The Pharmaceutical and Chemical Journal, 2023, 10(3):137-147

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Quinoxaline Derivatives: Synthesis and Biological Significance

Ridhima Chauhan, N. S. Chundawat and Girdhar Pal Singh

Department of Chemistry, Bhupal Nobles' University, Udaipur-313001, India
Email id: girdharpal@gmail.com

Abstract Quinoxaline is a well-known and important nitrogen-containing heterocyclic compound with a complex ring consisting of a benzene ring and a pyrazine ring. Different modified quinoxalines and their derivatives with various functional groups are an important part of biological science, and important research projects are introduced in this course. Many methods have been developed to combine them. The demonstration that many quinoxaline derivatives have many biological activities encourages research in this field. There are many useful drugs such as antibiotics, antibiotics, antibiotics, antibiotics, antibiotics, disease antibiotics, antiviral drug, antiviral drug, antiviral drug, antiviral drug. For this reason, a large number of such quinoxalines prepared using different synthetic methods have been described in the medical literature. This review gives an idea about the synthesis and biological activities of quinoxalines.

Keywords Quinoxaline, pharmaceuticals, anticancer, kinase inhibitory activities, dehydrogenative coupling

1. Introduction

Quinoxaline is a heterocyclic compound consisting of a benzene ring fused with a pyrazine ring [1]. It is a bicyclic molecule with molecular formula $C_8H_6N_2$ Figure 2.1. Quinoxaline is known for its diverse range of applications in various fields including chemistry [2], pharmaceuticals [3], and materials science [4].

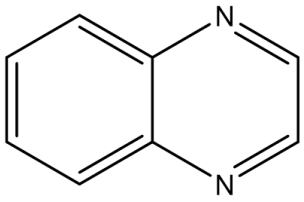
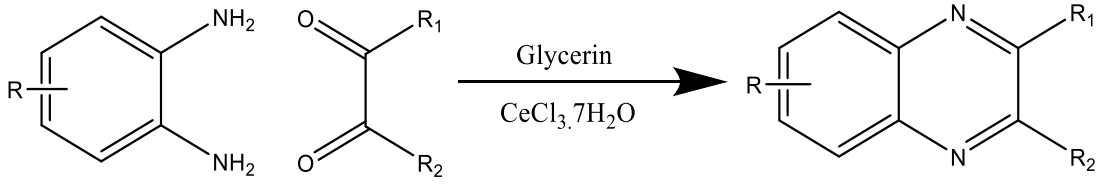


Figure 1: Structure of Quinoxaline

In terms of its chemical structure, quinoxaline possesses an aromatic character due to the presence of conjugated double bonds in the benzene and pyrazine rings. This molecular arrangement contributes to its stability and reactivity [5]. Quinoxaline derivatives can be synthesized by various methods, including condensation reactions and cyclizations [2]. Quinoxalines are a versatile class of nitrogen-containing heterocyclic compounds, and they constitute useful intermediates in organic synthesis [6]. Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including antimicrobial [7], antiviral [8], anti-inflammatory [9], anticancer [10], and kinase inhibitory activities. [11]

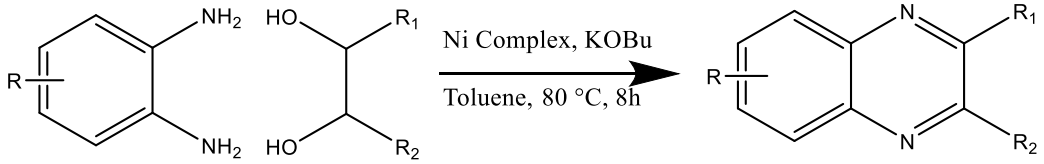
1. General methods for synthesis of Quinoxaline.

Scheme 1- In a typical experiment, equimolar amounts of benzil and 1,2-phenylenediamine were reacted in glycerine (2 ml) using $CeCl_3.7H_2O$ as catalyst to obtain the corresponding product 2,3-diphenylquinoxaline in excellent yields, as shown in the Scheme 1.1. [11]. The reaction medium was recovered and reused for further reactions without any problem.



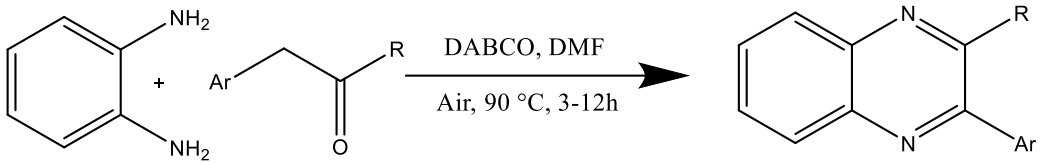
Scheme 1. General reaction for the synthesis of quinoxalines with aromatic-1,2-diamines.

Scheme 2: An efficacious, nickelcatalyzed synthesis of important heterocycle quinoxazline. In a typical reaction, a 5 ml vial was charged with ethanediol (1.1 mmol), o-phenylenediamine (1 mmol), KO^{t}Bu (0.5 mmol), and bis-(azophenolate) nickel complex (5 mol %) in 2 ml toluene and was closed with a rubber septum. The resulting solution was kept under a O_2-filled balloon added to the neck of the reaction flask. The reaction mixture was stirred at 80 °C for 8 h. The reaction mixture was cooled to room temperature upon completion. Desired product was obtained with 70% yield [12].



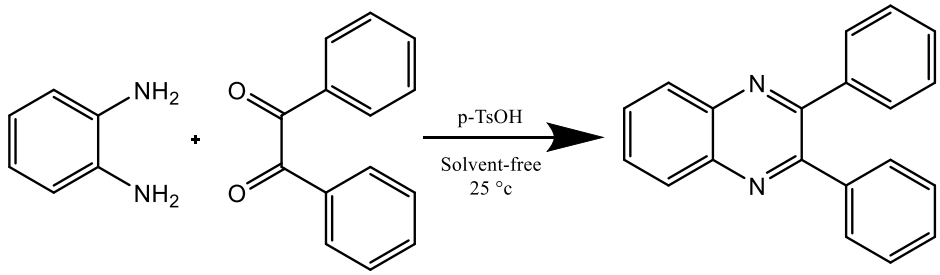
Scheme 2: General reaction for the synthesis of quinoxalines via dehydrogenative coupling.

Scheme 3- Aerobic oxidation of deoxybenzoins could be efficiently catalyzed by 1,4-diazabicyclo [2.2.2]octane (DABCO) with air as the sole oxidant to give the corresponding benzils in excellent yields [13]. A mixture of ketone 1 (0.5 mmol) and DABCO (0.2 eq) in DMF (1.5 ml) was stirred at 90 °C for 12 h in air.



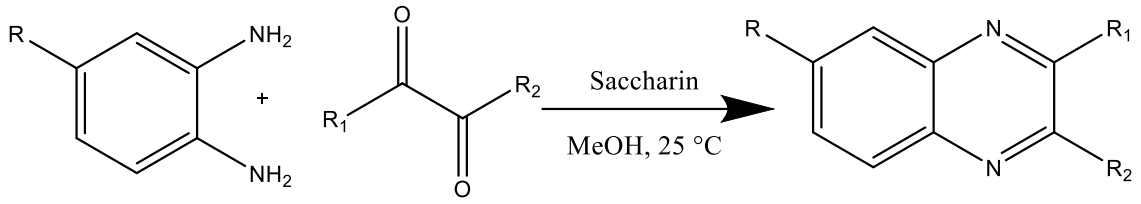
Scheme 3: One-Pot Synthesis of Quinoxalines from Benzyl Ketones and o-Phenylenediamines.

Scheme 4- A series of quinoxaline derivatives were efficiently synthesized in excellent yields by the reaction of 1,2-diamines and 1,2-diketones with grinding catalyzed by p-toluenesulfonic acid under solvent-free conditions at room temperature [14]. 1,2-Diamine(1 mmol), 1,2-diketone(1 mmol), and p-TsOH (0.1 mmol) were added to a mortar. The mixture was ground by mortar and pestle at room temperature for 1–5 min and was kept at room temperature for a period.



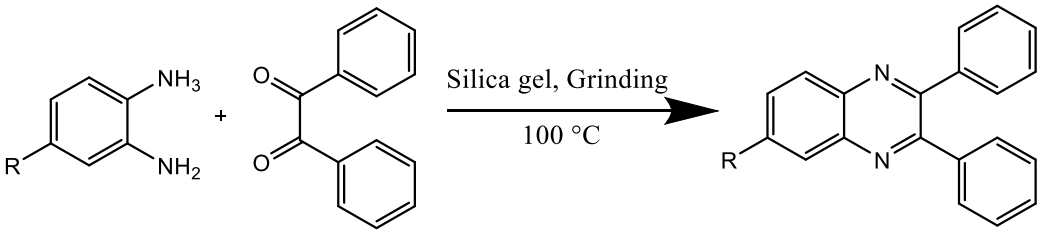
Scheme 4: The synthesis of 2,3-diphenylquinoxaline.

Scheme 5- A safe and economical process for the catalytic synthesis of quinoxaline from 1,2-arylenediamines and 1,2- dicarbonyl compounds at room temperature. The reusability of saccharin, a catalyst easy to handle, its availability and commercial low cost, its environmental acceptability and absence of toxicity, the mild reaction conditions, and the short reaction times are the strong practical points of the presented method. To the required 1,2-dicarbonyl (10 mmol) in methanol (10 ml) were successively added saccharin (92 mg, 0.5 mmol) and the required 1,2-arylenediamine (10 mmol). The mixture was stirred for the appropriate time at room temperature, and poured into water (10 ml). The solid was collected by filtration and dried to afford the product [15].



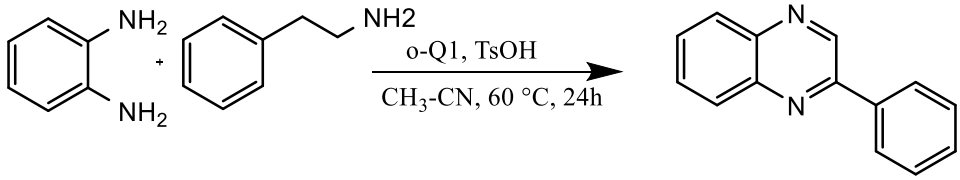
Scheme 5: General Procedure for the Quinoxalines

Scheme 6- A mixture of 1,2-dicarbonyl (1 mmol), 1,2-diamine (1 mmol), and 1.0 g of silica gel were taken in a mortar and ground with a pestle thoroughly at room temperature for 15 min. After the completion of the reaction, $CHCl_3$ was added to dissolve the product. Silica gel was filtered off, and the solvent was evaporated under vacuum to give the crude products, which were crystallized from ethanol [16].



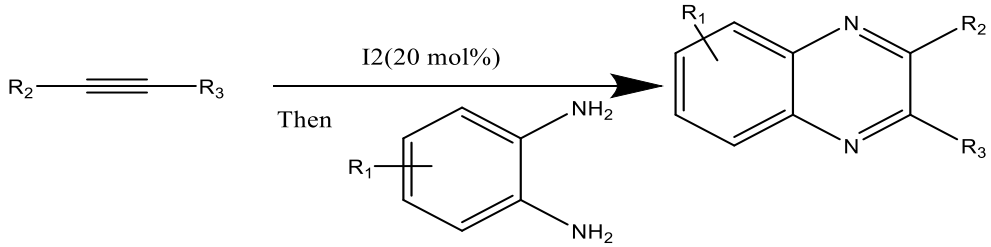
Scheme 6: Synthesis of quinoxalines from benzil with 1,2-diamines.

Scheme 7- The oxidative coupling of 2-phenethylamine and o-aminoaniline as the model substrates to synthesize quinoxaline. 4-Methoxy-5-tert-butyl-o-quinone (o-Q1) (10 mol %) was a catalyst in acetonitrile at 60 °C and , TsOH (10 mol %) was added. The reaction afforded quinoxaline as the major product 24 h and benzimidazole as a minor product [17].



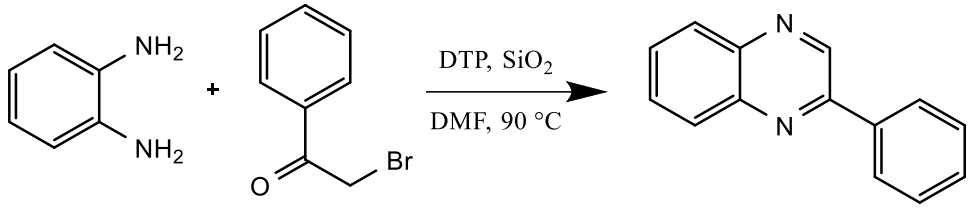
Scheme 7: Synthesis of quinoxalines by oxidative coupling of 2-phenethylamine.

Scheme 8- The reaction of 1,2-diphenylethyne in the presence of 20 mol% of iodine as the catalyst in DMSO at 130 °C for 24 h followed by addition of 1.5 equiv. of o-phenylenediamine at room temperature for 1 h afforded the product in 92% yield [18].



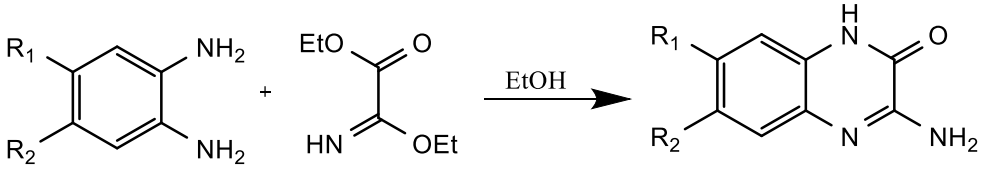
Scheme 8: Iodine-catalyzed one-pot synthesis of quinoxaline

Scheme 9- A mixture of phenacyl bromide (0.001 moles) and DTP/SiO_2 (20 mole%) was stirred in 10 ml DMF solvent at room temperature for 5 min. Then o-phenylenediamine (0.001 moles) was added slowly and the resultant mixture was stirred for 10 min at room temperature and heated for a stipulated time [19].



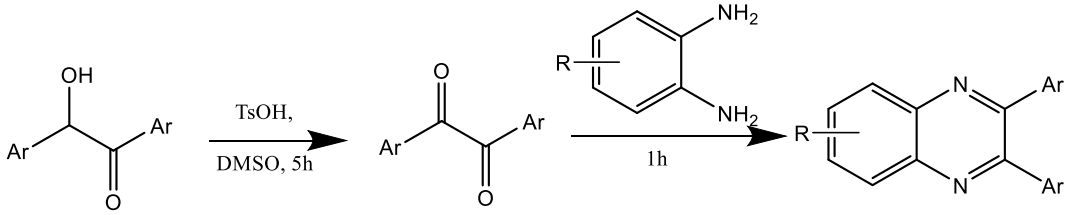
Scheme 9: Synthesis of quinoxalines using DTP/SiO_2 catalyst.

Scheme 10- Reaction of the hydrochloride salt of Ethyl carboethoxyformimidate with 1,2-phenyl-enediamine gave only polymeric material. When the free imidate was used, however, reaction proceeded smoothly but slowly at room temperature when ethanol was used as solvent. At reflux temperature reaction was complete after one hour, and 3-aminoquinoxalin-2(1*H*)-one was obtained in quantitative yield [20].



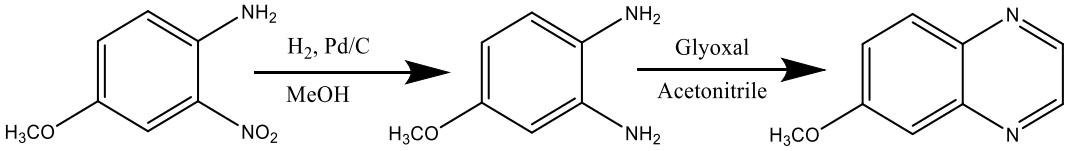
Scheme 10: Synthesis of quinoxalin.

Scheme 11- In a round bottom flask 1,2-diaryl-2-hydroxyethanone (1.0 mmol) and p-Toluenesulfonic acid (0.5 mmol) were taken and solvent DMSO (2 ml) was also added. The reaction mixture was then heated to 100 ^oC for 5h. To monitor progress of reaction TLC was checked and then o-diaminobenzene (1 mmol) was added to the reaction mixture. After 1h the reaction gets complete and desired product is obtained [21].



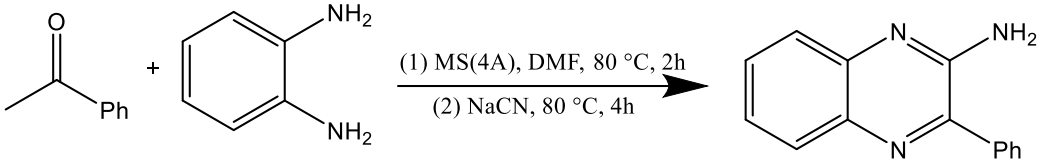
Scheme 11: PTSA-catalyzed One-pot Synthesis of Quinoxalines.

Scheme 12- 4-Methoxy-2-nitroaniline (16.8 g, 0.1 mol) was dissolved in methanol (200 ml) and hydrogenated in Parr hydrogenator using 10% Pd/C catalyst at 60^oC for 6h. After cooling, the reaction mass was filtered to separate the catalyst and then concentrated in rotavapour. 4-Methoxy-1,2-phenylenediamine so obtained was dissolved in acetonitrile (350 ml) and to this solution was added glyoxal (40%, 32.0 ml, 2.6 mol). The reaction mixture was then stirred at 60^oC for 6h and cooled [22].



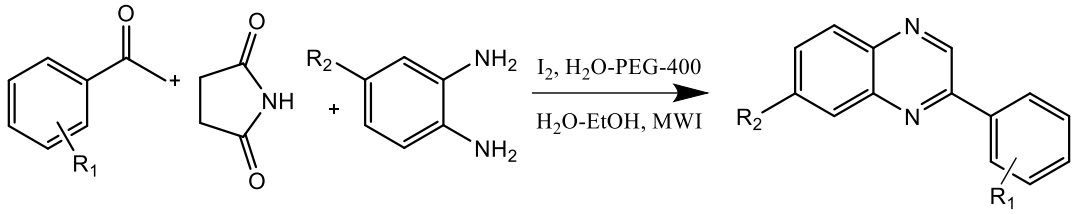
Scheme 12: Synthesis of 6-methoxyquinoxaline.

Scheme 13- 1,2-Phenylenediamine (0.20 mmol; 1.0 equiv) and aldehyde (0.22 mmol; 1.1 equiv) and the 4A molecular sieve (10 mg) were dissolved in DMF (1.0 ml). The reaction mixture was stirred at 80 °C in an open flask for 2h and monitored by TLC. On the complete consumption of compound, NaCN (11 mg; 0.22 mmol; 1.1 equiv) was added to the above reaction mixture with continue heating at 80'c for 4h to obtain the desired product [23].



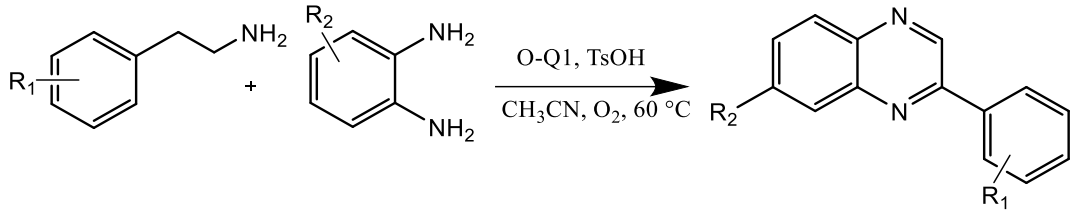
Scheme 13: One-Pot Cyanide-Based synthesis of quinoxalines.

Scheme 14- A mixture of succinamide (1.2 mmol) in water–PEG-400 (1:2), silver iodide (1.5 mmol), catalytic amount of iodine, and substituted acetophenone (1 mmol) stirred at room temperature till homogeneous to added iodine (20 mol%) and were microwave irradiated power at 350 W at 95–100 °C. Progress of the reaction was monitored on thin-layer chromatography (TLC) to obtain α-iodo acetophenone, then 1,2-diphenylamine (1 mmol) and water-ethanol (1:1) were added to the reaction mixture and irradiated for appropriate time and power 300 W at 90 °C [24].



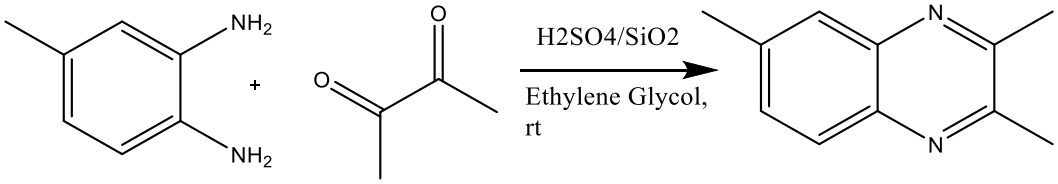
Scheme 14: One-pot multicomponent microwave-assisted green synthesis of Quinoxaline.

Scheme 15- In a borosil round bottom flask Substituted phenylenediamine (0.20 mmol), Substituted phenethylamine (0.20 mmol) were dissolved in Acetonitrile (1.0 ml). To the above reaction mixture ortho-quinone (10 mol %), p-Toluenesulfonic acid (20 mol %) were added with O2 balloon. Then the reaction mixture was heated at 60 °C for about 36 h. The reaction was monitored using analytical techniques and the reaction was switched off after completion. The desired product was further purified [17].



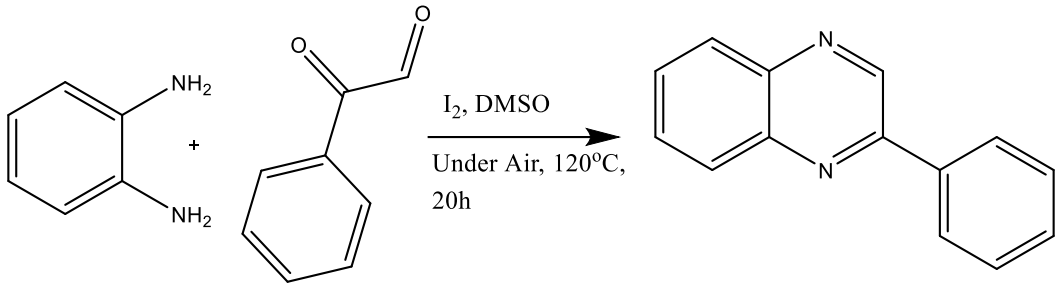
Scheme 15: Oxidative Synthesis of Quinoxalines by ortho-Quinone Catalysis.

Scheme 16: To a mixture of an appropriate o-phenylenediamine (1 mmol, 0.108 g) and a 1,2-dicarbonyl compound (1 mmol) in ethylene glycol (3 ml), a catalytic amount of H2SO4/SiO2 (0.3 g) was added and the mixture was stirred at room temperature [25].



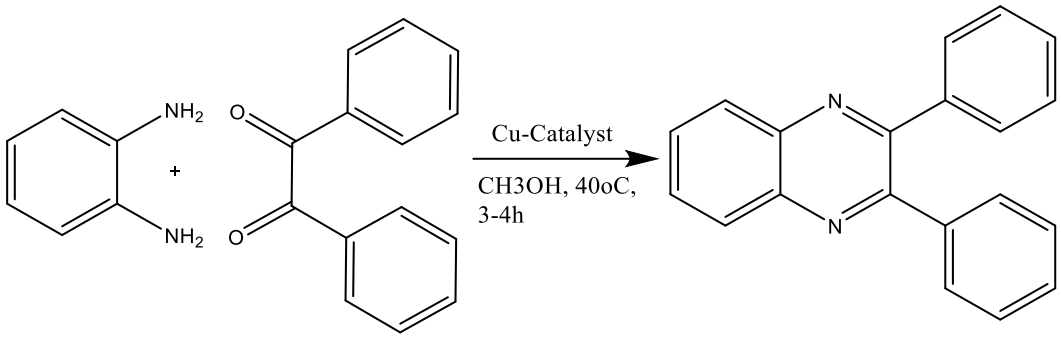
Scheme 16: Synthesis of quinoxaline derivatives using α-diketones.

Scheme 17: Synthesis of 2-aryquinoxalines from o-phenylenediamines and aryl methyl ketones in the presence of molecular-iodine was demonstrated. The reaction occurred at 120 °C, under air for 20h in DMSO [26].



Scheme 17: I_2 catalysed sunthesis of quinoxaline.

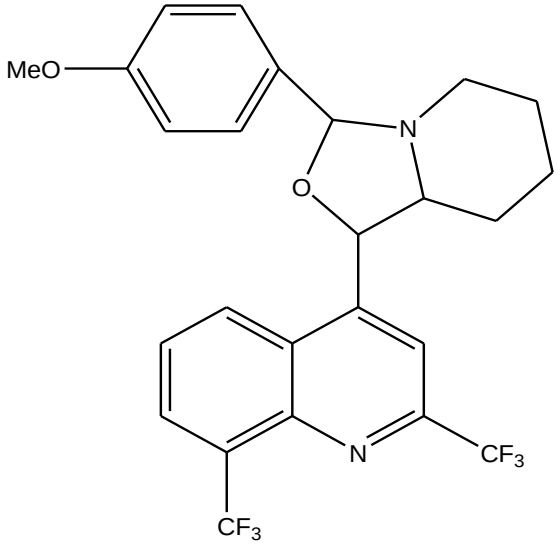
Scheme 18: A mixture of substituted benzil (1 mmol), o-phenylene diamine (1 mmol), copper catalyst (2.5 mol%) and methanol (3 mL) was taken in a 50 mL round bottom flask and heated in an oil bath at 40 oC with proper stirring on a magnetic stirrer for 3-4h [27].



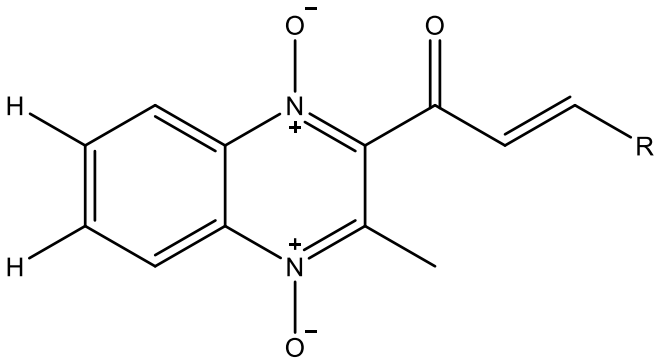
Scheme 18: Copper catalysed synthesis of quinoxaline.

2. Biological activity of Quinoxaline

Anticancer activity: A series Quinoxaline–oxazolidine derivatives, 4- [3-(aryl)hexahydro [1,3]oxazolo [3,4-a]pyridin-1-yl]-2,8-bis(trifluoromethyl)quinolines, derived from (R*, S*)-(±)-mefloquine and arenealdehydes, have been evaluated for their activity against four cancer cell lines (HCT-8, OVCAR-8, HL-60, and SF-295) [28].

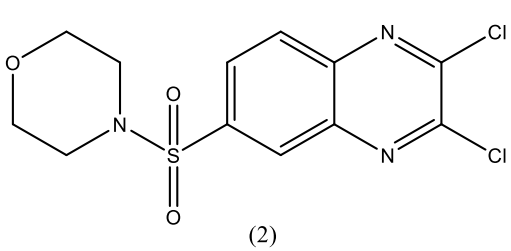


Antimalarial activity: Eighteen quinoxaline and quinoxaline 1,4-di-N-oxide derivatives have been synthesized with the aim of studying their antimalarial activity. The SAR study suggested that the chalcone and inverted chalcone moieties can act as useful linkers in the search for antimalarial ligands. Compounds 1a and 2a showed the best antiplasmodial activity [29].

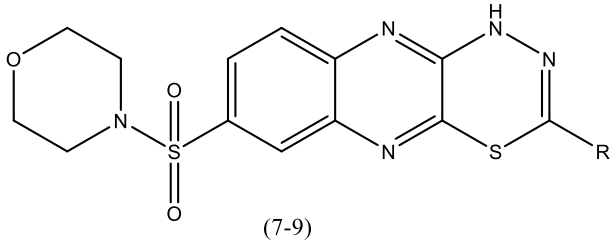


(1a,2a)

Antimicrobial activity: compounds showed moderate to good antimicrobial activities. Compounds 2, 7, 9, 10, 12 and 13c showed a significant antimicrobial activities with MICs value (1.95–31.25) µg/ mL. The results of antimicrobial activity revealed that compounds can inhibit the growth of the selected microorganisms with MIC values between 1.95 and 333 µg/mL. All the synthesized compounds exhibited adequate to good potential against various microbes [30].

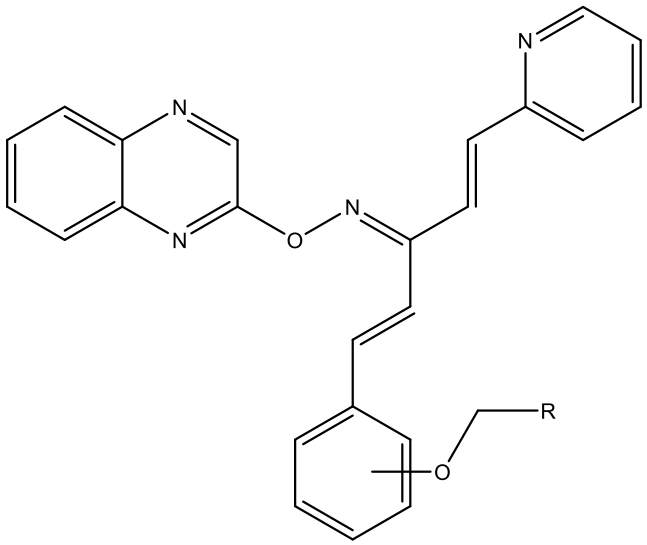


(2)



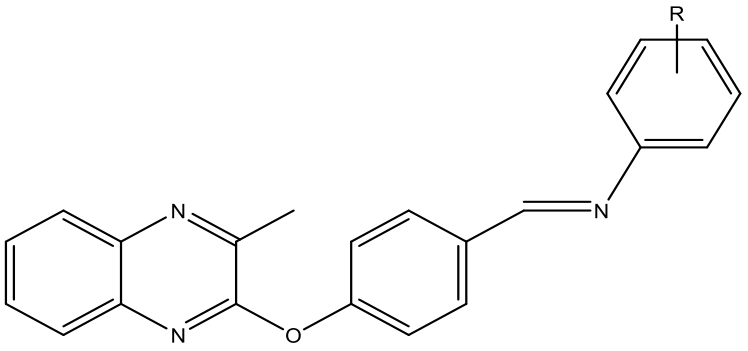
(7-9)

Anti-viral activity: a series of penta-1,4-dien-3-one oxime derivatives containing quinoxaline fragments in order to obtain novel and efficient agents with better biological activities. Their biological activities against TMV, Xac, Xoo and Rs were evaluated. The action mechanism of the title compounds against plant bacteria and virus has been studied. Compound **6i** showed remarkable curative, protective and inactivation activity [31].

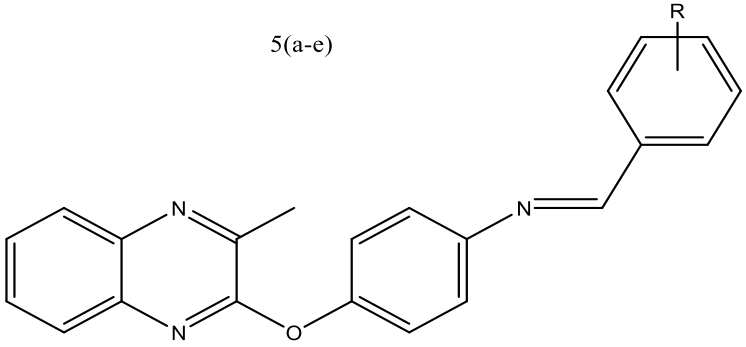


Antibacterial activity: The antibacterial activity was determined by the disc diffusion method at the concentration of 50 µg per disk. All the synthesized compounds were tested in vitro for their antibacterial activity against microorganisms such as Staphylococcus aureus, Bacillus subtilis (Gram positive), Escherichia coli, Pseudomonas

aeruginosa (Gram negative), using ciprofloxacin as standard antibacterial. Compounds **5a, 5c, 5d, 5e, 7a** and **7c** were highly active against both Gram positive and Gram negative bacteria [32].

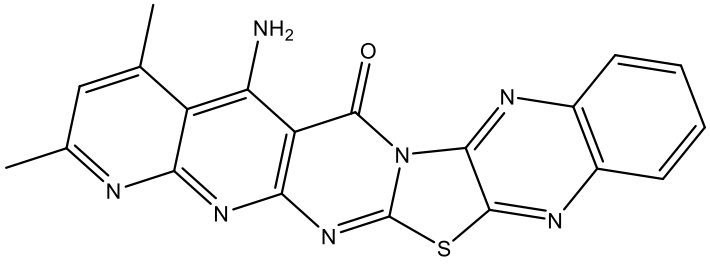


5(a-e)



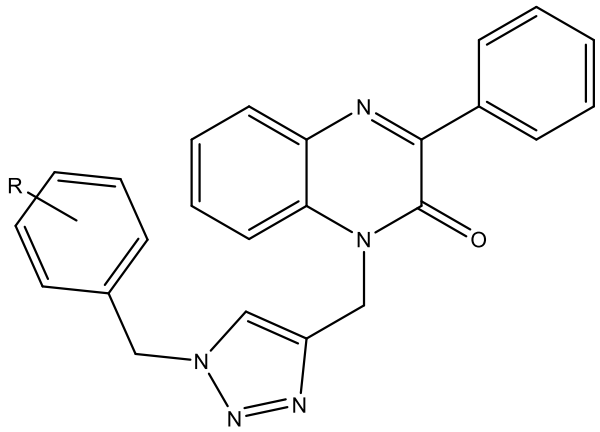
7(a-e)

Analgesic activity: The analgesic activity was determined by the hot-plate test (central analgesic activity) and acetic acid induced writhing assay. The results revealed that all tested compounds exhibited significant activity. Most of the tested compounds have nearly the same activity as the reference drug, and the remaining tested compounds have good activities in central analgesic activity. Also, compound **10** exhibited activities higher than the reference drug in peripheral analgesic activity testing. The remaining compounds have the same activity in peripheral analgesic activity testing [33].



(10)

Antihyperglycemic activity: Derivatives exhibited hypoglycemic activity. A model of insulin resistance is established by high glucose induction in LO2 cells, which is used to detect the effect of synthetic derivatives on changes in the level of glucose in the model. The study showed that, of the tested compounds, the activities of **5i** and **6b** were better than those of the lead compounds and comparable to that of the positive control Pioglitazone [34].



Compound	R
5i	p-br
6b	m-F

Conclusion

In conclusion, Quinoxaline derivatives are an important class of heterocycle compounds, where N replaces some carbon atoms in the ring of naphthalene [35]. Its molecular formula is $C_8H_6N_2$, formed by the fusion of two aromatic rings, benzene and pyrazine. It is rare in natural state, but their synthesis is easy to perform. By modifying quinoxaline structure it is possible to obtain a wide variety of biomedical applications, namely antimicrobial activities and chronic and metabolic diseases treatment.

The conclusive importance of quinoxaline lies in its diverse array of biological activities, making them important in the field of pharmaceuticals [8]. These compounds have been studied for their potential as antibacterial, antifungal, antiviral, antitumor, and anti-inflammatory agents [36]. The presence of nitrogen atoms in the heterocyclic ring system allows for interactions with biological targets, leading to diverse pharmacological effects.

References:

[1]. Taek Han, Y., J.-W. Jung, and N.-J. Kim, *Recent advances in the synthesis of biologically active cinnoline, phthalazine and quinoxaline derivatives.* Current Organic Chemistry, 2017. 21(14): p. 1265-1291.

[2]. Nageswar, Y., et al., *Recent developments in the synthesis of quinoxaline derivatives by green synthetic approaches.* Organic Preparations and Procedures International, 2013. 45(1): p. 1-27.

[3]. Irfan, A., et al., *A review on biological studies of Quinoxaline derivatives.* World J Pharm Pharmaceu Sci, 2017. 6(2): p. 11-30.

[4]. Hendrich, C.M., et al., *Homogeneous and heterogeneous gold catalysis for materials science.* Chemical Reviews, 2020. 121(14): p. 9113-9163.

[5]. Achelle, S., C. Baudequin, and N. Plé, *Luminescent materials incorporating pyrazine or quinoxaline moieties.* Dyes and Pigments, 2013. 98(3): p. 575-600.

[6]. Amin, A., et al., *A Review on The Medicinal And Industrial Applications of N-Containing Heterocycles.* The Open Medicinal Chemistry Journal, 2022. 16(1).

[7]. Vieira, M., et al., *Antimicrobial activity of quinoxaline 1, 4-dioxide with 2-and 3-substituted derivatives.* Microbiological Research, 2014. 169(4): p. 287-293.

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

[9]. Burguete, A., et al., *Synthesis and biological evaluation of new quinoxaline derivatives as antioxidant and anti-inflammatory agents.* Chemical biology & drug design, 2011. 77(4): p. 255-267.

[10]. Noolvi, M.N., et al., *Synthesis and in vitro antitumor activity of substituted quinazoline and quinoxaline derivatives: search for anticancer agent.* European journal of medicinal chemistry, 2011. 46(6): p. 2327-2346.
[11]. Narsaiah, A.V. and J.K. Kumar, *Glycerin and CeCl3· 7H2O: A new and efficient recyclable reaction medium for the synthesis of quinoxalines.* Synthetic Communications, 2012. 42(6): p. 883-892.
[12]. Bains, A.K., V. Singh, and D. Adhikari, *Homogeneous nickel-catalyzed sustainable synthesis of quinoline and quinoxaline under aerobic conditions.* The Journal of Organic Chemistry, 2020. 85(23): p. 14971-14979.
[13]. Qi, C., et al., *DABCO-catalyzed oxidation of deoxybenzoins to benzils with air and one-pot synthesis of quinoxalines.* Synthesis, 2011. 2011(03): p. 387-396.
[14]. Shi, D.-Q. and G.-L. Dou, *Efficient synthesis of quinoxaline derivatives catalyzed by p-toluenesulfonic acid under solvent-free conditions.* Synthetic Communications®, 2008. 38(19): p. 3329-3337.
[15]. Lassagne, F., F. Chevallier, and F. Mongin, *Saccharin as an organocatalyst for quinoxalines and pyrido [2, 3-b] pyrazines syntheses.* Synthetic Communications, 2014. 44(1): p. 141-149.
[16]. Nandi, G.C., et al., *Silica-gel–catalyzed efficient synthesis of quinoxaline derivatives under solvent-free conditions.* Synthetic Communications®, 2011. 41(3): p. 417-425.
[17]. Zhang, R., et al., *Oxidative synthesis of benzimidazoles, quinoxalines, and benzoxazoles from primary amines by ortho-quinone catalysis.* Organic letters, 2017. 19(20): p. 5629-5632.
[18]. Zi, J., et al., *Synthesis of quinoxalines through iodine-catalyzed one-pot annulation of alkynes with o-phenylenediamines.* Synthetic Communications, 2018. 48(8): p. 915-920.
[19]. Hebade, M.J., T.R. Deshmukh, and S.T. Dhumal, *Silica supported dodecatungstophosphoric acid (DTP/SiO_2): An efficient and recyclable heterogeneous catalyst for rapid synthesis of quinoxalines.* Synthetic Communications, 2021. 51(16): p. 2510-2520.
[20]. McKillop, A., et al., *Applications of ethyl carboethoxyformimidate to heterocyclic synthesis: Preparation of condensed pyrazinones and 1, 4-oxazinones.* Synthesis, 1997. 1997(03): p. 301-304.
[21]. Zhang, Z., et al., *PTSA-catalyzed one-pot synthesis of quinoxalines using DMSO as the oxidant.* Synthetic Communications, 2016. 46(18): p. 1507-1518.
[22]. Jagtap, A.R., et al., *The synthesis and characterization of novel coumarin dyes derived from 1, 4-diethyl-1, 2, 3, 4-tetrahydro-7-hydroxyquinoxalin-6-carboxaldehyde.* Dyes and Pigments, 2009. 82(1): p. 84-89.
[23]. Cho, Y.-H., K.-H. Kim, and C.-H. Cheon, *Synthesis of 2-aminoquinoxalines via one-pot cyanide-based sequential reaction under aerobic oxidation conditions.* The Journal of Organic Chemistry, 2014. 79(3): p. 901-907.
[24]. Jadhav, S.A., et al., *Expeditious one-pot multicomponent microwave-assisted green synthesis of substituted 2-phenyl Quinoxaline and 7-bromo-3-(4-ethylphenyl) pyrido [2, 3-b] pyrazine in water–PEG and water–ethanol.* Synthetic Communications, 2017. 47(18): p. 1661-1667.
[25]. Bashirzadeh, M. and F.K. Behbahani, *Green synthesis of quinoxaline derivatives at room temperature in ethylene glycol with H2SO4/SiO2 catalyst.* European Chemical Bulletin, 2020. 9(1): p. 33-37.
[26]. Van Tien, H., B.T. Ha, and N. Van Hoa, *Molecular iodine for the synthesis of 2-arylquinoxalines.* Journal of Science Technology and Food, 2022. 22(3): p. 66-79.
[27]. Saha, B., et al., *Organo-Cu (II) Catalyst: An efficient synthesis of substituted n-heterocycles via double condensation/tandem oxidation-cyclization/elimination-cyclization reactions from easily accessible precursors.* Rasayan Journal of Chemistry, 2021. 14(4).
[28]. Rodrigues, F.A., et al., *Mefloquine–oxazolidine derivatives: a new class of anticancer agents.* Chemical biology & drug design, 2014. 83(1): p. 126-131.
[29]. Gil, A., et al., *Synthesis, biological evaluation and structure-activity relationships of new quinoxaline derivatives as anti-Plasmodium falciparum agents.* Molecules, 2014. 19(2): p. 2166-2180.
[30]. Ammar, Y.A., et al., *Antimicrobial evaluation of thiadiazino and thiazolo quinoxaline hybrids as potential DNA gyrase inhibitors; design, synthesis, characterization and morphological studies.* Bioorganic Chemistry, 2020. 99: p. 103841.

[31]. Xia, R., et al., *Synthesis, antiviral and antibacterial activities and action mechanism of penta-1, 4-dien-3-one oxime ether derivatives containing a quinoxaline moiety.* New Journal of Chemistry, 2019. 43(42): p. 16461-16467.

[32]. Singh, D.P., et al., *Synthesis and antimicrobial activity of some new quinoxaline derivatives.* Pharmaceuticals, 2010. 3(8): p. 2416-2425.

[33]. Abu-Hashem, A., M. Gouda, and F. Badria, *Synthesis of some new pyrimido [2', 1': 2, 3] thiazolo [4, 5-b] quinoxaline derivatives as anti-inflammatory and analgesic agents.* European journal of medicinal chemistry, 2010. 45(5): p. 1976-1981.

[34]. Jia, W., et al., *Synthesis and hypoglycemic activity of quinoxaline derivatives.* Frontiers in Chemistry, 2023. 11.

[35]. Pereira, J.A., et al., *Quinoxaline, its derivatives and applications: A State of the Art review.* European Journal of Medicinal Chemistry, 2015. 97: p. 664-672.

[36]. Cör Andrejč, D., Ž. Knez, and M. Knez Marevci, *Antioxidant, antibacterial, antitumor, antifungal, antiviral, anti-inflammatory, and nevro-protective activity of Ganoderma lucidum: An overview.* Frontiers in Pharmacology, 2022. 13: p. 934982.