

METAL COMPLEXES OF SCHIFF BASES DERIVED FROM QUINOXALINE-2-CARBOXALDE –A PROMISING CANDIDATE IN CATALYSIS, MEDICINE AND MATERIAL SCIENCE-REVIEW

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Abstract

The present review is designed to cover the environmentally benign methods for the synthesis of quinoxaline based ligands. These ligands offer advantageous aspects which can be utilised in the preparation of metal complexes, especially of transition metals having various optical, catalytic, pharmacological applications. Many of these complexes are extensively reported for their anticancerous, antifungal and antimicrobial properties. The different facets of quinoxaline synthesis from the conventional methods to the improved synthetic protocols incorporated for better yield and increasing the green aspects etc. are discussed.

Keywords: quinoxaline, metal complexes transition metals, green synthesis, catalytic activity

Abstract

The sketching of a chelating system for a specific application depends largely on the ligand environment and the nature of the metal ion. Adequate modifications in the ligand moiety like introduction of heteroatoms in the ring or varying the substituents etc. can induce useful features and hence induce intended properties. Schiff bases derived from quinoxaline-2-carboxaldehyde are heterocyclic analogues of salicylidene ethylenediamine (SALEN) ligand in which two of the ring carbon atoms are replaced by two nitrogen atoms. Quinoxaline derivatives have extensively attracted interest as microbicidal, fungicidal and anticancer agents, fluorescent materials in the design of OLEDs, fabrication of catalysts, building units for covalent organic framework etc. However there is a need for intensive research in this area as the factors governing the electronic effects, oxygenation activity etc. are rather intricate and various synthetic strategies have been explored for quinoxaline based ligands and its applications in diverse fields. Here we make an attempt to review the chelating ligands having the quinoxaline framework in a brief and systematic manner giving an emphasis to the synthetic strategies adopted for quinoxaline derivatives.

Introduction

The understanding of the mixed valence compounds, electron transfer processes etc. is central to the design of molecular systems such as catalysts, photosensitizers etc. Schiff base complexes are versatile in the crafting of synthetic models of ligand environment around the metal which can impart the properties of choice to the resulting metal complexes. The NMR spectral studies and the electrochemical data indicate how the redox potential of the chelates which is a function of its electron density distribution is influenced by the substituents like nitro group, halogen etc. [1-3] The specific biological functions of the complexes are often greatly influenced by coordination geometry and the donor group of the ligand moiety. The substituent effects and donor properties of the ligand will be reflected in the catalytic activity and various spectroscopic properties of the chelate.

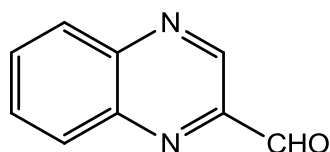


Fig. 1. Quinoxaline-2-carboxaldehyde

Quinoxalines which are also known by the names, 1,4-diazanaphthalene, 1,4-benzodiazine, or benzopyrazine are reported as excellent bridging ligand among nitrogen heterocycles. Reports of complexes derived from its derivatives are to be explored further [4-9]. Quinoxaline derivatives are occurring widely in nature in various forms like Echinomycin, triostin A, riboflavin (vitamin B12) flavoenzymes etc. Quinoxaline derivatives were reported to be catalytically, biologically and pharmacologically active. [10-25]. Quinoxaline moiety has proven to be forbidding the action of many gram positive bacteria and is present in a number of antibiotics and also active against various transplantable tumours. The structural nucleus of quinoxaline is the key factor for the advantageous features of the quinoxaline based ligands. The enhancement in the properties by combining the bridging nature of quinoxaline and the chelating properties of 2,2' bipyridine are observed and could be utilized in areas like catalysis and anticancer studies. Quinoxaline based cyclometalating agents for metal ions such as Ir (III) and Pt (II) as are found to exhibit excellent luminescence properties and emission attributes compared to systems containing quinoline or 2-phenyl pyridine etc [26].

Synthetic strategies and Properties of Quinoxaline Schiff bases

The synthesis of quinoxaline based ligands in a mild and green pathway was reported in the catalytic presence of a Zr complex developed by by Rezaeifard et al in 2013. The catalyst was prepared by the reaction of (z)- N-benzylidene-2-hydroxypropane-1-amine (HL) and $ZrCl_4$ yielding the monomeric compound (ZrL_2Cl_2). [27] The further preparation of the complexes of these ligands in an environmentally amiable solvent ethanol, excellent reusability and turn over number of the catalyst

are the advantages offered by this catalyst.

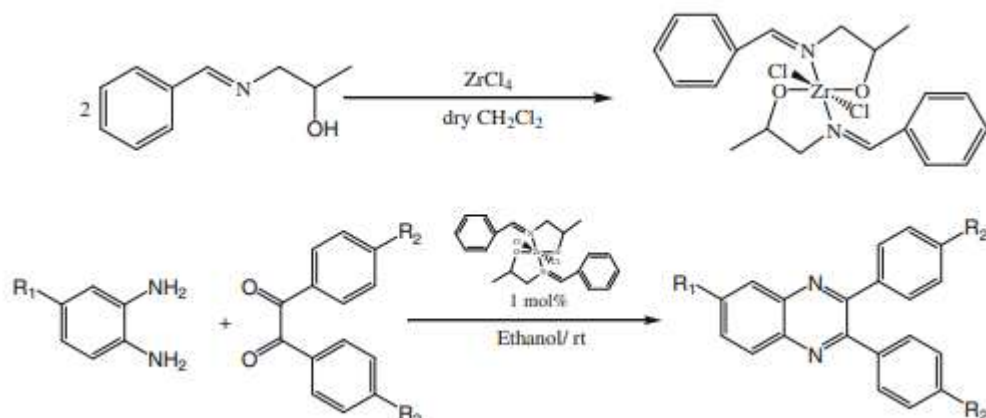


Fig.2. Synthesis of quinoxaline derivatives in the presence of ZrL_2Cl_2 (1 mol %) in ethanol at room temperature.

In 2016, Dhanaraj et al has reported the synthesis of a ligand N_2, N_3 -bis(3-nitrophenyl) quinoxaline-2,3-diaminequinoxaline-2,3-(1,4H)-dione by mixing methanolic solutions of quinoxaline-2,3-(1,4H)-dione to that of 3-nitroaniline drop wise with constant stirring at room temperature (Fig. 3). After refluxing the mixture for two hours the product was isolated by cooling the reaction mixture and filtration.

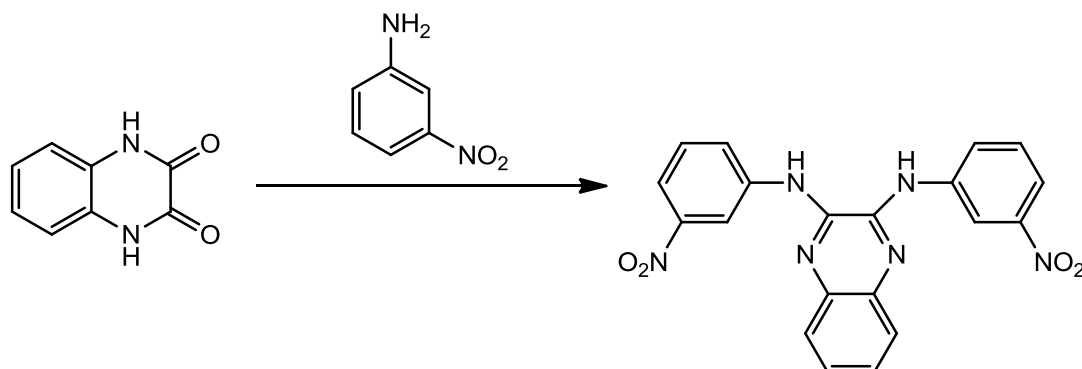


Fig. 3. Preparation of N_2, N_3 -bis(3-nitrophenyl) quinoxaline-2,3-diaminequinoxaline-2,3-(1,4H)-dione

In 2010, the formation of a heterocyclic perimidine, 2-(quinoxalin-2-yl)-2,3-dihydro-1H-perimidine was reported by Yusuff et al., which exhibited the characteristics of both π deficient and π excessive systems [28]. The compound was obtained by the reaction of 1,8-diaminonaphthalene [29,30] and 4-hydroxy-3-methoxy benzaldehyde in methanol at room temperature for 3 hours. The Schiff base formation takes place accompanying C-N coupling through the nucleophilic attack of the amino group at the imino carbon. The complex exhibits bands at 3284 cm^{-1} (NH) and 1599 cm^{-1} (C=N), of the quinoxaldehyde ring. The structural investigation was made by ^1H and ^{13}C NMR spectral and single crystal analyses. The studies reveal a monoclinic structure for the compound [31]. The UV-Visible spectrum of the compound does not show solvatochromism. The fluorescence spectrum on the other hand exhibits positive fluorescent solvatochromism. Also the compound exhibited superior antibacterial efficacy towards the common clinical isolates.

The reaction of (z)- N-benzylidene-2-hydroxypropane-1-amine (HL) and $ZrCl_4$ yielded the monomeric compound (ZrL_2Cl_2) (Fig.4) which acts as catalyst in the synthesis of various quinoxaline ligands, in a relatively milder and greener conditions. The preparation of the complexes in an environmentally amiable solvent ethanol, excellent reusability and turn over number of the catalyst are the advantages offered by this catalyst.

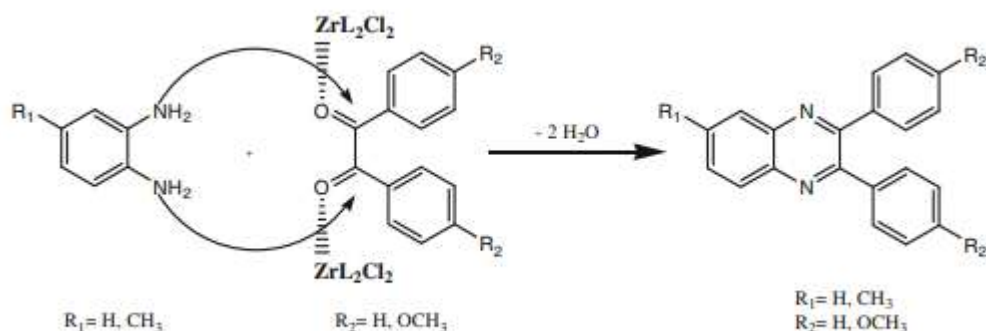


Fig. 4. The proposed mechanism of ZrL_2Cl_2 catalysed synthesis of quinoxaline

Complexes of 2-chloroquinoxaline with the biologically active silver (I) ion have been reported recently by Badr et al. [32]. The excellent. The one – pot synthetic protocol furnished a polymeric complex $[Ag(2Clquinox)(NO_3)]_n$, which conforms to 2D layers connected through Ag-O and Ag-Ag bonding and a second complex whose structure consists of alternating arrays of polymeric $[Ag(2Clquinox)(NO_3)]_n$ and monomeric $[Ag(2Cl-quinox)_2(NO_3)]$. The structure and crystal packing of the complexes are very much related to the presence of H-bonding and π stacking interactions. The quinoxaline derivative behaves as a terminal monodentate ligand. The complexes are found to inhibit the action of a wide range of multi drug resistant (MDR) bacteria. The antibacterial potency of the $[Ag(2Clquinox)(NO_3)]_n$ complex is greater than that of many antibiotics and its anticancer activity is greater than that of the second complex [33].

Compound	A-549	MCF-7
Complex 1	9.11±0.96	17.41±1.83
Complex 2	5.93±0.52	9.77±0.74
2Cl-quinox	143.14±9.78	205.04±11.92
AgNO ₃	14.70±0.53	2.81±0.97
Cis-platin	7.5±0.69	4.59±0.53

Table 1

Table 1. IC₅₀ values (in $\mu\text{g/mL}$) for the Ag(I) complexes, 2Cl-quinox, AgNO₃ and cis-platin against selected cancer cell lines.

The synthesis of a wide range of quinoxaline derivatives had been designed and carried out in environmentally benign manner by Jafarpour et al in the catalytic presence of a Zr(II)Schiff base complex [34]. The synthetic pathway involves mild reaction conditions and environmentally harmless solvent. The yield and reusability of the catalysts were excellent.

The synthesis of quinoxaline derivatives was reported in 2012 by Romelli in the presence of a molybdophosphovanadates which belong to heteropolyoxometalates (AlCuMoVP and AlFeMoVP) catalysts at room temperature. The are catalysts are reusable for several cycles. An acid catalysed condensation is proposed as the mechanism of conversion during the formation of quinoxalines [35].

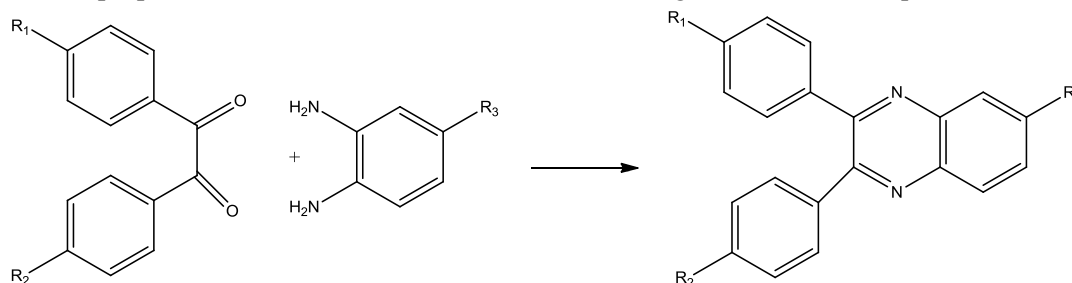


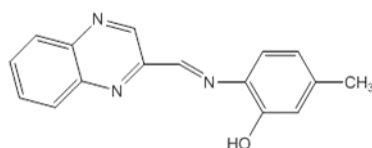
Fig.5 Synthesis of quinoxaline derivatives catalyzed by MoVP heteropolyoxometalates.

Dhanaraj et al carried out synthesis, structural studies, antimicrobial studies and molecular modelling of a quinoxaline based ligand, 3-[N'-(2-Hydroxy-3-methoxy-benzylidene)-hydrazino]-1H-quinoxalin-2-one and its transition metal complexes [36]. The antimicrobial assays were carried out against various bacterial and fungal strains. The significant DNA activity was revealed by superoxide dismutase (SOD) activity. Molecular docking studies show the binding of DNA to the complexes through the outer groove.

Hadjiliadis reported few Schiff base complexes of an accidentally formed ligand 2-(2'-pyridyl)quinoxaline on the reaction of 1,2-phenylenediamine with 2-acetylpyridine. [37]. It is a binucleating ligand which offers the bridging properties of quinoxaline together with the chelating properties of 2,2'-bipyridine. The synthetic method of 2-(2'-Pyridyl)quinoxaline involves adding 2-acetylpyridine to 1,2 phenylenediamine in 2:1 molar ratio along with methylchloroformate (~ 0.5 mol) in 2-propanol. The reaction mixture was stirred for 48 h at 50 °C. The structure of the ligand was investigated by the ¹HNMR, mass and other micro analytical studies. All the peaks could be assigned using 2D COSY NMR. The metal complexes [MLCl₂] (M = Co, Ni, Cu, Zn) were synthesised. The Zn(II) complex is reported to be having monomeric pseudo tetrahedral geometry, where only two nitrogen atoms of the ligand moiety are involved in complex formation. All the three nitrogen atoms of the Schiff base ligand are involved in complex formation in the polymeric complexes Co(II), Ni(II) and Cu(II) complexes and it is also reported that the Co(II) complex exhibits a five coordinate geometry and Ni(II) and Cu(II) complexes assumes six coordinate geometries respectively. The above results are showing the structural flexibility of the ligand in varying metal environments. Such tuning of electronic environment can impart many advantageous aspect having wide range of applications. Transition metal complexes in which the ligand environment is composed of nitrogen and phenolic oxygen is an interesting as it may generate unique properties due to the modification of the electronic properties due to the introduction of the hetero atoms to the ring.

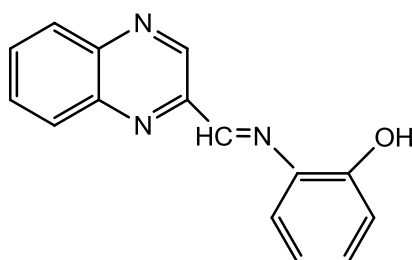
A new series of the metal complexes of quinoxaline-2-carboxalidine-2-amino-5-methylphenol with Mn(II), Ni(II), Cu(II) and Zn(II) ions was reported by Yusuff et al. [40]. The structures were explored in detail by various physicochemical and spectroscopic studies. Ni(II) complex was analysed by X-ray crystallographic studies also which indicated a distorted octahedral structure for the complex, in which N₄O₂ donor set of the ligand, which assumes a cis arrangement exhibits a 2-dimensional polymeric structure parallel to [0 1 0] plane. The reported geometries for Mn(II) complex is tetrahedral, Fe(III) complex is square pyramidal and Cu(II) complex is square planar.

respectively. The Mn(II), Fe(III) and Cu(II) complexes which have vacant coordination position proved to be very effective in catalysing the hydroxylation of phenol whereas Ni(II) complex is not exhibiting any catalytic activity which is a coordinatively saturated complex.



Schiff base complexes of quinoxaline -2-carboxaldehyde with semicarbazide (QSC) and furfurylamine (QFA) were reported by Yusuff et al. [41]. The complexes of QSC were having the general formula $[M(QSC)Cl_2]$ ($M = Mn(II)$ Co(II), Ni(II) and Cu(II)). A tetrahedral geometry was reported for the former three complexes and a square planar structure for the Cu(II) complex from the spectral, magnetic and conductance studies. For the QFA complexes where the structural formula is $[M(QFA)_2Cl_2]$ the studies are indicating an octahedral structure. All the complexes except Ni (II) complex exhibited appreciable catalytic activity towards the oxidation of 3,5-di-tert-butylcatechol (DTBC) to 3,5-di-tert-butylquinone (DTBQ) in the presence of air. The cobalt(II) complex of the ligand QFA exhibited the maximum activity in this reaction.

Yusuff et al also reported Schiff base complexes of first row transition metal ions of quinoxaline-2-carboxaldehyde with 2-aminophenol [42]. The analytical data along with spectral magnetic and conductance studies are indicative of a tetrahedral geometry for the Mn(II), Co(II),



Ni(II) and Cu(II) complexes and a dimeric structure for Fe(III) complex which is indicating the existence of antiferromagnetic coupling.

Diverse synthetic strategies like the interaction between α -diketones or ester like glyoxalates with *o*-phenylenediamine are available in the literature. The use of green protocol with glycerol-water as solvent or a solvent free environment based on organocatalyst are described [43-45]. The bioavailability of the quinoxalines and the pharmacological functions of the quinoxaline system are of very high significance in medicinal chemistry. Many quinoxaline are found to be very effective in the design of photo-initiating systems in both UV and visible range [46].

Conclusion

The aim of the review was to give an insight to the researchers of the field an update on the progress made on the Schiff bases derived from quinoxaldehyde. A comparison of this to the Schiff bases derived from salicylaldehyde will be helpful to design the ligand environment for better properties of the synthesised complexes. The presence of electron releasing or electron withdrawing groups or aromatic rings in the ligand becomes decisive in determining the chemical, physical and electronic properties of the chelating complexes. The green synthetic methods developed for the preparation of

quinoxaline based ligand systems has been the major focus of this review. The catalytic efficiency of the complexes with quinoxaline systems stems from the deactivated electronic environment existing in this ring system. The scope of utilising such catalyst for the large scale production of products is to be explored further.

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Conflicts of interest

There are no conflicts of interests to declare

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