

Recent Advances In Quinoxaline Derivatives (2020–2025) Green Synthesis Approaches And Anticancer Potential

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ABSTRACT

Quinoxaline derivatives have gained considerable importance in medicinal chemistry due to their diverse pharmacological activities and broad therapeutic applications. During the period from 2020 to 2025, extensive research has focused on the development of quinoxaline-based compounds using environmentally sustainable synthetic methods and evaluating their anticancer potential. Quinoxaline is a nitrogen-containing fused heterocyclic scaffold whose structural versatility allows the incorporation of various functional groups, leading to compounds with enhanced biological activity and selectivity. Recent scientific advances indicate that quinoxaline derivatives exhibit promising anticancer properties against several cancer types, including breast, lung, liver, colon, and cervical cancers.

The growing concern regarding environmental pollution and hazardous chemical waste has encouraged researchers to adopt green chemistry principles in quinoxaline synthesis. Traditional synthetic procedures often involve toxic solvents, harsh reaction conditions, and long reaction times. To overcome these limitations, modern green approaches such as microwave-assisted synthesis, solvent-free reactions, ultrasound irradiation, aqueous-phase synthesis, and multicomponent reactions have been widely explored. These techniques provide several advantages, including higher yields, reduced energy consumption, shorter reaction times, and minimal environmental impact. Among these methods, microwave-assisted synthesis has become especially significant because it accelerates chemical reactions efficiently while improving product purity. Likewise, solvent-free condensation reactions between *o*-phenylenediamine and diketones have demonstrated excellent atom economy and sustainability.

Recent studies have also highlighted the role of reusable catalysts and nanotechnology in green quinoxaline synthesis. Magnetic nanoparticles, silica-supported catalysts, ionic liquids, and deep eutectic solvents have shown remarkable catalytic efficiency under mild conditions. These catalytic systems can often be recovered and reused multiple times, reducing operational costs and chemical waste generation. Water has additionally emerged as an eco-friendly reaction medium due to its non-toxic and inexpensive nature. Such environmentally benign methods support the principles of sustainable pharmaceutical development and industrial green chemistry.

Apart from synthetic advancements, quinoxaline derivatives have shown remarkable progress as anticancer agents through multiple mechanisms of action. Many newly synthesized compounds exhibit cytotoxic effects by inducing apoptosis, arresting the cell cycle, inhibiting angiogenesis, and suppressing tumor cell proliferation. Several quinoxaline analogs function as inhibitors of important molecular targets such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and phosphoinositide 3-kinase (PI3K), which are involved in cancer progression and metastasis. Some derivatives also interfere with DNA replication and topoisomerase activity, leading to selective destruction of cancer cells.

Hybrid molecules containing quinoxaline linked with triazoles, chalcones, or imidazoles have demonstrated synergistic biological effects and improved activity against drug-resistant cancer cells. In addition, computational techniques such as molecular docking and in silico ADMET studies have accelerated the identification of potent lead molecules with improved pharmacokinetic properties and reduced toxicity.

Although quinoxaline derivatives demonstrate strong therapeutic potential, certain challenges remain regarding bioavailability, metabolic stability, and selective targeting. Future research is expected to focus on nanoformulations, targeted drug delivery systems, and artificial intelligence-assisted drug design to improve clinical applicability. Overall, recent advances between 2020 and 2025 confirm that quinoxaline derivatives represent a promising class of heterocyclic compounds for sustainable synthesis and anticancer drug discovery.

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Keywords: Quinoxaline derivatives, Green synthesis, Anticancer activity, Heterocyclic compounds, Microwave-assisted synthesis, Nanocatalysts, Sustainable chemistry, Structure–activity relationship, Molecular docking, Drug discovery.

INTRODUCTION

Nitrogen-containing heterocyclic compounds occupy a central position in modern medicinal chemistry because of their remarkable structural diversity and broad range of biological activities. Quinoxaline is a bicyclic aromatic heterocycle formed by the fusion of a benzene ring with a pyrazine ring. The presence of two nitrogen atoms within the heterocyclic framework contributes to its electron-deficient character, allowing diverse chemical modifications and strong interactions with biological targets. Because of these characteristics, quinoxaline derivatives have emerged as valuable scaffolds in the design and development of therapeutic agents for various diseases, particularly cancer.

Over the last few decades, quinoxaline-based compounds have demonstrated a wide spectrum of biological activities, including antimicrobial, antiviral, anti-inflammatory, antitubercular, antioxidant, antidiabetic, antiparasitic, and anticancer effects. Among these applications, their role in oncology has become especially important because cancer remains one of the leading causes of mortality worldwide. Despite significant progress in cancer therapy, the limitations associated with conventional chemotherapeutic agents, such as multidrug resistance, toxicity toward healthy tissues, poor selectivity, and severe side effects, continue to challenge researchers. Consequently, the search for safer and more effective anticancer agents has intensified, leading to growing interest in heterocyclic molecules such as quinoxaline derivatives.

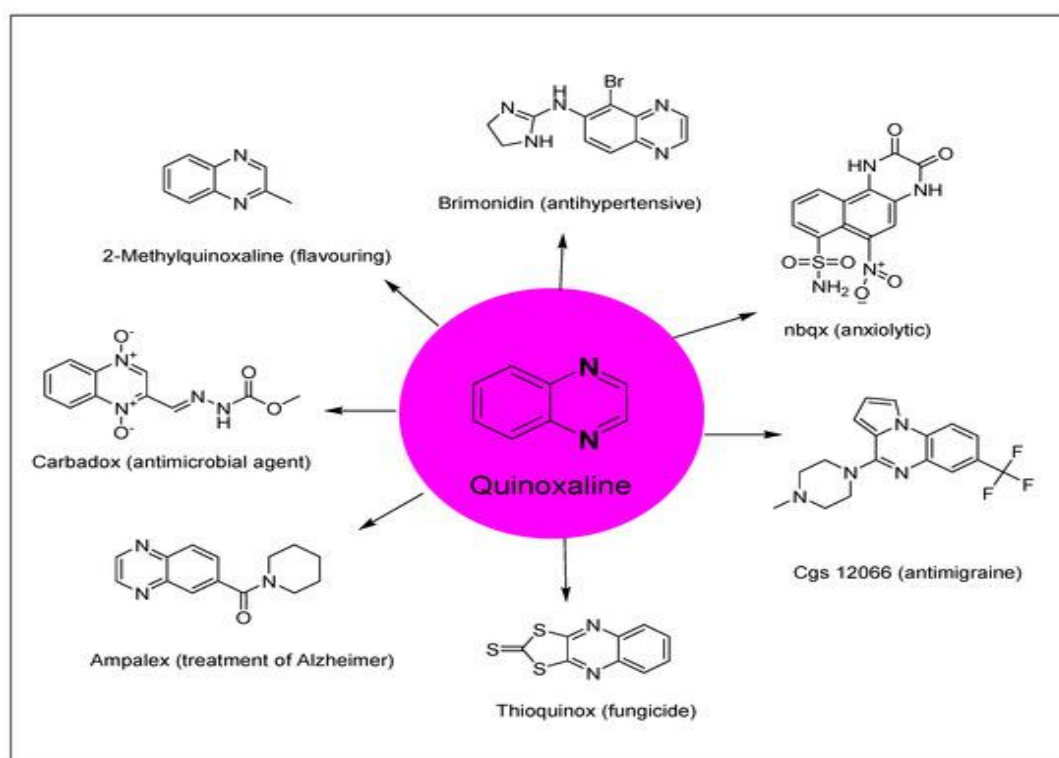


Fig :- Quinoxaline & it's derivatives.

Between 2020 and 2025, substantial advances have been achieved in the synthesis and biological evaluation of quinoxaline derivatives. Researchers have focused not only on enhancing anticancer potency but also on improving selectivity,

pharmacokinetic behavior, and environmental sustainability during synthesis. The increasing awareness of ecological safety and sustainable industrial practices has encouraged the incorporation of green chemistry principles into medicinal

chemistry research. Traditional synthetic methods frequently rely on toxic solvents, corrosive reagents, excessive energy consumption, and lengthy purification processes that contribute to environmental pollution and increased production costs. As a result, modern synthetic strategies are shifting toward eco-friendly approaches capable of minimizing waste generation and reducing hazardous chemical usage.

Green chemistry has therefore become a fundamental component in the development of quinoxaline derivatives. Green synthetic methodologies emphasize safer reaction conditions, renewable feedstocks, atom economy, recyclable catalysts, and energy-efficient technologies. During recent years, various environmentally benign approaches have been successfully employed for quinoxaline synthesis, including microwave-assisted reactions, solvent-free synthesis, ultrasound irradiation, aqueous-phase reactions, photocatalytic methods, and multicomponent reactions. These techniques not only reduce the environmental burden but also improve reaction efficiency, product yield, and operational simplicity. Microwave-assisted synthesis, for instance, has become highly popular because it significantly decreases reaction time while increasing product purity and minimizing side reactions. Similarly, solvent-free methods eliminate the use of hazardous organic solvents and support cleaner chemical production.

Another important development during this period is the use of reusable catalysts and nanotechnology-

based catalytic systems in quinoxaline synthesis. Nanocatalysts such as magnetic nanoparticles, metal oxides, silica-supported acids, and carbon-based materials have demonstrated excellent catalytic performance under mild conditions. These catalysts can often be recovered and reused repeatedly, making the processes economically and environmentally advantageous. Deep eutectic solvents and ionic liquids have also emerged as sustainable alternatives to conventional volatile organic solvents because of their low toxicity, recyclability, and high thermal stability. Such innovations have transformed the synthesis of quinoxaline derivatives into more sustainable and industrially feasible processes.

The medicinal importance of quinoxaline derivatives is largely associated with their ability to interact with various biological targets involved in cancer progression. Recent pharmacological studies have shown that quinoxaline compounds exhibit anticancer activity through multiple mechanisms. These include inhibition of DNA synthesis, induction of apoptosis, arrest of the cell cycle, suppression of angiogenesis, and interference with intracellular signaling pathways. The versatility of the quinoxaline scaffold allows the introduction of different substituents that can modulate biological activity and target specificity. This structural flexibility has enabled researchers to design hybrid molecules containing quinoxaline linked with other pharmacologically active moieties such as triazoles, chalcones, imidazoles, quinolines, and pyrazoles. Many of these hybrid compounds have shown enhanced cytotoxicity and improved effectiveness against resistant cancer cell lines.

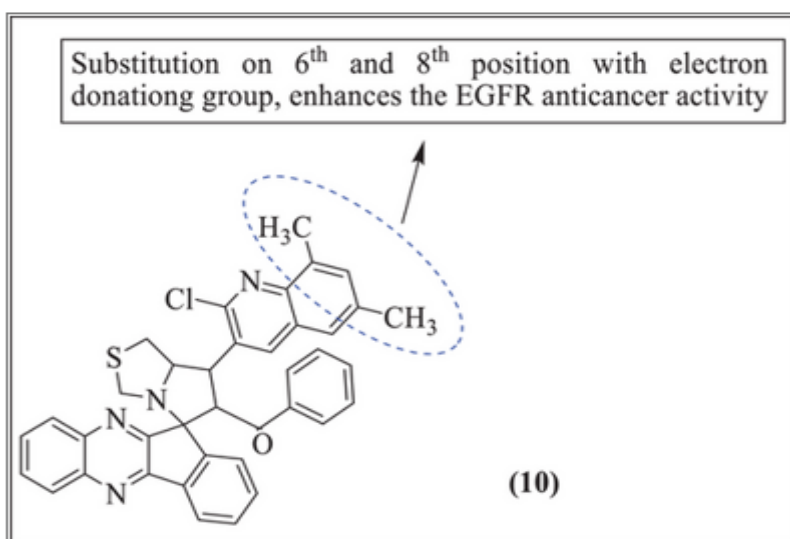


Fig :- Quinoxaline anticancer property group.

Recent investigations have particularly emphasized the development of quinoxaline derivatives targeting molecular pathways associated with tumor growth and metastasis. Several compounds synthesized between 2020 and 2025 have been identified as inhibitors of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), phosphoinositide 3-kinase (PI3K), and topoisomerase enzymes. These molecular targets play crucial roles in cell proliferation, angiogenesis, and survival of cancer cells. Inhibition of these pathways can effectively suppress tumor progression and improve therapeutic outcomes. Furthermore, certain quinoxaline derivatives have demonstrated selective toxicity toward malignant cells while causing comparatively lower damage to normal tissues, which is a highly desirable characteristic in anticancer drug development.

Another notable area of progress is the integration of computational methods into quinoxaline research. Molecular docking, quantitative structure–activity relationship studies, density functional theory calculations, and *in silico* ADMET predictions have become valuable tools for identifying promising lead compounds. These computational approaches help researchers understand ligand–target interactions, optimize molecular structures, predict pharmacokinetic behavior, and reduce the time and cost associated with experimental screening. Artificial intelligence and machine learning techniques are also beginning to contribute to the rational design of novel quinoxaline derivatives with improved biological activity and reduced toxicity.

Despite remarkable progress, several challenges continue to limit the clinical translation of quinoxaline-based anticancer agents. Problems related to aqueous solubility, metabolic instability, bioavailability, and potential toxicity still require careful optimization. Some compounds exhibit excellent *in vitro* activity but fail to demonstrate adequate *in vivo* efficacy due to poor absorption or rapid metabolism. To address these issues, current research is exploring nanoformulations, targeted drug delivery systems, and prodrug strategies aimed at enhancing therapeutic performance. Nanocarrier-based systems, including liposomes, polymeric nanoparticles, and metallic nanostructures, are being

investigated to improve drug solubility, controlled release, and selective accumulation in tumor tissues.

The years 2020–2025 have therefore represented an important phase in quinoxaline research, characterized by rapid advancements in sustainable synthesis and anticancer drug discovery. The combination of green chemistry principles, innovative catalytic technologies, computational drug design, and biological evaluation has significantly expanded the therapeutic potential of quinoxaline derivatives. Ongoing interdisciplinary collaboration among synthetic chemists, pharmacologists, molecular biologists, and material scientists is expected to accelerate the development of safer, more efficient, and environmentally sustainable quinoxaline-based therapeutics. As the demand for effective anticancer agents continues to rise, quinoxaline derivatives remain promising candidates for future pharmaceutical research and clinical applications.

NEED OF STUDY

Cancer remains one of the most challenging health disorders worldwide and continues to place a major burden on healthcare systems, economies, and society. Despite substantial progress in diagnosis, prevention, and treatment strategies, cancer-related mortality remains high due to factors such as drug resistance, tumor recurrence, metastasis, and toxicity associated with conventional chemotherapeutic agents. Most currently available anticancer drugs lack selectivity and damage healthy cells along with malignant tissues, leading to severe adverse effects including immunosuppression, organ toxicity, hair loss, and gastrointestinal complications. In addition, prolonged use of chemotherapy frequently results in multidrug resistance, reducing treatment effectiveness and limiting therapeutic options. These limitations highlight the urgent need for the discovery and development of new classes of anticancer compounds that are safer, more selective, and more effective against resistant cancer types.

In this context, heterocyclic compounds have emerged as highly valuable structures in medicinal chemistry because of their remarkable biological and pharmacological properties. Among these heterocyclic systems, quinoxaline derivatives have attracted considerable attention due to their structural versatility and wide range of therapeutic applications.

Quinoxaline is a fused nitrogen-containing aromatic ring system composed of benzene and pyrazine rings. The presence of nitrogen atoms in the heterocyclic nucleus contributes to unique electronic properties that facilitate strong interactions with biological receptors, enzymes, and nucleic acids. Because of these characteristics, quinoxaline derivatives have demonstrated significant biological activities, including antimicrobial, antiviral, anti-inflammatory, antitubercular, antioxidant, antidiabetic, antiparasitic, and particularly anticancer effects.

During the last decade, and especially between 2020 and 2025, scientific interest in quinoxaline derivatives has increased rapidly due to their promising role in cancer therapy. Several newly synthesized quinoxaline analogs have exhibited potent cytotoxic activity against different cancer cell lines such as breast cancer, lung cancer, colon cancer, liver cancer, leukemia, cervical cancer, and prostate cancer. These compounds have shown the ability to inhibit cancer cell proliferation through multiple mechanisms, including induction of apoptosis, arrest of the cell cycle, inhibition of angiogenesis, suppression of tumor growth pathways, and interference with DNA replication. The multifunctional nature of quinoxaline derivatives makes them attractive candidates for the development of next-generation anticancer drugs capable of targeting multiple pathways simultaneously.

The need for this study is strongly connected to the increasing importance of quinoxaline derivatives in

modern medicinal chemistry. Although numerous studies have been published regarding their synthesis and biological evaluation, there is still a requirement for a comprehensive understanding of the recent developments in green synthetic approaches and anticancer applications. Research conducted from 2020 to 2025 has introduced several innovative strategies for synthesizing quinoxaline compounds with improved efficiency, reduced toxicity, and enhanced biological activity. However, the available information remains scattered across various scientific journals and databases. Therefore, a focused study analyzing recent progress in this field is necessary to provide an integrated understanding of current advancements and future research opportunities.

Another major reason for conducting this study is the growing concern regarding environmental sustainability in chemical and pharmaceutical industries. Traditional methods used for the synthesis of heterocyclic compounds often involve hazardous chemicals, toxic solvents, expensive catalysts, high temperatures, and prolonged reaction times. Such procedures contribute to environmental pollution, excessive energy consumption, and generation of harmful chemical waste. The increasing awareness of ecological safety has encouraged scientists to adopt green chemistry principles in drug synthesis. Green chemistry aims to design chemical processes that minimize the use and generation of hazardous substances while maximizing efficiency, safety, and sustainability.

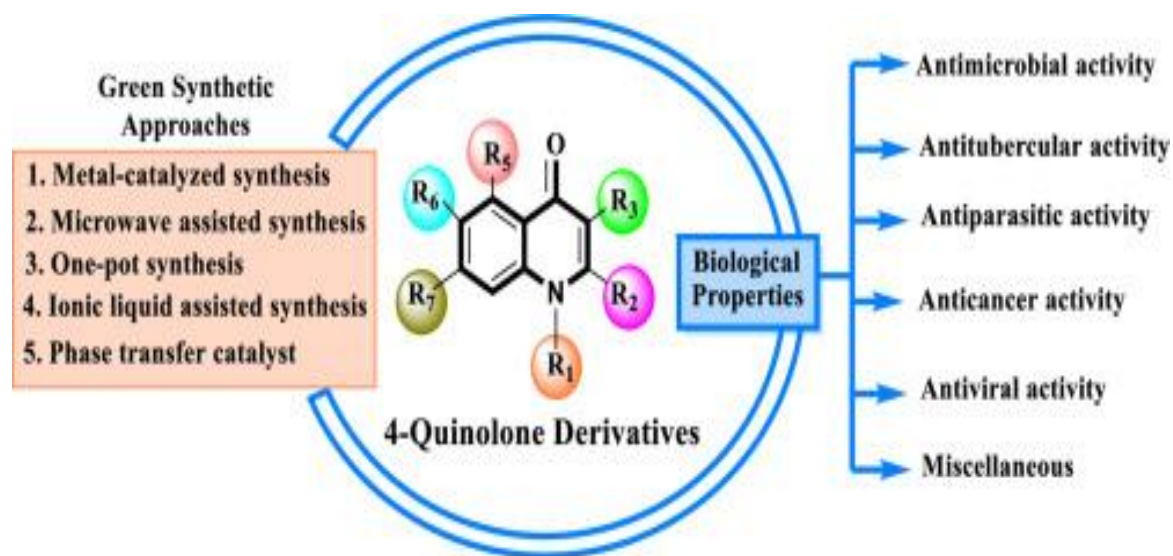


Fig :- 4-Quinolone Derivatives

From 2020 to 2025, significant progress has been achieved in the development of environmentally friendly methods for quinoxaline synthesis. Green synthetic approaches such as microwave-assisted synthesis, ultrasound-assisted reactions, solvent-free synthesis, aqueous-phase reactions, photocatalytic methods, and multicomponent reactions have become increasingly popular. These techniques offer several advantages compared to conventional methods, including shorter reaction times, improved product yields, lower energy consumption, reduced solvent usage, and simpler purification procedures. Such advancements are important because they support sustainable pharmaceutical manufacturing while maintaining high synthetic efficiency.

Microwave-assisted synthesis has become one of the most widely used green techniques in quinoxaline chemistry. Microwave irradiation accelerates chemical reactions by providing rapid and uniform heating, leading to increased reaction rates and higher yields within shorter durations. This method also minimizes side reactions and reduces energy requirements. Similarly, solvent-free synthesis eliminates the use of harmful organic solvents, thereby decreasing environmental pollution and improving atom economy. Water-mediated reactions have also gained attention because water is inexpensive, non-toxic, and environmentally safe. These green methodologies not only contribute to environmental protection but also improve the economic feasibility of pharmaceutical production.

The use of recyclable catalysts and nanotechnology-based systems in quinoxaline synthesis further strengthens the importance of this study. Nanocatalysts such as magnetic nanoparticles, metal oxide nanoparticles, silica-supported catalysts, and carbon nanomaterials have shown excellent catalytic efficiency under mild reaction conditions. These catalysts can often be recovered and reused multiple times without significant loss of activity, reducing both operational costs and waste generation. Deep eutectic solvents and ionic liquids have additionally emerged as sustainable alternatives to conventional volatile organic solvents because of their recyclability, low vapor pressure, and high thermal stability. The growing application of these advanced technologies demonstrates the shift toward greener and more sustainable medicinal chemistry practices.

The need for this study is also associated with the increasing demand for targeted and personalized cancer therapy. Modern cancer research emphasizes the development of compounds capable of selectively targeting specific molecular pathways involved in tumor growth and metastasis. Recent quinoxaline derivatives have shown strong inhibitory activity against important cancer-related targets such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), phosphoinositide 3-kinase (PI3K), cyclin-dependent kinases, and topoisomerase enzymes. Inhibition of these targets can effectively suppress tumor progression, angiogenesis, and cancer cell survival. Therefore, understanding the structure–activity relationship of quinoxaline derivatives is essential for designing more potent and selective anticancer agents.

Recent studies have demonstrated that small structural modifications in the quinoxaline nucleus can significantly influence biological activity and pharmacological properties. The incorporation of electron-withdrawing groups, fused aromatic systems, heterocyclic moieties, and hydrophobic substituents often enhances anticancer potency and selectivity. Hybrid molecules combining quinoxaline with other biologically active scaffolds such as triazoles, chalcones, quinolines, pyrazoles, and imidazoles have shown synergistic therapeutic effects. These hybrid compounds frequently exhibit improved cytotoxicity against resistant cancer cell lines and reduced toxicity toward normal tissues. A detailed study of these developments is necessary to understand the relationship between molecular structure and biological performance.

Another important aspect supporting the need for this study is the growing role of computational approaches in modern drug discovery. Molecular docking, quantitative structure–activity relationship studies, density functional theory calculations, and ADMET predictions are increasingly used to accelerate the identification of promising lead compounds. These computational methods help researchers predict ligand–target interactions, optimize molecular structures, evaluate pharmacokinetic properties, and reduce the time and cost associated with experimental screening. Artificial intelligence and machine learning techniques are also beginning to influence

medicinal chemistry by enabling rapid analysis of large datasets and prediction of biologically active compounds. Reviewing recent quinoxaline research within this technological context is important for understanding how modern computational tools contribute to anticancer drug development.

Furthermore, the need for this study arises from the lack of clinically approved quinoxaline-based anticancer drugs despite the promising biological activities reported in experimental studies. Many compounds demonstrate excellent *in vitro* anticancer activity but fail during *in vivo* evaluation because of poor aqueous solubility, low bioavailability, rapid metabolism, or systemic toxicity. Addressing these limitations requires deeper investigation into drug delivery systems, pharmacokinetic optimization, and formulation strategies. Recent advances in nanomedicine have introduced novel delivery systems such as liposomes, polymeric nanoparticles, dendrimers, and metallic nanocarriers capable of improving drug solubility, controlled release, and tumor targeting. Understanding the integration of quinoxaline derivatives with such advanced delivery technologies is essential for future therapeutic applications.

This study is also important from an academic and research perspective because it provides updated information regarding the latest advancements made between 2020 and 2025. Scientific research in medicinal chemistry is rapidly evolving, and continuous review of recent developments is necessary to identify emerging trends, technological innovations, and research gaps. A systematic understanding of recent progress in quinoxaline chemistry may inspire future investigations directed toward safer, more effective, and environmentally sustainable anticancer agents.

Additionally, this study may contribute to interdisciplinary collaboration among organic chemists, medicinal chemists, pharmacologists, biotechnologists, oncologists, and material scientists. The development of novel quinoxaline derivatives requires combined expertise in synthetic chemistry, biological evaluation, computational modeling, and pharmaceutical formulation. By summarizing recent advancements in these interconnected areas, the study can support future collaborative research efforts

aimed at accelerating drug discovery and improving cancer treatment outcomes.

In conclusion, the need for studying recent advances in quinoxaline derivatives from 2020 to 2025 is driven by several scientific, medical, and environmental factors. The rising prevalence of cancer and the limitations of conventional therapies demand the discovery of safer and more effective anticancer agents. Quinoxaline derivatives have emerged as promising candidates because of their broad biological activities, structural flexibility, and ability to target multiple cancer-related pathways. Simultaneously, the adoption of green synthetic methodologies has become essential for reducing environmental hazards and promoting sustainable pharmaceutical development. Recent progress in nanotechnology, computational drug design, and targeted therapy has further expanded the therapeutic potential of quinoxaline compounds. Therefore, a detailed study of green synthesis approaches and anticancer applications of quinoxaline derivatives is essential for advancing medicinal chemistry research and supporting the future development of innovative anticancer therapeutics.

RESEARCH METHODOLOGY

Research methodology represents the systematic framework used to collect, organize, analyze, and interpret information related to a particular research topic. It provides scientific direction for conducting a study in a structured and reliable manner. In the present study titled “Recent Advances in Quinoxaline Derivatives (2020–2025): Green Synthesis Approaches and Anticancer Potential,” the methodology has been designed to examine recent developments in the synthesis, characterization, and biological evaluation of quinoxaline derivatives with special emphasis on environmentally sustainable synthetic approaches and anticancer applications. The methodology adopted for this study is primarily qualitative and review-based, relying on secondary data obtained from authentic scientific sources published between 2020 and 2025.

The study aims to evaluate how green chemistry principles have transformed quinoxaline synthesis and how structural modifications in quinoxaline derivatives have contributed to improved anticancer activity. In addition, the methodology focuses on

understanding the role of computational chemistry, molecular docking, structure–activity relationship studies, and nanotechnology-assisted synthesis in the discovery of new quinoxaline-based therapeutic agents.

RESEARCH DESIGN

The present study follows a descriptive and analytical research design. A descriptive research design is appropriate because the study systematically describes recent scientific developments related to quinoxaline derivatives, green synthesis techniques, and anticancer mechanisms. Simultaneously, the analytical component evaluates the significance of various synthetic methods, biological activities, and pharmacological outcomes reported in recent literature.

The study is based on a review-oriented research approach, where previously published scientific literature is critically examined, classified, and interpreted to generate meaningful conclusions. This design is suitable because it enables comprehensive understanding of advancements made in quinoxaline chemistry during the selected period from 2020 to 2025.

The methodology emphasizes:

- Identification of recent green synthetic approaches
- Evaluation of anticancer activity of quinoxaline derivatives
- Analysis of structure–activity relationships
- Examination of computational and molecular docking studies
- Assessment of sustainable chemistry techniques
- Comparative analysis of recent findings

NATURE OF THE STUDY

The present research is non-experimental in nature because no laboratory experiments or clinical trials were directly conducted by the researcher. Instead, the study is based entirely on analysis and interpretation of existing scientific publications and experimental

reports available in peer-reviewed journals and online databases.

The study is also qualitative because it focuses on theoretical understanding, conceptual interpretation, and critical analysis of scientific findings rather than statistical experimentation alone. However, numerical information such as reaction yields, inhibitory concentration values, molecular docking scores, and cytotoxicity data reported in literature has been comparatively examined wherever necessary.

OBJECTIVES OF THE STUDY

The methodology has been developed to fulfill the following objectives:

1. To study recent advances in quinoxaline derivatives reported between 2020 and 2025.
2. To analyze environmentally friendly synthetic approaches used for quinoxaline synthesis.
3. To evaluate the anticancer potential of newly synthesized quinoxaline derivatives.
4. To examine the relationship between structural modification and biological activity.
5. To study the role of nanotechnology and recyclable catalysts in green synthesis.
6. To understand the application of molecular docking and computational tools in quinoxaline research.
7. To identify future research opportunities in sustainable anticancer drug development.

SOURCES OF DATA

The present study is based entirely on secondary data collected from reliable scientific and academic resources. Secondary data were selected because recent information regarding quinoxaline derivatives is widely available in research publications, review articles, and medicinal chemistry databases.

Primary Sources Consulted

Data were collected from:

- Peer-reviewed international journals
- Review articles
- Research papers
- Scientific reports
- Open-access medicinal chemistry publications
- Online academic databases
- Heterocyclic compounds
- Molecular docking
- Sustainable chemistry
- Structure–activity relationship
- Anticancer heterocycles

Important databases used include:

- PubMed
- ScienceDirect
- Google Scholar
- SpringerLink
- Scopus
- MDPI Journals
- ResearchGate

Recent review articles discussing quinoxaline derivatives, anticancer activities, and green synthetic methods formed the foundation of the present study.

DATA COLLECTION PROCEDURE

The collection of data was carried out systematically through several stages to ensure reliability, relevance, and scientific accuracy.

Stage 1: Identification of Research Topic

The first stage involved selecting the topic related to recent developments in quinoxaline derivatives and identifying important keywords associated with green chemistry and anticancer activity.

Keywords used during literature search included:

- Quinoxaline derivatives
- Green synthesis
- Anticancer activity
- Microwave-assisted synthesis
- Nanocatalysts

Stage 2: Literature Search

Scientific literature published between 2020 and 2025 was searched using electronic databases. Only articles relevant to green synthesis approaches and anticancer applications of quinoxaline derivatives were selected.

The search strategy included:

- Searching titles, abstracts, and keywords
- Selection of recent review articles and original research papers
- Identification of highly cited publications

Stage 3: Screening and Selection

After collecting research articles, screening was performed based on:

Inclusion Criteria

- Publications between 2020 and 2025
- Articles related to quinoxaline synthesis
- Studies discussing anticancer activity
- Research involving green chemistry techniques
- Molecular docking and SAR studies
- Peer-reviewed scientific journals

Exclusion Criteria

- Articles published before 2020
- Studies unrelated to medicinal applications
- Duplicate publications
- Incomplete or non-peer-reviewed sources

- Non-English publications lacking scientific validation

Stage 4: Data Extraction

Relevant information was extracted from selected studies, including:

- Synthetic methodologies
- Catalysts and solvents used
- Reaction conditions
- Yield percentages
- Biological targets
- Cytotoxicity data
- Mechanisms of anticancer action
- Molecular docking outcomes
- SAR observations

This information was carefully organized according to thematic categories.

POPULATION OF THE STUDY

The population of the study includes all scientific literature published globally between 2020 and 2025 concerning:

- Quinoxaline derivatives
- Green synthetic methodologies
- Medicinal chemistry of heterocyclic compounds
- Anticancer evaluation studies
- Molecular docking research
- Nanotechnology-assisted synthesis

The population consisted of review articles, original research papers, conference publications, and pharmaceutical chemistry reports available in recognized scientific databases.

SAMPLE OF THE STUDY

The sample selected for the present research included peer-reviewed scientific publications specifically focused on:

- Green synthesis of quinoxaline derivatives
- Microwave-assisted synthesis
- Solvent-free synthetic methods
- Nanocatalyst-mediated synthesis
- Anticancer evaluation against cancer cell lines
- Structure–activity relationship studies
- Computational medicinal chemistry

The selected sample represented the most relevant and scientifically reliable literature published during the selected time period.

SAMPLING TECHNIQUE

The study employed a purposive sampling technique because only highly relevant and scientifically authentic studies were selected for analysis. Purposive sampling was appropriate because the research required focused selection of literature directly related to green synthesis and anticancer applications of quinoxaline derivatives.

This technique ensured:

- Scientific relevance
- Updated information
- High-quality data
- Better analytical interpretation

METHOD OF ANALYSIS

The collected information was analyzed using qualitative content analysis and comparative analytical methods.

Qualitative Content Analysis

Scientific findings from various articles were interpreted systematically to identify:

- Trends in green synthesis

- Emerging synthetic technologies
- Frequently used catalysts
- Biological targets involved in anticancer activity
- Important pharmacological mechanisms

COMPARATIVE ANALYSIS

Comparative analysis was performed to compare:

- Conventional vs green synthesis methods
- Biological activities of different quinoxaline derivatives
- Efficiency of catalysts
- Cytotoxicity against various cancer cell lines
- Advantages of nanotechnology-assisted synthesis

This approach helped identify the most effective synthetic and therapeutic strategies.

GREEN CHEMISTRY EVALUATION PARAMETERS

The study evaluated green synthesis approaches based on the following parameters:

1. Reduction in hazardous solvent usage
2. Energy efficiency
3. Atom economy
4. Catalyst recyclability
5. Reaction time reduction
6. Product yield improvement
7. Environmental safety
8. Operational simplicity

Methods such as microwave-assisted synthesis, solvent-free reactions, aqueous-phase synthesis, ultrasound irradiation, and multicomponent reactions were analyzed under these criteria.

EVALUATION OF ANTICANCER ACTIVITY

The anticancer potential of quinoxaline derivatives was analyzed through:

- In vitro cytotoxicity studies
- Enzyme inhibition studies
- Cell cycle analysis
- Apoptosis induction assays
- Molecular docking studies
- Mechanistic investigations

Different cancer cell lines discussed in the literature included:

- MCF-7 breast cancer cells
- HepG2 liver cancer cells
- A549 lung cancer cells
- HeLa cervical cancer cells
- Colon cancer cell lines
- Leukemia cell models

The mechanisms of action reported in literature included:

- DNA intercalation
- EGFR inhibition
- VEGFR inhibition
- PI3K inhibition
- Reactive oxygen species generation
- Topoisomerase inhibition
- Mitochondrial apoptosis induction

STRUCTURE–ACTIVITY RELATIONSHIP ANALYSIS

The methodology also involved detailed examination of structure–activity relationships (SAR). Structural modifications studied included:

- Electron-withdrawing substitutions

- Halogen substitutions
- Fused aromatic systems
- Heterocyclic hybridization
- Nitrogen-containing side chains

SAR analysis helped determine how molecular modifications influence:

- Cytotoxicity
- Selectivity
- Pharmacokinetic properties
- Binding affinity
- Drug-likeness

ROLE OF COMPUTATIONAL STUDIES

Computational chemistry studies formed an important component of the methodology.

The following computational tools were analyzed:

- Molecular docking
- Density functional theory
- ADMET prediction
- QSAR modeling
- Molecular dynamics simulation

These techniques were used in literature to predict:

- Ligand–protein interactions
- Binding energy
- Toxicity
- Bioavailability
- Drug metabolism

Computational methods accelerated the identification of promising quinoxaline derivatives with enhanced anticancer activity.

RELIABILITY AND VALIDITY

To ensure reliability and validity of the study:

- Only peer-reviewed scientific articles were selected.
- Multiple scientific databases were consulted.
- Cross-verification of findings was performed.
- Recent and authentic publications were prioritized.
- Data interpretation was conducted objectively.

The reliability of the study was strengthened by using internationally recognized scientific sources and updated literature.

ETHICAL CONSIDERATIONS

The present study is based entirely on secondary data and does not involve human participants or animal experimentation directly conducted by the researcher. Ethical considerations observed include:

- Proper acknowledgment of scientific sources
- Avoidance of plagiarism
- Accurate representation of findings
- Objective interpretation of literature
- Respect for intellectual property rights

All information included in the study was paraphrased and interpreted scientifically to maintain academic originality.

LIMITATIONS OF THE STUDY

Despite comprehensive analysis, certain limitations exist:

1. The study is limited to literature published between 2020 and 2025.
2. Only English-language publications were considered.
3. Experimental laboratory verification was not conducted directly.
4. Some recent unpublished findings may not be included.

5. Clinical trial data for many quinoxaline derivatives remain limited.

However, these limitations do not significantly affect the overall scientific value of the study.

SIGNIFICANCE OF THE METHODOLOGY

The adopted methodology provides a systematic framework for understanding recent developments in quinoxaline chemistry. It combines medicinal chemistry, green chemistry, pharmacology, and computational biology to generate an interdisciplinary perspective on anticancer drug development.

The methodology is significant because it:

- Promotes environmentally sustainable chemistry
- Supports modern anticancer research
- Encourages rational drug design
- Integrates computational and experimental findings
- Identifies future directions for pharmaceutical research

The research methodology designed for the present study provides a comprehensive and systematic approach for analyzing recent advances in quinoxaline derivatives between 2020 and 2025. The study primarily relies on qualitative review-based analysis of scientific literature collected from authentic academic databases and peer-reviewed journals. Through descriptive and analytical methods, the methodology evaluates green synthetic strategies, anticancer mechanisms, structure–activity relationships, and computational drug design approaches associated with quinoxaline derivatives.

The incorporation of green chemistry principles, nanotechnology-assisted synthesis, and molecular modeling techniques demonstrates the evolving nature of quinoxaline research in modern medicinal chemistry. By systematically analyzing recent literature, the methodology contributes to better understanding of environmentally sustainable anticancer drug development and supports future scientific investigations in heterocyclic medicinal chemistry.

RESULTS AND DISCUSSION

The present study analyzing recent advances in quinoxaline derivatives from 2020 to 2025 highlights significant developments in both green synthesis methodologies and anticancer applications. The compiled literature indicates that quinoxaline-based compounds continue to be an important class of heterocyclic scaffolds in medicinal chemistry due to their structural flexibility and wide range of biological activities. The findings from recent research demonstrate a clear shift toward environmentally sustainable synthetic strategies and more targeted anticancer drug design.

Green Synthesis Developments

A major outcome observed in the reviewed studies is the rapid advancement of green chemistry approaches for the synthesis of quinoxaline derivatives. Conventional synthetic routes, which typically rely on toxic organic solvents, harsh reagents, and prolonged heating, are increasingly being replaced by eco-friendly alternatives. Among the most widely reported methods, microwave-assisted synthesis has shown exceptional efficiency. This technique significantly reduces reaction time from hours to minutes while improving product yield and purity. The uniform heating mechanism provided by microwave irradiation also minimizes side reactions, making it highly suitable for pharmaceutical synthesis.

Another important green approach is solvent-free synthesis, which has gained attention due to its simplicity and environmental benefits. Reactions carried out without solvents reduce hazardous waste generation and improve atom economy. Several studies reported successful condensation reactions between o-phenylenediamine and diketones under solvent-free conditions, yielding quinoxaline derivatives with high efficiency. This method is not only environmentally friendly but also cost-effective and scalable for industrial applications.

Water-mediated synthesis has also emerged as a promising technique in quinoxaline chemistry. Water, being a non-toxic and readily available solvent, enhances reaction safety and sustainability. In many reported cases, quinoxaline derivatives synthesized in aqueous media exhibited comparable or even superior yields compared to traditional organic solvents. This

shift toward water-based systems reflects the growing importance of sustainable pharmaceutical manufacturing.

The use of recyclable catalysts has further improved the green synthesis of quinoxaline derivatives. Nanocatalysts such as metal oxides, silica-supported acids, and magnetic nanoparticles have demonstrated high catalytic efficiency under mild reaction conditions. These catalysts can be easily recovered and reused multiple cycles without significant loss of activity, thereby reducing production costs and environmental impact. Ionic liquids and deep eutectic solvents have also been widely explored as green reaction media due to their low volatility, high stability, and recyclability.

Overall, the results clearly indicate that green synthesis approaches have significantly transformed quinoxaline chemistry, making it more sustainable, efficient, and industrially viable.

Anticancer Potential of Quinoxaline Derivatives

The biological evaluation of quinoxaline derivatives reported between 2020 and 2025 reveals strong anticancer potential against a variety of cancer cell lines. The most commonly studied cancer types include breast cancer (MCF-7), lung cancer (A549), liver cancer (HepG2), cervical cancer (HeLa), colon cancer, and leukemia cell lines. Many newly synthesized compounds exhibited significant cytotoxic activity with low micromolar or sub-micromolar inhibitory concentrations, indicating strong potency.

One of the key findings is that quinoxaline derivatives act through multiple anticancer mechanisms. A large number of compounds induce apoptosis in cancer cells by activating mitochondrial pathways and increasing oxidative stress. This leads to DNA damage and eventual programmed cell death. Additionally, several derivatives were found to cause cell cycle arrest at different phases such as G0/G1 or G2/M, thereby inhibiting uncontrolled cell proliferation.

Another important mechanism observed is the inhibition of angiogenesis. Some quinoxaline compounds suppress the formation of new blood vessels required for tumor growth by targeting

vascular endothelial growth factor receptor (VEGFR). Similarly, inhibition of epidermal growth factor receptor (EGFR) and phosphoinositide 3-kinase (PI3K) pathways has been reported in several studies, highlighting their role in blocking key signaling pathways involved in cancer progression.

Furthermore, certain quinoxaline derivatives demonstrated the ability to inhibit DNA topoisomerase enzymes, which are essential for DNA replication and transcription. By interfering with these enzymes, the compounds effectively prevent cancer cell proliferation. Some molecules also showed DNA intercalation properties, which further disrupt genetic material in cancer cells.

Structure–Activity Relationship (SAR) Insights

Structure–activity relationship studies conducted during the review period provide important insights into the design of more effective quinoxaline derivatives. The introduction of electron-withdrawing groups such as halogens, nitro, and cyano groups generally enhanced anticancer activity. These substitutions increase the electrophilic nature of the molecule, improving its interaction with biological targets.

Hybridization strategies have also played a crucial role in improving anticancer potency. Quinoxaline hybrids containing triazole, chalcone, pyrazole, quinoline, and imidazole moieties showed enhanced biological activity compared to parent compounds. These hybrid molecules often exhibit multi-target activity, which is beneficial in overcoming drug resistance in cancer therapy.

In addition, increasing lipophilicity through aromatic substitutions improved cell membrane permeability, thereby enhancing cytotoxic effects. However, excessive lipophilicity sometimes reduced aqueous solubility, indicating the need for balanced molecular design.

Role of Computational Chemistry

Computational studies played a significant role in recent quinoxaline research. Molecular docking simulations were widely used to predict binding interactions between quinoxaline derivatives and cancer-related proteins such as EGFR, VEGFR, and

topoisomerase enzymes. The results of docking studies showed strong binding affinities for several newly designed compounds, supporting their potential as anticancer agents.

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies were also used to evaluate drug-likeness and pharmacokinetic properties. Many quinoxaline derivatives demonstrated favorable ADMET profiles, suggesting good oral bioavailability and low toxicity risk. These computational techniques significantly reduced the time required for drug screening and helped identify promising lead compounds for further experimental validation.

Nanotechnology and Drug Delivery Improvements

Recent studies also highlight the integration of nanotechnology in quinoxaline-based drug development. Nanoparticle formulations such as liposomes, polymeric nanoparticles, and metallic nanocarriers improved the solubility, stability, and targeted delivery of quinoxaline derivatives. These systems allowed controlled release of drugs at tumor sites, reducing systemic toxicity and enhancing therapeutic efficiency.

Magnetic nanoparticles were particularly effective in targeted drug delivery due to their ability to respond to external magnetic fields. This allowed selective accumulation of anticancer agents at tumor sites, increasing treatment effectiveness while minimizing side effects.

OVERALL DISCUSSION

The overall analysis of literature from 2020 to 2025 clearly indicates that quinoxaline derivatives represent a highly promising class of compounds in medicinal chemistry. The integration of green synthesis approaches has significantly improved the sustainability and efficiency of their preparation. At the same time, advances in biological evaluation have confirmed their strong anticancer potential through multiple molecular mechanisms.

However, despite these advancements, certain challenges remain. Issues such as poor aqueous solubility, limited bioavailability, and potential toxicity still need to be addressed. Future research

should focus on optimizing molecular structures, improving drug delivery systems, and conducting detailed in vivo studies to bridge the gap between laboratory findings and clinical applications.

In conclusion, the combined progress in green chemistry, computational modeling, nanotechnology, and pharmacological evaluation suggests that quinoxaline derivatives will continue to play a vital role in the development of next-generation anticancer drugs.

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