

# QUINOXALINE-CENTRED HETEROCYCLES IN ANTICANCER DRUG DISCOVERY: RECENT TRENDS AND FUTURE DIRECTIONS

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## ABSTRACT

Cancer has grown as the life-threatening diseases worldwide, surpassing many other disorders due to its increasing incidence and aggressive progression. The continuous rise in drug resistance and uncontrolled cellular proliferation has intensified the need for the establishment of newer and effective therapeutic agents. In this context, synthetic and medicinal chemistry play a major role in identifying novel bioactive scaffolds for cancer treatment. Among various heterocyclic systems, quinoxaline derivatives have extensively explored because of their broad spectrum of biological and pharmacological activities, making them valuable candidates in modern drug discovery. Therefore, this review focuses on recent synthetic approaches for the preparation of functionalized quinoxaline analogues and discusses their potential applications in anticancer drug development. More than 35 million cancer cases will be detected by 2050. The present review highlights the significance of the quinoxaline scaffold as a versatile and privileged heterocyclic system with considerable potential in anticancer drug development. The structural flexibility of the quinoxaline nucleus enables extensive chemical modifications, facilitating the design of molecules with enhanced potency, selectivity, and favourable pharmacokinetic properties. The incorporation of quinoxaline into hybrid molecular architectures and target-directed drug design strategies has further expanded its therapeutic potential in oncology. These findings underscore the importance of quinoxaline-based compounds as valuable leads for the discovery of next-generation anticancer agents.

**KEYWORDS:** Quinoxaline, anticancer activity, scaffold, pharmacokinetic, target directed drug design

## INTRODUCTION

Cancer is a major determinant of death worldwide and poses a significant global health concern, mainly in developing countries where a large proportion of cancer-related mortality occurs<sup>1</sup>. The global impact of cancer continues to rise, with projections indicating a substantial increase in cancer-associated deaths in the coming years<sup>1,2</sup>. At the molecular level, cancer develops primarily due to genetic mutations that change the normal DNA function, following to uncontrolled cell growth and proliferation. These abnormal cells can affect neighbouring tissues and eventually spread to distant organs through metastasis<sup>2,3</sup>.

The greatest obstacles in successful cancer treatment are the creation of multidrug resistance (MDR), which significantly reduces the effectiveness of existing chemotherapeutic agents. The increasing incidence of resistance to currently available anticancer drugs has intensified the search for new bioactive molecules with improved therapeutic potential<sup>4,5</sup>. Abnormal cell proliferation culminates in the formation of tumours, which may be benign or malignant. While benign tumours generally remain localized, malignant tumours are cancerous and require effective therapeutic intervention to prevent disease progression<sup>5,6</sup>.

Among the various heterocyclic scaffolds investigated for anticancer drug development, imidazoquinoxalines have gained recognition owing to their promising biological activities. Their anticancer activity is associated with modulation of key signalling pathways, including triggering of the p38MAPK pathway and suppression of the PI3K pathway, leading to altered tumour cell persistence and proliferation<sup>4,5</sup>. Additionally, thymidine kinase 1 (TK1) and thymidine phosphorylase (TYMP) have developed as important molecular targets in cancer therapy. Compounds like thymidine–quinoxaline conjugates have demonstrated remarkable antiproliferative activity through the regulation of cytosolic thymidine metabolic pathways<sup>7</sup>.

Given the growing impact of cancer worldwide, extensive research efforts have focused on the synthesis and evaluation of nitrogen-containing heterocyclic compounds as potential anticancer agents<sup>7</sup>. Several clinically proven anticancer drugs contain heterocyclic frameworks, including benzimidazole-, quinazoline-, pyrimidine-, and quinoline-based derivatives<sup>8,9</sup>. These compounds have played a crucial role in modern chemotherapy and continue to inspire the establishment of new therapeutic candidates<sup>9,10</sup>.

Heterocyclic compounds are the extensively studied classes of molecules in organic and medicinal chemistry. They form the structural core of numerous biologically active natural products, secondary metabolites, and nucleic acid components. Among them, quinoxaline, a member of the benzodiazine family, possesses nitrogen atoms at the 1 and 4 positions of its fused heterocyclic ring system. Recent studies have highlighted quinoxaline as a privileged scaffold due to its versatile chemical properties, broad applications in materials science, and diverse pharmacological activities. These attributes make quinoxaline an attractive platform for the generation and evaluation of novel anticancer agents. Consequently, a comprehensive review of quinoxaline-based compounds may enhance our understanding of their therapeutic potential and facilitate the discovery of future anticancer drug candidates<sup>8,11,12</sup>.

## PHYSICAL PROPERTIES OF QUINOXALINE

Quinoxaline, also known as 1,4-benzodiazine or benzoparadiazine, is a nitrogen-containing fused heterocyclic compound with the molecular formula  $C_8H_6N_2$  and a molecular weight of 130.15 g/mol. It exists as a low-melting crystalline solid, exhibiting a melting point in the range of 29-32 °C and a boiling point of approximately 220-223 °C. The compound possesses weak basic characteristics, with a pKa value of 0.60, and is readily miscible with water. Furthermore, quinoxaline has a reported density of 1.124 g/mL at 25 °C<sup>8,9,10</sup>.

The quinoxaline scaffold is predominantly obtained through synthetic approaches and has gained considerable attention in medicinal chemistry due to its structural versatility<sup>13</sup>. The introduction of one or more phenyl groups into the quinoxaline nucleus, as well as fusion with related heterocyclic systems such as phenazine, enhances the degree of electron delocalization by increasing the number of possible resonance structures. This extended conjugation contributes significantly to the physicochemical and biological properties of quinoxaline derivatives, making them good candidates for pharmaceutical research and drug development<sup>13,14,15</sup>.

## OVERVIEW OF CANCER

Cancer is a complex and multidimensional disorder that stemming from the interplay of genetic changes and environmental influences. Exposure to carcinogenic agents present in air, water, food, industrial chemicals, and UV radiation has been recognised as a significant risk factor to cancer initiation and progression<sup>16</sup>. Such environmental factors may drive molecular alterations that compromise normal cellular homeostasis and promote malignant transformation<sup>17,18</sup>.

The majority of human cancers started from epithelial tissues, which line the external and internal surfaces of the body, particularly skin, respiratory tract, and gastrointestinal system<sup>19</sup>. Owing to their steady exposure to environmental agents and their active involvement in the metabolism of potentially harmful substances, epithelial cells are at greater risk to carcinogen-induced damage. Consequently, epithelial malignancies account for a substantial proportion of cancer cases worldwide<sup>20,21,22</sup>.

At the molecular scale, cancer development is driven by the buildup of mutations affecting genes that control regulating cell growth, division, and genomic integrity. Alterations in these critical genes impair the mechanisms that normally repair damaged DNA and eliminate dysfunctional cells<sup>23,24</sup>. As a result, abnormal cells acquire the ability to divide uncontrollably and affect normal growth-regulatory signals. Recent studies have highlighted the significance of DNA repair pathways in cancer progression. Inhibition of DNA2, a key enzyme involved in DNA replication and repair, has been shown to lower double-strand break end resection and suppress homologous recombination-mediated DNA repair<sup>25,26</sup>. Chemical inhibition of DNA2 also selectively restricts the progression of cancer cells experiencing oncogene-induced replication stress, underscoring its relevance as a therapeutic target<sup>27,28</sup>.

Not likely normal cells, which maintain tightly regulated metabolic and signalling networks, tumour cells demonstrate marked changes in metabolic reprogramming to support continuous expansion, resistance to death, and metabolic adaptation to hostile microenvironments<sup>29</sup>. These alterations enable tumour cells to evade growth suppression mechanisms and resist programmed

cell death<sup>30</sup>. Several signalling pathways play major roles in cancer progression and metastasis, including transforming growth factor-beta (TGF- $\beta$ ), Wnt/ $\beta$ -catenin, Notch, Src, and Ras signalling cascades<sup>31,32,33,34</sup>. These pathways contribute significantly to epithelial–mesenchymal transition (EMT), a cellular process through which epithelial cells acquire migratory and invasive characteristics. Transcription factors belonging to the zinc finger E-box-binding homeobox family, particularly ZEB1 and ZEB2, are recognized as important regulators of EMT and tumour dissemination<sup>35,36,37</sup>.

A defining characteristic of cancer is the loss of normal cellular differentiation accompanied by uncontrolled cell proliferation<sup>22,38</sup>. This phenomenon results from dysregulation of proteins and enzymes that govern cell-cycle progression, cellular growth, and signal transduction<sup>22,23,35</sup>. The cumulative effect of these molecular abnormalities promotes tumour initiation, progression, and metastatic spread. In addition to genetic and molecular factors, dietary interventions have emerged as promising tool for cancer prevention and management<sup>24</sup>. Recent evidence suggests that reduced protein intake may be associated with a lower incidence rate of certain cancers and improved clinical outcomes<sup>25,26</sup>. Experimental studies have demonstrated that protein restriction can block tumour growth through modulation of the mechanistic target mTOR signalling pathway, a central regulator of energy metabolism and proliferation<sup>39,40</sup>. Other mechanisms which provide anticancer effects of low-protein diets include alterations in IGF-1 signalling, amino acid metabolism, FGF21 activity, and autophagy regulation<sup>41</sup>.

The potential therapeutic value of reduced dietary protein intake has been supported by several preclinical investigations. In animal models of cancer, diets containing lower protein levels have produced substantial inhibition of tumour growth compared with isocaloric diets containing higher protein concentrations<sup>31</sup>. These findings proved that nutritional modulation may complement conventional therapeutic approaches and represent a valuable strategy for reducing tumour burden and improving cancer-related outcomes<sup>42</sup>.

## CAUSES OF CANCER

Cancer arises through a multifaceted interplay between genetic predisposition and environmental exposures. Although the molecular events leading to malignant transformation vary among cancer types, several modifiable and non-modifiable risk factors have been strongly associated with increased cancer incidence. Major contributors include tobacco usage, alcohol intake, poor dietary practices, excess body weight, inadequate physical activity, chronic infections, environmental pollutants, and inherited genetic abnormalities. Understanding these factors is needful for the establishment of effective preventive strategies and public health interventions<sup>42</sup>.

### Tobacco Use

Tobacco smoking remains the most significant preventable cause of cancer worldwide. Cigarette smoke contains thousands of chemical compounds, many of which possess carcinogenic properties capable of inducing DNA damage and genomic instability. Long-term exposure to tobacco smoke promotes the accumulation of genetic mutations, particularly in tumour suppressor genes and oncogenes that regulate cellular expansion and survival. Tobacco use is strongly associated with cancers of the mouth, larynx, lungs, oesophagus, pancreas, bladder, kidney, and several other organs<sup>43</sup>.

At the molecular level, smoking-related cancers often exhibit a high mutational burden characterized by specific DNA alterations, including G-to-T transversions and frequent mutations in the TP53 gene. Other than this increasing cancer disease, smoking has been associated with poorer prognosis, reduced treatment response, and higher cancer-related mortality among affected individuals. Smoking cessation is a most effective measures for decreasing cancer risk and optimizing long-term health outcomes<sup>44,45</sup>.

## **Alcohol Intake**

Alcohol intake is recognized as a significant modifiable determinant of cancer development. Ethanol is metabolized into acetaldehyde, a highly reactive compound capable of damaging DNA and interfering with normal cellular repair mechanisms<sup>46,47</sup>. Furthermore, alcohol usage can elevate oxidative stress, alter hormone levels, and enhance the penetration of other carcinogens into tissues<sup>43,48</sup>.

Numerous epidemiological studies have demonstrated a positive association between alcohol intake and cancers of the mouth, pharynx, larynx, oesophagus, liver, colorectum, and breast. The risk generally increases with both the quantity and duration of alcohol consumption. Combined exposure to alcohol and tobacco produces a synergistic effect, further elevating the likelihood of cancer development. Consequently, limiting alcohol intake is considered an important component of cancer control approaches<sup>49,50</sup>.

## **Dietary Factors**

Diet plays an important role in determining cancer risk. A balanced diet rich in fresh fruits, vegetables, whole grain products, and dietary fibre provides essential nutrients and bioactive compounds that protect cells against oxidative stress and chronic inflammation. In contrast, diets characterized by excessive consumption of processed foods, saturated fats, refined carbohydrates, and red or processed meats have been connected to an elevated risk of several malignancies<sup>51</sup>.

Growing evidence suggests that plant-derived phytochemicals, including flavonoids, polyphenols, and phytoestrogens, may give favourable effects through antioxidant, anti-inflammatory, and antiproliferative mechanisms<sup>52</sup>. Dietary patterns also influence metabolic parameters such as blood glucose, cholesterol, and triglyceride levels, which have been connected with the risk and progression of certain cancers, particularly breast and colorectal cancers. Therefore, dietary modification represents a practical and cost-effective approach to reducing cancer burden at the population level<sup>53,54</sup>.

## **Obesity and Excess Body Weight**

Obesity has emerged as a significant global health issue and is now recognized as a well-established determinant for multiple cancer types. Excess adipose tissue contributes to chronic low-grade inflammation, altered immune responses, insulin resistance, and dysregulated production of hormones such as insulin, estrogen, and leptin. These biological changes create a favourable environment for tumour initiation and progression<sup>53,55</sup>.

Studies have linked obesity to increased risks of breast, colorectal, endometrial, pancreatic, kidney, liver, and oesophageal cancers<sup>55</sup>. Weight gain following cancer identification has also been associated with poorer clinical outcomes in certain malignancies, whereas weight management and maintenance of a healthy BMI may contribute to improved prognosis and quality of life<sup>55,56</sup>. As obesity rates continue to rise worldwide, addressing abnormal body weight has become a major priority in cancer prevention programs<sup>57</sup>.

### **Physical Inactivity**

Regular physical activity is widely known for its protective effects against cancer and other chronic diseases. Exercise contributes to the regulation of body weight, improvement of immune function, reduction of systemic inflammation, and maintenance of hormonal balance. Individuals who engage in consistent physical activity generally exhibit a little risk of developing multiple cancer types such as breast, colorectal, and endometrial cancers<sup>58,59</sup>.

Among cancer survivors, good physical activity has been associated with increased quality of life, improved functional capacity, reduced treatment-related complications, and better overall survival. Although the precise biological mechanisms remain under investigation, reductions in circulating estrogen, insulin, and inflammatory mediators are believed to provide the needed effects of exercise on cancer outcomes<sup>58,59,60,61</sup>.

### **Inherited Genetic Factors**

While environmental and lifestyle related determinants account for a major proportion of cancer cases, inherited genetic mutations also play an important role in cancer susceptibility. Germline alterations in genes responsible for DNA repair, cell-cycle regulation, and tumour suppression can substantially increase an individual's lifetime risk of developing cancer<sup>50,62</sup>.

Familial cancer syndromes are commonly associated with mutations in genes such as BRCA1, BRCA2, TP53, APC, and mismatch repair genes involved in Lynch syndrome. Individuals carrying these mutations often develop cancer at an earlier age than those with sporadic disease<sup>63</sup>. Loss of function in tumour suppressor genes or impairments in DNA repair pathways can lead to genomic instability and uncontrolled cellular proliferation, thereby facilitating malignant transformation<sup>64</sup>.

### **Emerging Risk Factors**

Recent research has highlighted additional contributors to cancer development, including chronic infections, environmental pollution, occupational exposure to carcinogens, and prolonged exposure to ultraviolet radiation<sup>59</sup>. Human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Helicobacter pylori* are among the most widely explored biological carcinogens<sup>60,61</sup>. Furthermore, air pollution and exposure to industrial chemicals have been increasingly recognized as important factors contributing to the global cancer burden<sup>62</sup>.

In total, these details emphasize that cancer is a multifunctional disease influenced by both inherited and environmental determinants. Consequently, effective cancer prevention requires an integrated approach that combines lifestyle modification, early detection, vaccination programs, environmental protection measures, and genetic risk assessment<sup>63,64</sup>.

## FREQUENTLY DIAGNOSED CANCER TYPES

Cancer encompasses a diverse group of diseases that differ in their tissue of origin, molecular characteristics, and clinical manifestations. Among the most prevalent and clinically significant forms are lung cancer, leukaemia, colorectal cancer, hepatocellular carcinoma, and breast cancer<sup>65,66,67</sup>.

### Lung Cancer

Lung cancer is a leading cause of cancer-related mortality worldwide. It is broadly classified into NSCLC and SCLC, with NSCLC accounting for the more cases<sup>68</sup>. Tobacco smoking is the principal risk factor, while exposure to second-hand smoke, air pollutants, radon gas, and occupational carcinogens also contributes significantly to disease development<sup>68,69</sup>. Common symptoms include persistent cough, chest discomfort, shortness of breath, hemoptysis, and recurrent respiratory infections. Although SCLC often shows an initial response to chemotherapy, both major subtypes continue to present significant therapeutic challenges due to recurrence and drug resistance<sup>70,71</sup>.

### Leukaemia

Leukaemia is a hematological malignancy originating from abnormal proliferation of blood-forming cells in the bone marrow. The disease disrupts normal blood cell production and may spread throughout the body via the circulatory system. leukaemia is generally categorized into acute and chronic forms, with acute lymphoblastic leukaemia (ALL) being one of the rapidly progressing variants<sup>71,72</sup>. Several risk factors have been identified, including exposure to ionizing radiation, toxic chemicals, viral infections, and inherited genetic disorders. Current treatment approaches involve chemotherapy, targeted therapy, radiotherapy, immunotherapy, and hematopoietic stem cell transplantation<sup>72,73</sup>.

### Colorectal Cancer

Colorectal cancer develops in the colon or rectum and is among the most frequently diagnosed malignancies globally. The disease commonly arises from precancerous polyps that gradually undergo malignant transformation over time. Lifestyle-related factors such as diets rich in processed or red meat, obesity, physical inactivity, smoking, and high alcohol intake have been associated with elevated risk<sup>67</sup>. Clinical manifestations may include rectal bleeding, abdominal discomfort, fatigue, unexplained weight loss, and alterations in bowel habits. Early detection through screening programs is the most effective strategies for reducing disease burden and improving survival rates<sup>74,75</sup>.

### Liver Cancer

Liver cancer, particularly hepatocellular carcinoma, is a major public health problem in many developing regions. Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) constitutes the primary risk factor worldwide<sup>76</sup>. Additional contributors include aflatoxin-contaminated food, chronic liver disease, cirrhosis, metabolic disorders, and excessive alcohol consumption. Depending on disease stage, management options include surgical resection, liver

transplantation, local ablation techniques, trans arterial chemoembolization, targeted therapy, and immunotherapy<sup>77</sup>.

## Breast Cancer

Breast cancer is the widely diagnosed malignancy among women and originates primarily from epithelial cells lining the mammary ducts or lobules<sup>65</sup>. Disease progression frequently involves dissemination through the lymphatic system and distant metastasis<sup>78</sup>. Several factors contribute to breast cancer susceptibility, including genetic predisposition, hormonal influences, obesity, alcohol consumption, and sedentary lifestyle. Advances in early diagnosis, molecular profiling, targeted therapies, and personalized treatment strategies have significantly improved patient outcomes over recent decades<sup>78,79,80</sup>.

## Malignant Tumours

Malignant tumours arise when genetically altered cells acquire the ability to proliferate uncontrollably, invade surrounding tissues, and spread to distant organs. Depending on their tissue of origin, malignant neoplasms are classified into several categories, including carcinomas, sarcomas, leukaemia's, lymphomas, and gliomas. Among these, carcinomas are the most frequently encountered in clinical practice<sup>71</sup>.

Tumour development is a multistep process involving the accumulation of genetic and epigenetic abnormalities. Disease progression typically advances from cellular hyperplasia and dysplasia to carcinoma in situ and ultimately invasive cancer. Unlike benign tumours, malignant growths possess metastatic potential and can severely compromise the action of affected organs. Early diagnosis plays an important role in improving treatment outcomes. Modern diagnostic techniques, including molecular analysis, advanced imaging modalities, and spectroscopic methods, facilitate the identification of malignant lesions at earlier stages, thereby increasing the likelihood of successful therapeutic intervention<sup>79</sup>.

## QUINOXALINE – A VERSATILE HETEROCYCLIC PHARMACOPHORE

Quinoxaline has emerged as the most valuable privileged scaffolds in medicinal chemistry due to its good structural versatility and broad spectrum of biological activities. The ease of functionalization of the quinoxaline nucleus enables the innovation of diverse derivatives with enhanced pharmacological properties, polishing it an attractive platform for drug discovery and development. Over the past decades, extensive research has demonstrated the potential of quinoxaline-based compounds in various therapeutic areas, particularly in anticancer drug design<sup>10,12,79</sup>.

The incorporation of quinoxaline into hybrid molecular frameworks has generated compounds with promising biological profiles. For instance, quinoxaline–carbohydrate conjugates have been studied for their selective cytotoxic properties and their action to induce DNA cleavage under photochemical conditions, highlighting their potential application in targeted cancer therapy. Such hybrid systems offer opportunities to improve selectivity and therapeutic efficacy while minimizing adverse effects on normal cells<sup>12,79,80</sup>.

Several quinoxaline derivatives have also exhibited significant antineoplastic activity through interference with critical cellular targets. Among these, certain quinoxaline-based molecules function as topoisomerase II inhibitors, thereby disrupting DNA replication and cell division in rapidly proliferating cancer cells. This mechanism has attracted considerable attention because topoisomerase enzymes play a crucial role in maintaining DNA topology during cellular proliferation<sup>81</sup>.

Another important class of quinoxaline derivatives is represented by quinoxaline 1,4-di-N-oxides (QdNOs), which have demonstrated a range of biological activities. Of particular interest are hypoxia-activated QdNO derivatives that remain relatively non-toxic under normal physiological conditions but become activated within the oxygen-deficient microenvironment of solid tumours. This selective activation strategy has emerged as a promising approach for improving the therapeutic index of anticancer agents while reducing systemic toxicity. Several quinoxaline-based compounds have demonstrated significant therapeutic potential and have served as important lead molecules in anticancer drug discovery. The broad range of biological activities exhibited by these derivatives highlights the versatility of the quinoxaline scaffold in medicinal chemistry<sup>82</sup>.

Among these compounds, Q-85 HCl, a quinoxaline dioxide derivative, has been investigated for its antihypoxic and cytotoxic properties, indicating its potential utility in targeting hypoxic tumour environments. Another notable derivative, RPR 101511A, a 6,7-dimethoxy-substituted quinoxaline analogue, has shown activity as a tyrosine kinase inhibitor, a class of agents widely employed in targeted cancer therapy. Similarly, AG-1296 has been identified as a potent protein tyrosine kinase inhibitor, further emphasizing the ability of quinoxaline derivatives to modulate signalling pathways involved in tumour growth and progression<sup>83,84</sup>.

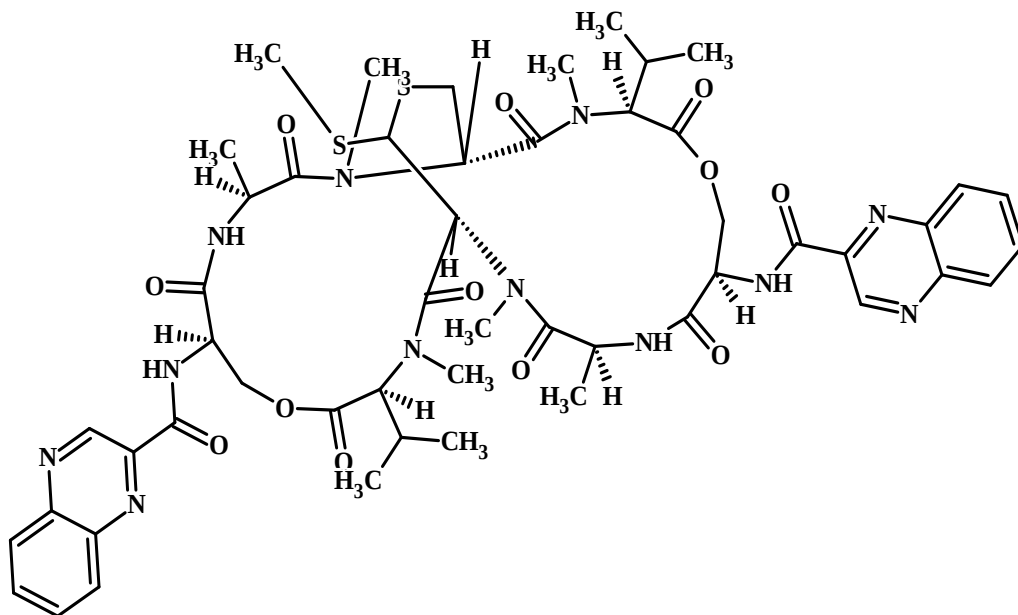
The therapeutic versatility of the quinoxaline framework is further illustrated by compounds such as Tinamast, which functions as a tumour necrosis factor (TNF) antagonist and may contribute to the regulation of inflammatory processes associated with cancer development. In addition, XK-469 (NSC-656889), a quinoxaline-containing antineoplastic agent, has attracted considerable interest because of its promising antitumour activity and has served as an important lead compound for the establishment of new anticancer therapeutics<sup>85</sup>.

Along with their direct cytotoxic effects, quinoxaline derivatives have been explored as modulators of key signalling pathways involved in cancer progression. Certain quinoxaline-based compounds have shown potent kinase inhibitory activity, resulting in suppression of tumour growth and cellular proliferation. Other derivatives have been developed as inhibitors of molecular targets associated with myeloproliferative disorders and various solid tumours, further emphasizing the versatility of the quinoxaline scaffold in oncology research<sup>86</sup>.

The growing number of quinoxaline-based molecules undergoing preclinical and clinical evaluation underscores the importance of this heterocyclic framework in contemporary medicinal chemistry. Collectively, these findings establish quinoxaline as a privileged pharmacophore with significant potential for the development of next-generation anticancer agents possessing improved efficacy, selectivity, and safety profiles<sup>87,88</sup>.

## QUINOXALINE MOTIFS IN NATURAL PRODUCTS

Although quinoxaline derivatives are predominantly synthesized in the laboratory, several naturally occurring compounds contain the quinoxaline framework and exhibit noteworthy biological activities<sup>89</sup>. The most prominent examples are echinomycin, a quinoxaline-containing cyclic peptide antibiotic isolated from bacterial species such as *Streptomyces echinatus* and *Streptomyces lasaliensis*. Echinomycin has attracted considerable interest because of its potent antitumour and antimicrobial properties<sup>90,91</sup>.



**Echinomycin**

The biological activity of echinomycin is largely associated with its ability to interact strongly with double-stranded DNA, thereby interfering with transcriptional processes and suppressing RNA synthesis<sup>92</sup>. Owing to this mechanism of action, echinomycin has been extensively investigated as a potential anticancer agent. Biosynthetically, the molecule originates from quinoxaline-2-carboxylic acid, a key intermediate derived from *L*-tryptophan through a series of enzymatic transformations. This biosynthetic pathway shares similarities with those involved in the development of other biologically active microbial metabolites<sup>93</sup>.

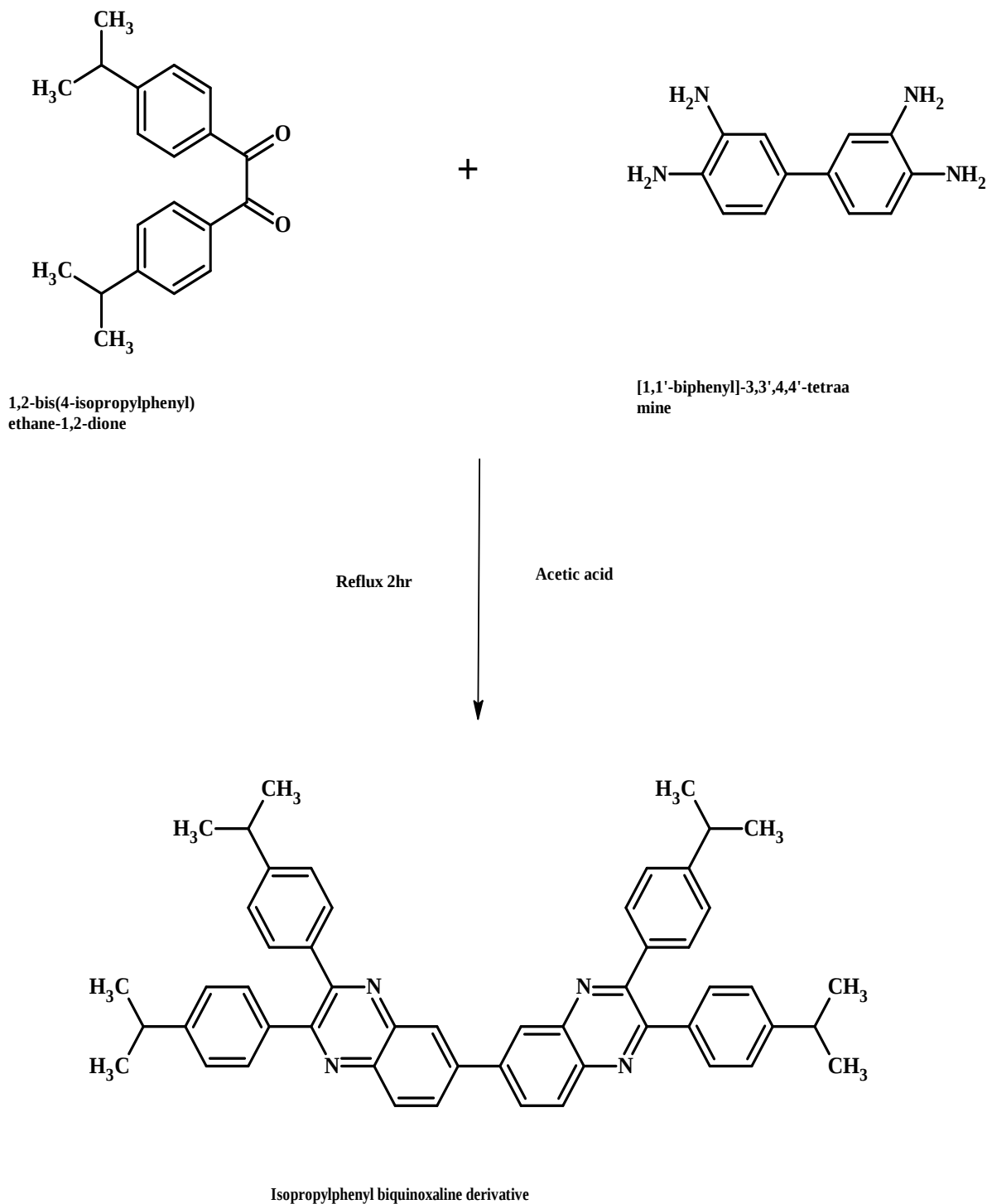
Structurally, quinoxaline belongs to the benzopyrazine family of heterocyclic compounds. Related pyrazine-containing motifs are distributed in nature and have been identified in several biologically important molecules. For example, the pyrazine ring system occurs in aspergillic acid, a metabolite produced by certain fungal species. Similar heterocyclic frameworks are also present in luciferin molecules found in bioluminescent beetles, including fireflies, where they contribute to the light-emitting biochemical reactions characteristic of these organisms<sup>92,94</sup>.

In addition to their occurrence in natural products, pyrazine derivatives play important roles in food chemistry. Methoxypyrazines, in particular, are responsible for the characteristic aroma and flavour profiles of various fruits and vegetables, including peas and *Capsicum* species. These compounds also contribute significantly to the sensory properties of several wines and other plant-derived products. The occurrence of quinoxaline-related structures in diverse natural

systems highlights their biological significance and further supports continued interest in quinoxaline-based compounds for pharmaceutical and medicinal applications<sup>95,96</sup>.

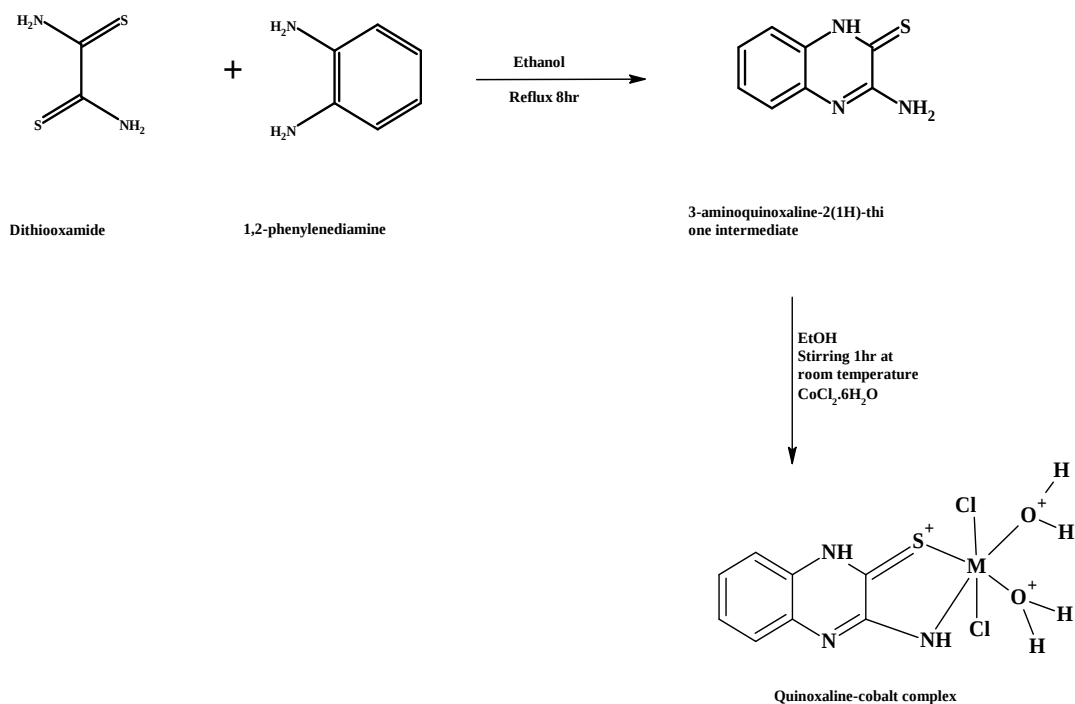
## SYNTHESIS OF VARIOUS DERIVATIVES OF QUINOXALINE

(i) The condensation of 1,2-bis(4-isopropylphenyl) ethane-1,2-dione with [1,1'-biphenyl]-3,3',4,4'-tetraamine in glacial acetic acid under reflux conditions for 2 hr, affording the corresponding isopropylphenyl biquinoxaline derivative<sup>97</sup>.



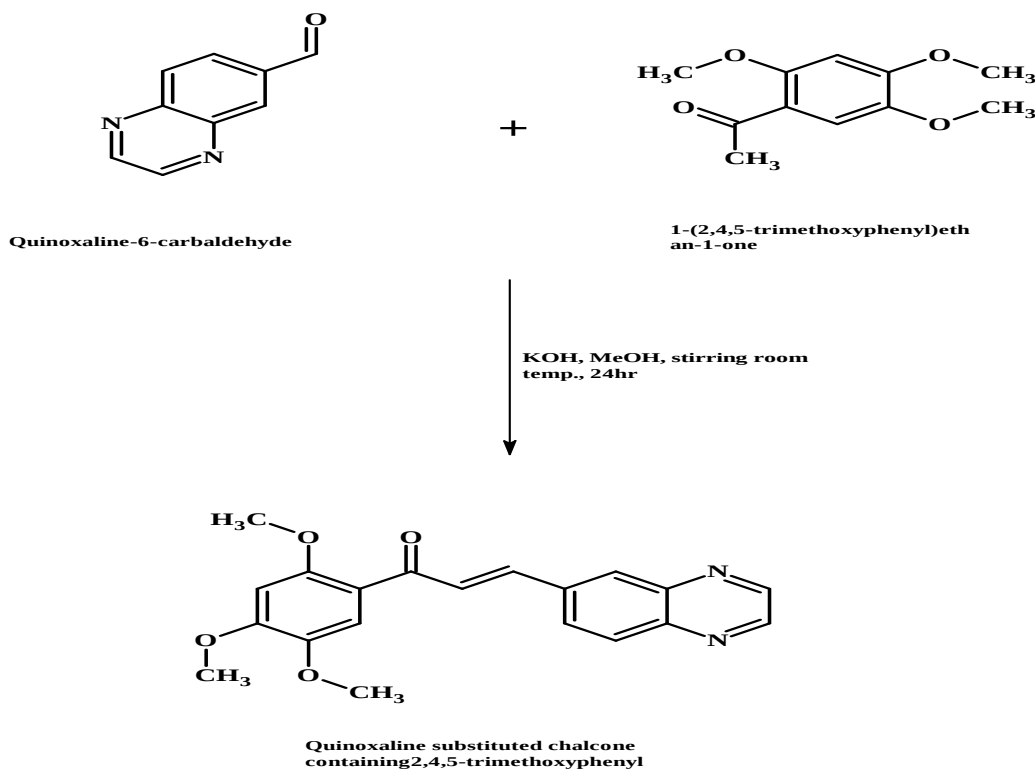
**Scheme 1**

(ii) The condensation of dithiooxamide and 1,2-phenylenediamine under reflux in ethanol, followed by complexation of the resulting 3-aminoquinoxaline-2(1H)-thione intermediate with  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  to afford the corresponding quinoxaline-cobalt complex<sup>97</sup>.



**Scheme 2**

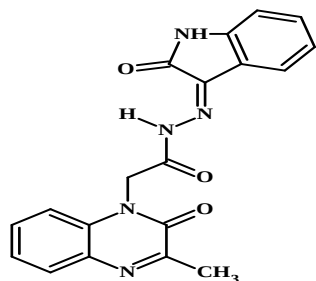
(iii) The synthesis of the desired quinoxaline-chalcone hybrid was accomplished through an aldol condensation between quinoxaline-6-carbaldehyde and 1-(2,4,5-trimethoxyphenyl) ethan-1-one, affording the corresponding trimethoxyphenyl-substituted product<sup>98</sup>.



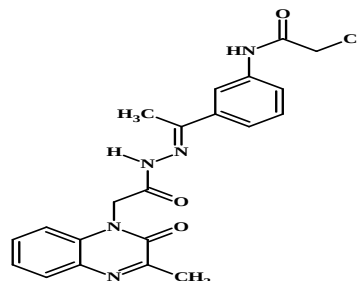
**Scheme 3**

## QUINOXALINE CANDIDATES AS ANTICANCER AGENTS

In 2025, Eman K.A. Abdelall et al. synthesized a group of compounds based on 3-methyl-2-oxoquinoxaline scaffold having acetohydrazide, benzohydrazide or acetamide substituents and evaluated the cytotoxic potential and assessed against HL-60 and PC-3 cells. Compounds 1 and 2 is having highest cytotoxic activity. HL-60 cell lines of compound 1 and 2 having  $IC_{50}=0.803 \pm 0.02$  and  $1.619 \pm 0.05 \mu M$  and PC-3 cell lines of compound 1 and 2 having  $IC_{50}=3.047 \pm 0.14$  and  $3.506 \pm 0.11 \mu M$ , compared to the reference drug sorafenib<sup>99</sup>.

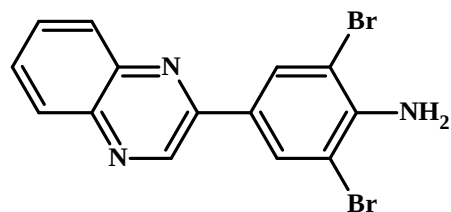


**Compound 1**

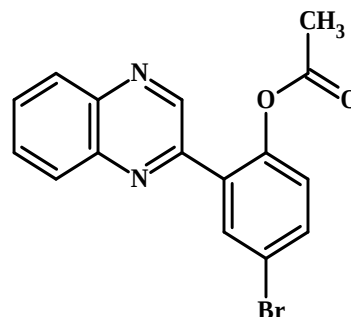


**Compound 2**

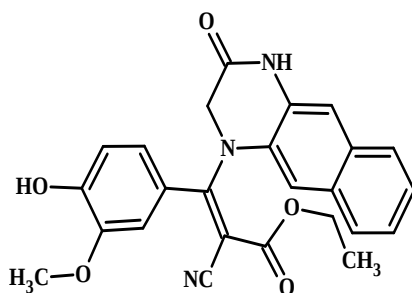
In 2024, ESH El-Sayed et al. synthesized a group of quinoxaline derivatives and it assessed against MCF-7 cell line using doxorubicin as the reference drug. New derivatives from 2-substituted quinoxaline were synthesized using o-phenylenediamine with aryl bromomethyl ketones. Compounds 3,4,5,6 exhibited the most potent anti-cancer activity with  $IC_{50}$  values of  $8.59 \pm 0.38$ ,  $4.80 \pm 0.21$ ,  $3.79 \pm 0.17$  and  $6.24 \pm 0.28 \mu M$ . The promising compound is 9 assessed for the ability to disrupt polymerization of  $\beta$ -tubulin which is having tubulin inhibition activity with  $IC_{50}$  value of  $0.814 \pm 0.03 \mu M$ <sup>100</sup>.



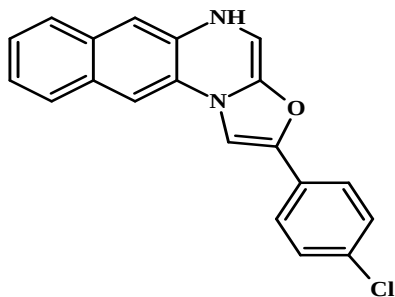
**Compound 3**



**Compound 4**

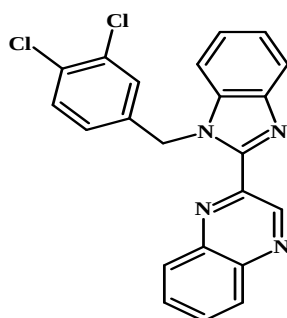


**Compound 5**



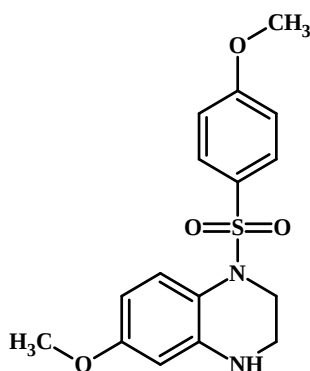
**Compound 6**

In 2023, O. Ommi et al. synthesized and evaluated novel quinoxaline-benzimidazole hybrids against three cancer cell lines HCT-116, A549 and SK-ML and one mouse cell line B16F10, colchicine is used as the reference drug. Compound 7 showed the highest activity among all the derivatives with  $IC_{50}$  values of  $7.13 \pm 0.19$ ,  $4.37 \pm 0.09$ ,  $6.25 \pm 0.59$  and  $16.64 \pm 1.51 \mu M^{101}$ .



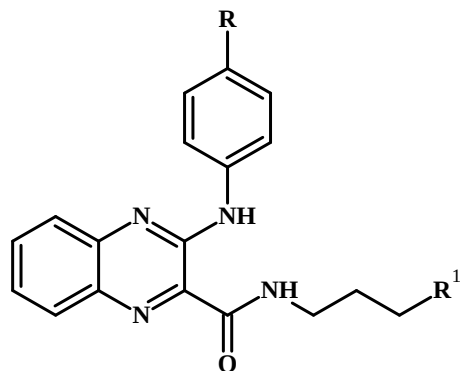
**Compound 7**

In the same year H. Dong et al. synthesized tetrahydro-quinoxaline sulphonamide derivatives and the anti-tumour action was evaluated using HT-29 cancer cells. Compound 8 was evaluated against HT-29, HepG-2, HeLa and MCF-7 cells. The compound 8 had moderate activity against all cell lines,  $IC_{50}$  values are  $2.20 \pm 0.07$ ,  $4.64 \pm 0.57$ ,  $2.84 \pm 0.15$ ,  $7.52 \pm 1.86 \mu M$  compared with ABT-751 reference drug<sup>102</sup>.



**Compound 8**

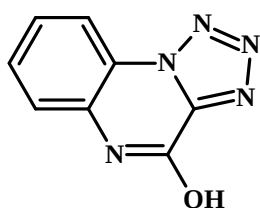
In 2021, N.Y. Chen et al. synthesized new derivatives of 3-aryl amino quinoxaline-2-carboxamide and evaluated anti-proliferative activity against five cancer cell lines such as MGC-803, A549, HeLa, HepG-2 and T24. Compound 9 with  $IC_{50}$  values of  $3.3 \pm 0.29$ ,  $4.2 \pm 0.36$ ,  $6.6 \pm 0.41$ ,  $4.2 \pm 0.33$ ,  $3.8 \pm 0.24$  and  $7.4 \pm 0.66 \mu M$ . Compound 10 with  $IC_{50}$  values of  $5.5 \pm 0.65$ ,  $10.1 \pm 0.84$ ,  $9.9 \pm 0.75$ ,  $10.1 \pm 0.83$ ,  $7.8 \pm 0.78$  and  $13.2 \pm 0.78 \mu M$ . Compound 11 with  $IC_{50}$  values of  $4.4 \pm 0.33$ ,  $5.83 \pm 0.31$ ,  $5.6 \pm 0.37$ ,  $6.3 \pm 0.49$ ,  $4.1 \pm 0.52$  and  $7.6 \pm 0.93 \mu M$ , these having potent antiproliferative activities compared with LY294002<sup>103</sup>.



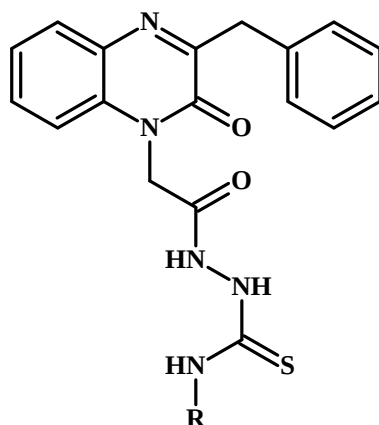
- |               |              |
|---------------|--------------|
| 9, R= 4-Cl.   | R¹= NH₂      |
| 10, R= 4-CH₃. | R¹= N(C₂H₅)₂ |
| 11, R= 4-CH₃. | R¹= NH₂      |

### Compound 9-11

In the same year, M. S. Ayoup et al. synthesized some of the new quinoxaline derivatives, those are inhibitors of MMP-9 and MAO-A. The compounds were tested against HCT-116 cancer cells, the doxorubicin is used as the reference drug. From the derivatives synthesized compound 12-16 has the highest anti-proliferative activity with IC<sub>50</sub> values in between  $5.567 \pm 0.229$  to  $8.815 \pm 0.069$  nM. They have good inhibitory effects against MMP-9 with IC<sub>50</sub> values of  $23.06 \pm 1.193$ ,  $5.074 \pm 0.267$ ,  $8.407 \pm 0.427$ ,  $4.502 \pm 0.230$  and  $9.301 \pm 0.477$  nM, it is compared with the positive control quercetin. Compound 13 and 15 were the potent MAO-A inhibitors and compound 13 and 14 were the effective MAO-B inhibitors<sup>104</sup>.

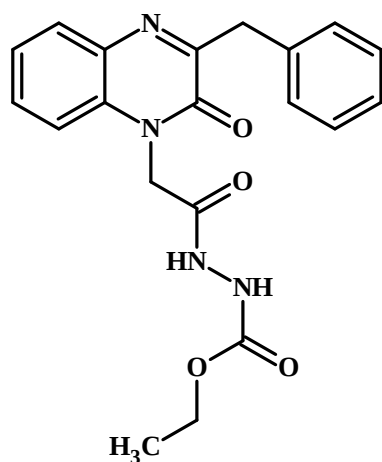


Compound 12

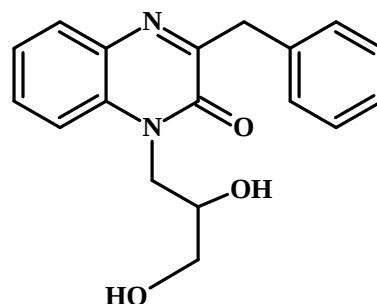


- |            |
|------------|
| 13, R=H    |
| 14, R=C₆H₅ |

### Compound 13,14

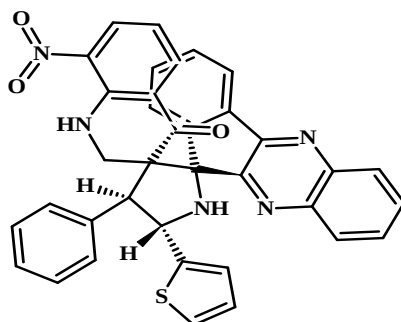


### Compound 15



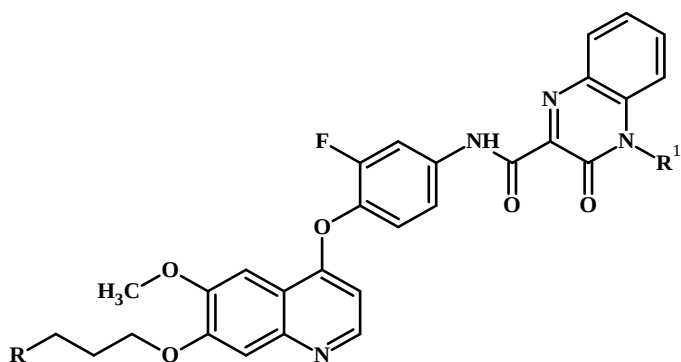
### Compound 16

In 2020, S. Shyamsivappan et al. synthesized new series of quinoxaline compounds. The cytotoxic activity performed in two cell lines MCF-7 and HeLa and reference drug for the study is doxorubicin. Compound 17 exhibited the potent inhibitory activity against the cell lines, with  $AI_{C_{50}}$  values of  $17 \pm 1.3$  and  $19 \pm 1.2 \mu M^{105}$ .



**Compound 17**

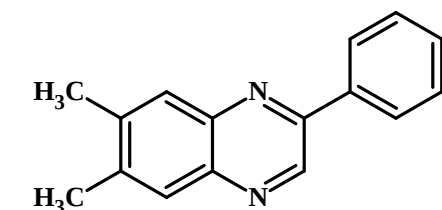
In 2019, Y. Yang et al. synthesized 4 phenoxy quinoline bearing 3-oxo-3,4-dihydroquinoxaline derivatives and assessed for cytotoxic activities against five cancer cell lines such as A549, H460, HT-29, MKN45 and U87MG, the reference drug used is foretinib. The compound 18 with  $IC_{50}$  values of  $0.48 \pm 0.03$ ,  $0.62 \pm 0.02$ ,  $0.38 \pm 0.05$ ,  $0.25 \pm 0.01$  and  $1.96 \pm 0.06 \mu M$ . Compound 19 with  $IC_{50}$  values of  $0.39 \pm 0.03$ ,  $0.18 \pm 0.03$ ,  $0.38 \pm 0.02$ ,  $0.18 \pm 0.02$  and  $0.81 \pm 0.04 \mu M$ . Compound 20 with  $IC_{50}$  values of  $0.32 \pm 0.03$ ,  $0.23 \pm 0.02$ ,  $0.23 \pm 0.03$ ,  $0.23 \pm 0.02$ ,  $0.56 \pm 0.04 \mu M$ . The compound 18-20 are more potent than foretinib<sup>106</sup>.



**Compound 18-20**

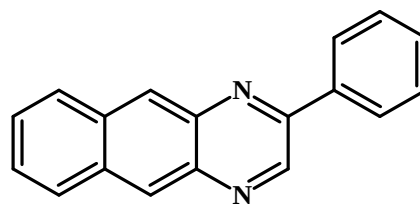
|                              |                                 |
|------------------------------|---------------------------------|
| 18, R= 4-methylpiperidinyl.  | R <sup>1</sup> = 4-Fluro-benzyl |
| 19, R= morpholinyl.          | R <sup>1</sup> = cyclohexyl     |
| 20, R= N-methyl piperazinyl. | R <sup>1</sup> = cyclohexyl     |

In 2018, Z. Ghanbarimasir et al. studied some quinoxaline to treat cancer. The quinoxaline coded AG 1295 (compound 21) and AG 1385 (compound 22) found to selectively block EGFR-TK. Clinical trials presently performed for these compounds<sup>107</sup>.



**6,7-dimethyl-2-phenylquinoxaline**

**Compound-21**



**2-phenylbenzo[g]quinoxaline**

**Compound-22**

## CONCLUSIONS AND FUTURE PERSPECTIVES

Cancer continues to represent a deathly global health concern owing to its complex pathogenesis, high mortality rate, and the emergence of resistance to conventional therapies. Despite remarkable advances in diagnosis and treatment, the need for safer, more selective, and highly effective anticancer agents remains a critical priority in modern drug discovery. Within the framework, heterocyclic compounds have emerged as valuable molecular frameworks for the innovation of new therapeutic agents, among which quinoxaline occupies a prominent position.

Despite these greater developments, several challenges remain to be addressed before the full clinical potential of quinoxaline derivatives can be realized. Future investigations should focus on improving target selectivity, overcoming multidrug resistance, minimizing systemic toxicity, and optimizing pharmacokinetic and pharmacodynamic profiles. In addition, a deeper understanding of structure–activity relationships, molecular targets, and mechanisms of action will facilitate the rational design of more effective quinoxaline-based therapeutics.

Overall, the extensive body of evidence reviewed herein establishes quinoxaline as a highly promising pharmacophore in anticancer research. Continued interdisciplinary efforts involving medicinal chemistry, molecular biology, computational drug design, and pharmacological evaluation are expected to accelerate the translation of quinoxaline derivatives from laboratory research to clinical application. Consequently, quinoxaline-based compounds are likely to play an increasingly important role in the establishment of innovative anticancer therapies and future oncology drug discovery programs.

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