International Journal on Science and Technology (IJSAT)

E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Modern Synthetic Strategies and Biological Applications of Quinoxaline Derivatives

Hrushikesh Deokar[1], Jaheer Pinjari[2], Vinit Kantela[3], Karan Nadage[4], Amol Fadvale[5]

[1,2,3,4,5]Sonopant Dandekar Arts, V.S. Apte Commerce and M.H. Mehta Science College, Palghar

Abstract

Heterocyclic compounds have garnered significant attention in synthetic and medicinal chemistry. This paper we tried to explore the nitrogen containing heterocyclic compound particularly Quinoxaline and its derivatives. This paper reviews a collection of modern and classical methods for the synthesis of quinoxaline derivatives.

Keywords: Quinoxaline, Synthetic strategies, Biological applications , Derivatives, Modern.

1. Introduction

Heterocyclic chemistry is an important and fascinating branch of chemistry due to its application of the heterocyclic compounds in the diverse field ranges from agrochemicals, pharmaceuticals and material sciences. Nitrogen containing heterocyclic compounds constitute a vital class of compounds due to its diversity in structure and versatility it show in medicinal and martial chemistry.

Quinoxaline and its derivatives are an important class of nitrogen containing heterocycles due to their fused benzene-pyrazine framework. The continuous development of efficient, scalable, and eco-friendly synthetic routes, as highlighted by numerous researchers in the past two decades, underscores the enduring importance of the Quinoxaline scaffold in contemporary chemical research. Quinoxaline and compounds exhibit a broad spectrum of biological activities which is depicted in the image given below.

For synthesis of quinoxaline significant advances has been achieved by the researchers which includes conventional methods, catalytic and green route for synthesis. In this review article we tied to summarize recent methodologies in synthesis, biological significance of that derivative.

3. METHDOLOGIES AND QUINOXALINE SYNTHESIS

The synthesis of the quinoxaline ring system can be achieved through various strategic approaches, ranging from traditional condensation reactions to modern catalytic protocols. The literature highlights a clear trend towards methods that are more efficient, environmentally friendly, and versatile.

A comprehensive review by Saifina and Mamedov[1] (Fig.1) covers both classical and modified methods for Quinoxaline synthesis, providing a baseline for subsequent innovations. Where various catalyst explore for synthesis.

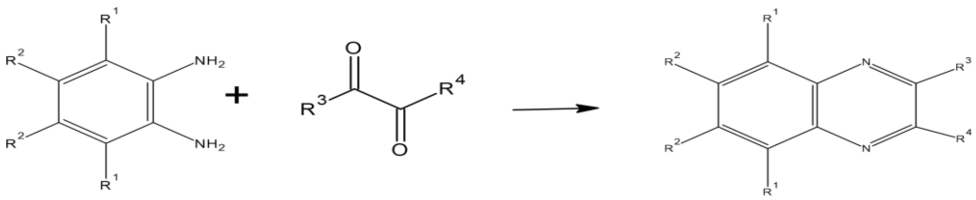


Fig.1

For synthesis simple metals like zinc iodide (ZnI_2), as explored by Sangshetti, Kokare, and Shinde 2007 [2] (Fig.2) and niobium pentachloride ($NbCl_5$), studied by Hou, Liu, and Zhang (2009), to sophisticated systems like palladium catalysts, nanoparticles, and visible-light photoredox catalysis.

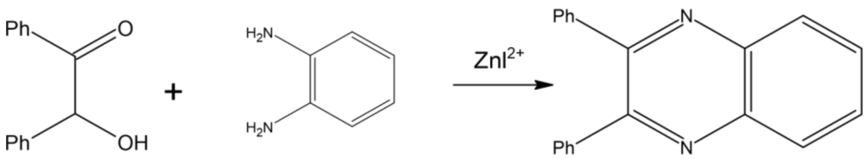


Fig.2

International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

3.1. GREEN SYNTHETIC APPROCHES

The development of a green, scalable, and catalyst-free one-minute synthesis of quinoxalines is reported by Elumalai and Hansen (2021)[3] (Fig.3) utilizing green chemistry principle. This method involves the cyclocondensation of aryldiamines and 1,2-dicarbonyls in methanol at room temperature, offering a rapid and eco-friendly alternative to traditional methods.

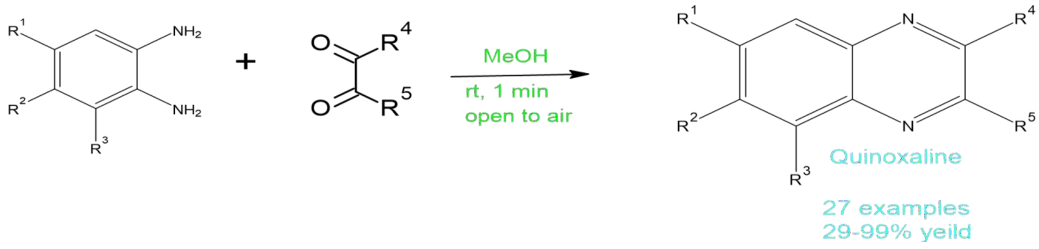


Fig.3

An innovative biomimetic synthesis of quinoxalines conducted in water, which avoids the use of hazardous organic solvents and mimics natural biological processes is introduced by Madhav et al. (2009).[4] (Fig.4) These methods demonstrate that complex heterocyclic structures can be formed efficiently under mild and environmentally conscious conditions.

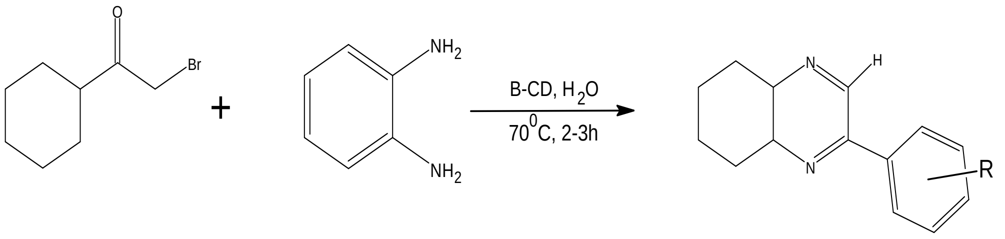


Fig.4

3.2. CONVENTIONAL AND SPECALIZED SYNTHETIC ROUTES

Beyond catalyst-free methods, numerous syntheses rely on specific precursors and reaction conditions to yield unique quinoxaline derivatives.

Kolshorn and Meier (2001)[5] (Fig.5)described a versatile synthesis of 4,5-dihydropyrrolo[1,2a]quinoxalines through the condensation of 1-(2-aminophenyl)pyrrole with various aromatic and heteroaromatic aldehydes.

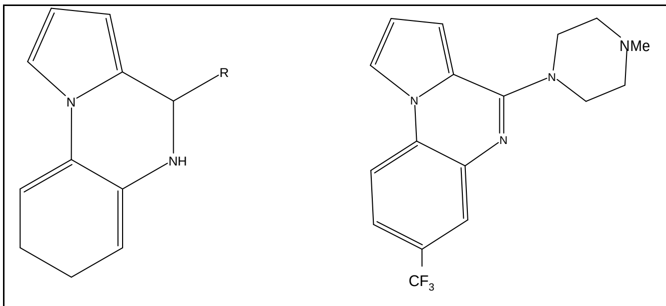


Fig.5

From epoxide and ene-1,2-diamines Antoniottia and Dun˜ach (2002)[6] (Fig.6) detailed an oxidative catalytic approach for the direct synthesis of quinoxaline derivatives

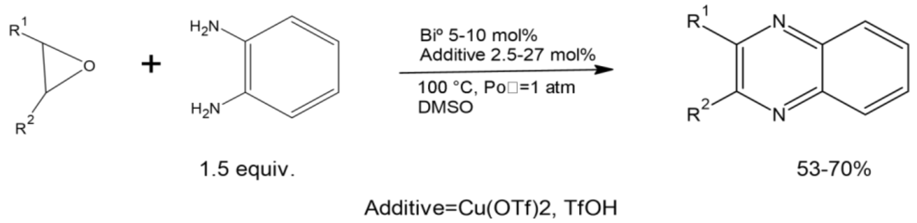


Fig.6

El-Faham et al. (2002)[7] (Fig.7) outlined a versatile synthetic route to create chiral quinoxaline derivatives using amino acid precursors, providing a pathway to form heterocyclic α-amino acids.

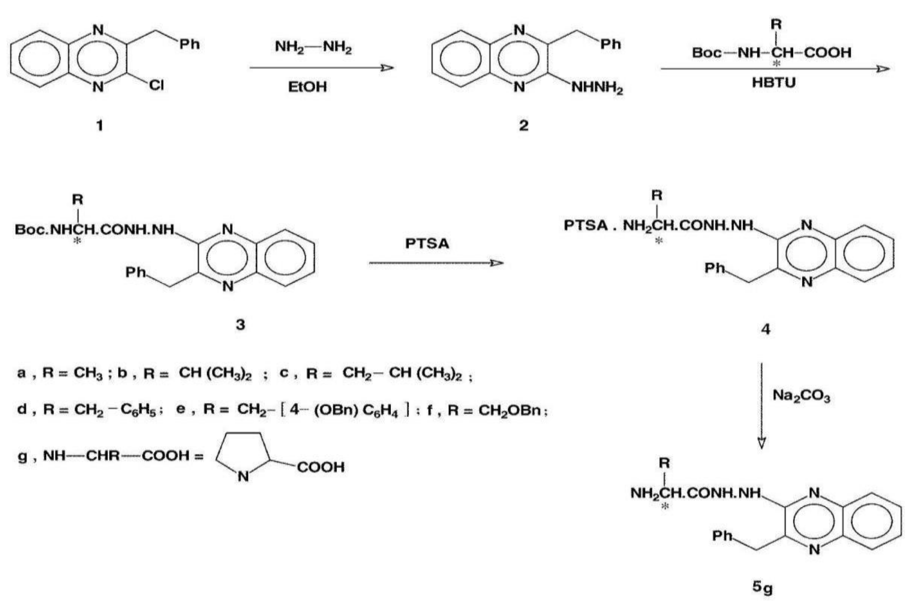


Fig.7

For applications in peptide chemistry, Staszewska, Stefanowicz, and Szewczuk (2005)[8] (Fig.8) developed a direct solid-phase synthesis for producing quinoxaline-containing peptides, facilitating the integration of this scaffold into peptide chains.

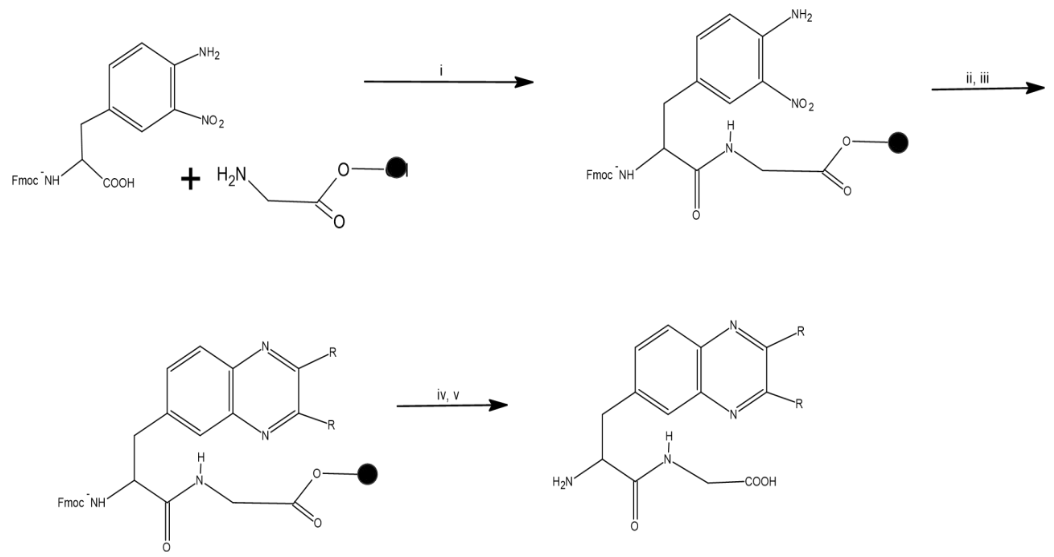


Fig.8

One pot tandem protocol is developed by Anil Kumar et al. (2011)[9] (Fig.9) for synthesis of highly functionalized derivatives like pyrrolo[1,2-a]quinoxalines, streamlining the synthetic process by minimizing intermediate isolation steps.

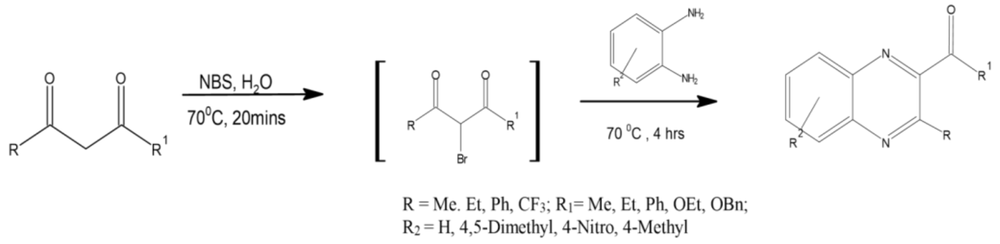


Fig.9

Nanoparticle-Mediated Catalysis: Nanomaterials have emerged as highly effective catalysts due to their large surface area-to-volume ratio.

Hasaninejad, Shekouhya, and Zare (2011)[10] (Fig.10) demonstrated that silica nanoparticles could efficiently catalyze the synthesis of quinoxalines.

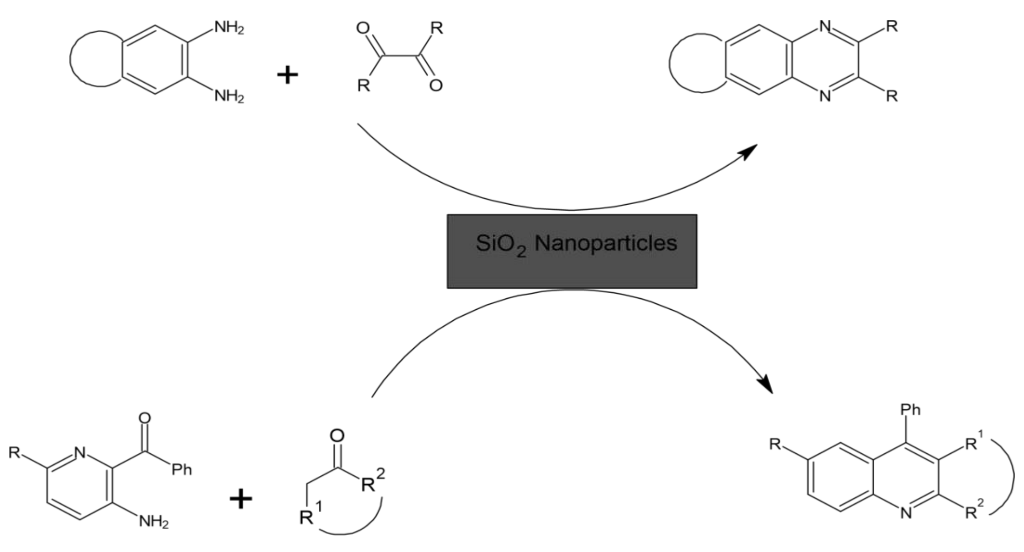


Fig.10

Similarly, Kumar et al. (2007)[11] (Fig.11)showed that Ni-nanoparticles also serve as an efficient catalyst for this transformation. The use of nanoparticles represents a significant step towards developing reusable and highly active catalytic systems.

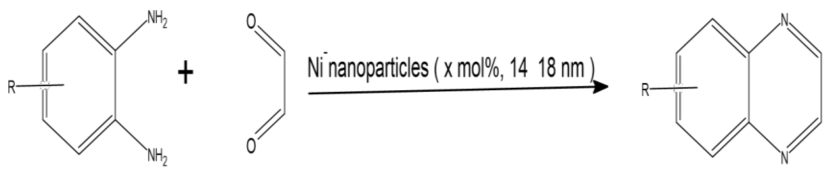


Fig.11

Silica modifies Fe3O4 nanoparticles was utilized by the Sajjadifar et al for the snynthesis of quinoxaline n ethanol as a solvent.

(S. Sajjadifar, I. Amini, G. Mansouri and S. Alimohammadi, Eurasian Chem. Commun., 2020, 2(5), 626–633.)[12] (Fig.12)

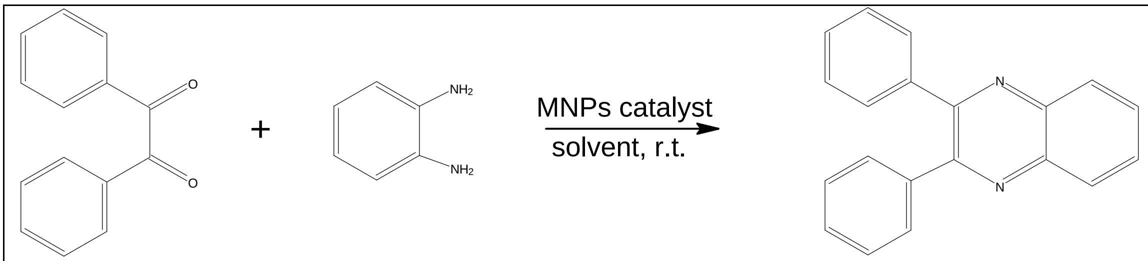


Fig.12

Fe3O4@SiO2-imidazole PMA magnetic nanoparticles were employed by the Javidi et al. for the synthesis of quinoxaline.

J. Javidi and M. Esmaeilpour, Mater. Res. Bull., 2016, 73, 409–422.[13] (Fig.13)

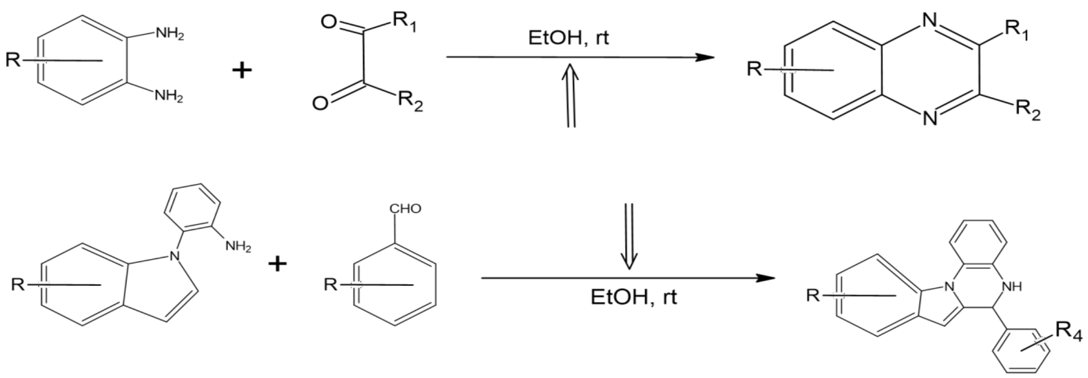


Fig.13

3.3. Metal-Based Catalytic Systems

Lewis acid was utilized by Cai et al. (2008)[14] (Fig.14) to described the use of gallium(III) triflate as an effective catalyst for quinoxaline synthesis.

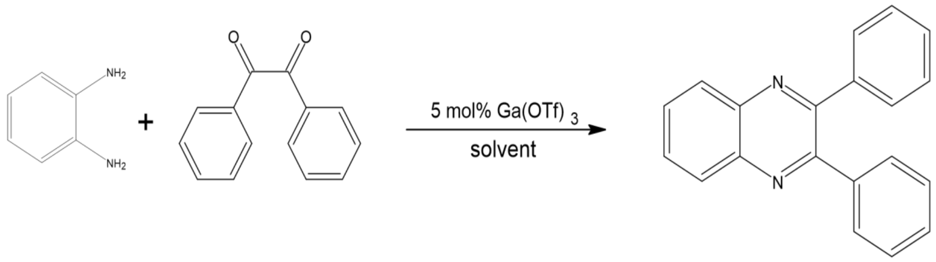


Fig.14

Similarly transition metal work of lace et al. (2008)[15] (Fig.15) highlights the importance of Palladium (Pd) in catalyzing the synthesis of quinoxaline derivative.

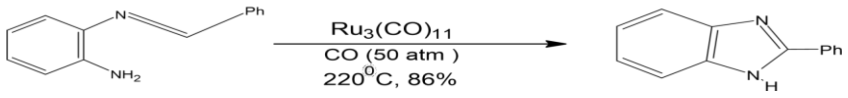


Fig.15

Other Metal Compounds like lead oxide (PbO) have been shown by Kotharkar and Shinde (2006)[16] (Fig.16) to mediate the synthesis of quinoxalines.

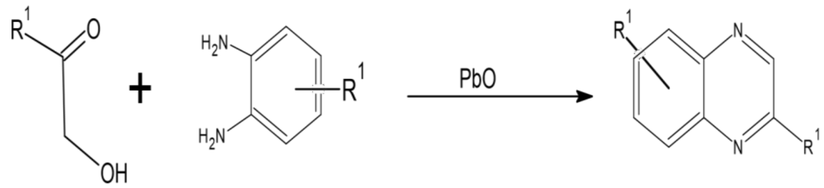


Fig.16

3.4. Environmentally Benign and Novel Catalysts:

The push towards sustainable chemistry has led to the exploration of catalysts that are non-toxic, inexpensive, and readily available.
More et al. (2005)[17] (Fig.17) demonstrated that molecular iodine (I_2) is a cheap and powerful catalyst for the easy and efficient synthesis of quinoxalines.

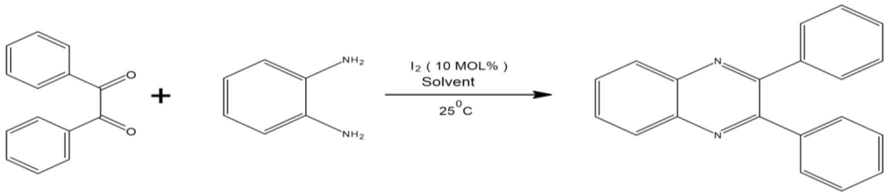


Fig.17

Solid acids as a catalyzed is used by Ahmad and Maleki (2007)[18] (Fig.18)which showed that an efficient synthesis of quinoxaline derivatives at room temperature.

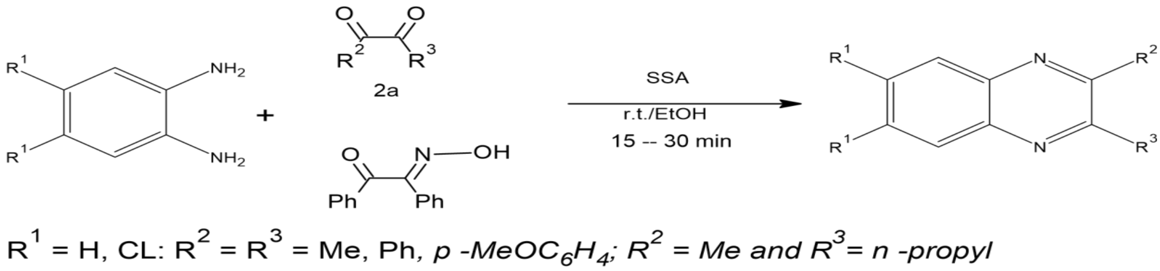


Fig.18

Visiblei-light photoredox catalysis was developed by He et al. (2014)[19] (Fig.19) to synthesize highly functionalized polycyclic quinoxaline derivative.

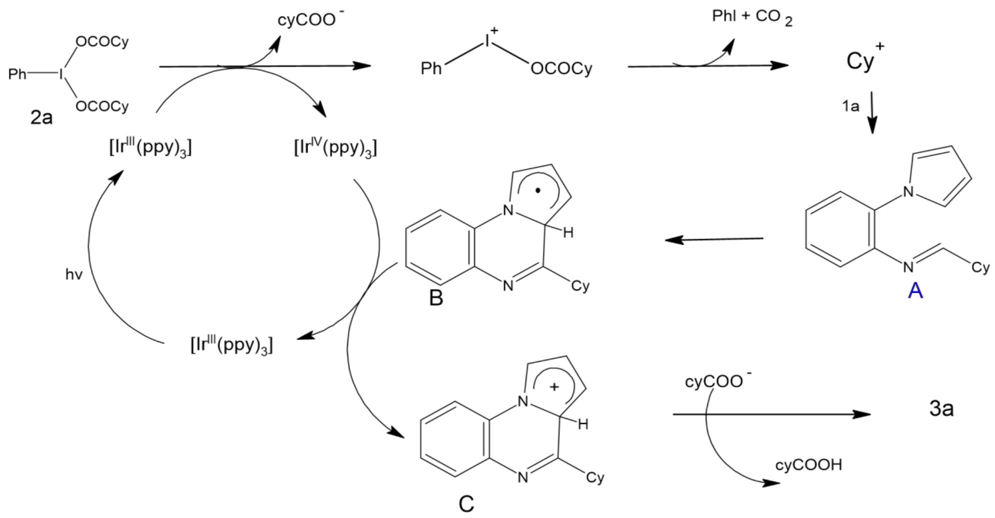


Fig.19

3.5. Quinoxaline Derivatives Applications

The significant interest in synthesizing quinoxalines is largely driven by their diverse applications, especially in pharmacology and materials science.

Pharmacological:

Singh et al. (2010)[20] (Fig.20), report the synthesis and antimicrobial evaluation of new quinoxaline derivatives.

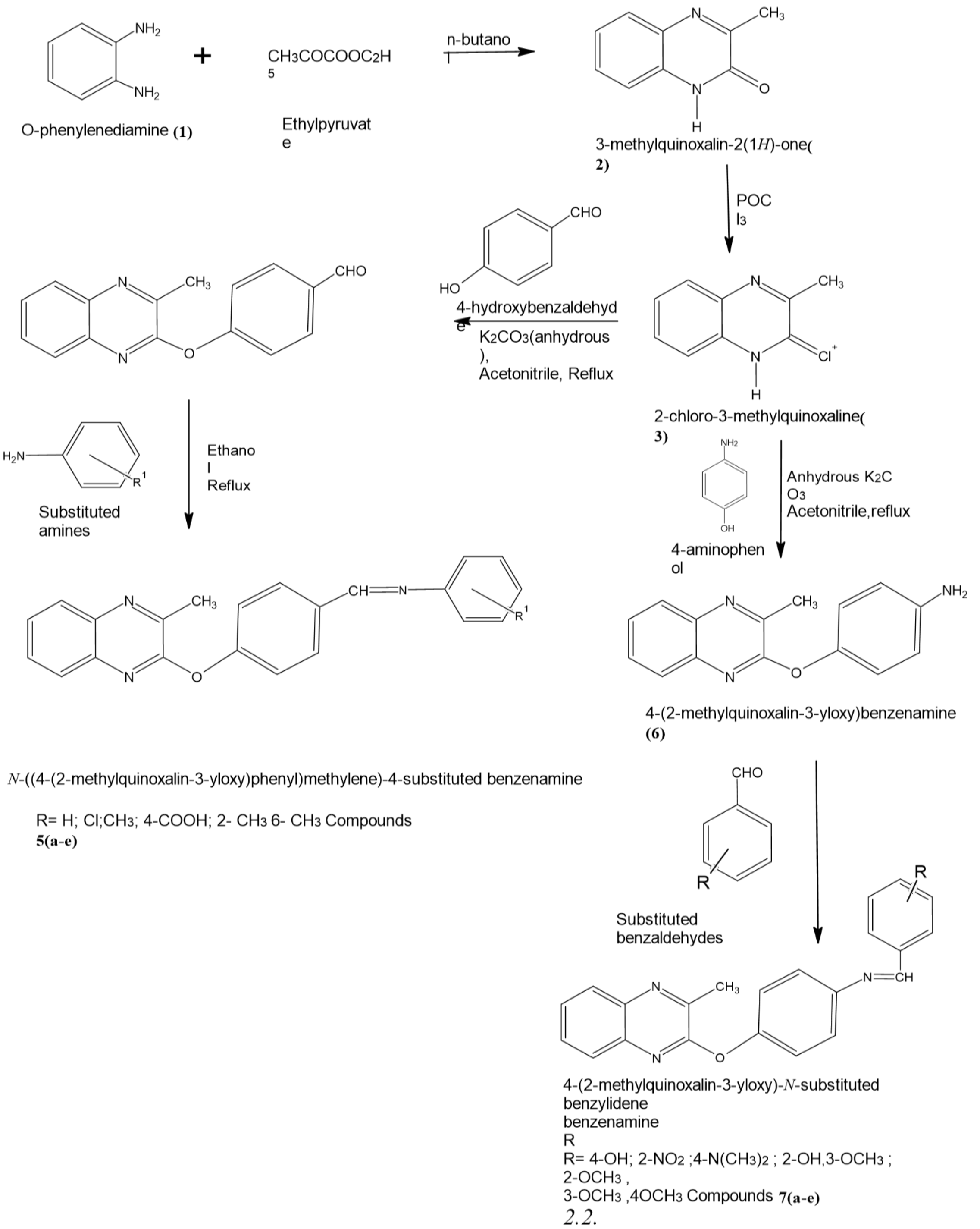


Fig.20

Taiwo, Obafemi, and Akinpelu (2021)[21] (Fig.21) synthesized quinoxaline sulfonamides and assessed them as potential antibacterial agents.

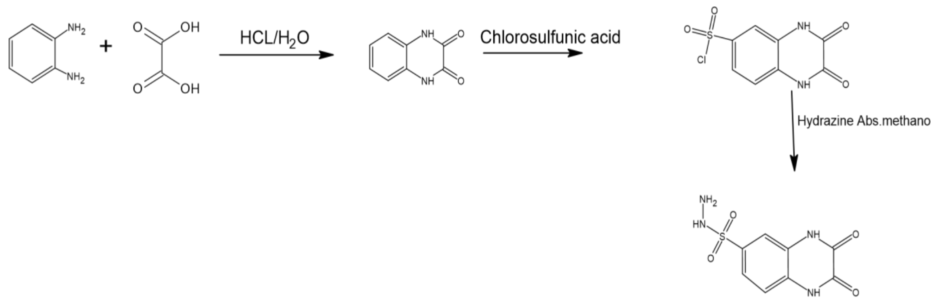


Fig.21

New quinoxaline-2-carboxylate 1,4-dioxide derivatives and showed them to possess in vitro activity against Mycobacterium tuberculosis were reported by Jaso et. al. in 2004.[22] (Fig.22)

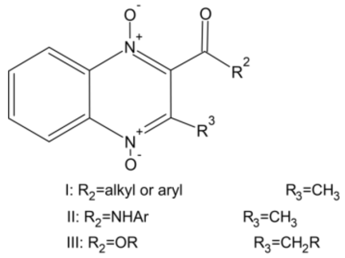


Fig.22

Acyclic quinoxaline nucleosides by Ali et al. (2008)[23] (Fig.23) yielded compounds with potent anti-HIV-1 activity, with one compound exhibiting a high therapeutic index of 73.

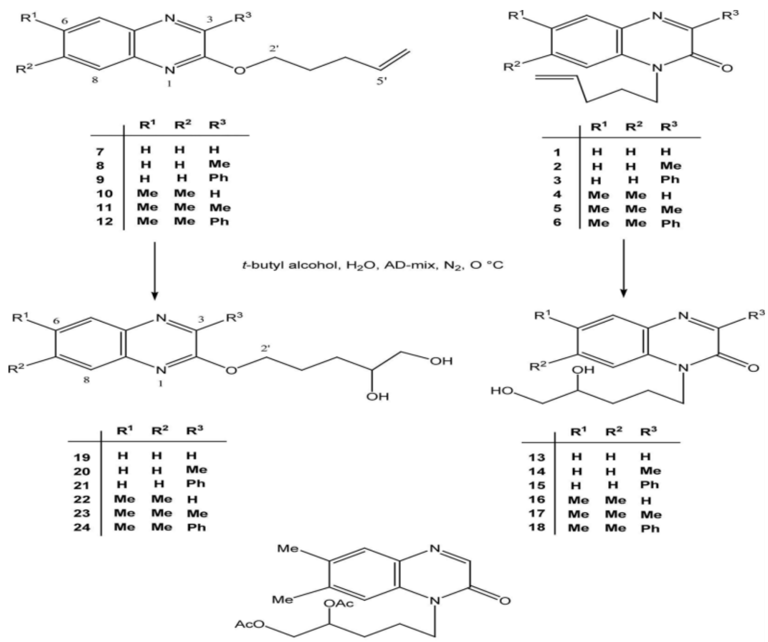


Fig.23

7484829 new quinoxaline derivatives against the protozoan parasite Leishmania donovani was reported by Hui et al. (2005).[24] (Fig.24)

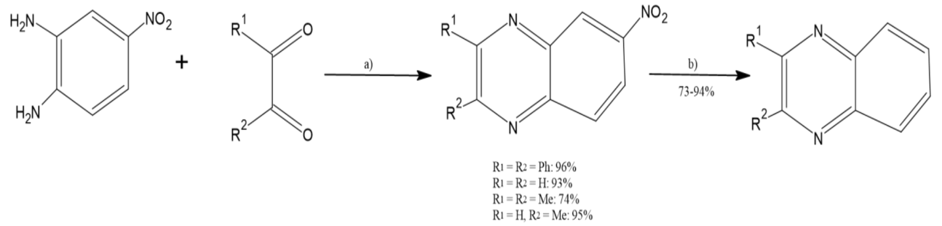


Fig.24

Galal et al. (2010)[25] (Fig.25) synthesized novel derivatives and evaluated their cancer chemopreventive activity, supported by molecular docking studies.

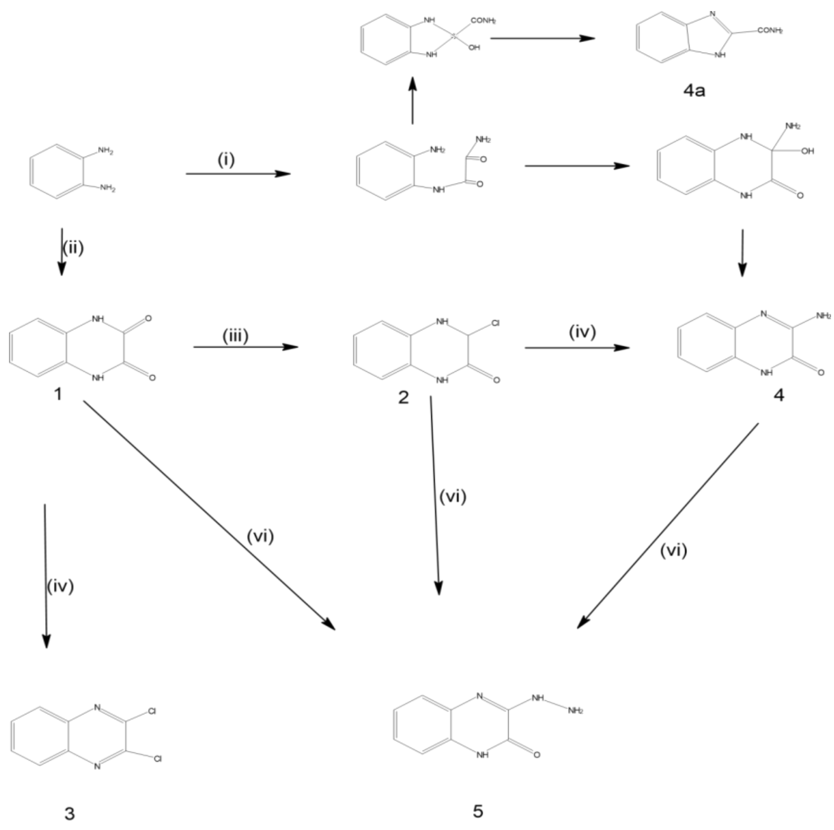


Fig.25

Work of Makhloufi et al. (2011)[26] (Fig.26) also described the synthesis of new derivatives for both antimicrobial and anticancer evaluation.

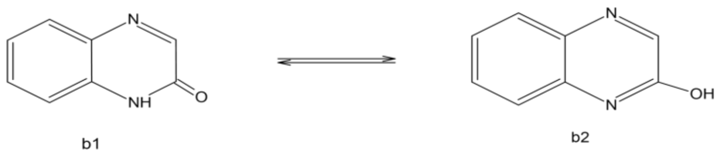


Fig.26

Material Science:

In 2010, Chen et al. [27] (Fig.27) synthesized quinoxaline-benzoxale conjugates that exhibit hexagonal columnar liquid crystalline phases, demonstrating their potential in display technologies.

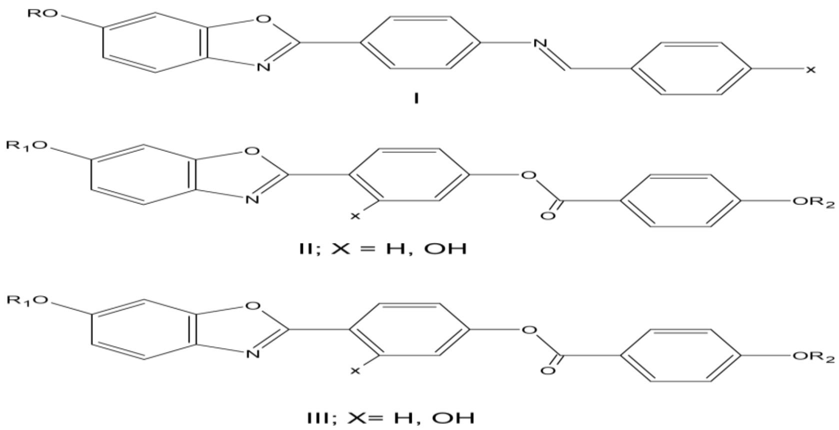
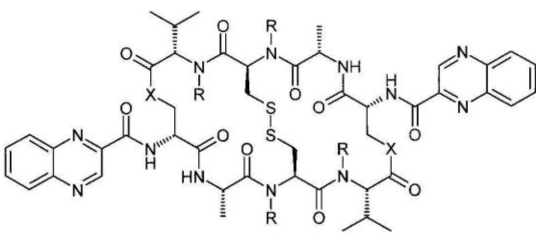


Fig.27

Using quinoxalines as chromophores Dietrich and Diederichsen (2005)[28] (Fig.28) synthesized cyclopeptidic analogues of Triostin highlighting their application in designing molecules with specific optical properties.



Triostin A (**1**): R = CH_3, X = O
Des-*N*-Tetramethyltriostin (**2**): R = H, X = O
Azatriostin (**3**): R = CH_3, X = NH
Des-*N*-Tetramethylazatriostin (**4**): R = H, X = NH

Fig.28

Long-chain quinoxaline metallocyclophanes synthesized by Howard, Heirtzler, and Dias (2007)[29] (Fig.29) points their utility in supramolecular chemistry and the construction of complex molecular architectures.

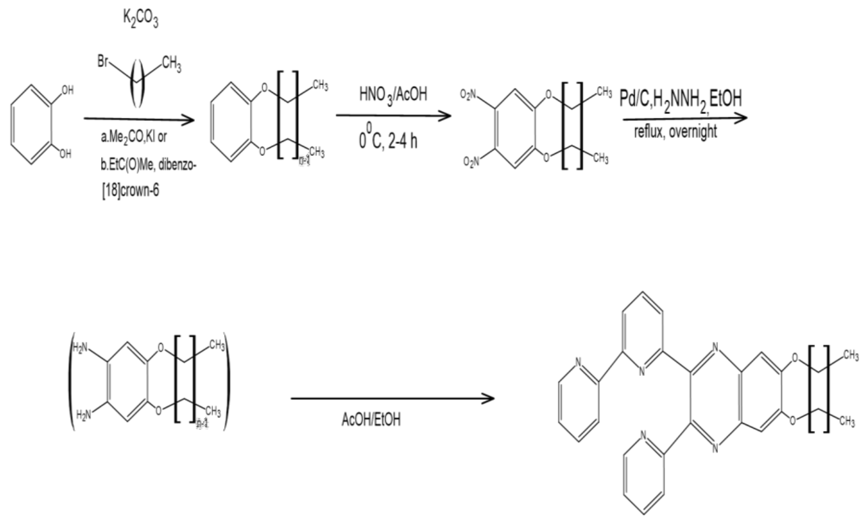


Fig.29

4. CONCLUSION

Chemistry of quinoxaline has evolved from fundamental study to multidisciplinary innovation which leads to high tech application using sustainable routes. This review demonstrate, Quinoxaline derivatives transition towards green chemistry using catalyst free and aqueous pathway that reduces environmental footprints. Nanotechnology were also introduced and revolutionized the synthetic process by solving industrial challenges regarding catalyst separation and recyclability. Immense versatility of this fused benzene-pyrazine framework allows development of targeted pharmaceutical agents which are ranging from activities like antitubercular and antimicrobial leads to potent anticancer compounds as well as advanced materials for OLEDs and liquid crystals. Process oriented design of the molecule is the future scope that lies with quinoxaline, where atom economy and energy efficiency through photoredox or microwave activation become the standard.
Ultimately quinoxaline is a vital and inspiring scaffold which can show potential for the development of next generation smart materials and biologically active molecules through collaborative and scientific efforts.

REFERENCES

1. Saifina DF, Mamedov VA. New and modified classical methods for the synthesis of quinoxalines. Russian Chemical Reviews, 2010; 79 (5): 351-370.
2. Sangshetti JN, Kokare ND, Shinde DB. Efficient One-Pot Synthesis of Quinoxalines in the Presence of Zinc Iodide as Catalyst. Russian Journal of Organic Chemistry, 2009;45(7):1116-1118.
3. Elumalai V, Hansen JH. A Green, Scalable, and Catalyst-Free One-Minute Synthesis of Quinoxalines. SynOpen, 2021;5:43-48.

4. Madhav B, et al. Biomimetic synthesis of quinoxalines in water. Tetrahedron Letters, 2009;50:6025-6028.
5. Abonia R, Insuasty B, Quiroga J, Kolshorn H, Meier H. A Versatile Synthesis of 4,5-Dihydropyrrolo[1,2-a] quinoxalines. Journal of Heterocyclic Chemistry, 2001;38:671.
6. Antoniotti S, Dunach E. Direct and catalytic synthesis of quinoxaline derivatives from epoxides and ene-1,2-diamines. Tetrahedron Letters, 2002;43:3971-3973.
7. El-Faham A, El Massry AM, Amer A, Gohar YM. A versatile synthetic route to chiral quinoxaline derivatives from amino acids precursors. Letters in Peptide Science, 2002;9:49-54.
8. Staszewska A, et al. Direct solid-phase synthesis of quinoxaline-containing peptides. Tetrahedron Letters, 2005;46:5525-5528.
9. Kumar Anil BSP, et al. Quinoxaline synthesis in novel tandem one-pot protocol. Tetrahedron Letters, 2011;52:2862-2865.
10. Hasaninejad A, Shekouhya M, Zare A. Silica nanoparticles efficiently catalyzed synthesis of quinolines and quinoxalines. Catalysis Science & Technology, 2012;2:201-214.
11. Kumar A, et al. Ni-nanoparticles: An efficient catalyst for the synthesis of quinoxalines. Catalysis Communications, 2008;9:778-784.
12. Sajjadifar S, Amini I, Mansouri G, Alimohammadi S. Fe3O4@APTES@isatin-SO3H as heterogeneous and efficient catalyst for the synthesis of quinoxaline derivatives. Eurasian Chemical Communications, 2020;2: 626-633.
13. Javidi Jaber, Mohsen Esmaeilpour. Fe3O4@SiO2–imid–PMAn magnetic porous nanosphere as recyclable catalyst for the green synthesis of quinoxaline derivatives at room temperature and study of their antifungal activities. Materials Research Bulletin, 2016;73:409-422.
14. Cai JJ, et al. Gallium(III) triflate-catalyzed synthesis of quinoxaline derivatives. Tetrahedron Letters, 2008;49:7386-7390.
15. Wallace JM, et al. Palladium-catalyzed synthesis of quinoxaline derivatives. Tetrahedron, 2008;64:9675-9684.
16. Kotharkar SA, Shinde DB. Lead Oxide (PbO) Mediated Synthesis of Quinoxaline. Journal of the Iranian Chemical Society, 2006;3(3):267-271.
17. More SV, et al. Molecular iodine a powerful catalyst for the easy and efficient synthesis of quinoxalines. Tetrahedron Letters, 2005;46:6345-6348.
18. Shaabani AHMAD, ALI Maleki. An Efficient Solid Acid Promoted Synthesis of Quinoxaline Derivatives at Room Temperature. Chinese Journal of Chemistry, 2007;25(6):818-821.
19. He Zhi, Bae Minwoo, Wu Jie, Jamison TF. Synthesis of Highly Functionalized Polycyclic Quinoxaline Derivatives Using Visible-Light Photoredox Catalysis. Angewandth Chemie, 2014;126: 14679-14683.
20. Singh DP, Deivedi SK, Hashim SR, Singhal RG. Synthesis and Antimicrobial Activity of Some New Quinoxaline Derivatives. Pharmaceuticals, 2010;3:2416-2425.
21. Taiwo Festus O, et al. Synthesis of Some Quinoxaline Sulfonamides as a Potential Antibacterial Agent. Journal of Pharmaceutical Research International, 2021;33(51B):116-132.
22. Jaso A, Zarranz B, Aldana I, Monge A. Synthesis of New Quinoxaline-2-carboxylate 1,4-Dioxide Derivatives as Anti-Mycobacterium tuberculosis Agents. Journal of Medicinal Chemistry, 2005;48(6):2019-2025.
23. Ali IAI, Al-Masoudi IA, Aziz NM, Al-Masoudi NA. NEWACYCLIC QUINOXALINE

24. NUCLEOSIDES. SYNTHESIS ANDANTI-HIV ACTIVITY. Nucleosides, Nucleotides and Nucleic Acids, 2008;27: 146-156.
25. Hui X, et al. Synthesis and antiprotozoal activity of some new synthetic substituted quinoxalines. Bioorganic & Medicinal Chemistry Letters, 2006;16:815-820.
26. Galal SA, et al. Part I: Synthesis, cancer chemopreventive activity and molecular docking study of novel quinoxaline derivatives. European Journal of Medicinal Chemistry, 2011;46:327-340.
27. Makhloufi A, Baitiche M, Merbah M, Benachour D. SYNTHESIS OF NEW QUINOXALINE DERIVATIVES. Synthetic Communications, 2011;41(23): 3532-3540.
28. Chen CJ, et al. Synthesis of quinoxalineebenzoxale conjugates and mesomorphic properties. Tetrahedron, 2011;67:114-124.
29. Dietrich B, Diederichsen U. Synthesis of Cyclopeptidic Analogues of Triostin A with Quinoxalines or Nucleobases as Chromophores. European Journal of Organic Chemistry, 2005: 147- 153.
30. Howard MJ, Heirtzler FR, Dias SIG. Synthesis and Stereochemistry of Long-Chain Quinoxaline Metallocyclophanes. Journal of Organic Chemistry, 2008;73:2548-2553.