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Recent Advances In The Chemistry And Biological Activities Of Quinoxaline Derivatives: A Comprehensive Review

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Abstract

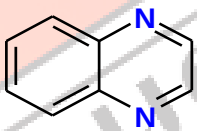
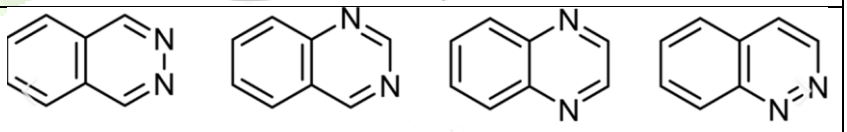
Quinoxaline and its fused heterocyclic derivatives constitute an important class of nitrogen-containing heterocyclic compounds possessing remarkable chemical versatility and extensive biological activities. Owing to their electron-deficient aromatic framework and facile functionalization, quinoxaline derivatives have attracted considerable attention in medicinal chemistry, pharmaceutical sciences, and synthetic organic chemistry. The present review summarizes the chemistry, synthetic methodologies, structural modifications, and pharmacological significance of quinoxaline derivatives reported over the years. Various synthetic approaches including condensation of o-phenylenediamines with 1,2-dicarbonyl compounds, intramolecular cyclization reactions, ring contraction methods, and synthesis of quinoxaline-N-oxides have been discussed systematically. Particular emphasis has been placed on the diverse biological applications of quinoxaline analogues such as antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, antituberculosis, anti-HIV, antidepressant, and antiglaucoma activities. Structure–activity relationship studies reveal that substitution patterns and fused heterocyclic systems significantly influence biological potency. In addition, recent developments in fused quinoxaline systems and their pharmaceutical relevance are highlighted. This review demonstrates that quinoxaline derivatives remain promising scaffolds for the development of novel therapeutic agents and functional organic materials.

Keywords: Quinoxaline, Heterocyclic compounds, Anticancer activity, Antibacterial activity, Quinoxaline-N-oxides, Medicinal chemistry, Fused quinoxalines

1. Introduction

Nitrogen-containing heterocyclic compounds represent one of the most important classes of organic molecules due to their widespread occurrence in biologically active natural products (**Table: 1)**, pharmaceuticals, agrochemicals, and advanced functional materials. Among these heterocyclic systems, quinoxaline derivatives occupy a special position because of their unique structural features and remarkable pharmacological properties. Quinoxaline is a bicyclic aromatic heterocycle obtained by fusion of a benzene ring with a pyrazine nucleus. The presence of two nitrogen atoms in the aromatic framework imparts electron-deficient characteristics to the ring system, making quinoxaline derivatives highly reactive toward various electrophilic and nucleophilic substitution reactions. Furthermore, the quinoxaline scaffold serves as an important pharmacophore in medicinal chemistry and drug design [1-57].

Table: 1 Introduction to Quinoxaline Derivatives

Definition of Quinoxaline	Quinoxaline is a bicyclic heterocyclic compound formed by fusion of a benzene ring with a pyrazine ring. It contains two nitrogen atoms in the heteroaromatic system and exhibits remarkable chemical and biological properties.
Importance of Heterocyclic Compounds	Nitrogen-containing heterocyclic compounds are among the most important classes of organic molecules due to their extensive pharmaceutical, industrial, and biological applications. Quinoxaline derivatives occupy a significant position because of their broad spectrum of activities.
General Formula	Quinoxaline nucleus consists of a fused benzopyrazine ring system represented as 
Isomeric form	 Phthalazine Quinazoline Quinoxaline Cinnoline
Nature of Quinoxaline Ring	The quinoxaline ring is aromatic, planar, electron deficient, and capable of undergoing electrophilic and nucleophilic substitution reactions.
Historical Background	Quinoxaline chemistry has attracted considerable attention due to the discovery of biologically active derivatives such as antibacterial, antifungal, antiviral, anticancer, and antituberculosis agents.

The chemistry of quinoxaline has received continuous attention owing to the broad spectrum of biological activities associated with its derivatives. Numerous quinoxaline analogues have been synthesized and investigated for antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, antituberculosis, antidepressant, and anti-HIV activities [82-83]. Several marketed drugs and biologically active compounds contain quinoxaline or fused quinoxaline nuclei as essential structural components.In recent years, considerable efforts have been devoted toward the synthesis of novel substituted and fused quinoxaline derivatives using environmentally benign and efficient synthetic methodologies. Modern research has focused not only on improving synthetic efficiency but also on enhancing biological efficacy through rational structural modifications.

The present review aims to provide a comprehensive overview of: The chemistry and structural features of quinoxalines, Synthetic methodologies for quinoxaline derivatives, Biological and pharmaceutical activities, Structure–activity relationships and Future perspectives in quinoxaline research.

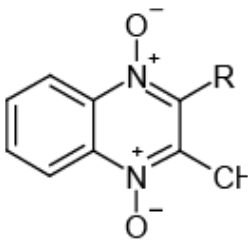
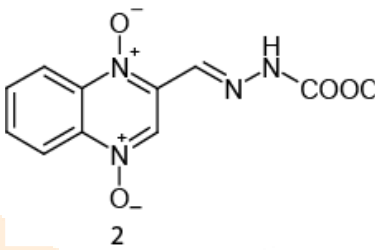
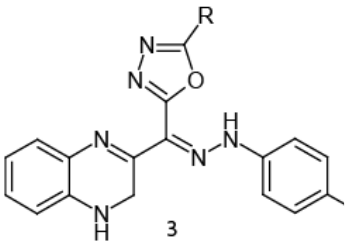
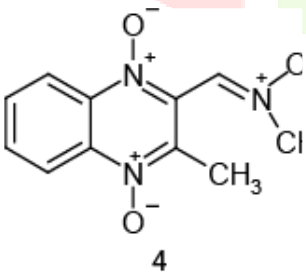
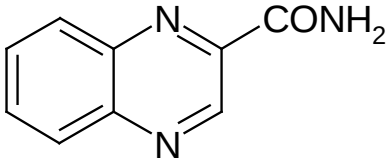
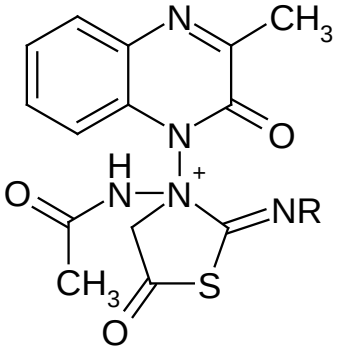
2. Structural Features and Chemistry of Quinoxaline

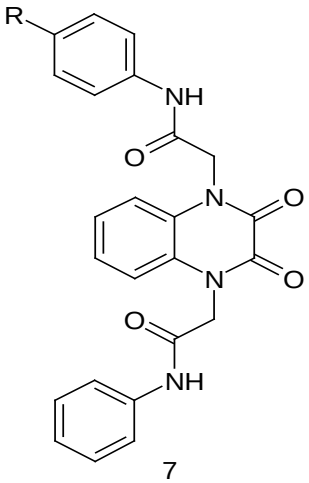
2.1 Structure of Quinoxaline

Quinoxaline consists of a fused bicyclic aromatic ring system containing a benzene ring condensed with a pyrazine ring. The molecular formula of quinoxaline is

The aromaticity and electron-deficient nature of the heterocyclic ring significantly influence its chemical behavior. The nitrogen atoms withdraw electron density from the ring system, facilitating nucleophilic substitution reactions while decreasing susceptibility toward electrophilic attack under normal conditions.

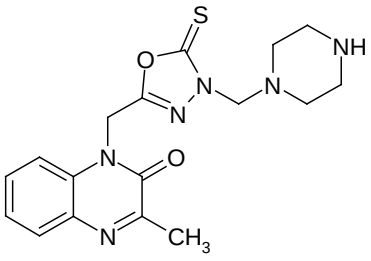
Table: 2 Biological Activities of Quinoxaline Derivatives

Biological Activity	**Important Features**	**Representative Compounds/Examples**
Antibacterial Activity	Several quinoxaline-1,4-di-N-oxide derivatives exhibit potent antibacterial properties against Gram-positive and Gram-negative bacteria.	Carbadox, quinoxaline diones, triazoloquinoxalines
 1 2- hydroxy methyl 3-methyl quinoxaline 1,4-di-N-oxide (1, R= CH_2OH) and a metabolite of 2,3- dimethyl quinoxaline-1,4- di-N-oxide (1, R= CH_3) are highly active against Gram negative bacteria [1].	 2 Carbadox (2), a quinoxaline -1,4-di-N-oxide of commercial importance, is usually used in research as a reference antibacterial agent [2].	 3 quinoxaline derivatives R=H,CH_3 (3) containing an oxadiazole moiety demonstrated marked antibacterial activity [3].
 4 The methyl nitrone of 3-methyl quinoxaline 2-carboxaldehyde- 1,4-di-N-oxide (4) showed exceptional activity against prot.mirabilis and different Salmonella species in experimental infections in mice [4].	 5 Pyrazinamide (5) is a well known synthetic antibacterial agent and still be used for treatment of tuberculosis. This compound contains the pyrazine moiety, common to all quinoxaline derivatives [5].	 6 Some quinoxaline derivatives containing thiazolidinone residue (6) R= C_2H_5,$CH_2CH=CH_2$,C_6H_5 [6].



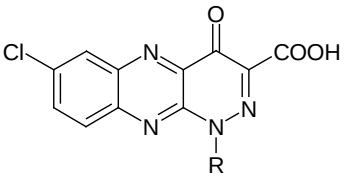
7

In1996, a new series of quinoxaline diones (7) R= CH_3,OCH_3 were prepared and tested for antibacterial activity. [7].



8

Additionally, a group of research workers [8] synthesized a quinoxaline derivative (8) that showed considerable antibacterial activity against the Gram positive bacteria B.subtilis .



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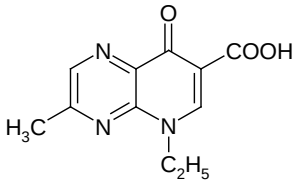
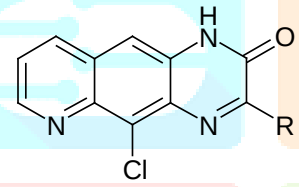


10

Several pyridazino quinoxaline derivatives (9) were prepared as analogues of nalidixic acid (10). [9].



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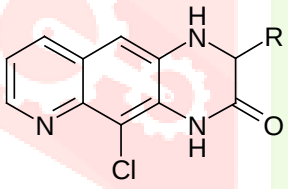
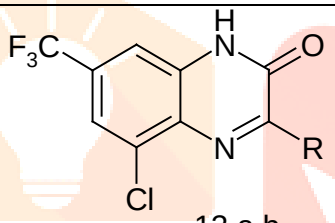
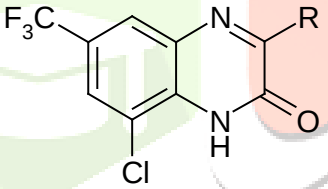


12

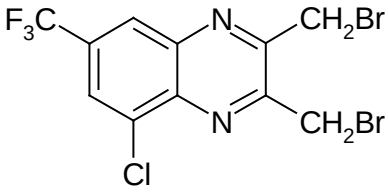
In 2001, new derivatives of quinoxaline (11,12) R= CH_2Br,$CH(CH_3)_2$ were synthesized and submitted to a preliminary in vitro evaluation for antibacterial [10].



13 a,b

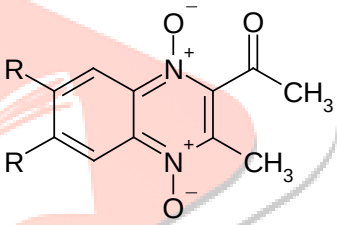


13 c



13 d

In 2003 Antonio Carta et al[11], synthesized a new series of quinoxaline derivatives(13a-d) R= $CH(CH_3)_2$,CF_3 .



14

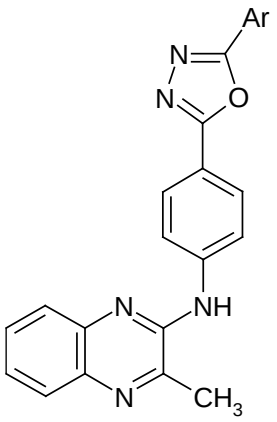
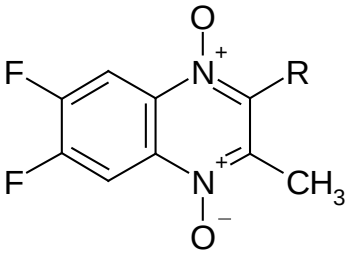
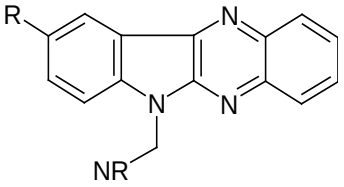
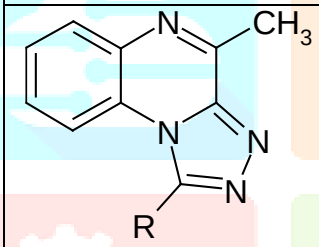
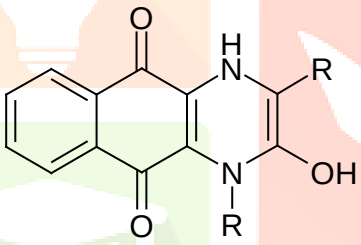
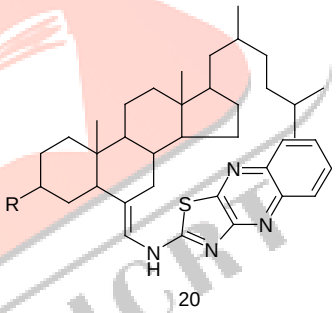
Andres Jaso et al [12] synthesized 2- acetyl -3 methyl quinoxaline- 1,4 – di-N-oxide derivatives (14a-d) 14a H H

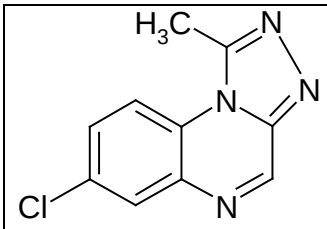
14b Cl H

14c CH_3 H

14d OCH_3 H

and found that they showed antitubercular activity.

 15 In 2004, substituted oxadiazoles attached to the quinoxaline nucleus (15) were prepared and their antibacterial activities were evaluated [13].	 16 Furthermore, a series of quinoxaline derivatives (16a-z) was prepared and evaluated as antibacterial, antifungal, antitrichomonas and antimycoplasma activities [14].	 17 A year later, some indolo quinoxaline derivatives (17a-i) had been described as antibacterial and anti-inflammatory agents [15].
 18 In 2005, a group of research workers [16] synthesized a series of traizolo quinoxaline derivatives (18a-m) showed antimicrobial activity	 19 In 2006 Vishnu et al [17] synthesized a series of 1,2,3-trisubstituted-1,4-dihydrobenzo[g] quinoxaline-5,10-diones (19) which showed in vitro antibacterial activity against Klebs. pneumoniae and E. coli.	 20 In 2007 Salman Ahmad et al [18] synthesized different steroidal thaizolo quinoxaline derivatives (20) as antibacterial agents against E. coli. better than amoxicillin.
Antifungal Activity	Triazoloquinoxaline and pyrazoloquinoxaline derivatives showed significant activity against fungal strains such as *Candida albicans.*	Tetrazoloquinoxalines, triazoloquinoxalines



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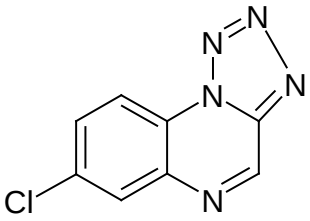
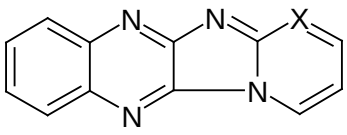


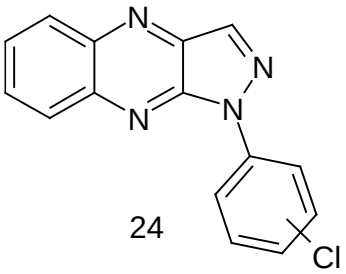
22

In 1985, a group of Japanese research workers developed a synthetic route for the preparation of triazolo and tetrazolo quinoxaline (21, 22), which were found to exhibit significant fungicidal activity [19].



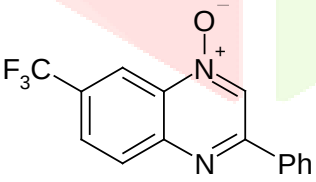
23

Additional, imidazo[4, 5-b] quinoxaline fused to heterocyclic rings (pyridine or pyrimidine) (23), was found to possess remarkable fungicidal activity [20].



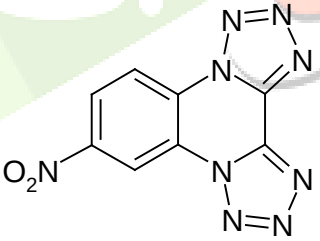
24

Kurasawa and co-workers [3] prepared a series of pyrazoloquinoxalines(24), which was found to possess antifungal activity.



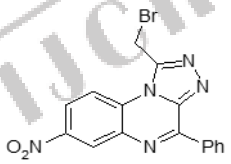
25

In 1990, it is worth to mention that 3-phenyl-7-tri Fluro methyl quinoxaline –N- oxide (25), was reported to possess anti-cand.



26

Bis- tetrazolo quinoxaline (26) was prepared in 1999 and found to have mild antifungal activity against certain fungi [22].



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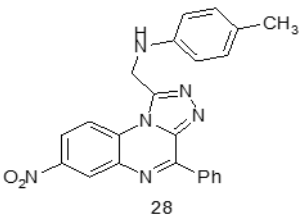
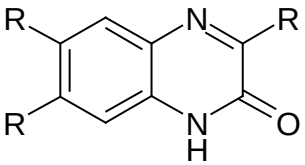
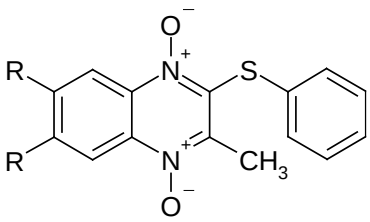
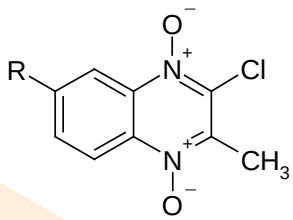
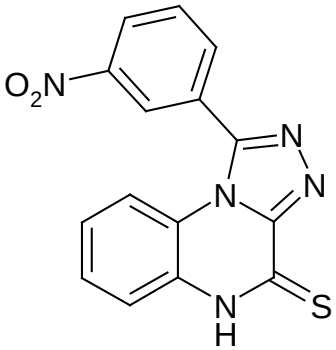
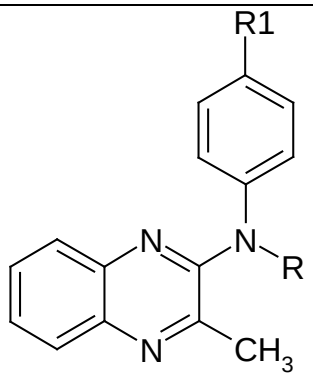
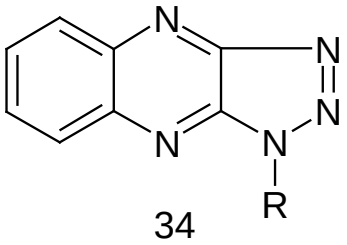
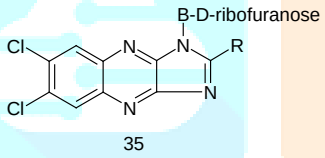
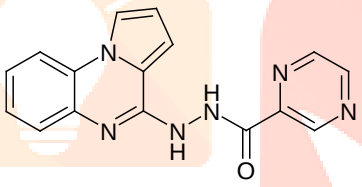
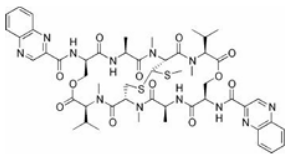
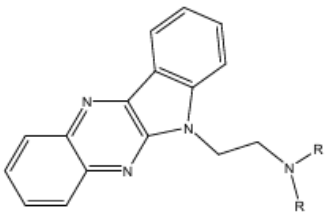
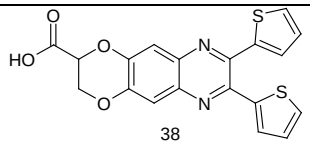
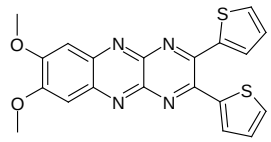
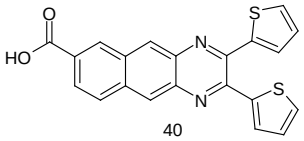
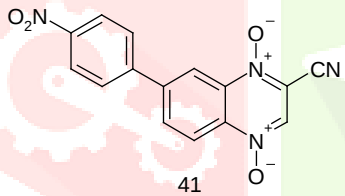
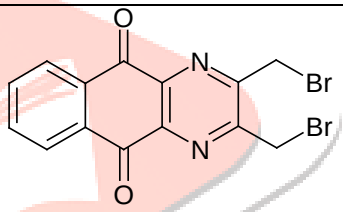
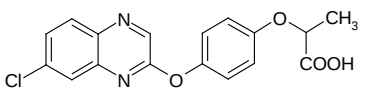


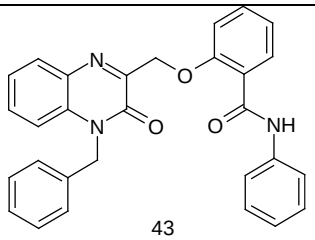
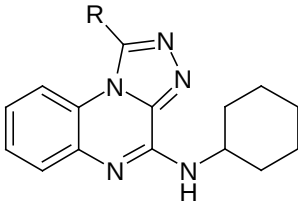
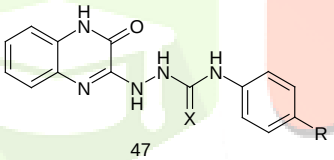
28

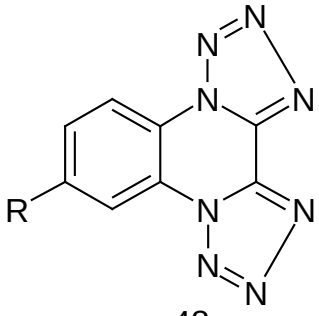
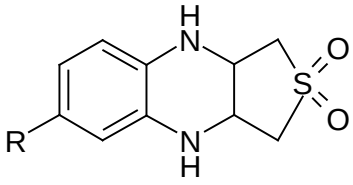
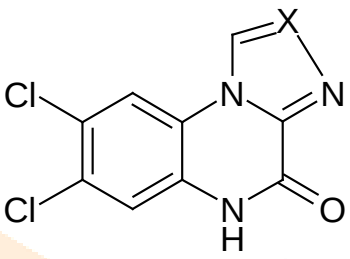
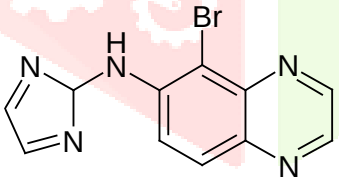
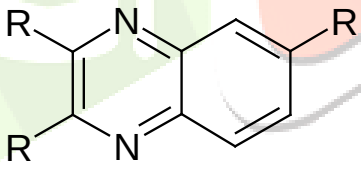
In 1999, certain triazoloquinoxaline derivatives were synthesized and screened for antibacterial and antifungal activities. Two of these compounds (27) and (28) were found to have highly significant antifungal activity exceeding that of

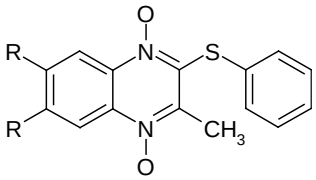
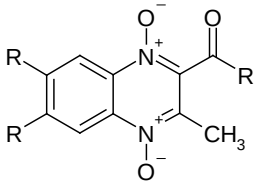
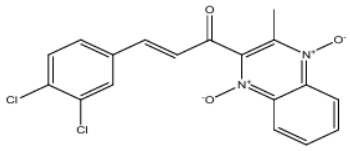
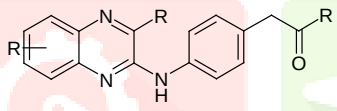
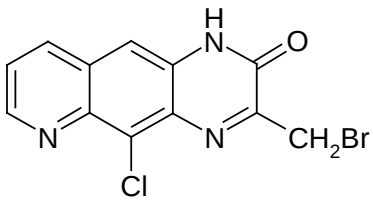
parapsilosis in vitro activity [21].		Nystatin [23].
 29 In the same year, new derivatives of quinoxaline (29a-f) were synthesized, evaluated and showed an inhibition activity against various strains of candida [24].	 30  31 After three years, Antonio Carta et al [25] prepared new compounds which showed antitubercular activity, in addition they have anticandida activity, while compound (30a-e)&(31) were the most active against C. krusei .	 32 Among triazolo quinoxaline thione derivatives which have been prepared by Badran and co-workers [26], 1-(3-nitrophenyl) –(1,2,4) triazolo (4,3-a) quinoxalin – 4 (5H)- thione (32) showed moderate antifungal activity against Cand. albicans.
In 2004 Hanan R. et al [13] synthesized a new series of quinoxalines and published that compound (33a-c) and tested for the antifungal activity which showed moderate activities against Cand.ablicans .	The synthesized new derivatives of traizolo quinoxaline (34a,b) [27] were screened for antifungal activities against Rhiz. solani and Rhiz. pythium and showed moderate to excellent activities under different concentrations.	

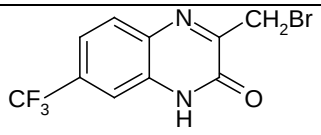
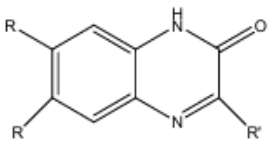
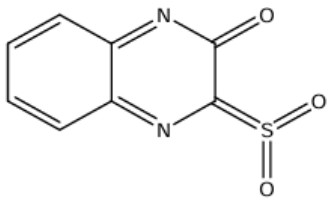
 33	 34	
Antiviral Activity	Some imidazoquinoxaline and pyrroloquinoxaline derivatives inhibit viral replication and reverse transcriptase activity.	HIV reverse transcriptase inhibitors
 35 The synthesized Imidazo [4,5-b] quinoxaline ribonucleosides (35) showed significant antiviral activity against human cytomegalovirus and herpes virus[28].	 36 In 2001, a new pyrroloquinoxaline derivatives (36) in which a heteroaroyl moiety is linked to the heterocyclic system via hydrazine spacer, was prepared as a prototypic antiviral agent of a new class of reverse transcriptase inhibitors [29].	 Y. B. Kim, Y. H. Kim, J. Youn park , S. K. Kim , Synthesis and biological activity of new quinoxaline antibiotics of echinomycinanalogues, Bio.Org &Med. Chem. Lett, 14, 2004, 541.
	 M. O. Shibinskaya, S. A. Lyakhov, A. V. Mazepa, S. A. Andronati, A. V. Turov,	

 38  39  40 In 2005, a series of novel tricyclic quinoxaline analogues (37-40) as SRPK- 1 inhibitors with advantageous physicochemical properties [30].	N. M. Zholobak and N. Y. Spivak, Synthesis, cytotoxicity, antiviral activity and interferon inducing ability of 6- (2-amino ethyl)-6-H-indolo [2,3-b] quinoxalines, Eur. J. Med. Chem, 45, 2010, 1237.	
Antineoplastic activity  41	N-oxides have been prepared and tested for tumor inhibiting activity. Compound(41) was found to be highly active as a cytotoxic agent [31].	 42 On the other hand, a benzoquinoxalinedione derivative (42) showed remarkable cytotoxic effect against different Sarcoma types [8].
Moreover, a quinoxalinone derivative (43) was reported as a synergistic chemotherapeutic agent for the treatment of resistant neoplastic diseases [32].	In 2005, quinoxaline derivative (45) proved to be among of the most highly and broadly active antitumor agents [34].  45	

 43		
Antidepressant Activity	Triazoloquinoxalines act as selective adenosine antagonists and exhibit antidepressant activity.  46	N-arylcarbamoyl hydrazino quinoxalinones Several [1, 2, 4] triazolo [4, 3-a] quinoxalines (46) have been synthesized and found to possess potent antidepressant activity by virtue of their selective adenosine antagonistic activity [35].
Hypoglycemic Activity	Hydrazino quinoxalinones showed mild hypoglycemic effects comparable to tolbutamide.  47	N-arylcarbamoyl hydrazino quinoxalinones 3- (N-arylcarbamoyl and N-aryl thiocarbamoyl) hydrazine quinoxalin – 2 (1H) ones (47) has been reported as mild hypoglycemic agents comparable to that of tolbutamide [36].
Anti-inflammatory Activity	Certain triazoloquinoxaline and thienoquinoxaline derivatives act as anti-inflammatory agents.	Bis-tetrazoloquinoxalines
In 1990, a series of bis-tetrazoloquinoxalines (48) has been synthesized. Some of the prepared compounds were found to possess anti-inflammatory activity [21]	1, 3, 3a, 4, 9, 9a – Hexahydro thieno [3, 4-b] quinoxaline – 2, 2- dioxide (49) has been reported as a potent anti-inflammatory agent, which has been prepared in 1990, among a series of thieno [3, 4-b]	

 48	quinoxaline derivatives [37  49]	
Excitatory amino acid antagonistic activity Substituted imidazol and triazoloquinoxaline derivatives (50) were developed in 1991 as excitatory amino acid receptor modulators.	 50	These compounds were suggested to play a role in alleviating the new neurological damage associated with disorders such as cerebral ischemia, huntington's chorea, epilepsy and alzheimer's disease [38].
Antiglaucoma Activity	Quinoxaline derivatives such as Brimonidine reduce intraocular pressure in glaucoma patients.	Brimonidine
 51	 52 Recently, new quinoxaline derivatives (52a-i) were prepared and showed interesting activities against several parasites [40].	The importance of quinoxalines as pharmaceutical agents was manifested by the marketing of Brimonidins (Alphagan) (5-bromo – N – (4, 5-dihydro 1H-imidazol-2-y1) -6-quinoxaline amine (51). The drug acts through reducing the intraocular pressure, thus alleviating the symptoms of glaucoma [39].
Antituberculosis Activity	Several substituted quinoxaline-1,4-di-N-oxides possess strong antimycobacterial activity comparable to rifampicin.	6(7)-Substituted quinoxaline derivatives

 53  54	 D. Umashankar , D. Swagathika and J.R. Dimmock , E-2-[3, (3,4-dichloro phenyl)-1-oxo-2-propenyl]- 3- methyl quinoxaline-1,4–dioxide : A lead anti tubercular agent which alters mitochondrial respiration in rat liver, Eu. J. med. chem , 45, 2010, 4682 .	In 2002,a group of research workers synthesized a series of 6(7)-substituted-3-methyl-2-phenylthio-quinoxaline-1,4-di-N-oxides (53a-e) showed antituberculosis activity exhibiting MIC between 0.39 and 0.78 µg mL-1 (rifampicin MIC= 0.25 µg mL-1)[25]. The same group research workers also synthesized a new derivatives of quinoxaline-1,4-di-N-oxide (54a-g) which have been found to exhibit a good antituberculosis activity [12,41].
Anticancer Activity  57	Quinoxaline derivatives have shown cytotoxicity against various human tumor cell lines including leukemia, breast, and colon cancers.	Quinoxaline diones, quinoxaline N-oxides
In 1999, a group of research workers [24] have synthesized a new series of quinoxaline and submitted to preliminary in vitro evaluation for anticancer and results showed interesting anticancer activity for compound (55).	Two years later, Antonio et al [10] have prepared a series of compound (56) pyrido[2,3-g] quinoxalines and submitted them to preliminary in vitro evaluation for anticancer testing.  56	A year later[42], a new series of quinoxaline derivatives(57 a-g) were prepared and tested for anticancer in vitro and the results showed that compound (57a) was the most active agent followed in decreasing order by (57b)=(57c),(57d),(57e),(57f),(57g).

 55		
Anti-HIV Activity 	Quinoxalinones have been reported as potent HIV-1 reverse transcriptase inhibitors. 	3,3-Disubstituted quinoxalinones

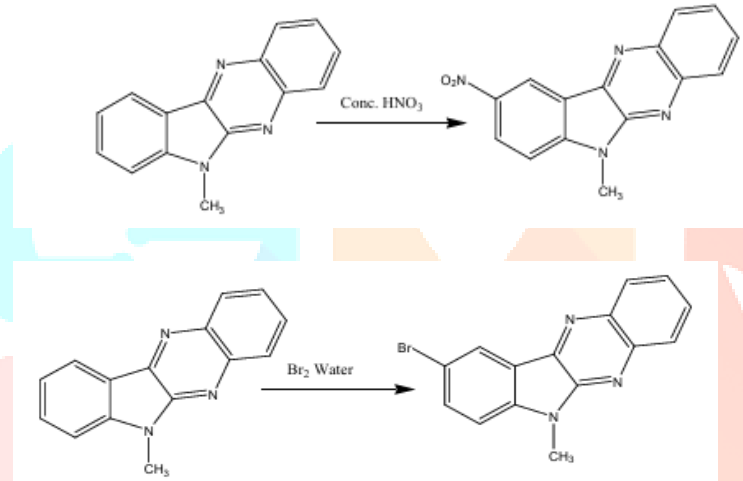
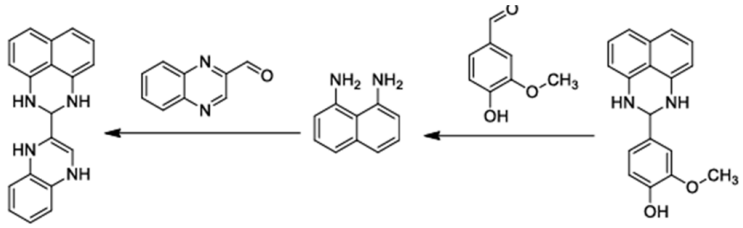
1.1 Chemistry of Quinoxalines

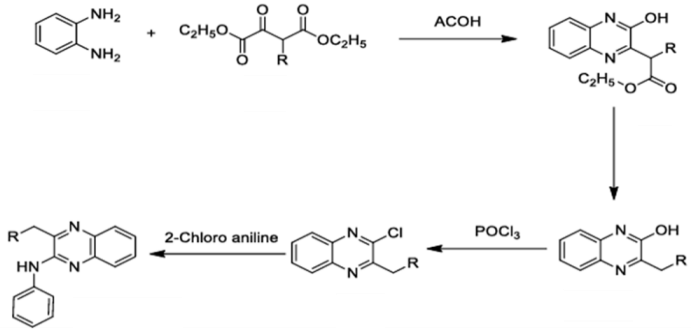
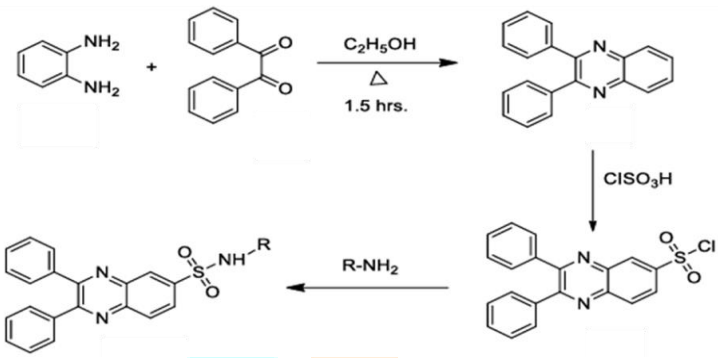
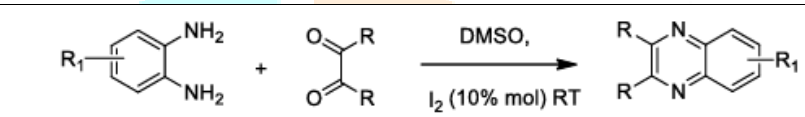
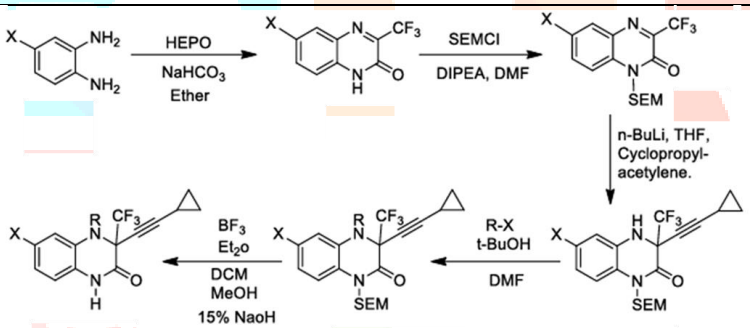
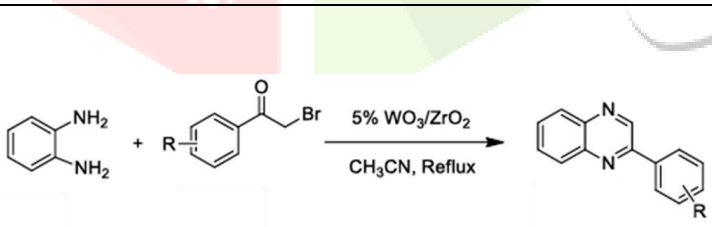
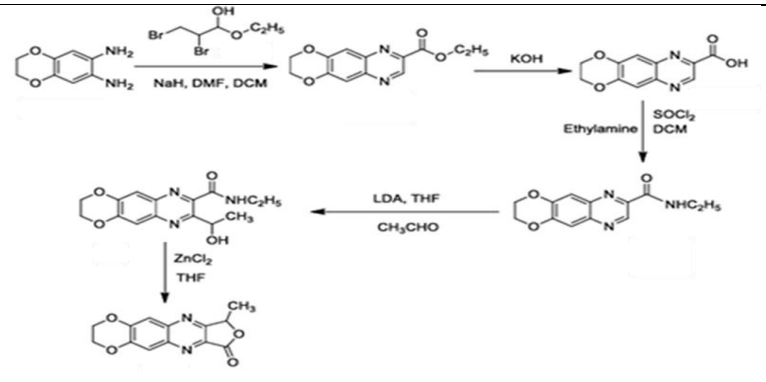
1.2 Synthesis of Quinoxaline Derivatives

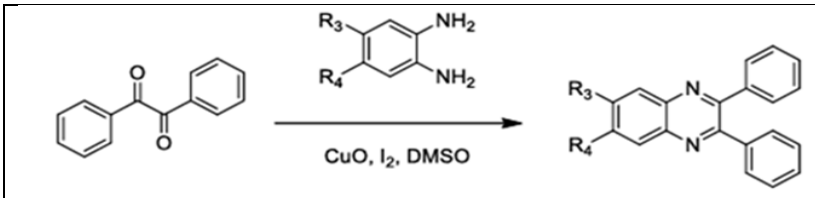
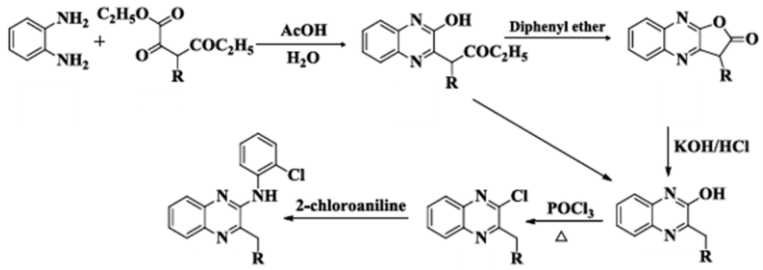
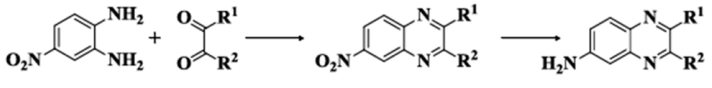
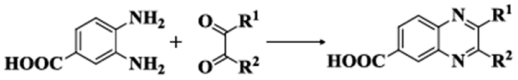
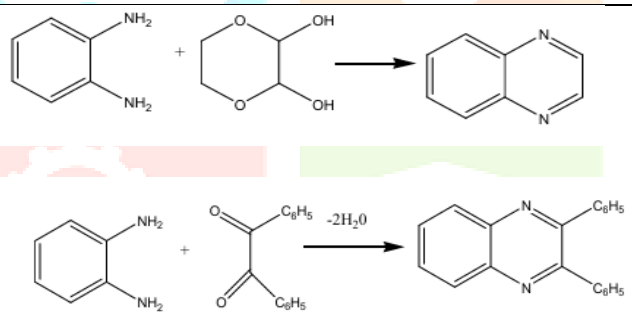
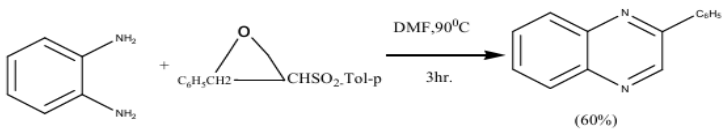
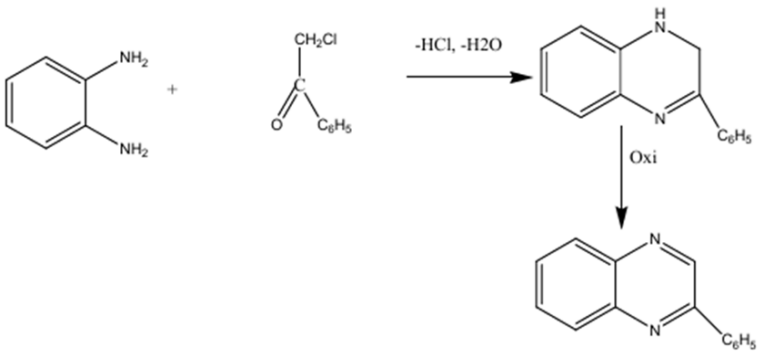
Synthetic Method	Reaction Description	Key Reagents
Condensation of 1,2-Diamines with 1,2-Dicarbonyl Compounds	Most common method involving cyclocondensation between o-phenylenediamine and diketones or glyoxal derivatives.	o-Phenylenediamine, glyoxal, diketones
Reaction with Oxalic Acid	Formation of quinoxaline-2,3-dione derivatives through condensation with oxalic acid.	Oxalic acid
Intramolecular Cyclization	Cyclization of substituted intermediates to yield fused quinoxaline systems.	Sodium hydride, DMF
From α-Arylimino Oximes	Cyclization of arylimino oximes produces substituted quinoxalines.	Hydroxylamine, acetic anhydride

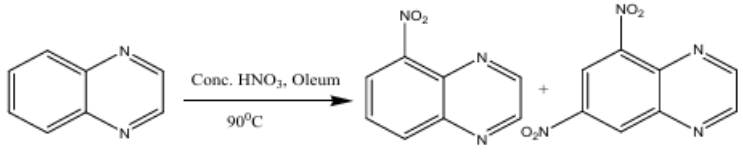
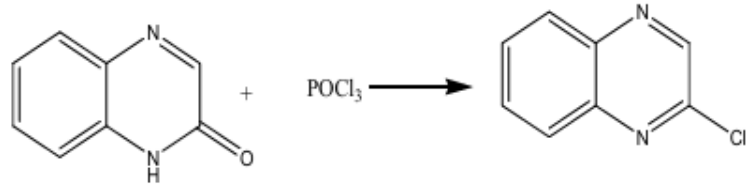
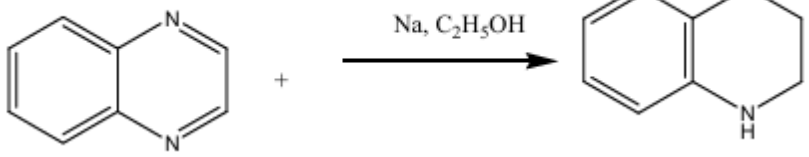
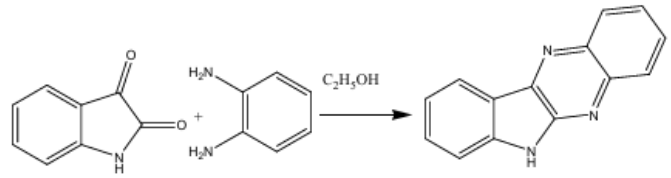
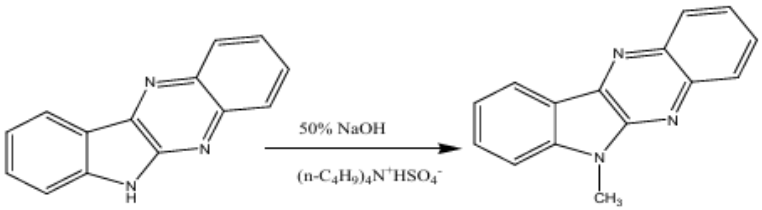
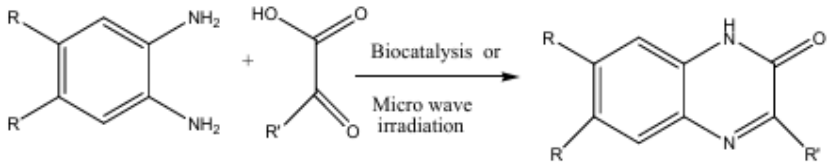
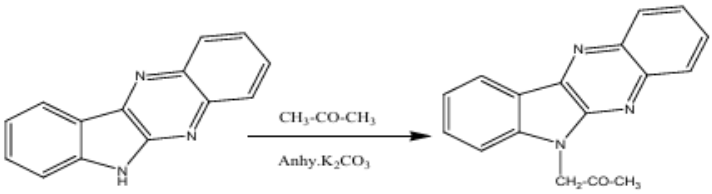
Preparation of Quinoxaline N-Oxides	Cyclization of o-nitroacetanilides affords quinoxaline-N-oxide derivatives.	Sodium ethoxide
Ring Contraction of Diazepines	Photochemical conversion of benzodiazepines into quinoxaline derivatives.	Oxidative conditions

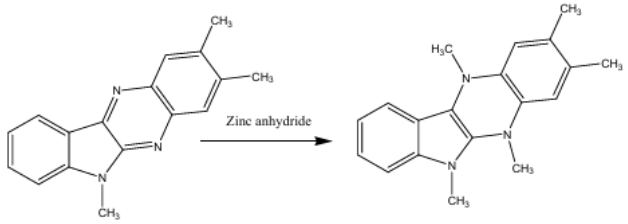
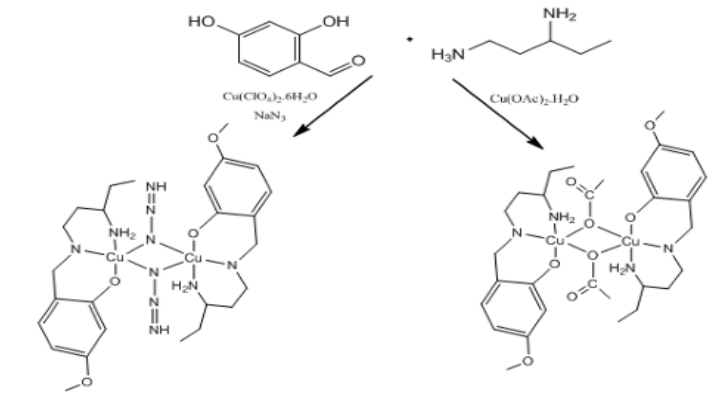
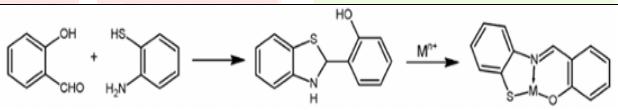
A. Reactions of Quinoxaline Derivatives

Reaction Type	**Description**
Electrophilic Substitution	
	Reference [58]
Cyclization Reactions	Hydrazino quinoxalines cyclize to produce triazoloquinoxalines and fused heterocyclic systems.
	Reference [59]

	Reference [60]
	Reference [61]
	Reference [62]
	Reference [63]
	Reference [64]
	Reference [65]

	Reference [66]
	Reference [67]
 R¹ = H, Me, Ph; R² = H, Me, Ph  R¹ = H, Me, Ph; R² = H, Me, Ph	Reference [68]
	Reference [69]
 (60%)	Reference [70]
	Reference [71]

	Reference [72]
	Reference [73]
	Reference [74]
	Reference [75]
	Reference [76]
	Reference [77]
Acylation	
	Reference [78]
Oxidation and Reduction	Quinoxalines can be oxidized to N-oxides or reduced under catalytic conditions.

	Reference [79]
Metal Complex Formation	Quinoxaline derivatives containing donor atoms form stable metal complexes with transition metals such as copper.
	Reference [80]
	Reference [81]

1.3 Spectroscopic Characterization of Quinoxaline Derivatives

Technique	Purpose
FT-IR Spectroscopy	Identification of functional groups such as C=N, N–H, C=O, and aromatic vibrations
^{1}H NMR Spectroscopy	Determination of proton environments and structural confirmation
^{13}C NMR Spectroscopy	Carbon skeleton analysis and substitution pattern determination
Mass Spectrometry	Molecular weight determination and fragmentation analysis

UV–Visible Spectroscopy	Electronic transition analysis and conjugation studies
Single Crystal X-ray Diffraction (SCXRD)	Precise molecular geometry and crystal structure determination

Conclusion:

Quinoxaline derivatives constitute a versatile and pharmacologically important class of heterocyclic compounds. Extensive research over the years has demonstrated their broad spectrum of biological activities including antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, antituberculosis, and anti-HIV properties. Advances in synthetic methodologies have enabled the preparation of structurally diverse quinoxaline analogues with improved biological efficacy. The presence of electron-withdrawing groups, fused heterocyclic systems, and N-oxide functionalities significantly enhances pharmacological properties. Owing to their remarkable therapeutic potential and structural diversity, quinoxaline derivatives continue to attract considerable attention in medicinal chemistry and pharmaceutical research. Further exploration of structure–activity relationships and modern computational approaches may lead to the development of novel quinoxaline-based therapeutic agents in the future.

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