College of Pharmaceutical Sciences and Drug Manufacturing
A college accredited by "NAQAAE"

Journal of Pharmaceutical Sciences and Drug Manufacturing
ISSN: 3009-6553 (Print)
ISSN: 3009-6677 (Online)

JPSDM

Section B: Organic, Analytical and Pharmaceutical Chemistry.

Review Article

Green and Conventional Synthetic Strategies for Quinoxaline Derivatives: Toward a Sustainable Future

Aya A. Abdelaziz[1], Ahmed Moustafa[2], Youssif Ibrahim[2], Noha Ryad [1*]

[1] Pharmaceutical Organic Chemistry Department, College of Pharmaceutical Sciences and Drug Manufacturing, Misr University for Science and Technology (MUST), 6th of October City, Giza, P.O. Box 77, Egypt.

[2] College of Pharmaceutical Sciences and Drug Manufacturing, Misr University for Science and Technology (MUST), 6th of October City, Giza, P.O. Box 77, Egypt.

*Correspondence: Noha.gabr@must.edu.eg.

Received: 15 May 2025
Accepted: 13 June 2025
Published: 28 June 2025

Editors
Nehad Eldydamony
Mahmoud Eltahan

Keywords
Quinoxaline
Green Chemistry
Conventional Heating
Sustainable Synthesis
Eco-Friendly

Abstract

Introduction:
Quinoxaline derivatives are a prominent class of nitrogen-containing heterocyclic compounds known for their unique chemical and physical properties. The quinoxaline ring, characterized by two nitrogen atoms at the 1 and 4 positions of a benzene ring, has gained significant attention due to its pharmacological relevance and synthetic versatility. This makes it an essential scaffold in drug design.

Aim of review:
The review aims to highlight recent advancements in the synthesis of quinoxaline derivatives, focusing specifically on the incorporation of green chemistry principles. The objective is to demonstrate how sustainable approaches can be effectively integrated into quinoxaline synthesis.

Concepts of review:
The study explores various green synthetic strategies, including solvent-free reactions, catalytic processes, and the use of alternative energy sources. Emphasis is placed on the application of green reagents, the reduction of toxic byproducts, and waste minimization.

Conclusion:
Key sustainable methods for synthesizing quinoxaline derivatives were identified and evaluated. These methods have shown potential in improving the environmental profile of synthetic processes without compromising efficiency or yield. The integration of green chemistry into quinoxaline synthesis offers a promising path for developing environmentally friendly and efficient synthetic routes. This approach not only addresses sustainability concerns but also enhances the potential application of quinoxaline-based compounds in the pharmaceutical and chemical industries.

1. Introduction

A significant type of heterocycle molecule is quinoxaline derivatives, in which *N* substitutes for some of the carbon atoms in the naphthalene ring[1]. Two aromatic rings, pyrazine and benzene, fused to generate quinoxaline[2]. It has attracted significant interest in modern medicinal chemistry[3]. Since quinoxaline has emerged as a considerable chemical moiety with a variety of physicochemical and biological functions[4], including anti-cancer[5], anti-diabetic[6], anti-bacterial[7], anti-convulsant [8], anti-leishmanial[9], anti-amoebic[10], anti-trypanosomal[11], anti-HCV[12] and anti-oxidant/anti-inflammatory properties[13]. Additionally, they have strong biological activity[14] that selectively targets receptors, such as AMPA receptor antagonist activity[15]. Natural quinoxaline derivatives are uncommon and the majority of quinoxaline derivatives are synthetic, such as echinomycin and triostin-A[1]. The numerous medical and industrial uses of quinoxaline derivatives make them advantageous substances. They are widely recognized for their use in pharmacological drugs, polymers and organic light-emitting devices. Quinoxaline-containing polymers' low band gap and thermal stability make them suitable for use in optical devices[16]. According to their pharmacokinetic characteristics, medications containing quinoxaline cores are very simple to give as oral capsules, intramuscular injections, or rectal suppositories[17].

Derivatives of quinoxaline 1,4-dioxide (QdNOs) have been utilized extensively as anti-bacterial and growth-promoting agents. The traditional members of QdNOs include carbadox (CBX), olaquindox (OLA), quinocetone (QCT), cyadox (CYA) and mequindox (MEQ) as illustrated in **Fig.1**.[18]. Quinoxaline synthesis has been extensively researched in the past, particularly due to the wide range of biological activity attributed to several members of this class of chemicals[19]. As a result, a wide range of synthetic techniques for creating functionalized quinoxalines have been documented in the literature.

2. Materials and methods

There are several ways to synthesize quinoxalines and each one uses a different set of conditions and reagents. Based on the above search results, the following are the most common synthetic methods for making quinoxalines. Green synthesis has significantly raised the present environmental safety requirements while avoiding the traditional processes that use hazardous or toxic solvents or catalysts. At the laboratory and commercial levels, green chemistry research has consistently contributed significantly to the creation of heterocyclic scaffolds[20]. The overall goal of green chemistry is to

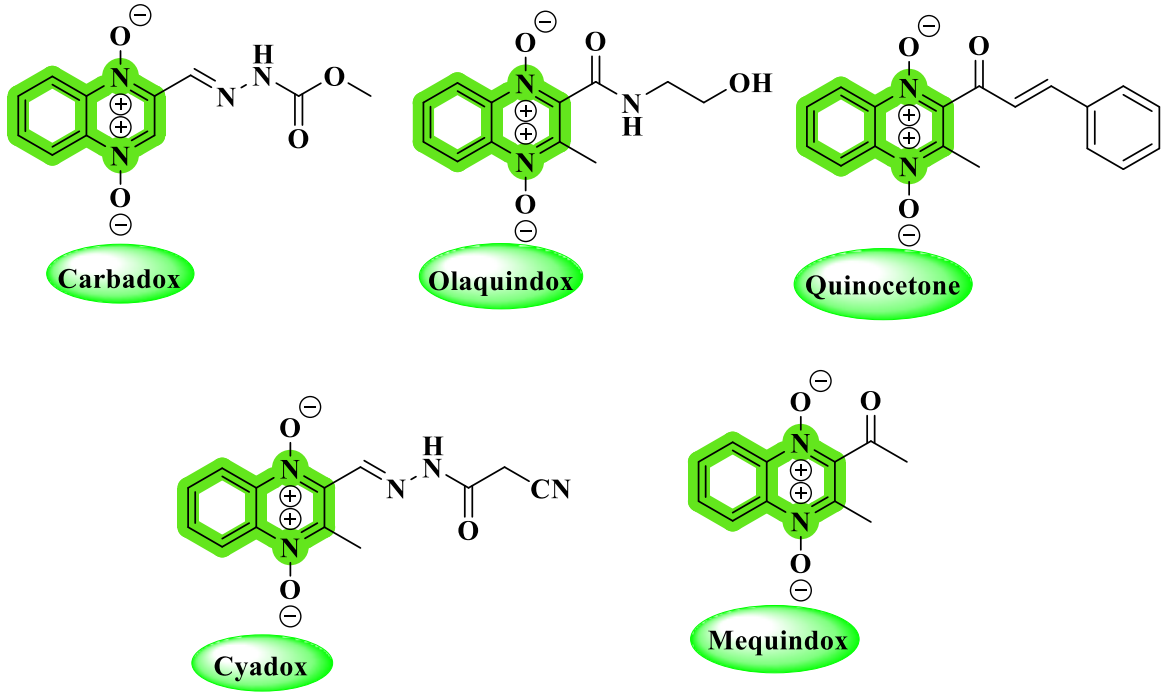
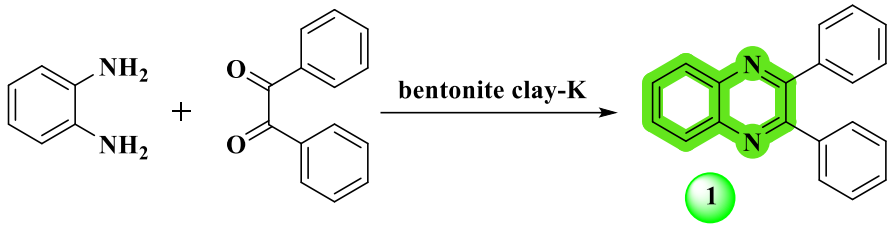


Figure 1. Derivatives of quinoxaline 1,4-dioxide (QdNOs).



Scheme 1. Synthesis of quinoxaline analog **1** using bentonite clay K-10.

maximize the conversion of reactants into products while minimizing waste and byproducts, using the least amount of energy possible, and using fewer harmful chemicals and solvents. The practice of conducting organic reactions in water is becoming more popular due to the benefits of using water as a solvent medium[21].

2.1. Synthetic pathways to prepare quinoxaline derivatives *via* cost-effective and green synthetic approach

2.1.1. Using bentonite clay K-10

To safeguard human health and the environment[22], a great deal of research has been done since the advent of green chemistry to create safe and ecologically friendly chemical processes[23]. Research on the green organic synthesis approach is gaining momentum due to its environmental friendliness and the ability to overcome drawbacks including harsh reaction conditions, costly reagents and low yield. Clay[24] is an easily accessible, heterogeneous, and inexpensive green reagent[25]. Due to its low energy consumption and recyclable nature, heterogeneous catalysis has found widespread application in green organic chemistry[26]. Quinoxaline derivative **1** was created using bentonite clay K-10. The reaction proceeds by mixing the reactants *O*-phenylenediamine and benzil with ethanol and bentonite clay, which paves the path for organic synthesis using green chemistry, offering remarkably mild conditions such as quick reaction times, excellent yields, low costs and straightforward isolation and experimentation processes. Similar research on the creation of effective and eco-friendly processes in organic synthesis should be established, as this synthesis complies with green chemistry regulations. Table **1** provides a briefing of the findings. *O*-phenylenediamine and benzil condense in room-temperature ethanol with varying concentrations of bentonite clay K-10. As shown in Table **2**, a range of solvents was selected to identify the best solvent for the synthesis of 2,3-diphenyl quinoxaline **1** (Scheme 1) **[27]**.

Table 1: The effect of clay concentration on the percentage of isolated yield % at room temperature.

Entry	Grams of clay	Time(min.)	Isolated Yields %
1	0.5	720	38
2	1	120	43
3	1.5	90	65
4	2	60	93
5	2.5	20	95
6	3	20	95

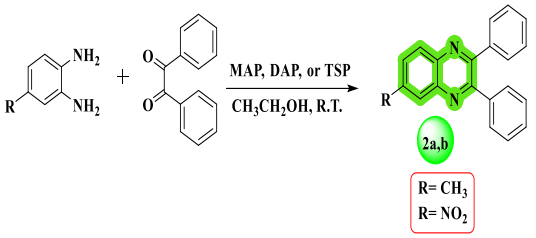
Table 2: The impact of various solvents on the reaction between *O*-phenylenediamine and benzil when bentonite clay K-10 at ambient temperature.

Entry	Solvent	Time(min.)	Isolated yields %
1	CH_3CH_2OH	20	95
2	CH_3OH	30	91
3	H_2O	120	Trace
4	$CHCl_3$	30	87
5	CH_2Cl_2	30	82
6	CH_3CN	35	92
7	THF	30	89

2.1.2. Using phosphate-based heterogeneous catalyst (MAP, DAP, TSP)

To create quinoxaline derivatives using heterogeneous catalyst fertilizers based on phosphates[28], such as triple-super phosphate (TSP)[26, 29], di-ammonium phosphate (DAP)[30], or mono-ammonium phosphate (MAP)[31]. Various *O*-phenylenediamines were condensed with

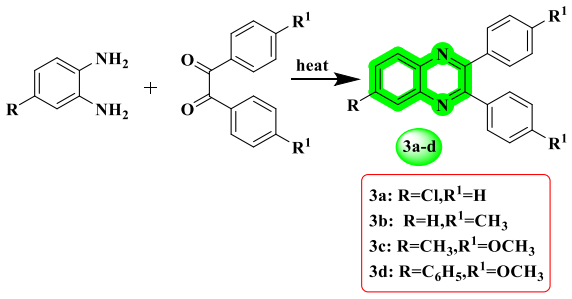
benzil in ethanol and phosphate-based catalysts MAP, DAP, or TSP to verify the protocol's dependability, as illustrated in the reaction**.** Ethanol was used to recrystallize the resulting product **2a,b** and dried for 6hrs. (Scheme 2).



Scheme 2. Synthesis of substituted quinoxaline analogs **2a**,**b** using MAP, DAP, TSP.

2.1.3. Using lanthanide reagent (CAN)

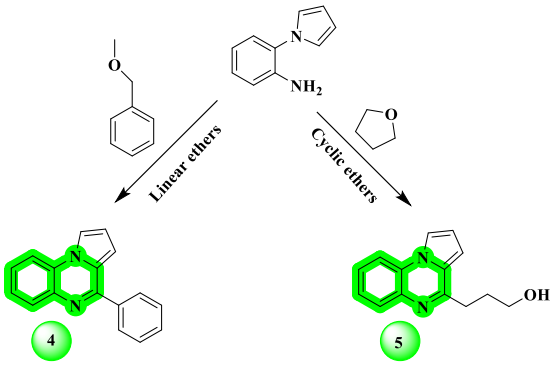
Cerium (IV)ammonium nitrate (CAN), one of the lanthanide reagents[32], has drawn a lot of interest in organic chemistry because of its high reactivity, low cost, and water miscibility. One safe green chemistry method is to use CAN as a catalyst in chemical synthesis[21]. Consequently, Yao *et al* used a catalytic quantity of CAN in water to create physiologically significant quinoxalines. The quinoxaline derivatives **3a-d**, were generated by the reaction of substituted benzil with *O*-phenylenediamine derivatives using a catalytic quantity of CAN in methyl cyanide or any protic solvent. Without any byproducts, the product was completed in 20 minutes. The anti-microbial qualities of quinoxaline's derivatives **3a-d** include anti-viral, anti-bacterial, anti-fungal, and many more. As a green chemical strategy, quinoxaline synthesis employing lanthanides as a catalyst ought to be investigated (Scheme 3)[21].



Scheme 3. Methods for synthesizing quinoxaline analogs **3a-d** using CAN as a catalyst.

2.1.4. Using Fe as a Catalyst

Pyrrolo[1,2-*a*] quinoxalines are an example of *N*-heterocyclic compound that is frequently found in nature and has appropriate pharmacological activities. Because of its amazing applications, pyrrolo[1,2-*a*] quinoxalines have drawn a lot of attention for synthesis *via* various routes. Zheyu *et al*. developed synthetic pathways for the preparation of pyrrolo[1,2-*a*] quinoxalines using Fe catalysis with 1-(2-aminophenyl) pyrroles and cyclic ethers[33]. Pyrroloquinoxaline synthesis was developed because of the reagents' accessibility and affordability. The synthesis pathway for both linear and cyclic ethers is established, reaction was initially concentrated on 1-(2-aminophenyl) pyrrole using tert-butyl hydroperoxide (TBHP), THF and Fe as a catalyst, with stirring at room temperature for ten hrs. The yield of the desired product was 46%. The inclusion of CF_3SO_3H as an additive raised the percentage to 94%. In summary, this reaction creates pyrrolo[1,2-*a*] quinoxalines by breaking the C–O link of cyclic ethers to produce C–C and C–N bonds (Scheme 4) [34, 35].

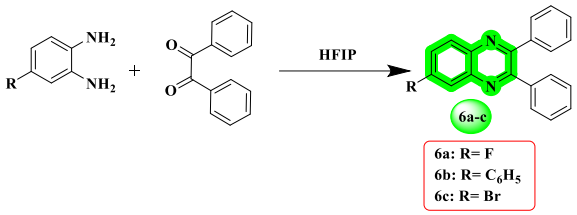


Scheme 4. The synthetic pathway for both linear **4** and cyclic ethers **5**.

2.1.5. Using Fluorinated Alcohols (HFIP)

The fluorinated alcohol's strong hydrogen bond-donating ability, high polarity, low nucleophilicity, and capacity to solvate water have all led to their increased attention in organic processes[33]. Additionally, fluorinated alcohols can stabilize protein helix conformations[36]. Khaskar *et al*. demonstrated the ability of fluorinated alcohol to create quinoxaline derivatives[37]. The reaction was carried out in hexafluoroisopropanol (HFIP) with benzil and *O*-phenylenediamine at room temperature for one hr to produce 2,3-diphenylquinoxaline **6a-c** with a 95% yield. A typical method that has issues with long reaction times, high reaction temperatures, low yields, the use of

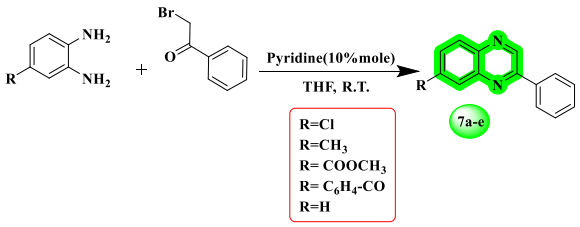
hazardous organic solvents, and many other issues is the condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds in ethanol or acetic acid. Since the HFIP can be recycled at least five times without experiencing a substantial change in activity, it also offers an excellent green chemical feature. This process can be used to prepare quinoxalines on a big scale (Scheme5) [38, 39].



Scheme 5. Methods for synthesizing quinoxaline analogs **6a-c** using Fe as a catalyst.

2.1.6. Using pyridine as a catalyst

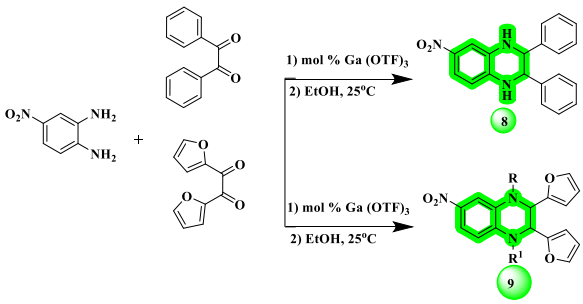
Quinoxaline derivatives can be made with *O*-phenylenediamine and two carbon synthones, including *α*-dicarbonyls, *α*-halogen carbonyls, *α*-hydroxy carbonyls, *α*-azo carbonyls, epoxides and *α*, *β*-dihalides. By reacting phenacyl halides with substituted *O*-phenylenediamine, a condensation-oxidation reaction that necessitates a pyridine and/or media catalyst, quinoxaline derivatives can also be produced and completed within two hrs. Phenacyl bromide and an equimolar amount of *O*-phenylenediamine derivatives react in THF with pyridine to produce the intended product, 2-phenyl quinoxaline **7a-e** (Scheme 6)[40].



Scheme 6. Synthetic pathway to prepare quinoxaline derivatives **7a-e** using pyridine as a catalyst.

2.1.7. Using a solid acid catalyst, TiO_2-Pr-SO_3H

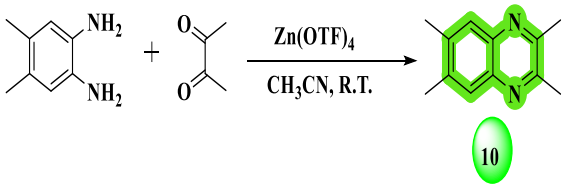
Catalysts can be used to increase the rate of organic processes. Because of green chemical synthesis, organic chemists have been very interested in recyclable catalysts, such as solid acid catalysts like TiO_2-Pr-SO_3H. The method of making quinoxaline analogs can proceed with shorter reaction durations at room temperature. Despite their importance, these processes have drawbacks, such as lengthy reaction times and possible risks during catalyst preparation. A straightforward one-step synthesis of quinoxaline analogs. A variety of solvents, including ethanol, THF, MeCN, EtOAc and toluene, as well as solvent-free conditions, are used to assess the reaction between substituted *O*-phenylenediamine and benzil using a 95% yield only after 10 minutes. The best results were obtained using TiO_2-Pr-SO_3H and ethanol[41]. In the past, quinoxalines like alumina have been prepared using a variety of catalysts[42], such as montmorillonite K-10[43], sulfated TiO_2[44], clayzic[45], Zirconium(IV) modified silica gel [46], PEG-400[47], hetero-polyacid[48], ZrO_2/MxOy/MCM-41[49], cellulose sulfuric acid[50] and $Ga(OTf)_3$ (Scheme 7) [51].



Scheme 7. Synthetic pathway to prepare quinoxaline derivatives **8** and **9** using solid acid catalyst TiO_2, Pr-SO_3H as a catalyst.

2.1.8. Zinc triflate catalyst

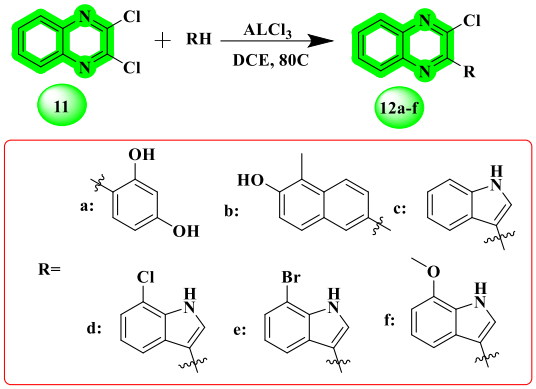
Trifluoromethanesulfonic acid's zinc salt is called zinc triflate. It is a very efficient and environmentally friendly catalyst. It is a catalyst for green chemistry. Acetonitrile solvent or a microwave-assisted reactor can be used to finish the reactions carried out by the zinc triflate catalyst without the need for a solvent. Using a zinc triflate catalyst, *O*-phenylenediamine and α-diketones were reacted in acetonitrile to produce quinoxaline derivative **10** in a good yield of 90% (Scheme 8)[52].



Scheme 8. Preparation of quinoxaline derivative **10** using zinc triflate as a catalyst.

2.1.9. Intramolecular arylation using Lewis acid catalyst

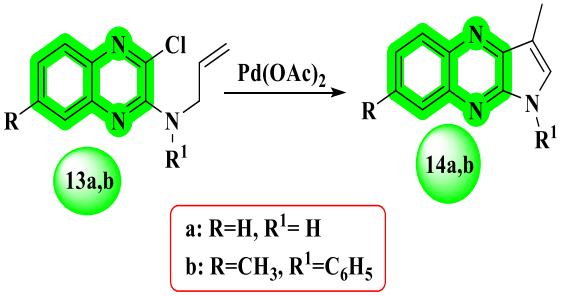
Using a Lewis acid catalyst ($AlCl_3$), dichloro quinoxalines and aryl derivatives were reacted to yield aryl derivatives of quinoxalines **12a-f** after 60 minutes. (Scheme 9) [53, 54].



Scheme 9. Method-induced arylation *via* C-C bond formation.

2.1.10. Intramolecular cyclization of quinoxalines

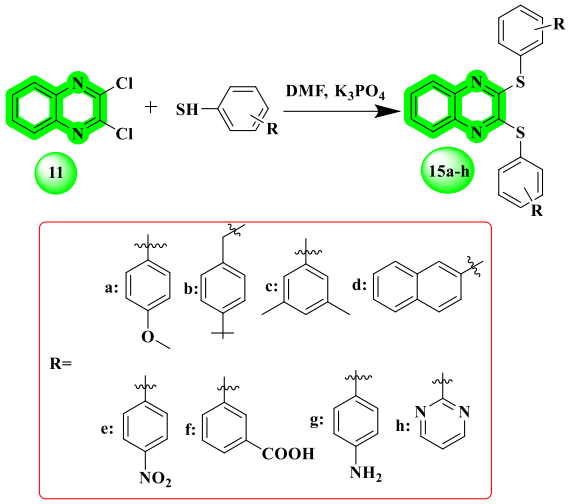
Substituted pyrrolo [2,3-*b*]quinoxaline **14a,b** from allyl-3-chloroquinoxaline-2-ylamine **13a,b** with aromatic amine and terminal alkene derivatives was made with a Pd-mediated catalyst $Pd(OAc)_2$ (Scheme 10) [55].



Scheme 10. Synthesis of quinoxaline analogs **13a**,**b** and **14a**,**b** via cyclization reaction.

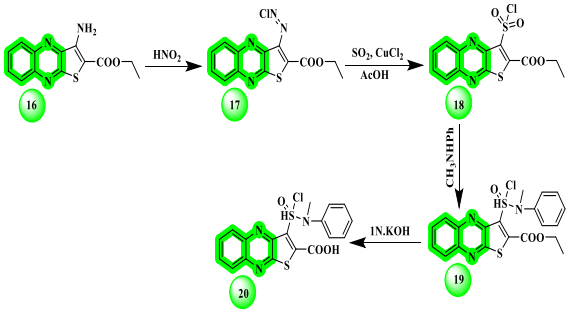
2.2. Synthetic pathways to prepare quinoxaline derivatives *via* conventional heating

Hena *et al,* 2024 created a new novel of quinoxaline derivatives, including 2,3-bis(aryl thiol)quinoxaline, 4-chloro-12*H*-quinoxalino [2,3-*b*] and 5-nitro-1*H*-benzo and 1,4-benzothiazine [d]Imidazole-2-thiol by reacting 2,3-dichloroquinoxaline with aromatic thiols (Scheme 11) [56].



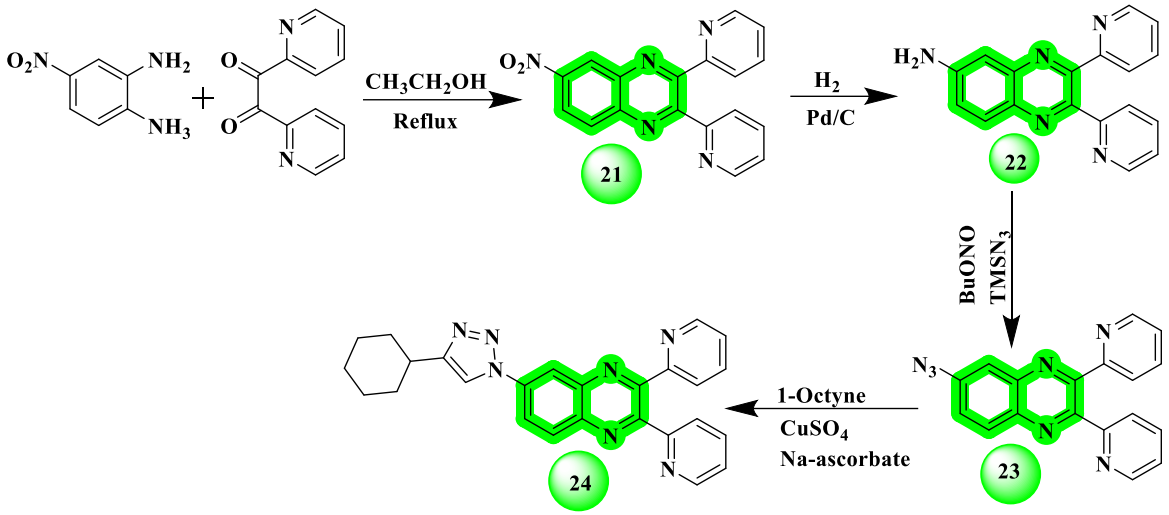
Scheme 11. 2,3-dichloroquinoxaline's reaction with aryl mercaptans to produce derivatives of 2,3-bis(arylthiol) quinoxaline **15a-h**.

Osama and his team's goal in this work was to create several heterocycle fused systems with thieno[2,3-*b*] quinoxaline in the hopes that they would have potent biological activity. 2-ethoxycarbonylthieno[2,3-*b*] quinoxaline-3-sulfonyl chloride **18** was produced by the reaction of 3-amino-2-ethoxycarbonylthieno[2,3-*b*] quinoxaline **16** with nitrous acid, followed by sulfur dioxide and cupric chloride in acetic acid, *via* the diazonium salt **17**. 3-sulfamoyl thienoquinoxaline **19** was produced by the reaction of **18** with N-methylaniline, and upon hydrolysis, 3-sulfamoyl-2-carboxylic acid **20** was obtained (Scheme 12) [57].



Scheme 12. Some quinoxaline analogs are synthesized *via* a diazotization reaction.

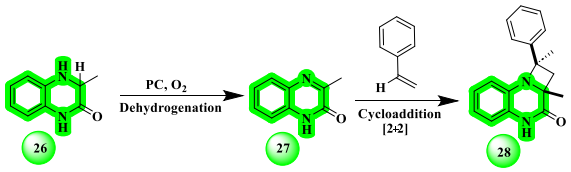
Some researchers illustrated that simple methods that do not require sophisticated equipment or an inert atmosphere can synthesize the **24**, as explained below. Using 4-nitro-1,2-phenylenediamine and 2,2′-pyridyl, nitroquinoxaline **21** was prepared[58]. Amine derivative **22** was prepared by reducing this substance with palladium on carbon. Adams' catalyst (PtO_2) can also be utilized for this phase, but this reagent requires longer



Scheme 13. Synthesis of azide **23** and triazole analog **24**.

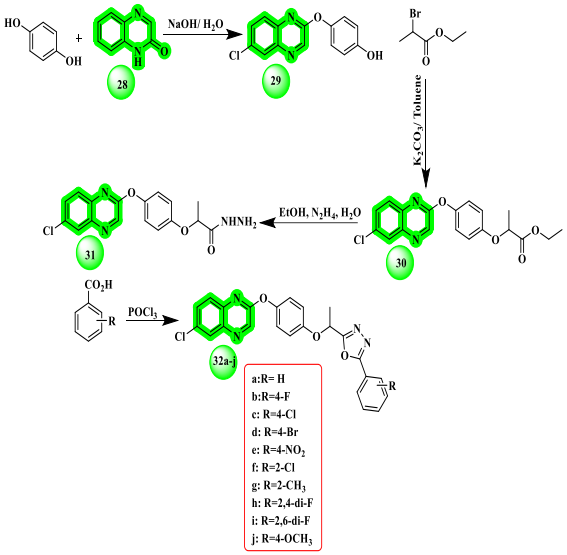
reaction times. To create azide derivative **23**, diazotization and azide transfer were used. Compound **23** was synthesized by reacting aminoquinoxaline **22** with BuONO in DMSO, and then product **23** reacted with 1-octyne in DMSO to obtain compound **24** (Scheme 13) [59].

Shivangi *et al* synthesized a novel of azetidine derivatives using a photocatalytic method by aerobic dehydrogenative [2 + 2] cycloaddition from quinoxalinones and substituted alkene. Dihydro quinoxalinone substituent **25** started the Aza Paterno-Buchi reactions process, forming through photo redox oxidation with an iridium catalyst. In the subsequent steps, an intermolecular cycloaddition reaction produced azetidine derivatives 27 by substituting styrene **25** with **26** in the presence of an Ir-based sensitizer (Scheme 14) [60].



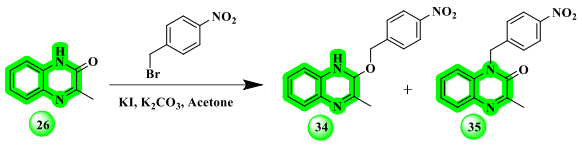
Scheme 14. Synthesis of azetidine by photocatalysis using [2+2] cycloadditions **28**.

Bnagar and his associates created a new series of quinoxaline-oxadiazole analogs. Adding 2,6 dichloroquinoxaline, compound **28,** and hydroquinone was the planned strategy. In an aqueous sodium hydroxide (NaOH) solution, compound **28** and hydroquinone reacted to start the synthesis process to form compound **29**. This intermediate **29** then reacts with ethyl 2-bromo propanoate [EBP] to generate quizalofop ethyl, compound **30**. Upon heating compound **30** and hydrazine hydrate, produced compound **31**. Compound **31** is cyclized with various substituted aromatic carboxylic acids in phosphoryl chloride ($POCl_3$) in the final step. As a result of this method, the hybrid chemicals **32a-j** are synthesized (Scheme 15) [61].



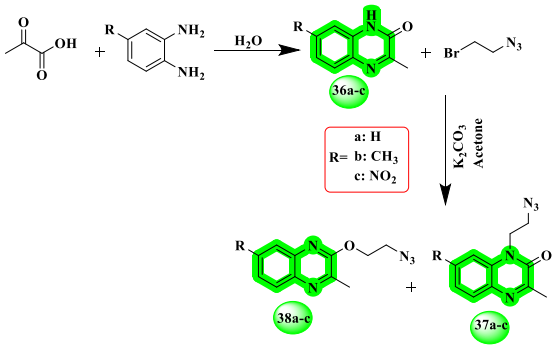
Scheme 15. Diagrammatic representation of the process used to create quinoxaline and oxadiazole hybrid compounds.

Sheena *et al* created new analogs of quinoxaline ring by reacting 3-methyl quinoxaline-2 (1*H*)-one **26** with *p*-nitro benzyl bromide to give 2-methyl-3-((4-nitrobenzyl)oxy)quinoxaline **34** and 3-methyl-1-(4-nitrobenzyl) quinoxaline-2 (1*H*)-one **35** in two different ratios (40% and 47%, respectively) (Scheme 16) [62].



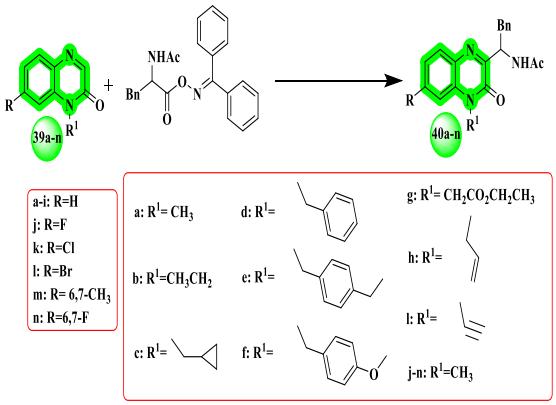
Scheme 16. Method for synthesis of some quinoxaline derivatives.

Manan and her group created a novel set of quinoxaline analogs through certain steps. Combining substituted O-phenylenediamine with pyruvic acid in water produced 3-methyl quinoxaline-2(1H)-one derivative 36a-c. These products then reacted with 1-azido-2-bromoethane, to produce products **37a-c** and **38a-c**. Finally, a dropwise addition of azido bromoalkane was added (Scheme 17) [63].



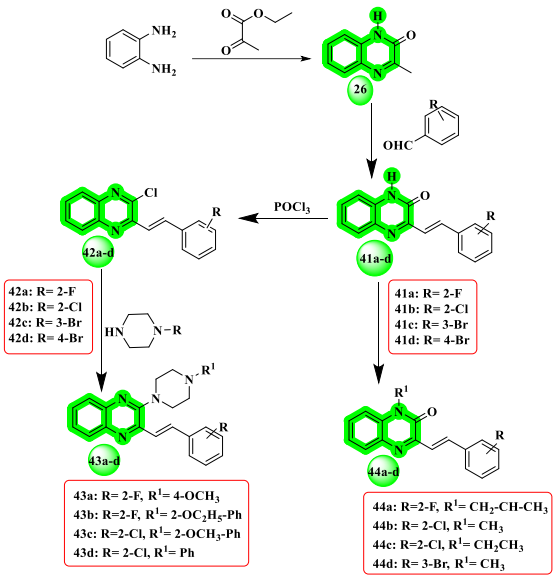
Scheme 17. Synthetic pathway to obtain quinoxaline analogs **37a-c** and **38a-c**.

In 2025, Bin and some researchers illustrated that substituted methyl quinoxaline-2 (1*H*)-one **39a-n** and an oxime ester made from acetyl phenylalanine, demonstrated good results from the photoinduced decarboxylative reaction of oxime amino acid ester, which produced derivatives of quinoxaline-2 (1*H*)-one **40a-n** (Scheme 18)[64].



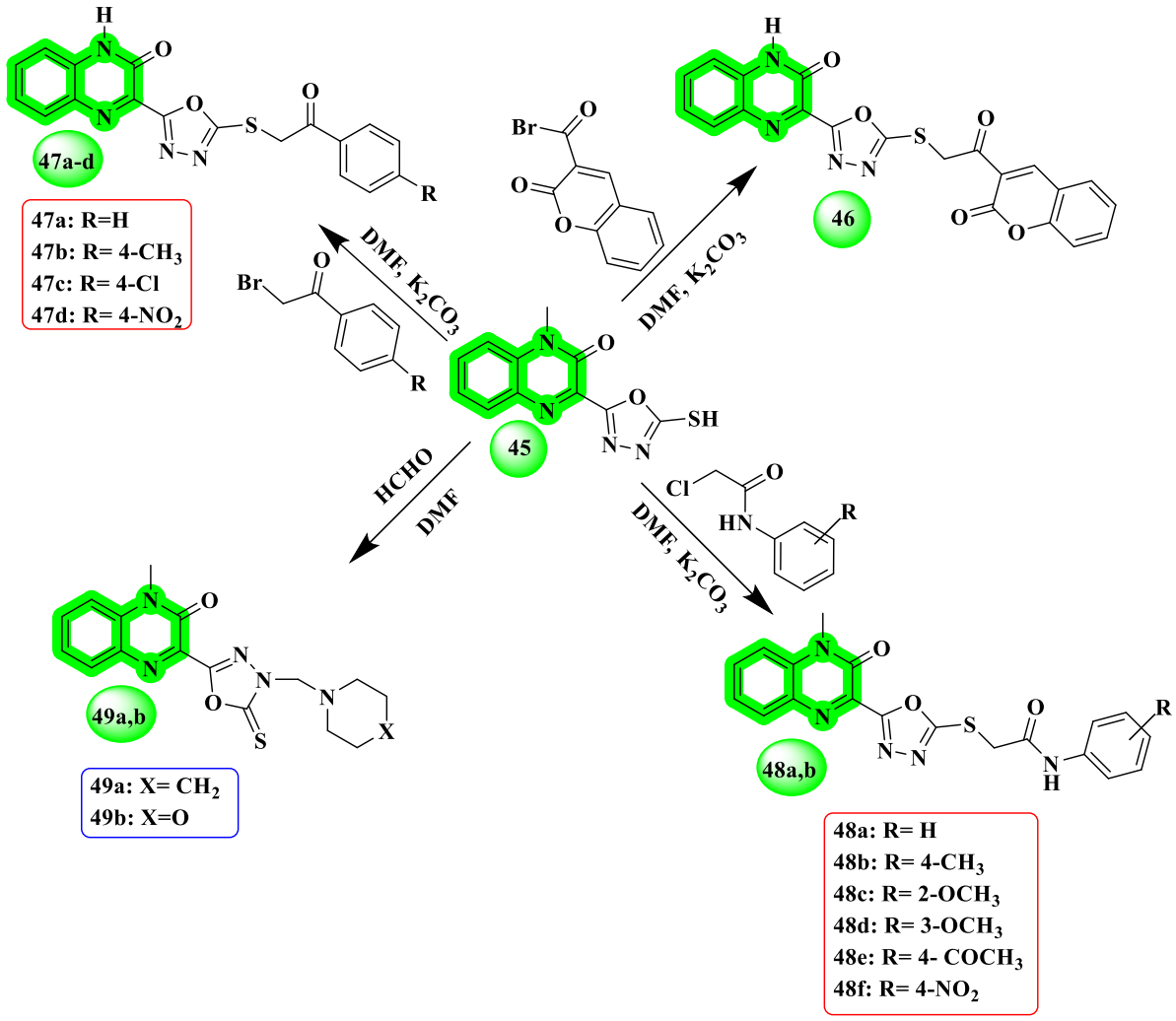
Scheme 18. Synthetic pathway to obtain quinoxaline analogs **40a-n**.

Mohga *et al* created new derivatives of quinoxaline ring. The reaction of *O*-phenylenediamine with ethyl pyruvate using a documented technique produced the starting material, 3-methyl quinoxaline-2(1H)-one **26** [65]. In the presence of piperidine, compound **26** reacted with certain aromatic aldehydes using acetic anhydride to generate 3-substituted styrylquinoxalin-2(1*H*)-ones **41a-d**. Compounds **41a**–**d** were chlorinated with phosphorus oxychloride to get Styrylquinoxalines 2-chloro-3-substituted **42a-d**. Meanwhile, 2-(4-substituted piperazin-1-yl) was produced by amining compounds **42a-d** with specific substituted piperazines in n-butanol that are 3-substituted **43a-d**. *N*-alkylated quinoxalinone derivatives were the only byproduct of the alkylation of quinoxalin-2-ones, according to a publication[66]. Consequently, the required Compounds **41a**, **41c** or **41d** were heated to create 1-(alkyl or allyl)-3-substituted styrylquinoxalin-2(1*H*)-ones **44a-d** (Scheme 19) [67].



Scheme 19. Synthetic pathway to synthesize quinoxaline derivatives **43a-d** and **44a-d**.

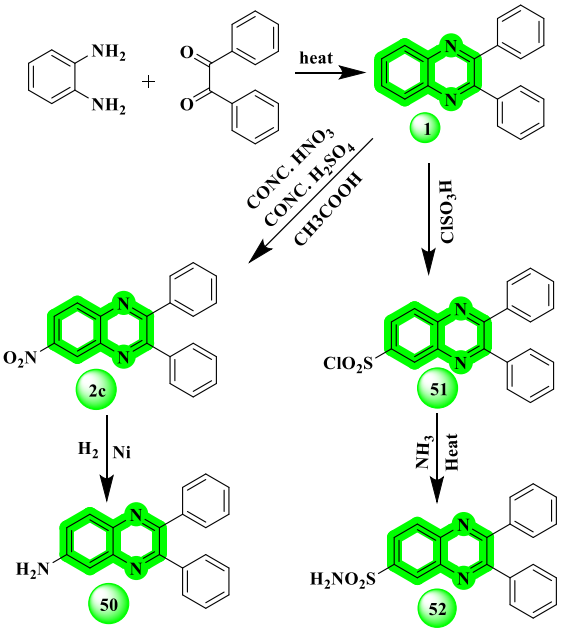
Mamdouh and some collaborators created a new series of quinoxaline-1,3,4-oxadiazole derivatives. 1-methyl-3-(5-thioxo-4,5-dihydro-1,3,4oxadiazol-2-yl)quinoxalin-2(1*H*)-one **45** was manufactured by reacting 4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carbohydrazide with carbon disulfide[68]. Compound **45** was further reacted with several 2-bromoacetophenone derivatives to produce 1-methyl-3-(5-(2-oxo-2-arylethylthio)-1,3, 4-oxadiazol-2-yl) quinoxaline-2 (1*H*)-one **47a-d**. Likewise, α-bromoketones reacted with mercaptoxadiazole **45** to obtain 1-methyl-3-(5-(2-oxo-2-(2-oxo-2*H*-chromen-3-yl)ethylthio)-1,3,4-oxadiazol-2-yl)quinoxalin2(1*H*)-one



Scheme 20. Synthetic strategy of quinoxaline 1,3,4-oxadiazole hybrids **46**, **47a-d**, **48a**,**b** and **49a**,**b**.

46. Moreover, compound **45** reacted with different 2-chloro-*N* arylacetamide to produce compounds **48a-f**. Furthermore, analog **45** was aminoacylated to produce mannich base **49a,b** (Scheme 20) **[69]**.

Some researchers created a new series of quinoxaline analogs. 2,3-diphenyl quinoxaline **1** was produced by reacting benzil with *O*-phenylenediamine, then compound **1** interacted with concentrated nitric acid in the presence of concentrated sulphuric acid to obtain 6-nitro-2,3-diphenyl quinoxaline **2b**, after that it reacted with nickel to produce 6-amino-2,3-diphenyl quinoxaline **50**. Moreover, compound **1** interacted with $ClSO_3H$ to produce 2,3-diphenyl quinoxaline-6-sulphonyl chloride **51**. Furthermore, it reacted with ammonia to produce 2,3-diphenylquinoxaline-6-sulphonamide **52** (Scheme 21) **[70].**



Scheme 31. Synthetic pathway to produce different quinoxaline analogs.

3. Conclusion

This review summarizes synthetic methods and structural modification of quinoxaline-based compounds, highlighting strategies that enhance their chemical diversity and synthetic accessibility. Special emphasis was placed on the influence of different substituents and reaction conditions on the efficiency and sustainability of synthetic routes. Although significant progress has been achieved, developing more environmentally friendly and scalable methods remains a critical challenge. Future efforts should optimize synthetic strategies to support the sustainable development of quinoxaline.

4. Acknowledgment

I would like to express my sincere gratitude to my colleague, Bassant Ibrahim, for her continuous support and encouragement. Her contribution has been truly appreciated.

5. Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

6. References

[1] J.A. Pereira, A.M. Pessoa, M.N.D. Cordeiro, R. Fernandes, C. Prudêncio, J.P. Noronha, M. Vieira, Quinoxaline, its derivatives and applications: A State of the Art Review, European Journal of Medicinal Chemistry 97 (2015) 664-672.

[2] M. Montana, F. Mathias, T. Terme, P. Vanelle, Anti-tumoral activity of quinoxaline derivatives: A systematic review, European Journal of Medicinal Chemistry 163 (2019) 136-147.

[3] S. Tariq, K. Somakala, M. Amir, Quinoxaline: An insight into the recent pharmacological advances, European Journal of Medicinal Chemistry 143 (2018) 542-557.

[4] G. Yashwantrao, S. Saha, Recent advances in the synthesis and reactivity of quinoxaline, Organic Chemistry Frontiers 8(11) (2021) 2820-2862.

[5] R. Ingle, R. Marathe, D. Magar, H.M. Patel, S.J. Surana, Sulphonamido-quinoxalines: Search for anti-cancer agent, European Journal of Medicinal Chemistry 65 (2013) 168-186.

[6] M.K. Ibrahim, I.H. Eissa, A.E. Abdallah, A.M. Metwaly, M. Radwan, M. ElSohly, Design, synthesis, molecular modeling and anti-hyperglycemic evaluation of novel quinoxaline derivatives as potential PPARγ and SUR agonists, Bioorganic & medicinal chemistry 25(4) (2017) 1496-1513.

[7] X. Tang, Q. Zhou, W. Zhan, D. Hu, R. Zhou, N. Sun, S. Chen, W. Wu, W. Xue, Synthesis of novel anti-bacterial and anti-fungal quinoxaline derivatives, RSC advances 12(4) (2022) 2399-2407.

[8] A.-G.A. El-Helby, R.R. Ayyad, K. El-Adl, A. Elwan, Quinoxalin-2 (1 H)-one derived AMPA-receptor antagonists: Design, synthesis, molecular docking and anti-convulsant activity, Medicinal Chemistry Research 26 (2017) 2967-2984.

[9] J. Cogo, V. Kaplum, D.P. Sangi, T. Ueda-Nakamura, A.G. Correa, C.V. Nakamura, Synthesis and biological evaluation of novel 2, 3-disubstituted quinoxaline derivatives as anti-leishmanial and anti-trypanosomal agents, European Journal of Medicinal Chemistry 90 (2015) 107-123.

[10] J. Soto-Sánchez, L.A. Caro-Gómez, A.D. Paz-González, L.A. Marchat, G. Rivera, R. Moo-Puc, D.G. Arias, E. Ramírez-Moreno, Biological activity of esters of quinoxaline-7-carboxylate 1, 4-di-N-oxide against E. histolytica and their analysis as potential thioredoxin reductase inhibitors, Parasitology research 119 (2020) 695-711.

[11] J. Cogo, J. Cantizani, I. Cotillo, D.P. Sangi, A.G. Correa, T. Ueda-Nakamura, B.P. Dias Filho, J.J. Martín, C.V. Nakamura, Quinoxaline derivatives as potential anti-trypanosomal and anti-leishmanial agents, Bioorganic & Medicinal Chemistry 26(14) (2018) 4065-4072.

[12] J. Chakraborty, A. Kanungo, T. Mahata, K. Kumar, G. Sharma, R. Pal, K.S. Ahammed, D. Patra, B. Majhi, S. Chakrabarti, Quinoxaline derivatives disrupt the base stacking of hepatitis C virus-internal ribosome entry site RNA: reduce translation and replication, Chemical Communications 55(93) (2019) 14027-14030.

[13] G. Cheng, W. Sa, C. Cao, L. Guo, H. Hao, Z. Liu, X. Wang, Z. Yuan, Quinoxaline 1, 4-di-N-oxides: biological activities and mechanisms of actions, Frontiers in pharmacology 7 (2016) 64.

[14] X. Jiang, K. Wu, R. Bai, P. Zhang, Y. Zhang, Functionalized quinoxalinones as privileged structures with broad-ranging pharmacological activities, European Journal of Medicinal Chemistry 229 (2022) 114085.

[15] A. Husain, D. Madhesia, Recent advances in pharmacological activities of quinoxaline derivatives, J. Pharm. Res 4(3) (2011) 924-929.

[16] M. Soleymani, M. Chegeni, The chemistry and applications of the quinoxaline compounds, Current Organic Chemistry 23(17) (2019) 1789-1827.

[17] O.O. Ajani, Present status of quinoxaline motifs: Excellent pathfinders in therapeutic medicine, European Journal of medicinal chemistry 85 (2014) 688-715.

[18] X. Wang, M.-A. Martínez, G. Cheng, Z. Liu, L. Huang, M. Dai, D. Chen, M.-R. Martínez-Larrañaga, A. Anadón, Z. Yuan, The critical role of oxidative stress in the toxicity and metabolism of quinoxaline 1, 4-di-N-oxides in vitro and in vivo, Drug Metabolism Reviews 48(2) (2016) 159-182.

[19] S.K. Suthar, N.S. Chundawat, G.P. Singh, J.M. Padrón, Y.K. Jhala, Quinoxaline: A comprehension of current pharmacological advancement in medicinal chemistry, European Journal of Medicinal Chemistry Reports 5 (2022) 100040.

[20] I. Ali, R. Bhatia, Green and Eco-friendly Synthetic Strategies for Quinoxaline Derivatives, Current Green Chemistry 11(1) (2024) 37-49.

[21] Y. Nageswar, K.H.V. Reddy, K. Ramesh, S.N. Murthy, Recent developments in the synthesis of quinoxaline derivatives by green synthetic approaches, Organic Preparations and Procedures International 45(1) (2013) 1-27.

[22] P.T. Anastas, M.M. Kirchhoff, Origins, current status, and future challenges of green chemistry, Accounts of chemical research 35(9) (2002) 686-694.

[23] P. Anastas, N. Eghbali, Green chemistry: principles and practice, Chemical Society Reviews 39(1) (2010) 301-312.

[24] M.R. Dintzner, P.R. Wucka, T.W. Lyons, Microwave-assisted synthesis of a natural insecticide on basic montmorillonite K10 Clay. Green chemistry in the undergraduate organic laboratory, Journal of chemical education 83(2) (2006) 270.

[25] A. Hasaninejad, A. Zare, M. Shekouhy, A. Reza Moosavi-Zare, Bentonite Clay K-10 as an Efficient Reagent for the Synthesis of Quinoxaline Derivatives at Room Temperature, Journal of Chemistry 6 (2009) S247-S253.

[26] B. Malek, İ. Bahammou, O. Zımou, A. El Hallaouı, R. Ghaılane, S. Boukhris, A. Souızı, Eco-friendly synthesis of quinoxaline derivatives using mineral fertilizers as heterogeneous catalysts, Journal of the Turkish Chemical Society Section A: Chemistry 7(2) (2020) 427-440.

[27] H. Khatoon, E. Abdulmalek, Novel synthetic routes to prepare biologically active quinoxalines and their derivatives: A synthetic review for the last two decades, Molecules 26(4) (2021) 1055.

[28] A. Amini, A. Fallah, A. Sedaghat, A. Gholami, C. Cheng, A.R. Gupta, Natural vs. synthetic phosphate as efficient heterogeneous compounds for synthesis of quinoxalines, International Journal of Molecular Sciences 22(24) (2021) 13665.

[29] H. Anahmadi, M. Fathi, Z. Benzekri, S. Sibous, B.C. El Idrissi, A. Souizi, S. Boukhris, Synthesis, characterization and application of α-Ca3 (PO4) 2 as a heterogeneous catalyst for the synthesis of 2.3-diphenylquinoxaline derivatives and knoevenagel condensation under green conditions, Journal of Molecular Structure 1248 (2022) 131449.

[30] R. Wang, R. Ramaraj, T. Okajima, F. Kitamura, N. Matsumoto, T. Thiemann, S. Mataka, T. Ohsaka, Electrochemical behavior of conjugated quinoxaline derivatives, Journal of Electroanalytical Chemistry 567(1) (2004) 85-94.

[31] S. Tariq, O. Alam, M. Amir, Synthesis, anti-inflammatory, p38α MAP kinase inhibitory activities and molecular docking studies of quinoxaline derivatives containing triazole moiety, Bioorganic Chemistry 76 (2018) 343-358.

[32] S. ul Hassan, M.A. Farid, Y. Wang, A series of lanthanide–quinoxaline-2, 3 (1 H, 4 H)-dione complexes containing 1D chiral Ln 2 O 3 (Ln= Eu, Tb, Sm, Dy) chains: luminescent properties and response to small molecules, RSC advances 11(53) (2021) 33309-33318.

[33] Z. An, L. Zhao, M. Wu, J. Ni, Z. Qi, G. Yu, R. Yan, FeCl 3-Catalyzed synthesis of pyrrolo [1, 2-a] quinoxaline derivatives from 1-(2-aminophenyl) pyrroles through annulation and cleavage of cyclic ethers, Chemical Communications 53(84) (2017) 11572-11575.

[34] R. Sarges, H.R. Howard, R.G. Browne, L.A. Lebel, P.A. Seymour, B.K. Koe, 4-Amino [1, 2, 4] triazolo [4, 3-a] quinoxalines. A novel class of potent adenosine receptor antagonists and potential rapid-onset anti-depressants, Journal of medicinal chemistry 33(8) (1990) 2240-2254.

[35] M. Montana, V. Montero, O. Khoumeri, P. Vanelle, Quinoxaline derivatives as anti-viral agents: a systematic review, Molecules 25(12) (2020) 2784.

[36] J.-P. Begue, D. Bonnet-Delpon, B. Crousse, Fluorinated alcohols: A new medium for selective and clean reaction, Synlett 2004(01) (2004) 18-29.

[37] J.F. Povey, C.M. Smales, S.J. Hassard, M.J. Howard, Comparison of the effects of 2, 2, 2-trifluoroethanol on peptide and protein structure and function, Journal of Structural Biology 157(2) (2007) 329-338.

[38] S. Khaksar, F. Rostamnezhad, A novel one-pot synthesis of quinoxaline derivatives in fluorinated alcohols, Bulletin of the Korean Chemical Society 33(8) (2012) 2581-2584.

[39] M. Faul, Organic Syntheses, Volume 94, John Wiley & Sons2018.

[40] S.B. Wadavrao, R.S. Ghogare, A.V. Narsaiah, A simple and efficient protocol for the synthesis of quinoxalines catalyzed by pyridine, Organic Communications 6(1) (2013) 23.

[41] S.V. Atghia, S.S. Beigbaghlou, Nanocrystalline titania-based sulfonic acid (TiO 2-Pr-SO 3 H) as a new, highly efficient, and recyclable solid acid catalyst for preparation of quinoxaline derivatives, Journal of Nanostructure in Chemistry 3 (2013) 1-8.

[42] M. Jafarpour, A. Rezaeifard, M. Danehchin, Easy access to quinoxaline derivatives using alumina as an effective and reusable catalyst under solvent-free conditions, Applied Catalysis A: General 394(1-2) (2011) 48-51.

[43] T.-k. Huang, R. Wang, L. Shi, X.-x. Lu, Montmorillonite K-10: an efficient and reusable catalyst for the synthesis of quinoxaline derivatives in water, Catalysis Communications 9(6) (2008) 1143-1147.

[44] B. Krishnakumar, M. Swaminathan, Solvent free synthesis of quinoxalines, dipyridophenazines and chalcones under microwave irradiation with sulfated Degussa titania as a novel solid acid catalyst, Journal of Molecular Catalysis A: Chemical 350(1-2) (2011) 16-25.

[45] A. Dhakshinamoorthy, K. Kanagaraj, K. Pitchumani, Zn2+-K10-clay (clayzic) as an efficient water-tolerant, solid acid catalyst for the synthesis of benzimidazoles and quinoxalines at room temperature, Tetrahedron letters 52(1) (2011) 69-73.

[46] R. Sharma, C. Sharma, Zirconium (IV)-modified silica gel: Preparation, characterization and catalytic activity in the synthesis of some biologically important molecules, Catalysis Communications 12(5) (2011) 327-331.

[47] X.Z. Zhang, J.X. Wang, Y.J. Sun, H.W. Zhan, Synthesis of quinoxaline derivatives catalyzed by PEG-400, Chinese Chemical Letters 21(4) (2010) 395-398.

[48] M.M. Heravi, K. Bakhtiari, F.F. Bamoharram, M.H. Tehrani, Wells-Dawson type heteropolyacid catalyzed synthesis of quinoxaline derivatives at room temperature, Monatshefte für Chemie-Chemical Monthly 138 (2007) 465-467.

[49] S. Ajaikumar, A. Pandurangan, Efficient synthesis of quinoxaline derivatives over ZrO2/MxOy (M= Al, Ga, In and La) mixed metal oxides supported on MCM-41 mesoporous molecular sieves, Applied Catalysis A: General 357(2) (2009) 184-192.

[50] A. Shaabani, A.H. Rezayan, M. Behnam, M. Heidary, Green chemistry approaches for the synthesis of quinoxaline derivatives: Comparison of ethanol and water in the presence of the reusable catalyst cellulose sulfuric acid, Comptes Rendus Chimie 12(12) (2009) 1249-1252.

[51] J.-J. Cai, J.-P. Zou, X.-Q. Pan, W. Zhang, Gallium (III) triflate-catalyzed synthesis of quinoxaline derivatives, Tetrahedron Letters 49(52) (2008) 7386-7390.

[52] C.S. Subrahmanyam, S. Narayanan, Synthesis of Quinoxalines in Presence of Zinc Triflate, Asian Journal of Chemistry 23(3) (2011) 1331.

[53] K.S. Kumar, D. Rambabu, S. Sandra, R. Kapavarapu, G.R. Krishna, M.B. Rao, K. Chatti, C.M. Reddy, P. Misra, M. Pal, AlCl3 induced (hetero) arylation of 2, 3-dichloroquinoxaline: a one-pot synthesis of mono/disubstituted quinoxalines as potential anti-tubercular agents, Bioorganic & medicinal chemistry 20(5) (2012) 1711-1722.

[54] K.S. Kumar, D. Rambabu, S. Sandra, R. Kapavarapu, G.R. Krishna, M.B. Rao, K. Chatti, C.M. Reddy, P. Misra, M. Pal, AlCl3 induced (hetero) arylation of 2, 3-dichloroquinoxaline: a one-pot synthesis of mono/disubstituted quinoxalines as potential anti-tubercular agents, Bioorganic & medicinal chemistry 20(5) (2012) 1711-1722.

[55] P.V. Babu, S. Mukherjee, G.S. Deora, K.S. Chennubhotla, R. Medisetti, S. Yellanki, P. Kulkarni, S. Sripelly, K.V. Parsa, K. Chatti, Ligand/PTC-free intramolecular Heck reaction: synthesis of pyrroloquinoxalines and their evaluation against PDE4/luciferase/oral cancer cell growth in vitro and

zebrafish in vivo, Organic & Biomolecular Chemistry 11(39) (2013) 6680-6685.

[56] H. Khatoon, E. Abdul Malek, S.M. Faudzi, Y. Rukayadi, Synthesis of a series of quinoxaline derivatives and their anti-bacterial effectiveness against pathogenic bacteria, ChemistrySelect 9(7) (2024) e202305073.

[57] O.S. Moustafa, M.Z. Badr, T.I. El-Emary, New fused quinoxalines: Synthesis and reactions of pyrimidothienoquinoxaline and oxadizolylthienoquinoxalines, Bulletin-Korean Chemical Society 23(4) (2002) 567-570.

[58] P. Ledwon, R. Motyka, K. Ivaniuk, A. Pidluzhna, N. Martyniuk, P. Stakhira, G. Baryshnikov, B.F. Minaev, H. Ågren, The effect of molecular structure on the properties of quinoxaline-based molecules for OLED applications, Dyes and pigments 173 (2020) 108008.

[59] Y. Lysandrou, T. Newsome, K. Duty, O. Mohamed, J.T. Markiewicz, Synthesis, optical and electronic studies of a "clickable" quinoxaline-based pH sensor, Journal of Photochemistry and Photobiology A: Chemistry 433 (2022) 114183.

[60] S. Jaiswal, N. Arya, D. Kishore, J. Dwivedi, S. Sharma, Exploring Azetidine Containing Heterocycles: From green synthesis to applications, Tetrahedron (2025) 134491.

[61] B.R. Vancha, M. Sreeshitha, K.P. Vasikarla, S.S. Vyshnava, V. Srikanth, M. Makhkamov, J. Razzokov, A. Islam, P.V.G. Reddy, New quinoxaline-oxadiazole hybrids as tubulin inhibitors: Synthesis, cytotoxicity, and molecular dynamics simulations, Journal of Molecular Structure 1322 (2025) 140355.

[62] S. Mahajan, V. Sharma, R.P. Sharma, Y. Saini, V.K. Gupta, K.K. Kapoor, Synthesis, structural elucidation, physico-chemical quantum properties and in silico interaction analysis of 2-methyl-3-((4-nitrobenzyl) oxy) quinoxaline, Journal of Molecular Structure 1295 (2024) 136654.

[63] M. Kothari, K. Kannan, R. Sahadevan, S. Sadhukhan, Novel molecular hybrids of EGCG and quinoxaline: Potent multi-targeting anti-diabetic agents that inhibit α-glucosidase, α-amylase, and oxidative stress, International Journal of Biological Macromolecules 263 (2024) 130175.

[64] B. Wang, R. Gao, X. Geng, J. Wang, L. Wang, H. Chen, B. Zhu, Photocatalyzed C3-α-aminoalkylation of quinoxalin-2 (1H)-ones with amino acid-derived oxime esters under metal-free conditions, Molecular Catalysis 573 (2025) 114795.

[65] G. Westphal, H. Wasicki, U. Zielinski, F. Weber, M. Tonew, E. Tonew, Potential virostatics. 1. Quinoxalines, Die Pharmazie 32(10) (1977) 570-571.

[66] M. Ali, M. Ismail, M. El-Gaby, M. Zahran, Y. Ammar, Synthesis and anti-microbial activities of some novel quinoxalinone derivatives, Molecules 5(6) (2000) 864-873.

[67] M.M. Badran, A.A. Moneer, H.M. Refaat, A.A. El-Malah, Synthesis and anti-microbial activity of novel quinoxaline derivatives, Journal of the Chinese Chemical Society 54(2) (2007) 469-478.

[68] E.A. Ahmed, M.F. Mohamed, O.A. Omran, Novel quinoxaline derivatives as dual EGFR and COX-2 inhibitors: synthesis, molecular docking and biological evaluation as potential anti-cancer and anti-inflammatory agents, RSC advances 12(39) (2022) 25204-25216.

[69] M.F. Mohamed, E.A. Ahmed, O. Alshazly, O.A. Omran, R.A. Soomro, A. Nafady, Synthesis, anti-cancer and anti-inflammatory evaluation of novel quinoxaline-1, 3, 4-oxadiazole derivatives as EGFR and COX-2 inhibitors, Journal of Molecular Structure (2025) 141651.

[70] G. Meka, R. Chintakunta, Analgesic and anti-inflammatory activity of quinoxaline derivatives: design synthesis and characterization, Results in Chemistry 5 (2023) 100783.