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Review Article

Quinoxaline-Based Scaffolds Targeting Tyrosine Kinases and Their Potential Anticancer Activity

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Quinoxaline derivatives, also called benzopyrazines, are an important class of heterocyclic compounds. Quinoxalines have drawn great attention due to their wide spectrum of biological activities. They are considered as an important basis for anticancer drugs due to their potential activity as protein kinase inhibitors. In this review, we focus on the chemistry of the quinoxaline derivatives, the strategies for their synthesis, their potential activities against various tyrosine kinases, and on the structure–activity relationship studies reported to date.

Keywords: Anticancer / Kinase inhibitors / Quinoxalines / SAR / Synthetic strategies

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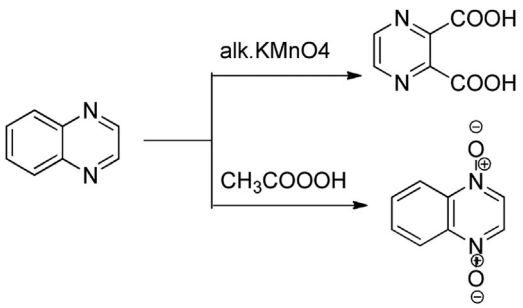
Introduction

Quinoxalines are derivatives of [1,4]diazine, also named as benzo[b][1,4]diazine [1]. It is a heterocyclic compound containing a benzene ring and a pyrazine ring [2]. Quinoxaline is described as a bioisostere of quinoline, naphthalene, and benzothiophene [3]. It possesses a low melting point (29–30°C), it is miscible with water, and it is a weakly basic compound (pK_a 0.56) forming salts with acids.

Oxidation of quinoxaline is dependent on the nature of the oxidizing agent being used. When using alkaline potassium permanganate, quinoxaline is oxidized to give pyrazine 2,3-dicarboxylic acid, while quinoxaline di-*N*-oxide results when using peracid [3].



Quinoxalines have drawn great attention due to their wide spectrum of biological activities. It is considered an important basis for anticancer drugs. Screening of quinoxaline as anticancer scaffold has been started since 1980s, where some quinoxalinone derivatives were synthesized and tested for anticancer activity. Moreover (1998–2002) Sanna et al. [4] reported the synthesis and anticancer *in vitro* evaluation

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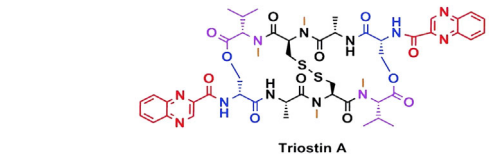
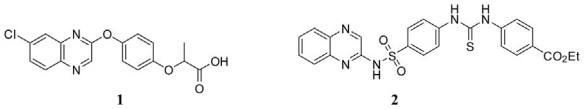
Abbreviations: Abl, Abelson tyrosine-protein kinase; **AML,** acute myeloid leukemia; **ATP,** adenosine triphosphate; **CDK,** cyclin-dependent kinase; **c-Met,** c-Met proto-oncogene; **DMSO,** dimethylsulphoxide; **EGFR,** epidermal growth factor receptor; **Eph,** ephrin receptors; **FAK,** focal adhesion kinase; **FGFRs,** fibroblast growth factor receptor; **FL,** full-length; **FLT3,** FMs-related tyrosine kinase 3; **HER,** human epidermal growth factor receptor; **HGF,** hepatocyte growth factor; **JAK2,** Janus kinase inhibitors; **JH1,** JAK homology 1; **KDR,** kinase insert domain receptor; **Lck,** lymphocyte-specific protein tyrosine kinase; **NRTK,** non-receptor tyrosine kinase; **PDGFR,** platelet-derived growth factor receptor; **PlGF,** placental growth factor; **PI3K,** phosphoinositide 3-kinase; **PTK,** protein tyrosine kinase; **RTK,** receptor tyrosine kinase; **SAR,** structure–activity relationship; **Src TK,** proto-oncogene non-receptor tyrosine-protein kinase; **VEGFR,** vascular endothelial growth factor receptor; **Wt,** wild-type.

of over 130 quinoxalin-2-ones after a wide study of the biological properties of this nucleus. Results of those screenings showed that some compounds were with promising anti-proliferative activity [4]. The quinoxaline scaffold has received much attention in recent years as part of a large number of potential therapeutic entities as such [5] or in their form *N*-oxide or *N*,*N*′-dioxide [6]. Being isosteric to purine antimetabolites, quinoxalines developed a promising platform for the discovery of active chemotherapeutic agents [7]. The antineoplastic antibiotic quinoxaline triostin A is characterized by cross-linked octa-peptide rings bearing two quinoxalines and is stabilized at its center by a cysteine pair. The two quinoxaline rings representing the planar aromatic ring structure are important for intercalation [8]. In 2001, Ding et al. [9] synthesized a quinoxaline phenoxypropionic acid derivative, compound **1** (XK469), as a topoisomerase II inhibitor. Later on, Ghorab et al. [10] designed compound **2**, the (quinoxalin-2-yl)-benzenesulfonamide derivative (CTBS), which possesses potent anticancer activity against a human liver cancer cell line ($HEPG_2$).





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Cancer is the second leading cause of death; despite advances in diagnosis and treatment, overall survival of patients remains poor. Scientific advances in recent years have enhanced our understanding of the biology of cancer. Human protein tyrosine kinases (PTKs) play a central role in human carcinogenesis [11], whereas cell cycle progression, cell division, and proliferation are viewed as a sequence of events controlled by a cascade of those protein kinases, so (PTKs) have emerged as the promising new targets [12].

PTKs constitute one of the largest and most important of protein families [13]. They are called phosphor-transferases regulating the biological activity of proteins by phosphorylation of specific amino acids with ATP as the source of phosphate, thereby inducing a conformational change from an inactive to an active form of the protein [14]. Phosphorylating substrate proteins resulted in modifying the activity, location, and affinities of up to 30% of all cellular proteins, and directing most cellular processes, particularly in signal transduction and coordination of complex pathways [13] (Fig. 1).

Protein kinases (PKs) are classified according to the amino acid side chain that they phosphorylate [14].

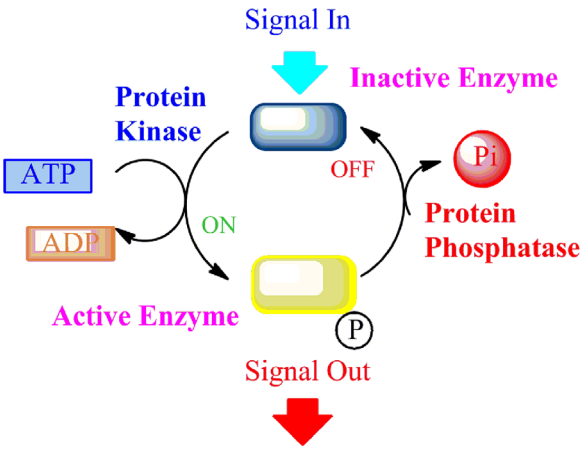


Figure 1. Protein kinases and protein phosphatases.

- Tyrosine kinases (TKs): Those phosphorylate the tyrosine phenolic hydroxyl. Ninety tyrosine kinase genes have been identified (58 receptor tyrosine kinases (RTKs) and 32 non-receptor tyrosine kinases [NRTKs]). Based on their extracellular and non-catalytic domain sequences, the RTKs and NRTKs have been further grouped into 20 and 10 subfamilies, respectively [15].
- Serine-threonine kinases: Six groups have been identified whose kinases primarily phosphorylate serine and threonine residues [16].
- Dual-specificity kinases: Phosphorylate all three amino acids, tyrosine, serine, and threonine amino acids [17].
- Histidine kinases: Recently discovered, they phosphorylate the nitrogen of histidine residues [14].

Tyrosine kinases

Tyrosine kinases are classified into RTKs and NRTKs (Table 1). RTKs transversing the cell membrane and have dual roles as enzymes and as receptors. These proteins have an extracellular domain that recognizes an external messenger (growth hormones, growth factors) and an intracellular kinase active site that becomes activated upon binding of the messenger, triggering a signaling cascade that ultimately controls the transcription of specific genes related to cellular proliferation and differentiation [15]. RTKs are essential for the transduction of extracellular signals into the cell [18]. Tyrosine kinase family also includes NRTKs. These proteins have no extracellular domain, they are activated by upstream signaling molecules such as G-protein-coupled receptors and immune system receptors, and also by receptor TKs [15]. They accomplish intracellular communication [18].

A RTK monomer consists of an N-terminal extracellular ligand-binding domain, a transmembrane domain, and a C-terminal intracellular domain with tyrosine kinase activity. The kinase domain has a bi-lobar structure, with an ATP-binding cleft located between the N- and C-terminal lobes. The ATP-binding site can be divided into three subregions:

Table 1. Types of tyrosine kinases.

Types of tyrosine kinase	
RTKs	**NRTKs**
• Epidermal growth factor receptor (EGFR). • Platelet-derived growth factor receptors (PDGFR). • Fibroblast growth factor receptors (FGFRs). • Vascular endothelial growth factor receptors (VEGFR).	• Proto-oncogene non-receptor tyrosine-protein kinase (Src). • Abelson tyrosine-protein kinase (Abl). • Focal adhesion kinase (FAK). • Janus kinase (JAK).

the adenine region, the sugar region, and the phosphate-binding region [18] (Fig. 2).

Ligand binding to the extracellular domain of the receptor promotes receptor dimerization, resulting in auto-phosphorylation of specific tyrosine residues of the cytoplasmic kinase domain [19]. Besides these phosphorylation sites for regulation of their own kinase activity, other phosphorylation sites of kinases are being used to control protein interactions. The activated receptor recruits interacting proteins that bind to certain phosphorylation sites [20]. Recruited and phosphorylated signaling proteins are subsequently able to phosphorylate other proteins. Activation of multiple signaling pathways leads to biological responses [21] including cell activation, proliferation, differentiation, migration, survival, and vascular permeability [22].

Most kinase inhibitors discovered till now are ATP competitive and present one to three hydrogen bonds to the amino acids located in the hinge region of the target kinase, thereby mimicking the hydrogen bonds that are normally formed by the adenine ring of ATP. The majority of kinase inhibitors do not exploit the ribose binding or the triphosphate binding site of ATP [23].

Herein, we describe various synthetic aspects for quinoxalines and their inhibitory activity against various tyrosine kinases.

Synthetic strategies for quinoxalines

Numerous synthetic strategies have been outlined for the synthesis of quinoxaline nucleus which is incorporated in

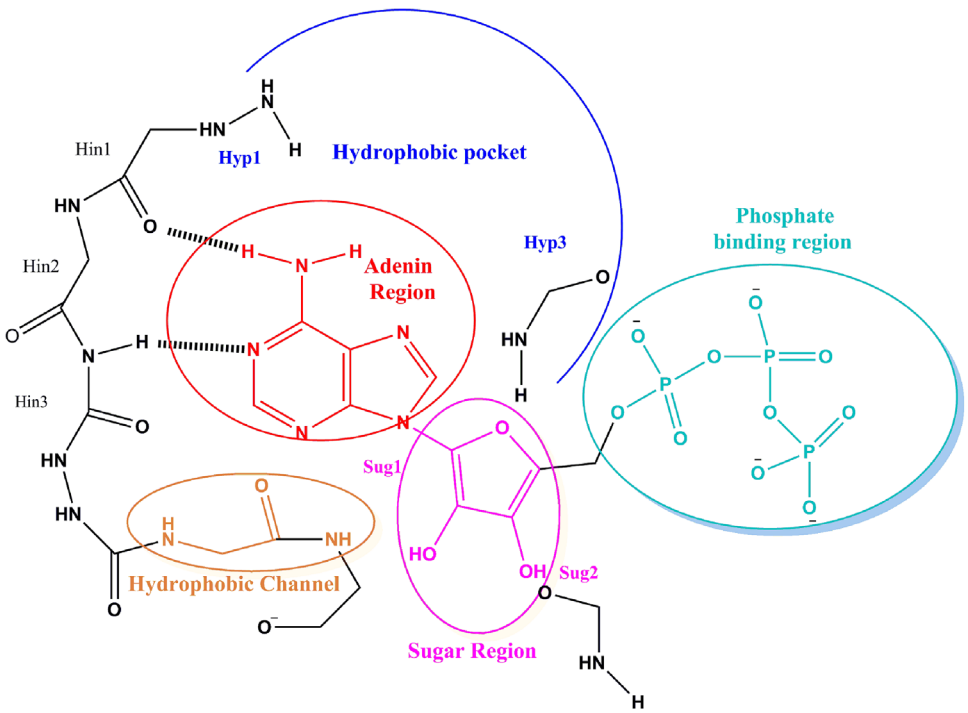


Figure 2. Model of the ATP-binding site of protein kinases.

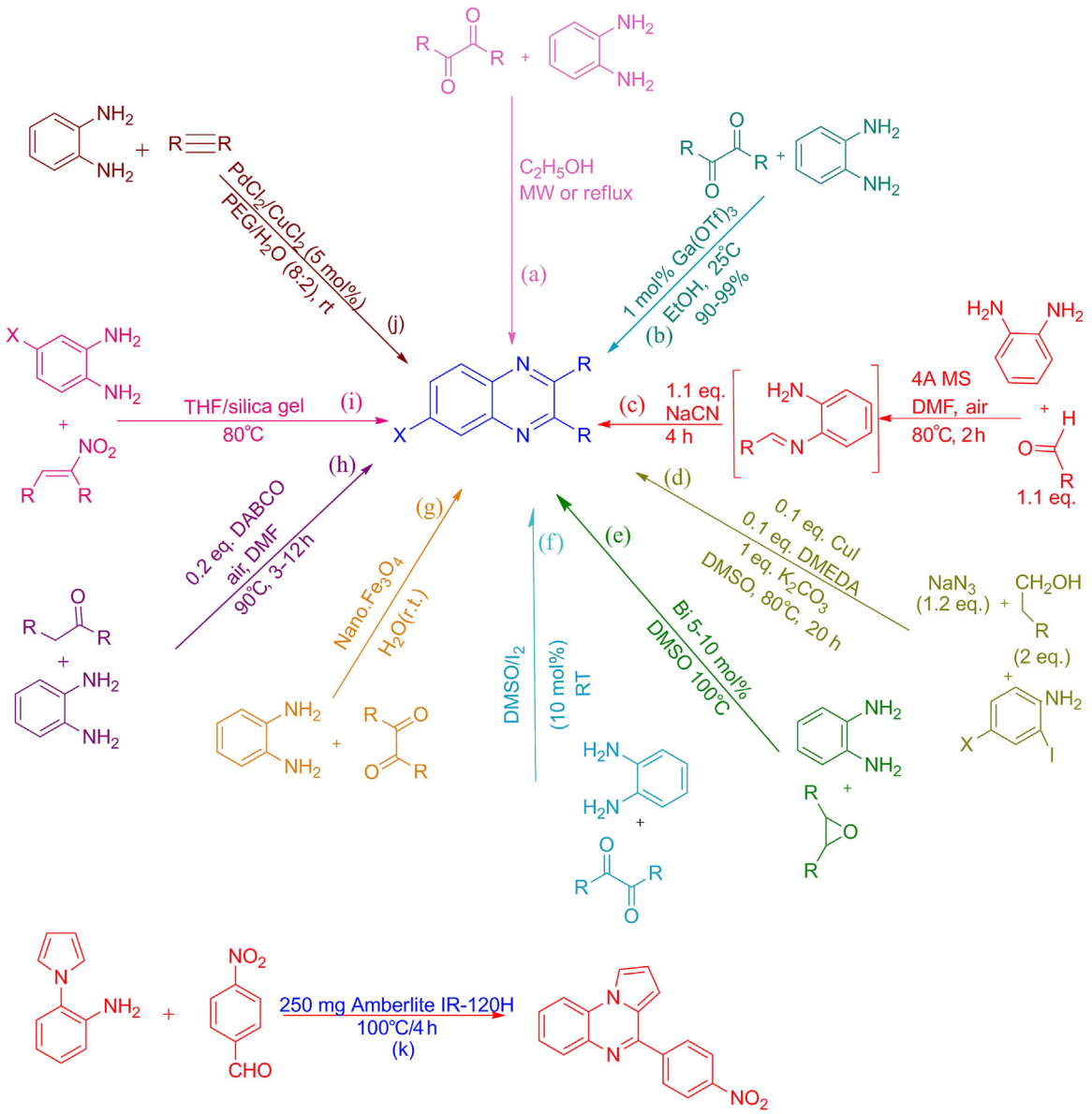


Figure 3. Synthetic approaches for quinoxalines.

various kinase inhibitors (Fig. 3). Quinoxaline itself is prepared by the reaction of *o*-phenylenediamine and α-ketocarboxylic acids [24] through different methods including one-pot and microwave methods [25, 26]. One-pot efficient green synthesis of 1,4-dihydroquinoxaline-2,3-dione derivatives has been achieved in a one-pot reaction at room temperature under solvent free conditions by a simple grinding method [27].

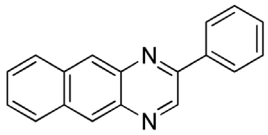
Kowalski et al. [28] in 2006 reported the synthesis of quinoxaline through refluxing *o*-phenylenediamine with 1,2-dicarbonyl compounds in ethanol under microwave irradiation. High yield, short reaction time, pure products without purification and using only ethanol instead of toxic and expensive solvents for isolation of the products, were the advantages of this method (Route a). Cai et al. [29], in 2008, have reported gallium(IIII) triflate-catalyzed reactions of phenylene-1,2-diamines and 1,2-diketones which produce quinoxalines in excellent to quantitative yields (Route b).

In 2014, Cho et al. [30] have reported one-pot two-step cyanide-mediated sequential reactions of *ortho*-phenylenediamines with aldehydes under aerobic oxidation conditions affording 2-aminoquinoxalines in 90% yields (Route c). In

2013, Yuan et al. [31] reported copper-catalyzed condensation and C–N bond formation of 2-iodoanilines, aryl acetaldehydes, and sodium azide, in a one-pot three-component reaction, enabling the synthesis of quinoxalines in good yields (Route d). Direct and catalytic synthesis of quinoxaline derivatives from epoxides and ene-1,2-diamines by a bismuth-catalyzed oxidative coupling, by using Bi (5 mol%) as catalyst in the presence of DMSO solvent at 100°C gave 53–70% yield [32] (Route e). Bhosale et al. [33] have reported use of molecular iodine as the catalyst for a one-pot synthesis of quinoxaline derivatives at room temperature (95% yield) (Route f). In 2010, Lü et al. [34] reported a novel environmentally friendly procedure for the synthesis of quinoxaline derivatives in the presence of magnetic Fe_3O_4 nanoparticles through the reaction between 1,2-diamines and 1,2-dicarbonyl compounds in water to afford quinoxaline derivatives in high yield (Route g). In 2011, Qi et al. [35] have reported aerobic oxidation of deoxybenzoins is efficiently catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) with air as the sole oxidant to give the corresponding benzyls in excellent yields. The process has been successfully extended to a one-pot synthesis of quinoxalines from benzyl ketones and aromatic 1,2-diamines (Route h). In 2014, Li et al. [36] reported the synthesis of quinoxalines via reacting nitroolefins and *o*-phenylenediamine with silica gel catalyst in THF at 80°C (yield = 90%), but gave benzimidazoles efficiently in water. The reaction was solvent-dependent chemoselective reaction, affording two cyclized products selectively with the same substrate, short reaction time, operational simplicity, as well as available starting materials and non-toxic catalysts (Route i). Oxidation of alkynes efficiently using the catalytic amount of $PdCl_2$ and $CuCl_2$ in PEG-400 in the presence of water have been reported by Chandrasekhar et al. [37] in 2010. Their study provided excellent yields of the corresponding 1,2-diketones. A variety of alkynes were well-suited substrates for the oxidation under the described conditions. Further, the optimized conditions were successfully utilized for the one-pot synthesis of 2,3-disubstituted quinoxaline derivatives (Route j). In 2015, Kamal et al. [38] reported an environmentally benign efficient method for the synthesis of pyrrolo[1,2-*a*]quinoxalines by reacting 1-(2-aminophenyl)pyrrole and 4-nitrobenzaldehyde in the presence of green and recyclable catalyst Amberlite IR-120H resin under solvent-free condition. Optimization of the reaction was carried out through reacting 250 mg of Amberlite IR-120H at 100°C for 4 h with an electron withdrawing groups on the aldehyde giving a yield of 92% (Route k).

Quinoxalines as kinase inhibitors and potential anticancer agents

Quinoxalines are proved to be selective ATP competitive inhibitors in many kinases as compounds **3** and **4** (AG1385, AG1295) which are quinoxaline derivatives that were shown to selectively block the EGFR kinase [39].



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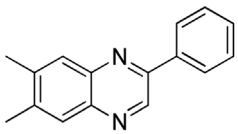

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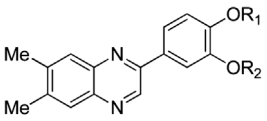
Novartis claimed a series of quinoxaline amides (38) as inhibitors of kinases including FGFR3, KDR, c-Kit, PDGFR, LCK, and c-ABL for use in PTK mediated diseases [40].

Quinoxalines as vascular endothelial growth factor receptor (VEGFR) inhibitors

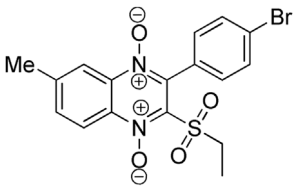
It has been validated that multiple tyrosine kinases are involved in angiogenesis [41]. VEGF has settled to be the most important regulator of angiogenesis [42, 43]. VEGFs regulate vascular development, angiogenesis, and lymph angiogenesis by binding to a number of receptors [44]. EC proliferation and migration, two crucial steps in angiogenesis, are mediated through a specific VEGF receptor, the kinase insert domain-containing receptor (KDR or VEGFR-2) [45]. The VEGF family comprises five family members VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). This family of growth factors regulate angiogenesis and lymphangiogenesis through differentially binding to Class V RTKs (VEGFR1–3) and their co-receptors such as neuropilins (NRP1 and NRP2) [46]. These (VEGFR1–3) receptors are transmembrane tyrosine kinases which upon binding of their ligands to the extracellular domain of the receptor activate a cascade of downstream proteins after the dimerization and autophosphorylation of the intracellular receptor tyrosine kinases. The receptors identified so far are designated VEGFR-1, VEGFR-2, and VEGFR-3 [47].

In 2002, Jacqueline et al. [48] compared the effects on VEGF-induced angiogenesis of a number of known anti-angiogenic agents together with some novel derivatives including isoflavone, indomethacin, the 3-arylquinoxaline compound **5** (SU1433) and its derivatives, the benzoic acid derivative, the oxindoles, together with their simple *N*-benzyl derivatives [48]. The study revealed that 3-arylquinoxaline (**5**) is a potent TK inhibitor, inhibiting downstream effects of VEGF both *in vitro* and *in vivo* [49]. The results support this since 10 μM of compound **5** almost fully inhibited angiogenesis. Three relatively simple *O*-substituted derivatives were synthesized in order to assess the importance of the phenolic OH groups. Converting one of the phenolic OH groups of **5** into methyl and benzyl derivatives **6** and **7** reduced activities compared to **5**, whereas the acetyl derivative **8** has the same activity of that of the parent compound.



5 R_1=R_2=H (SU1433)
6 R_1=Me, R_2=H
7 R_1=Bn, R_2=H
8 R_1=Ac, R_2=H

In 2011, Weng et al. [50] studies revealed that compound **9** suppresses hypoxia-induced HIF-1α protein accumulation and VEGF expression in human hepatoma (SMMC-7721) cells but has no significant inhibitory effects on HIF-1α mRNA levels.



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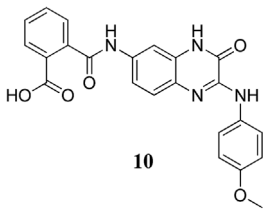
In 2012, Shahin et al. [51] designed a series of new quinoxaline-based derivatives which were further biologically evaluated for their inhibitory activity against VEGFR-2.

A profound study of the structure–activity relationship (SAR) of type-II VEGFR-2 inhibitors was carried out in order to design the target compounds. Among the synthesized compounds, compound **10** displayed the best inhibition percentage against VEGFR-2 which is 69% at a concentration of 10 μM and compound **11** displayed the best IC_{50} value of 10.27 μM.



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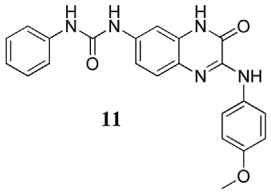

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Quinoxalines as platelet-derived growth factor receptor (PDGFR) inhibitors

The platelet-derived growth factor (PDGF, a potent mitogen) plays a vital role as a regulator of cell growth. Binding of PDGF to its transmembrane receptor (PDGFR) results in tyrosine phosphorylation of natural substrates that act by a number of pathways [52]. The PDGF AA, AB, and BB isoforms interact differentially with PDGF α- and β-receptors. They are transmembrane tyrosine kinases whose activation by ligand binding is essential for cellular signaling. PDGF and its receptors are involved in regulation of vital aspects of embryogenesis [53]. PDGFRs belong to the type III tyrosine kinase family. They are not expressed in normal tissues but only in fibroblasts, smooth muscle cells in lungs and pericytes of the vascular wall. PDGFR activation has been reported in a number of malignancies, including non-small cell lung cancer (NSCLC) and gliomas [54].

In 1996, Gazit et al. [53] prepared a series of 3-indoleacrylonitrile tyrphostins, 2-chloro-3-phenylquinolines, and 3-arylquinoxalines and tested for inhibition of platelet-derived growth factor receptor tyrosine kinase (PDGF-RTK) activity. The potency of the inhibitors was found to be quinoxalines > quinolones > indoles. Concerning quinoxaline, the SAR studies were as shown in Fig. 4 and Table 2.

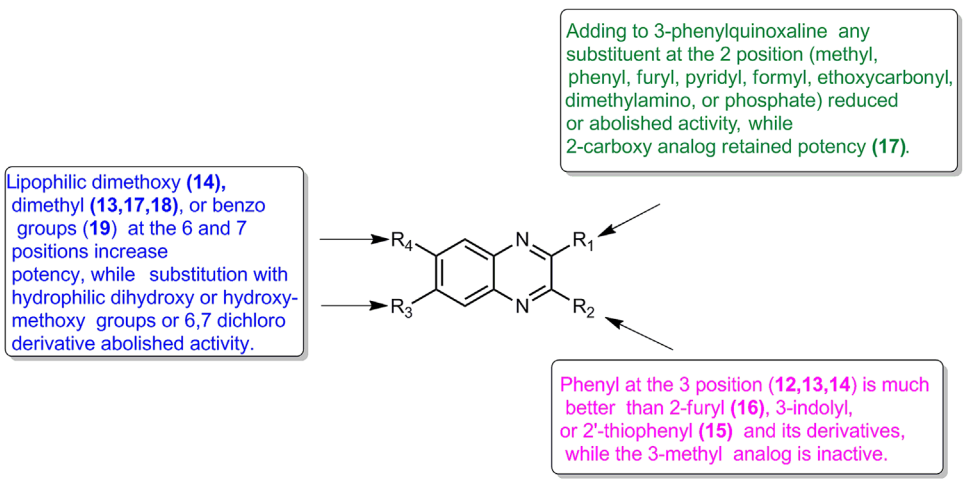
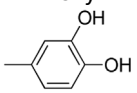
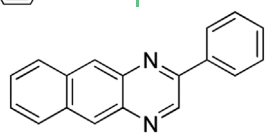
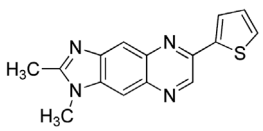


Figure 4. Structure–activity relationship for 3-arylquinoxalines as (PDGFR) inhibitors.

Table 2. 3-Arylquinoxaline derivatives and their cytotoxic activity.

Compound no.	R_1	R_2	R_3	R_4	IC_{50} (μM)
12	H	Phenyl	H	H	10
13	H	Phenyl	CH_3	CH_3	0.4
14	H	Phenyl	OCH_3	OCH_3	0.8
15	H	2-Thiophene	H	H	100
16	H	2-Furan	H	H	>100
17	COOH	Phenyl	CH_3	CH_3	1.0
18	H		CH_3	CH_3	0.6
19					0.9

Gazit et al. [55] reported in 2003, tricyclic quinoxalines as highly potent and selective inhibitors of the type III receptor tyrosine kinases PDGFR, FLT3, and KIT. These compounds were generated in order to improve bioavailability over the highly hydrophobic bicyclic quinoxalines studied in their previous study [53]. Imidazolo-quinoxalines, which are potent and selective class III tyrosine kinase inhibitors possess balanced solubility properties and seem to be non-cytotoxic. Therefore, they are more suitable than the highly hydrophobic bicyclic quinoxalines for development as anticancer agents. Substituents at position-2 greatly diminished potency. It seems that the 7,8-positions area is less congested and amenable to further SAR study [55]. Compounds **20/21** (AGL 2043/44) were designed in order to obtain quinoxalines with enhanced solubility compared to the hydrophobic compounds. The study revealed that the most active inhibitor (**20**) is 15–20 times more potent than its isomer (**21**) [55].



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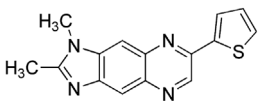

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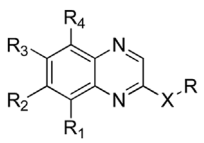
The quinoxalines inhibitors of PDGF receptor possess 1,4-diaza substitution and lack the four amino radical making them less similar to adenine. Besides the main pharmacophore, all these inhibitors contain an aryl group that interacts with a lipophilic pocket near the ATP binding site, not available to ATP which is essential for the potency of the inhibitors and seems to be an important factor in their selectivity, as the aryl attachment position is position 3 in the quinoxalines [56].

Myers et al. [57] in 2003 have found novel substituted 2-anilino- and 2-cycloalkylamino quinoxalines to be useful and selective inhibitors of PDGF-R autophosphorylation. Replacement of an anilino-substituent with substituted cyclohexylamino- or norbornylamino substituents led to significant improvements in the pharmacokinetic profile of these analogs.

The dimethoxy groups at R_2, R_3 positions were essential for activity, removing both of them (**22**, $IC_{50} = 5.1$ μM) lowers the potency in comparison with the prototype PDGF-R inhibitor (**28**, $IC_{50} = 0.461$ μM). However, a single methoxy substitution can improve potency by up to 100-fold depending on the position of substitution. The fact that the 6,7-dimethyl substituted anilinoquinoxaline (**23**) is 60-fold less potent than the dimethoxyl analog (**25**) seems to suggest that the two oxygen atoms might be involved in hydrogen bonding and that this region of the quinoxaline could be used as a handle for chemical manipulations in order to change the chemical and physical properties of target molecules. Exchange of the amine or oxo (**26**) linker for sulfur (**27**) also leads to a dramatic loss in activity for the cyclohexyl analog (Table 3) [57].

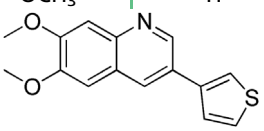


Quinoxalines as Src kinase inhibitor

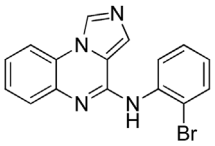
The Src family of TKs belongs to a class of non-receptor TKs, which are present in the cytoplasm and participate in signaling pathways controlling proliferation, migration, and angiogenesis. As a cytoplasmic protein, c-Src has a critical role in mediating signal transduction via interactions with multiple proteins and protein complexes [58].

Although anilino-substituted quinoxalines are known inhibitors of tyrosine kinases, Chen et al. [59], in 2002, present a novel tyrosine kinase inhibitor where an imidazo

Table 3. **2-Anilino- and 2-cycloalkylamino quinoxaline derivatives and their cytotoxic activity.**

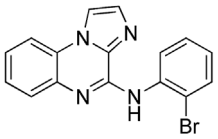
Compound no.	R_1	R_2	R_3	R_4	X	R	IC_{50} (μM)
22	H	H	H	H	NH	Ph	5.1
23	H	CH_3	CH_3	H	NH	Ph	0.34
24	H	H	OCH_3	H	NH	Ph	1.6
25	H	OCH_3	OCH_3	H	NH	Ph	0.006
26	H	OCH_3	OCH_3	H	O	Cyclohexyl	0.065
27	H	OCH_3	OCH_3	H	S	Cyclohexyl	0% @ 1 μM
28							0.461

group is fused to the quinoxaline ring. A series of 1,5-imidazoquinoxalines have been identified as inhibitors of Lck with excellent potency ($IC_{50} < 5$ nM) as well as good cellular activity against T cell proliferation ($IC_{50} < 1$ mM). Herein, the requirements for the core heterocycle were fully explained through the SAR studies with an optimal 2,6-disubstituted aniline group (Fig. 5).



29

Lck $IC_{50} = 170$ nM



30

Lck $IC_{50} > 50000$ nM

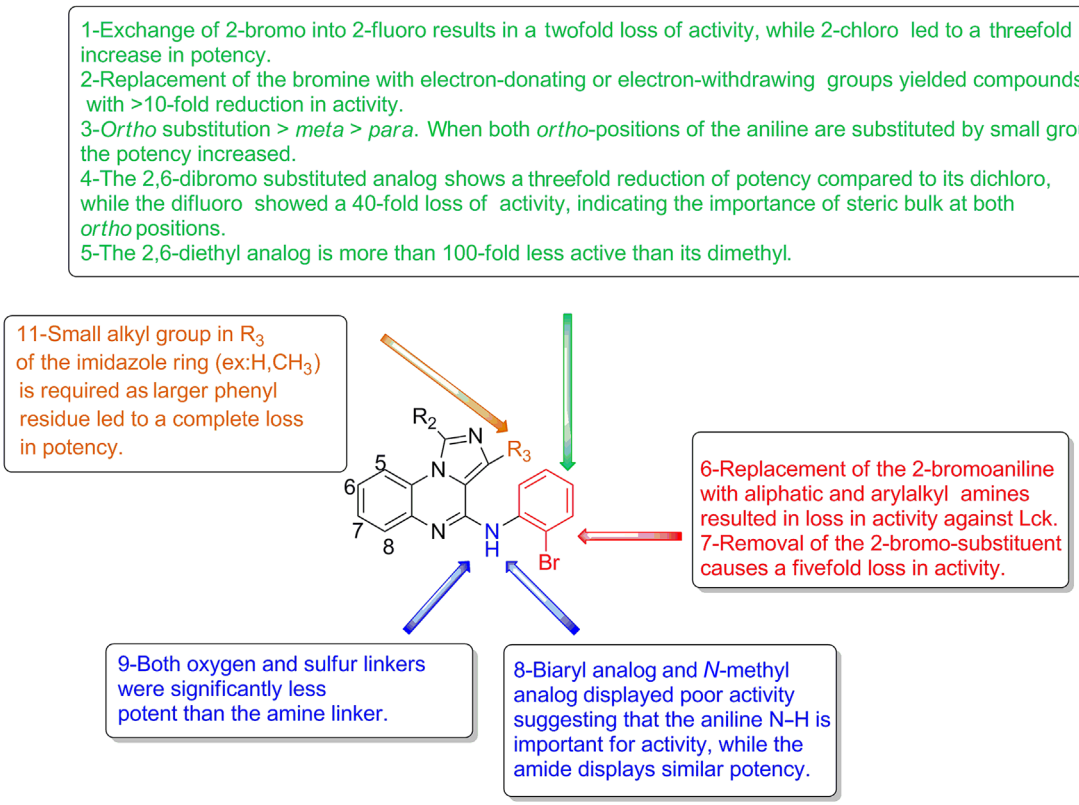


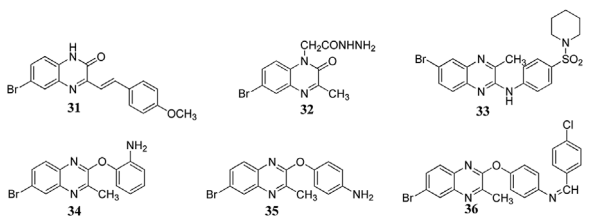
Figure 5. SAR of 1,5-imidazoquinoxalines as Lck inhibitors.

Chen et al. studies revealed that N-2 nitrogen of the imidazole ring plays an important role in enzyme binding (presumably as a hydrogen bond acceptor) and that 1,2-imidazoquinoxaline was formed as a mixture (1:1) of two regioisomers (**29**, **30**), in which compound **30** displays poor activity against Lck compared with **29** [59].

Quinoxalines as inhibitors of c-Met kinase

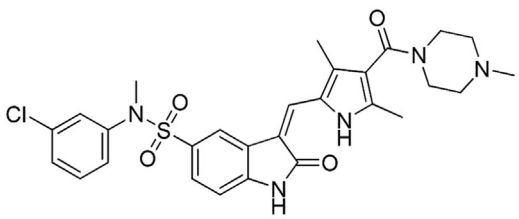
Met kinase, as a member of RTK family, is important for normal mammalian development together with its ligand, hepatocyte growth factor (HGF) [60]. HGF c-Met is regulating many critical cellular processes including embryological development, cell growth, differentiation, neovascularization, and tissue regeneration [61, 62]. It has been shown to be deregulated and associated with high tumor grade and poor prognosis in a number of solid tumors, as it can become activated by a variety of mechanisms, including gene amplification and mutation inducing motility, invasiveness, and tumorgenicity into the transformed cells. Leading to receptor dimerization and recruitment of several SH2 domain containing signal transducers that activate various pathways [60]. Therefore, inhibition of HGF/c-Met signaling pathway has shown great therapeutic benefit as novel cancer therapy [63–66].

In 2015, Abbas et al. [67] reported the design and synthesis of novel quinoxaline derivatives, considering the number and position of the substituent which are considerably important for cytotoxicity. The designed compounds were screened *in vitro* for their anti-proliferative activity against three tumor cell lines: breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460), and CNS cancer (SF-268). It was found that six of these compounds (**31–36**) exhibited the highest binding affinity with CDOCKER energy score, and the lowest IC_{50} values against the three cancer cell lines (Table 4). Among these compounds, **32** and **34** were more potent than the reference doxorubicin.



Wu et al. [68], in 2012, have designed two series of new analogs by replacing the quinoline scaffold of their lead with quinoxaline and pyrido[2,3-*d*]pyrimidine frameworks. Their study took the advantage of the widely used quinoxazoline skeleton as a privileged scaffold of RTK inhibitors and modified it in order to design new series of quinoxaline analog where moderate c-Met inhibitory activity was observed [68]. Their SAR is illustrated in Fig. 6.

A series of quinoxaline inhibitors of c-Met kinase have been studied by Porter et al. [60] in 2009 and their SAR is illustrated in Fig. 7 and Table 5. X-ray crystal structure of the c-Met-28-c-butyrolactone complex revealed a conformational change to Met1229 and Tyr1230 similar to that observed in the crystal structure of SU11274 forming a H-bond to the backbone NH of Asp1222. They believe that the electron withdrawing effect of the nitro group in **46** enhances pi-stacking with the phenyl ring of Tyr1230 and forms a H-bond with Asp1222, since it produced 30-fold increasing in potency (c-Met $IC_{50} = 0.035$ μM). Benzoxadiazole, as an isosteric replacement for the nitro group in a PDE4D inhibitor [69], showed equal potency (c-Met $IC_{50} = 0.031$ μM) with **46**, suggesting a similar mode of binding [60].



Pyrrolo[3,2-*b*]quinoxaline derivatives as type $I_{1/2}$ and II Eph tyrosine kinase inhibitors

Eph receptors are the largest subfamily of RTKs. Their ephrin ligands are important mediators of cell–cell communication regulating cell attachment, shape, and mobility. Their signaling is essential for the development of many tissues and organs such as the nervous and cardiovascular systems. EphB4 overexpression has been linked to several types of cancer, including breast [70], colon [71], and ovarian [72]. Both Ephs and ephrins are membrane-bound and their interactions at sites of cell–cell contact initiate unique bi-

Table 4. The quinoxaline derivatives and their cytotoxicity in comparison with doxorubicin.

Compound no.	MCF-7 (μM)	NCI-H460 (μM)	SF-268 (μM)
31	0.06 ± 0.006	0.06 ± 0.006	0.2 ± 0.08
32	0.01 ± 0.001	0.02 ± 0.004	0.06 ± 0.002
33	1.62 ± 0.48	0.67 ± 0.16	1.8 ± 0.06
34	0.02 ± 0.001	0.03 ± 0.006	0.06 ± 0.008
35	0.81 ± 0.04	0.52 ± 0.04	0.08 ± 0.006
36	0.08 ± 0.002	0.08 ± 0.003	0.02 ± 0.002
Doxorubicin	0.04 ± 0.008	0.09 ± 0.008	0.09 ± 0.007

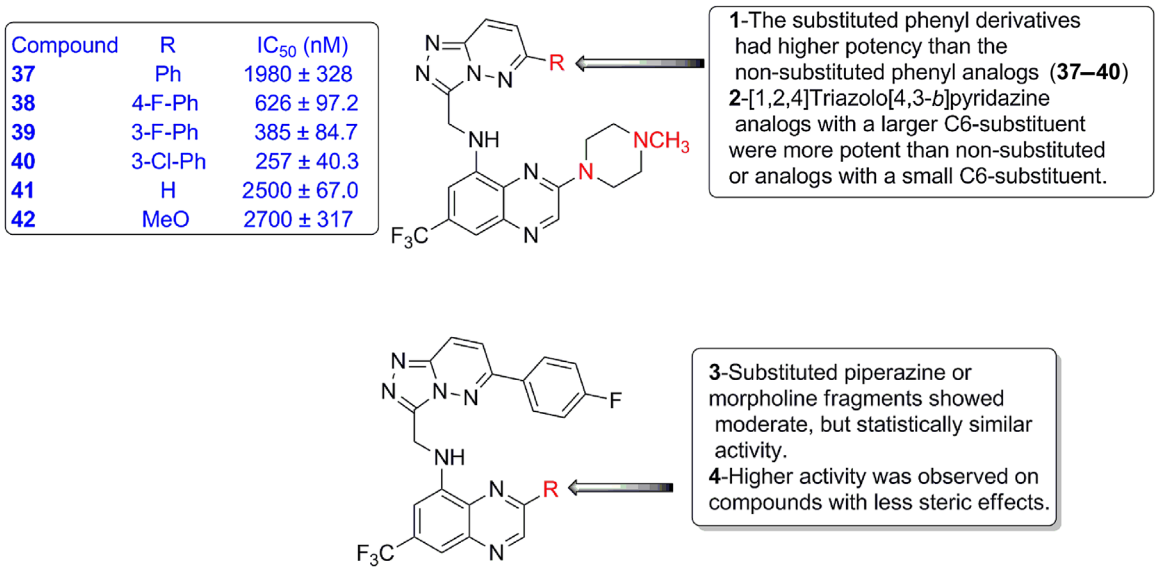
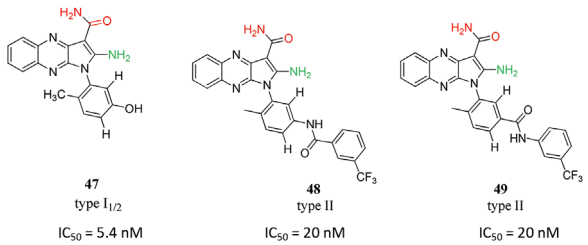


Figure 6. SAR studies for new series of quinoxalines as c-Met inhibitors.

directional signaling cascades where information is transduced in both the receptor and the ligand-expressing cells [73].

Unzue et al. [74] in 2014 synthesized about 25 pyrrolo[3,2-*b*]quinoxaline derivatives, three of which (compounds **47**–**49**) having low IC_{50} values for Eph kinases *in vitro* and a good selectivity profile on a panel of 453 human kinases.



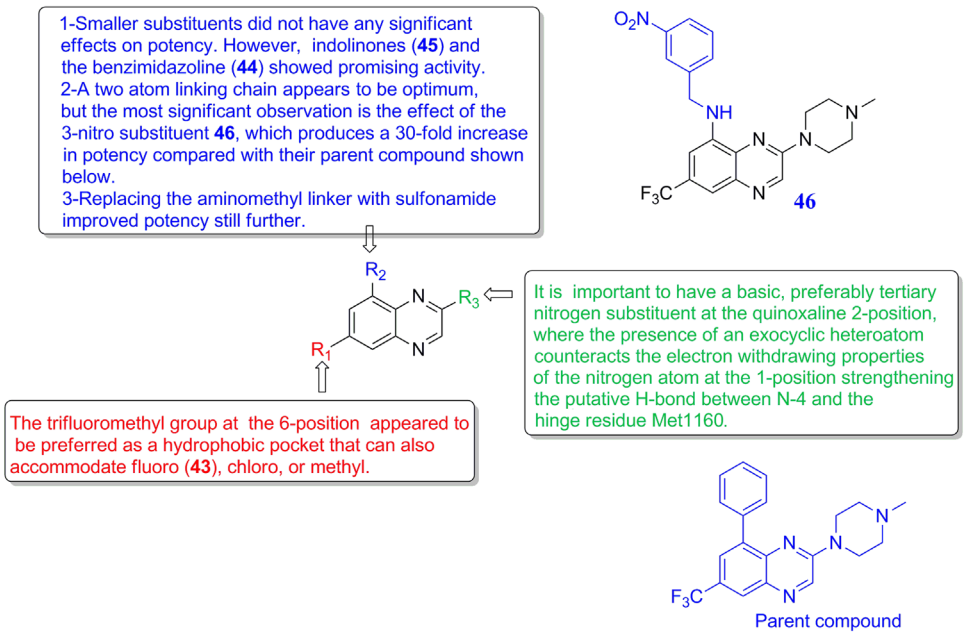
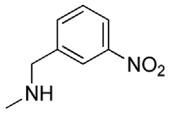


Figure 7. Structure–activity relationship for quinoxalines as c-Met inhibitors.

Table 5. **Effect of substituents on the biological activity of quinoxalines.**

Compound no.	R_1	R_2	R_3	IC_{50} (μM)
43	F	Phenyl	*N*-Methyl piperazinyl	3.9
44	CF_3	Benzimidazoline	Piperazine	0.39
45	CF_3	Indolinone	Piperazine	0.17
46	CF_3		Piperazine	0.035

The X-ray crystal structures of the EphA3 kinase in complex with two high-nanomolar inhibitors based on the 2-amino-1-phenyl-pyrrolo[3,2-*b*]quinoxaline-3-carboxamide scaffold showed that it occupied the ATP binding site with the phenyl substituent located into the so-called hydrophobic pocket. The amino substituent at position 2 of the pyrrole ring is involved in a hydrogen bond with the side chain hydroxyl of the Thr693 gatekeeper and the backbone carbonyl of Glu694. Furthermore, the amide substituent at position 3 of the pyrrole ring is optimally oriented for two hydrogen bonds with the backbone polar groups of Met696 providing a total of three hydrogen bonds with the backbone of the hinge region [74].

This structural information was used to design type $I_{1/2}$ and II derivatives by taking advantage of the existing knowledge on privileged chemical motif:

(1) For designing type $I_{1/2}$ hydroxyl group should be located in *meta* position of the phenyl ring.
(2) For designing type II hydrophobic moieties should be connected to the phenyl ring by amide or urea linkers.
(3) It is possible to "elongate" a type $I_{1/2}$ into a type II inhibitor by introducing an amide or urea linked to a bulky hydrophobic group. These type II linkers are involved in the same hydrogen bonds as the type $I_{1/2}$ bearing a hydroxyl group in the same position, whereas the hydrophobic moiety occupies the pocket resulting from the displacement of the Phe side chain of the DFG motif.
(4) The similar selectivity profiles of types $I_{1/2}$ and II inhibitors show that the moiety in contact with the gatekeeper's side chain and hinge region is crucial for determining specificity [74] (Fig. 8).

Quinoxaline derivatives as novel EGFR/HER-2 dual inhibitors

The epidermal growth factor receptor (EGFR) is a transmembrane PTK playing a crucial role in regulating cell proliferation, adhesion, migration, differentiation, survival, and apoptosis. It has been implicated in many types of cancer [75]. The EGFR family includes the human epidermal growth factor receptor (EGFR/ErbB-1), human epidermal growth factor receptor 2 (HER-2/ErbB-2), human epidermal growth factor receptor 3 (HER-3/Erb-3), and human epidermal growth factor receptor 4 (HER-4/Erb-4) [76]. Among these, EGFR and HER-2 play a crucial role in the development and malignancy of many human neoplasms [77], such as NSCLC, breast, stomach, colon, prostate, and ovarian cancers [78]. Therefore, compounds that inhibit the kinase activity of EGFR and/or HER-2 (after binding to their ATP binding sites) are of potential interest as new anticancer therapeutics [79].

In 2015, Zong et al. [78] designed 25 pyrazole–quinoxaline derivatives functioning as EGFR and HER-2 kinases inhibitors, most of the synthesized compounds exhibited promising affinity for EGFR or HER-2 kinase as well as potent antiproliferative activity [78]. Taking the advantage of pyrazole ring which has been reported as EGFR or HER-2 inhibitors (thiazolyl–pyrazoline scaffold) [80, 81], and quinoxaline derivatives which have been described as potential candidates for the treatment of cancer [82–84]. SAR analysis indicated that electron-donating substituent at the R_1 and/or R_2 position might increase the inhibitory activity against EGFR/HER-2 (Fig. 9). Compound **57** showed excellent EGFR/HER-2 inhibitory activities and better antiproliferative activity

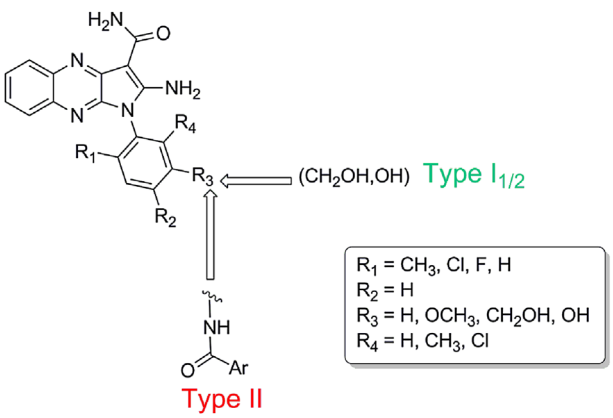


Figure 8. Design of type $I_{1/2}$ and II derivatives.

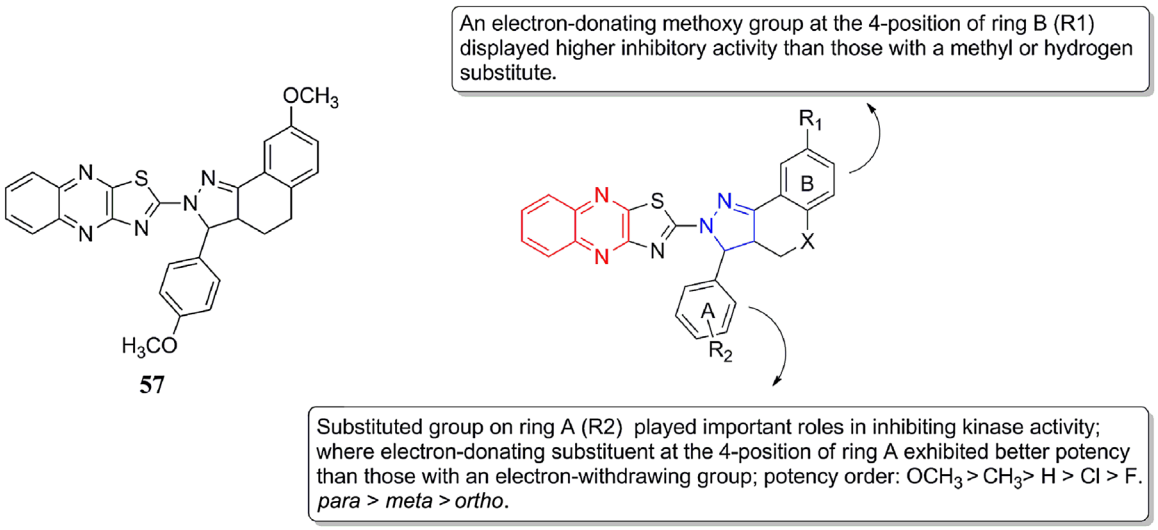


Figure 9. Structure–activity relationship of pyrazole–quinoxaline analogs.

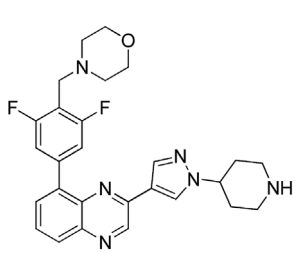
against A549 (3.04 μM) and MCF-7 (1.91 μM) cell lines than erlotinib (4.28 μM), (2.32 μM), receptively (Table 6).

Zong et al. [78] mentioned that the quinoxaline moiety might play a crucial role in the compounds' EGFR inhibition activity by forming π–π interactions and hydrogen bonding interactions with the residues in the binding pocket [78].

Quinoxalines as JAK2 inhibitors

The acquired activating point mutation discovery in the pseudo kinase domain of JAK2 (Janus kinase inhibitors, also known as jakinibs [85]), valine 617 to phenylalanine mutation has brought much attention to this kinase [86–88]. This mutation is found in nearly every patient with polycythemia vera (PV) and every second patient suffering from essential thrombocythemia and primary myelofibrosis [89]. In 2010, Baffert et al. [90] reported a novel substituted quinoxaline, compound **58** (termed NVP-BSK805), which was found to be potent and selective ATP-competitive inhibitor of JAK2 and JAK2 wild-type enzymes. Molecular modeling and drug design based on the structure of the JAK2 tyrosine kinase domain in complex with a pan-JAK inhibitor tool compound, whereas compound **58** displays more than 20-fold selectivity toward JAK2 over the other JAK family members and more than 100-fold selectivity over a panel of kinases *in vitro*. It was found to have favorable absorption, distribution, metabolism, and excretion properties.

Besides exhibiting good oral bioavailability and a long half-life *in vivo*, **58** was efficacious in suppressing recombinant human erythropoietin-induced polycythemia and extramedullary erythropoiesis in mice and rats [90] (Table 7).



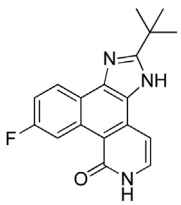


Table 6. Effect of substituents in the biological activity of pyrazole–quinoxaline.

Compound no.	R_1	R_2	X	A549 IC_{50} (μM)	MCF-7 IC_{50} (μM)	Hela IC_{50} (μM)	HepG2 IC_{50} (μM)
50	H	H	C	8.32	6.88	2.98	4.38
51	H	4-OCH_3	C	4.38	3.28	8.25	2.58
52	H	4-F	C	28.26	15.26	5.38	10.08
53	H	4-Cl	C	15.26	11.33	15.24	17.18
54	H	3-Cl	C	15.26	18.26	9.28	10.08
55	–OCH_3	H	C	5.38	3.48	6.28	4.18
56	H	H	O	4.12	6.83	5.88	12.56
57	–OCH_3	4-OCH_3	C	3.04	1.91	7.38	5.76

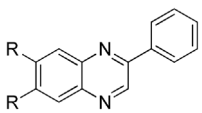
Table 7. Activity of compound 58 over three types of JAK2 kinases.

JAK2 types	58 IC_{50} (nmol/L)	JAK inhibitor 1, IC_{50} (nmol/L)
JAK2 JH1	0.48 ± 0.02	1.04 ± 0.04
FL JAK2 V617F	0.56 ± 0.04	1.73 ± 0.05
FL JAK2 wt	0.58 ± 0.03	1.59 ± 0.09

Quinoxaline as FLT3 inhibitors

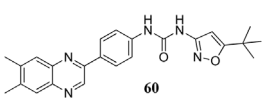
FMS-like tyrosine kinase 3 (FLT3) is a class III receptor tyrosine kinase including FMS, c-KIT, and two genes encoding PDGFR α and β [91]. It is the most common mutated gene in AML (was cloned in 1993 [92]) and has been expressed in most tissues including hematopoietic organs (spleen and bone marrow), prostate, ovary, heart, lung, kidney, and placenta [93, 94]. FLT3 structure is composed of an N-terminal extracellular ligand binding domain with five immunoglobulin-like motifs, a transmembrane domain followed by an intracellular juxtamembrane domain, and a C-terminal tyrosine kinase domain [95].

Two classes of activating FLT3 mutations have been identified and are present in 30% of all AML cases: FLT3 internal tandem duplications (ITDs) (23% of all AML patients) [96] and point mutations at residues D835 or I836 in the activation loop of FLT3 (7% of AML cases) [94, 97, 98], both types of mutations constitutively induce the tyrosine kinase activity. Quinoxalines AG1295 (**4**) and AG1296 (**59**) were the first inhibitors developed for FLT3 [99, 100].



4 R = Me
59 R = OMe

In 2009, Chao et al. [101] identified bisarylurea and they were evaluated as a uniquely potent and selective FLT3 inhibitor. In 2015, Göring et al. [95] designed a set of diverse quinoxaline-bisarylureas, which were profiled in an FLT3 kinase activity assay. Their study used the pharmacophore features of different known inhibitors as a starting point for a new optimization algorithm for type II TKIs, starting from an *in silico* library pharmacophore search and induced-fit docking in the known FLT3 structure. These *in silico* hits were synthesized and evaluated in biological assays resulting in tenfold increased inhibitory potency relative to that of compound **4**. The most active compounds were **60** and **61**, exhibiting IC_{50} values of 71 (**60**) and 32 nM (**61**), respectively. Then the toxicity of compound **60** against **4** was evaluated in *in vivo* (zebrafish) embryo phenotype assay, observing no toxicity below 20 mM for both compounds.



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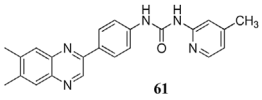


61

Future studies will focus on the development of quinoxaline-based inhibitors of the active kinase state to overcome increasing resistance to type II inhibitors caused by the FLT3 D835Y mutation [95].

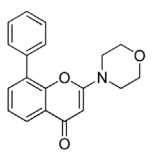
Quinoxalines as PI3Kα inhibitors

The PI3Ks are lipid kinases and considered to be one of the most highly activated and mutated signaling cascades for a wide spectrum of cancers [102, 103]. Among these, PI3Kα has emerged as a promising target for cancer therapy due to prevalent gain-of-function mutations which have been observed in PI3Kα [104]. Several studies are currently being focused on developing inhibitors targeting PI3K, especially PI3Kα, for the treatment of cancer [105–107].

In 2012, Wu et al. [108] built up a pharmacophore model of PI3Kα inhibitors, this model revealed a series of morpholino–quinoxalines as potential PI3Kα inhibitors. Synthesized target compounds exhibited good to excellent *in vitro* cytotoxicity against tested human cell lines [108].

Their lead compound was 2-morpholino-3-phenyl-sulfonyl-quinoxaline with a predictive PI3Kα IC_{50} of 1.0 μM, containing a morpholino-aryl scaffold, as shown in the widely studied PI3K inhibitor **62** (LY294002) which was believed to be one of the privileged structures for PI3K inhibition; it has been chosen for further synthesis and biological evaluation. Mapping analysis and docking study showed that both the sulfonyl group and the morpholino group (R2) are important for the PI3K inhibitory activity in this series of compounds.

Electron-donating (methyl and methoxy groups) and electro-withdrawing (fluoro and bromo) groups at the 4-position of the sulfonyl phenyl ring also exhibited favorable PI3Kα inhibitory activities ranging from 1.58 to 2.89 μM, while compound **69** with a thio group at the 3-position of the quinoxaline ring showed an IC_{50} value bigger than 50 μM, and compound **68** with a piperidinyl group at the 2-position of the quinoxlaine ring showed an IC_{50} value of 21.63 μM [108] (Table 8).



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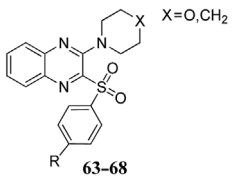
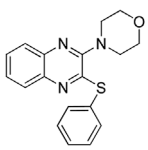


63–68



69

Quinoxaline as a potent CDK1,2,4,6 inhibitor

Cyclin-dependent kinases (CDKs) are a family of serine/threonine protein kinases whose members are small proteins composed of little more than the catalytic core involved in all protein kinases [109]. They are involved in critical cellular

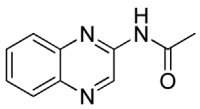
Table 8. The biological activity of morpholino-quinoxalines.

Compound no.	R	X	IC_{50} (μM)
63	H	O	0.44
64	Methyl	O	1.58
65	Methoxy	O	1.40
66	Bromo	O	2.89
67	Fluoro	O	2.49
68	H	CH_2	21.63
LY294002		O	0.63

processes, such as cell cycle or transcription, whose activity requires association with specific cyclin subunits [110].

CDKSs have a central role in coordinating the eukaryotic cell division cycle, and serve to integrate diverse growth-regulatory signals [111]. The human genome contains 21 genes encoding CDKs and five additional genes encoding a more distant group of proteins known as CDK-like (CDKL) kinases [110]. Genetic or epigenetic changes that lead to cyclin overexpression, beside absence or reduction of CDK-inhibitor proteins, are commonly observed in human malignancy. Consequently, CDK1, 2, 4, and 6 are attractive targets for new anticancer drugs [112].

In 2012, Kumar et al. [113] designed a *N*-(quinoxalin-2-yl)-acetamide (**70**) as a potent kinase (CDK2) inhibitor.

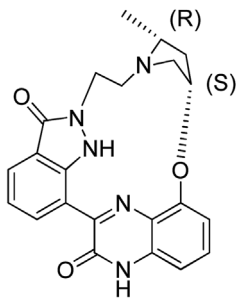


70

In 2006 Kawanishi et al. [112] designed a novel series of quinoxaline-2-ones as cyclin-dependent kinase (CDK) inhibitors. Their study based on their previously reported diaryl-urea as a novel selective CDK4 inhibitor [114, 115]. Compound **71** was considered to be their lead compound for the structure-based drug design of a potent CDK1,2,4,6 inhibitor [112]. The urea hydrogen and carbonyl group in compound **71** formed hydrogen bonds with Val83 in the ATP-binding hinge region of the protein. It was coplanar with an intramolecular hydrogen bond between pyridine and the urea hydrogen and insufficiently potent so they hypothesized that conversion of the linear system to a ring to force coplanarity would improve potency. Compound **72**, which had a cyclic urea structure, was found with no activity against CDK4 due to steric hindrance, which might make coplanarity difficult. On the other hand, the quinoxaline-2-one compound **73** could take a coplanar conformation and fit like compound **71** in the ATP-binding pocket of CDK4 (with moderate inhibitory activity) (Fig. 10).

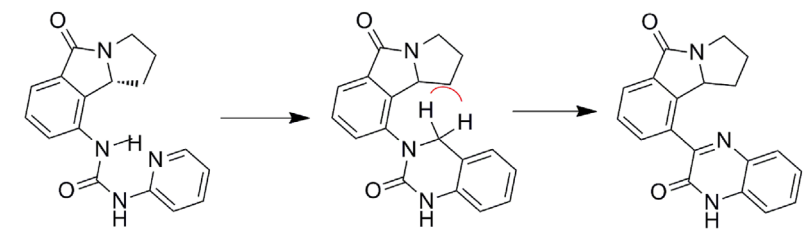
For improving potency, they introduced a chain of 4–6 carbon atoms to link the quinoxaline-2-one and the benzoisothiazol-1-one. These linkers filled the void space around the ribose site of the ATP-binding pocket, and the CDK4-inhibitory activities were measured finding that the compound with 5-carbon linker showed the best activity (IC_{50}% CDK4 = 3.6 nm).

Furthermore, the cellular potency was improved by the introduction of a pyrrolidine ring and the incorporation of a methyl group to this pyrrolidine ring, which improved the binding affinity to CDK4 by means of additional lipophilic interactions with Ala144, Leu134, and Asn132. Finally compound **74** was the most potent against CDK4 in both the enzyme and the cell-based assay [112].



74

CDK1	CDK2	CDK4	CDK6
1.0 nM	3.4 nM	6.4 nM	12 nM



71 **72** **73**

IC_{50} =	42 nM	>10,000 nM	480 nM

Figure 10. Structures of compounds **71–73** showing **72**'s steric hindrance.

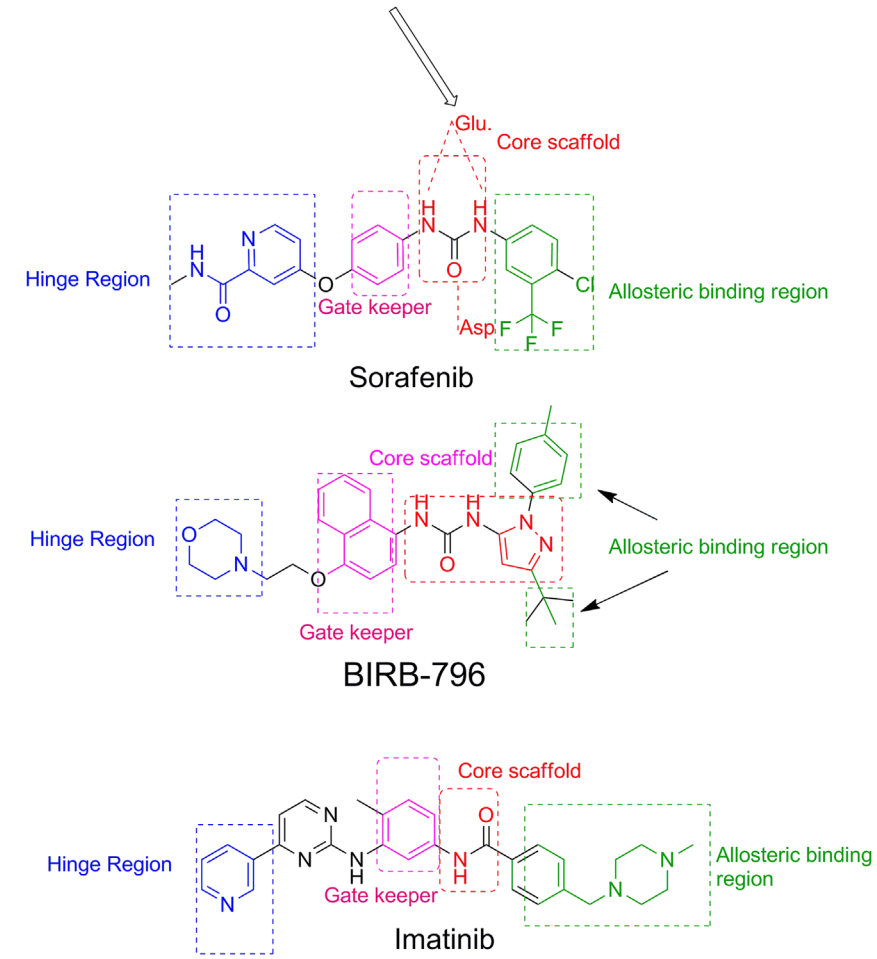


Figure 11. The essential interacting features of three type II TK inhibitors.

Designing new quinoxaline scaffolds as type II tyrosine kinase inhibitors

Most of kinase inhibitors that have been developed so far target the ATP binding site of the kinase in its active conformation – they are so called type I inhibitors, in which the activation loop is phosphorylated. Recently, crystal structures of inhibitors such as imatinib (Gleevec), BIRB796, and sorafenib (Nexavar) (known as type II inhibitors) have revealed a new binding mode that exploits an additional binding site immediately adjacent to the region occupied by ATP. This pocket is accessible by an activation-loop rearrangement that is characteristic of kinases in an inactive conformation. Here, we present a structural analysis of binding modes of the three mentioned drugs as type II inhibitors and demonstrate them as a pharmacophore model that is currently being used to design a new generation of kinase inhibitors.

In 2010, Dietrich et al. [116] presented a structural comparison of the important and similar interactions necessary for three important drugs (Gleevec, Nexavar, and BIRB-796) to bind to their respective DFG-out allosteric binding pockets and the selectivity of each with respect to c-Abl, B-Raf, and p38α, so designing new quinoxaline derivatives as type II inhibitors targeting VEGFR-2 should keep the essential interacting features (Fig. 11):

(1) Hydrogen-bonding interactions with the core scaffold (shown in red).
(2) Hydrophobic interactions in the allosteric binding region (shown in green).

(3) Hydrophobic interactions in the gatekeeper region (shown in pink).
(4) Hydrogen-bonding interactions with the hinge region (shown in blue).

Conclusion

Quinoxalines represent an important class of nitrogen-containing heterocycles and have been shown to possess a broad spectrum of biological activities including anticancer and kinase inhibitors. In this review, we have compiled and discussed different synthetic aspects for quinoxalines, as well as the anticancer activity of quinoxaline derivatives through inhibition of various kinase enzymes. Considering synthesis, the most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in different conditions. Regarding the important anticancer activity of quinoxalines, studies proved that quinoxalines were selective ATP competitive inhibitors in many kinases example: VEGFR, PDGFR, Src, c-Met kinase, EGFR/HER-2, JAK-2, FLT-3, and CDK1,2,4,6. Number of studies has explored their SAR, as well as conformation and orientation requirements for kinase binding site through modeling studies. This could provide insight to a medicinal chemist for a comprehensive and target oriented information required for the development of clinically viable quinoxaline-based anticancer drugs.

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