML cells, **83** effectively inhibited proliferation with a GI_{50} of 0.098 μM and reduced c-MYC expression, similar to the pan-BET inhibitor OTX-015. In vivo studies in AML xenograft mouse models revealed that **83** significantly delayed tumor growth, with a 90 % reduction in tumor volume compared to controls ($P < 0.001$). Tumor samples from treated animals showed increased PARP cleavage, indicating apoptosis induction. **83**'s selectivity for BD1 over BD2, combined with its strong anticancer activity, highlights its potential as an oral bioavailable AML therapeutic with an improved safety profile compared to non-selective BET inhibitors.

Xu et al. did a similar study, which synthesized a series of quinoxalinone derivatives targeting BRD4, a critical protein for transcriptional regulation in hepatocellular carcinoma (HCC) [85]. The most potent compound, **84** (Fig. 13), exhibited an IC50 value of 82.3 nM against BRD4 and demonstrated strong antiproliferative activity with an IC50 of 1.13 μM in HepG2 liver cancer cells while showing significantly less toxicity in normal GES-1 gastric cells (IC_{50} = 57.24 μM). **Eighty-four** inhibited HepG2 colony formation by approximately 80 % at 10 μM and effectively reduced migration in wound healing assays, showing dose-dependent inhibition of key metastasis markers like Snail and MMP-9. It also upregulated E-cadherin and Occludin, further confirming its anti-metastatic potential. Mechanistically, **84** downregulated c-Myc expression and induced G0/G1 cell cycle arrest, leading to apoptosis through increased expression of cleaved caspase-3 and p21 proteins. Molecular docking studies revealed that **84** forms key interactions with BRD4's active site, supporting its potential as a promising therapeutic for liver cancer treatment.

In addition to BET bromodomains, non-BET bromodomains like BRD9 play significant roles in chromatin remodeling and cancer progression. Gazzillo et al. explored this by designing functionalized [1,2,4] triazolo[4,3-a]quinoxaline-based compounds targeting BRD9 [86]. They identified key structural features that enhanced selectivity and binding, such as an amine linker at C-4 and bulky alkyl substituents at C-1. Among their findings, **85** and **86** (Fig. 13) showed the most promise, with IC_{50} values of 3.93 μM and 6.73 μM for BRD9, respectively, and demonstrated good antiproliferative effects, especially in the CCRF-CEM

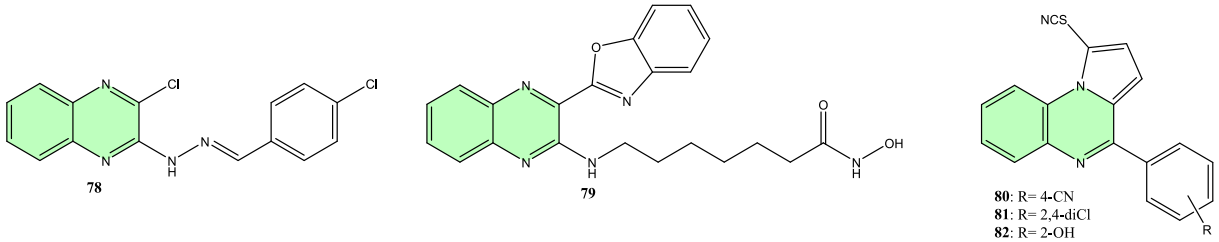


Fig. 12. Structures of compounds **78–82** as HDAC inhibitors.

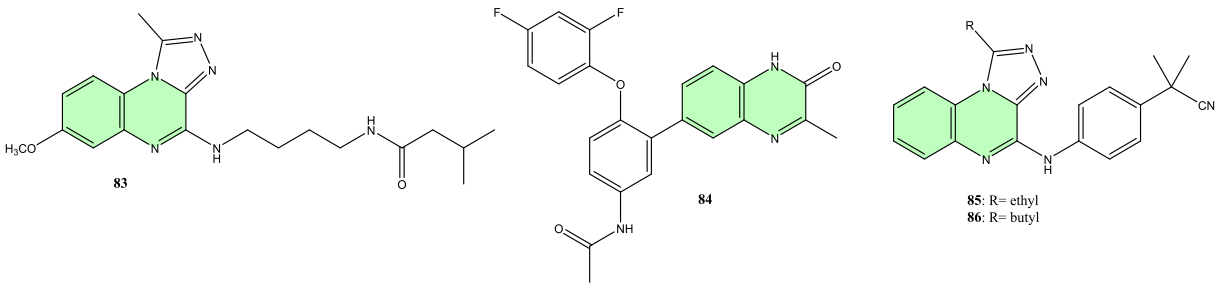


Fig. 13. Structures of compounds **83–86** as BRD inhibitors.

leukemia cell line. These compounds also showed activity against BRPF1, revealing them as dual BRD9/BRPF1 inhibitors with potential therapeutic applications in leukemia.

Tubulin polymerization inhibitors

Tubulin polymerization inhibitors play a crucial role in cancer therapy by disrupting the dynamic instability of microtubules, which are essential for mitotic spindle formation and chromosome segregation during cell division. Inhibitors that target the colchicine binding site on β-tubulin prevent the polymerization of tubulin heterodimers into microtubules, leading to mitotic arrest at the G2/M phase. This arrest triggers apoptosis by activating various pro-apoptotic pathways [87]. These inhibitors impede microtubule dynamics, inhibiting cancer cell proliferation and inducing programmed cell death.

Some recent studies have highlighted quinoxaline derivatives as potent agents for inhibiting tubulin polymerization, selectively targeting the colchicine binding site, and demonstrating significant antiproliferative activity against cancer cells. Liang et al. developed and evaluated a series of 1,2,3,4-tetrahydroquinoxaline derivatives aimed at inhibiting tubulin polymerization by targeting the colchicine binding site, a critical area for cancer treatment [88]. Among the synthesized compounds, **87** (Fig. 14) stood out as the most potent, displaying IC_{50} values of 0.16 μM and 0.18 μM against HeLa and HT-29 cancer cell lines, respectively. It effectively inhibited tubulin polymerization, as confirmed through cell-free and cellular assays, showing a comparable effect to standard inhibitors like colchicine and combretastatin A-4 (CA-4). Further biological evaluations revealed that **87** disrupted microtubule dynamics, leading to G2/M cell cycle arrest and triggering apoptosis in a dose-dependent manner. Immunofluorescence assays supported these findings, showing **87** caused microtubule depolymerization in cancer cells. Molecular docking studies highlighted its strong binding affinity at the colchicine site, forming hydrogen bonds with key residues such as βN258 and βK352, essential for its inhibitory activity. Moreover, **87** exhibited significantly lower toxicity in normal human LO2 cells than its effects on cancer cells, indicating its selectivity and potential as a promising candidate for further development as a targeted anticancer agent.

In another notable study, Goel et al. investigated a series of 34 imidazo[1,2-a]quinoxaline derivatives as potential anti-tubulin agents with anticancer properties using in silico and in vitro approaches [89]. Molecular docking studies identified compound **88** (Fig. 14) as the most promising candidate, showing a high binding affinity (glide score of −11.45 kcal/mol) within the colchicine-binding site of tubulin. Further in vitro assays demonstrated that **88** effectively inhibited tubulin polymerization, similar to colchicine, validating its potential mechanism of action. Antiproliferative assays against MCF-7, MDA-MB-231, HCT-116, and A549 cancer cell lines revealed IC_{50} values of 4.33 μM, 6.11 μM, 5.87 μM, and 5.44 μM, respectively, confirming its cytotoxic efficacy comparable to colchicine. Molecular dynamics simulations showed stable protein–ligand interactions, supporting the compound's potential as an anticancer agent. These results suggest that **88** is a viable lead for further anticancer drug development targeting tubulin polymerization.

Guan et al. further contributed by developing a green synthesis method for 3-benzoylquinoxalinones [90], with compound **89** (Fig. 14) showing the most significant antiproliferative activity. This compound effectively disrupted tubulin polymerization, causing G2/M cell cycle arrest and apoptosis in cancer cells, similar to known tubulin inhibitors like CA-4. It exhibited IC_{50} values of 0.17 μM, 0.24 μM, and 0.28 μM against HT-1080, SGC-7901, and A549 cell lines, respectively. Molecular docking studies confirmed that **89** effectively binds to the colchicine site of tubulin, overlapping with the binding pose of CA-4 and establishing hydrogen bonds with key residues, explaining its strong inhibitory activity.

Other anticancer mechanisms

Aromatase inhibition is crucial in hormone-dependent cancers, as it reduces estrogen production, a key driver of tumor growth in breast cancer [91]. In this context, Lekgau et al. designed and synthesized a series of 6-amino-quinoxaline-alkynyl derivatives as potential aromatase (CYP19A1) inhibitors [92]. Among the synthesized compounds, **90**, **91**, and **92** (Fig. 15) exhibited promising anticancer properties against MCF-7 breast cancer cells with IC_{50} values of 69.7, 35.6, and 69.8 μM, respectively. Notably, compounds **90** and **91** also demonstrated significant inhibition of aromatase with IC_{50} values of 12.2 and 66.7 μM,

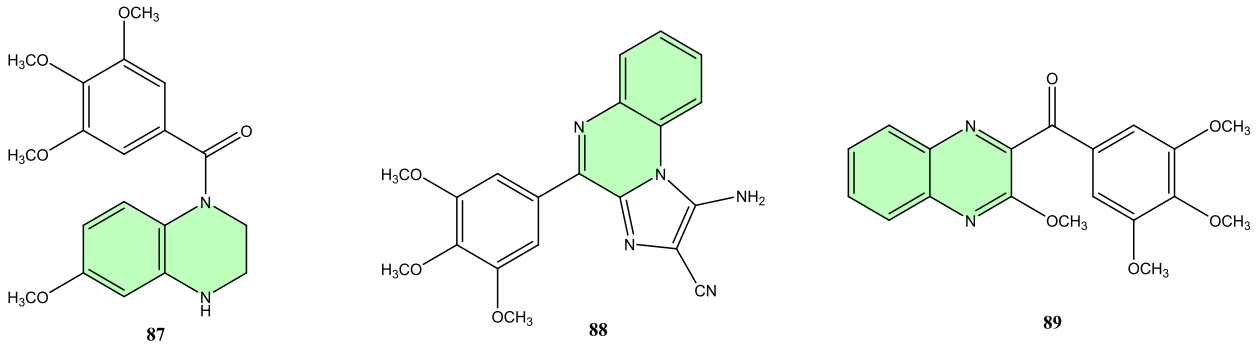


Fig. 14. Structures of compounds **87–89** as tubulin polymerization inhibitors.

suggesting their potential mechanism of action. Molecular docking and MD simulations further validated these compounds' stability and binding interactions within the active site of aromatase. The study highlighted that these quinoxaline derivatives have a promising profile for further development as targeted breast cancer therapies.

Inhibiting Bcl-2 is vital for promoting apoptosis in cancer cells, as this protein allows cancer cells to evade programmed cell death. Building on this mechanism, Ono et al. synthesized quinoxaline-1,3,4-oxadiazole hybrid derivatives targeting the anti-apoptotic Bcl-2 protein [93]. The compounds were evaluated for their antiproliferative activity against HL-60 leukemia cells. The most potent compounds, **93**, **94**, and **95** (Fig. 15), showed IC_{50} values of 2.1 μM, 2.3 μM, and 2.4 μM, respectively. Compound **93** demonstrated a notable apoptotic effect by reducing Bcl-2 mRNA levels to 10 % of the control and increasing apoptotic markers such as caspase-3. Molecular docking confirmed that these compounds interact strongly with Bcl-2's hydrophobic pockets, enhancing their pro-apoptotic activity. This study suggests that these quinoxaline-1,3,4-oxadiazole hybrids are promising for further development as Bcl-2 inhibitors.

Targeting A2B receptors can modulate tumor progression, as these receptors influence signaling pathways linked to cancer growth. Based on this rationale, Ezzat et al. synthesized a series of [1,2,4]triazolo[4,3-a]quinoxaline derivatives as A2B receptor antagonists with potential anticancer properties [94]. Among the compounds tested, six derivatives (**96**, **97**, **98**, **99**, **100,** and **101**) (Fig. 15) showed promising activity against the MDA-MB-231 breast cancer cell line, with IC_{50} values ranging from 1.9 to 6.4 μM. Molecular docking studies indicated that these compounds effectively bind to the A2B receptor, interacting with key amino acids such as Asn273, Leu81, and Val256 through hydrogen bonding and hydrophobic interactions. The structure–activity relationship (SAR) analysis suggested that modifying the hydrophobic tail and linker groups significantly impacts receptor affinity and cytotoxicity. Compound **99** demonstrated the most potent activity with an IC_{50} of 1.9 μM, showing potential as a lead compound for further development as a chemotherapeutic agent targeting A2B receptors.

HIF-1α inhibition is critical in tumors thriving in hypoxic conditions, where limited oxygen supply promotes cancer survival and metastasis. Addressing this need, Buravchenko et al. synthesized and evaluated a series of 6(7)-amino-3-phenylquinoxaline-2-carbonitrile 1,4-dioxides as hypoxia-selective HIF-1α inhibitors [95]. Among the synthesized compounds, **102** (Fig. 15) exhibited the highest hypoxia selectivity and potency, with an IC_{50} of 0.1 μM under hypoxic conditions in MCF7 breast cancer cells, compared to 4.7 μM under normoxia. It showed a hypoxic cytotoxicity ratio (HCR) of 36.3, significantly surpassing the reference compound, tirapazamine (HCR of 5.4). This compound also effectively reduced HIF-1α expression and ERα activity, demonstrating strong antiestrogenic effects in breast cancer cells. The study highlights **102** as a promising dual HIF-1α/ERα blocker for further development as an anticancer agent under hypoxic conditions.

Inhibiting enzymes like MMP-9 and MAO-A is key to preventing cancer metastasis, as these enzymes facilitate extracellular matrix breakdown and tumor cell migration. Leveraging this approach, Ayoup et al. designed and synthesized quinoxaline-based dual inhibitors targeting MMP-9 and MAO-A to inhibit CRC metastasis [96]. Compound **103** (Fig. 15) emerged as the most potent, showing IC_{50} values of 4.50 nM for MMP-9 and 5.41 nM for MAO-A, with a selectivity index of 2.07, indicating a preference for MAO-A over MAO-B. In functional assays using HCT116 CRC cells, **103** effectively inhibited cell migration by 28.82 % and significantly downregulated HIF-1α expression by more than five-fold, demonstrating its ability to reduce the metastatic potential of these cells. Molecular docking simulations revealed that compound **103** interacted strongly with key residues such as Glu402 in MMP-9 and Tyr407 in MAO-A, confirming its ability to bind effectively to the active sites of both enzymes. The compound also exhibited favorable drug-like properties in ADMET predictions, supporting its potential as a lead compound for further development as a CRC metastasis inhibitor.

Overcoming multidrug resistance (MDR) is a major challenge in cancer therapy, as cancer cells develop mechanisms to pump out chemotherapeutic drugs. To counteract this, Ibba et al. synthesized a series of pyridoquinoxaline derivatives targeting P-glycoprotein (P-gp) to overcome MDR in cancer cells [97]. The most potent compound, **104** (Fig. 16), demonstrated significant P-gp inhibition, particularly in HCT-15 colorectal cancer cells, which overexpress P-gp. At 0.1 μM, **104** increased the retention of a fluorescent dye substrate, indicating effective inhibition of P-gp activity. Co-administration of **104** with vincristine at 0.2 μM enhanced its cytotoxicity, reducing cell viability by over 50 % compared to vincristine alone. Compound **104** showed minimal

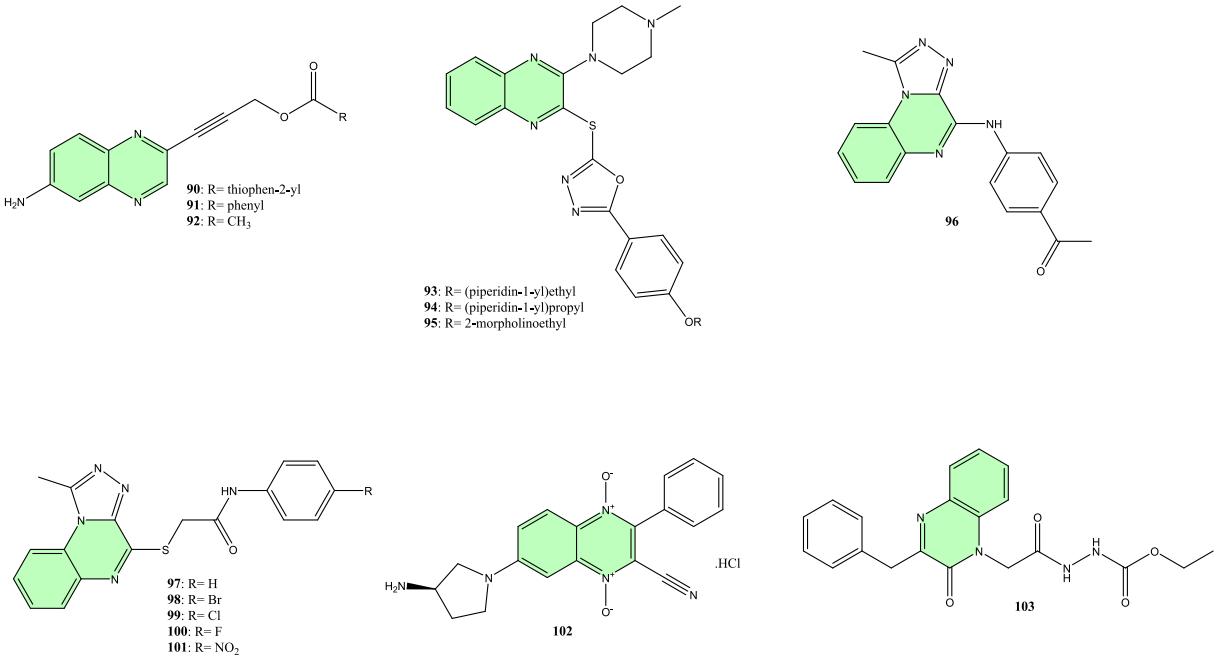


Fig. 15. Structures of compounds **90–103** as anticancer agents.

cytotoxicity in healthy cells, highlighting its potential as a selective MDR reversal agent.

Targeting NPM1c mutations is pivotal in treating specific leukemias, particularly acute myeloid leukemia (AML), where these mutations drive abnormal cell growth. To address this, Skayneh et al. investigated the effects of **105** (Fig. 16), an imidazoquinoxaline derivative, on NPM1c-mutant AML [98]. The compound selectively induced apoptosis in NPM1c-expressing cells by modulating SENP3/ARF-mediated SUMOylation. In xenograft models of NPM1c AML, **105** significantly prolonged survival, with treated mice living up to 100 days compared to 40 days for controls ($p = 0.003$). The compound reduced leukemic burden in the bone marrow from 47 % to 25 % ($p < 0.05$). Mechanistically, **105** induced NPM1c SUMOylation and subsequent proteasomal degradation while activating the p53 pathway by downregulating HDM2. These results support the potential of **105** as a targeted therapy for NPM1c-mutant AML.

PARP-1 inhibitors are essential in cancers with defective DNA repair mechanisms, such as BRCA1-mutated breast cancers. Recognizing this, Syam et al. synthesized a series of quinoxaline-based PARP-1 inhibitors using 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline as a scaffold, designed to mimic the structure of Olaparib [99]. Among the compounds tested, **106** and **107** (Fig. 16) showed the most potent inhibitory activities, with IC_{50} values of 2.31 nM and 3.05 nM, respectively, compared to Olaparib's 4.40 nM. Compound **107**, specifically, demonstrated notable antiproliferative effects against BRCA1-mutated MDA-MB-436 breast cancer cells, with an IC_{50} of 2.57 μM, which is approximately four times more potent than Olaparib ($IC_{50} = 8.90$ μM). In vitro studies indicated compound **107** induced cell cycle arrest at the G2/M phase and promoted apoptosis and autophagy, contributing to its anticancer effects. Molecular docking studies highlighted key interactions between compound **107** and the PARP-1 active site, reinforcing its inhibitory potential. ADMET analysis confirmed favorable drug-like properties, positioning compound **107** as a promising candidate for further development as a PARP-1-targeted anticancer agent.

Carbonic anhydrase IX (CA IX) inhibition is particularly relevant in hypoxic tumors, where the enzyme helps cancer cells survive by regulating pH in low-oxygen environments. To exploit this vulnerability, Buravchenko et al. synthesized and evaluated a series of sulfonamide derivatives of quinoxaline 1,4-dioxides as carbonic anhydrase inhibitors [100]. The most potent compound, **108** (Fig. 16), demonstrated a Ki value of 42.2 nM against the CA IX isoform, comparable to the reference acetazolamide (Ki = 25.7 nM). Compound **108** also exhibited significant antiproliferative effects, particularly under hypoxic conditions, showing an IC_{50} of 0.9 μM in MCF-7 breast cancer cells. Its hypoxic cytotoxicity ratio (HCR) was 4.7, indicating strong hypoxia selectivity similar to tirapazamine. Molecular docking studies revealed that **108** forms coordination bonds with Zn^{2+} and hydrogen bonds with Thr200 in the CA IX active site, explaining its inhibitory potency. These findings highlight the potential of compound **108** for further development as a dual carbonic anhydrase inhibitor and anticancer agent under hypoxic conditions.

Critical analysis and future Directions for quinoxaline derivatives in anticancer therapy

The comprehensive exploration of quinoxaline derivatives reveals their significant therapeutic potential across a range of anticancer targets, including kinases, DNA intercalators, histone deacetylase (HDAC) inhibitors, bromodomain (BRD) inhibitors, and tubulin polymerization inhibitors. Each target represents a distinct pathway in cancer progression, making quinoxaline derivatives versatile candidates in anticancer drug development.

Mechanistically, these compounds demonstrate strengths across various targets. For instance, kinase inhibitors such as VEGFR-2, EGFR, and c-Met inhibitors show potent antiproliferative and pro-apoptotic activities, often comparable to or exceeding standard treatments like sorafenib and erlotinib. In VEGFR-2 inhibitors, fused quinoxaline ring systems are employed to form bulkier structures, enhancing binding affinity to the hinge region at the active site. EGFR inhibitors demonstrate remarkable adaptability; for example, replacing the methyl indole ring in Osimertinib with a dihydroquinoxalinone scaffold has facilitated new hydrogen bond formations, improving interactions with key amino acid residues. Similarly, in c-Met inhibitors, quinoxalinone serves as a crucial five-atom linker between the 4-phenoxythienopyridine core and the substituted phenyl ring, a structural necessity for type II c-Met inhibitors.

DNA intercalators and Topoisomerase II inhibitors leverage vulnerabilities in DNA replication and repair mechanisms. Here, fused triazoloquinoxaline moieties act as planar, polyaromatic chromophores

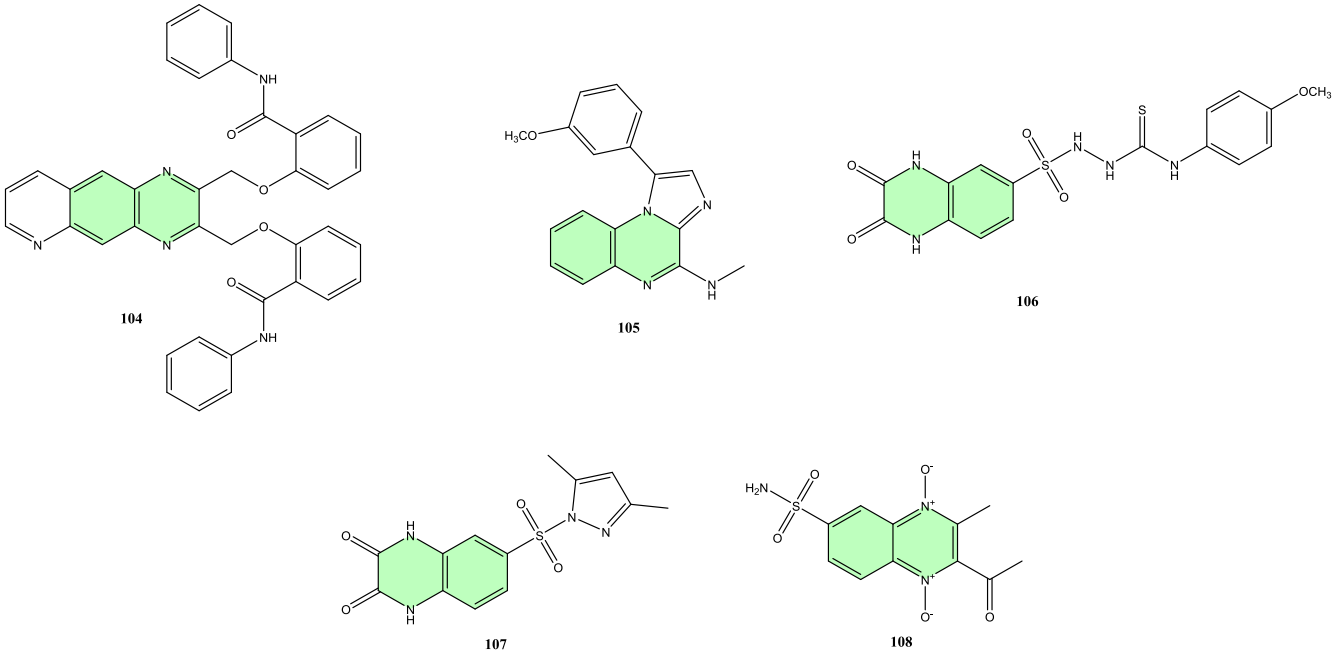


Fig. 16. Structures of compounds **104–108** as anticancer agents.

that facilitate stable intercalation into DNA, making these compounds robust approaches for inducing apoptosis, particularly in resistant cell lines. Epigenetic modulators such as HDAC and BRD inhibitors provide another dimension to therapeutic versatility. For instance, quinoxaline derivatives serve as heterocyclic aromatic caps that occupy the narrow tubular pocket of HDAC1, offering at least one H-bond acceptor critical for binding the Zn^{2+}-binding group. Selective BD1 inhibitors among BRD inhibitors also demonstrate reduced toxicity relative to pan-BET inhibitors.

Furthermore, tubulin polymerization inhibitors effectively disrupt microtubule dynamics, inducing mitotic arrest and apoptosis. The quinoxaline ring plays a pivotal role in these inhibitors, contributing to their selectivity for cancer cells over normal cells, which is a significant therapeutic advantage. Mechanisms targeting tumor microenvironment challenges, such as hypoxia, extracellular pH regulation, or specific receptors like HIF-1α, A2B, and carbonic anhydrase IX, showcase the adaptability of quinoxaline derivatives in addressing niche oncogenic pathways.

Despite their promising activities, several limitations and challenges emerge from the studies. While many compounds exhibit excellent in vitro activity, only a subset has undergone in vivo evaluation, leaving significant uncertainty about their pharmacokinetics, systemic toxicity, and therapeutic windows. Moreover, while some studies provide structure–activity relationship (SAR) analyses, their depth and scope are inconsistent, highlighting the need for systematic optimization to improve potency, selectivity, and pharmacokinetic profiles. Off-target effects and potential toxicity remain underexplored, particularly for compounds targeting multiple kinases or DNA intercalators, which may pose risks of adverse side effects. Additionally, the lack of translational studies on these derivatives raises questions about their scalability, manufacturability, and cost-effectiveness in real-world therapeutic contexts.

To address these gaps, future studies should prioritize comprehensive preclinical validation through in vivo models, including xenograft and orthotopic models, to better mimic the tumor microenvironment. Mechanistic studies should explore resistance pathways, such as those associated with EGFR mutations or multidrug resistance (MDR) proteins, to design compounds that can overcome these barriers. Combination therapies with existing treatments, such as DNA-damaging agents or immune checkpoint inhibitors, should be investigated to enhance efficacy and reduce the likelihood of resistance. Advanced drug delivery systems, including nanoparticles or liposomes, could improve the bioavailability, stability, and tumor-targeting capabilities of quinoxaline derivatives. Expanding the scope of these compounds beyond cancer to other diseases, such as inflammatory or neurodegenerative disorders, could also uncover broader therapeutic applications.

Antimicrobial activity

Antibacterial activity

Quinoxaline derivatives have shown great promise in combating *Mycobacterium tuberculosis*, one of the leading causes of death due to infectious diseases worldwide [101,102]. As tuberculosis is a global health challenge, discovering novel antimycobacterial agents, particularly against drug-resistant strains, is critical [103]. Several research efforts have focused on developing quinoxaline-based compounds that target key bacterial enzymes and pathways, demonstrating significant potential in preclinical studies (Fig. 17).

In a notable effort, Li et al. developed a series of novel 3-arylvinylquinoxaline-2-carboxylic acids using a streamlined one-pot synthetic approach combining Arbuzov, Horner-Wadsworth-Emmons (HWE), and ester hydrolysis reactions [104]. The compounds were tested for their inhibitory effects against *Mycobacterium tuberculosis* Leucyl-tRNA synthetase (Mtb LeuRS), an essential enzyme for protein synthesis in bacteria. Among the synthesized compounds, (E)-3-(3-nitrostyryl) quinoxaline-2-carboxylic acid (**109**) (Fig. 18) showed the highest potency with an IC_{50} value of 14.7 μmol/L, outperforming the standard drug AN2679. Molecular docking simulations suggested that compound **109** interacts strongly with critical residues in the enzyme's active site, such as Met576, His52, and Asp80, forming stable hydrogen bonds that may explain its superior activity. Furthermore, compound **109** exhibited significant antitubercular activity against *Mycobacterium smegmatis*, with an MIC of 15.6 μg/mL, matching the efficacy of the standard drug rifampicin. These findings underscore the potential of **109** as a lead compound for further development of anti-tubercular agents targeting Mtb LeuRS.

Meanwhile, Arumugam et al. synthesized a series of spiropyrrolidine-tethered indenoquinoxaline hybrids using an ionic liquid-accelerated multicomponent 1,3-dipolar cycloaddition reaction [105]. These compounds were evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv using the Microplate Alamar Blue Assay (MABA). Among the derivatives, compound **110** (Fig. 18), which features a 3-nitrophenyl group, exhibited the most potent activity with an MIC value of 1.56 μg/mL, equating to the standard drug ethambutol. Additionally, compound **110** demonstrated a favorable safety profile, showing no cytotoxic effects on Raw 264.7 macrophage cell lines at concentrations up to 50 μg/mL. These findings suggest that the electron-withdrawing nitro group significantly enhances the anti-tubercular potency of spiropyrrolidine-indenoquinoxaline hybrids, making compound **110** a promising lead for further drug development against tuberculosis.

In another study, Kanchrana et al. synthesized a series of spiroquinoxaline-1,2,4-oxadiazoles using a [3+2] cycloaddition reaction under ultrasonic irradiation, aiming to develop novel anti-mycobacterial agents [106]. The synthesized compounds were evaluated against *Mycobacterium tuberculosis* H37Rv. Among them, compound **111** (Fig. 18) exhibited the most potent activity, with an MIC99 value of 0.78 μg/mL, surpassing the standard drug ethambutol (MIC99 = 1.56 μg/mL). Compounds **112**, **113**, and **114** (Fig. 18) also showed notable activity, each with an MIC99 value of 6.25 μg/mL. Cytotoxicity tests on the RAW 264.7 cell line revealed that these compounds had low toxicity, with compound **111** showing a 26.4 μg/mL toxicity level. Molecular docking studies indicated strong binding interactions between these compounds and the *Mycobacterium tuberculosis* protein 5OEQ, with compound **113** displaying the lowest binding energy of −12.19 kcal/mol. These findings suggest that the synthesized spiroquinoxaline-1,2,4-oxadiazoles, particularly **111**, have significant potential as anti-tubercular agents.

In a related approach, Srinivasarao et al. synthesized a series of 1,2,3-triazole-based quinoxaline-1,4-di-N-oxide derivatives, evaluating their anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv and two clinical isolates (Spec. 210 and Spec. 192) [107]. Among the tested compounds, **115** (Fig. 18) demonstrated the most potent activity, with a MIC value of 30.35 μM against all three strains, making it more effective than other analogs. Compound **115** exhibited low cytotoxicity in HEK 293 cells, with an IC_{50} value of 62.71 μM, showing a selectivity index of approximately 4. Molecular docking studies on **115** revealed its interactions with MTB DNA Gyrase, demonstrating a glide score of −7.4 kcal/mol and forming two halogen bonds with the ARG-128 residue, suggesting a strong binding affinity and potential for further development as an anti-tubercular agent.

Moreover, Zhang et al. synthesized a series of quinoxaline-1,4-di-N-oxides containing various nitrogenous heterocyclic moieties at the R6 position, targeting antimycobacterial activity [108]. Four compounds (**116**, **117**, **118**, and **119**) (Fig. 18) showed the most potent activity against *Mycobacterium tuberculosis* strain H37Rv, each with a 0.25 mg/mL MIC. Among them, compound **119** also demonstrated significant antimycobacterial efficacy in a macrophage infection model, inducing a disruption in the membrane integrity and disturbing energy homeostasis of *M. tuberculosis*. Furthermore, compound **119** elevated ROS levels, leading to autophagy in infected macrophages, suggesting a mechanistic pathway for its activity. The selectivity index (SI) 6o was 328.2,

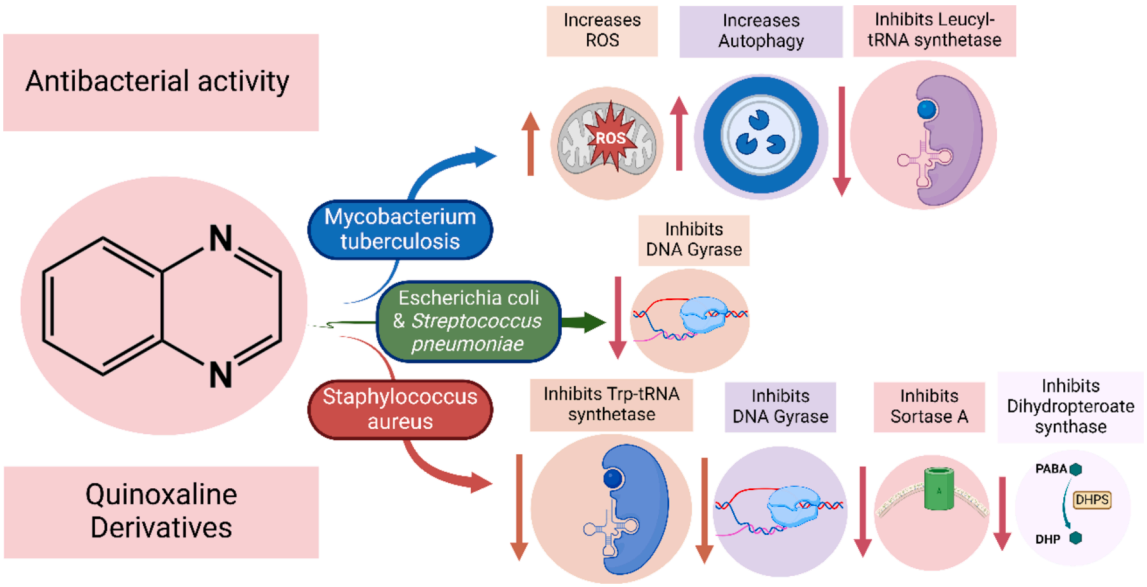


Fig. 17. Quinoxaline derivatives as antibacterial agents.

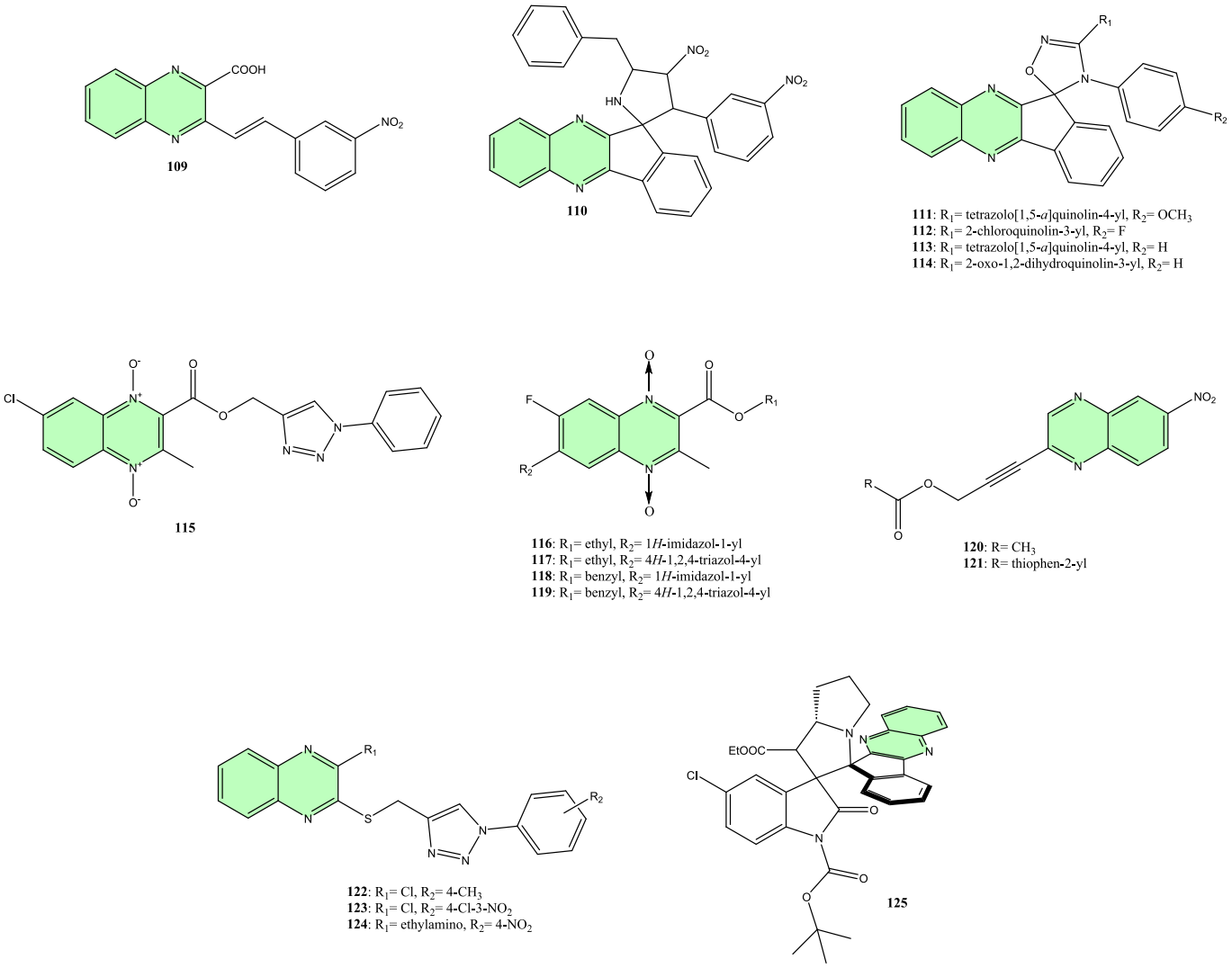


Fig. 18. Structures of compounds **109–125** as antibacterial agents.

indicating a favorable safety profile with minimal cytotoxicity in VERO cells. Pharmacokinetic studies of **119** revealed an acceptable safety margin and suitable PK properties, making it a promising candidate for further development as an antimycobacterial agent.

Similarly, Raphoko et al. synthesized a series of quinoxaline-alkynyl derivatives using Sonogashira coupling, esterification, and oxidation reactions, aiming to develop potent antimycobacterial agents against *Mycobacterium tuberculosis* H37Rv [109]. Among the tested compounds, the most effective was compound **120** (Fig. 18), a nitro derivative with a MIC90 value of 1.80 μM, indicating superior activity compared to other derivatives. Compound **121** (Fig. 18), a nitro-containing derivative, followed by a MIC90 of 2.74 μM. The study highlighted that nitro substitutions at the 6-position significantly enhanced the antimycobacterial efficacy, as 4 of the 7 most potent compounds contained this substituent. Additionally, cytotoxicity tests using the RAW 264.7 cell line demonstrated that these nitro derivatives maintained an acceptable selectivity index (SI), supporting their potential for further development as antitubercular agents.

Shifting the focus from *M. tuberculosis*, Keivanloo and colleagues synthesized a series of 1,2,3-triazole-based 3-substituted 2-thioquinoxalines and evaluated them for their antibacterial activities against *Bacillus subtilis* and *Micrococcus luteus* [110]. Compounds **122**, **123**, and **124** (Fig. 18) exhibited significant activity against bacteria with inhibition zones of 10 mm, 15 mm, 12 mm against *Bacillus subtilis* and 14 mm, 18 mm, and 16 mm against *Micrococcus luteus*, respectively. Molecular docking studies supported these findings, revealing that compound **122** had the strongest binding affinity ($\Delta G = -8.52$ kcal/mol), forming stable hydrophobic interactions and hydrogen bonds within the bacterial protein active sites. The study highlights the influence of substituent orchestration, particularly electron-donating groups, on both biological activity and binding affinity, suggesting these compounds are promising candidates for antibacterial drug development.

Ren et al. synthesized a series of spirooxindole–indenoquinoxaline derivatives as potential inhibitors of tryptophanyl-tRNA synthetase (TrpRS) using a one-pot, diastereoselective cycloaddition method involving azomethine ylides [111]. Among these compounds, **125** (Fig. 18) showed the most potent inhibitory activity with IC_{50} values of 225 nM and 74 nM against human mitochondrial TrpRS (hmTrpRS) and *E. coli* TrpRS (ecTrpRS), respectively. One hundred twenty-five displayed significant antibacterial activity against *Staphylococcus aureus* with a MIC90 of 4 μg/mL. It demonstrated cytotoxic effects on diffuse large B-cell lymphoma (DLBCL) cell lines, with IC_{50} values ranging from 2.9 to 4.8 μM. The compound induced apoptosis and cell cycle arrest at the G0/G1 phase in DLBCL cells, suggesting its potential as an antibacterial and anticancer agent. Molecular docking studies revealed that **125** effectively binds to key residues in the TrpRS active site, forming hydrogen bonds and π–π interactions, highlighting its promise as a lead compound for further development.

Abbaspour et al. synthesized a series of 3-aminoquinoxaline-2-alkynyl carboxylate esters via a multi-component, copper-free Sonogashira coupling reaction [112]. These compounds were evaluated for antibacterial activity against *Micrococcus luteus* and *Pseudomonas aeruginosa*. The most potent compounds, **126**, **127**, and **128** (Fig. 19), exhibited MIC values of 62.5 μg/mL against *M. luteus*, comparable to the standard antibiotic tetracycline. Compound **129** (Fig. 19) also showed significant activity with an MIC of 62.5 μg/mL against *P. aeruginosa*. Molecular docking studies indicated that these compounds could effectively occupy the pterin and p-aminobenzoic acid binding pockets of the bacterial dihydropteroate synthase (DHPS) enzyme, suggesting that they inhibit bacterial growth by interfering with the folate biosynthetic pathway.

Ragab et al. synthesized a series of spiro[1,3]dithiine-4,11′-indeno [1,2-b]quinoxaline derivatives to evaluate their inhibitory activity against *Staphylococcus aureus* Sortase A (SrtA), an enzyme critical for

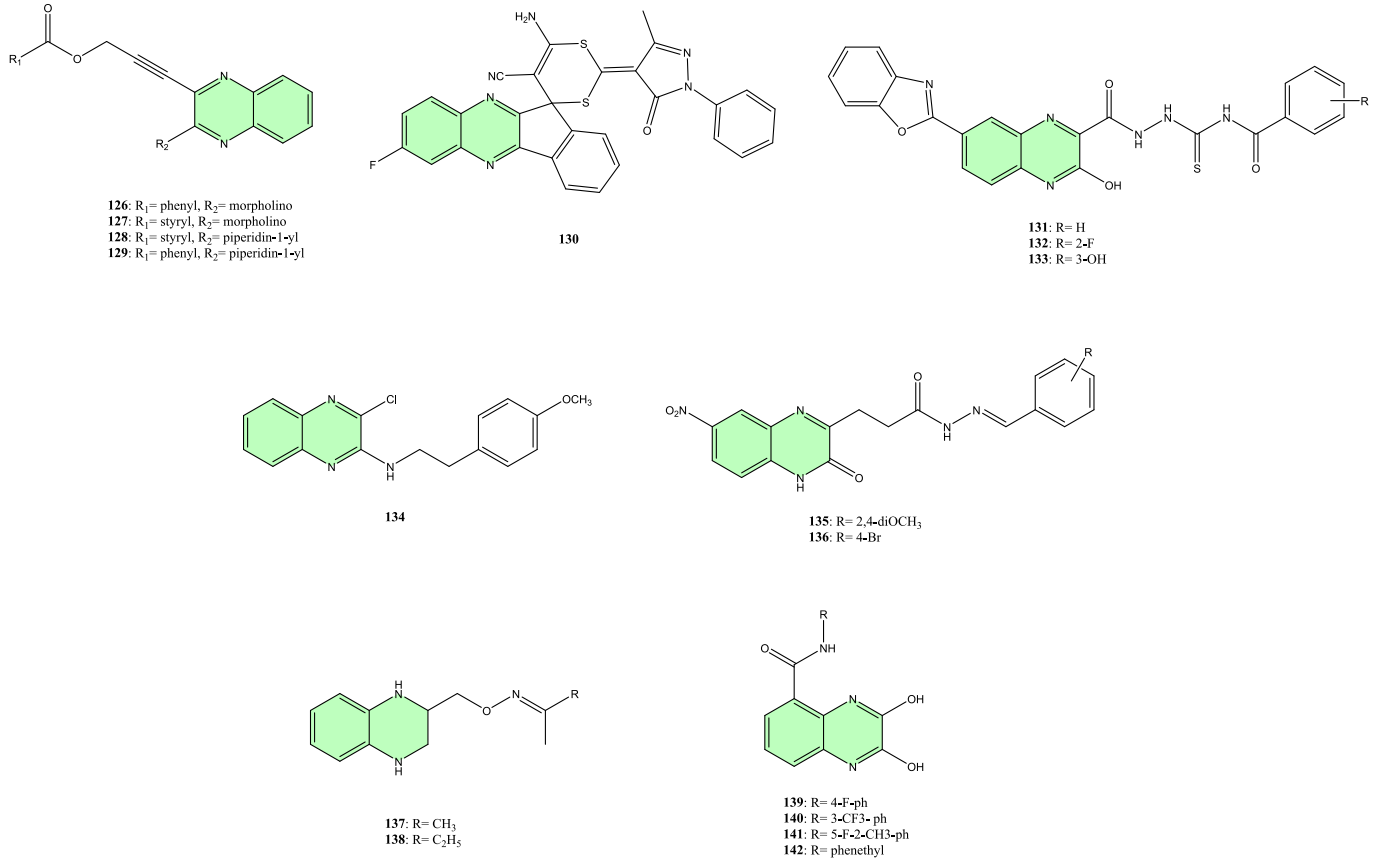


Fig. 19. Structures of compounds **126–142** as antibacterial agents.

bacterial adhesion and biofilm formation [113]. Among the synthesized compounds, **130** (Fig. 19) demonstrated the most potent activity, showing an IC_{50} value of 22.15 μM against SrtA. This compound also significantly reduced bacterial adhesion to fibrinogen by 39.22 % and decreased biofilm biomass formation by 32.27 % at a concentration of 200 μM. The study further explored the use of gamma radiation as a sterilization method, finding that a dose of 5 kGy effectively eradicated microbial contamination without degrading the physicochemical properties of the compounds. Molecular docking simulations confirmed that **130** interacts with key residues within the SrtA active site, highlighting its potential as a promising anti-virulence agent for combating drug-resistant *S. aureus*.

In their search for new antibacterial agents, Eppakayala et al. synthesized a series of N-{2-[7-(1,3-benzoxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl]hydrazinecarbonothioyl}benzamide derivatives. Using the agar well diffusion method, they evaluated their antibacterial activity against gram-positive and gram-negative bacterial strains [114]. Among the derivatives, compounds **131**, **132**, and **133** (Fig. 19) exhibited the most significant antibacterial activity, with inhibition zones measuring 15.5 mm against *Escherichia coli* and *Staphylococcus aureus*. Molecular docking studies targeting DNA gyrase revealed that these compounds formed stable hydrogen bonds with key residues such as Arg78, Gly79, and Asp75, alongside π–π-cation and π–π-anion interactions with Glu52 and π-stacking interactions with Asn48. Compound **131**, in particular, showed the highest docking score of −9.85 kcal/mol, correlating well with its antibacterial activity. These findings suggest that these benzamide derivatives could be promising candidates for developing new antibacterial agents.

Xie et al. synthesized a series of novel quinoxaline derivatives and evaluated their antibacterial activity and preliminary antibacterial mechanisms [115]. Among these, compound **134** (Fig. 19) exhibited the most potent activity, with MIC values of 4 μg/mL against *Staphylococcus aureus* and *Bacillus subtilis* and 16 μg/mL against *Escherichia coli* and *Pseudomonas aeruginosa*. Further studies showed **134**'s effectiveness against multidrug-resistant strains, including MRSA and *Klebsiella pneumoniae*, with MICs of 4–16 μg/mL. One hundred thirty-four displayed a lower tendency for developing bacterial resistance than controls like norfloxacin. The compound showed bactericidal activity against MRSA at 3 MIC, leading to a >7 log10 CFU/mL reduction after 7 h. In vivo studies using a mouse wound model confirmed that **134** at 5 mg/mL reduced bacterial survival by 75 %. These results highlight **134**'s potential as a promising antibacterial agent.

Saleh et al. designed and synthesized a series of 3-(7-nitro-3-oxo-3,4-dihydroquinoxalin-2-yl)propanehydrazide derivatives targeting bacterial DNA gyrase inhibition [116]. Among these, compounds **135** and **136** (Fig. 19) exhibited the most potent antibacterial activity, with MIC values of 9.40 μM and 9.00 μM, respectively, against *Staphylococcus aureus* and 4.70 μM and 4.50 μM against *Streptococcus pneumoniae*, outperforming ciprofloxacin (MIC = 12.07 μM). DNA gyrase inhibition assays revealed IC_{50} values of 0.242 μM for **135** and 0.177 μM for **136**, significantly lower than ciprofloxacin's IC_{50} of 0.768 μM. In cytotoxicity assays, compounds **135** and **136** showed IC_{50} values of 288.69 μM and 227.64 μM in WI-38 cells, indicating favorable selectivity. Molecular docking confirmed their strong binding affinity, particularly for **135**, which displayed a binding energy of −7.51 kcal/mol, surpassing ciprofloxacin's score of −7.29 kcal/mol. These findings suggest that compounds **135** and **136** are promising candidates for further development as DNA gyrase inhibitors.

In another promising study, Zarenezhad et al. synthesized a series of oxime ether derivatives containing a quinoxaline moiety and evaluated their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* [117]. Among these derivatives, compounds **137** and **138** (Fig. 19) demonstrated the most significant antibacterial effects, with MIC values of 62.5 μg/mL against *S. aureus*, outperforming penicillin (MIC = 125 μg/mL) in similar conditions. In contrast, both compounds showed MIC values of 125 μg/mL against *E. coli*. Molecular docking studies revealed that compounds **137** and **138** formed stable hydrogen bonds with key residues in the active sites of *S. aureus* Gyrase B and *E. coli* MurB. Specifically, the NH group of the quinoxaline moiety **137** interacted with Glu325 in *E. coli* MurB and Asn54 in *S. aureus* Gyrase B, highlighting the critical role of these interactions in antibacterial activity. These findings suggest that small substitutions, such as methyl and ethyl groups, enhance these derivatives' binding and antibacterial efficacy.

Srinivas et al. synthesized a series of novel 2,3-dihydroxyquinoxaline-5-carboxamide derivatives and evaluated their antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pyogenes* [118]. Among these, compounds **139**, **140**, **141**, and **142** (Fig. 19) exhibited the most potent antibacterial activity, with zones of inhibition ranging from 27 to 28 mm against *E. coli* and *S. aureus*. These compounds also demonstrated strong activity against *P. aeruginosa* and *S. pyogenes* with 22–24 mm inhibition zones. SAR analysis indicated that electronegative groups, such as fluoro and trifluoromethyl substituents, enhanced antibacterial efficacy. Additionally, the deprotection of dimethoxy groups from hydroxyl groups in the quinoxaline moiety further improved activity. These findings highlight the potential of these derivatives as promising candidates for antibacterial drug development.

Antifungal activity

Quinoxaline derivatives have shown considerable potential as antifungal agents, offering promising avenues for combating clinical and agricultural fungal infections [119]. In recent studies, these compounds have been explored for their ability to inhibit key fungal enzymes and disrupt cellular processes, targeting human pathogens like *Candida* species and phytopathogenic fungi affecting agriculture. Focusing on inhibiting ergosterol biosynthesis, Fayed et al. synthesized quinoxaline derivatives to inhibit ergosterol biosynthesis in *Candida* species [120]. The study identified compounds **143**, **144**, **145**, **146**, and **147** (Fig. 20) as the most potent, exhibiting MIC50 values ranging from 0.78 to 3.12 μg/mL across multiple *Candida* strains, including *C. albicans*, *C. krusei*, and *C. glabrata*. Compound **143** emerged as the most effective, showing superior antifungal activity compared to standard drugs like Ketoconazole and Fluconazole, with an MIC50 of 0.78 μg/mL against all tested strains. Mechanistic studies confirmed that these compounds inhibited ergosterol synthesis by targeting the 14α-demethylase enzyme (CYP51), which is crucial for fungal cell membrane integrity. Cytotoxicity assays demonstrated compound **9** had an IC_{50} value above 500 μg/mL in NIH/3T3 cells, indicating a high selectivity index and minimal cytotoxicity. ADMET analysis and molecular docking further supported the potential of these compounds as promising antifungal agents.

Exploring other mechanisms, El Newahie et al. synthesized a series of hybrid styryl-quinoxaline analogs to investigate their antifungal activity against *Candida albicans* [121]. The most potent compound, N-(3-chlorophenyl)-2-(3-(2-hydroxystyryl)quinoxalin-2-yl)hydrazinecarboxamide (**148**) (Fig. 20), exhibited an MIC50 value of ≤ 0.25 μg/mL, which is comparable to fluconazole (MIC50 = 0.125 μg/mL). Molecular docking studies indicated that compound **148** targets the fungal squalene epoxidase enzyme, similar to allylamine antifungals, forming hydrogen bonds and hydrophobic interactions that inhibit the enzyme's function. The compound showed minimal cytotoxicity in human embryonic kidney cells (HEK293) and no hemolytic activity at 32 μg/mL concentrations in human red blood cells. These findings suggest that **148** is a promising candidate for further development as an antifungal agent.

Addressing antifungal resistance, Guillon et al. synthesized two series of piperazinyl-pyrrolo[1,2-a]quinoxaline derivatives, aiming to evaluate their inhibitory effects on *Candida albicans* multidrug transporters CaCdr1p and CaMdr1p, which contribute to antifungal resistance [122]. Most of the tested compounds exhibited dual inhibitory activity against both transporters. Compounds **149** and **150** (Fig. 20) were particularly effective, displaying MIC80 values ranging from 5 to 14 μM in yeast strains overexpressing CaMdr1p. Further synergy testing through checkerboard assays revealed that these two compounds

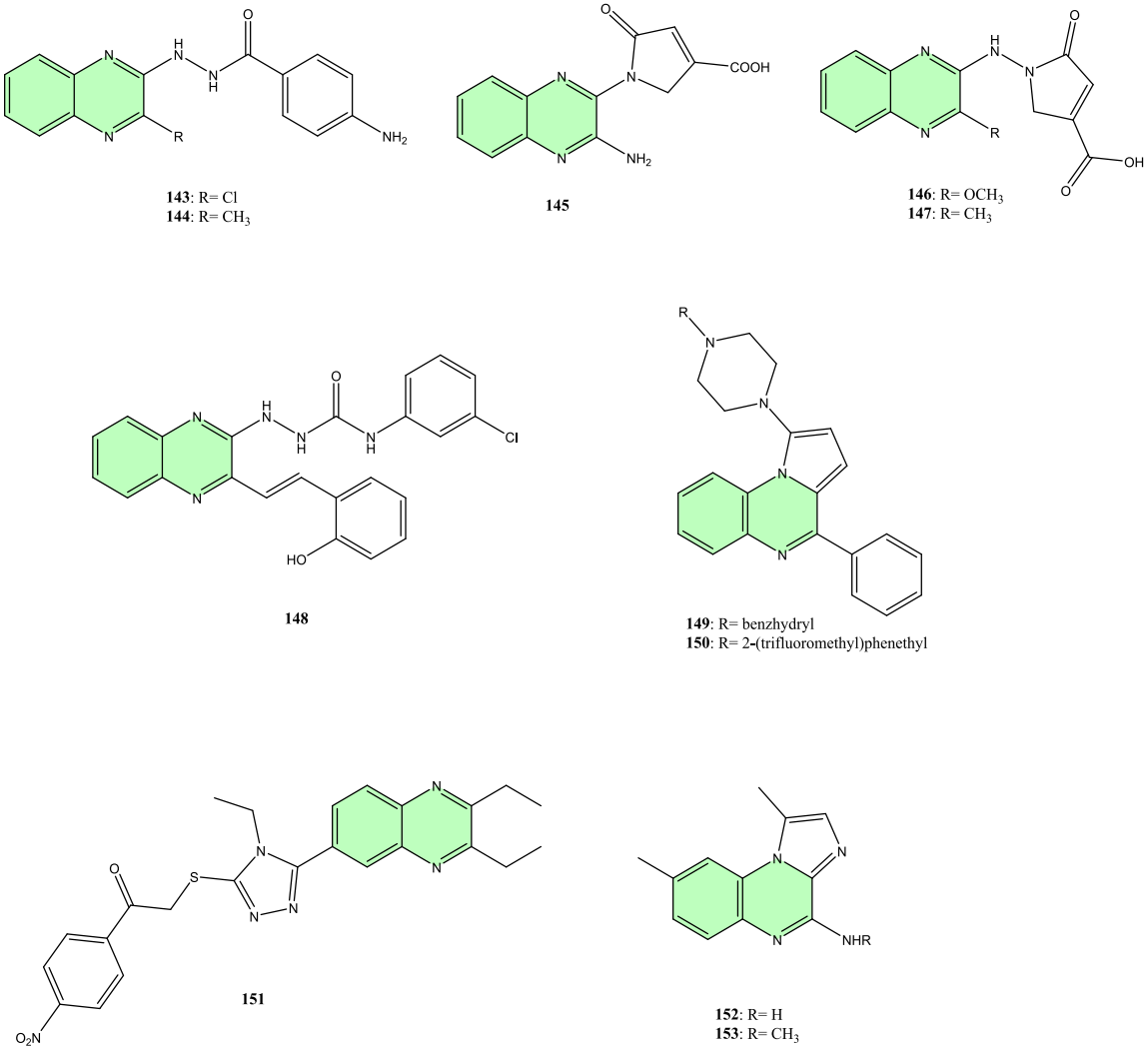


Fig. 20. Structures of compounds **143–153** as antifungal agents.

significantly enhanced the activity of fluconazole, achieving fractional inhibitory concentration index (FICI) values of 0.15 and 0.4, respectively, which reduced the fluconazole concentration required by up to 129-fold. Molecular docking studies showed that **149** and **150** effectively interact with the binding sites of the efflux pumps, stabilizing their structure and preventing drug efflux. These findings suggest that compounds **149** and **150** have the potential to act as chemosensitizers, providing a promising approach for overcoming multidrug resistance in *C. albicans*.

Turning to the challenge of biofilm formation, Osmaniye et al. synthesized novel quinoxaline-triazole compounds and evaluated their antifungal activity against various *Candida* strains [123]. The most potent compound, **151** (Fig. 20), exhibited promising activity, with MIC90 values of 2 μg/mL against *Candida glabrata* and *Candida krusei*. Compound **151** outperformed fluconazole against *C. krusei*, demonstrating an eightfold higher efficacy (fluconazole MIC90 = 16 μg/mL). Biofilm inhibition studies revealed that compound **151** reduced *Candida tropicalis* biofilm formation by 70–77 % at twice the MIC concentration. Molecular docking studies showed that the nitro group **151** formed stable interactions with the CYP51 enzyme's active site, including cation–π and π–π interactions. Molecular dynamics simulations confirmed these interactions' stability over 100 ns, further supporting compound **151**'s potential as an antifungal agent against drug-resistant *Candida* species.

Shifting the focus to agricultural applications, Ma et al. synthesized thirty-six imidazo[1,2-a]quinoxaline derivatives to evaluate their antifungal properties against ten phytopathogenic fungi commonly found in agriculture [124]. The compounds exhibited broad-spectrum activity, with **152** and **153** (Fig. 20) showing the most promising results. Compound **152** had an EC_{50} value of 5.6 μg/mL against *Valsa mali*, while compound **153** demonstrated an EC_{50} value of 5.1 μg/mL against *Fusarium solani*, surpassing commercial fungicides like hymexazol. The study suggests that these compounds disrupt hyphal differentiation, spore germination, and germ tube growth, as observed via microscopy. Cytotoxicity assays on BV2 cells showed these compounds have low toxicity, with cell viability above 82.7 % at 100 μg/mL. The results highlight the potential of imidazo[1,2-a]quinoxaline derivatives as effective and safe agricultural fungicides.

Antiviral activity

Quinoxaline derivatives have emerged as promising antiviral agents, showing significant potential in targeting various viral proteins and mechanisms across multiple viral strains. Research has demonstrated their effectiveness in inhibiting key enzymes and proteins associated with viral replication, offering hope for developing broad-spectrum antiviral therapies. Below are examples of recent studies exploring quinoxalines as antiviral agents (Fig. 21).

In the search for novel flavivirus inhibitors, Zephyr et al. discovered a new class of quinoxaline-based allosteric inhibitors targeting the flavivirus NS2B/NS3 protease using a fragment-based drug discovery

approach [125]. These inhibitors, which include cyclic amine and proline moieties linked to a quinoxaline core, displayed non-competitive inhibition mechanisms against the Zika virus (ZIKV) protease. Enzymatic assays confirmed that these compounds bind to an allosteric site, competing with the NS2B cofactor. Among the tested derivatives, compound **154** (Fig. 22) demonstrated the most promising activity, with an IC_{50} value of 30 μM. It also exhibited antiviral effects in cellular assays, showing EC_{50} values of 2.7 μM against dengue virus (DENV) and 3.2 μM against Japanese encephalitis virus (JEV). Molecular docking studies supported the binding of these compounds within the allosteric site, confirming their potential to shift the protease dynamics toward an inactive conformation. These findings highlight the potential of quinoxaline-based scaffolds as candidates for developing broad-spectrum antiviral therapies against flaviviruses.

Turning their focus to HIV, Fabian et al. designed, synthesized and evaluated a series of quinoxaline compounds as anti-HIV agents targeting the HIV reverse transcriptase (RT) enzyme [126]. Using structure-based development, they created a virtual chemical library, screening it with molecular docking and 3D-QSAR techniques to identify promising candidates. Twenty-five quinoxaline derivatives were synthesized based on their docking scores and ease of synthesis. Compounds **155** and **156** (Fig. 22) demonstrated significant RT inhibitory activity, with IC_{50} values of 0.63 μM and 64 μM, respectively. Compound **155**, in particular, showed potent antiviral activity with an EC_{50} of 3.1 nM in HIV-infected MT2 cells and a selectivity index (SI) of 31,798, comparable to the commercial drug nevirapine (NVP). Cytotoxicity assays confirmed that both compounds exhibited minimal toxicity at therapeutic doses. These results suggest that compound **155** is a strong candidate for further development as a novel anti-HIV agent targeting the reverse transcriptase enzyme.

Amid the growing need for COVID-19 treatments, Chemboli et al. explored the potential of quinoxaline derivatives to address the severe inflammatory responses associated with the disease [127]. Their pyrrolo [2,3-b]quinoxalines series was designed to attenuate the cytokine storm. These compounds were evaluated for their inhibitory effects on phosphodiesterase 4B (PDE4B) and tumor necrosis factor-alpha (TNF-α), both critical in the inflammatory response. Compound **157** (Fig. 22) emerged as the most promising, exhibiting 77.3 % TNF-α inhibition at 10 μM with an IC50 of 5.14 μM. Molecular docking studies confirmed strong binding of **157** to the N-terminal RNA-binding domain (NTD) of the SARS-CoV-2 nucleocapsid protein. In silico ADME analysis, they - predicted favorable pharmacokinetic properties, including high gastrointestinal absorption and low toxicity, positioning compound **157** as a strong candidate for further development as a therapeutic agent to mitigate the cytokine storm in COVID-19 patients.

Taking a computational approach to COVID-19 treatment, Shahinshavali et al. synthesized a series of 3-alkynyl substituted 2-chloroquinoxaline derivatives using ultrasound-assisted Cu-catalysis to explore their potential as ligands for the NTD of the SARS-CoV-2N-protein [128]. The compounds were designed based on known antiviral scaffolds and synthesized using a green methodology involving PEG-400 as a solvent. Molecular docking studies identified compound **158** (Fig. 22) as the most promising, with a binding energy of −6.5 kcal/mol, outperforming others in the series. This compound showed effective π–π interactions with Tyr110 and formed hydrophobic contacts with key residues like Arg150 and Ala157. In silico analysis of the series, they revealed that derivatives containing hydroxycycloalkyl or aryl moieties exhibited better binding affinity due to their ability to stabilize hydrophobic interactions within the protein's binding site. These findings suggest that **158** and similar derivatives are potential candidates for further in vitro and in vivo studies as anti-COVID-19 agents.

In another effort to target SARS-CoV-2, Missioui et al. synthesized a novel compound, Diethyl 2-(2-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl) acetyl)hydrazono)malonate (**159**) (Fig. 22), as a potential COVID-19 therapeutic agent [129]. Computational studies using DFT strongly correlated the theoretical and experimental structures. Molecular docking simulations revealed binding energies of −7.0 and −6.9 kcal/mol for two disordered molecular forms **159** when docked against the SARS-CoV-2 main protease, indicating potential inhibitory activity. These scores were comparable to several approved antiviral drugs. The docking analysis suggested that **159** establishes multi-hydrogen bonds and hydrophobic interactions with key residues, including Arg188 and

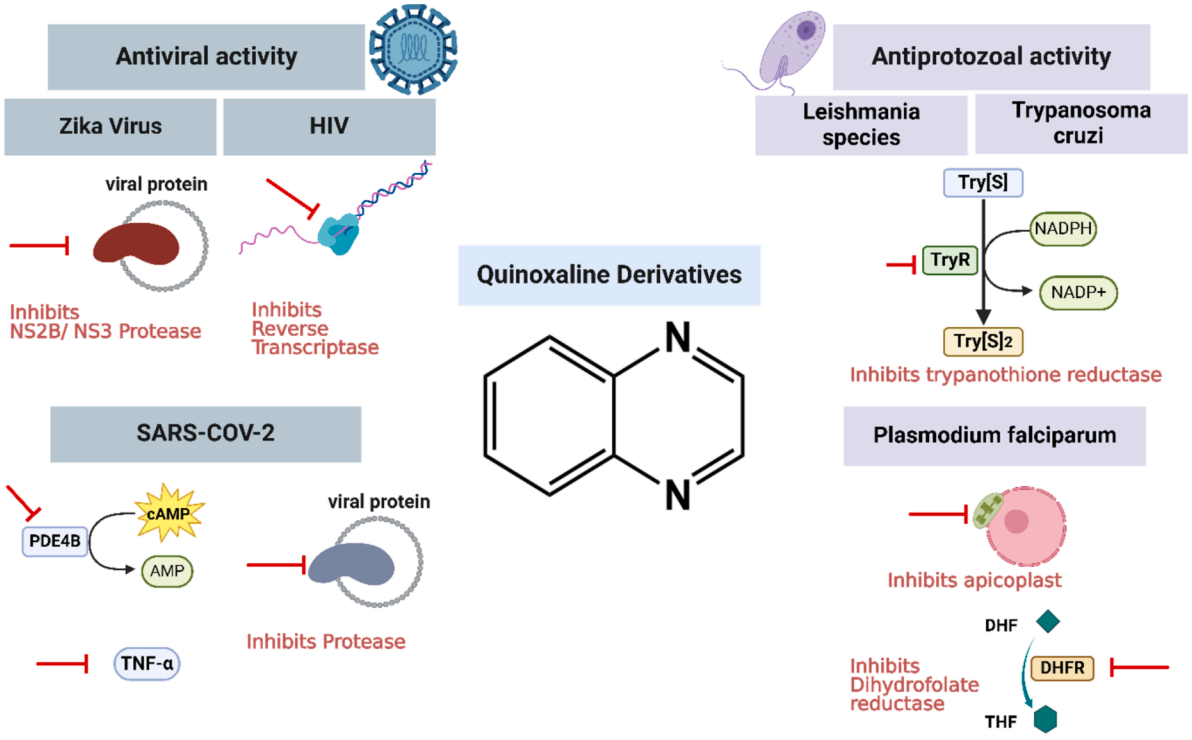


Fig. 21. Quinoxaline derivatives as antiviral and antiprotozoal agents.

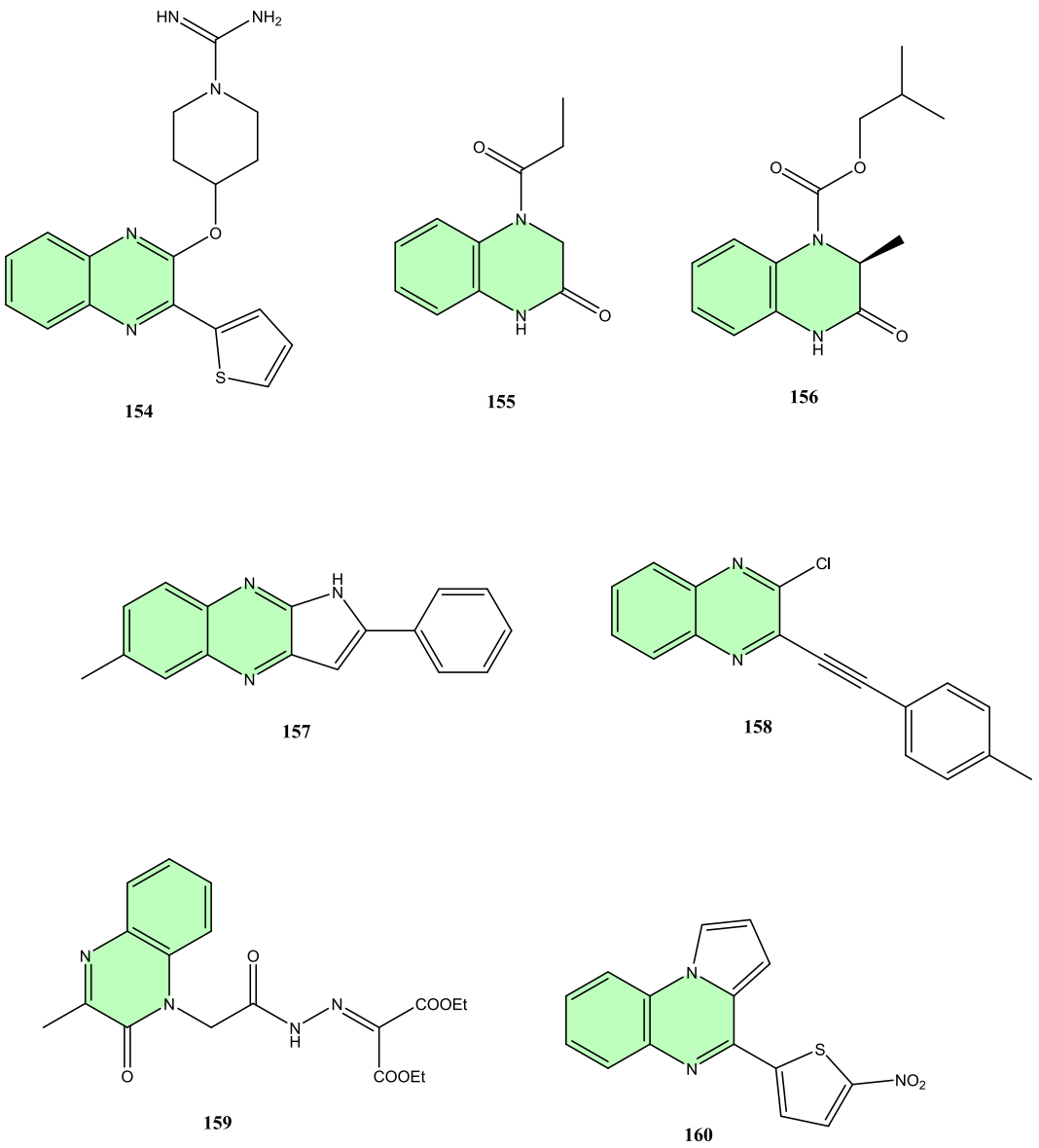


Fig. 22. Structures of compounds **154–160** as antiviral agents.

His41. Additionally, in silico ADMET analysis and PASS predictions indicated that **159** has favorable pharmacokinetic properties and potential antiviral activity against picornaviruses, warranting further exploration as a therapeutic agent for COVID-19.

Continuing the search for effective COVID-19 therapies, Divya et al. synthesized 4-(5-nitro-thiophen-2-yl)-pyrrolo[1,2-a]quinoxaline (**160**) (Fig. 22) and evaluated its potential as a SARS-CoV-2 main protease (3CLpro) inhibitor [130]. Molecular docking studies demonstrated that **160** binds effectively to the active site of 3CLpro with a binding energy of −7.95 kcal/mol, surpassing the binding affinities of approved drugs such as hydroxychloroquine and remdesivir. The docking analysis revealed key interactions, including hydrogen bonds with Gly143 and Cys145 and hydrophobic interactions with residues such as Glu166 and His164. Energy framework analysis indicated that dispersion energy was dominant in crystal packing stability. The findings suggest that **160** shows promising inhibitory activity against SARS-CoV-2 and warrants further investigation as a potential therapeutic agent.

Antiprotozoal activity

Protozoal diseases like malaria, Chagas disease, and leishmaniasis remain major global health challenges, particularly in regions where drug resistance is widespread. Researchers have explored various chemical scaffolds to identify new antiprotozoal agents, including quinoxalines, which have shown considerable promise due to their diverse biological activities (Fig. 21). Targeting the essential organelles of *Plasmodium falciparum*, Amrane et al. synthesized a series of 2-thiophenoxy-3-trichloromethyl quinoxalines, aiming to target the apicoplast of *Plasmodium falciparum*, an essential organelle involved in the parasite's survival and proliferation [131]. These compounds were evaluated for their antiplasmodial efficacy against the multidrug-resistant K1 strain. Compound **161** (Fig. 23) emerged as the most potent, with an EC_{50} value of 0.3 μM, significantly inhibiting parasite growth. Cytotoxicity assays showed that **161** had a CC_{50} value of 56.0 μM in HepG2 cells, indicating a high selectivity index 175. Additional safety profiling confirmed that **161** was non-genotoxic and exhibited minimal toxicity in both VERO and CHO cell lines, supporting its safety profile. Mechanistic studies revealed that **161** disrupts apicoplast biogenesis, leading to a delayed death phenotype consistent with compounds targeting this essential organelle. This suggests that **161** could be a viable candidate for developing novel antimalarial therapies.

In the search for treatments against Chagas disease, González-González et al. synthesized a series of n-butyl and isobutyl quinoxaline-

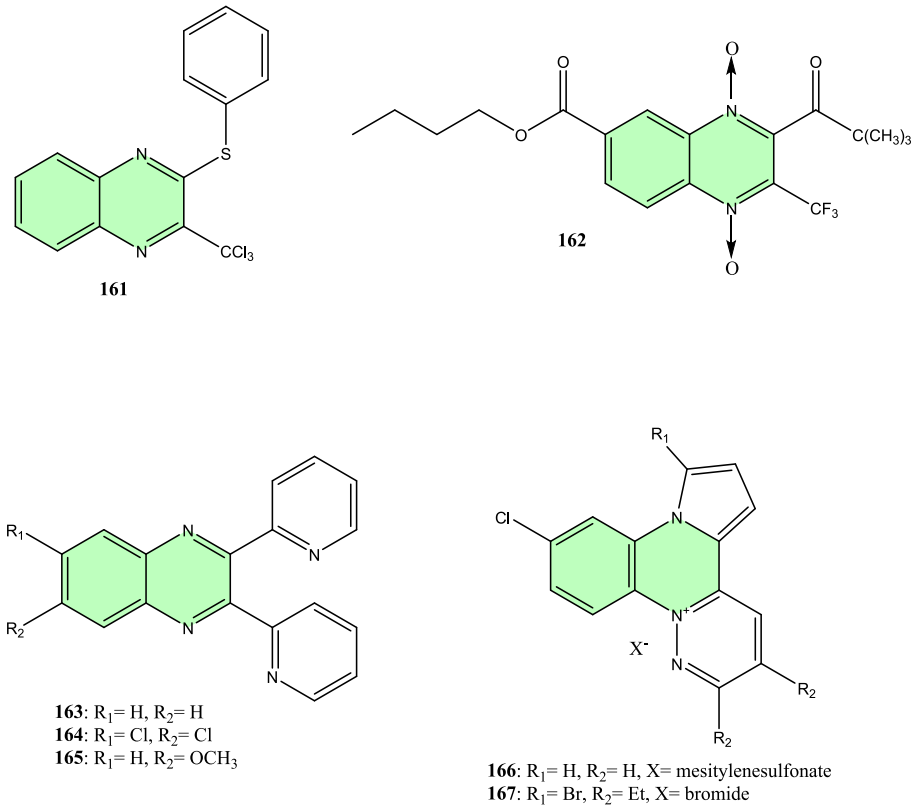


Fig. 23. Structures of compounds **161–167** as antiprotozoal agents.

7-carboxylate 1,4-di-N-oxide derivatives to evaluate their antitrypanosomal activity against *Trypanosoma cruzi* [132]. Among these, compound **162** (Fig. 23) demonstrated the most potent trypanocidal effect with an LC_{50} value of 44 μM against the NINOA strain. Enzyme inhibition assays revealed that **162** acted as a mixed-type inhibitor of trypanothione reductase (TR), with Ki and Ki' values of 11.4 μM and 60.8 μM, respectively, comparable to the reference TR inhibitor mepacrine (Ki = 19 μM). Molecular docking studies confirmed that **162** interacts with key residues in the TR active site, including Val-59 and Phe-396, indicating its potential mechanism of action. These findings suggest that **162** could serve as a promising lead compound for further development as a treatment for Chagas disease.

With a focus on antileishmanial activity, Kumar et al. synthesized six quinoxaline derivatives, each with distinct substitutions (Br, Cl, F, OCH3, and CF3). They assessed their antileishmanial activity against promastigote forms of *Leishmania major* and *tropica* [133]. The chloro-substituted compounds, specifically derivatives **163** and **164** (Fig. 23), along with the methoxy-substituted compound **165** (Fig. 23), showed the most significant inhibitory effects, with IC_{50} values of 23.30, 19.03 and 20.12 μM against *L. major*, respectively. This potency was comparable to the standard antileishmanial drug miltefosine, which had an IC_{50} of 25.78 μM under the same conditions. Importantly, all compounds demonstrated no cytotoxic effects on BJ human fibroblast cells at a concentration of 30 μM, indicating a favorable safety profile. Supramolecular analysis revealed that these compounds' structural stability and intermolecular interactions, including H-Br, H-Cl, H-C, and H-F bonding, contributed significantly to their activity and stability. These findings suggest that the chloro and methoxy derivatives, in particular, hold promise for further development as antileishmanial agents.

Further broadening the investigation into antileishmanial agents, Lucio et al. synthesized a series of pyridazine-pyrrole-quinolinium salts to investigate their antileishmanial activity against *Leishmania infantum* [134]. Among these, 11 compounds showed potent leishmanicidal effects, with EC_{50} values in the nanomolar range. Compounds **166** and **167** (Fig. 23) stood out, achieving selectivity indices above 300 due to their low cytotoxicity against the THP-1 human monocytic cell line (LC_{50} values > 10 μM). Notably, compound **167** demonstrated the most potent intracellular activity, with an EC_{50} of 1.23 μM, closely matching the activity of the reference drug miltefosine (EC_{50} = 0.55 μM). Mechanistic studies revealed that **167** acts as a hyperbolic noncompetitive inhibitor of the *L. infantum* trypanothione disulfide reductase (LiTryR) when tested with varying trypanothione (TS2) concentrations. This noncompetitive inhibition suggests compound **167** stabilizes the enzyme-substrate complex but reduces its catalytic efficiency. The findings highlight the potential of pyridazino-pyrrolo-quinoxalinium salts as promising candidates for developing new leishmanicidal agents targeting LiTryR.

Critical analysis of antimicrobial potential in quinoxaline derivatives

Quinoxaline derivatives have demonstrated remarkable potential as antimicrobial agents, with significant activities spanning antibacterial, antifungal, antiviral, and antiprotozoal applications. Their structural versatility and ability to target diverse biological pathways make them promising candidates for combating challenging infections and diseases. In the realm of antibacterial activity, these derivatives have shown exceptional promise against *Mycobacterium tuberculosis* (Mtb), where some quinoxalines such as quinoxline N-oxides stood out as an important feature for the antimycobacterial activity. Compounds such as **109**, **110**, and **111** have exhibited potent activity, with MIC values comparable to or surpassing standard drugs like rifampicin and ethambutol. These compounds target essential bacterial enzymes like Leucyl-tRNA synthetase and leverage favorable structural features, such as nitro groups, to enhance efficacy. However, while these derivatives perform well in preclinical studies, their limited testing against drug-resistant strains and lack of in vivo validation present significant challenges. Similarly, other bacterial targets, such as *Staphylococcus aureus* and *Escherichia coli*, have seen promising results with compounds like **120** and **125**, though comprehensive clinical validation is still needed. While

some derivatives demonstrate lower resistance development tendencies, their long-term efficacy against multidrug-resistant (MDR) strains requires further investigation.

Quinoxaline derivatives also exhibit notable antifungal potential, particularly in targeting ergosterol biosynthesis in Candida species. Compounds such as **143** and **148** have shown superior activity to standard drugs like fluconazole, with minimal cytotoxicity and high selectivity indices. These derivatives target fungal enzymes like CYP51 and squalene epoxidase, effectively disrupting fungal cell membrane integrity. Furthermore, compounds like **151** have demonstrated the ability to inhibit biofilm formation, a key factor in fungal resistance. Despite these advancements, concerns remain regarding antifungal resistance and toxicity, emphasizing the need for expanding structural diversity and optimizing activity against resistant fungal strains.

In antiviral applications, quinoxaline derivatives like **155** and **157** have shown potent activity by targeting critical viral proteins such as HIV reverse transcriptase and the SARS-CoV-2 nucleocapsid protein. These compounds exhibit strong inhibitory effects and favorable pharmacokinetics, making them promising candidates for addressing global pandemics like COVID-19 and HIV. However, their activity has predominantly been assessed through computational and in vitro studies, with limited translation into in vivo validation. For example, compounds like **160**, which show strong molecular docking results, have yet to be evaluated in clinical settings. The focus moving forward should be on transitioning from computational findings to preclinical and clinical investigations to confirm their broad-spectrum antiviral potential.

Quinoxaline derivatives have also proven effective as antiprotozoal agents, with compounds like **161** and **167** exhibiting strong activity against protozoal diseases such as malaria and leishmaniasis. These compounds target essential parasite organelles and enzymes, such as the apicoplast in *Plasmodium falciparum* and trypanothione reductase in *Leishmania infantum*. Despite these successes, their antiprotozoal applications are limited by insufficient safety profiling, resistance evaluations, and compatibility with existing therapeutic regimens.

Future research should prioritize several areas to maximize the therapeutic potential of quinoxaline derivatives. Expanding their structural libraries and leveraging advanced drug design techniques, such as AI-driven optimization, could enhance activity and selectivity. More comprehensive preclinical and clinical validation is essential to establish their safety, efficacy, and pharmacokinetics. Resistance profiling, particularly against MDR strains, should be a focus to ensure long-term efficacy. Additionally, exploring these derivatives as multifunctional agents capable of tackling infections caused by mixed microbial communities could be a valuable direction. Systematic studies on their safety, cytotoxicity, and bioavailability will further support their development as viable therapeutic agents. In conclusion, while quinoxaline derivatives hold immense promise as antimicrobial agents, addressing these challenges will be critical to realizing their full therapeutic potential.

Antidiabetic activity

Quinoxaline derivatives have garnered significant attention as potential antidiabetic agents due to their diverse mechanisms of action in managing glucose levels and improving insulin sensitivity. Recent studies have explored these compounds' abilities to inhibit key enzymes, enhance glucose uptake, and modulate oxidative stress, contributing to their promising role in treating type II diabetes (Fig. 24).

In one study, Pedrood et al. designed and synthesized a series of diphenyl quinoxaline-6-carbohydrazide hybrids as potential α-glucosidase inhibitors for managing type II diabetes [135]. The compounds exhibited inhibitory activity with IC_{50} values ranging from 110.6 to >750 μM, compared to the standard acarbose (IC = 750.0 μM). Compound **168** (Fig. 25), which features a 3-fluorophenyl moiety, showed the most potent activity with an IC = of 110.6 μM. Kinetic studies revealed that **168** acts as a competitive inhibitor, binding directly to the active site. Molecular docking supported these findings, showing that **168** formed hydrogen bonds and aromatic interactions within the enzyme's active site, correlating with its high potency. These results suggest compound **168** could be a promising lead for developing new antidiabetic agents targeting α-glucosidase.

Exploring the dual enzyme inhibition route, Missioui et al. synthesized a novel quinoxaline derivative, 2-(4-((3-methyl-2-oxoquinoxalin-1(2H)-yl)methyl)-4,5-dihydro-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (**169**) (Fig. 25), to evaluate its antidiabetic activity [136]. In vitro studies showed that **169** inhibited α-glucosidase and α-amylase enzymes with IC_{50} values of 288.6 μM and 246.6 μM, respectively, demonstrating better activity than the reference drug acarbose (IC_{50} = 115.6 μM for α-amylase). Molecular docking revealed that **169** formed stable interactions with key residues in both enzymes, including hydrogen bonds with SER566 and ARG189 in α-glucosidase. ADMET analysis predicted that **169** has favorable pharmacokinetic properties, including good oral bioavailability and minimal toxicity, making it a promising candidate for further development as an antidiabetic agent.

Similarly, Phongphane et al. synthesized a series of quinoxaline-isoxazole hybrids and evaluated their antidiabetic activity by inhibiting α-amylase and α-glucosidase enzymes [137]. Among the derivatives, compound **170** (Fig. 25) exhibited the most potent dual inhibition with IC_{50} values of 17.0 μM for α-amylase and 40.1 μM for α-glucosidase, outperforming the control drug acarbose. Compound **171** (Fig. 25), with a cyano group, showed selective inhibition of α-glucosidase, achieving an IC_{50} of 16.6 μM. Molecular docking studies supported these findings, revealing binding energies ranging from −8.3 to −9.1 kcal/mol. Compound **170** demonstrated stability in molecular dynamics simulations, interacting strongly with key residues, suggesting its potential as an effective anti-hyperglycemic agent. Drug-likeness assessments confirmed that the compounds comply with Lipinski's rules, supporting their development as oral antidiabetic drugs.

Turning to another important target in diabetes management, García-Marín et al. synthesized and evaluated a series of pyrrolo[1,2-a]quinoxalines as selective inhibitors of protein tyrosine phosphatase 1B (PTP1B), a therapeutic target for type 2 diabetes [138]. The compounds exhibited low- to sub-micromolar inhibitory activity, with the 4-benzyl derivative (compound **172**) (Fig. 25) being the most potent (IC_{50} = 0.24 μM) and demonstrating a selectivity index (SI) of over 40 against the closely related enzyme TCPTP. In cell-based assays using C2C12 cells, compound **172** increased glucose uptake, mimicking insulin action by enhancing the phosphorylation of insulin receptor substrate 1 (IRS1) and AKT without affecting STAT3. Molecular docking and dynamics simulations indicated that these compounds bind to the allosteric α3/α6/α7 pocket of PTP1B, supporting their selectivity. Despite showing aggregation tendencies in enzyme kinetics assays, the compounds, particularly **172**, show promise for further development as antidiabetic agents targeting PTP1B.

Further exploring PTP1B inhibitors, Sánchez-Alonso et al. synthesized pyrrolo[1,2-a]quinoxal-5-inium salts and 4,5-dihydropyrrolo[1,2-a]quinoxalines to evaluate their inhibitory activity against PTP1B [139]. The compounds demonstrated inhibition percentages between 37 % and 53 % at a concentration of 1 μM, with IC_{50} values ranging from 0.25 to 1.90 μM. Among them, 4,5-dihydropyrrolo[1,2-a]quinoxalines showed slightly higher activity and selectivity for PTP1B than T-cell protein tyrosine phosphatase (TC-PTP). The most selective compound, **173** (Fig. 25), exhibited an IC_{50} of 0.45 μM and a selectivity index greater than 11. In C2C12 cells, 3 g enhanced glucose uptake by about 150 %, mimicking insulin's effect, though it was slightly less potent than insulin. Molecular docking studies revealed that these compounds preferentially bind the α3/α6/α7 allosteric tunnel of PTP1B, forming key interactions with residues like Phe196 and Glu276, supporting their potential as selective PTP1B inhibitors for antidiabetic therapy.

Turning attention to DPP-4 inhibition, Syam et al. synthesized new quinoxaline derivatives featuring the 1,4-dimethyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide scaffold and evaluated their

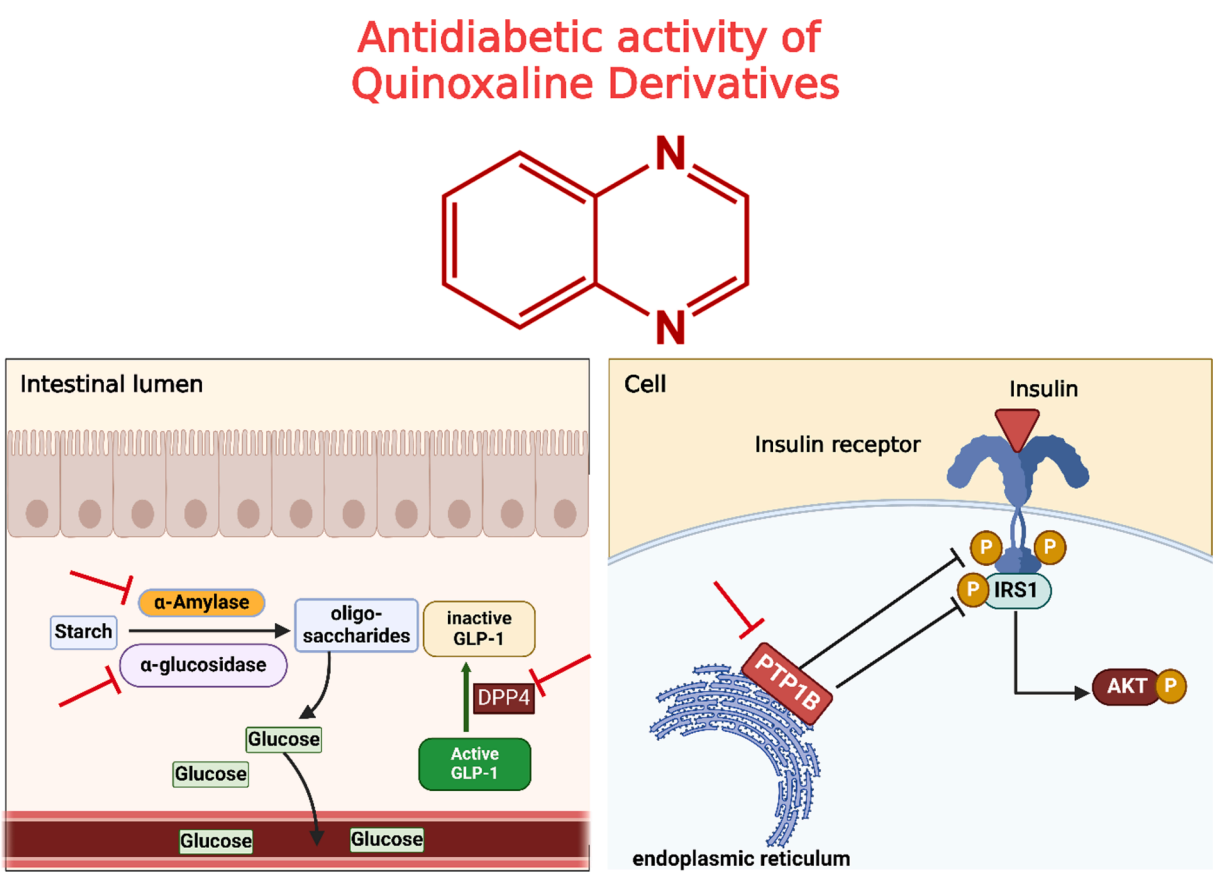


Fig. 24. Quinoxaline derivatives as antidiabetic agents.

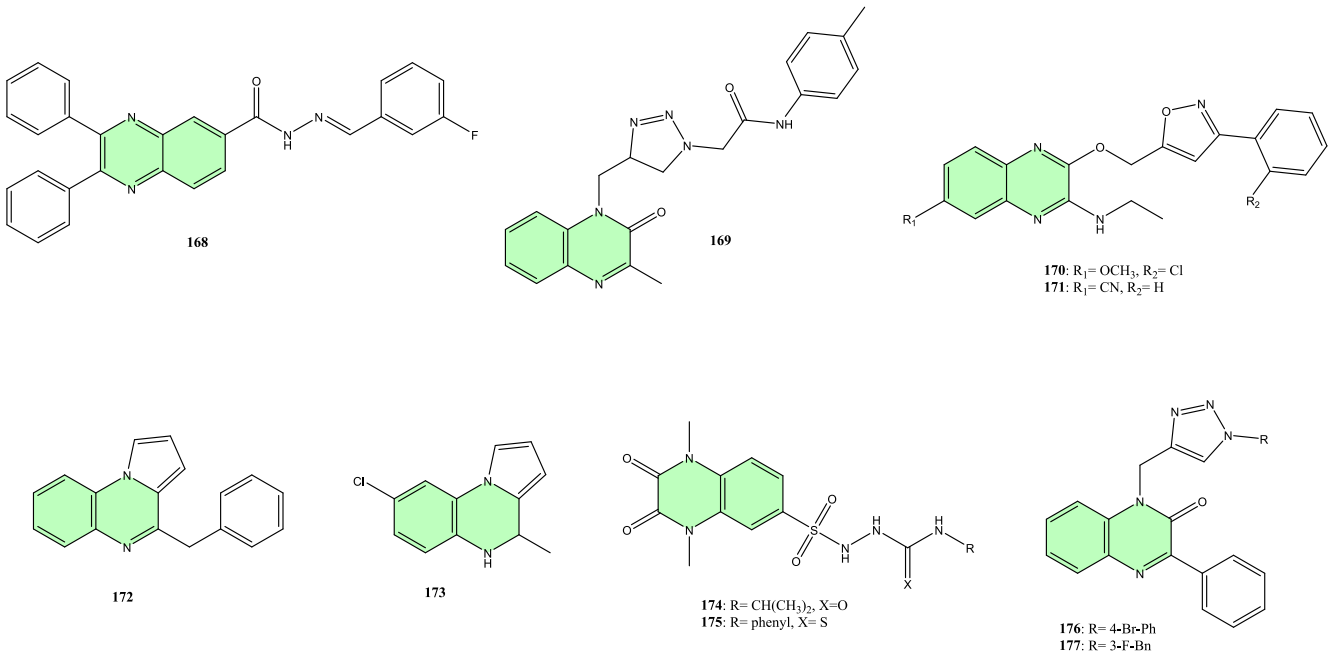


Fig. 25. Structures of compounds **168–177** as antidiabetic agents.

biological potential as dipeptidyl peptidase-IV (DPP-4) inhibitors for type II diabetes management [140]. Compounds **174** and **175** (Fig. 25) exhibited significant DPP-4 inhibition, with IC_{50} values of 35.4 μM and 28.7 μM, respectively, outperforming the standard drug linagliptin. Molecular docking studies revealed these compounds fit well within the DPP-4 active pocket, forming hydrogen bonds with key residues. Additionally, molecular dynamics simulations confirmed the stability of these interactions. Both compounds also adhered to Lipinski's rule of five, indicating favorable oral bioavailability. Furthermore, radiolabeling of compound **174** allowed for biodistribution studies, showing

accumulation in visceral organs, aligning with DPP-4's secretion sites, and highlighting its therapeutic potential.

In a different approach, Jia et al. synthesized quinoxalinone derivatives to assess their hypoglycemic potential [141]. Among these, compounds **176** and **177** (Fig. 25) demonstrated significantly enhanced hypoglycemic activity, outperforming the initial lead compounds and showing effects comparable to the standard Pioglitazone. Specifically, compound **177** emerged as the most potent, effectively reducing blood glucose levels while alleviating oxidative stress (OS) in LO2 cells. This compound modulated key glucose transporter proteins (GLUT4, SGLT2, and GLUT1), improving glucose uptake efficiency. In vitro assays highlighted that **177** lowered ROS levels more efficiently than compound **176**, suggesting superior antioxidant properties. Molecular docking studies supported these findings, showing that **177** had strong binding affinities to diabetes-related targets, particularly SGLT2, forming stable interactions that enhance activity. These results suggest compound **177** is a promising candidate for further development as an antidiabetic agent with potential therapeutic applications.

This exploration of quinoxaline derivatives as antidiabetic agents reveals a promising avenue for combating type II diabetes, with diverse mechanisms of action and innovative synthetic strategies. However, several aspects warrant closer examination to assess their true potential as therapeutic candidates.

A notable strength lies in the variety of mechanisms targeted by these derivatives. Studies have demonstrated their efficacy in inhibiting key enzymes like α-glucosidase, α-amylase, and protein tyrosine phosphatase 1B (PTP1B), which are central to glucose metabolism and insulin sensitivity. Compounds like **168** and **172** show impressive potency and selectivity, supported by detailed molecular docking and dynamic simulation studies. Moreover, compounds such as **176** and **177** exhibit hypoglycemic effects by modulating glucose transporters, addressing oxidative stress, and improving glucose uptake efficiency. This multifaceted approach underscores the versatility of quinoxaline derivatives in addressing different aspects of diabetes pathology.

Despite these advancements, certain limitations and challenges remain. The reported IC_{50} values, although potent in some cases, vary significantly across studies, with some compounds showing only moderate activity compared to standard drugs. For example, while compound **168** demonstrates superior α-glucosidase inhibition, the inhibitory activity of **169** against α-amylase remains less compelling. This variation raises questions about the consistent efficacy of quinoxaline derivatives across different enzymatic targets.

Another concern lies in the aggregation tendencies observed during enzyme kinetics assays for some compounds, such as **172**. Such tendencies may complicate their development as clinical drugs, requiring further structural optimization to enhance solubility and stability. Similarly, the bioavailability and distribution profiles of these derivatives, despite adherence to Lipinski's rules, remain underexplored, particularly for compounds targeting systemic or organ-specific glucose regulation.

Furthermore, while compounds like **174** and **175** show significant dipeptidyl peptidase-IV (DPP-4) inhibition, outperforming standard drugs like linagliptin, the lack of detailed in vivo efficacy studies prevents a complete understanding of their therapeutic potential. The reliance on computational predictions and isolated enzyme studies, without accompanying biological validation, weakens the translational impact of these findings.

Analgesic and anti-inflammatory activity

Inflammation, a complex immune response to injury or infection, can be modulated by targeting key pathways like cytokines, enzymes, and receptors, allowing for precise treatment and reducing harmful immune responses [142,143]. Quinoxaline derivatives have been extensively studied for their potential in managing pain and inflammation, making them valuable candidates for therapeutic development. In a detailed study, Meka and Chintakunta synthesized a variety of quinoxaline derivatives, including biphenyl quinoxaline, quinoxaline dione, and quinoxaline-2-one, to assess their analgesic and anti-inflammatory properties [144]. Several compounds stood out for their analgesic effects, with compounds **178**, **179**, **181**, **183**, and **185** (Fig. 26) exhibiting percentage protection values of 56.90 %, 68.68 %, 67.70 %, 66.33 %, and 68.79 %, respectively, comparable to aspirin's 70.50 % at 30 mg/kg. Compounds **180**, **182**, **184**, and **186** (Fig. 26) displayed anti-inflammatory effects, reducing edema by 53.91 %, 48.72 %, 46.77 %, and 46.85 %, respectively, similar to indomethacin (49.00 % reduction). The structure–activity relationship analysis indicated that electron-withdrawing groups (e.g., nitro groups at C-6) enhanced anti-inflammatory efficacy, while other substitutions influenced analgesic properties. The findings suggest the potential of these quinoxaline derivatives as therapeutic agents for pain and inflammation management.

Another study was performed by Doğan et al., where they synthesized a series of twelve 1,2,4-triazolo[4,3-a]quinoxaline derivatives to investigate their anti-inflammatory activity [145]. The anti-inflammatory potential was assessed using LPS-induced RAW264.7 murine macrophage cells, with the nitrite levels measured to evaluate inflammation. Among the tested compounds, **187** (Fig. 26) exhibited the most potent effect, reducing nitrite levels by 65.12 %, comparable to the standard drug indomethacin (63.83 %). Compounds **188** and **189** (Fig. 26) also showed notable activity, reducing nitrite levels by 51.56 % and 51.13 %, respectively. Molecular docking studies supported these findings, revealing that the compounds formed key interactions with the active site of inducible nitric oxide synthase (iNOS), which is responsible for elevated nitrite levels during inflammation. These results suggest that 1,2,4-triazolo[4,3-a]quinoxaline derivatives, particularly compound **187**, are promising candidates for anti-inflammatory drug development.

In Alzheimer's disease

Alzheimer's disease continues to be a major target for drug development, with numerous studies exploring various pathways involved in the disease's progression [146]. Quinoxaline derivatives have emerged as promising candidates, particularly for their potential to inhibit key enzymes related to Alzheimer's pathology, such as cholinesterases and monoamine oxidases.

In one investigation, Almansour et al. synthesized a series of spiropyrrolidine-tethered imidazole hybrids using a [bmim]Br-mediated 1,3-dipolar cycloaddition approach [147]. These compounds were evaluated for their cholinesterase inhibitory activities against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The most potent compounds, **190** and **191** (Fig. 27), displayed IC_{50} values of 2.02 μM and 2.05 μM against AChE and 12.40 μM and 11.45 μM against BChE, respectively, showing comparable activity to the standard drug galanthamine. Docking studies revealed that these compounds interact effectively with key residues within the cholinesterase active site, forming multiple hydrogen bonds and hydrophobic interactions. The electron-donating groups on the aryl ring of these derivatives were crucial for their high potency, suggesting their potential as promising candidates for Alzheimer's disease treatment.

In another approach, Elhag et al. synthesized a series of indolo[2,3-b]quinoxaline derivatives using microwave-assisted techniques to evaluate their potential as AChE inhibitors for Alzheimer's disease treatment [148]. In vitro screening revealed that the derivatives exhibited potent AChE inhibitory activity, with IC_{50} values as low as 0.02 μM for the most active compound, **192** (Fig. 27), which featured electron-withdrawing groups such as nitro and benzoyl moieties. DFT calculations provided insights into the electronic and thermal properties. At the same time, molecular docking studies highlighted critical pi-pi and hydrogen bonding interactions with key amino acids (e.g., TRP286) within the catalytic gorge of AChE. These results support the indole-quinoxaline hybrids as promising candidates for dual-binding site

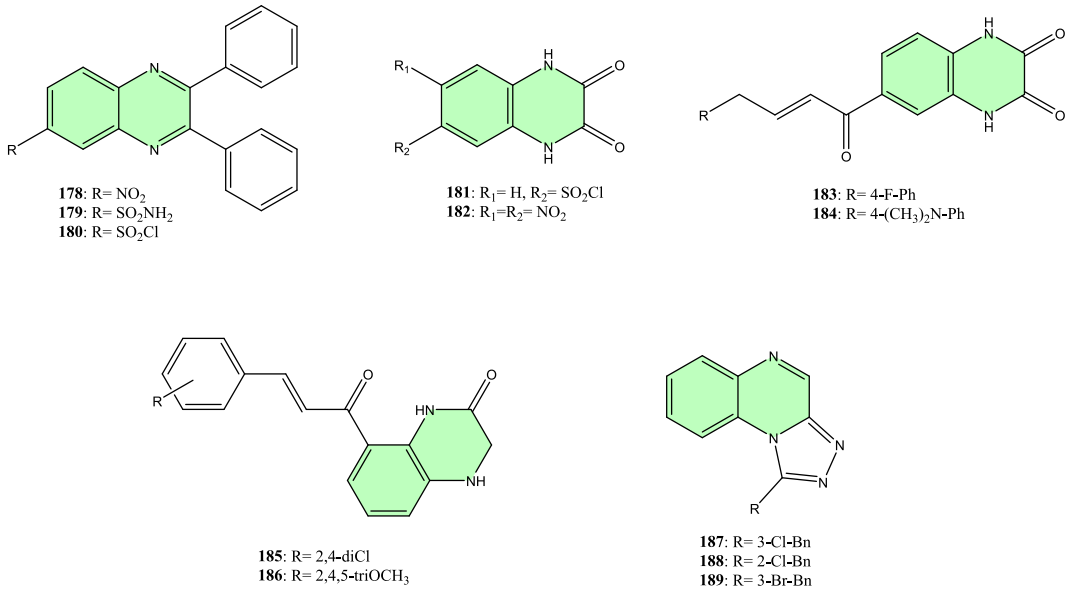


Fig. 26. Structures of compounds **178–189** as analgesic and anti-inflammatory agents.

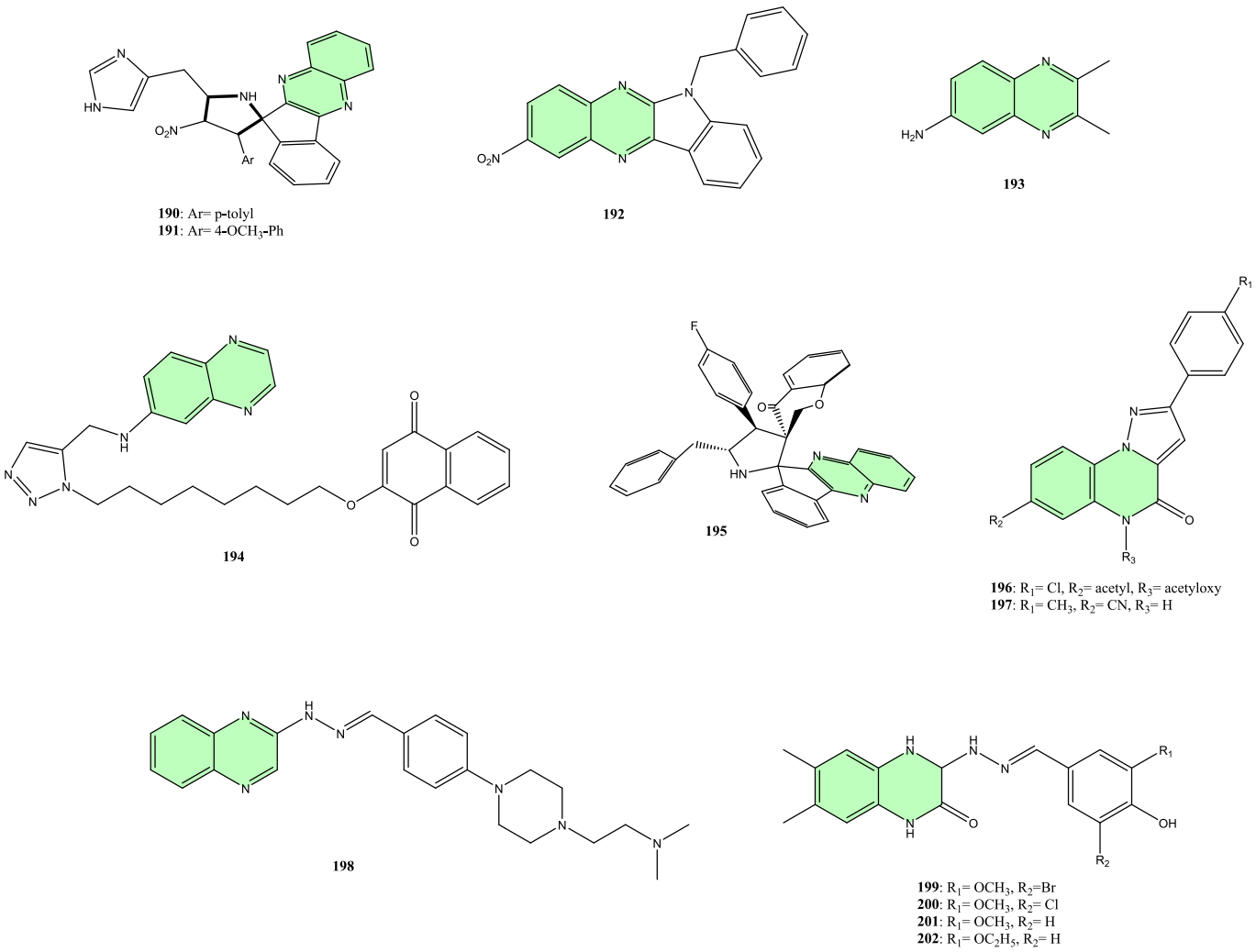


Fig. 27. Structures of compounds **190–202** used in Alzheimer's disease.

AChE inhibitors, offering the potential for developing multifunctional anti-Alzheimer agents.

Continuing the search for effective inhibitors, Suwanhom et al. synthesized twelve quinoxaline derivatives to evaluate their AChE and BChE inhibitory activities [149]. Among these, compound **193** (Fig. 27) exhibited the most potent AChE inhibitory activity with an IC_{50} value of 0.077 μM, outperforming standard inhibitors like tacrine (IC_{50} = 0.11 μM). This compound also showed moderate selectivity, with lower BChE inhibition (IC_{50} = 42.02 μM). Kinetic studies revealed that **193** acts as a mixed-type inhibitor, primarily targeting the peripheral anionic site (PAS) of AChE, which was confirmed through molecular docking. The docking results showed strong interactions between **193** and key residues at the PAS site, such as Trp286 and Tyr341. Additionally, **193** demonstrated no cytotoxicity against SH-SY5Y human neuroblastoma cells, highlighting its potential as a safe and effective anti-Alzheimer's agent.

Expanding on their findings, Suwanhom's group further designed lawsone–quinoxaline hybrids to target both the catalytic and peripheral anionic sites of AChE [150]. Among the synthesized compounds, **194** (Fig. 27) exhibited the highest potency, showing IC_{50} values of 20 nM for AChE and 220 nM for BChE. In vitro, cytotoxicity assays confirmed that **194** was non-toxic to SH-SY5Y neuronal cells at concentrations up to 100 μM. Kinetic studies and in silico analyses revealed that **194** binds to the catalytic and peripheral anionic sites of human AChE, forming key interactions with residues such as Trp80 and Tyr118. This dual-site interaction approach suggests that Lawsone–quinoxaline hybrids, particularly **194**, hold promise for further development as effective anti-Alzheimer agents.

Arumugam et al. also contributed to the field, synthesizing spiroquinoxalinopyrrolidine-embedded chromanone hybrids to investigate their cholinesterase inhibitory activities [151]. The most potent compound, **195** (Fig. 27), featuring a fluorine substitution on the phenyl ring, showed IC_{50} values of 3.20 μM for AChE and 18.14 μM for BChE, comparable to the standard drug galantamine (AChE IC_{50} = 2.09 μM). Molecular docking and dynamics simulations revealed that **195** had a higher binding affinity for AChE (−10.5 kcal/mol) than galantamine (−7.56 kcal/mol). The MMPBSA analysis further confirmed that **195** exhibited stronger binding energy (−93.5 kcal/mol) than galantamine (−66.2 kcal/mol), indicating superior binding stability. These findings suggest that the fluorinated spiroquinoxaline derivatives, particularly **195**, are promising candidates for developing new cholinesterase inhibitors for Alzheimer's therapy.

Expanding beyond cholinesterase inhibition, Panova et al. synthesized 22 pyrazolo[1,5-a]quinoxalin-4-one derivatives and evaluated their inhibitory activity against monoamine oxidases (MAOs) MAO-A and MAO-B [152]. Eight derivatives exhibited potent MAO-A inhibition with submicromolar IC_{50} values, and three derivatives showed similar activity against MAO-B. The most effective MAO-A inhibitor, compound **196** (Fig. 27), had an IC_{50} of 0.028 μM, displaying 50-fold selectivity over MAO-B. Component 197 (Fig. 27) for MAO-B was the most potent, with an IC_{50} of 0.617 μM and an 8-fold selectivity advantage. Molecular docking studies indicated that **196** forms pi-interactions and hydrogen bonds with key residues in the active site of MAO-A, suggesting an induced fit mechanism involving water molecule displacement. ADME predictions indicated high gastrointestinal absorption for most compounds, though few were predicted to penetrate the blood–brain barrier, highlighting compound **197**'s potential as a centrally active MAO-B inhibitor.

Targeting multiple mechanisms, Çevik et al. synthesized quinoxaline-hydrazone derivatives to evaluate their potential as multifunctional agents targeting AChE and MAO for Alzheimer's disease treatment [153]. Among the synthesized compounds, **198** (Fig. 27) emerged as the most potent, with IC_{50} values of 0.028 μM for AChE and 0.046 μM for MAO-B, showing activity comparable to donepezil and selegiline. Molecular docking studies indicated compound **198** binds effectively to AChE and MAO-B, forming critical interactions such as π-π stacking and hydrogen bonds with key residues like Trp286 in AChE and Tyr435 in MAO-B. These findings suggest that **198**, with its dual inhibition properties, could be a promising candidate for further development as a treatment for Alzheimer's disease.

Shifting to kinase inhibition, Jain et al. synthesized a series of 6,7-dimethyl quinoxaline analogs targeting glycogen synthase kinase-3β (GSK3β), an enzyme involved in Alzheimer's pathology through its role in tau protein hyperphosphorylation [154]. Compounds **199** and **200** (Fig. 27), containing bromo and chloro groups, displayed high selectivity and potency for GSK3β, with IC_{50} values of 0.270 μM and 0.390 μM. Molecular docking studies revealed that both compounds formed stable hydrogen bonds with the Val135 residue and additional non-covalent interactions with Arg141 and Thr138, enhancing their selectivity. These interactions were confirmed through molecular modeling, which showed a strong fit of the compounds in the active site, mimicking the binding pattern of known GSK3β inhibitors. The selective inhibition of GSK3β by compounds **199** and **200** over other kinases, like DYRK1A and CLK1, underscores their therapeutic potential for Alzheimer's disease treatment.

Continuing their work, Jain's group also focused on cyclin-dependent kinase 5 (CDK5), another enzyme implicated in Alzheimer's. They synthesized 6,7-dimethylquinoxaline derivatives to assess their potential as CDK5 inhibitors [155]. The study revealed that compounds **201** and **202** (Fig. 27), featuring methoxy and hydroxy substituents, exhibited the highest potency against CDK5 with IC_{50} values of 1.24 μM and 1.88 μM, respectively. These compounds showed selectivity for CDK5 over other kinases such as DYRK1A and CLK1. Molecular docking studies confirmed that these derivatives interact with the CDK5 active site, specifically forming hydrogen bonds with Cys83 and Glu81, crucial for their inhibitory action. DFT calculations supported these findings, showing that the compounds with lower hydrophobicity achieved optimal binding. The study highlighted the importance of substituent modulation in optimizing the activity and selectivity of quinoxaline derivatives, offering insights for further development of CDK5 inhibitors as potential Alzheimer's therapeutics.

The diverse approaches utilized in these studies underscore the versatility of quinoxaline derivatives as a scaffold for addressing Alzheimer's disease (AD). From cholinesterase and MAO inhibition to kinase modulation, these compounds have demonstrated the capacity to target multiple pathological mechanisms involved in AD. While the studies underscore their therapeutic potential, critical aspects warrant further exploration to optimize these compounds for clinical use.

One of the key strengths of the reported derivatives is their structural diversity, which allows for the modulation of different biological targets. The spiropyrrolidine-tethered imidazole hybrids synthesized by Almansour et al. demonstrate potent cholinesterase inhibitory activity, comparable to established drugs like galantamine. Similarly, lawsone-quinoxaline hybrids effectively target both catalytic and peripheral anionic sites of acetylcholinesterase (AChE), emphasizing their potential as dual-binding inhibitors. These findings illustrate the capacity of quinoxaline scaffolds to be fine-tuned for specific enzymatic targets, enhancing their pharmacological efficacy.

Despite the promising enzyme inhibitory activities of these derivatives, critical gaps in their development remain. While molecular docking and dynamics studies provide valuable insights into binding interactions, further experimental validation, such as protein crystallography, is essential to confirm these computational predictions. Additionally, the selective inhibition demonstrated by certain compounds, such as 6,7-dimethylquinoxalines targeting CDK5 over DYRK1A, highlights the need for more robust selectivity profiling to ensure minimal off-target effects, particularly for enzymes with overlapping roles in neurodegeneration.

Another notable limitation is the insufficient exploration of blood–brain barrier (BBB) permeability in many of these studies. AD therapies require compounds with efficient CNS penetration, and while ADME predictions indicate favorable properties for some derivatives,

experimental validation through in vitro BBB models or in vivo pharmacokinetic studies remains crucial. This is particularly relevant for kinase inhibitors like CDK5-targeting derivatives, where CNS accessibility is paramount for therapeutic efficacy.

Lastly, while the multifunctionality of compounds like quinoxaline-hydrazones targeting both AChE and MAO-B is commendable, the potential for drug-drug interactions and cumulative toxicity needs to be addressed in future studies. Given the complexity of AD pathology and the requirement for long-term treatment, the safety and tolerability profiles of these compounds must be rigorously evaluated.

Future directions

Quinoxaline derivatives have demonstrated significant therapeutic potential across multiple disease areas, but several key challenges remain to be addressed for their advancement into clinical use. One important area for future research involves optimizing the pharmacokinetics of these compounds. Although many quinoxaline derivatives show strong in vitro activity, their bioavailability and metabolic stability in vivo often limit their effectiveness. To overcome this, future studies should modify their chemical structures to improve solubility, permeability, and resistance to metabolic degradation. Additionally, approaches such as prodrug development or the incorporation of drug delivery systems, like nanoparticles, could enhance their pharmacokinetic profiles and clinical utility.

Another critical challenge is overcoming drug resistance, particularly in cancer and infectious diseases. For example, resistance to kinase inhibitors in cancer often arises through mutations in target proteins. Designing next-generation quinoxaline derivatives that bind to novel, allosteric sites or irreversibly interact with their targets could help bypass common resistance mechanisms. Similarly, in the realm of antimicrobial and antiviral therapies, future efforts should be directed toward developing quinoxaline derivatives that can overcome resistance mechanisms, such as efflux pumps or enzyme modifications, which reduce the effectiveness of current treatments.

Further exploration of novel molecular targets is another promising avenue for quinoxaline derivative development. While their ability to inhibit kinases, histone deacetylases (HDACs), and topoisomerases is well-established, expanding the investigation to other emerging targets, such as bromodomain proteins and nuclear receptors involved in inflammation and metabolism, could unlock new therapeutic opportunities. Developing multitargeted quinoxaline derivatives that can simultaneously modulate multiple biological pathways may be particularly effective for treating complex diseases like cancer and neurodegenerative disorders.

Neurodegenerative diseases represent another important area for future research. Quinoxaline derivatives with neuroprotective properties, such as those that reduce oxidative stress and inflammation, have shown promise in models of neurodegeneration. Future work could focus on developing these compounds to inhibit the aggregation of misfolded proteins like amyloid-β or tau, which play key roles in conditions such as Alzheimer's and Parkinson's. Improving the ability of quinoxaline derivatives to cross the blood–brain barrier will be essential for their effectiveness in treating central nervous system disorders.

The potential of quinoxaline derivatives in combination therapies also deserves attention. In oncology, combining quinoxaline-based kinase inhibitors with immunotherapies, such as checkpoint inhibitors, could yield synergistic effects, enhancing immune responses while directly targeting tumor cells. These compounds could be combined with existing antibiotics to combat multidrug-resistant pathogens more effectively in infectious diseases.

Finally, the application of quinoxaline derivatives could expand beyond traditional therapeutic areas. Recent studies suggest their potential roles in metabolic disorders such as diabetes, obesity, and cardiovascular diseases, where they may modulate pathways related to lipid metabolism and inflammation. Their potential in immunomodulation, particularly in autoimmune diseases, also presents a promising avenue for further investigation. Given their ability to modulate key immune system regulators, quinoxaline derivatives could emerge as important tools in treating diseases characterized by dysregulated immune responses.

Conclusion

Quinoxaline derivatives are versatile bioactive molecules with strong therapeutic potential across various diseases, including cancer, neurodegenerative disorders, and infectious diseases. Their ability to inhibit key enzymes and receptors and their structural adaptability have made them valuable in drug development. Despite these advancements, challenges remain, particularly in improving their pharmacokinetic properties, such as bioavailability and metabolic stability, and overcoming drug resistance in cancer and microbial treatments. Future research should focus on optimizing drug-likeness, reducing toxicity, and exploring novel delivery systems to enhance their therapeutic impact. Additionally, expanding the application of quinoxaline derivatives into less-explored areas, such as neurological and metabolic disorders, offers further potential. With continued efforts in SAR optimization and innovative molecular designs, quinoxaline derivatives have the potential to play a pivotal role in the development of next-generation therapeutics, addressing critical unmet medical needs.

CRediT authorship contribution statement

Aly M. Waseem: Methodology, Conceptualization. **Ranya Mohammed Elmagzoub:** Writing – original draft, Validation, Investigation. **Mervat Mohammed Mazhar Abdelgadir:** Software, Formal analysis, Data curation. **Areej Al Bahir:** Resources, Funding acquisition. **N.S. Abd EL-Gawaad:** Resources, Funding acquisition. **Ahmed S. Abdel-Samea:** Writing – review & editing, Writing – original draft, Visualization. **Devendra Pratap Rao:** Validation, Supervision. **Konstantinos Kossenas:** Software, Investigation, Data curation. **Stefan Bräse:** Supervision, Project administration, Funding acquisition. **Hamada Hashem:** Writing – review & editing, Supervision, Project administration, Conceptualization.

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Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

Data will be made available on request.

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