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An insight into medicinal chemistry of anticancer quinoxalines

Tanu Kaushal[a,b], Gaurava Srivastava[a,b], Ashok Sharma[a], Arvind Singh Negi[a,b,*]

[a] CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP), P.O. CIMAP, Kukrail Picnic Spot Road, Lucknow 226 015, UP, India
[b] Academy of Scientific and Innovative Research (AcSIR), New Delhi 110001, India

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ABSTRACT

Quinoxalines are benzopyrazines containing benzene and pyrazine rings fused together. In the recent past, quinoxalines have attracted Medicinal Chemists considerably for their syntheses and chemistry due to their distinct pharmacological activities. Diverse synthetic protocols have been developed *via* multicomponent reactions, single pot synthesis and combinatorial approach using efficient catalysts, reagents, and nano-composites etc. Further, the versatility of the quinoxaline core and its reasonable chemical simplicity devise it extremely promising source of bioactive compounds. Therefore, a wide variety of bioactive quinoxalines has been realised as antitumour, antifungal, anti-inflammatory, antimicrobial, and antiviral agents. Already, a few of them are clinical drugs while many more are under various phases of clinical trials. Present review focuses on chemistry and pharmacology (both efficacy and safety) of quinoxalines and also provides some insight in to their structure–activity relationship.

1. Introduction

Heterocyclic compounds are one of the vast areas of research in medicinal chemistry. Quinoxaline is a member of family of benzodiazine with its 1,4-nitrogens as heteroatoms. These are pharmacologically important compounds possessing diverse biological activities i.e. antibacterial,[1] antifungal,[2] anticancer,[3] analgesic,[4] antimalarial,[5] antitumor,[6] antiamoebic,[7] antiepileptic,[8] anticonvulsant,[9] antitubercular,[10] antiproliferative[11], anti-HCV[12], and anti-inflammatory[13] etc. Quinoxaline core is an attractive nucleus for Medicinal Chemists to achieve various biologically active compounds. Echinomycin,[14] a natural antibiotic, possesses two terminal quinoxaline-2-carboxylic acid nuclei linked to a cyclic octadepsipeptide containing a sulphur cross-linkage. It is structurally related to triostin (Fig. 1). Echinomycin, SW-163s, and triostin A are important secondary metabolites from quinomycin families. These non-ribosomal peptides act as bisintercalators by placing quinoxaline unit preferably adjacent to cytosine-guanine (C-G) base pairs of DNA. Subsequently, several novel quinoxaline antibiotics of echinomycin class have been developed through synthetic modifications. Moreover, quinoxaline moieties also find prominent uses in agrochemicals as herbicides,[15] insecticides,[16] pesticides[17] and also as high performance phosphorescence light emitting diodes and solar cells.[18] Present review aims at recent updates of quinoxaline derivatives in chemical and biological applications in order to provide an important class for therapeutic targets in drug discovery and future drug development. It mainly focuses on anticancer aspects of quinoxaline class of compounds.

2. Chemistry

2.1. Synthesis of quinoxaline derivatives

Over the years, researchers have established relatively simpler methods to prepare quinoxaline core. To attain high diversity, numerous synthetic approaches have been realised to prepare quinoxalines and their polycyclic derivatives. Thus, a large number of derivatives with diverse pharmacophores have been synthesized.

Several important synthetic protocols are summarised;

2.1.1. Condensation between O-Phenylenediamines and diketones

Substituted diketones are usually condensed with *O*-phenylenediamines to synthesize the quinoxaline derivatives at refluxing temperature in ethanol, benzene, or acetic acid.[19] This condensation was activated by iodine,[20] indium(III) chloride,[21] copper(II) sulfate,[22] ceric ammonium nitrate,[23] *o*-iodoxybenzoic acid,[24] phosphorus oxychloride,[25] silica gel,[26] gallium(III) triflate,[27] and clayzic[28]. Furthermore, other heterogeneous catalysts such as, cellulose sulphuric acid (CSA),[29] molecular I_2,[30] ferric perchlorate,[31] Zn[(L) proline],[32] silica bonded S-sulfonic acid (SBSSA),[33] Montmorillonite *K*10,[34] $Cu_2H_2PMo_{11}VO_{40}$[35] and ZrO_2/Ga_2O_2/MCM-4,1[36–38] Graphite,[39] Cu/

* Corresponding author.
E-mail address: arvindcimap@rediffmail.com (A. Singh Negi).

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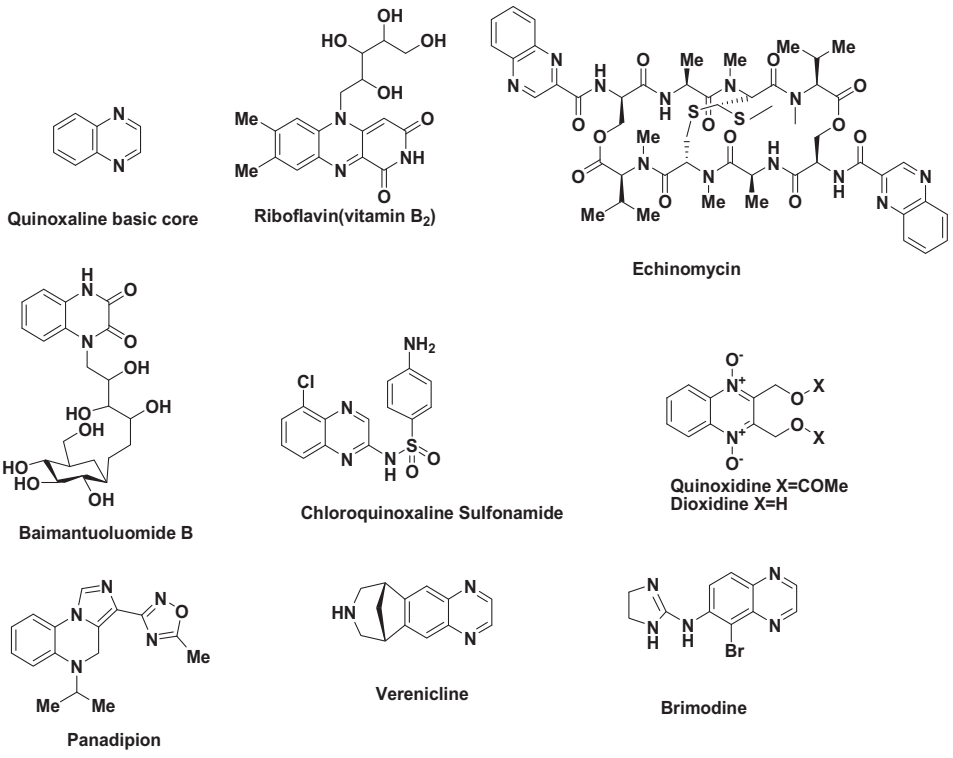
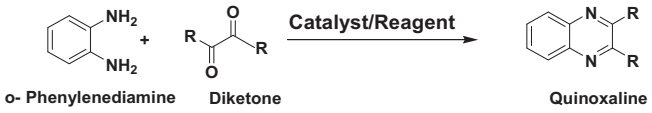
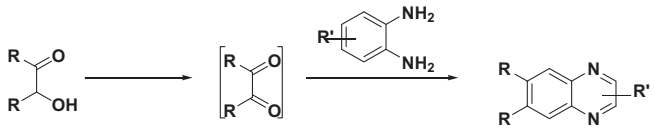


Fig. 1. A few representative drugs, bioactive and naturally occurring compounds possessing quinoxaline scaffold.



Scheme 1.



Scheme 1B.

SBA-15,[40] $PdCl_2/PPh_3$,[41] $MgSO_4{\cdot}7H_2O$,[42] $HClO_4.SiO_2$,[43] zirconium(IV)-modified silica gel,[44] acidic alumina[45] as well as nano-catalysts *viz.* $MnFe_2O_4$[46], Ni-nanoparticles[47], nanocrystalline CuO[48] and g-Maghemite-silica nanocomposite[49] are divergent routes to prepare quinoxaline derivatives suitably (Scheme 1).

An environment friendly and economic synthesis of quinoxaline core was reported in glycerol–water system without a catalyst (Scheme 1A).[50]

Further, a one pot tandem oxidation process has been developed using different oxidants like manganese dioxide,[51] mercuric iodide,[52] silica gel[53] in diglyme and ferric chloride/morpholine (Scheme 1B).[54]

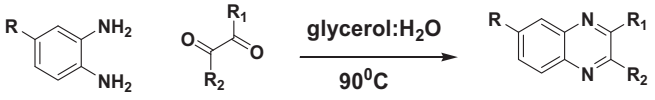
2.1.2. Condensation of 1-(p-tolylsulfonyl)-2-phenyloxirane with o-phenylenediamine

On refluxing 1-(*p*-tolylsulfonyl)-2-phenloxirane with *o*-phenylenediamine in dimethylformamide yielded 2-phenylquinoxaline.[55] Substrate phenloxirane was obtained on condensation of chloromethyl-*p*-tosylsulfone with benzaldehyde (Scheme 2).

III. Cyclization of phenacyl bromides

Phenacyl bromides were condensed with phenylenediamines and then cyclised in presence of pyridine (10% mol) in THF at room temperature in 8 h to afford the quinoxaline moiety (Scheme 3A).[56]

Another effective one-pot synthesis of 2-substituted quinoxalines



Scheme 1A.

was developed by catalysing with *K*10-montmorillonite (*K*10 clay) at 50 °C in acetonitrile medium.[57] In the plausible mechanism quinoxaline was formed *via* dehydration–dehydrohalogenation–cyclization sequence. Additionally, the *K*10 clay catalyst was recycled up to six times without any catalytic loss (Scheme 3B).

2.1.3. Condensation between o-phenylenediamine and α-hydroxy-ketones

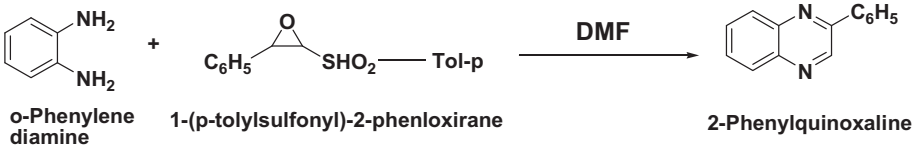
The quinoxaline core was formed either by refluxing transition metals catalysed reaction mixture in acetic acid such as Mn,[58] Pd,[59] Ru,[60] Cu,[61] and Pb[62] or by microwave irradiation[63] to afford quinoxalines. Recently, synthesis of quinoxaline core was performed by the condensation of α-hydroxyketones with *o*-phenylenediamine in presence of KF and alumina (2:3) on refluxing at 80 °C (Scheme 4).[64]

V. Three-component tandem reaction of (2-arylsulfanyl-3-aryl-2-oxiranyl) (aryl) methanones and o-phenylenediamine

The starting substrates for the synthesis of quinoxaline nucleus, namely, (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl) methanones (**B**) was obtained successively by the reaction of 1,3-diaryl-2-(arylsulfanyl)-2-propen-1-ones (**A**) with alkaline hydrogen peroxide in ethanol at room temperature in excellent yields (95–98%).[65] Compound **B** was further condensed with o-phenylenediammine catalysed by acetic acid to afford 2,3-disubstituted quinoxalines (Scheme 5). The tandem reaction presumably moves via oxirane aminolysis–cyclisation–elimination–air oxidation–condensation sequence.

2.1.4. One-pot tandem oxidation process (TOP) using a variety of oxidants

This methodology possessed several advantages like shorter reaction times, higher yields as well as less number of synthetic steps. A



Scheme 2.

number of TOP-mediated quinoxaline syntheses were duly developed using different oxidants like manganese dioxide,[51] mercuric iodide,[52] silica gel[53] in diglyme and ferric chloride/morpholine system (Scheme 6).[54]

2.1.5. Condensation between terminal/internal alkynes and o-phenylenediamine

An interesting preparation of quinoxalines was developed through cyclization of terminal alkyne and *o*-phenylenediamine catalysed by Cu (II) in presence of a base. The reaction proceeded smoothly to furnish the products in modest yields (Scheme 7A).[66]

For internal alkynes, a transition metal free approach was developed to achieve quinoxaline core with high structural diversity using diacetoxyiodobenzene as a catalyst under heating condition (Scheme 7B).[67]

Further, a one-pot, three-component synthesis was established for the preparation of quinoxalinyl triphenylphosphoranes as useful synthetic targets as well as fascinating intermediates. This procedure provided preparation of quinoxalines with diverse functionalities (Scheme 7C).[68]

2.1.6. Copper (II)-catalyzed synthesis of quinoxalines from o-phenylenediamines and nitro olefins

Another efficient protocol was developed for synthesizing quinoxaline core *via* $CuBr_2$-catalysed reductive cyclisation of *o*-phenylenediamine and nitro olefins without a base (Scheme 8).[69]

2.1.7. Reaction of substituted O-diamines with phenylacetaldehyde

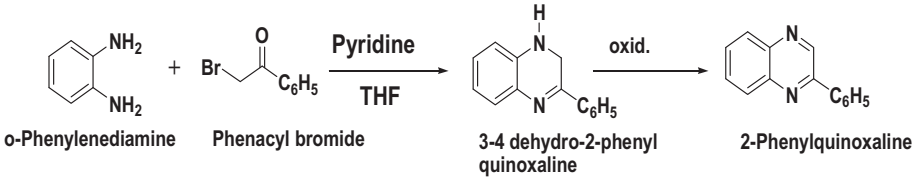
This one-pot procedure goes smoothly even in absence of transition-metal catalyst. However, an inorganic base (K_2CO_3) was required in the reaction mixture. The protocol is convenient, economical, highly efficient and eco-friendly to achieve quinoxalines (Scheme 9).[70]

2.1.8. Pd catalyzed synthesis of dihydroquinoxalines

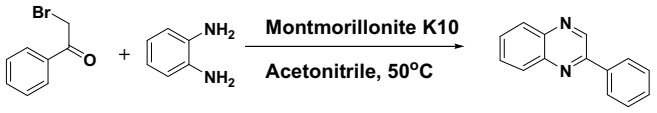
Wallace et al.[71] developed a palladium-catalyzed reductive *N*-hetero-annulation of enamines derived from 2-nitrobenzenamines to give a mixture of 1,2-dihydroquinoxalines and 3,4-dihydroquinoxalin-2-one. The reaction progressed with bis (dibenzylidene acetone) palladium(0), 1,3-bis-(diphenylphosphino)propane, and 1,10-phenanthroline in DMF under 6 atm of carbon monoxide at 70 °C (Scheme 10).

2.1.9. Multicomponent reactions

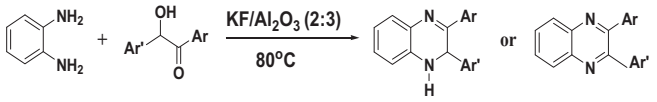
Synthesis of heterocyclic compounds through multicomponent reactions has emerged as most felicitous approach. An effective and concise synthesis of quinoxalines was deployed through Ugi-based unified approach. This procedure used readily available commercial reagents and simple intermediates. Overall, this protocol represents a simple and convenient synthesis of quinoxaline library (Scheme 11).[72]



Scheme 3A.



Scheme 3B.



Scheme 4.

2.1.10. One-pot cyanide-based sequential reaction under aerobic oxidation conditions

An effective preparation of 2-aminoquinoxalines was established *via* one-pot two-step cyanide-mediated sequential reaction of *ortho*-phenylenediamines with aldehydes under aerobic oxidation conditions. Diverse substrates, including aliphatic aldehydes with acidic α-protons, underwent this reaction to give the targeted 2-aminoquinoxalines in excellent yields (Scheme 12).[73]

2.1.11. Condensation of aliphatic diamines with ethyl gallate to get tetrahydroquinoxalines

A Green Chemistry approach was developed to synthesize Quinoxalines from ethyl gallate through nucleophilic substitution reaction.[74] The desired products i.e. tetrahydroquinoxalines are formed in excellent yields within a very short duration of time (Scheme 13).

2.1.12. Iodine catalysed tandem synthesis via sp^3, sp^2 and sp C–H functionality

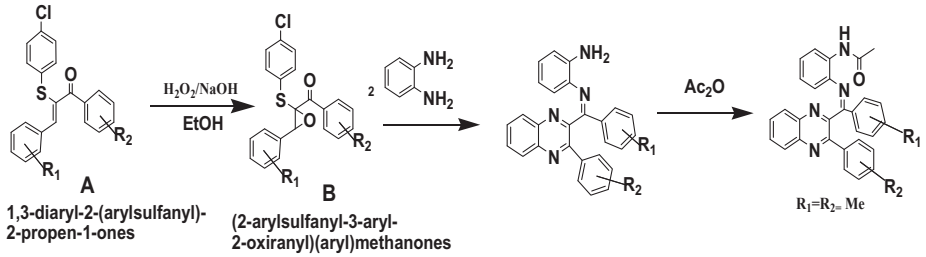
A simple, metal free, one pot synthesis of quinoxalines was developed from the condensation of aryl glyoxals with *o*-phenylenediamine. Molecular iodine was used as a catalyst and *t*-butylhydroxyperoxide (TBHP) as an oxidant in DMSO for this domino reaction involving oxidative cyclization (Scheme 14).[75]

2.1.13. Intramolecular cyclization of nitroketene of N, S-anilioacetal intermediates

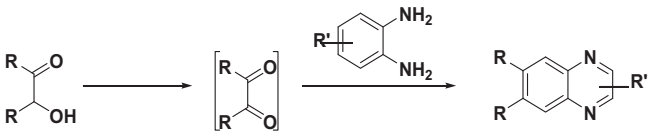
A regioselective and chemoselective efficient synthesis of substituted 3-(carboethoxy)-imidazo and diimidazo[1,5a: 5′,1′c] quinoxalines was developed *via* intramolecular cyclization of nitro ketene N,S-anilioacetal intermediates (Scheme 15).[76]

2.1.14. Beirut reaction

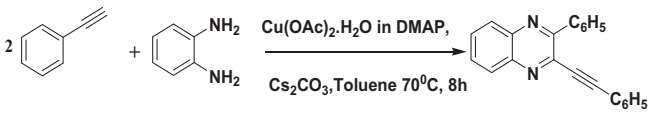
Dhabi and co-workers (2010) reported an extension of Beirut reaction for the synthesis of the 2-phosphorylated quinoxaline-1,4-bis-*N*-oxides. The methodology involved the reaction of benzo [c] [1,2,5] oxadiazole-1-oxide with dimethyl-2-oxopropylphosphonate in the presence of 3Å molecular sieves to get two phosphorylated derivatives or



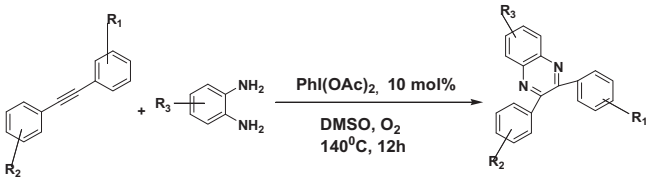
Scheme 5.



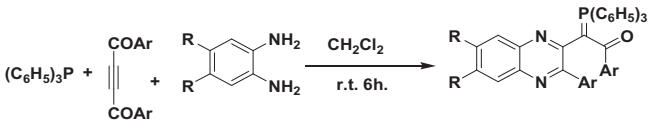
Scheme 6.



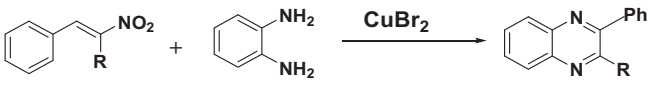
Scheme 7A.



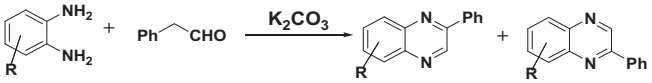
Scheme 7B.



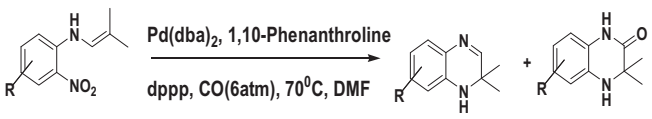
Scheme 7C.



Scheme 8.



Scheme 9.



Scheme 10.

with anhydrous cesium carbonate to yield single non-phosphorylated derivative (Scheme 16).[77]

2.1.15. Combinatorial parallel synthesis approach

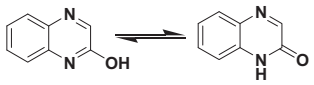
In the recent past, combinatorial synthesis emerged as a powerful approach in drug discovery. In this, two parallel synthetic strategies i.e. solid phase synthesis[78] and solution phase synthesis[79] have been advanced.

2.1.15.1. Solid phase synthesis. In this methodology, polymer-linked 2-nitrophenyl carbamate was condensed with α-bromoketone followed by stannous chloride mediated reduction of the nitro group, which further underwent intramolecular cyclization to yield polymer bound quinoxalines. Subsequent acidolysis yielded desired compounds *via* aerial oxidation in excellent yields and good purities (Scheme 17A).[78]

2.1.15.2. Solution phase strategy. Besides the advantages of solid-phase chemistry (use of excess reagents and simple isolation and purification), it has the advantages of solution chemistry conventional analysis. Polyethylene glycol (PEG), is successful as a polymer support and as a delivery vehicle for many low-molecular-weight drugs, polypeptides, and oligonucleotides. Conjugation to PEG increases water solubility and retention time and protects drugs against degrading enzymes. An efficient synthesis of quinoxaline was described by Fouad F. (2013), on PEG-4500 soluble polymer under microwave irradiation 3,4-dinitrobenzoic acid was hooked up to the hydroxyl termini of PEG-4500, and two adjacent nitro groups were subsequently reduced to the desired 1,2-diamine. This diamine was further condensed with α-diketones under microwave irradiation in the closed vessel system for 10 min. Finally, the cleavage of the quinoxaline from the PEG support was achieved by sodium methoxide in methanol (Scheme 17B).[79]

2.2. Reactions of quinoxalines

Quinoxalines are weakly basic (pKa ≈ 0.56), low melting solids forming salts with acid.[80] The phenomenon of tautomerism is reported in 2- hydroxy quinoxaline.[81]



2.2.1. Electrophilic substitution reactions

Quinoxaline doesn't undergo electrophilic substitutions easily. The symmetry of quinoxaline ring makes the 6- and 7- positions equivalent. When benzene ring possesses more activating substituents, substitution usually becomes more facile whereas presence of substitution at heterocyclic ring varies the situation depending upon the reaction conditions.[82]

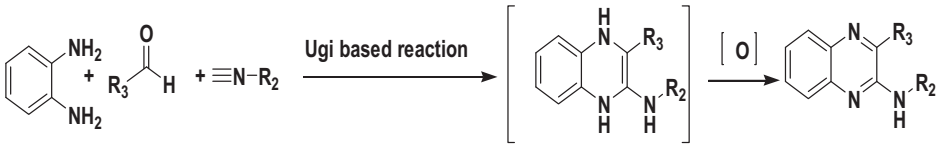
Nitration

Under drastic reaction conditions (98% conc. HNO_3, oleum at 90 °C) nitration is observed at 5- and dinitration occurs at 5,7- positions (Scheme 18).[83]

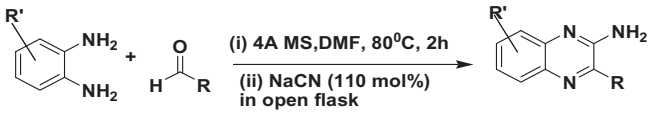
Sulfonation

Sulfonation of quinoxaline-1,4-dione with fuming sulfuric acid yields the 6-sulfonic acid. Similarly, if quinoxaline 2,3-dione is treated with chlorosulfonic acid at elevated temperature, the 6-sulfuryl chloride is obtained (Scheme 19).[84]

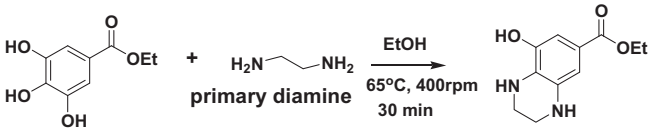
Free radical reaction



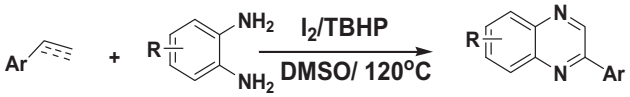
Scheme 11.



Scheme 12.



Scheme 13.



Scheme 14.

The radicals are generated under oxidising conditions with the H_2O_2 or *t*-butyl hydroperoxide and ferrous sulfate. The UV irradiation of quinoxaline in methanol yields radicals not by the hydrogen abstraction, but by the protonation of the first singlet excited state, followed by epiplex formation. Quinoxaline is transformed to 2-methylquinoxaline when treated with acidified methanol. The reaction is expected to go through free radical mechanism where there is an electron transfer from methanol to protonated quinoxaline (Scheme 20).[85]

2.2.2. Nucleophilic substitution reactions

Quinoxalines readily undergo nucleophilic substitutions.

Reaction with Grignard reagent

Two molecular proportions of Grignard reagent could be added across quinoxaline molecule (Scheme 21).

Whereas, 2-quinoxalinone added one molecule of Grignard reagent to yield the corresponding 3-substituted tetrahydroquinoxalinone (Scheme 22).[86]

6-substituted quinoxalines underwent unusual reaction with nucleophiles (Scheme 23). Thus, 2,3-diphenyl-6-nitroquinoxaline with potassium cyanide underwent substitution in the 5-position with simultaneous nucleophilic displacement of the nitro group to give I along with 5-aminoisoxazole[3,4-f] quinoxaline II (Scheme 23).[87]

2.2.3. Oxidation reactions

Quinoxaline and its derivatives undergo oxidation readily. However, the formation of product depends upon the nature of the oxidising agent used. Alkaline potassium permanganate yielded pyrazine-2,3-dicarboxylic acid, while peracid gave quinoxaline1,4-bis-N-oxide[88] (Scheme 24). The latter was biologically more potent. Substitution at 2- position generally inhibited the 1-oxide formation. 5-Substituted quinoxaline afforded mono-*N*-oxide presumably the 1-oxide and were resistant to further oxidation. 6-Substituted quinoxalines, as the substituents became more electron attracting, the yield of the 1,4-dioxide decreased more of the 2,3-dione was formed.[89]

2.2.4. Reduction of quinoxalines

Quinoxaline is converted to 1,2,3,4- tetrahydroquinoxaline either by the action of sodium in boiling ethanol or by treatment of lithium aluminium hydride (Scheme 25). The tetrahydro derivative is also achieved on catalytic hydrogenation. On treatment of quinoxaline with Na in THF, a distinct product was obtained. The sodium quinoxalide (**IVa**) bears a deep purple colour which on addition of absolute ethanol turns to light green. Further, addition of water precipitated a light tan solid i.e. 1,4- dihydroquinoxaline (**IVb**). Treatment of this compound with lithium aluminium hydride yielded 1,2,3,4-tetrahydroquinoxaline (**IVc**).[90] Sodium borohydride in acetic acid was taken for reduction in case of 6- substituted quinoxaline derivatives.[91]

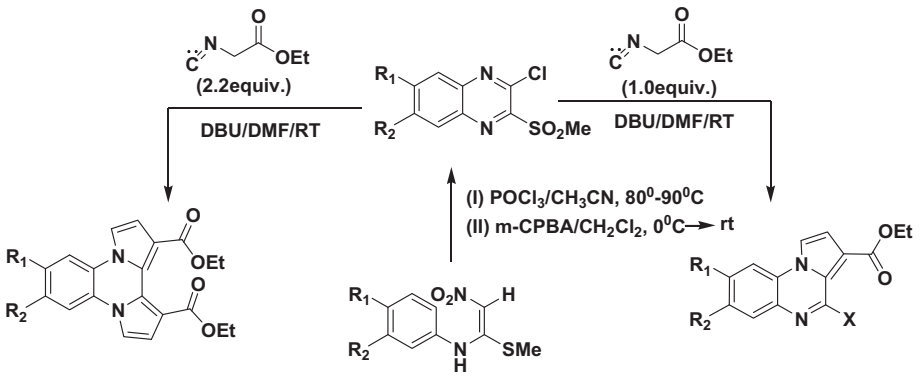
2.2.5. Quaternary salt formation

Cheeseman (1962) prepared 1,4-dimethylderivatives as quaternary ammonium salts by electrophilic substitution reaction of 2,3-dihydroxyquinoxalines. 2-Methyl quinoxaline and some of their 6,7- substituted derivatives were formed from 4-methylsulfates and perchlorates which on hydrolysis afforded quinoxalinone salts (Scheme 26).[92]

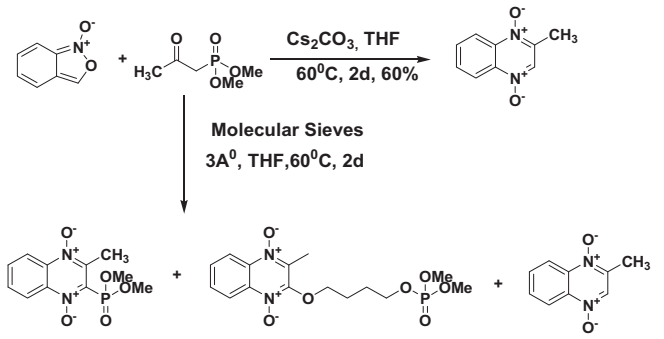
There are several quinoxaline based drugs in the clinical use. Table 1 shows sixteen marketed drugs; two are natural, one semi-synthetic and rest thirteen are synthetic.

2.3. Total synthesis of some quinoxaline clinical drugs

Riboflavin and echinomycin were isolated from naturally occurring sources, rest of all were synthetically produced. Total synthesis of some of the clinical drugs has been discussed in this section;



Scheme 15.



Scheme 16.

2.3.1. Industrial synthesis of riboflavin

Microbial process is used to produce riboflavin from renewable resources like sugar or plant oil. Three diverse microorganisms i.e. a filamentous fungus *Ashbya gossypil*, a yeast *Candida famata* and a Gram positive bacterium *Bacillus subtilis* are used for this transformation. The high concentration of riboflavin in the modified strain has a reddish/brownish colour which accumulates riboflavin crystals in the vacuoles, and finally burst the mycelium.

2.3.2. Chemical synthesis of riboflavin

Riboflavin is synthesized by chemical process also known as Kuhn synthesis (Scheme 27).[93] In the first step reductive condensation of 2-nitro-4,5,-dimethylaniline (**b1**) is done with D-ribose to get 2-nitro-4,5-dimethyl-*N*-D-ribitylaniline (**b2**). Compound **b2** is treated by hydrogen/palladium-charcoal to reduce nitro group to amine to get 2-amino-4,5-dimethyl-*N*-D-ribitylamine (**b3**), which on condensation with alloxan in presence of boric acid yields riboflavin.

2.3.3. Synthesis of varenicline

Varenicline was approved as an aid to smoking cessation treatment by US FDA in May 2006. It is a partial agonist of α4β2-nicotinic receptor. Coe *et al.* (2005)[94] synthesized it from benzazepine (**c1**) in four straight-forward steps as shown in Scheme 28. The heterocyclic nitrogen of **c1** was protected as trifluoroacetyl group by treating it with trifluoroacetic anhydride in pyridine-dichloromethane system to get compound **c2**. Compound **c2** was dinitrated in presence of exceptionally powerful and soluble nitrating agent, nitronium triflate i.e. nitric acid-trifilic acid (HNO_3-CF_3SO_3H) in dichloromethane to afford **c3**. Both the nitro groups were reduced to corresponding amino groups by reducing **c3** with H_2/$Pd(OH)_2$ in methanol to get compound **c4**. Diamino derivative **c4** was further condensed with ethylene glycol to get quinoxaline moiety as trifluoroacetamide **c5** which was converted to varenicline as hydrochloride salt. The overall yield of the final product varenicline hydrochloride was 44% in this complete process.

Another synthesis was done by Pasikanti *et al.* (2010)[95] as per Scheme 29, starting with 2,3,-dimethylpyrazine (**c6**). It was a six step synthesis with 10% overall yield. It employed conversion of 2,3-dimethylpyrazine c6 to 2,3-bis(dibromomethyl)pyrazine c7. Subsequent NaI catalysed Diels–Alder reaction between 2,3-bis(dibromomethyl)-pyrazine c7 and norbornadiene afforded the adduct c8. Olefin c8 on treatment with OsO_4 in the presence of NMO was transformed to its corresponding diol c9 which on oxidative cleavage with $NaIO_4$ provided an intermediate dialdehyde. Further, reductive amination with 4-methoxybenzyl amine yielded compound as amine-protected varenicline c10. Finally, the amino protective group PMB, was removed by Pd/C-ammonium formate-methanol system to furnish the desired product varenicline.

2.3.4. Synthesis of brimonidine

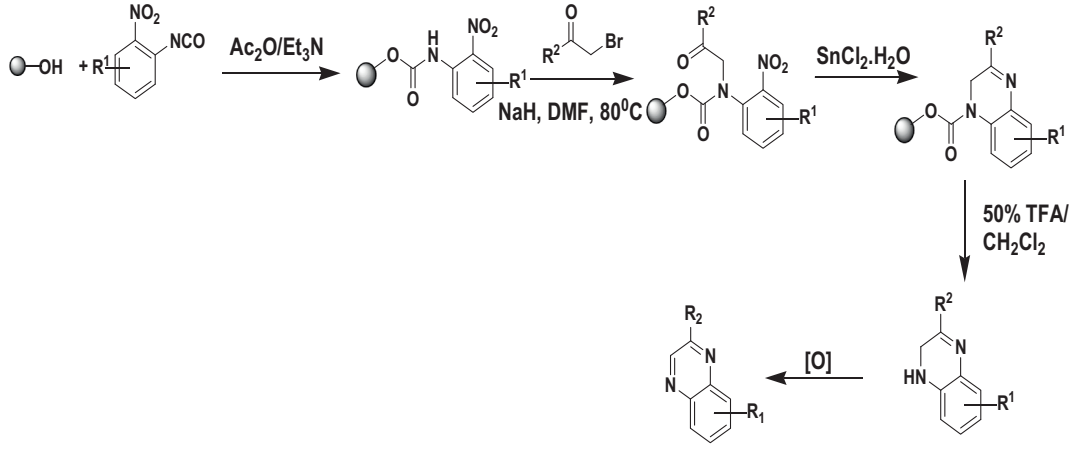
In the recent past Naik *et al.*[96] came up with a novel and environment friendly synthesis (Scheme 30) of brimonidine tartrate to rectify most of the disadvantages of previously reported protocols. First step involved formation of *N*-acetyl brimonidine using 6-amino-5-bromo quianoxaline (**d1**) and *N*-acetyl ethylene urea (**d2**) in presence of phosphorus oxychloride at 55–60 °C to yield a condensed product **d3** which on hydrolysis in methanolic-sodium hydroxide formed brimonidine base (**d4**). Base **d4** on reaction with tartaric acid in methanol produced brimonidine tartrate (**d5**) in good yield and high purity.

(e) Simultaneous synthesis of quinoxidine and dioxidine

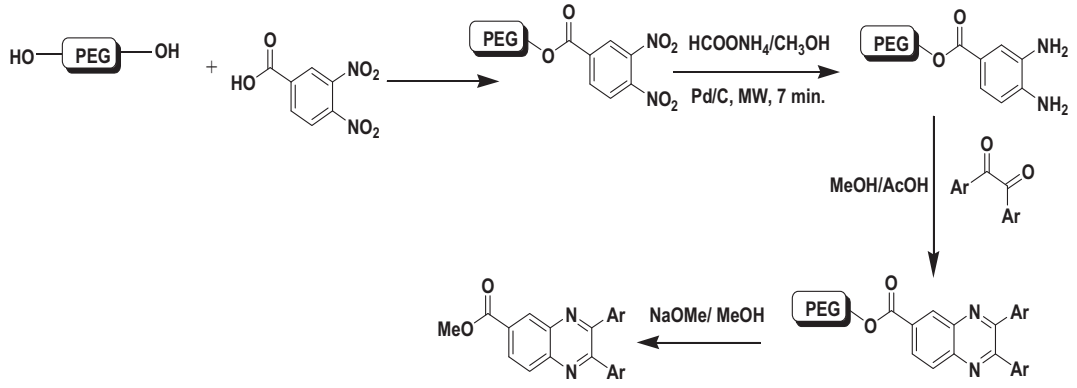
Musatova et al. [97] developed a method for the simultaneous synthesis of both quinoxidine (**e4**) and dioxidine (**e5**). As depicted in scheme 31, 5-fluorobenzofuroxan (**e1**) was reacted with ethyl methylketone in presence of *n*-butylamine to get 6-fluoro-2,3-dimethylquinoxaline di-*N*-oxide (**e2**). Both the 2,3-methyls of **e2** were brominated with bromine to get dibromoquinoxaline moiety (**e3**). Dibromo derivative **e3** was treated with triethylamine-acetic acid system to get quinoxidine i.e. 6-bromo-2,3-bis(acetoxymethyl) quinoxaline di-*N*-oxide (**e4**). Quinoxidine (**e4**) was hydrolysed with methanolic alkali to achieve dioxidine i.e. 6-fluoro-2,3,-bis (hydroxymethyl) quinoxaline di-*N*-oxide (**e5**).

3. Pharmacological profile of quinoxalines

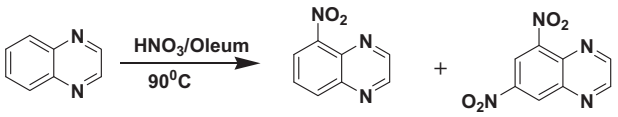
Various experimental studies have revealed diverse biological activities of quinoxaline motifs. The versatility of the quinoxaline core, its relative chemical simplicity, and accessibility makes it a promising pharmacophore for bioactive compounds which plays an important role in drug discovery. Fig. 2 depicts some of the important biological activities of quinoxaline class of compounds.



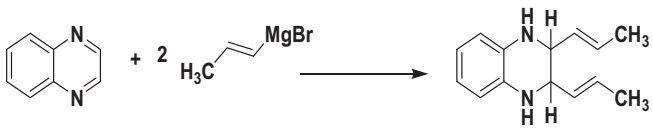
Scheme 17A.



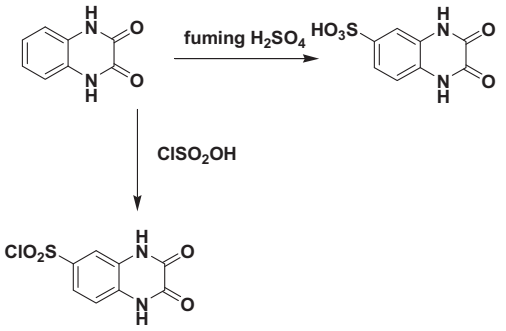
Scheme 17B.



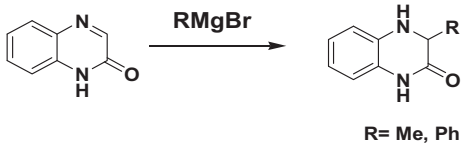
Scheme 18.



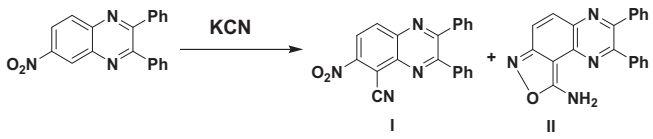
Scheme 21.



Scheme 19.



Scheme 22.

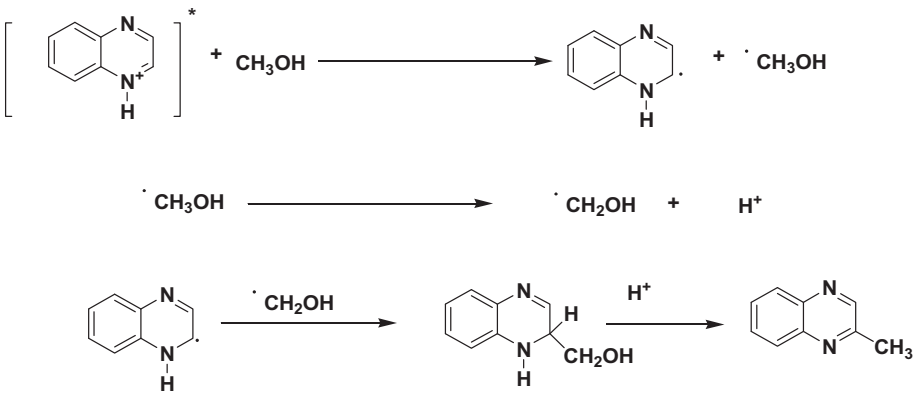


Scheme 23.

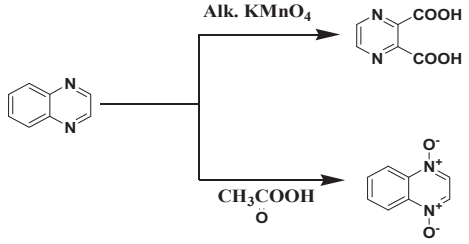
3.1. Anticancer activity

Antiproliferative cytotoxins that selectively kill rapidly dividing cells are used medicinally as anticancer drugs.[98] Various quinoxaline based compounds exhibited potential anticancer activity by inhibiting various biological targets (Fig. 3).

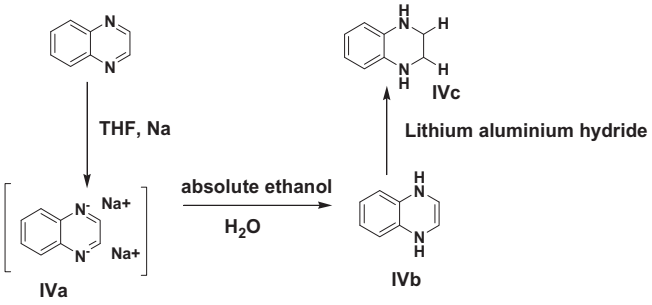
Compound **1** exhibited significant activity against four human cancer cell lines HCT-15, T-47D, MDA-MB-468 and SK-OV-3 at IC_{50} of 0.05, 0.08, 0.20 and 0.40 μM respectively.[99] Similarly, fluoroquinoxaline (**2**) was reported to possess potent anticancer activity with IC_{50} ranging from 11 to 21 nM in growth inhibition of cancer cells,[100] while the *N*-alkylated quinoxalinone **3** showed chemopreventive properties.[101] Porphyrin bearing quinoxaline **4** exhibited enhanced photocytotoxicity (IC_{50} = 0.06 μM) when compared to TMPyP (*meso*-tetra (4-*N*-methylpyridyl) porphyrin) against A549 cancer cells.[102] Further, there are many more reports about quinoxaline derivatives **5**,[103] **6**,[104] **7**,[105] **8**,[106] **9**,[107] and **10**[108] as potential anticancer agents of choice.



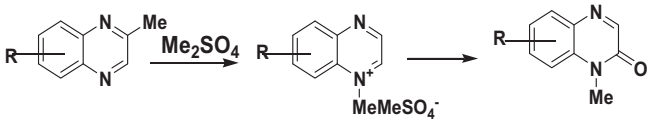
Scheme 20.



Scheme 24.



Scheme 25.



Scheme 26.

3.2. Target specific anticancer drugs

Target specific anticancer drugs is relatively recent approach of cancer drugs that can address many of the issues of cytotoxic drugs. These are divided into two groups; small molecules and antibodies. Small-molecules are developed for cancer targets that are located inside the cell because such compounds are able to enter into the cells relatively easily. Monoclonal antibodies are relatively larger in size and generally cannot enter into the cells, so they are used only for targets that are outside cells or on the cell surface.[109] Targeted therapies are designed to affect cellular proteins or processes that are utilized by the cancer cells. This allows a high dose to cancer tissues with a relatively low dose to the other tissues. Here some targets are discussed with the effective quinoxaline moiety of it (Fig. 4).[110]

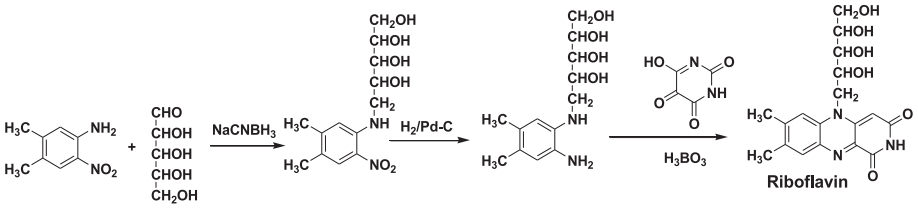
3.2.1. Angiogenesis inhibitors

Angiogenesis inhibitors block the growth of new blood vessels to tumours (a process called tumour angiogenesis). Tumour cells require blood supply because blood provides oxygen and nutrients for the continued growth of tumour cells. Compounds that interfere with angiogenesis process may block tumour growth.[111] Some targeted therapies that inhibit angiogenesis interfere with the action of vascular endothelial growth factor (VEGF), a substance that stimulates formation of new blood vessels. Quinoxaline-1,4-dioxides (QdNOs) acted as potent hypoxia selective cytotoxins modulating hypoxia inducible factor-1alpha (HIF-1α) expression. Out of many quinoxaline dioxides DCQ and BPQ showed significant activity for Lewis lung carcinoma (LLC) and EMT-6 mammary adenocarcinoma cells (**11** and **12**).[112] Recently, NBPQD (**13**) has been reported to cause bio-reductive alkylation. It cleaves DNA under hypoxic condition in presence of xanthine and xanthine oxidase.[113] Similarly, 3-(4-bromophenyl)-2-(ethylsulfonyl)-6-methylquinoxaline-1,4-dioxide (**14**) showed activity against K562, SMMC-7721, ECA-109, SGC-7901, PC-3 with IC_{50} values 0.18 μM, 3.17 μM, 6.38 μM, 8.88 μM, and 4.98 μM respectively.[114] 3-Arylquinoxalines SU1433 (**15**) and its derivatives (**16–18**) were potent inhibitors of Vascular Endothelial Growth Factor (VEGF) that stimulates angiogenesis (Table 2).[115] The methyl and benzyl derivatives (**16** and **17**) were less effective whereas acetyl derivative **18** was almost as active as the parent molecule. Further, the copper (II) complex (**19**) exhibited cytotoxic selectivity in hypoxia with promising antitumor activity[116] while compound **20** possessed potential hypoxic inhibitions in solid tumors.[117] All such compounds are represented in Fig. 5.

Some other examples of quinoxaline-1,4-dioxides include 7-(-4-nitrophenyl)-2-quinoxalinecarbonitrile-1,4-dioxide (**21**), 7-chloro- and 7-

Table 1
Quinoxaline based clinical drugs.

S. No.	Name of the drug	Nature	Application	Trade name
1.	Riboflavin (Vit. B2)	Natural	Dietary supplement, included in WHO list of Essential Medicines	Vitamin B2
2.	Echinomycin	Natural	Peptidic antibiotic, antibacterial, anticancer, and antiviral activities, Intercalates DNA, HIF-α inhibitor	Quinomycin A, Levomycin
3.	Chloroquinoxaline sulphonamide (CQS)	Synthetic	Coccidiosis in poultry, rabbit, sheep, and cattle, murine and human solid tumors (TOPO-II inhibitor)	CQS
4.	Quinoxidine	Synthetic	qHTS of small molecules that selectively kill *Giardia lamblia*: An antiarrhythmic medicine prescribed for abnormal heart rhythms such as atrial fibrillation, atrial flutter, and ventricular arrhythmias such as paroxysmal ventricular tachycardia.	Cardioquine, Cin-Quin, Duraquin, Quinidex, Quinora, Quinact, Quinatime, Quinaglute, Quinalan
5.	Dioxidine	Synthetic	Antibacterial	Dioxydine,
6.	Panadipion	Synthetic	Hepatoprotective	Used in combination with other hepatoprotective drugs.
7.	Varenicline	Synthetic	To treat nicotine addiction, also for tobacco smoking cessation, agonist of α_7 nicotinic acetylcholine receptors	Chantix and Champix
8.	Brimonidine	Synthetic	Ocular hypertension and rosacea, To treat open angle glaucoma, facial skin redness	Alphagan and Alphagan-P , Mirvaso gel
9.	Quinacillin	Semisynthetic	penicillase-resistant penicillin with antibacterial activity	Quinacilline
10.	Thioquinox	Synthetic	Its a trithiocarbonate derivative, fungicide	Quinothionate; Readex; Chinothionat;Thiaquinox; Eradex
11.	Desoxycarbadox	Synthetic	Swine growth promoter	Vetranal
12.	Carbadox	Synthetic	veterinary drug that combats bacterial infection in swine	Carbadox
13.	Olaquindox	Synthetic	Antibiotic, feed additive for growing pigs	Bay-o-nox (Bayer Co.)
14.	Quinacetone	Synthetic	antibiotic	—
15.	1-desoxyquinacetone	Synthetic	antibiotic	—
16.	Mequindox	Synthetic	An antibacterial drug which is based on quinoxaline-N,*N*-dioxide. It is useful to control bacterial enteritis in various food-producing animals	—



Scheme 27.

trifluoromethyl-/3-(dimethylaminopropyl)-amino-2-quinoxaline-1,4-dioxide (**22** and **23**) showed high potency at 0.4 μM and 0.3 μM with high Hypoxic Cytotoxic Ratio (HCR) 250 and 350 respectively.[118] The SAR studies revealed that the electronic and lipophilic properties of substitution at 3-phenyl modulates the antitumor activity of the entire molecule. At this phenyl-3-chloro substitution was the most favoured. However, 7-methyl or 7-methoxy groups also exhibited potential hypoxic selectivity against several cell lines.

3.2.2. Protein kinase inhibitors

Protein kinases behave as oncogenes by playing crucial roles in regulating most cellular functions like cell cycle, proliferation, DNA damage repair, cell metabolism, survival/apoptosis, cell motility, and response to the cellular microenvironment. Some of the kinases like c-Src, c-Abl, mitogen activated protein (MAP) kinase, phosphotidylinositol-3-kinase (PI3K)/AKT, and the epidermal growth factor (EGF) receptor are commonly activated in cancer cells, and contribute to tumorigenesis.[119] Many of these occur in the same signalling pathway, for example, HER-kinase family members (HER1 [EGFR], HER3, and HER4) transmit signals through MAP kinase and PI3 kinase to promote cell proliferation.[120] Therapeutic strategy involves, blocking of kinase-substrate interaction, or inhibit the enzyme's adenosine triphosphate (ATP) binding site.[121] A fair number of kinase inhibitors has already been developed and approved for cancer treatment. Many more are currently under clinical trial evaluation. Some of the notable quinoxalines derivatives of this class are shown in Fig. 6.

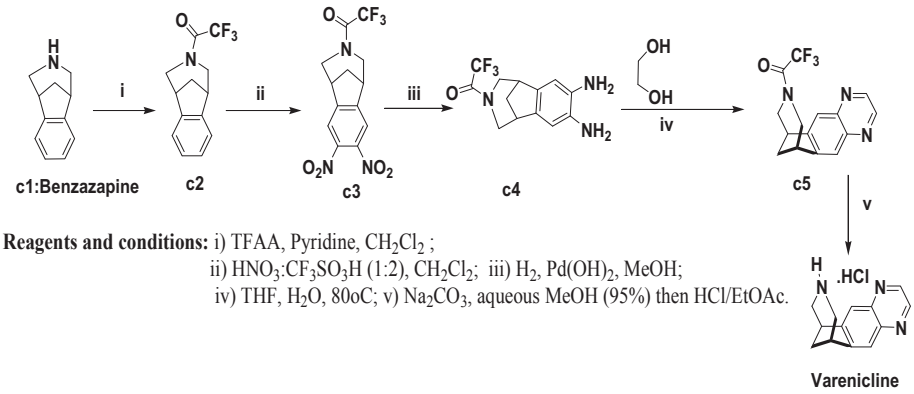
2-Amino-1-phenyl-pyrrolo[3,2-*b*]quinoxaline-3-carboxamide scaffold was optimised for type I type $I_{1/2}$ and type II tyrosine inhibitors. Compounds (**24–26**) based on this scaffold showed excellent activity with IC_{50} values of 230 nM, 5.4 nM and 21 nM respectively for type I, type $I_{1/2}$ and type II inhibitors.[122] AGL 2043 (**27**) was reported as a cell-permeable, tricyclic quinoxaline compound that acted as a potent, selective, ATP-competitive, and reversible inhibitor of type III receptor tyrosine kinases PDGFR (IC_{50} = 800 nM in 3 T3 cells; 90 nM against purified PDGF-β-receptor), Flt-3/Flk-2 (Flt3), and c-Kit (Kit) (IC_{50} ~ 1–3 μM). It weakly inhibits PKA, EGFR, IGF-1R, VEGFR, and Src kinases (IC_{50} > 30 μM).[123]

Various substituted 2(3)-(4-fluorophenyl)-3(2)-(pyridin-4-yl) quinoxalines were prepared as novel p38R MAP kinase inhibitors *via* different synthetic strategies for diverse chemical structures. An amino moiety introduction at *C*2 position of pyridine ring of 2(3)-(4-fluorophenyl)-3(2)-(pyridin-4-yl) quinoxalines afforded compounds exhibiting enzyme inhibition in nanomolar range (**28**; IC_{50} = 81 nM).[124] 4-Chlorotetrazolo[1,5-a] quinoxaline (**29**) was found to be effective in the treatment of allergic diseases mediated by mast cells by potentially inhibiting activation of syk kinase.[125] Moreover, quinoxaline derivatives **30**[126] and **31**[127] also emerged as potent kinase inhibitors. In other studies,. 2,3-di(thiophen-2-yl)benzo[*g*]quinoxaline-7-carboxylic acid (**32**) potentially inhibited SRPK-1 kinase at IC_{50} as low as 0.04 μM.[128] Merck explored and identified quinoxaline scaffolds **33**, **34**, and **35** as promising kinase inhibitors through high-throughput screening.[129] Interestingly, **36** specifically exhibited *in vitro* Pim-3 kinase inhibitory potencies.[130] A few more quinoxaline scaffolds with improved kinase inhibitory activity were **37**,[131] **38**,[132] **39**,[133] **40**,[134] **41**,[135] and **42**.[136]

3.2.3. Cell cycle regulator inhibitor

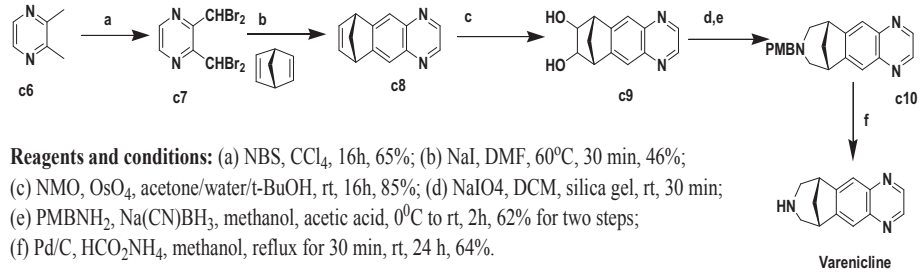
Cell proliferation is regulated by various growth factors and also by a variety of signals that allow cell cycle progression. For example, agents that damage DNA result in cell cycle arrest, presumably to allow time for the cell to repair the damage. In addition, cell contacts and a variety of extracellular factors act to inhibit rather than stimulate proliferation of their target cells. The effects of such inhibitory signals are also mediated by regulators of the cell cycle machinery, frequently *via* the induction of cyclin dependent kinase (Cdks) inhibitors.[137] A good number of Cdk inhibitors induce cell cycle arrest in response to DNA damage, which is mediated by the protein p53. The p53 protein is a transcriptional regulator that functions, at least in part, to stimulate expression of the Cdk inhibitor p21. The p21 protein inhibits several Cdk/cyclin complexes, and its induction by p53 appears to represent at least one mechanism of p53-dependent cell cycle arrest following DNA damage. In addition to inhibiting cell cycle progression *via* its interaction with Cdks, p21 may directly inhibit DNA replication. In particular, p21 binds to proliferating cell nuclear antigen (PCNA), a subunit of DNA polymerase δ. Thus, p21 may play a dual role in cell cycle arrest induced by DNA damage, not only blocking cell cycle progression by inhibiting Cdks but also directly inhibiting DNA replication in S phase of cells.[138]

Recently, some novel isoindolo[2,1-a] quinoxaline derivatives have shown dual inhibition of tubulin polymerization and topoisomerase I. Derivative **43** caused cell cycle arrest at G2/M phase and induced



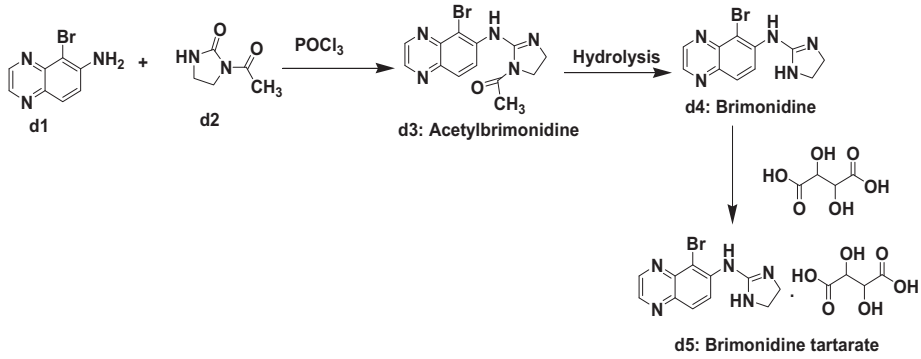
Reagents and conditions: i) TFAA, Pyridine, CH_2Cl_2 ;
ii) HNO_3:CF_3SO_3H (1:2), CH_2Cl_2; iii) H_2, $Pd(OH)_2$, MeOH;
iv) THF, H_2O, 80oC; v) Na_2CO_3, aqueous MeOH (95%) then HCl/EtOAc.

Scheme 28.

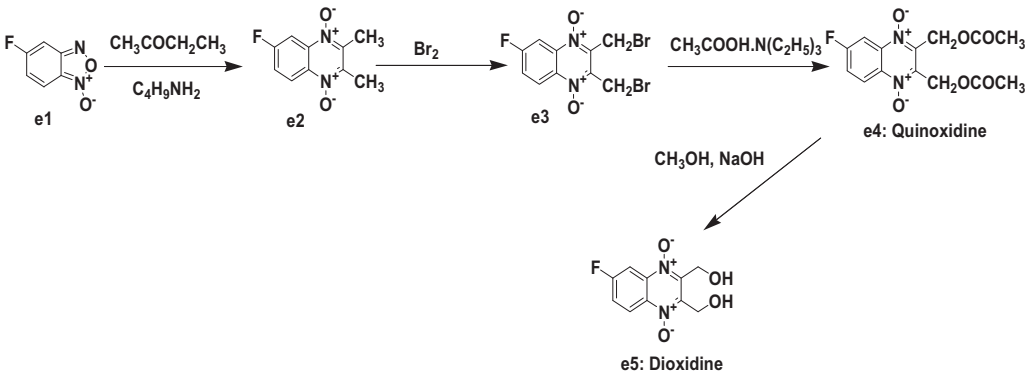


Reagents and conditions: (a) NBS, CCl_4, 16h, 65%; (b) NaI, DMF, 60°C, 30 min, 46%; (c) NMO, OsO_4, acetone/water/t-BuOH, rt, 16h, 85%; (d) NaIO4, DCM, silica gel, rt, 30 min; (e) $PMBNH_2$, $Na(CN)BH_3$, methanol, acetic acid, 0°C to rt, 2h, 62% for two steps; (f) Pd/C, HCO_2NH_4, methanol, reflux for 30 min, rt, 24 h, 64%.

Scheme 29.



Scheme 30.



Scheme 31.

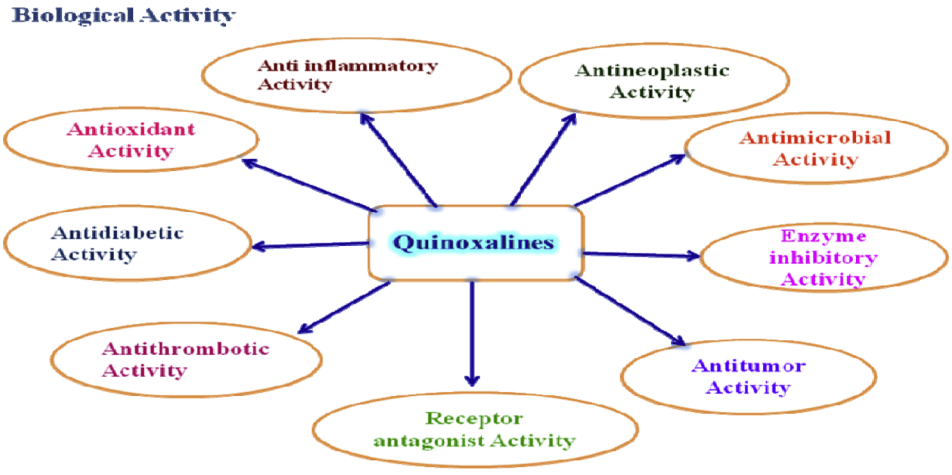


Fig. 2. Various pharmacological activities of quinoxalines.

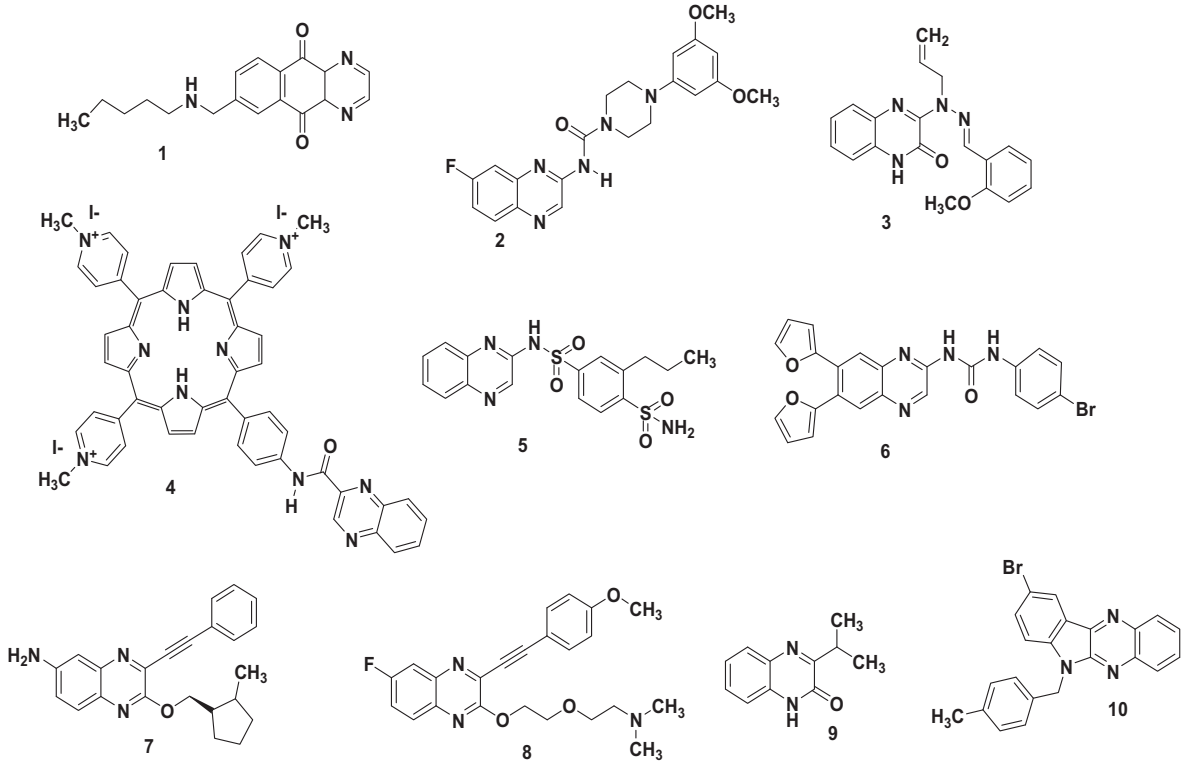


Fig. 3. Some of the quinoxaline motifs as anticancer agents.

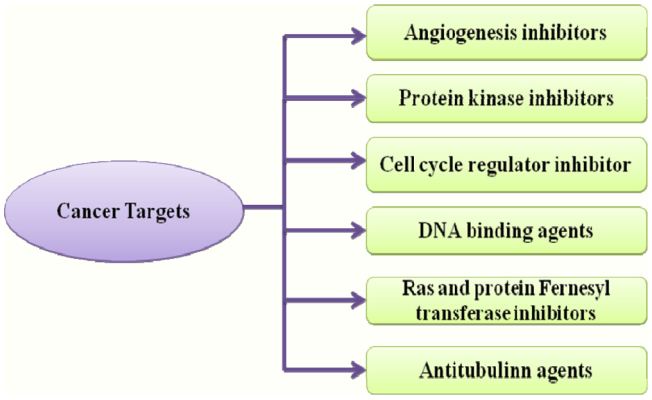


Fig. 4. Various cancer targets modulated by quinoxaline based anticancer agents.

Table 2
Antiangiogenic activity of arylquinoxalines in various related cells.

Compound	BE cells IC_{50} (μM)	U87 IC_{50} (μM)	HUVEGs IC_{50} (μM)
15	>50	>50	24.65 ± 6.63
16	>50	>50	>100
17	41 ± 5.4	15.9 ± 0.5	>100
18	>50	42.3 ± 3.2	54.4 ± 9.6

apoptosis, generation of reactive oxygen species, mitochondrial depolarization, and activation of caspase-3 and caspase-9 in the cells. Interestingly, it induced increase in the mitotic index, inhibited microtubule assembly and acted as topoisomerase I inhibitor.[139] Further, 3-amino-1*H*-pyrazolo[3,4-b] quinoxaline (**44**) showed excellent activity as Cdk and GSK inhibitor {Cdk1/cyclinB (IC_{50} = 600 nM), Cdk5/p25 (IC_{50} = 400 nM} and GSK-3B (IC_{50} = 1 μM)}.[140] Hydrochloride salt of quinoxaline macromolecule (**45**) also acted as Cdk 1,2,4,6 and E2F inhibitor having considerable IC_{50} values as 1.0, 3.4, 6.4, and 3.6 nM respectively.[141] Synthetic chalcones like **46**, **47** led to G1 phase arrest, AKT inhibition and ERK 1/2 activation.[142] Similarly, some bisquinoxaline moieties **48**, **49** exhibited good activity in *in vitro* studies for MCF-7 cell line.[143] XK469 (**50**) and chloroquinoxaline sulfonamide (CQS) (**51**) have been established as antineoplastic quinoxaline topoisomerase II inhibitors.[144] Likewise, there are novel piperazinylquinoxaline derivatives (**52–55**) targeting phosphoinositide 3-Kinase (PI3K) (IC_{50} ~ 40 nM).[145] Several important quinoxaline based cell cycle inhibitors have been represented in Fig. 7.

3.2.4. DNA binding agents

The interaction of small molecules with DNA is very important in designing new DNA targeting drugs. Some of the quinoxaline derivatives exhibited potential such an activity (Fig. 8). For instance, quinoxaline carbohydrate hybrid **56** displayed DNA photo-cleaving ability leading to DNA damage.[146] Aggarwal and co-workers (2011) reported applicability of triazoloquinoxaline **57** for probing DNA structure and for photodynamic chemotherapy.[147] Benzimidazoles also possessing a quinoxalin-2,3-dione core (**58**, **59**),[148] Ni(II) complex **60**[149] and thiophene-2-carbonyl derivative **61**[150] exhibited strong binding affinity and showed hypoxia-selective, enzyme-activated DNA-cleaving properties.

Moreover, quinoxaline 1,4-dioxide (**62**) exhibited hypoxia-selective DNA cleaving properties to provide a chemical basis for interpreting the cytotoxic and mutagenic activities of various antibiotics of this class. The DNA cleavage by **62** required enzymatic one-electron reduction in order to obtain an activated, oxygen-sensitive intermediate which upon homolytic cleavage of the hydroxyl free radical afforded mono oxide derivative **63**.[151]

Recently, some 9-Fluoro-6*H*-indolo [2,3b]-quinoxaline derivatives (**64a-c**) (Fig. 9) have been reported to possess DNA binding property and thus induce cytotoxicity. Di-cation quaternary ammonium salts of 6*H*-indolo [2,3b]-quinoxaline derivatives showed remarkably high affinity with DNA and potential cytotoxicity against breast cancer and lung cancer cell lines.[152]

Further, [1,2,4]triazolo[4,3-*a*]quinoxaline and bis ([1,2,4]triazolo)

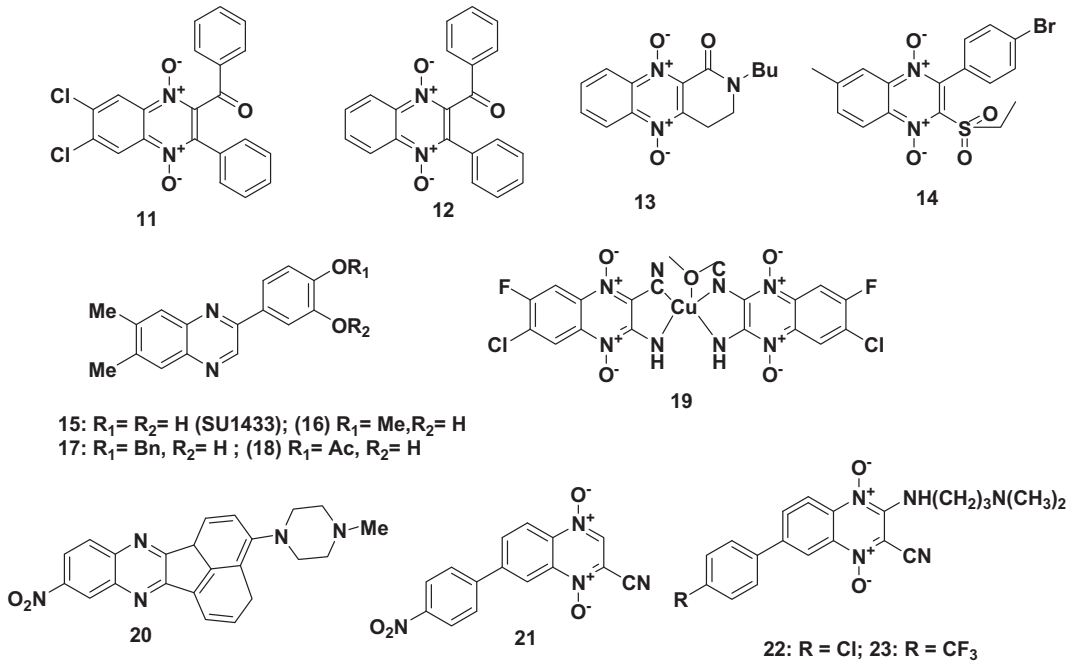


Fig. 5. Some quinoxaline motifs as antiangiogenic agents.

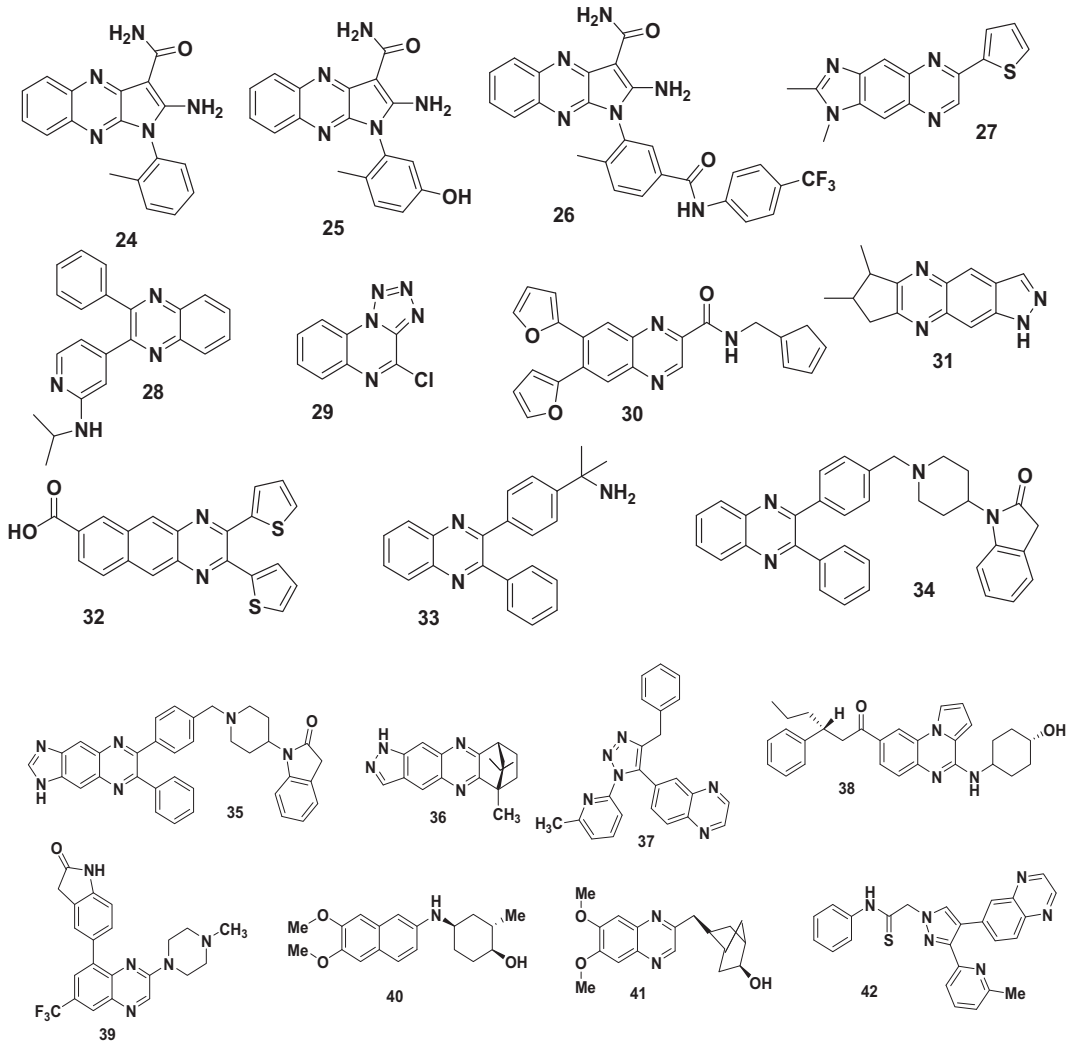


Fig. 6. Quinoxaline motifs as protein kinase inhibitors.

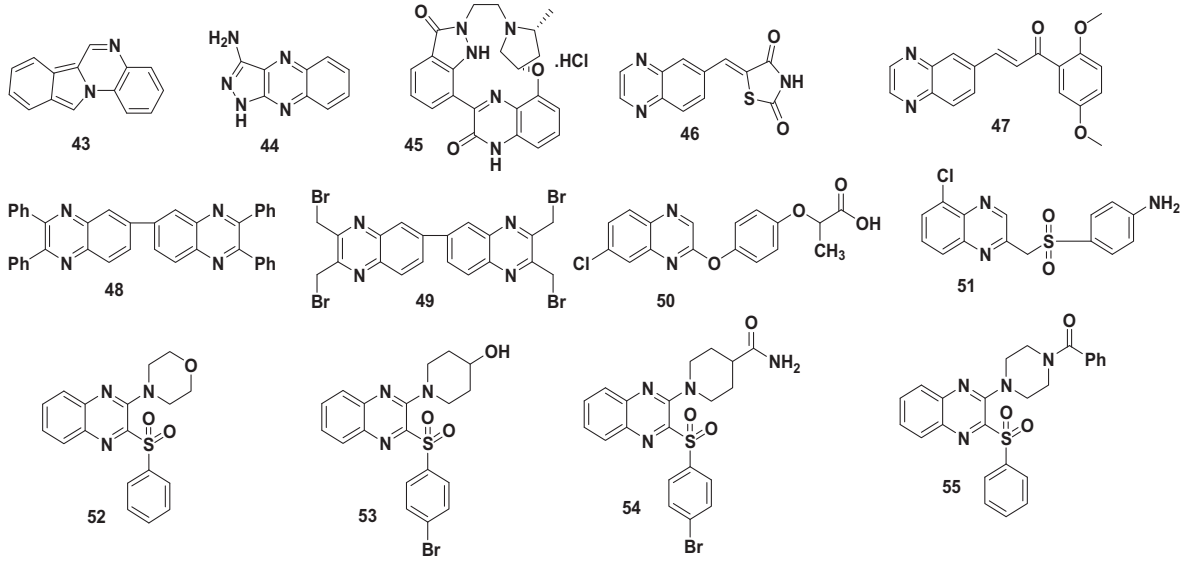


Fig. 7. Some quinoxaline motifs as cell cycle inhibitors.

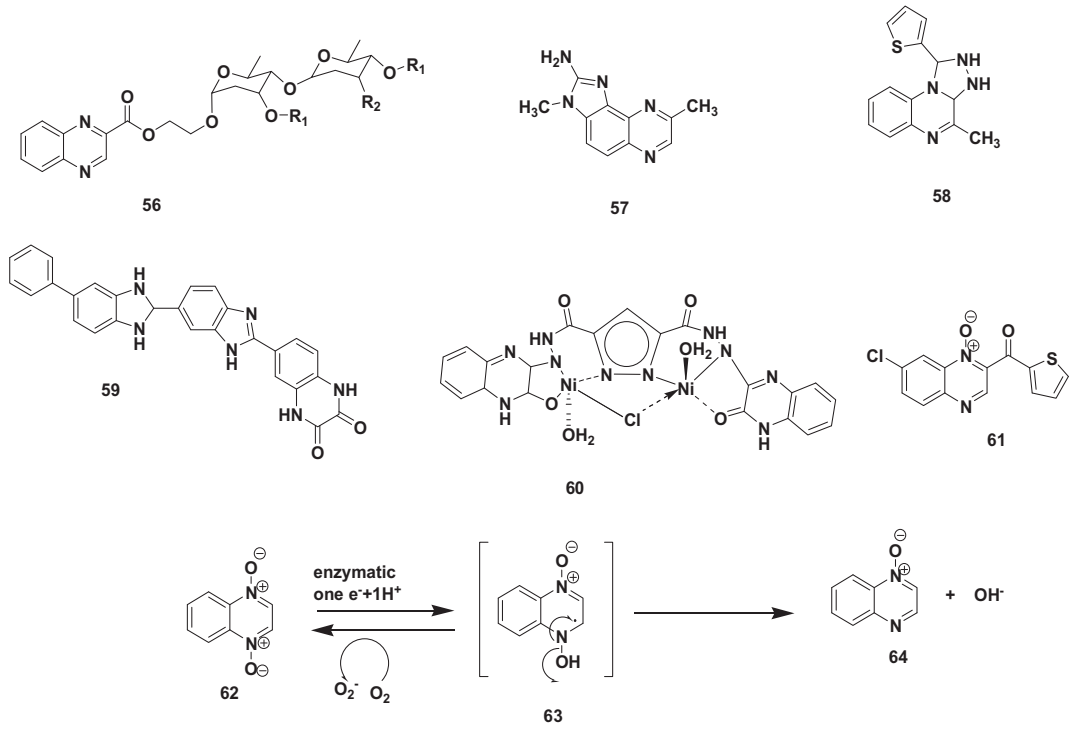


Fig. 8. Quinoxaline based DNA targeting agents.

[4,3-*a*:3′,4′-*c*] quinoxaline derivatives exhibited significant anti-proliferative activity against Caco-2 (Colorectal adenocarcinoma) cells. Compounds **65**, **66**, **67**, and **68** possessed potential cytotoxicity IC_{50} 0.46 μM, 0.57 μM, 0.39 μM and 0.80 μM respectively (Table 3). All the four compounds inhibited DNA topoisomerase-II (IC_{50} = 0.68–1.06 μM) and induced DNA intercalation significantly.[153]

3.2.5. Ras and protein Fernesyl transferase inhibitors

Farnesyl transferase inhibitors are relatively a new class of anticancer drugs. However, their mechanism of action is obscure. These drugs inhibit farnesylation of target proteins including Ras. It is believed that these agents do Ras inactivation through inhibition of farnesyl transferase enzyme and induce cell growth arrest. Farnesyl transferase inhibitors exhibited great potency against tumour cells in preclinical studies, but their efficacy in clinical studies, was surprisingly weak.[154] This unexpected and frustrating clinical outcome must be explored in the drug-development process.

Ras proteins are guanine nucleotide-binding proteins playing crucial roles in the control of normal and transformed cell growth. Ras proteins are among the most purposefully studied proteins of the last decade. Ras stimulates various growth factors and cytokines to meticulously activate several downstream effectors like Raf-1/mitogen-activated protein kinase pathway and the Rac/Rho pathway. Mutated proteins were produced by Ras genes in some of the human cancers like pancreatic and colon adenocarcinomas. Ras genes produce mutated proteins that remain locked in an active state, so that impart uncontrolled proliferative signals. Subsequent, post translational modifications in Ras allows its attachment to plasma membrane inner surface. Among

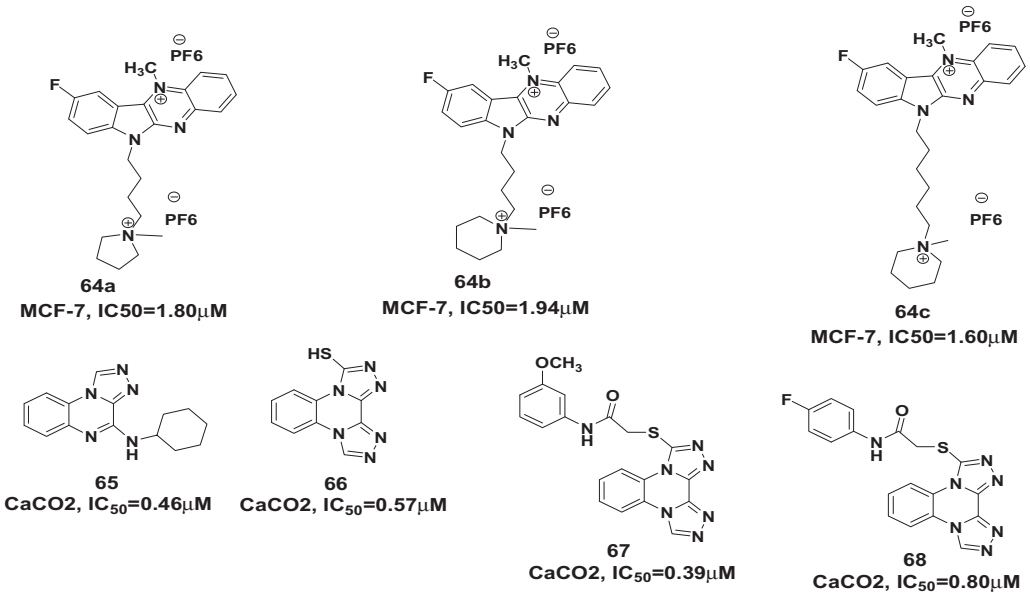


Fig. 9. Triazolo quinoxalines specifically targeting DNA topoisomerase-II enzyme.

Table 3
Cytotoxicity and DNA targeting activity of triazolo quinoxalines.

Activity	65	66	67	68
Cytotoxicity CaCO2 IC_{50} (μM)	0.46	0.57	0.39	0.80
DNA Topo-II (μM)	0.68	1.06	0.85	0.94
DNA intercalation IC_{50} (μM)	39.37	29.85	38.62	43.40

these post translational modifications, addition of farnesyl isoprenoid moiety is most critical step which is catalysed by farnesyltransferase (FTase) enzyme which cause Ras in its biologically inactive form. Hence, FTase is an important therapeutic target for cancer drug development.[155] Several 1,2,3,4- tetrahydroquinoxaline derivatives (**69–74**) acted as alpha-2C adrenoreceptor agonists along with potential antitumor activity (Fig. 10).[156] Similarly, tetrahydro (1-imidazolo) quinoxaline, hydrochloride and its carbomethoxy derivatives (**75** and **76**) potentially inhibited farnesyl transferase.[157]

3.2.6. Antitubulin agents

Microtubules are tubulin polymers which play important role in cell division in mitosis phase. Microtubules are in dynamic equilibrium with tubulin dimers. Disruption in microtubule dynamics leads to cell cycle arrest and induces apoptosis in cancer cells. Microtubules have been one of the most successful targets in cancer chemotherapy.

Qi *et al.* (2017) prepared several *N*-substituted 3-oxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid ester derivatives (Series A and B, **77**, Fig. 11). Some of the derivatives exhibited potential anticancer

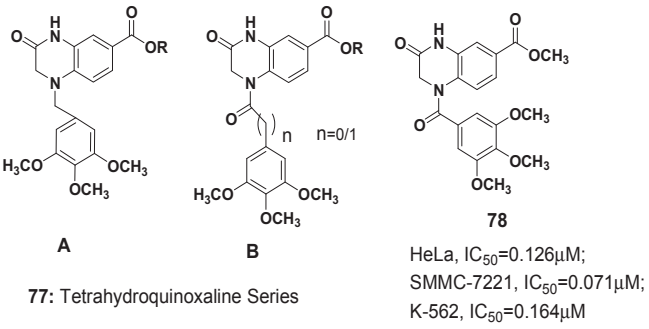


Fig. 11. Anticancer quinoxaline motifs targeting tubulin dynamics.

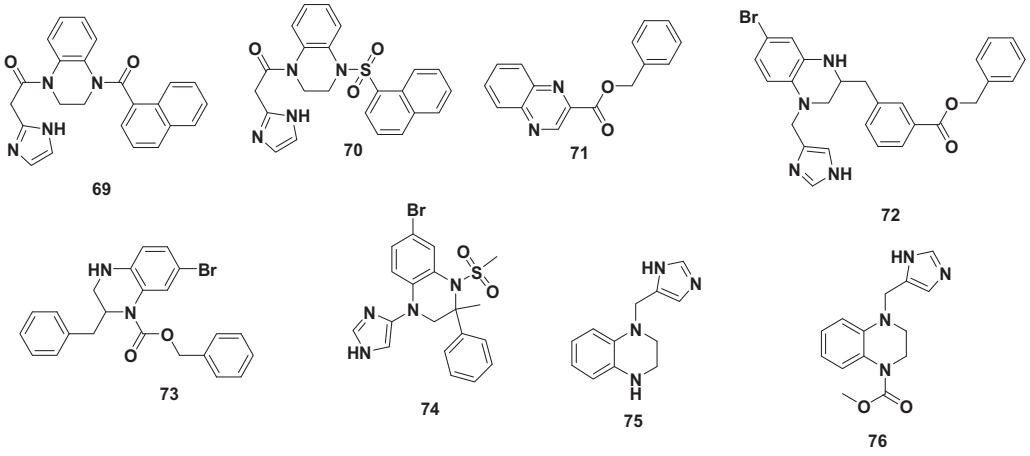


Fig. 10. Quinoxaline motif based Ras and protein farnesyl transferase inhibitors.

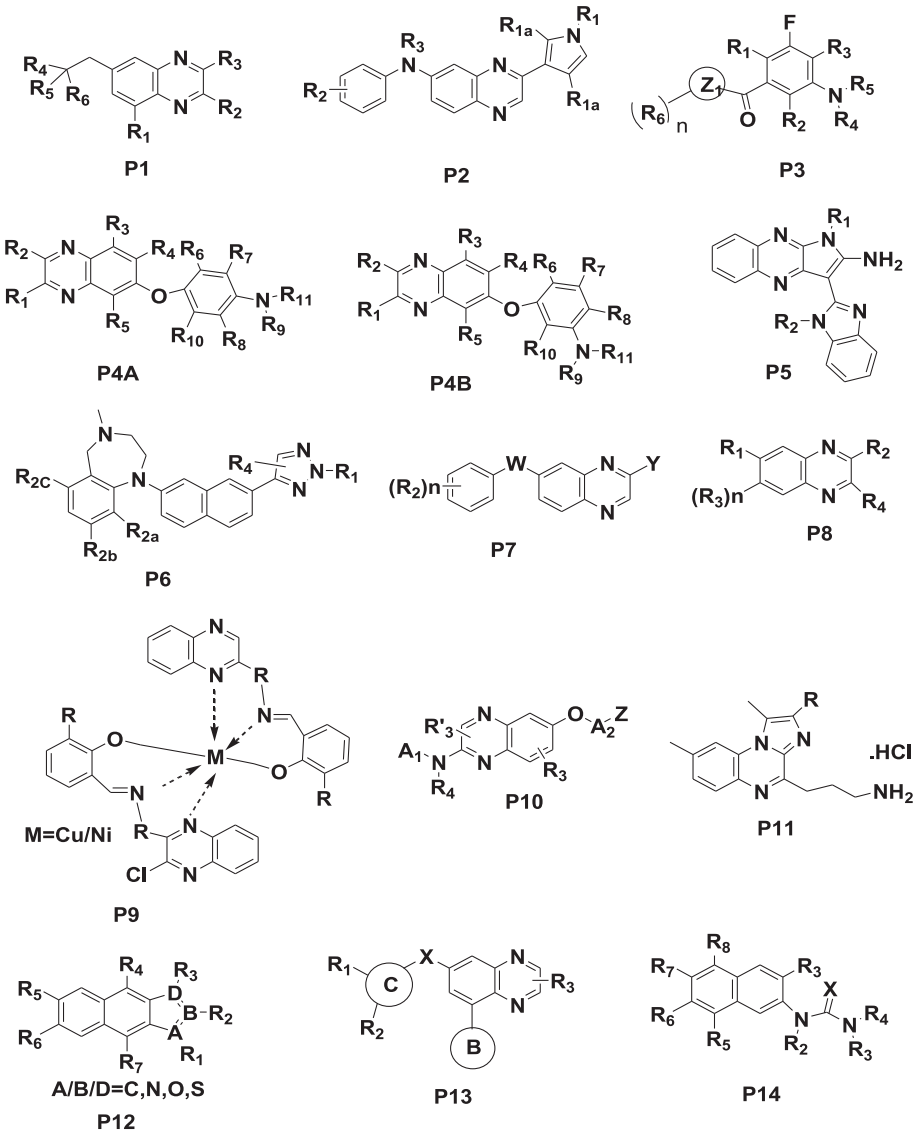


Fig. 12. Basic core of quinoxaline based patents.

activity against HeLa (Cervical cancer) cells, SMMC-7721 (Hepatocarcinoma), and K562 (Leukaemia) cell lines. Compound **78** possessed potent antiproliferative activity at IC_{50} ranged 71 nM to 164 nM. It was potential microtubule destabilizer (IC_{50} = 3.97 μM).[158]

In this study, two different series of compounds were prepared i.e. Series A, as *N*-benzyl derivatives and Series B as *N*-benzoyl derivatives. In Series A, compounds with 3,4,5-trimethoxybenzyl substitution on the 4-nitrogen atom exhibited better activity as compared to other substitutions. Carboxylic ester derivatives were more potent than their corresponding carboxylic acid derivatives. In series B, antiproliferative efficacy order in benzene substitution at 4-nitrogen atom was in the order; 3,4,5-trimethoxy > 3,4-dimethoxy > 4-methoxy = 4-Fluoro. Increasing carbon length in series B reduced the activity significantly. Converting carboxylic ester to amide derivatives lowered the activity. Comparing both the series A and B, series B compounds exhibited much better antiproliferative activity as compared to series A compounds.

3.3. Patent status of anticancer quinoxalines

Various patents have been filed and granted on quinoxaline nucleus by US patent office and WIPO (PCT). Most of the patents described new quinoxaline derivatives, their preparation and application in the treatment of cancer. Some of the important patents have been included in Fig. 12 represents the prototypes of these patents. Further details are given in Supplementary information.

3.4. Quinoxalines under clinical trials for the treatment of cancer

There are many quinoxaline motifs currently under clinical trials at different stages for cancers of different origins. Some of them are depicted in Table 4, Fig. 13.[159–170]

3.5. Structure activity relationship of Quinoxaline as anticancer pharmacophore

In Structure and activity relationship (SAR) studies, it was revealed that, in general the presence of 1,4-*N*-oxide is responsible for many biological activities like antibacterial (**93**), antitubercular and anticancer activities.[117-120] Studies for anticancer activity showed that presence of 1–4 *N*-oxide is responsible for the antiangiogenic effect thereby showing antitumor activity (Fig. 14 and Fig. 15). As shown by various quinoxalines, **87**[168] and **88**[169] under clinical trials and several others **11–14**,[112,113] **19**,[116] **21–23**,[118] **61**,[150] and **62**[151]. Further, presence of diketone at 5 and 8 positions also serves for antiproliferative effect as

shown by **1** and WDP1263 (**94**) as this was confirmed by comparison of quinonoid analogues with non quinonoid counterparts **95a-b**.[174] Similarly, comparative studies revealed that 1,2,3,4-tetrahydroquinoxaline derivatives show potent Ras and protein farnesyl transferase inhibitor thereby perform as attractive antitumour agents (**69**, **70**[156], **75-76**[157]).

3.6. Pharmacokinetic properties

3.6.1. Quinoxaline drug administration

Various routes of administration of quinoxaline drugs *viz.* carbadox (**1 0 0**),[175] desoxycarbadox **101**,[177] olaquindox (**1 0 2**), quincetone (**1 0 3**), 1-desoxyquincetone (**1 0 4**)[177] and mequindox (**1 0 5**)[178] have been reported for essential growth and development of livestock (Fig. 16).[175-178] The administered dose is many a times adjusted individually using either a prior or a posterior methods.[179] For example, due to poor solubility, a parent drug XB947 was intra-peritoneally administered in murine models, while its antitumor drug analogue XK469, **85** was water-soluble and much more efficacious. Many a time individual dose adjustments helps in managing toxicity during anticancer drug administration.[180]

3.6.2. Quinoxaline drug absorption

Quinoxaline drugs have been administered *via* oral, intramuscular and intravenous routes.[181] Drug pharmacokinetics varies with routes of administration, type of formulation, animal species, their age and physiological condition.[181] The relative rate of absorption of drug in the animal tissues depends on several factors related to intra-and inter-individual variables[183] which also influences efficacy and toxicity of drugs.[183] In a study mequindox (**1 0 5**)[184] on intramuscular administration was absorbed rapidly (t1/2a, 0.28 h) and almost completely in experimental goats.[185]

3.6.3. Quinoxaline drug distribution

Quinoxaline benzamide **106** (IN-1130), a novel ALK5 inhibitor and antimetastatic drug against breast cancer,[186] was readily distributed into lungs, liver, and kidneys when orally administered (Fig. 17).[186] It was metabolised in rat and mouse as 3-((4-(2-hydroxyquinoxalin-6-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2yl) methyl) benzamide **107** or 3-((4-(3-hydroxyquinoxalin-6-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2yl)methyl)benzamide **108**.[186]

3.6.4. Quinoxaline drug metabolism

The metabolism of quinoxaline drug derivatives has been an important aspect in human, rodents and non-primate animals.[187] The metabolism of quinoxaline (MeIQx) in human revealed that quinoxaline-8-carboxylic acid was a major detoxification pathway catalyzed by cytochrome P450 1A2 (Fig. 18).[188] The biotransformation of urinary metabolites of **109** following the oral administration in mouse, rabbit, and human. It is also metabolised by xanthine oxidase through oxidative metabolism to **110**.[190] Moreover, carbadox (**1 0 0**) and olaquindox (**1 0 2**) were metabolized to quinoxaline-2-carboxylic acid and methyl-3-quinoxaline-2-carboxylic acid.[191] Quincetone (**1 0 3**) was metabolised to 1-desoxyquinocetone (**1 0 3**), dideoxyquinocetone (**1 1 1**), and a reduced derivative as dideoxyquinocetone (**1 1 2**) in pigs.[192]

3.6.5. Quinoxaline drug elimination

In a study, XK469 (**85**) on intravenous administration had mean elimination half-life of 13.5 h in rats and 13.2 h in dogs.[182] In another study, XK469 (**1 0 6**) was eliminated only by 7% in the kidneys.[172] Olaquindox (**1 0 2**) was eliminated mainly in the urine with quite low amounts in the faeces of rats, pigs and dogs.[173] While, carbadox (**1 0 0**) was rapidly eliminated up to 90% in swine at 50 ppm dose level. About two-third (2/3) of the dose was eliminated in the urine and the rest in the faeces.[181]

3.7. Toxicity studies

Case. *study* 1: *Zhang et al.* (2012) [182] *studies toxicity effects of two quinoxaline*-1,4-*dioxide derivatives i.e. quincetone* (**1 0 3**) *and olaquindox* (**1 0 2**) *for cytotoxicity and genotoxicity against human healthy liver cells, Chang and L*-02. *Both the drugs were non-selective and showed cytotoxicity against cancer as well as healthy cells. However, quincetone was much more cytotoxic to both the normal liver cells than the olaquindox. Both the drugs at* 10–20 *μg/mL for* 4 *h exposure induced DNA damage in the tail length, tail DNA%, and oliver tail moment in both liver cells. Both the drugs exhibited mutagenic effects clearly*.[181]

Quinoxaline-1,4-dioxide derivatives have exhibited diverse toxicities.[182,183] Several severe side effects have also been observed like photo-allergy, mutagenicity, carcinogenicity and drug resistance by this types of quinoxaline derivatives.[184,185] It is now well established that quinoxaline-1,4-dioxide derivatives induce mutagenicity mainly due to their *N*-oxide groups.[186]

Case. *study* 2: *Huang et al.* (2010)[187] *undertook long term toxicity studies on mequindox* (**1 0 5**) *at four different doses i.e.* 25 *mg/kg,* 55 *mg/kg,* 110 *mg/kg and* 275 *mg/kg in Wistar rats for* 180 *days. Mequindox caused kidney cell damage at higher concentrations i. e.* 110 *mg/kg and* 275 *mg/kg by inducing cell loss, cell swelling, nuclei shrinkage, haemorrhages, cell atrophy, vacuolation, and necrosis. These effects were much more pronounced at* 275 *mg/kg dose. There were long term effects on intra- or extra adrenal-renin-angiotension-aldosterone system* (*RAAS*)

Overall, high doses of mequindox lead to oxidative damage and dysfunction of kidney and adrenal gland.

Case. *study* 3: *Another study was done by Ihsan et al.* (2010)[188] *on acute and subchronic toxicity of mequindox in Wistar rats. Three different doses of*

Table 4
Quinoxaline based investigational anticancer drugs under various phases of clinical trials.

S.No.	Drug	Target	Clinical Trial and Phase	and toxicity	Refs.
1.	ABT-737	BCL-2, BCL-X_L, and BCL-w	phase I/phase II NCT01440504; Ovarian cancer	No systemic toxicity	170
2.	BMS 354451	Inhibition of Ikappa β kinase (IKK) and IKK-related kinases	Failed in phase III (Merck), metastatic melanoma skin cancer Presently against (Bristol-Myers Squibb)–phase-I/II, INCT02419417– advanced tumour	–	171
3.	XK-469	DNA Topoisomerase-IIβ	phase I, Leukemia, murine cancer	Myelosuppression and Neutropaenia,	172
4.	Tirapazamine (SR-4233)	Angiogenesis, DNA damage	phase I/phase II, Solid tumours, hepatocellular carcinoma, head and neck cancer	Weight loss, muscle cramps, dermal adverse effects	173
5.	XL-765 (Voxtalisib)	PIK3CG, PIK3CA, PIK3CD, PIK3CB, PRKDC	phase I, Solid tumours, Glioblastoma etc.	Nausea, vimiting, decreased appetite etc.	167
6.	XL-147(Pilaralisib)	P13K inhibitor	phase I/phase II, Solid tumours, breast cancer, endometrial cancer, non-small lung cancer, ovarian cancer	Among Grade-3 toxicities: anemia, thrombocytopenia	168
7.	AG1295 (Tyrphostin)	Tyrosine kinase	preclinical/phase I Acute myeloid leukemia	–	169

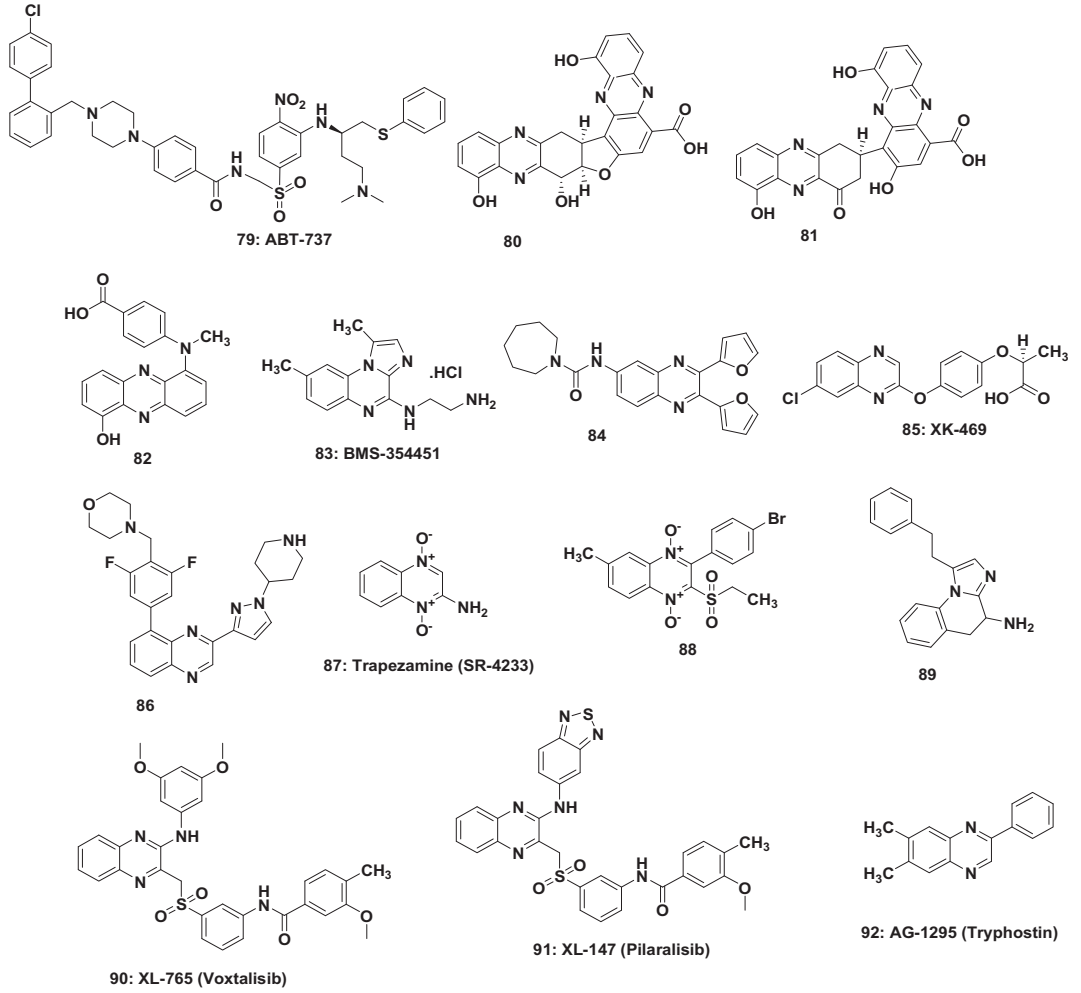


Fig. 13. Quinoxaline based various anticancer investigational drugs under clinical trials.

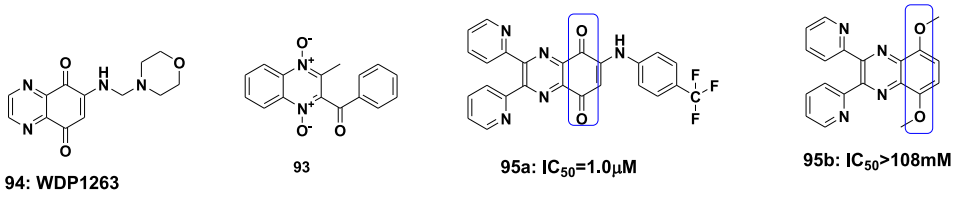


Fig. 14. Some of the potent anticancer pharmacophores on quinoxaline core.

mequindox were given at 175 *mg/kg,* 550 *mg/kg and* 2000 *mg/kg bodyweight as single dose each by oral gavage after suspending in* 0.5% *CMC solution. The* LD_{50} *was found to be at* 550 *mg/kg dose. All the animals were dead at* 2000 *mg/kg dose within* 24 *h while one rat was died in* 550 *mg/kg group. Loss in body weight was also observed. There were some signs of liver injury also. Overall, it showed moderate toxicity at higher doses.*

In subchronic experiment, three doses of mequindox were given to rats at 55 mg/kg, 110 mg/kg and 275 mg/kg orally for 90 days. There were multiple signs of toxicity by the drug. Weight reduction, reduced kidney weight, increased liver and adrenal weights and increased liver parameters alanineaminotransferase (ALT), malondialdehyde, and superoxidedismutase and aspartateaminotransferase in serum at 275 mg/kg dose group. Two rats were died in 275 mg/kg group. There were no significant changes in haematological parameters and biochemical parameters.

Overall, among the quinoxaline class of compounds, quinoxaline-1,4-dioxides have been reported to possess liver and adrenalin toxicities.[188] Toxicity is a major concern and should be addressed carefully.

4. Future prospects

Heterocycles are an important class of compounds possessing diverse pharmacological activities. Quinoxalines have been an important nucleus in designing various types of pharmacophores. Several drugs are already in clinics. But, toxicity has been a major issue associated with some of the quinoxaline based drugs. However, many quinoxaline based investigational drugs are under various phases of clinical trials. Many of them are being developed against advanced targets of cancer. The potential lead compounds should further be evaluated pre-clinically, against specific animal models. Hopefully, a few of them will emerge as clinical drugs in future. Further, many efficient synthetic methods have been developed to prepare diverse quinoxaline based pharmacophores. Chemists should now mainly focus on green chemistry approaches considering environmental concerns. Broad-spectrum

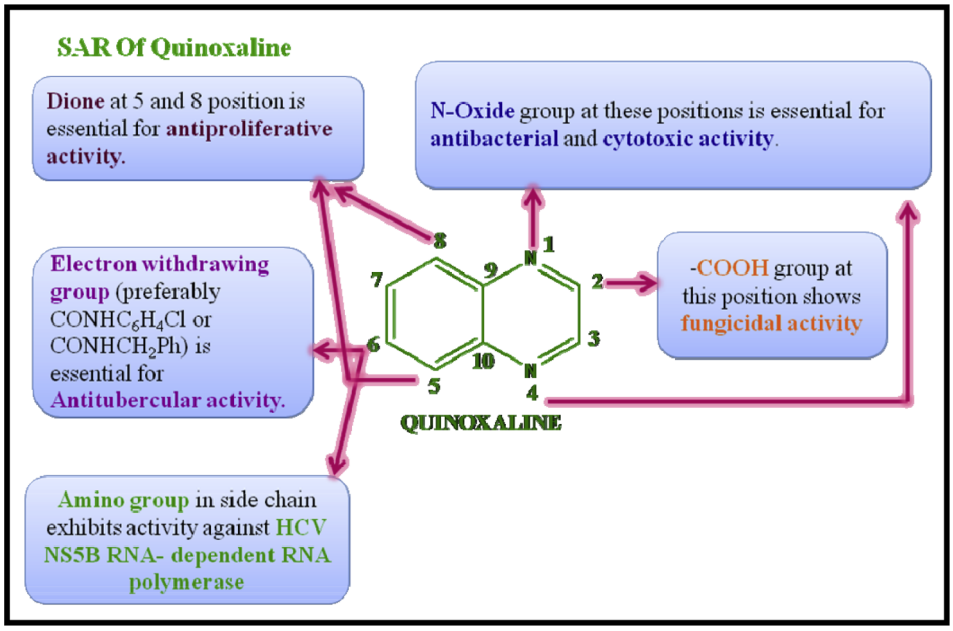


Fig. 15. Structure activity relationship of quinoxaline compounds for various biological activities.

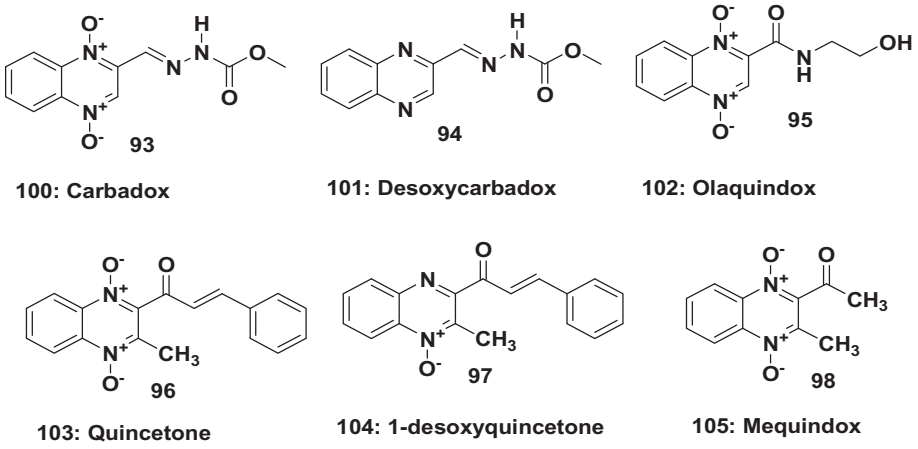


Fig. 16. Chemical structure of some of the quinoxaline based drugs for drug administration studies.

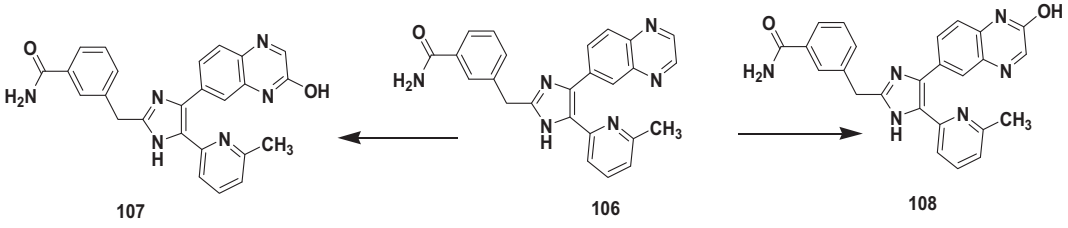


Fig. 17. Metabolites of quinoxaline benzamide in rat and mice.

pharmacological effect of quinoxalines is beyond doubt which makes it a pharmacophore of choice to the Medicinal Chemists. Nevertheless, quinoxaline pharmacophore has much scope still to be explored to establish modulation in biological response on changing the chemistry.

5. Concluding remarks

Therapeutic usefulness of quinoxalines makes them important scaffolds to design library of compounds by the Medicinal Chemists. Numerous compounds have been prepared based on diverse pharmacophores and many of them have exhibited potential pharmacological activities. Notably, quinoxalines have modulated diverse and specific anticancer targets, thus offering excellent framework for anticancer drug discovery. However, detailed SAR studies are still required to design quinoxaline based drug candidates meticulously. Synthetic Chemists have developed distinct magnificent protocols to prepare quinoxaline core. Fortunately, these methodologies also facilitate in the preparation of varied pharmacophores. Toxicity has been a major

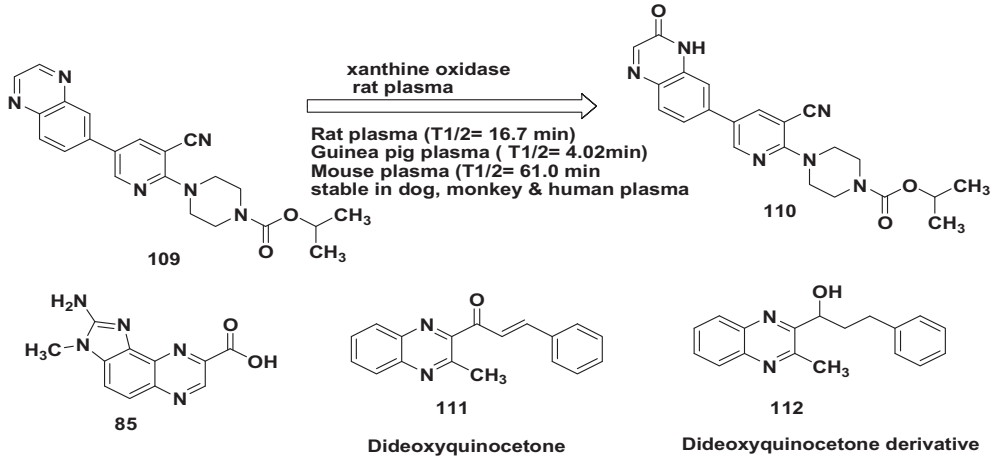


Fig. 18. Quinoxaline scaffolds used in drug metabolism evolution studies.

concern in case of quinoxaline based drugs which indicates soft drug design approach to undertake in future research. A justifiable proportion should be there between lipophilic-hydrophilic nature in the chemical structure to have a good pharmacokinetics profile of this class of drugs.

The present review provided a detailed status of quinoxaline based clinical drugs, drug candidates and potential lead compounds with varied anticancer targets and highlighting future scope for improvement in the development of quinoxaline based anticancer drugs.

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Declaration

Authors declare no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2018.11.021.

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