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# Quinoxaline Derivatives Anti-Cancer Activities Through Protein Kinases Inhibition: A review

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**Abstract**

Benzopyrazines, commonly known as quinoxaline derivatives, are a significant group of heterocyclic compounds. Due to the vast range of biological activities that quinoxalines exhibit, they have received a lot of interest. Derivatives of quinoxaline (benzopyrazine), which contain the pyrazoline ring structure, are a class of physiologically active compounds. They demonstrated broad range of biological activities; anticancer, anti-inflammatory, antibacterial, antidepressant, hypoglycemic, hypotensive, and antihistamic because of their ability to serve as protein kinase inhibitors, they are regarded as crucial starting point for anticancer medicines. Since quinoxalines have been shown to be selective ATP-competitive inhibitors of numerous kinases, including the Epidermal growth factor receptor EGFR/HER2 inhibitors, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), C-Met kinase inhibitor, Janus kinase receptor (JAK-2) and cyclin dependent kinase (CDK1,2,4,6). Quinoxaline derivatives' chemistry and their possible anti-protein kinase effects are the main topics of this paper.

Anticancer / Kinase inhibitors / Quinoxalines derivatives.

## 1. Introduction

In the twenty-first century, cancer is predicted to be the leading cause of death worldwide and the single biggest barrier to increasing life expectancy [29]. In the entire world, noncommunicable diseases (NCDs) are already the main cause of death. According to estimates from the World Health Organization (WHO) in 2020, cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries. The Distribution of Cases and Deaths for the 10 Most Common Cancers in 2021 are shown in Pie Chart (Figure 1) [17] . When anticancer medication has the ability to cause apoptosis of the cancer cells, its beneficial effects are taken into account [11] . An imbalance in the rate of cell division and death, or apoptosis, is what causes cancer. Unfortunately, because cancer is seen as a heterogeneous disease at the level of tissues, detecting and treating it in the body is extremely difficult [6] . Chemotherapy has been a key component of cancer treatment for the past three decades. However, efforts to further enhance conventional chemotherapy have been constrained by its undesirable side effects, which are dose dependent. Recent advancements in cancer treatment have been made possible by the introduction of molecularly targeted therapies with great selectivity for tumor cells and little toxicity in normal cells. However, molecularly focused therapy has clear drawbacks as well, namely drug resistance. As a result, there is a critical therapeutic need to investigate new anticancer medicines with enhanced efficacy and reduced adverse effects [21] . In the field of modern medical chemistry, quinoxaline, a fused heterocycle comprising benzene and pyrazine rings, has attracted a lot of interest. This

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moiety has a wide range of pharmacological actions, that encourages the pharmaceutical sector to synthesize and evaluate various substitutes of quinoxalines as crucial therapeutic agents [2] .

So, derivatives of quinoxaline (benzopyrazine), are a class of physiologically active chemicals [15] . They demonstrated a broad range of biological effects, including anticancer, anti-inflammatory, antibacterial, antidepressant, hypoglycemic, hypotensive, and antihistamic Figure 2) [22]. As they have been shown to be selective ATP-competitive inhibitors of numerous kinases, quinoxalines are regarded as a key building block for anti-cancer medicines [13] . As an illustration, quinoxalines derivatives consider as ATP-competitive inhibitors of the following proteins kinases ;Epidermal growth factor receptor EGFR/HER2 inhibitors, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), C-Met kinase inhibitor, Janus kinase receptor (JAK-2) and cyclin dependent kinase (CDK1,2,4,6). (Figure 3) [34] .

## 2. Quinoxaline derivatives targeting screening.

### *2.1. Epidermal growth factor receptor EGFR/HER2 inhibitors*

Human epidermal growth factor receptors (EGFR/ErbB1), human epidermal growth factor receptors 2 and 3 (HER-2/ErbB-2, HER-3/Erb-3), and human epidermal growth factor receptor 4 (HER-4/Erb4) are all members of the EGFR family [18] . Breast and stomach cancers, among other malignancies, are greatly influenced by EGFR and HER-2. Therefore, novel anticancer treatments that bind to the ATP binding sites of EGFR and/or HER-2 then block their kinase activity may be of interest [30] .

Normally, the activation of EGFR tyrosine kinase activity and receptor trans autophosphorylation are caused by the interaction of EGF at the cell surface, which causes the dimerization of EGFR [25] [11] . Large signaling complexes are formed when tyrosine autophosphorylation sites in the active EGFR interact with downstream signaling proteins. The activation of multiple signaling pathways is then started by the receptor-signaling protein complexes, which eventually promote cell survival and proliferation [12] .

Figure 4 shows the mechanism of action of epidermal growth factor receptor tyrosine kinase inhibitor (Gefitinib) which is considered one of the most effective quinoxaline derivatives act as EGFR inhibitor by binding and blocking the ATP binding sites of EGFR [13] .

In 2021 Kumar et al, designed and synthesized series of 30 non-covalent imidazole [1, 2-a] quinoxaline-based inhibitors of epidermal growth factor receptor (EGFR). Compounds 1, 2, 3, 4 and 5 were potent EGFR inhibitors with low IC50 values against cancer cell lines; A549 (lung), HCT-116 (colon), and MCF7 (breast). Table (1 ) illustrates the potential of these quinoxaline derivatives as anticancer candidates against tested cancer cell lines; The results showed that compound 1 was the most effective one against lung cancer cell line (A549) with IC50 value of 2.7 nM and compound 3 was the most effective one against breast cancer cell line (MCF7) with IC50 value of 2.2 nM [10] .

#### *2.1.1. Vascular endothelial growth factor receptor-2 inhibitors*

The process of angiogenesis is crucial for the development and regeneration of tissues. To stop ischemic necrosis and aid in the survival of injured tissues, such role is essential. During the normal state, a few protein kinases (PKs), which include VEGFRs, FGFRs, and EGFRs, regulate angiogenesis. Under pathological circumstances, PKs can become dysregulated, disrupting the angiogenesis process [13] . As a result, the rate of cell division accelerates, resulting in tumors. Many human malignancies, particularly solid tumors like gliomas and carcinomas, overexpress VEGFRs and their specific agonist (VEGF) [14] . The VEGF/VEGFR-2 signaling pathway is essential for tumor angiogenesis, the process by which oxygen and nutrients are delivered to the tumor to encourage its growth. VEGFRs are therefore regarded as one of the most significant regulators of angiogenesis and consequently, tumor formation. Both tumor angiogenesis and embryonic vasculogenesis are regulated by VEGFR-2. On the other hand, lymph angiogenesis is caused by VEGFR-3 [15] .

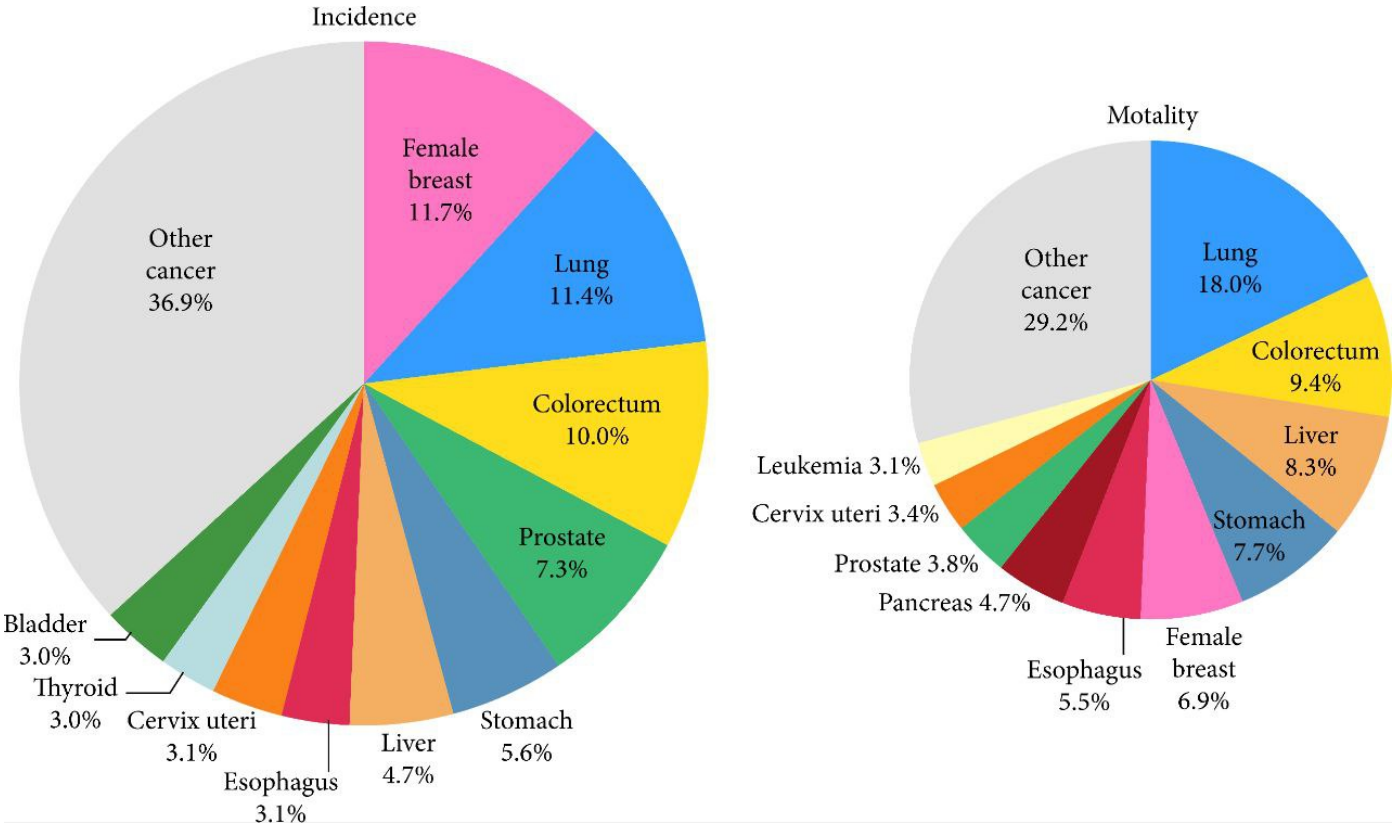



Figure 1: The Distribution of Cases and Deaths for the 10 Most Common Cancers in2021 are shown in Pie Charts [17]

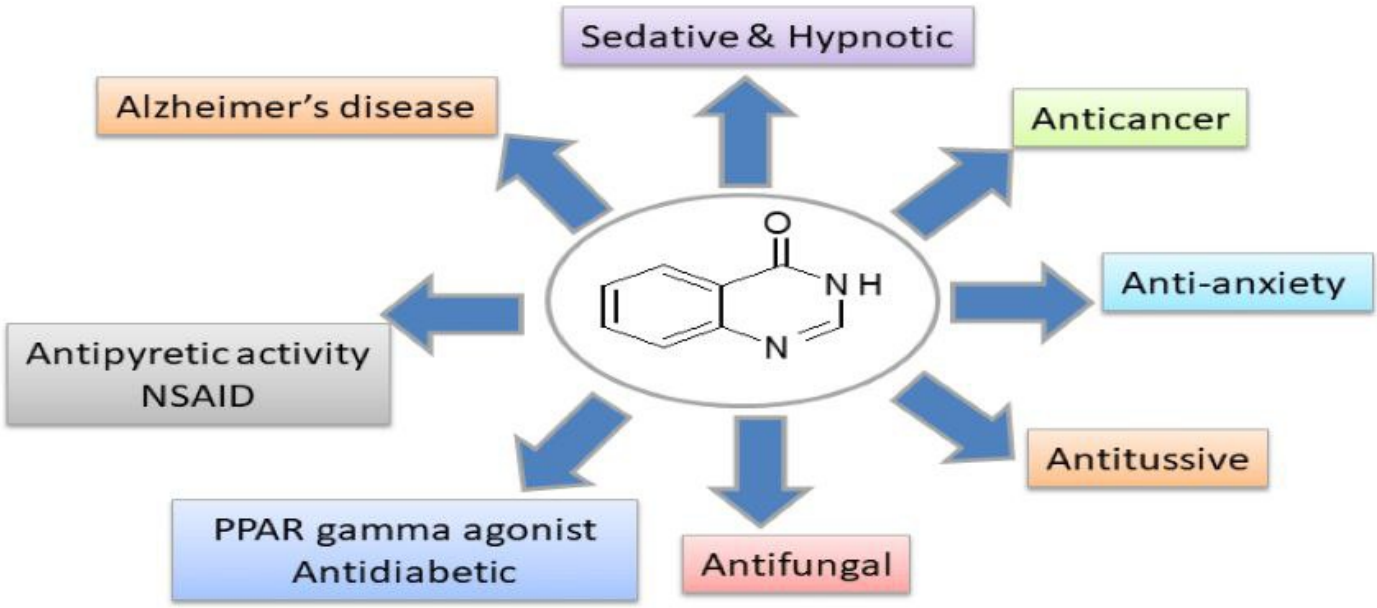



Figure 2: Bioactivity ofQuinoxaline derivatives for biological effects [15] .

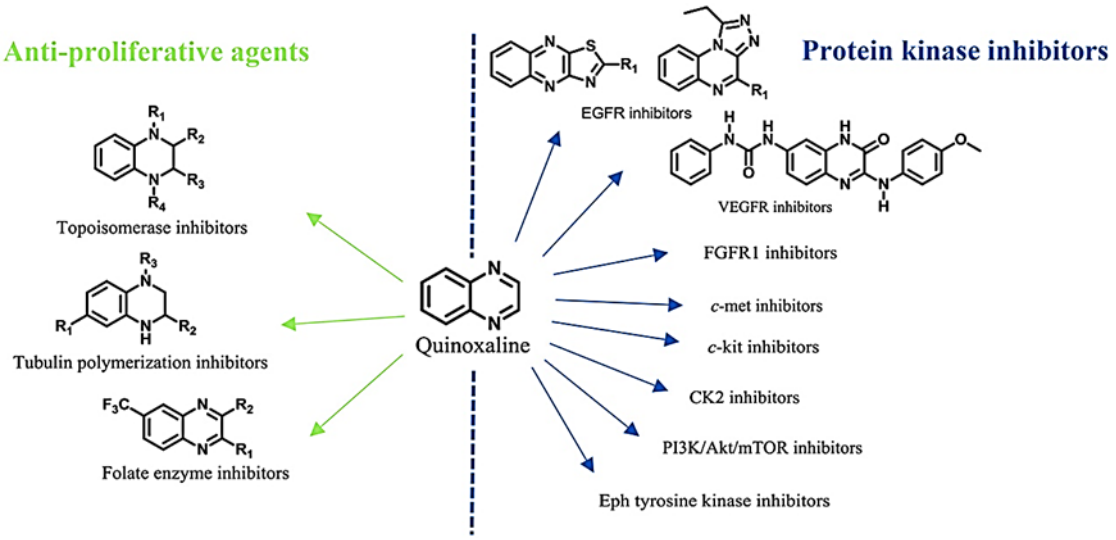



Figure 3: QuinoxalineAnti-proliferative agents and protein kinase inhibitors agents and protein kinase inhibitors [34]

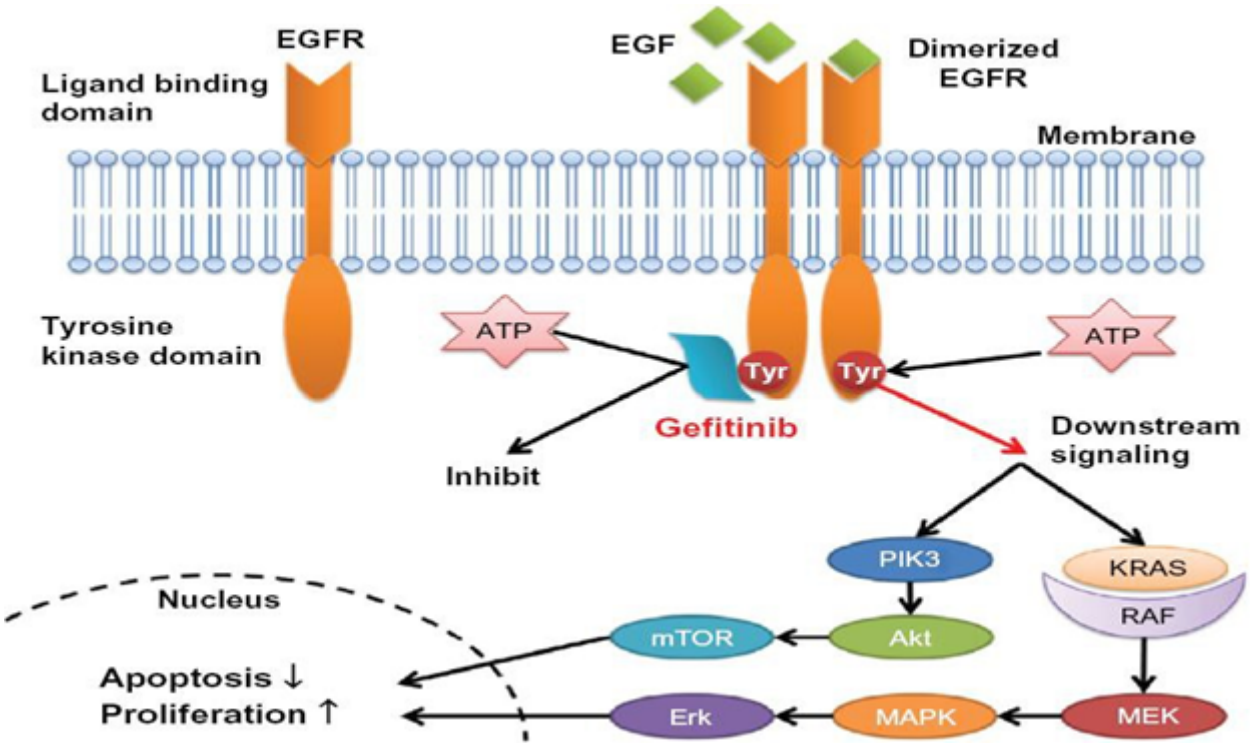
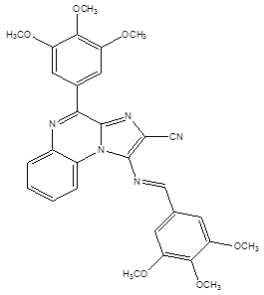
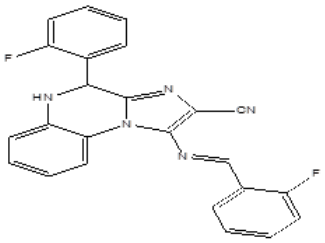
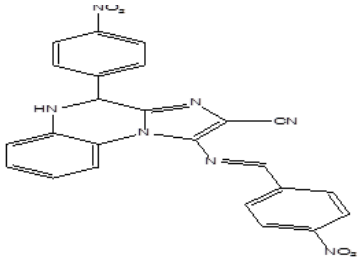
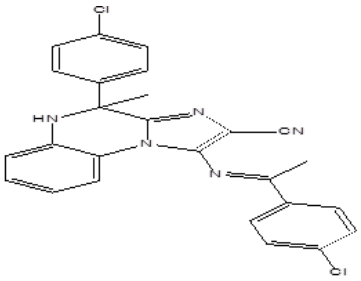
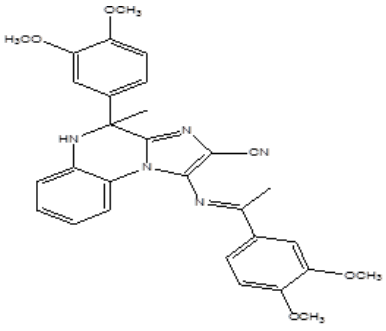



Figure 4: Mechanism of action of epidermal growth factor receptor tyrosine kinase inhibitors [13]

When VEGF binds to VEGFR, the receptor undergoes a conformational shift that is followed by dimerization of the receptor and tyrosine phosphorylation [15] .

In 2021 Mohammed M. Alanazia et al, [16] designed and synthesized two series of new 3-methylquinoxaline derivatives as VEGFR-2 inhibitors. The synthesized derivatives were evaluated in vitro for their cytotoxic activities against MCF-7 (breast) and HepG2 (liver) and HCT-116 (colon) cell lines. Compound 1 was the most potent VEGFR-2 inhibitor with potent IC50 against MCF-7 (breast) cell line as 3.95 nM and IC50 against HepG2 (liver) cell line as 3.08 nM and potent IC50 against HCT-116 (colon) cell line as 3.38 shown in table 2.

Table 1: $IC_{50}$ values for some quinoxalinederivatives against EGFR inhibitors$IC_{50}$ values for some quinoxalinederivatives against EGFR inhibitors

| Entry | Compound | Structure | Anti-cancer activity | Ref. |
|---|---|---|---|---|
| 1 | 1-[(3,4,5-Trimethoxy-benzylidene)-amino]-4-(3,4,5-trimethoxy-phenyl)-imidazo[1,2-a]quinoxaline-2-carbonitrile |  | Cell line IC50<br>A549 2.7 ± 0.032<br>HCT-116 5.1 ±_ 0.029<br>MCF-7 4.1 ± 0.031 | [12] |
| 2 | 1-[(2-Fluoro-benzylidene)-amino]-4-(2-fluoro-phenyl)-4,5-dihydro-imidazo[1,2-a]quinoxaline-2-carbonitrile |  | Cell line IC50<br>A549 4.09 ± 0.024<br>HCT-116 <1<br>MCF-7 11.2 ±0.022 | [12] |
| 3 | 1-[(4-Nitro-benzylidene)-amino]-4-(4-nitro-phenyl)-4,5-dihydro-imidazo[1,2-a]quinoxaline-2-carbonitrile |  | Cell line IC50<br>A549 8.75 ± 0.028<br>HCT-116 <1<br>MCF-7 2.2 ± 0.026 | [12] |
| 4 | 4-(4-Chloro-phenyl)-1-[1-(4-chloro-phenyl)-ethylideneamino]-4-methyl-4,5-dihydro-imidazo[1,2-a]quinoxaline-2-carbonitrile |  | Cell line IC50<br>A549 6.63 ± 0.031<br>HCT-116 >25<br>MCF-7 14.1 ± 0.021 | [12] |
| 5 | 4-(3,4-Dimethoxy-phenyl)-1-[1-(3,4-dimethoxy-phenyl)-ethylideneamino]-4-methyl-4,5-dihydro-imidazo[1,2-a]quinoxaline-2-carbonitrile |  | Cell line IC50<br>A549 12.06 ± 0.021<br>HCT-116 7.90 ±0.027<br><br>MCF-7 13.6 ± 0.028 | [12] |

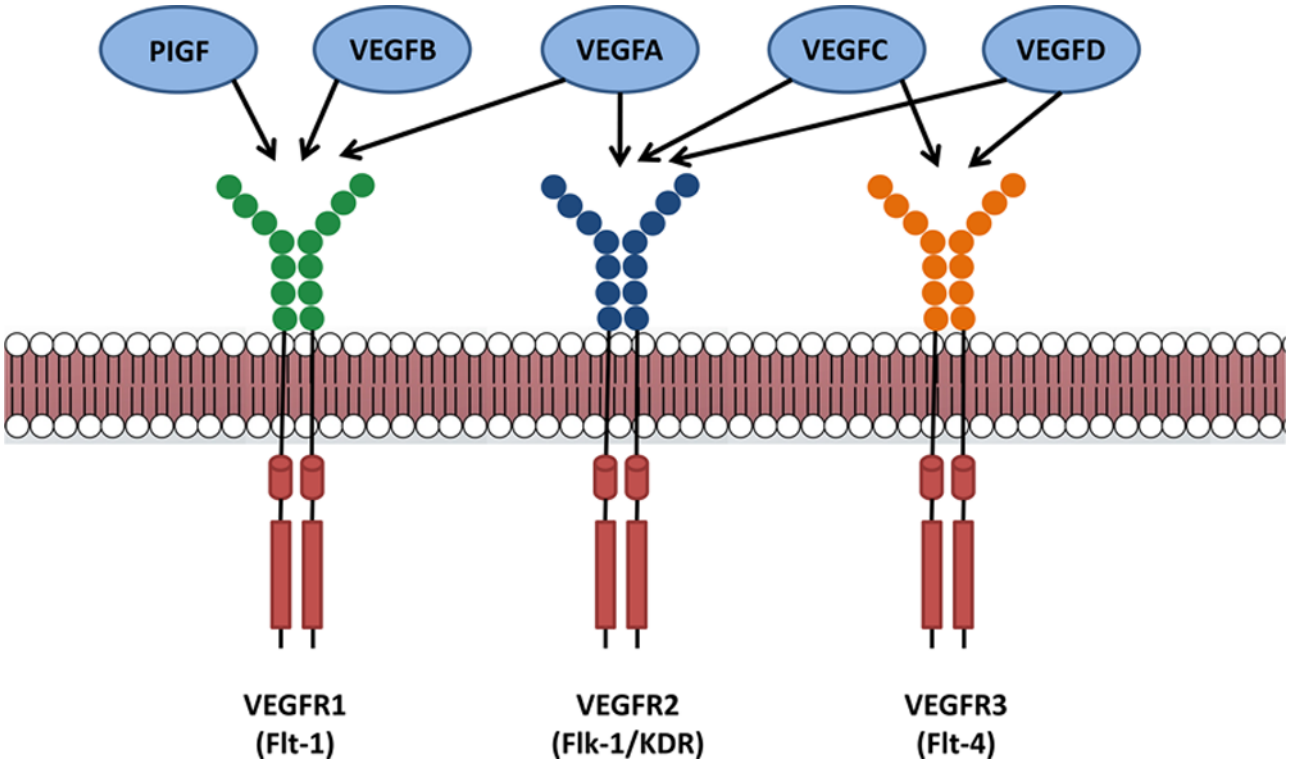



Figure 5: Vascular endothelial growth factor ligands and receptors [15] .

Also El-Adl in 2021 [18] arrested Compounds exhibited a strong cytotoxic effect against MCF-7 (breast) and HepG2 (liver) and HCT-116 (colon) cell lines. Respectively with potent IC50. Compound 2 was the most potent one against HepG2 (liver) cell line with IC50 value of 2.5 nM and most potent one against MCF-7 (breast) cell line with IC50 value of 9 nM. Compound 3 was the most potent one against HCT-116(colon) cell line with IC50 value of 7.8 nM as shown in table 2.

Ismail MMF et al, in 2023 designed and synthesized novel library of quinoxalin-2-one derivatives such as 3-furoquinoxaline carboxamides, 3-pyrazolylquinoxalines, and 3-pyridopyrimidylquinoxalines. Among them, 4 and 5 produced remarkable cytotoxicity against MCF-7 (breast) and HepG2 (liver) and HCT-116 (colon) cell lines using the MTT assay. They showed direct inhibition of VEGFR-2. Impressively, compound 5 was the most potent one against HepG2 (liver) cell line with IC50 value of 8.4 nM. But compound 4 was the most potent one against MCF-7 (breast) cell line with IC50 value of 15.5 nM and against HCT-116 (colon) cell line with IC50 value of 9.8 nM. [20] as shown in table 2 .

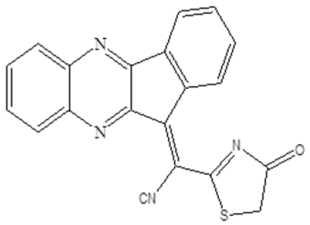
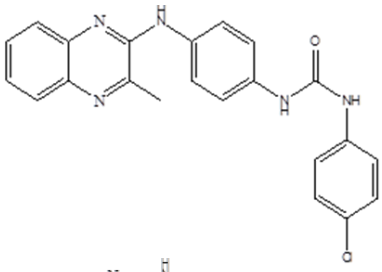
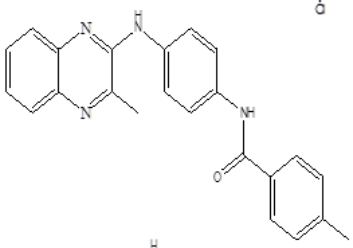
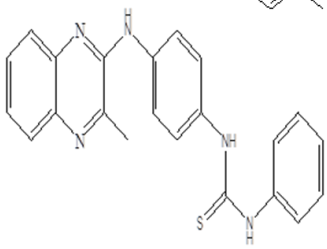
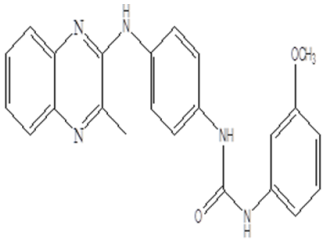
### *2.1.2. Platelet-derived growth factor receptor (PDGFR) inhibitors*

A crucial role in controlling cell development is played by the potent mitogen platelet-derived growth factor (PDGF). Tyrosine phosphorylation of natural substrates that function via a variety of pathways is a result of PDGF binding to its transmembrane receptor (PDGFR) [20] . Various PDGF isoforms have various interactions with the PDGF a- and b-receptors (Figure 6) . They are transmembrane tyrosine kinases, and ligand interaction activates them, which is necessary for cellular signalling. Important elements of embryogenesis are regulated by PDGF and its receptors [21] .

Numerous cancers, such as gliomas and non-small cell lung cancer (NSCLC), have been linked to PDGFR activation. derivatives of pyrazole exhibiting Inhibitors of the platelet-derived growth factor receptor (PDGFR) action [22] .

In many cancers as well as non-malignant conditions like atherosclerosis, balloon injury-induced restenosis, and restenosis after by-pass surgery, the

Table 2: $IC_{50}$ values for some quinoxaline derivatives against VEGFR inhibitors

| Entry | Compound | Structure | Anti-cancer activity | Ref. |
|---|---|---|---|---|
| 1 | 2-(Indeno[1,2-b]quinoxalin-11-ylidene-isocyano-methyl)-thiazol-4-one |  | Cell line IC50 HepG-2 3.08 ± 0.19 HCT-116 3.38 ± 0.21 MCF-7 3.95 ± 0.28 | [18] |
| 2 | 1-(4-Chloro-phenyl)-3-[4-(3-methyl-quinoxalin-2-ylamino)-phenyl]-urea |  | Cell line IC50 HepG2 2.5 HCT-116 22 MCF-7 9 | [19] |
| 3 | 4-Methyl-N-[4-(3-methyl-quinoxalin-2-ylamino)-phenyl]-benzamide |  | Cell line IC50 HepG2 25.7 HCT-116 7.8 MCF-7 60.3 | [19] |
| 4 | 1-[4-(3-Methyl-quinoxalin-2-ylamino)-phenyl]-3-phenyl-thiourea |  | Cell line IC50 HepG2 12.3 HCT-116 9.8 MCF-7 15.5 | [19] |
| 5 | 1-(3-Methoxy-phenyl)-3-[4-(3-methyl-quinoxalin-2-ylamino)-phenyl]-urea |  | Cell line IC50 HepG2 8.4 HCT-116 21.4 MCF-7 24.5 | [20] |

increased PDGFR receptor activity is crucial. The PDGF receptor tyrosine kinase is effectively inhibited by bicyclic quinoxaline derivatives [23] .

*2.1.3. C-Met kinase inhibitor*

The receptor for hepatocyte growth factor (HGF), C-Met (Mesenchymal-epithelial transition factor) tyrosine kinase, is a prototype member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs). When HGF binds to its receptor c-Met, it activates a number of intricate signaling cascades that cause cell motility, proliferation, survival, induction of cell polarity, scattering, and invasion. The HGF/c-Met signaling pathway's physiological roles are limited to processes of tissue regeneration, wound healing, and embryonic development [25] . Deregulation of the c-Met/HGF

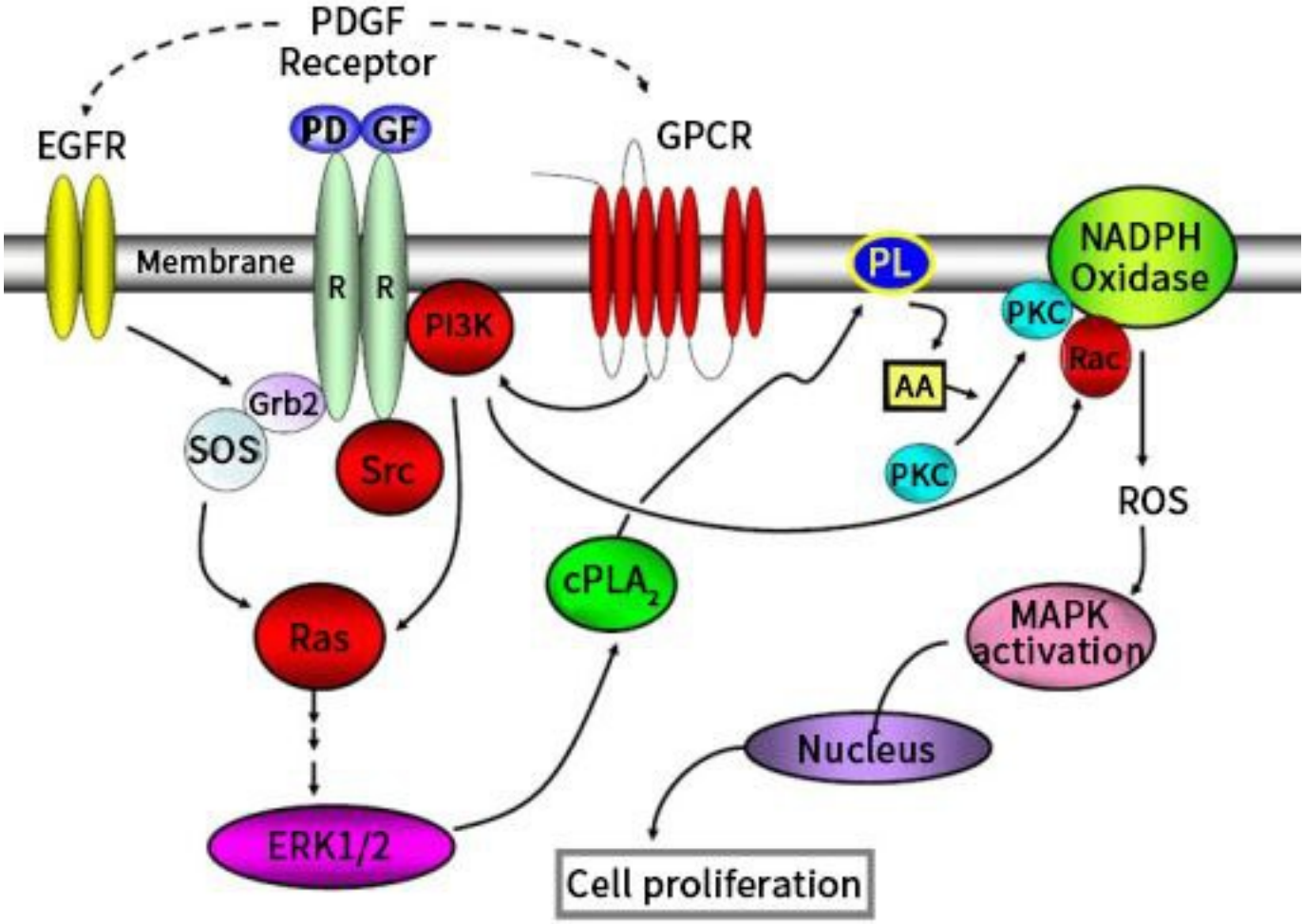



Figure 6: **Platelet-Derived Growth Factor (PDGF) Signaling Pathway** [21].

pathway, however, can result in tumor development and metastasis. Some of the deregulation mechanisms seen in many human malignancies include c-Met gene amplification, c-Met and/or HGF overexpression, and constitutive activation brought on by sequence changes. Consequently, one new approach to cancer treatment has been the pharmaceutical inhibition of c-Met activity [24] .

In 2015 Seung Chan Kim et al, synthesized and evaluated series of novel quinoxaline derivatives for their inhibitory activity against c-Met kinase enzyme. Most of the tested compounds exhibited potent inhibitory activity against breast cancer cell line (MCF7),lung cancer cell line ( NCI-H460) and human glioblastoma cancer cell line (SF-268). Among the synthesized compounds, compound 1 exhibited very potent IC50 value of 0.21 nM against breast cancer cell line (MCF7) and against lung cancer cell line ( NCI-H460) with IC50 value of 0.32 nM and against human glioblastoma cancer cell line (SF-268) with IC50 value of 0.16 nM as shown in table 3 [26] .

In an attempt to boost their potency by adjusting a new substituent at a different position in the quinoxaline scaffold, researchers designed new quinoxaline derivatives as c-Met kinase inhibitors after analyzing the interactions between freshly synthesized quinoxalines and c-Met kinase, Hebat-Allah S Abbas et al, in 2020 synthesized some substituted quinoxaline derivatives, all the tested compounds were screened in vitro for their cytotoxic effect on three tumor cell lines breast cancer cell line (MCF7),lung cancer cell line ( NCI-H460) and human glioblastoma cancer cell line (SF-268).

Compound 2 showed the lowest IC50 value

against lung cancer cell line ( NCI-H460) with IC50 value of 0.67 nM ,but compound 3 was the most potent one against breast cancer cell line (MCF7) with potent IC50 value of 0.81 nM and human glioblastoma cancer cell line (SF-268) with potent IC50 value of 0.08 nM as shown in table 3 [27] .

*2.1.4. JAK2 inhibitor*

The four non-receptor protein tyrosine kinases that make up the Janus kinase (JAK) family, JAK1, JAK2, JAK3, and TYK2, are crucial for cell survival, proliferation, and differentiation [28] . Our knowledge of the etiology of chronic myeloproliferative neoplasms (MPNs) was significantly advanced by the identification of somatic JAK2 mutations in individuals with these diseases. Considerable work is being done to find and develop small molecule inhibitors of JAK2's kinase activity because it provides a viable target for the therapy of MPNs [30] .

The identification of an acquired activating point mutation in JAK2, which results in the amino acid position 617 of phenylalanine being changed to valine, has greatly advanced our understanding of the molecular mechanism behind chronic myeloproliferative neoplasms. Remarkably, the JAK2V617F mutation is present in nearly all polycythemia patients and in about every other patient with primary myelofibrosis and essential thrombocythemia. Because of this, JAK2 is a target that shows promise for the treatment of myeloproliferative neoplasms, and a lot of work is being done to find and create JAK2 inhibitors. In 2010, Baffert et al, reported a novel substituted quinoxaline, compounds 1 and 2, which were found to be potent and selective ATP-competitive inhibitor of JAK2. Compounds 1 had potent IC50 value of 5.98 nM against HepG2 (liver) cell line and IC50 value of 7.70 nM against HCT-116 (colon) cell line and IC50 value of 6.35 nM against MCF-7 (breast) cell line as shown in Table 4 [30].

*2.1.5. CDKs inhibitors*

The class of enzymes known as cyclin-dependent kinases (CDKs) are serine/threonine protein kinases that only have the catalytic core common to all protein kinases, in eukaryotic cells, the cyclin-dependent kinase (CDK) protein family is essential for controlling the cell cycle. The expression of CDK's activator subunit, cyclin, is primarily responsible for controlling the advancement of the cell cycle in an orderly manner. The advancement of the G2/M phase depends on the interaction of CDK1 (CDC2) with cyclin B. Retinoblastoma protein is sequentially phosphorylated by CDK4 and CDK6 with cyclin D, and CDK2 with cyclin E or A to promote G1/S progression [31] .

A characteristic of cancer is the dysregulation of cell-cycle control. This makes cyclin-dependent kinases (CDK) a desirable target for the creation of anti-cancer medications. A highly effective macrocycle-quinoxalinone-structured pan-CDK inhibitor has been biologically characterized. CDK inhibitors are currently being actively developed by numerous pharmaceutical companies [32] .

IN 2006 a novel class of CDK inhibitors that comprise a macrocyclic quinoxaline-2-carboxylic acid had tested against (MV4-11) human AML cell line and HCT-116 (colon) cell line , compound 1 was the most potent one against ( MV4-11) human AML cell line with IC50 value of 32.9 nM and compound 2 was the most potent one against HCT-116 (colon) cell line with IC50 value of 35.3 nM as shown in table 5 [33] .

## 3. Conclusion

Quinoxalines are a significant group of nitrogen-containing heterocycles that have been found to have a wide range of biological functions. Derivatives of quinoxalines have been shown to have anticancer potential through the inhibition of several kinase enzymes such as Epidermal growth factor receptor EGFR/HER2 inhibitors, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), C-Met kinase inhibitor, Janus kinase receptor (JAK-2), and cyclin dependent kinase (CDK1,2,4,6). In this review, a number of quinoxaline derivatives were illustrated that have a good evaluation of their work as anti-cancer agents. We ultimately recommend conducting an evaluation of these compounds on experimental animals to ensure their effectiveness as anti-cancer agents without causing unwanted

Table 3: $IC_{50}$ values for some quinoxaline derivatives against C-Met kinase inhibitor

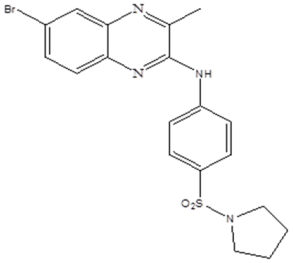
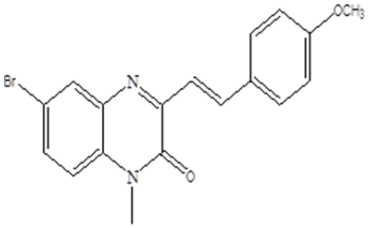
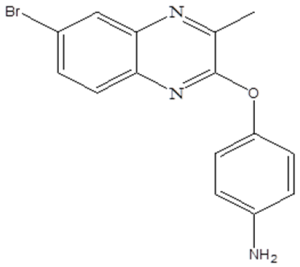
| Entry | Compound | Structure | Anti-cancer activity | Ref. |
|---|---|---|---|---|
| 1 | (6-Bromo-3-methyl-quinoxalin-2-yl)-[4-(pyrrolidine-1-sulfonyl)-phenyl]-amine |  | Cell line IC50 MCF-7 0.21 ± 0.001 NCI-H460 0.32 ± 0.004 SF-268 0.16 ± 0.002 | [27] |
| 2 | 6-Bromo-3-[2-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-quinoxalin-2-one |  | Cell line IC50 MCF-7 1.62 ± 0.48 NCI-H460 0.67 ± 0.16 SF-268 1.8 ± 0.06 | [28] |
| 3 | 4-(6-Bromo-3-methyl-quinoxalin-2-yloxy)-phenylamine |  | Cell line IC50 MCF-7 0.81 ± 0.04 NCI-H460 0.72 ± 0.04 SF-268 0.08 ± 0.06 | [28] |

Table 4: $IC_{50}$ values for some quinoxaline derivatives against JAK2 inhibitor

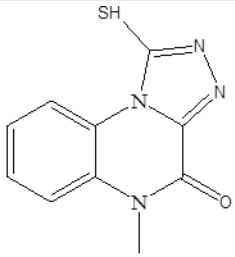
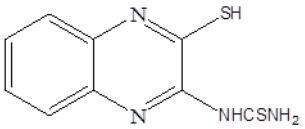
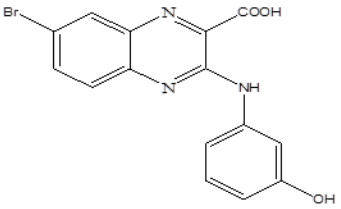
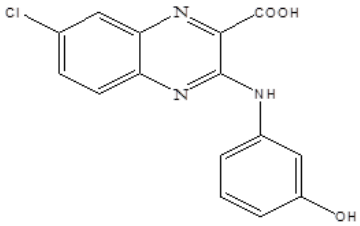
| Entry | Compound | Structure | Anti-cancer activity | Ref. |
|---|---|---|---|---|
| 1 | 1-Mercapto-5-methyl-5H-[1,2,4] [17, 29]triazolo[4,3-a]quinoxalin-4-one |  | Cell line IC50 HepG2 5.98±0.3 HCT-116 7.70±0.5 MCF-7 6.35±0.3 | [30] |
| 2 | (3-Mercapto-quinoxalin-2-yl)-thiourea |  | Cell line IC50 HepG2 7.6 ± 0.4 HCT-116 8.04 ± 0.7 MCF-7 8.34 ± 0.6 | [30] |

Table 5: $IC_{50}$ values for some quinoxaline derivatives against CDK inhibitors

| Entry | Compound | Structure | Anti-cancer activity | Ref. |
|---|---|---|---|---|
| 1 | 7-Bromo-3-(3-hydroxy-phenylamino)-quinoxaline-2-carboxylic acid |  | Cell line IC50 MV4-11 32.9 ± 9.6 HCT-116 40.7 ± 0.1 | [33] |
| 2 | 7-Chloro-3-(3-hydroxy-phenylamino)-quinoxaline-2-carboxylic acid |  | Cell line IC50 MV4-11 35.5 ± 1.1 HCT-116 35.3 ± 1.0 | [33] |

side effects such as poisoning or death in animals and then humans.

## 4. Conflict of interest:

The authors have declared no conflict of interest.

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