Review

Chemistry, Synthesis, and Structure Activity Relationship of Anticancer Quinoxalines

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Abstract: Quinoxaline is a fused heterocycle system of a benzene ring and pyrazine ring. It has earned considerable attention due to its importance in the field of medicinal chemistry. The system is of extensive importance due to its comprehensive array of biological activities. Quinoxaline derivatives have been used as anticancer, anticonvulsant, anti-inflammatory, antidiabetic, antioxidant, antibacterial, anti-TB, antimalarial, antiviral, anti-HIV, and many other uses. Variously substituted quinoxalines are significant therapeutic agents in the pharmaceutical industry. This review spotlights on the chemistry, physiochemical characters, synthesis, pharmaceutical products, and medicinal chemistry of various anticancer quinoxaline derivatives that were developed in the last period. It covers the period from 2016 to 2023.

Keywords: quinoxaline; development; discovery; design; synthesis; anticancer; applications; structure–activity relationship

1. Introduction

Heterocycles containing nitrogen have great importance in the pharmaceutical field including uses in drug discovery, synthesis, and development processes [1–3]. Diazine heterocycles are central components of several drug candidates [4,5]. The benzo-diazene systems of quinoxalines, cinnolines, quinazolines, phthalazines, naphthalenes, and quinolines are used in the preparation of various drugs [6,7]. They are also used in several research studies for the discovery of new drugs [8,9]. Among these heterocycles, quinoxaline plays an essential role in drug discovery and production [10–12]. Quinoxaline is a benzopyrazine system with the molecular formula $C_8H_6N_2$ [13]. It is formed of a benzene ring fused to the six-membered pyrazine ring [14]. It is a low-melting solid (29–30 °C), soluble in water, and a weak base (pKa = 0.56) [15]. Several studies were performed and displayed a wide range of pharmacological activities for quinoxaline derivatives (Figure 1) [16–30]. Additionally, quinoxalines are used for crop protection as a component of insecticides, herbicides, and fungicides [31–35]. Quinoxalines were linked to a metal center such as ruthenium or another heterocyclic moiety such as indole to be used as dyes in solar cell preparation, fluorescent materials, organic semiconductors, and inhibitors of corrosion in metals [36–38]. There are many commercially available quinoxalines that have an essential role in the pharmaceutical and industrial market [39,40]. The objective of this review is to gather the literature reported by researchers on quinoxaline derivatives, their preparations, and their structure–activity relationship (SAR) as anticancer agents.
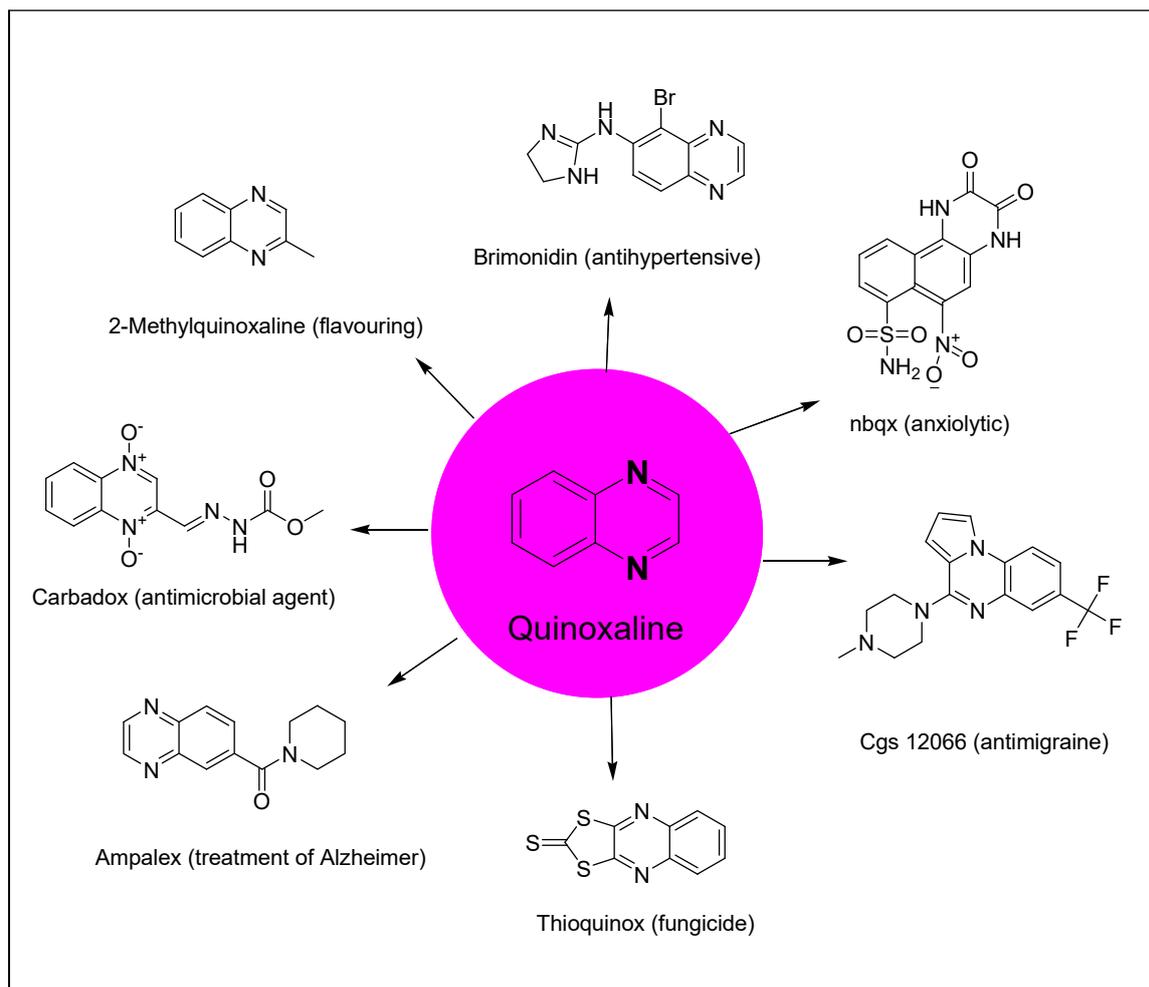
Figure 1. Quinoxaline and examples of its pharmacological activities.

2. Chemical Characters of Quinoxalines

Quinoxaline molecules are named benzopyrazines or 1,4-benzodiazines [41–43]. There are four benzodiazines: quinoxaline, quinazolines, phthalazines, and cinnolines. In addition, the bioisosteres of benzodiazines are benzothiophenes, naphthalenes, and quinolines (Figure 2) [14]. These systems have an aromatic nature, so they have a chemical stability by resonance characters [44–46]. Quinoxaline is a white crystalline solid at room temperature. It presents two ionization states. The first and the second ionization states were calculated by photon electron spectroscopy, and they were 8.99 and 10.72 eV, respectively [47–50]. The past twenty years have witnessed huge progress in the synthesis of quinoxaline derivatives [51–55]. These synthetic processes focused on function groups and their tolerance, product variation, selective catalysis, and substrates [56–58]. They also gave a mechanistic insight to correct and explain the different types of reactions [59–62]. These continuous scientific efforts supported the production of many pharmaceutical products and helped in the treatment of various diseases and infections [63–65]. The quinoxaline molecule has a specific electrostatic potential that influences its hydrophobic and hydrophilic interactions with the different molecules (Figure 3) [66]. Table 1 displays the physicochemical characteristics of the quinoxaline system [67]. There are many synthetic methods used for the preparation of biologically active quinoxaline derivatives [68–75].
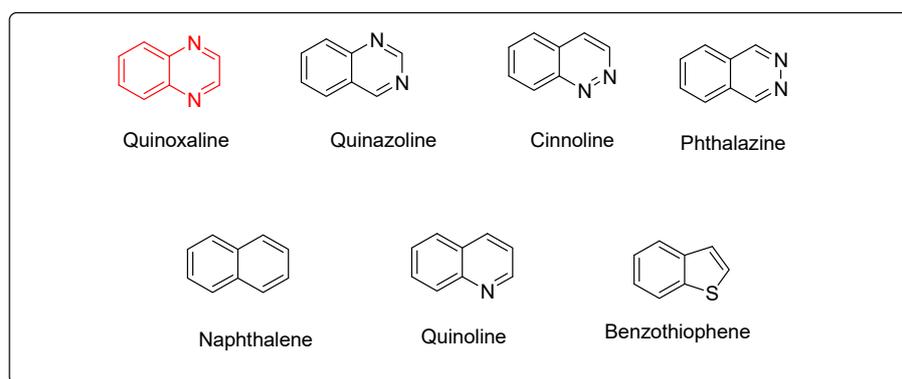
Figure 2. Benzodiazines (quinoxaline, quinazoline, cinnoline, phthalazine) and their bioisosteres (naphthalene, quinoline, benzothiophene).
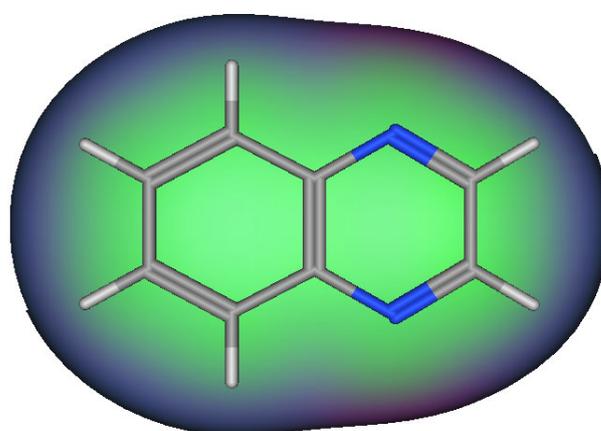

Figure 3. Surface map for interactions in the quinoxaline system. The pink color shows hydrogen bonding area, the green color indicates hydrophobic area, and the blue color indicates a mild polar area.

Table 1. The physicochemical characteristics of the quinoxaline system.

Characteristic	Quinoxaline
Molecular formula	$C_8H_6N_2$
Molecular weight	130.15 g/mol
Number of heavy atoms	10
Number of aromatic heavy atoms	10
Fraction Csp3	0
Number of rotatable bonds	0
Number of H-bond acceptors	2
Number of H-bond donors	0
Molar refractivity	39.54
Tropological polar surface area	25.78 A^2
Lipophilicity	1.47
Water solubility	Soluble
GI absorption	High
BBB permeation	Yes
Bioavailability score	0.55
Lipinski	Yes
Synthetic accessibility	Easy

3. Methods of Preparation of Quinoxalines

Due to the massive synthetic importance and the various therapeutic activities of quinoxaline derivatives, several attempts have been made by many researchers to prepare

a library of these molecules [76–91]. The methods of preparation of quinoxalines can be divided into two pathways:

1. The traditional chemistry pathway, which is based on the condensation between o-phenylenediamines and dicarbonyl compounds in the presence of special conditions such as organic solvents, high temperatures, long times, or strong catalysts. Additionally, the reaction yield may be low and side products may be produced. These types of reactions have negative effects on the environment.
2. The green chemistry pathway, which is a cost-effective pathway through using green chemistry methodologies to produce quinoxalines. This pathway is characterized by using an environmentally friendly recyclable catalyst, a low cost, lower consumption of energy, one-pot synthesis, no side products, short time, and high yield. It can be performed in an aqueous medium at room temperature or by the microwave reactor.

3.1. Traditional Chemistry Pathway

3.1.1. Condensation of o-Phenylenediamine and 1,2-Dicarbonyl Derivatives

Korner and Hinsberg in 1884 synthesized the first derivative of quinoxaline through a condensation of o-phenylenediamine with a 1,2-dicarbonyl derivative. Various derivatives were obtained from this reaction (Scheme 1) [76].

R= H, Me, Cl, NO_2
R_1= R_2 = H, Ph, Me, 4-Me-Ph, 2-Furyl
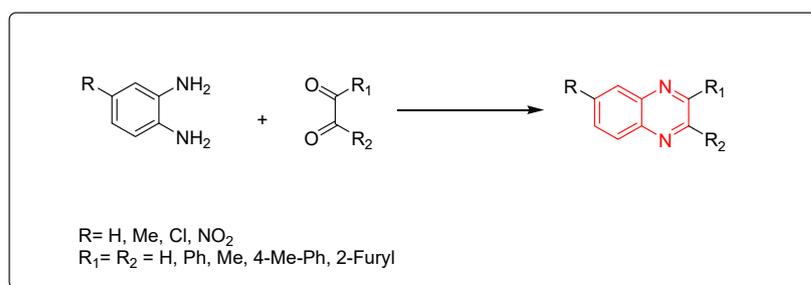
Scheme 1. Synthesis of quinoxaline by the condensation technique: diamine (1 mmol), dicarbonyl (1 mmol), glycerol (5 mL), water (2 mL), 90 °C, 4–6 min, yield (85–91%).

3.1.2. O-Phenylenediamine and In Situ Produced 1,2-Dicarbonyls

Quinoxalines were synthesized via catalytic iodine, which was used to accelerate the oxidative cyclization cascade between different 1,2-diamino compounds and hydroxyl ketones (Scheme 2) [77].

R = H, NO_2, Cl, Me
Ar = 4-OCH_3-Ph
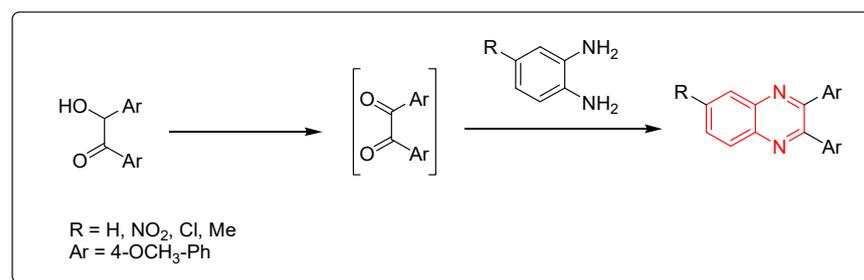
Scheme 2. Synthesis of quinoxaline from o-phenylenediamine and in situ generated 1,2-dicarbonyl derivatives: o-phenylenediamine (1 mmol), hydroxyl ketone (1 mmol), I_2 (0.25 mmol), DMSO (2 mL), RT, 12 h, yield (80–90%).

3.1.3. Metal-Catalyzed Cyclization of Imines and Azides

Ketimines and azides were used to create quinoxalines. This is a metal-catalyzed cyclization reaction that produces quinoxaline derivatives (Scheme 3) [78–80].
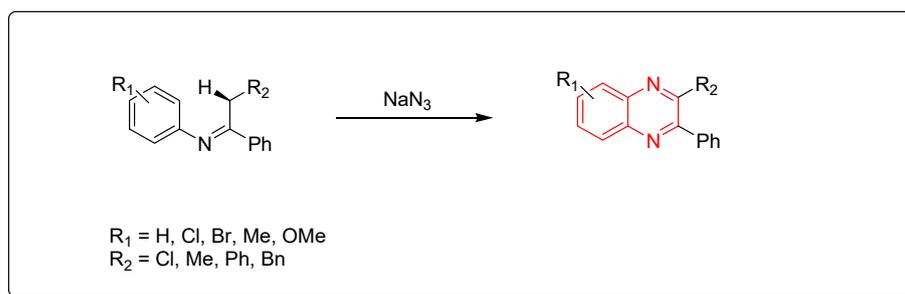
Scheme 3. Synthesis of quinoxalines from imines and azides: imine (1 mmol), sodium azide (3 mmol), (diacetoxyiodo)benzene (3 mmol), CuO (1 mmol), ethylacetate, Rt, 16 h, yield (35–80%).

3.1.4. Cyclocondensation of o-Phenylenediamine and Aromatic Alkynes

Quinoxalines were synthesized via cyclocondensation of phenylene diamine and aromatic alkynes in the presence of Cu(OAc)$_2$ as a catalyst (Scheme 4) [81].
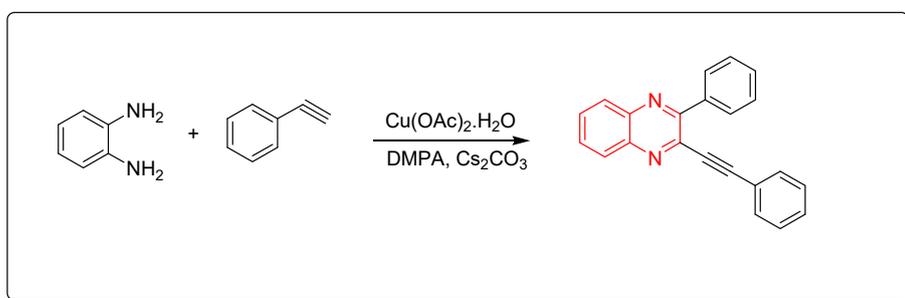
Scheme 4. Synthesis of quinoxalines from aromatic alkynes and amines: o-phenylenedia mine (0.25 mmol) in toluene, phenyl acetylene (1 mmol), Cs$_2$CO$_3$ (0.75 mmol), Cu(OAc)$_2$.H$_2$O (10 mol % from the o-phenylenediamine), DMPA (0.75 mmol), 70 °C, 8 h, yield (86%).

### 3.1.5. Cyclocondensation of o-Phenylenediamine and Nitro-Olefins

Using CuBr$_2$ as a catalyst, phenylenediamine and nitro-olefins reacted to produce quinoxalines (Scheme 5) [82].
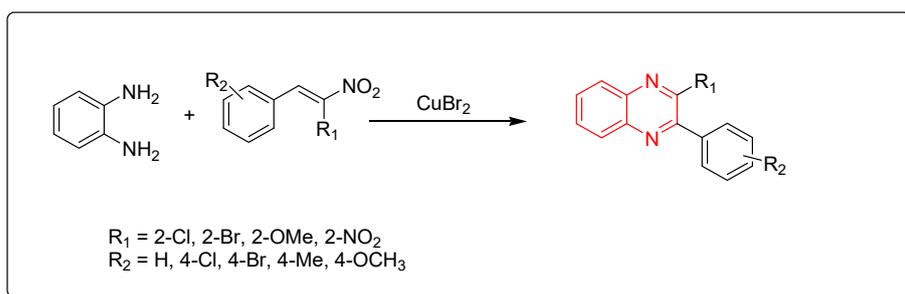
Scheme 5. Synthesis of quinoxalines from nitro-olefins and amines: phenylenediamine (1 mmol), nitro-olefins (1 mmol), CuBr2 (1 mmol), ethanol, 110 °C, 2–4 h, yield (35–90%).

3.1.6. Cyclocondensation of Aromatic Amines and DMF

A new strategy for the preparation of pyrrol [1,2-a]quinoxaline derivatives was described by using ferric chloride as a Lewis acid and an initiator for a straightforward reaction. DMF solvent was used as a source of carbon (Scheme 6) [83].
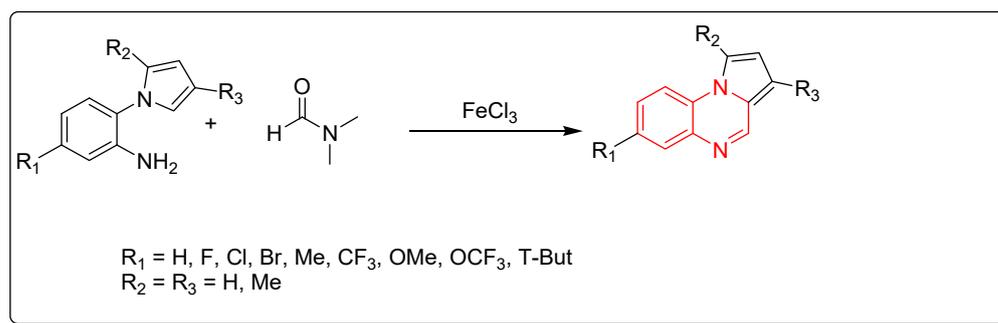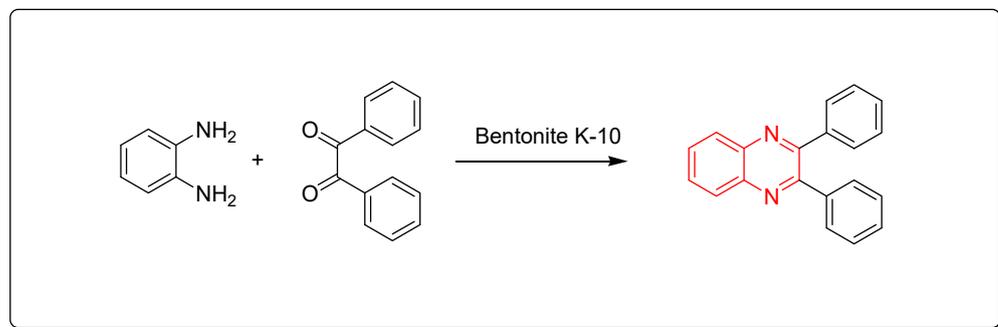
Scheme 6. Synthesis of quinoxalines from amines and DMF in Fe-mediated catalyst: aniline derivative (0.3 mmol), DMF (2 mL), FeCl$_3$ (0.3 mmol), TBPB (0.9 mmol), 120 °C, 5–12 h, yield (40–97%).

*3.2. Green Chemistry Pathway*

3.2.1. Clay-10 Based Method

This is a green synthetic pathway for the synthesis of quinoxalines. It is environmentally friendly with no traditional limitations such as high temperature, expensive reagents, low yield, and contamination. Clay is a cheap material, green reagent, and is continuously available. This reaction is performed by mixing the two reagents with bentonite K-10 at room temperature, then it is flowed on a celite pad and ethanol. The mixture is concentrated to 5 mL and diluted with 10 mL of water. The reaction is allowed to stand for 1 h. The clay can be recovered after formation of the product as pure crystals and can be used five times again. This method agrees with the green chemistry protocol, and it is recommended for the synthesis of different quinoxaline derivatives to avoid the problems of the traditional pathway. The reaction is shown in Scheme 7 [84].

Scheme 7. Synthesis of quinoxalines by one-pot cascade method: o-phenylene-diamine (1 mmol), benzil (1 mmol), bentonite K-10 (3 gm), ethanol 50 mL, RT, 20 min, yield (95%).

3.2.2. Zinc Triflate Catalyst

Zinc triflate is a zinc salt of trifluoromethanesulfonic acid. It is an ecologically friendly and highly effective catalyst. It is one of the green chemistry catalysts. The reactions performed by using zinc triflate catalyst can be completed without solvent (solvent-free) using a microwave-assisted reactor or by using acetonitrile solvent. Quinoxaline derivatives were prepared by the reaction of o-phenylenediamine and α-diketones using a zinc triflate catalyst at room temperature in acetonitrile. This reaction produced a yield up to 90% (Scheme 8) [85].
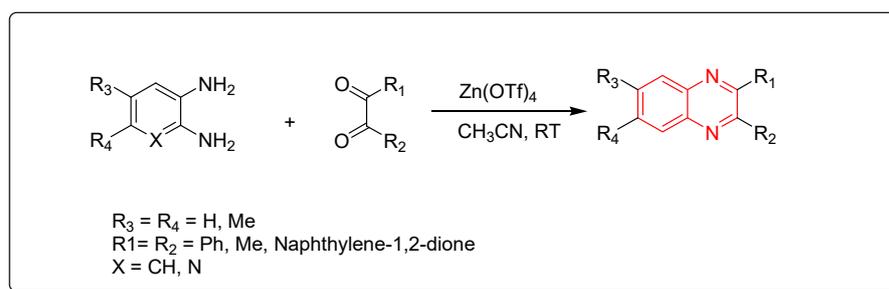
Scheme 8. Synthesis of quinoxaline by using zinc triflate catalyst: diamine (1.1 mmol), dicarbonyl (1 mmol), Zn(OTf)$_4$ (0.2 mmol), CH$_3$CN (5 mL), RT, yield (85–91%).

3.2.3. Phosphate-Based Catalyst

The phosphate catalysts include monoammonium phosphate (MAP), diammonium phosphate (DAP), and triple super phosphate (TSP), which is a constituent of fertilizer that mainly consists of monocalcium phosphate Ca(H$_2$PO$_4$)$_2$. The needed amount from this type of catalyst is a minute amount (0.006 gm) for performing the one molar equivalent reaction. The resulting product is crystallized from ethanol while the catalyst is recovered from the reaction by simple filtration, washing with hot ethanol, and drying for 6 h (Scheme 9) [86].
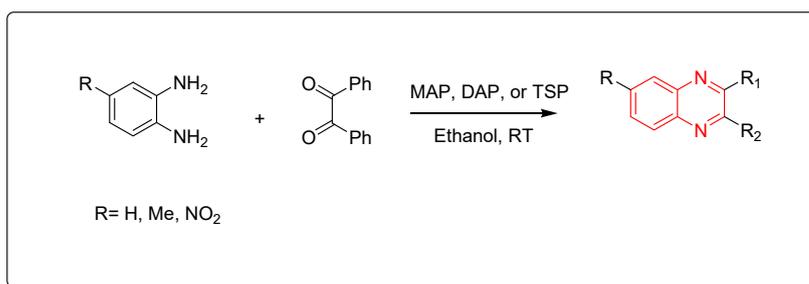
Scheme 9. Synthesis of quinoxaline by using phosphate-based catalyst: amine (1 mmol), benzil (1 mmol), MAP, DAP, or TSP (0.0006 gm), ethanol, RT, yield (85–91%).

### 3.2.4. Lanthanide-Based Catalyst

Cerium (IV) ammonium nitrate (CAN) is one of the lanthanide reagents. It has earned attention in synthetic reactions of organic chemistry due to its low cost, availability, miscibility in water, safety, and high reactivity. It is used in green chemistry due to its unique characters. The reaction between o-phenylenediamine and benzil derivatives in the presence of cerium (IV) ammonium nitrate (CAN) readily happens in 20 min without any side products at room temperature to produce a good yield reaching up to 98%. Additionally, it is performed in an aqueous medium. The CAN catalyst is mixed with acetonitrile or any aprotic solvent. It is one of the green chemistry protocols that are used for the synthesis of quinoxaline derivatives (Scheme 10) [87].
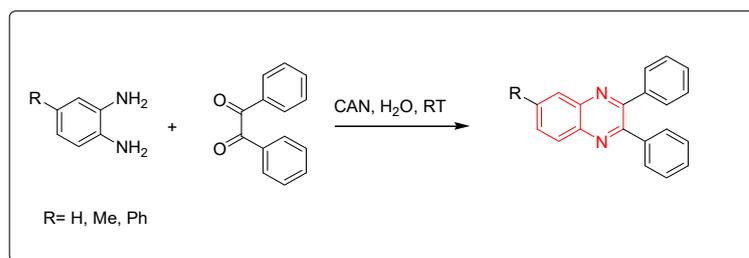
Scheme 10. Synthesis of quinoxaline by using lanthanide-based catalyst. Amine (1 mmol), benzil (1 mmol), CAN (5 mol), acetonitrile, RT, 20 min, yield (80–98%).

3.2.5. Fluorinated Alcohols Catalyst (HFIP)

Fluorinated alcohols are related to green chemistry catalysts. Recently, they have gained much attention due to their low nucleophilic characteristics, high polarity, their ability to strongly donate hydrogen bonds, and water solvation characteristics. They also can stabilize the helix conformation of proteins. The reaction between o-phenylenediamine and benzil derivatives in the presence of hexafluoroisopropanol (HFIP) was run at room temperature for one hour to produce quinoxaline derivatives with a 95% yield. It is a solvent-free reaction without side products and toxic solvents. Furthermore, the hexafluoroisopropanol can be recovered from the reaction without activity change. Therefore, it is a green chemistry pathway (Scheme 11) [87].
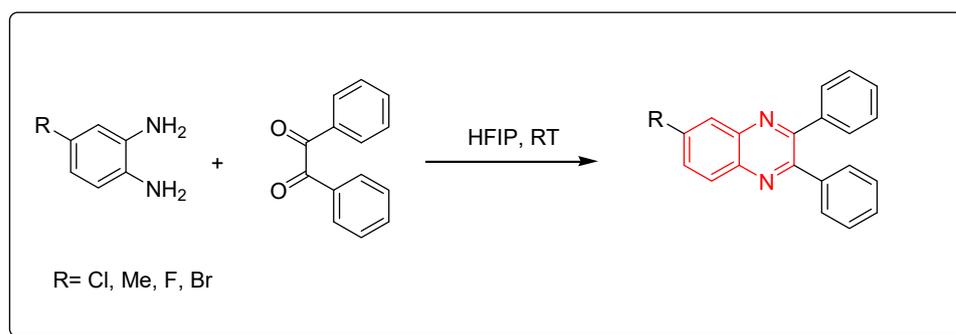
Scheme 11. Synthesis of quinoxaline by using fluorinated alcohols catalyst: amine (1 mmol), benzil (1 mmol), HFIP (5 mol), RT, 20 min, yield (95%).

3.2.6. Solid Acid Catalyst (TiO$_2$-Pr-SO$_3$H)

Nanocrystalline titania-based sulfonic acid (TiO$_2$-Pr-SO$_3$H) is a green chemistry catalyst. It is a sulfonic acid nano porous titania resulting from the reaction of (3-mercaptopropyl) trimethoxysilane and titanium oxide. It can be recovered from the reaction without a change in the activity. It is used to catalyze the reaction between o-phenylenediamine and benzil derivatives at room temperature. The product yield was 95% and it needed only 10 min to be accomplished. This reaction can be performed in the presence of ethanol or in the absence of any solvent. It is a one-step reaction without side products (Scheme 12) [87].
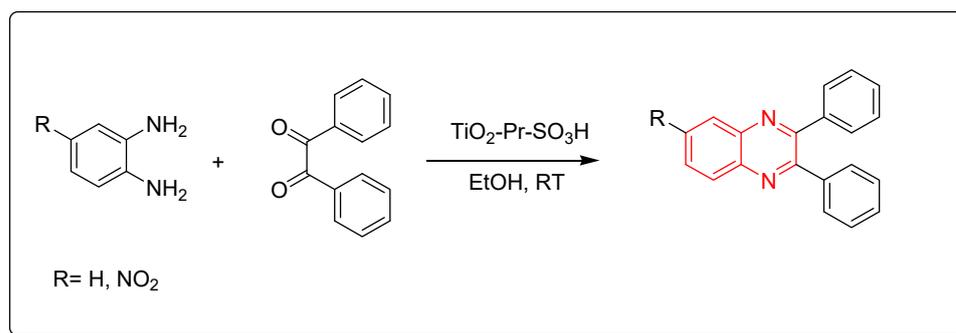
Scheme 12. Synthesis of quinoxaline by using solid acid catalyst: amine (1 mmol), benzil (1 mmol), TiO$_2$-Pr-SO$_3$H (1 mol), RT, 10 min, yield (95%).

3.3. Reaction of Quinoxalines

3.3.1. Intramolecular Arylation Using Lewis Acid Catalyst

Aryl derivatives of quinoxalines were produced via the reaction between dichloroquinoxalines and aryl derivatives using a Lewis acid catalyst (AlCl$_3$). The previous method induced arylation via C–C bond formation (Scheme 13) [88].
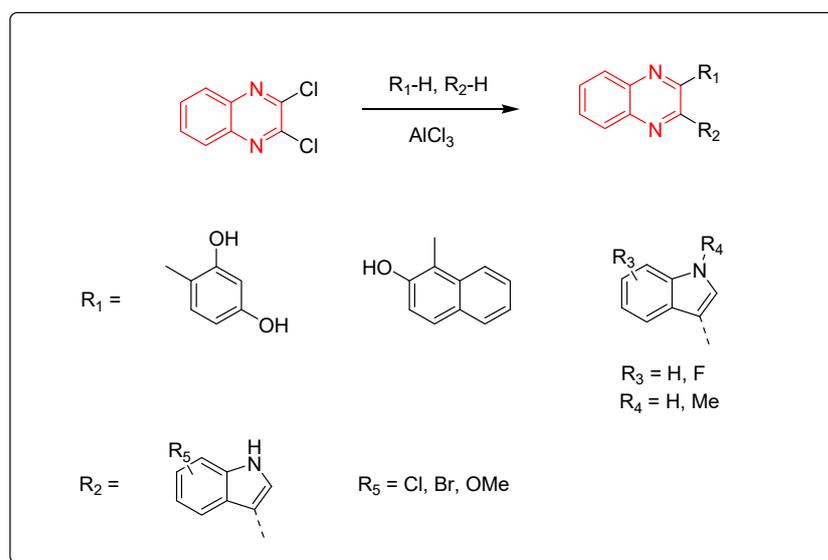
Scheme 13. Synthesis of quinoxalines derivatives by AlCl$_3$-induced arylation of dichloroquinoxalines: dichloroquinoxaline (1 mmol), R1-H (1 mmol), R2-H (1 mmol), AlCl$_3$ (2.2 mmol), DCE, 80 °C, 60 min, yield (87–85%).

3.3.2. Intramolecular Cyclization of Quinoxalines

Substituted pyrrolo[2,3-b]quinoxaline from allyl-3-chloroquinoxaline-2-ylamine having terminal alkene and aromatic amine derivatives was prepared using a Pd-mediated catalyst Pd(OAc)$_2$ (Scheme 14) [89].

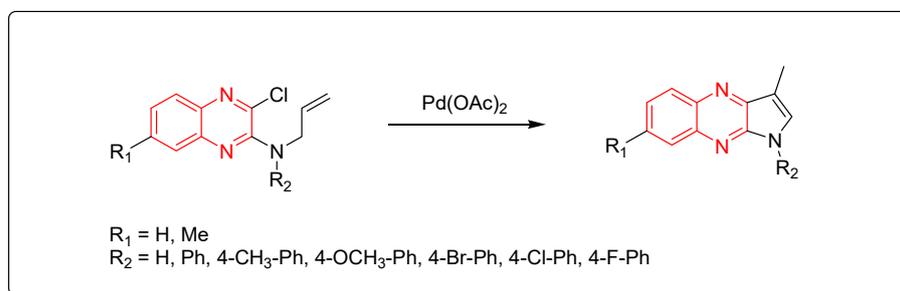**Scheme 14.** Synthesis of quinoxalines derivatives by Pd-mediated catalyst: amine (1 mmol), Pd(OAc)$_2$ (0.015 mmol), K$_2$CO$_3$ (3 mmol), DMF, 100 °C, 2 h, yield (80–91%).

4. Pharmaceutical Products of Anticancer Quinoxalines

Many anticancer drugs containing quinoxaline were developed. While some of them are still undergoing clinical trials or have been discontinued, others have FDA approval and are marketed as pharmaceutical products. Examples of some common derivatives are shown in Table 2, along with their generic names, formulas, and molecular weights [14,90].

1. Erdafitinib is an inhibitor of the subgroup tyrosine kinase fibroblast (FGFR). These receptors become unregulated and are exposed to angiogenesis, differentiation, and proliferation in certain types of tumors. Erdafitinib is used for the treatment of malignancy and some types of solid tumors. It has the brand name Balversa. It was discovered to overcome the toxicity profiles of other anticancer agents used for the treatment of gastric cancer, bile duct cancer, and lung cancer. It was invented for the first time by the Astex Pharmaceutical Company. The FDA approved it in 2018 for the management of urothelial tumors. In 2019 it was approved for the treatment of other types of tumors. It inhibits FGFR-1, FGFR-2, FGFR-3, and FGFR-4 with a strong IC$_{50}$ = 1.2, 2.5, 3, and 5.7 nM, respectively [14].

2. Chloroquinoxaline sulfonamide was listed as CQS, and it was used in the treatment of different types of tumors. It completed clinical trials (phase II) on colorectal and lung cancer cell lines. It works via the inhibition of topoisomerase IIα and topoisomerase IIβ. Therefore, it inhibits DNA replication. It showed a high toxicity profile, so it was discontinued after this phase II. It showed IC_{50} = 1.8 μM against B16 murine melanoma cells [14].

3. Tyrophostin is a tyrosine kinase inhibitor. It was used for the treatment of resistant melanoma cell platelet-derived growth factor receptor kinase (PDGFR), activates apoptosis, and reduces capability and movement of resistant melanoma cells of skin cancer. It has no effect on the epidermal growth factor receptor (EGFR), but it strongly inhibits PDGFR with an IC_{50} = 0.3 to 0.5 μM. It also works via the activation of apoptosis in tumor cell lines. It is used in the treatment of melanoma [14].

4. Pilaralisib is an effective and favorably selective inhibitor of class I phosphatidylinositol 3-kinase (PI3K). It inhibits the formation of PIP3 in the cell membrane, which leads to the inhibition of cell differentiation and proliferation. It was invented for the treatment of solid tumors by Sanofi and Exelixis. It significantly inhibited tumor growth but showed a high toxicity profile, so it was discontinued after phase II. It displayed an IC_{50} of 39, 383, 23, and 36 nM against PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ [14].

5. 2-(4-Chlorophenyl)-5-Quinoxalinecarboxamide is an example of an antineoplastic agent that inhibits the poly(ADP-ribose) polymerase enzyme. This enzyme participates in the base excision repair (BER) pathway by facilitating the poly(ADP-ribosyl)action of a select few acceptor proteins that are important for DNA metabolism and chromatin architecture. The quinoxaline derivative is still in the experimental stage [90].

6. PQ-10 is a quinoxaline and quinazoline derivative that works via the inhibition of cAMP and cAMP-inhibited cGMP 3′,5′-cyclic phosphodiesterase 10A. The latter enzyme controls the amount of cyclic nucleotides inside cells, which aids in signal transduction. It is capable of hydrolyzing both cAMP and cGMP but prefers cAMP more highly. This derivative is in the experimental stage as a new anticancer treatment with a quinoxaline system [90].

Table 2. Some pharmaceutical products of anticancer quinoxalines.
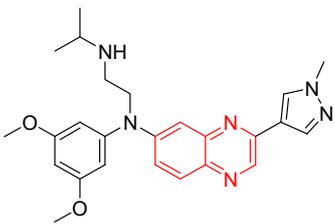
Molecular Structure	Generic Name	Chemical Name	Molecular Formula/ Molecular Weight
	Erdafitinib	N′-(3,5-dimethoxyphenyl)-N′-[3-(1-methylpyrazol-4-yl)quinoxalin-6-yl]-N-propan-2-ylethane-1,2-diamine	$C_{25}H_{30}N_6O_2$ 446.2
	Chloroquinoxaline sulfonamide	4-amino-N-(5-chloro-2-quinoxalinyl)-benzenesulfonamide	$C_{14}H_{11}ClN_4O_2S$ 334.03
	Tyrophostin	6,7-Dimethoxy-2-phenylquinoxaline	$C_{16}H_{14}N_2O_2$ 266.1
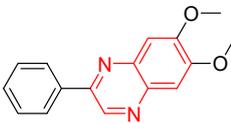
Table 2. *Cont.*

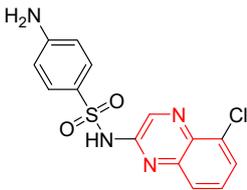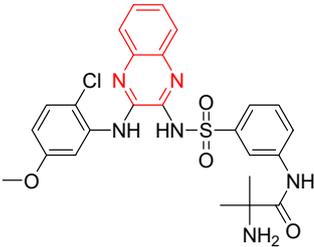| Molecular Structure	Generic Name	Chemical Name	Molecular Formula/ Molecular Weight
	Pilaralisib	2-amino-N-[3-[[3-(2-chloro-5-methoxyanilino)quinoxalin-2-yl]sulfamoyl]phenyl]-2-methylpropanamide	$C_{25}H_{25}ClN_6O_4S$ 540.13
	NA	2-(4-Chlorophenyl)-5-Quinoxalinecarboxamide	$C_{15}H_{10}ClN_3O$ 283.05
	PQ-10	6,7-Dimethoxy-4-[(3R)-3-(2-quinoxalinyloxy)-1-pyrrolidinyl]-quinazoline	$C_{22}H_{21}N_5O_3$ 403.43
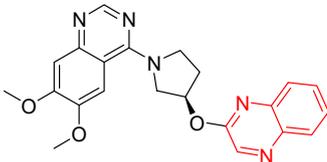
5. Anticancer Quinoxalines

Kamble and colleagues (2016) created hybrid derivatives of quinoxaline molecules linked with coumarin to test their anticancer potential. Compounds **1** and **2** were tested against 60 cancer cell lines among these derivatives. Compound **1** showed a 55.75% growth inhibition (GI) against a melanoma (MALME-M) tumor cell line. The SAR of these derivatives showed that unsubstituted aromatic rings (R_1, R_2 = H) have a higher activity than other substituents while the electron withdrawing group (Cl) produces higher activity than the electron withdrawing group (Br) and the electron releasing group (CH_3). Figure 4 shows the molecular structures of compounds **1**, **2**, and their SAR [91].
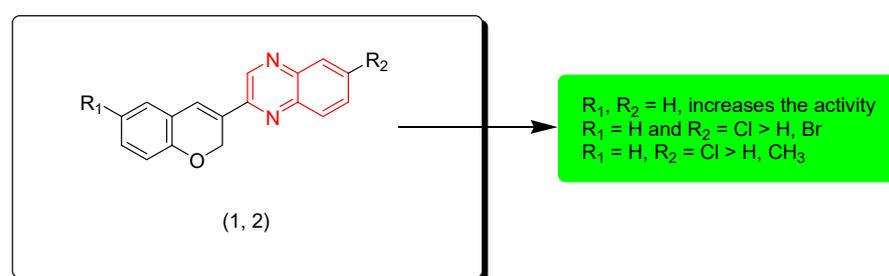
Figure 4. Anticancer quinoxaline **1** (R_1 = H, R_2 = H), **2** (R_1 H, R_2 = Cl), and their SAR.

Ali and coworkers (2017) designed and synthesized some quinoxaline derivatives with a triazole ring. These derivatives were screened for their anticancer activity against leukemia cell lines Ty-82 and THP-1. Compound **3** was the highest active compound. It showed an excellent potency on the two cell lines Ty-82 (IC_{50} = 2.5 μM) and THP-1 (IC_{50} = 1.6 μM). The SAR of these derivatives showed that the aliphatic linker CH_2 at the third position of quinoxaline is essential for the activity while N-linker decreases the activity. Electron releasing groups containing an oxygen atom (OCH_3, OC_2H_5) and phenyl substituents at R_2 decrease the activity while an isopropyl group ($CH(CH_3)_2$) increases the activity. Figure 5 shows the molecular structures of compound **3** and its SAR [92].
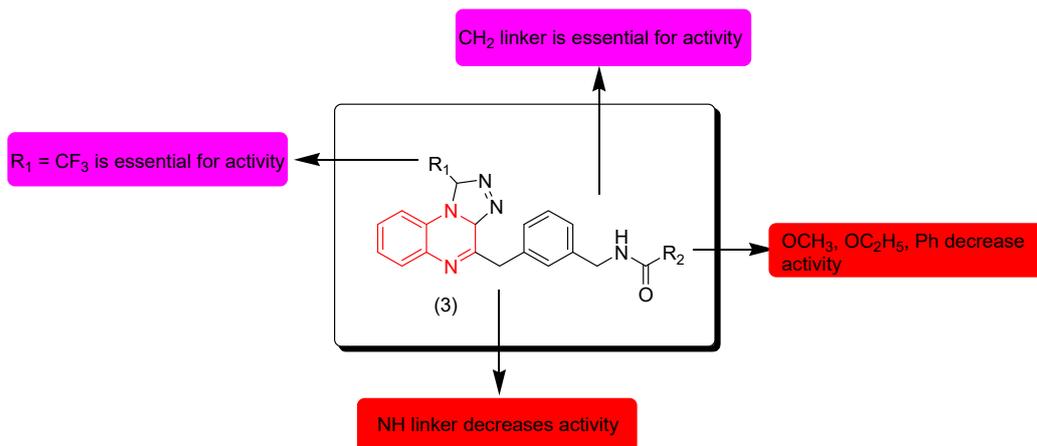
Figure 5. Anticancer quinoxaline **3** (R1 = CF$_3$, R$_2$ = CH(CH$_3$)$_2$ and its SAR.

Dong and coworkers (2018) identified new derivatives of quinoxalines containing ester and amide groups (**4**–**7**). They were tested for their anticancer activity against cervical cancer (HeLa), human hepatoma cancer cells (SMMC-7721), and leukemia (K562). Some compounds **4**, **6**, and **7** showed moderate activity, while compound **5** showed excellent activity against HeLa (IC$_{50}$ = 0.126 µM), SMMC-7721 (IC$_{50}$ = 0.071 µM), and K562 (IC$_{50}$ = 0.164 µM) compared to the reference doxorubicin. The SAR of these derivatives showed that the electron releasing group (OCH$_3$) at R$_1$, R$_2$, and R$_3$ is essential for the activity. Substitution of this group with an electron withdrawing group such as (F) decreases the activity while other electron releasing groups such as CH$_3$ or C$_2$H$_5$ decrease the activity. It also showed that the aliphatic linker CH$_2$ fused to the aromatic ring at the second position from the quinoxaline nucleus is essential for the activity. Figure 6 shows the molecular structures of compounds **4**–**7** and their SAR [93].
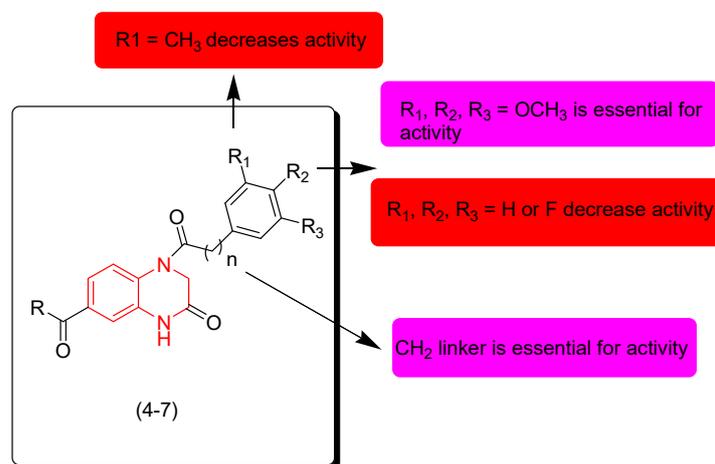
**Figure 6.** Anticancer quinoxalines **4** (R = OMe, (R = OMe, R$_1$ = OMe, R$_2$ = OMe, R$_3$ = H, n = 0, R$_1$ = OMe, R$_2$ = OMe, R$_3$ = H), **5** (R = OMe, R$_1$ = OMe, R$_2$ = OMe, R$_3$ = OMe, n = 0), **6** (R = OMe, R$_1$ = OMe, R$_2$ = OMe, R$_3$ = OMe, n = 1), **7** (R = -NH-Bu, R$_1$ = OMe, R$_2$ = OMe, R$_3$ = H, n = 0), and their SAR.

Liu and coworkers (2019) discovered new quinoxaline derivatives with benzoxazole, benzothiazole, and benzimidazole rings. They were evaluated for their anticancer activity against different cell lines (MGC-803, HepG-2, A549, Hela, and T24). Additionally, they were evaluated against normal cells (WI-38). Benzoxazole derivatives showed excellent activity while benzimidazole and benzothiazole were moderately active. Compound **8** displayed the highest activity among all compounds, including MGC-803 (IC$_{50}$ = 1.49 ± 0.18 µM),

Hep G2 (IC$_{50}$ = 5.27 ± 0.72 μM), A549 (IC$_{50}$ = 6.91 ± 0.84 μM), Hela (IC$_{50}$ = 6.38 ± 0.81 μM), T-24 (IC$_{50}$ = 4.49 ± 0.65 μM), and WI-38 (IC$_{50}$ = 10.99 ± 1.06 μM). The SAR of these derivatives showed that the NH linker at the third position from the quinoxaline nucleus is essential for the activity while the aliphatic linkers decrease the activity. The benzoxazole moiety at the second position from the quinoxaline nucleus produced higher activity than other heterocyclic systems. Figure 7 shows the molecular structure of compound **8** and its SAR [94].
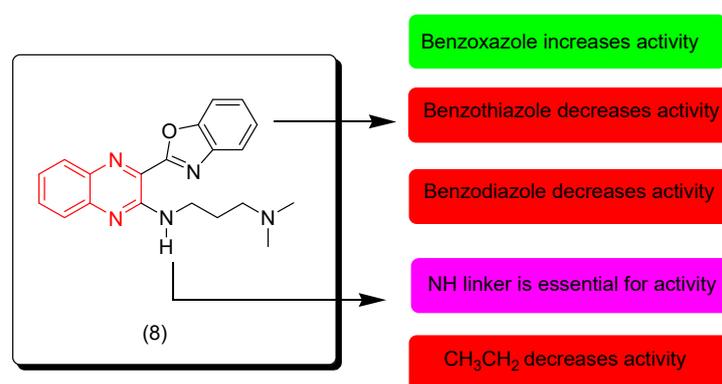
Figure 7. Anticancer quinoxaline **8** and its SAR.

Newahie and coworkers (2019) designed new quinoxaline derivatives including urea, thiourea, amide, and sulfonamide groups (**9–13**). The anticancer evaluation of these derivatives was performed against the breast cancer cell line (MCF-7), liver hepatocellular carcinoma Hep G2, and human colon carcinoma HCT116. Compounds containing sulfonamide and thiourea **12** and **13** were inactive. The compound with an amide group (**9**) showed moderate activity while compound **12** that had thiourea showed good results against HCT116 (IC$_{50}$ = 4.4 μM) and MCF-7 (IC$_{50}$ = 4.4 μM). Compound **11**, having a chloro-substitution at the fourth position from the phenyl ring, showed excellent activity against MCF-7 (IC$_{50}$ = 9 μM) and HCT116 (IC$_{50}$ = 2.5 μM). Doxorubicin was used as a standard drug to compare the activity. The SAR of these derivatives showed that the NH-CO linker at the second position from the quinoxaline nucleus increased the activity while aliphatic linkers decreased the activity. Electron releasing groups CH$_3$ and OCH$_3$ at R$_1$ decreased the activity. Sulfonamide and thiourea systems at R$_1$ blocked the activity. Figure 8 shows the molecular structures of compounds **9–13** and their SAR [95].
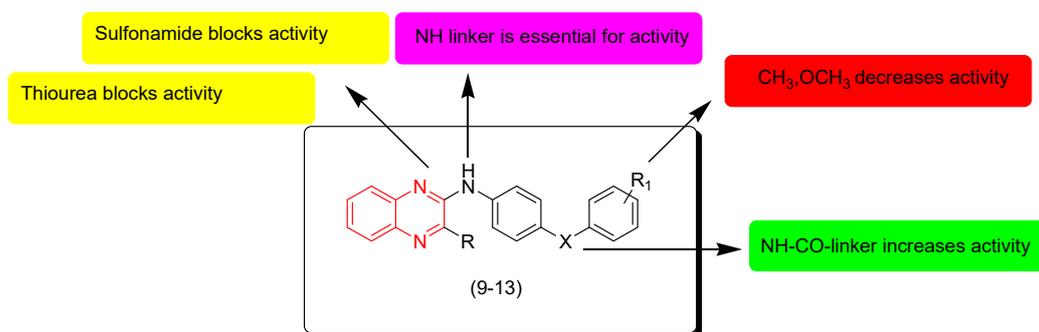

Figure 8. Anticancer quinoxalines **9** (R = Me, R1 = 4-Me, X = -NHCO-), **10** (R = Cl, R1 = H, X = -NHCO-), **11** (R = Me, R1 = 4-Cl, X = -NHCONH-), **12** (R = Me, R1 = H, X = -NHCSNH-), and **13** (R = Me, R1 = 4-Me, X = -NHSO$_2$-).

Cobouri and coworkers (2019) prepared some derivatives from 1-(N-substituted)-quinoxaline and tested their anticancer activity on a breast cancer cell line (MCF-7) and cervix cancer (Hela). Compound (**14**) was the most active among other derivatives with

IC_{50} = 2.61 μM on MCF-7, while other derivatives showed comparable anticancer activity with the reference doxorubicin. The SAR of these derivatives showed that replacement of the electron releasing group OCH_3 with an electron withdrawing group such as Cl decreases the activity. The CN group at the aliphatic chain fused to the nitrogen atom of the quinoxaline nucleus is essential for the activity. Replacement of the ester group $COOC_2H_5$ with the hydrazide group $CONHNH_2$ decreases the activity. Figure 9 shows the molecular structures of compound **14** and its SAR [96].
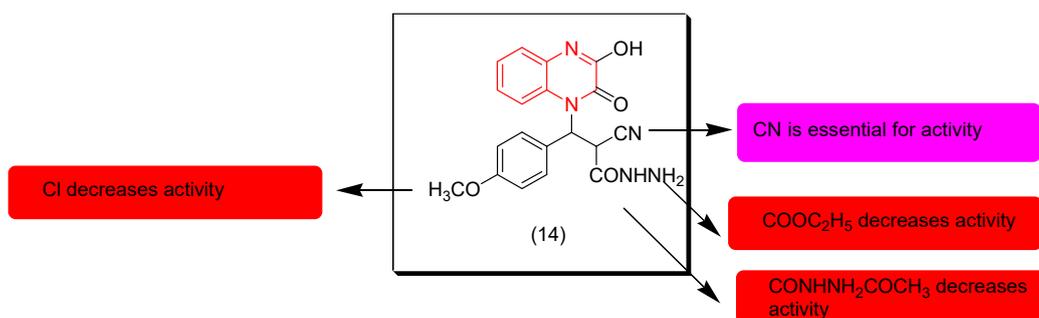
Figure 9. Anticancer quinoxaline **14** and its SAR.

Yuan and coworkers (2019) prepared two forms of naphthyl quinoxaline thymidine conjugates cis (**15**) and trans (**16**) as a novel class of cytotoxic molecules that efficiently induced in vivo antitumor activity through the vaccination application. The two conjugates **15** and **16** exhibited a pronounced cytotoxicity post 400 nm UVA activation at 3 mW/cm^2 for 20 min with the IC_{50} = 44.3 and 26.6 nM, respectively. This study connected the immunological effects and the antitumor activity of quinoxaline derivatives through this newly synthesized model. The structures of cis and trans isomers were separated by HPLC, and they were confirmed based on their chemical shifts. The measurement of antitumor activity was performed by measuring the immunogenic cell death markers after 2 h from UVA activation. The authors only synthesized two compounds, which was insufficient to study the SAR of these derivatives. The trans isomer was more active than the cis isomer. Figure 10 shows the molecular structures of compounds **15** and **16** [97].

Figure 10. Anticancer quinoxalines **15** and **16**.

Jin and coworkers (2020) synthesized sulfono-hydrazide and benzo-hydrazide derivatives of quinoxaline. These derivatives were tested against lung cancer cells (A549), breast adenocarcinoma cells (MCF-7), and colon cancer cells (HCT-116). Compound **18** had the highest activity against MCF-7 (IC_{50} = 22.11 ± 13.3 μM) compared to the reference (IC_{50} = 11.77 ± 4.57 μM). Compound **17** displayed moderate activity on (A549) and (HCT-116) with IC_{50} = 46.6 ± 7.41 μM and 48 ± 8.79 μM, respectively. The SAR of these derivatives showed that the sulfonyl linker at the third position from the quinoxaline system decreases the activity while the benzyl linker increases the activity. The electron withdrawing group NO_2 at the seventh position from the quinoxaline nucleus decreases the activity. Electron releasing groups at the aromatic ring fused to the second position from the quinoxaline system increase the activity while electron withdrawing groups decrease it. Figure 11 shows the molecular structures of compounds **17**, **18**, and their SAR [98].
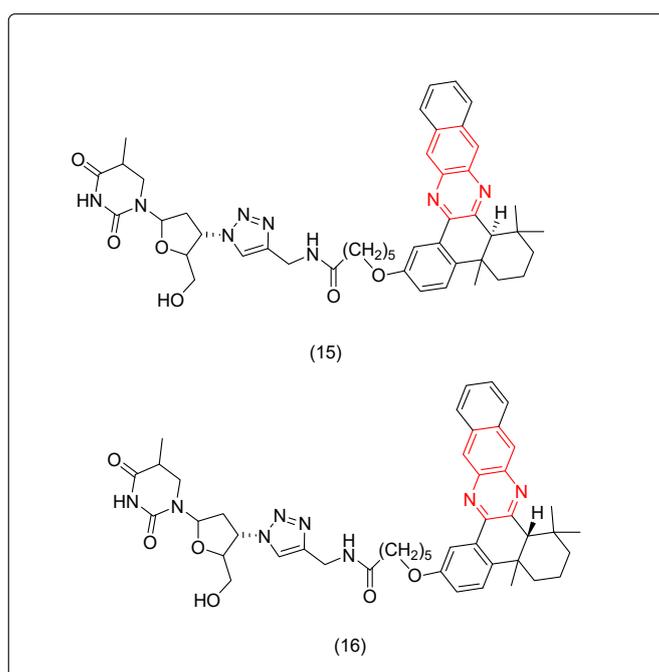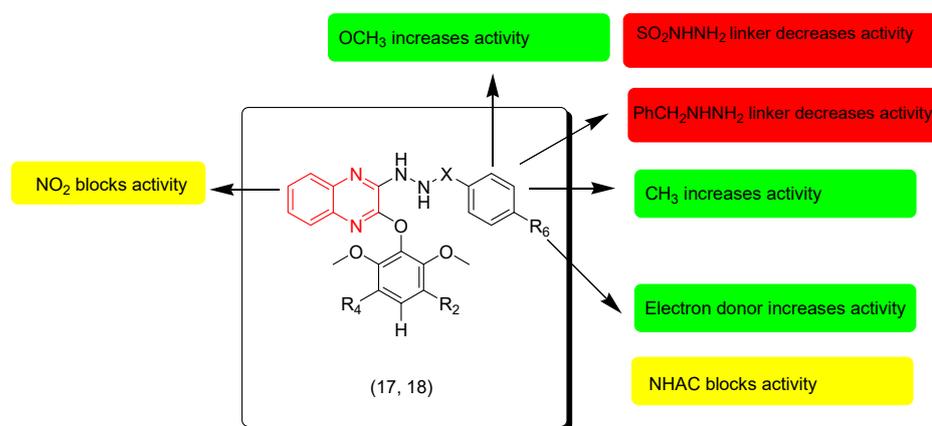

Figure 11. Anticancer quinoxalines **17** (R_2 = H, R_4 = H, R_6 = H, X = CO), **18** (R_2 = H, R_4 = H, R_6 = Me, X = CO), and their SAR.

Li and coworkers (2021) designed and synthesized a group of 1,3-diphenylurea-quinoxaline compounds and investigated their in vitro cytotoxic activity against MGC-803, HeLa, NCI-H460, HepG2, SMMC-7721, T-24, and HL-7702 cancer cell lines. Most of these compounds showed good results while compounds **19** and **20** were the highest active derivatives with IC_{50} = 9, 12.3, 13.3, 30.4, 17.6, 27.5, and 80.9 μM for compound **19** and IC_{50} = 17.2, 12.3, 40.6, 46.8, 95.4, 8.9, and 86.8 μM for compound **20** against the tested cell lines, respectively. The SAR of these derivatives showed that the replacement of the R group with electron donating groups increases the activity while electron withdrawing groups decrease the activity. Figure 12 shows the molecular structures of compounds **19**, **20**, and their SAR [99].
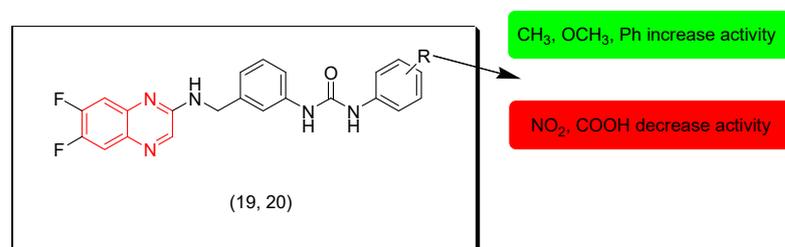
Figure 12. Anticancer quinoxalines **19** (R = 4-O-Ph), **20** (R = (3,5-$(Me)_2$)), and their SAR.

Pationate and coworkers (2021) investigated new quinoxaline derivatives with substituted imidazole-substitution. These derivatives were screened against the melanoma cells A375. Compound **24** showed an excellent activity (IC_{50} = 3 nM) 20-fold more potent than the reference Vemurafenib (IC_{50} = 139 nM). The other derivatives **21**, **22**, **23** showed moderate activities. The SAR of these derivatives showed that the o,o-dimethoxyphenyl

group at the second position from the quinoxaline nucleus increases the activity while CF_3 and OCF_3 decrease the activity. The N-linker at the third position increases the activity while the O-linker decreases the activity. The secondary amine at the third position from the quinoxaline ring increases the activity while primary and tertiary amines decrease the activity. The presence of NH or NCH_3 at the second position from the quinoxaline nucleus is essential for the activity. Figure 13 shows the molecular structures of compounds **21–24** and their SAR [100].
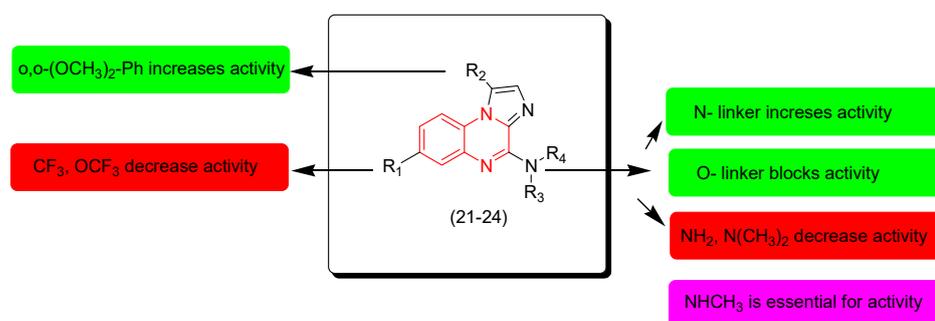
Figure 13. Anticancer quinoxalines **21** (R_1 = OCF_3, R_2 = H, R_3 = H, R_4 = Me), **22** (R_1 = OCF_3, R_2 = o,o-$(OCH_3)_2$-Ph, R_3 = H, R_4 = Me), **23** (R_1 = H, R_2 = o,o-(OCH3)$_2$-Ph, R_3 = Me, R_4 = Me), **24** (R_1 = H, R_2 = o,o-$(OCH_3)_2$-Ph, R_3 = H, R_4 = Me), and their SAR.

6. Quantitative Structure–Activity Relationship (QSAR) Modeling of Anticancer Quinoxalines

In a recent study, using some reported anticancer quinoxaline derivatives, a statistically verified 2D-QSAR model was developed by Abdullahi and coworkers (2023). By means of the created model, quinoxaline derivatives were virtually screened, and compound **25** with a high inhibiting capacity (pIC_{50} = 5.357) was chosen as the model for the design, and five potential better VEGFR-2 inhibitory compounds (**26–30**), having pIC_{50} values between 5.43 and 6.16, were created. The intended compounds were used as ligands in docking studies, and the active site residues of VEGFR-2 were discovered to have docking scores ranging from −171.384 to −182.241 kcal/mol, surpassing the score of −170.579 kcal/mol for the template ligand. MD simulation indicated that the ligands remained in the stable docked complex and that the molecules did not leave the VEGFR-2 active site during the 200 ns simulation. Figure 14 shows the molecular structure of the model **25** and the designed derivatives (**26–30**) while Table 3 shows the computed activities of these derivatives [101].

Figure 14. The molecular structure of the model **25** and the designed derivatives (**26–30**): **25** (Y = H, X = H), **26** (Y = H, X = CH_3), **27** (Y = H, X = OH), **28** (Y = H, X = OCH_3), **29** (Y = H, X = NH_2), **30** (Y = NH_2, X = NH_2).

Table 3. The selected quinoxaline model (**25**), the designed quinoxaline derivatives (**26**–**30**), and their computed VEGFR-2 inhibitive activities. GATS5e (Geary autocorrelation—lag 5/we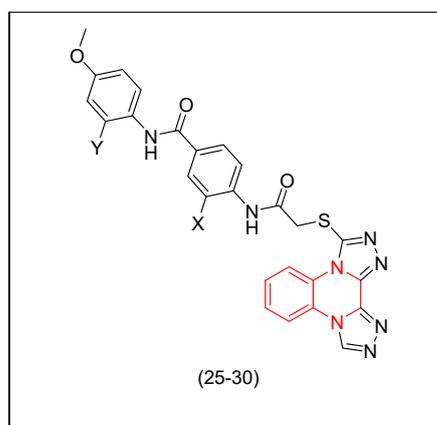ighted by Sanderson electronegativities), GATS3i (Geary autocorrelation—lag 3/weighted by Sanderson electronegativities), GATS8i (Geary autocorrelation—lag 8/weighted by Sanderson electronegativities), SpMax8_Bhs (the largest absolute eigenvalue of Burden modified matrix—n 8/weighted by relative I-state), VR2-Dt (normalized Randic-like eigenvector-based index from Detourn matrix).

ID	GATS5e	GATS3i	GATS8i	SpMax8_Bhs	VR2_Dt	Pred. pIC_{50}
25	-	-	-	-	-	5.270
26	0.84815	1.14294	1.10205	3.268138	13.5029	6.16
27	0.77563	1.11386	1.01902	3.511698	13.5029	5.59
28	0.78409	1.11669	0.93430	3.26897	12.6848	5.56
29	0.79970	1.12572	1.04414	3.274876	13.5029	6.13
30	0.82951	1.15402	1.03294	3.407978	12.3978	5.43

7. SAR of Anticancer Quinoxalines

From the previously discussed examples, we can conclude the following SAR of anticancer quinoxalines:

1. Quinoxaline moiety is an essential pharmacophore for the anticancer activity.
2. The main sites of substitutions are first, second, and third, sixth, and/or seventh positions.
3. The quinoxaline nucleus can be part of a hybrid molecule through a molecular hybridization process to potentiate the anticancer activity.
4. The quinoxaline system can be joined with a polycyclic aromatic system at the (B) junction.
5. There are two types of linkers that can be fused to the quinoxaline nucleus; in most cases the aliphatic linker is more reactive than the hetero-atomic linker.
6. The third position from the quinoxaline nucleus can be fused to the heterocyclic system or aromatic system via an aliphatic linker.
7. The aromatic ring of the quinoxaline nucleus can be substituted with halogens such as Cl or F at the sixth and/or seventh position/s to increase the activity.

8. Future Potentials

Heterocyclic molecules are an important class of derivatives with huge potential in medicinal activities. Quinoxaline is a heterocyclic system used in the design of many types of drugs. Many efficient methods were used for the synthesis of quinoxaline molecules. Chemists should use and develop green chemistry protocols as a new developed way for the future production of these molecules to avoid the problems of traditional reactions. The anticancer activity of quinoxaline compounds was reported in many studies, however the main problem associated with its anticancer activity was toxicity effects. Consequently, many quinoxaline derivatives are under development for lowering the toxicity profiles and increasing the activity. Quinoxaline pharmacophore possesses broad-spectrum pharmacological activities and still has many ranges to be discovered.

9. Conclusions

Drug development is a continuous job with limitless borders. It plays a major role in the progress of medicinal chemistry research. Nonstop research efforts in the field of drug discovery have resulted in the discovery of quinoxaline and its derivatives as versatile medicinal agents. A vast frame of scientific experiments proved the efficacy of quinoxalines in the treatment of many diseases and infections. Numerous molecules of quinoxalines were approved by the FDA and are available in the market. This review article sheds light on chemistry, physicochemical characteristics, methods of preparations, pharmaceutical products, molecular structures, and anticancer activities of some quinoxaline derivatives and their SAR characteristics. The study of SARs will be the major key for the development of efficient quinoxaline therapeutic agents. The improved quinoxaline derivatives will be identified via SAR-based studies. The structural optimization was performed with different

strategies such as molecular hybridization or biological isosteric replacement to produce more potent anticancer molecules.

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