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## Chapter - II

### Review of Literature

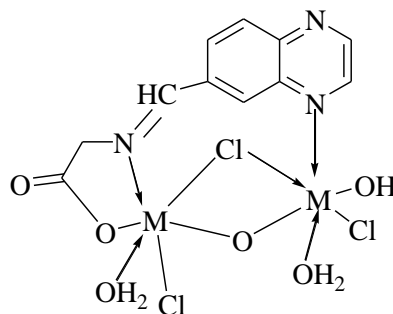
#### 2. 1. Quinoxalines

Quinoxaline is nitrogen containing six membered heterocyclic in which two nitrogen atoms are based on pyrazine so called as benzopyrazine.  $\alpha$ -dicarbonyl compounds react with aromatic ortho-diamine by consecutive addition-elimination mechanism to give quinoxaline. Quinoxalines have become an attractive target of extensive research due to its inherent properties and therapeutic uses. Quinoxaline finds many pharmacological activities like antibacterial, antifungal, antitubercular, antiinflammatory, antihyperglycemic, antitumor *etc.*,

##### 2.1.1. Review on quinoxaline derivatives and its transition metal complexes

Quinoxaline-based Schiff bases were synthesized and characterized by several workers. The review of the previous work is presented below.

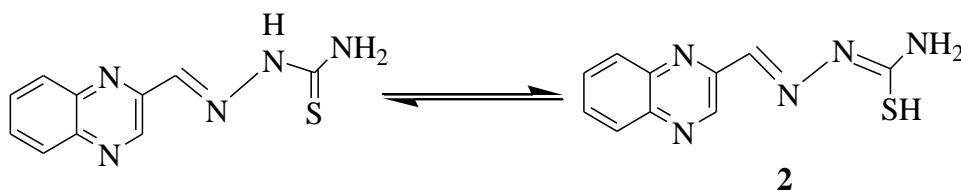
**K. K. M. Yusuff *et al.***, synthesized and characterized the Schiff base and its Fe(III), Co(II), Ni(II) and Cu(II) complexes (**1**) by template method<sup>1</sup>.



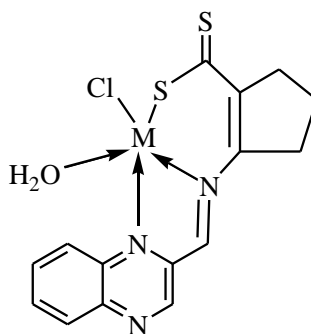
M= Fe(III), Co(II), Ni(II) and Cu(II))

**1**

**R. Sreekala and A. R. Karthikeyan *et al.***, derived a new Schiff base (**2**) from quinoxaline-2-carboxaldehyde and 2-aminocyclopent-1-ene-1-dithiocarboxylic acid and its Fe(III), Co(II), Ni(II) and Cu(II) complexes (**3**) were synthesized and characterized by various spectral and analytical techniques. From the results, the following structures were assigned for the complexes<sup>2,3</sup>.



**2**

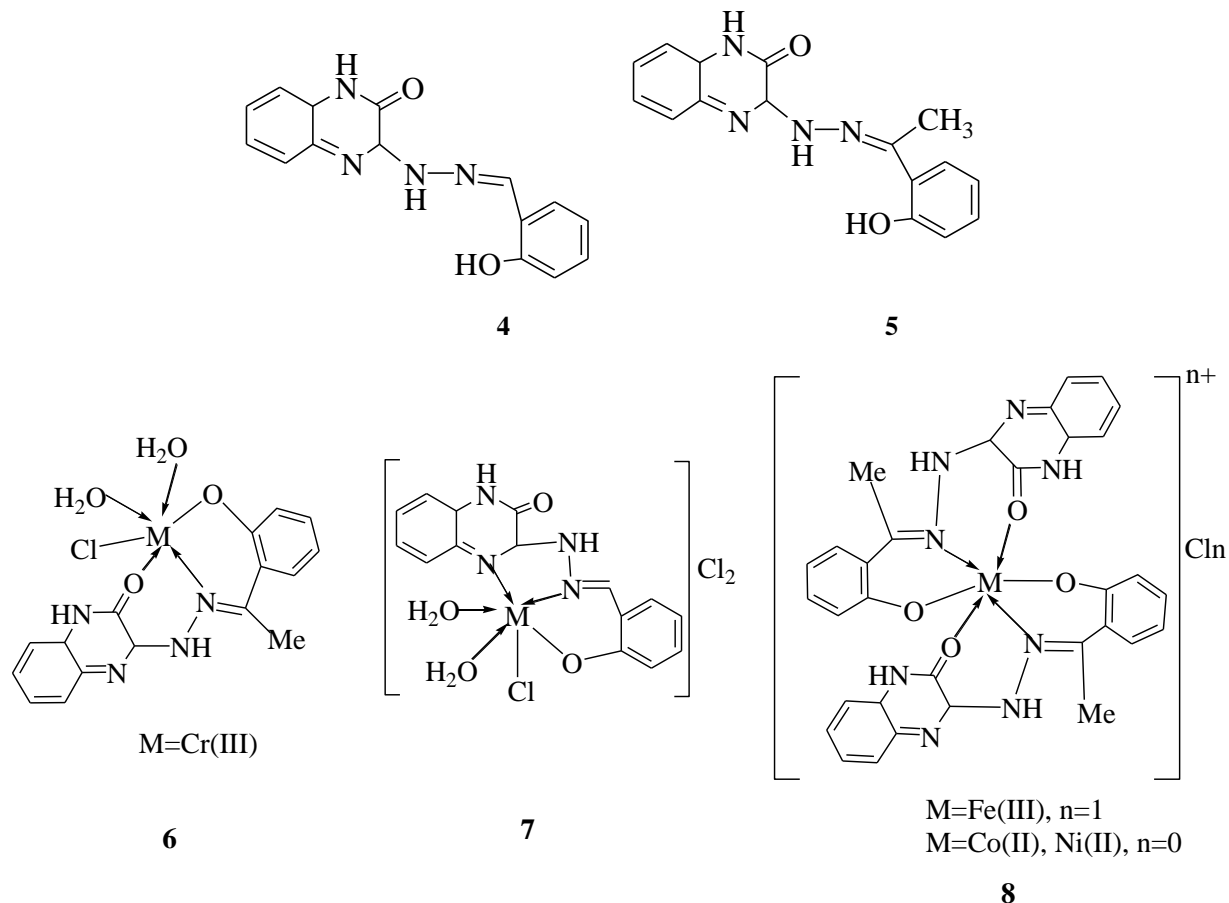


**3**

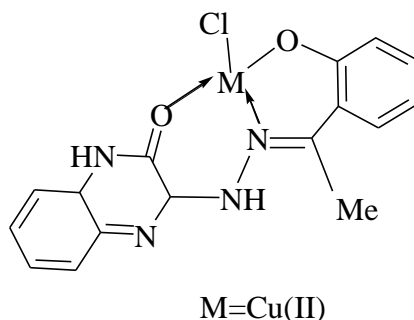
**R. Sreekala *et al.***, synthesized and characterized new Co(III), Ni(II) and Cu(II) complexes of quinoxaline-2-carboxaldehyde thiosemicarbazone. The ligand was a uninegative tridentate NNS donor in the Co(II) and Cu(II) complexes and neutral bidentate NS donor in the Ni(II) complex. The cytotoxicity of Co(III) complex was determined in vitro as well as in tissue culture methods<sup>4</sup>.

**D. S. Rani *et al.***, synthesized and characterized Mn(II), Fe(III), Co(II), Ni(II), Cu(II), and Zn(II) complexes of a new dibasic multidentate ligand<sup>5</sup>.

Lakshmi, *et al.*, prepared new tridentate oxygen–nitrogen donors, N-salicylidene-3-hydrazinoquinoxaline-2-one (**4**) and N-(2-hydroxy)acetophenoyl-3-hydrazino quinoxaline-2-one (**5**) and its complexes Cr(III), Mn(II), Fe(III), Co(II), Ni(II), and Cu(II) (**6-9**) and characterized them by various analytical techniques<sup>6</sup>.



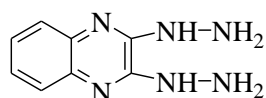
The analytical data indicated that M:L stoichiometry is 1 : 1 in Cr(III) and Mn(II) complexes and 1:2 in Fe(III), Co(II) and Ni(II) complexes.



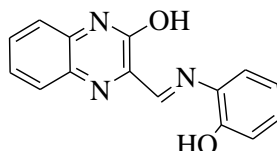
J. Mathew *et al.*, reported the synthesis, characterization, and catalytic activity studies of metal complexes of Schiff bases, N,N'-bis-(3-hydroxyquinoxaline-2-carboxalidene)-ethylenediamine, N,N'-bis-(3-hydroxyquinoxaline-2-carboxalidene)-o-phenyl enediamine-3-hydroxylquinoxalinhydrazone, and N,N'-bis-(3-

hydroxyquinoxaline-2-carboxaldehyde)diethylenetriamine were reported. The complexes exhibited anomalous magnetic behavior<sup>7</sup>.

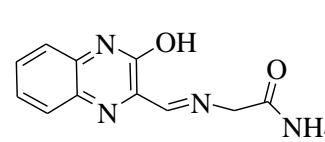
**S. G. Valavi *et al.***, synthesized and characterized new complexes of Mn(II), Fe(III), Co(II), Ni(II) and Cu(II) with 2,3-bis(hydrazinoquinoxaline) (**10**), 3-hydroxyquinoxaline-2-carboxaldehyde semicarbazone (**11**), 3-hydroxyquinoxaline-2-carboxaldehyde thiosemicarbazone (**12**), 3-hydroxyquinoxaline-2-carboxaldehyde furfurylamine (**13**), 3-hydroxyquinoxaline-2-carboxaldehyde thiosemicarbazone (**14**) and 2-[quinoxalin-2-ylmethyl(amine)]acetamide (**15**). The synthesized complexes have been screened for catalytic activity for oxidation of 3, 5-ditertbutylcatechol to the corresponding quinone using molecular oxygen as the oxidant<sup>8</sup>.



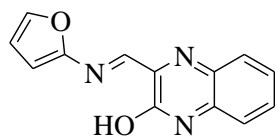
**10**



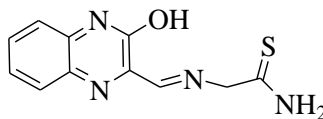
**11**



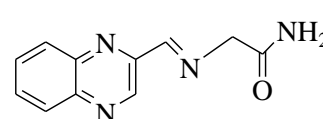
**12**



**13**

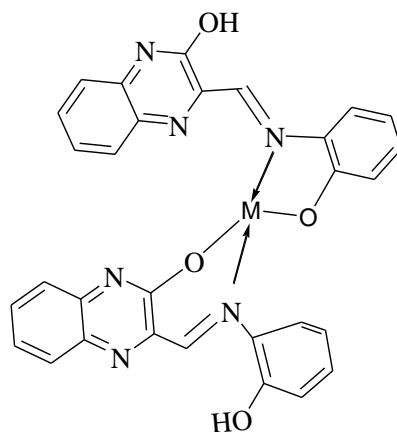


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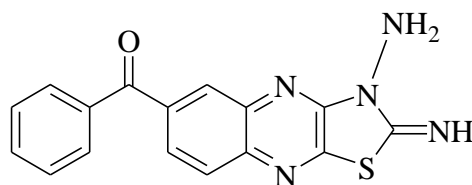
**15**

**S. Mayadevi *et al.***, synthesized some new transition metal complexes of the Schiff base deprotonated quinoxaline-2-carboxaldehyde-2-aminophenol(QAP) (**16**) and characterized by elemental analysis, molar conductance, magnetic measurements, IR and UV-vis studies. The complexes of Mn(II), Co(II), Ni(II) and Cu(II) have empirical formula  $[M(QAP)_2]$  and Fe(III) complex have the empirical formula  $[Fe(QAP)_2Cl]$ . The very low molar conductance values indicated the non-electrolytic nature of the complexes. A tetrahedral geometry was assigned for Mn(II), Co(II), Ni(II) and Cu(II) complexes and octahedral geometry for Fe(III) complex<sup>9</sup>.



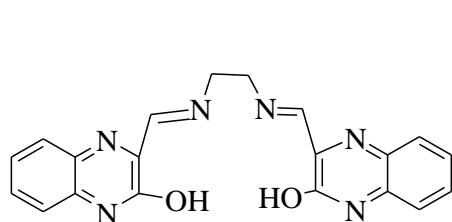
16

Y. A. Ammar *et al.*, have reported the synthesis of some Schiff bases from 6-benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-*b*]quinoxaline<sup>10</sup> (17).

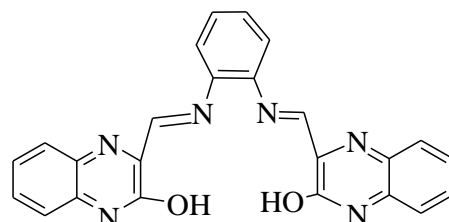


17

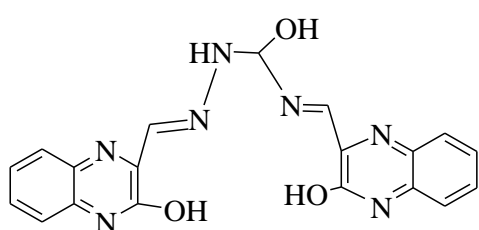
N. R. Suja *et al.*, studied zeolite-encapsulated Co(II), Ni(II) and Cu(II) complexes of N,N'-bis(3-hydroxyquinoxaline-2-carboxalidene)ethylenediamine (18), N,N'-bis(3-hydroxyquinoxaline-2-carboxalidene)o-phenylenediamine (19), 3-hydroxy quinoxaline-2-carboxaldehydehydrazone (20) and N,N'-bis(3-hydroxyquinoxaline-2-carboxalidene) diethylenetriamine (21)<sup>11</sup>.



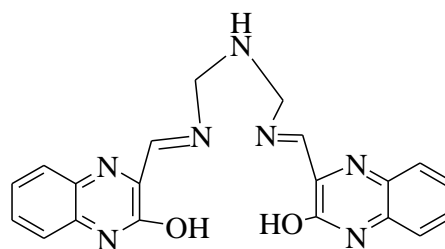
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19

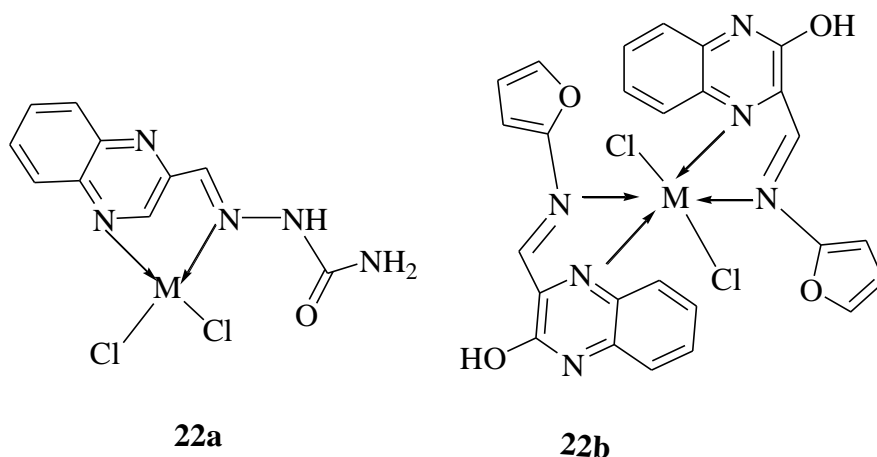


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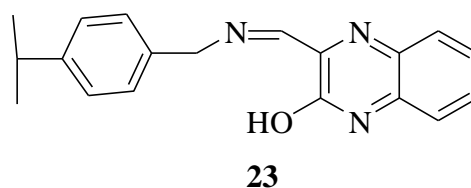


21

**S. Mayavi *et al.***, synthesized two series of transition metal complexes of Schiff base derived from quinoxaline-2-carboxalidene and semicarbazide and quinoxaline-2-carboxalidene and furfurylamine (**22a**, **22b**) and characterized by elemental analysis, molar conductance, magnetic susceptibility measurements, IR, electronic and electron paramagnetic resonance (EPR) spectral studies. The molar conductance values showed that the complexes are non-electrolytes. All the complexes exhibited catalytic activity towards oxidation of 3,5-ditert-butylalcohol to 3,5-di-tert-butylquinone using atmospheric oxygen<sup>12</sup>.



**N. R. Suja *et al.***, studied the synthesis, characterization and assignment of possible geometries of polymer anchored Schiff base (PS-HQAD) (**23**) complexes of Co(II), Ni(II), and Cu(II) metal ions. PS-HQAD was prepared by the condensation of polymer-bound amine with 3-hydroxyquinoxaline-2-carboxaldehyde<sup>13</sup>.



**Y. B. Dong *et al.***, synthesized four new polymeric Ag(I) complexes based on 2,5-bis(2-benzodiazine)-3,4-diaza-2,4-hexadiene with disubstituted quinoxalinediazenes. The complexes were characterized by IR, elemental analysis, and single-crystal X-ray diffraction<sup>14</sup>.

**Wang *et al.***, reported the design and synthesis of a chemo selective sensor for mercury ion containing quinoxaline<sup>15,16</sup>.

**Gamo *et al.***, reported the synthesis of Ni(II) and Cu(II) complexes with 2,3-quinoxalinedioxime and their characterization using physico-chemical

techniques. Metal complexes of a new multidentate ligand with two different N-heterocyclic constituents were synthesized<sup>17</sup>.

**M. Yohannes *et al.***, synthesized N,N'-bis(3-quinoxaline-2-one)diamino propane and its Cd(II), Ni(II), Zn(II), Fe(II), Cr(III), Mn(II) and VO(IV) complexes. They were characterized by IR, <sup>1</sup>H and <sup>13</sup>C NMR, electronic spectra, and elemental analysis<sup>18</sup>.

**X.Q.Che *et al.***, reported the synthesis of Zn(II) complexes of 8-carboxyindolenol[1,2-b]-quinoxaline-11-onethiosemicarbazone. The Zn(II) complex was five-coordinated and situated in a distorted square-pyramidal environment<sup>19</sup>.

**X. Wu *et al.***, synthesized Ru(III) complexes of deprotonated quinoxaline-2-carboxalidene-2-aminophenol,N,N'-bis(3-hydroxyquinoxaline-2-carboxalidene)-o-phenylenediamine and Schiff base derived from 3-hydroxyquinoxaline-2-carboxaldehyde and 2-aminobenzimidazole and characterized by elemental, spectral (IR, UV-vis, EPR and FABmass), thermogravimetric, molar conductance and magnetic moment analysis<sup>20</sup>. The synthesized new ligands and their complexes have been tested for *in-vitro* growth-inhibitory activity against one strain of gram-positive bacteria *Klebsiella pneumoniae* and gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. The complexes are active while the ligands were inactive towards the bacteria under study.

**P. S. Chittilapilly *et al.***, synthesized and characterized zeolite-Y-encapsulated Ru(III) complexes. The Ru(III) complex was used as a catalyst for catechol oxidation by H<sub>2</sub>O<sub>2</sub> to 1,2,4-trihydroxy benzene<sup>21</sup>.

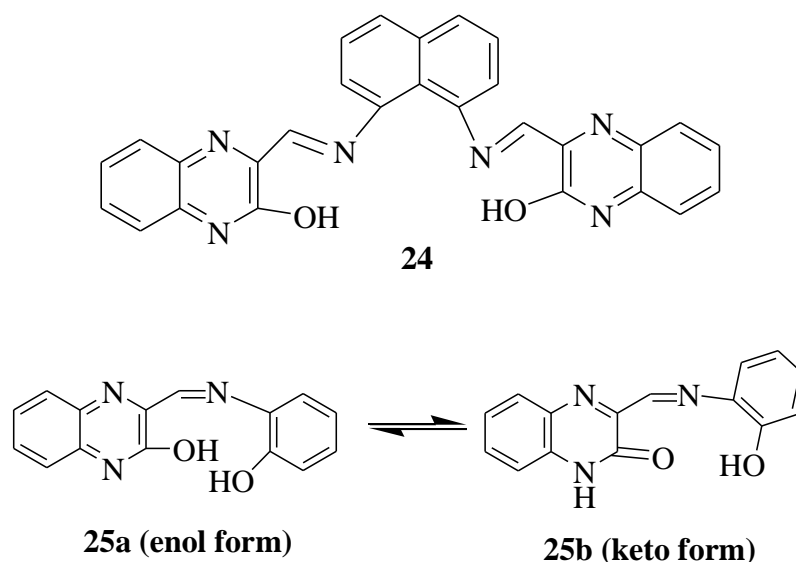
**Lakshmi *et al.***, synthesized new Cr(III), Mn(II), Fe(III), Ni(II), and Cu(II) complexes of NBHQO and characterised using various spectral techniques like elemental analysis, molar conductance, thermal, spectral and magnetic data. Analytical data confirmed the metal-to-ligand stoichiometry as 1 : 2 except in Cu(II) complex where it is 1 : 1. Cr(III) and Fe(III) complexes were 1 : 1 electrolytes, Ni(II) complex was 1 : 2 electrolyte, and Mn(II), Co(II), and Cu(II) complexes were non-electrolytes. Octahedral geometries have been proposed for all the complexes, except for Cu(II) which had square planar geometry<sup>22</sup>.

**X. Chittilapilly *et al.***, synthesized ruthenium(III) complexes of the Schiff bases derived from 3-hydroxyquinoxaline-2-carboxaldehyde and *o*-phenylenediamine, *o*-aminophenol and 2-aminobenzimidazole and the Schiff bases derived from salicylaldehyde and *o*-phenylenediamine, *o*-aminophenol or 2-aminobenzimidazole

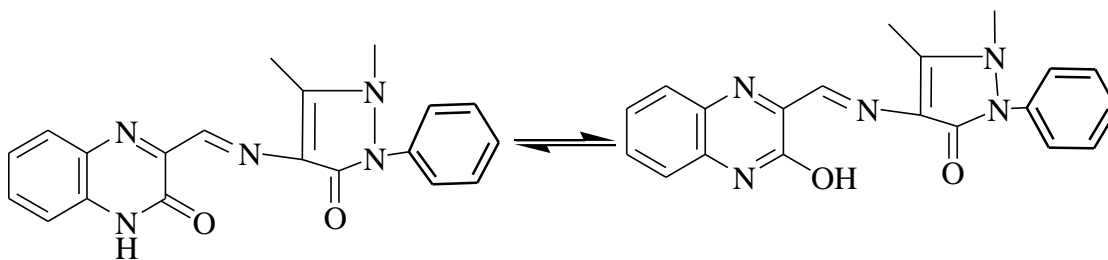
and characterized by elemental, spectral (FT IR, UV-vis, EPR and FAB mass), thermogravimetric, conductance and magnetic moment analyses. An octahedral structure has been tentatively proposed for all the new complexes. The synthesized ligands and complexes have been tested for *in vitro* growth inhibitory activity against gram positive bacteria *Klebsiella pneumoniae*, gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. The complexes were active while the ligands were inactive towards the bacteria under study<sup>23, 24</sup>.

**A. G. Budie *et al.***, synthesized metal complexes of heterocyclic multidentate ligands containing triazine and quinoxaline by template method and characterized by various spectral techniques. The ligand was coordinated to the metal as a dibasic tridentate (ONN) ligand. The studies revealed tetrahedral and octahedral geometries for the Zn(II) and Cu(II) complexes, respectively<sup>25</sup>.

**V. Arun *et al.***, reported the VO(IV), Cu(II), and Ru(II) complexes of N,N'-bis(3-hydroxyquinoxaline-2-carboxalidene)1,8-diamino naphthalene (**24**), N,N'-bis(3-hydroxyquinoxaline-2-carboxalidene)trans (R,R')1,2-diaminocyclohexane (**25**), 3-hydrazinoquinoxaline-2-carboxalidene-2-aminophenol, and 3-hydroxyquinoxaline-2-carboxalidene-4-aminoantipyrine (**26**) and their catalytic activities towards oxidation and hydrogenation reactions<sup>26</sup>. The ligands exhibited two tautomeric forms, enol and keto forms.

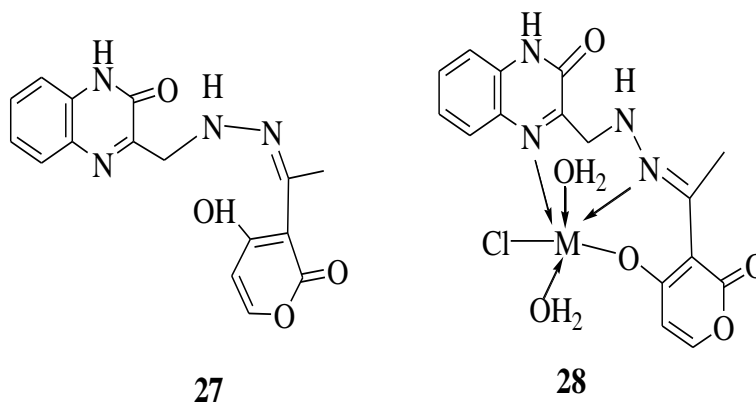






**26 (keto and enol forms)**

**P. V. A. Lakshmi *et al.***, synthesized and characterised a series of new Cr(III), Mn(II), Fe(III), Co(II), Ni(II), and Cu(II) complexes of Schiff base derived from 3-hydrazinoquinoxaline-2-one and dehydroacetic acid (**28**) and characterized. The Schiff base (**27**) exhibited bi-ambidenticity, as monobasic tridentate ONN donor in Cr(III), Mn(II), Co(II), and Ni(II) complexes<sup>27</sup>.

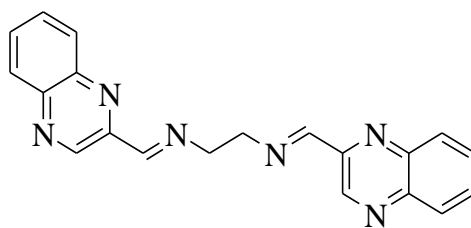


**27**

**28**

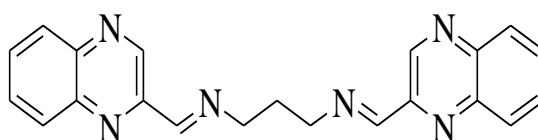
**V. Arun *et al.***, synthesized two new complexes of  $[ML(H_2O)] \cdot H_2O$  {where  $M=Ni(II)$  or  $Ru(II)$ } and characterized by elemental analysis, IR, UV-vis, diffuse reflectance spectroscopy, FAB-mass, TG-DTA, atomic absorption spectroscopy, cyclic voltammetry, molar conductance and magnetic susceptibility measurements. The complexes had a distorted octahedral structure and were effective catalysts for hydrogenation of benzene<sup>28, 29</sup>.

**D. Varghese *et al.***, have reported the synthesis and crystal structure of *N,N'*-bis[(*E*)-quinoxalin-2-ylmethylidene]ethane-1,2-diamine (**29**). The quinoxaline ring was nearly planar, with a maximum deviation of 0.021(2) Å from the mean plane. The crystal structure was stabilized by intermolecular C-H...N interactions, leading to the formation of a layer-like structure<sup>30</sup>.

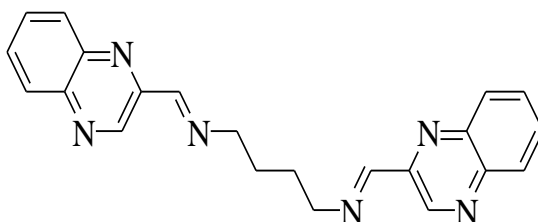


**29**

**D. Varghese *et al.***, synthesized Schiff bases by the condensation of quinoxaline-2-carboxaldehyde and ethylenediamine. The crystal structures of the Schiff bases, N,N'-bis[(E)-quinoxalin-2-ylmethylidene]propane-1,3-diamine (**30**) and N,N'-bis[(E)-quinoxalin-2-ylmethylidene]butane-1,4-diamine were determined (**31**). These Schiff bases crystallized in a monoclinic crystal system. Molecular conformations of the crystal structures were stabilized by aromatic  $\pi$ - $\pi$  stacking<sup>31</sup>.



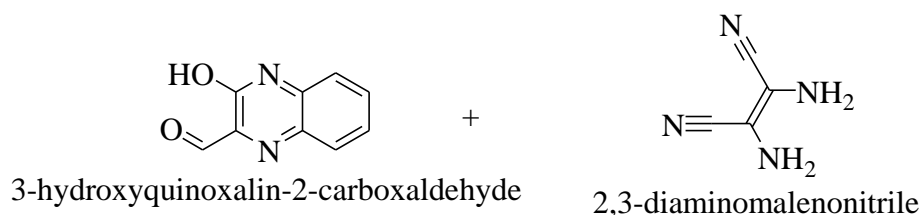
**30**



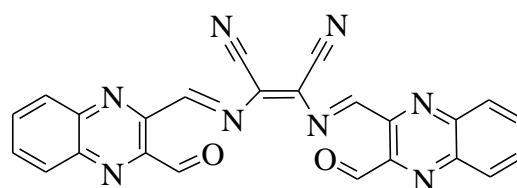
**31**

**V. Arun *et al.***, have synthesized a bis-azomethine Schiff base by the condensation of 3-hydroxyquinoxaline-2-carboxaldehyde and 2,3-diaminomaleonitrile and characterized it by IR, <sup>1</sup>H and <sup>13</sup>C NMR, HPLC, cyclic voltammetry, thermogravimetry-differential thermal analysis (TG-DTA) and DSC studies. The studies revealed that the Schiff base existed in two major tautomeric forms, *i.e.*, minor enol and major keto forms<sup>32</sup> (**32**).

**Leeju *et al.***, reported the synthesis and crystal structure of N-[(E)-quinoxalin-2-ylmethylidene]-1H-indazole-5-amine<sup>33</sup> (**33**).

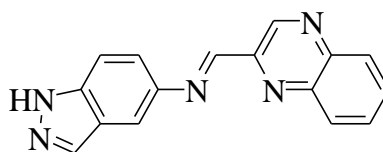


2H<sub>2</sub>O



Major Keto form

**32**



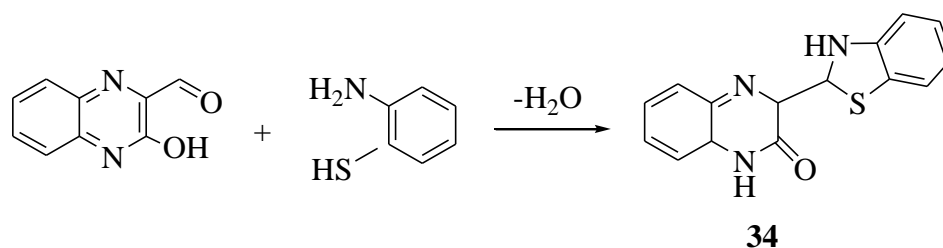
**33**

**M. Sebastian *et al.***, synthesized mononuclear Co(II) complex [CoL<sub>2</sub>].H<sub>2</sub>O (where HL=quinoxaline-2-carboxalidene-2-amino-5-methylphenol) and characterized by elemental analysis, conductivity measurements, IR, UV-vis, TG-DTA and XRD. The crystallographic study showed that Co(II) had a distorted octahedral geometry with each tridentate NNO Schiff base. They also reported the synthesis and characterization of Mn(II), Fe(III), Ni(II), Cu(II), and Zn(II) complexes. The structure of [NiL<sub>2</sub>].H<sub>2</sub>O was studied by single-crystal XRD. All the prepared complexes were screened for their catalytic activity for liquid phase hydrogenation of phenol<sup>34, 35</sup>.

**S. Budagumpi *et al.***, reported the synthesis and characterization of a series of Co(II), Ni(II), Cu(II) and Zn(II) complexes of 1*H*-pyrazolo-3,5-dicarboxylic(2-hydroxy-3-hydrazinoquinoxaline). DNA binding/cleavage studies revealed stronger binding of the Ni(II) complex, confirmed by absorbance, viscometric and gel electrophoresis studies. Cu(II) complex showed growth-inhibitory activity<sup>36</sup>.

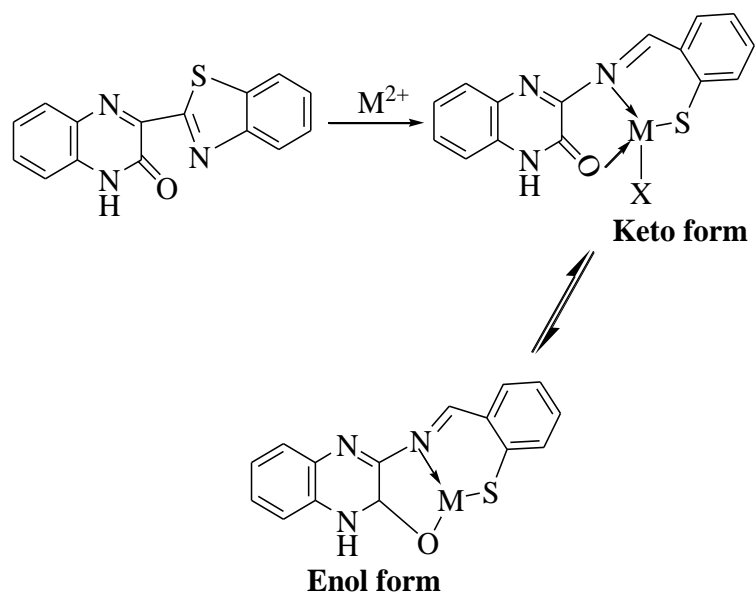
**B. K. Rai *et al.***, reported the synthesis, characterization, and antimicrobial screening of Co(II), Ni(II), and Cu(II) complexes with Schiff base derived from

2-arylquinoxalinesemicarbazone (**34**) which behaved as a neutral bidentate chelating agent, bonded through azomethine nitrogen and oxygen of semicarbazone<sup>37</sup>.



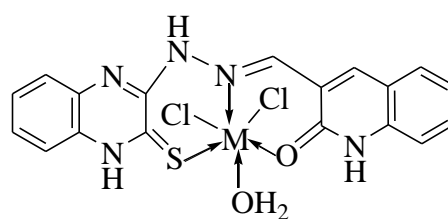
**M. Sebastian *et al.***, reported a new benzothiazoline derivative, 3-(2,3-dihydro-1,3-benzothiazol-2-yl)quinoxaline-2(1H)-one. The Schiff base was prepared by condensation of 3-hydroxyquinoxaline-2-carboxaldehyde with 2-mercaptoaniline. They prepared complexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II). All compounds have been characterized by elemental analysis, IR, electronic spectra, TG, molar conductance and magnetic susceptibility measurements. Complex formation proceeds with rearrangement of benzothiazoline to form corresponding Schiff base chelates. The quinoxaline moiety of the ligand and its complexes exhibited keto–enol tautomerism. All complexes showed octahedral geometry, except Cu(II) and Zn(II) which have square planar and tetrahedral geometries, respectively<sup>38</sup>.

**G. S. Kurdekar *et al.***, reported a series of Co(II), Ni(II), Cu(II), and Zn(II) complexes of bi and tridentate hydrazones prepared by the condensation of 2-mercapto-3-hydrazinoquinoxaline with 2-hydroxy-3-formylquinoline and 3-acetyl coumarin respectively. The compounds, characterized by various analytical techniques and magnetic moment studies, were monomeric and non-electrolytes. All the complexes exhibited octahedral geometry except Cu(II) which had square-pyramidal geometry (**35-38**)<sup>39</sup>.



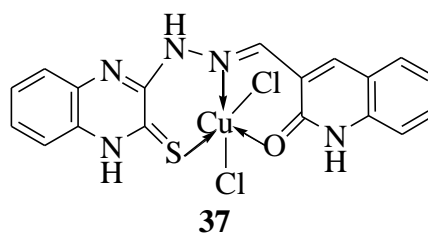
**M= Mn, Cu or Zn**

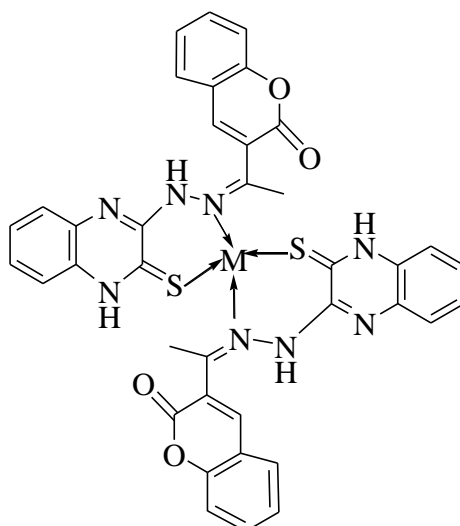
**35**



**M=Co(II), Ni(II) or Zn(II)**

**36**



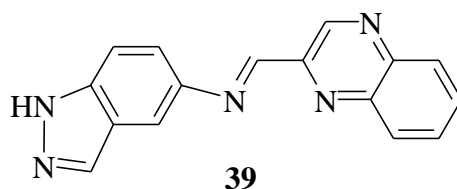


**M=Cu(II), Co(II), Ni(II)**  
**38**

**N. V. Kulkarni *et al.***, synthesized new binuclear transition metal complexes of bicompartamental SNONS-donor Schiff base obtained by condensation of 3-hydrazinyl quinoxalin-2(1*H*)-thione with 2,6-diformyl-4-methyl phenol. The synthesized compounds were characterized by various physico-chemical techniques. Influence of two metal centers in terms of cooperative effect on electronic, magnetic, electrochemical, and structural properties were investigated<sup>40</sup>.

**Y. Hu *et al.***, synthesized the Schiff base compounds, N,N'-((5,5'(quinoxaline-2,3-diyl)bis(1*H*-pyrrole-5,2-diyl))bis(methanylylidene)bis(4-methoxy aniline) and N,N'-((5,5'(quinoxaline-2,3-diyl)bis(1*H*-pyrrole-5,2-diyl))bis(methanylylidene)dianiline). These compounds displayed good sensitivity toward transition-metal ions with Cd(II) and Zn(II) turn-on and Cu(II) and Hg(II) turn-off fluorescence. The fluorescence and crystal structure data indicated a 1:1 stoichiometry complex was formed<sup>41</sup>.

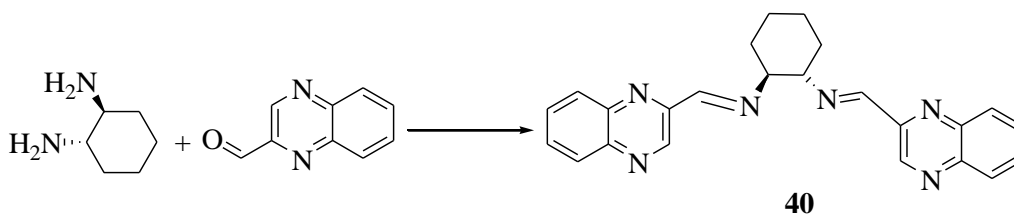
**N. V. Kulkarni *et al.***, reported the ligational behavior of Schiff base (**39**) prepared by condensation of 3-hydrazinylquinoxaline-2(1*H*)-thione with isatin and quinoxaline-2,3(1,4*H*)-dione and their metal complexes with first-row transition metal ions. The compounds were characterized by spectro-analytical techniques and magnetic susceptibility measurements. All the complexes show octahedral geometry and were mononuclear. In the crystal structure, the mean planes of quinoxaline and indazole fragments formed dihedral intermolecular N–H...N hydrogen bonds. The crystal packing also exhibited  $\pi$ – $\pi$  interactions<sup>42</sup>.



In the crystal, weak intermolecular N–H...N hydrogen bond linked the molecule into zigzag chains extending in the [0 0 1] direction. The crystal packing also exhibited  $\pi$ – $\pi$  interactions.

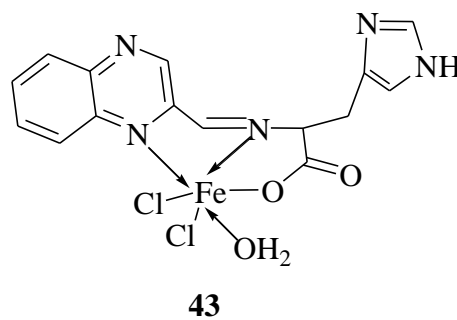
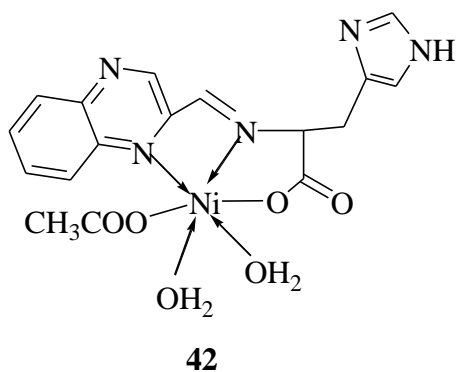
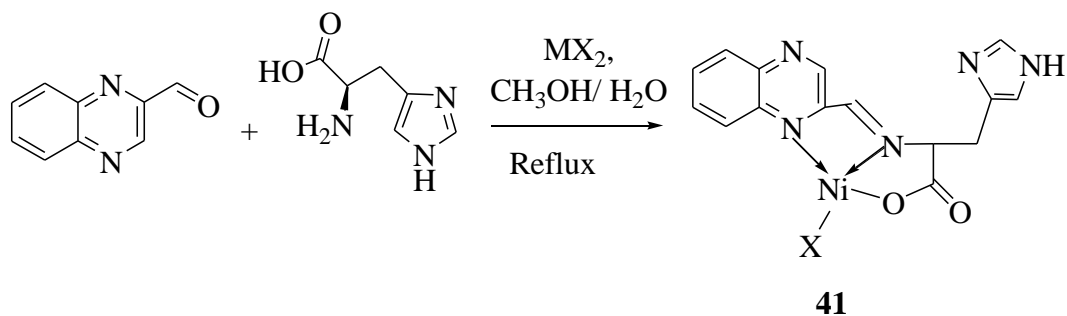
**V. G. Ratnadeep *et al.***, have reported the synthesis and characterization of a series of Schiff bases of quinoxaline-2(1*H*)-one<sup>43-45</sup>. The synthesized Schiff bases were screened for their anti-inflammatory, anticonvulsant and antimicrobial activities.

**Y. Zhengfeng, *et al.***, reported the synthesis and crystal structure of Schiff bases (*N,N'*-Bis-quinoxalin-2-ylmethylene-cyclohexane-1,2-diamine(**40**)) derived from quinoxaline-2-carboxaldehyde with (1*S*,2*S*)-1,2-diaminocyclohexane and 1,1'-binaphthyl-2,2'-diamine<sup>46</sup>.



**B. Kumar *et al.***, synthesized quinoxaline based complexes and characterized using analytical and spectral data. Electronic spectra and magnetic susceptibility values revealed octahedral geometry for the complexes. The low molar conductance value of the complexes confirmed their non-electrolytic nature. The ligand and its metal complexes have been screened for antibacterial and antifungal activity<sup>47</sup>.

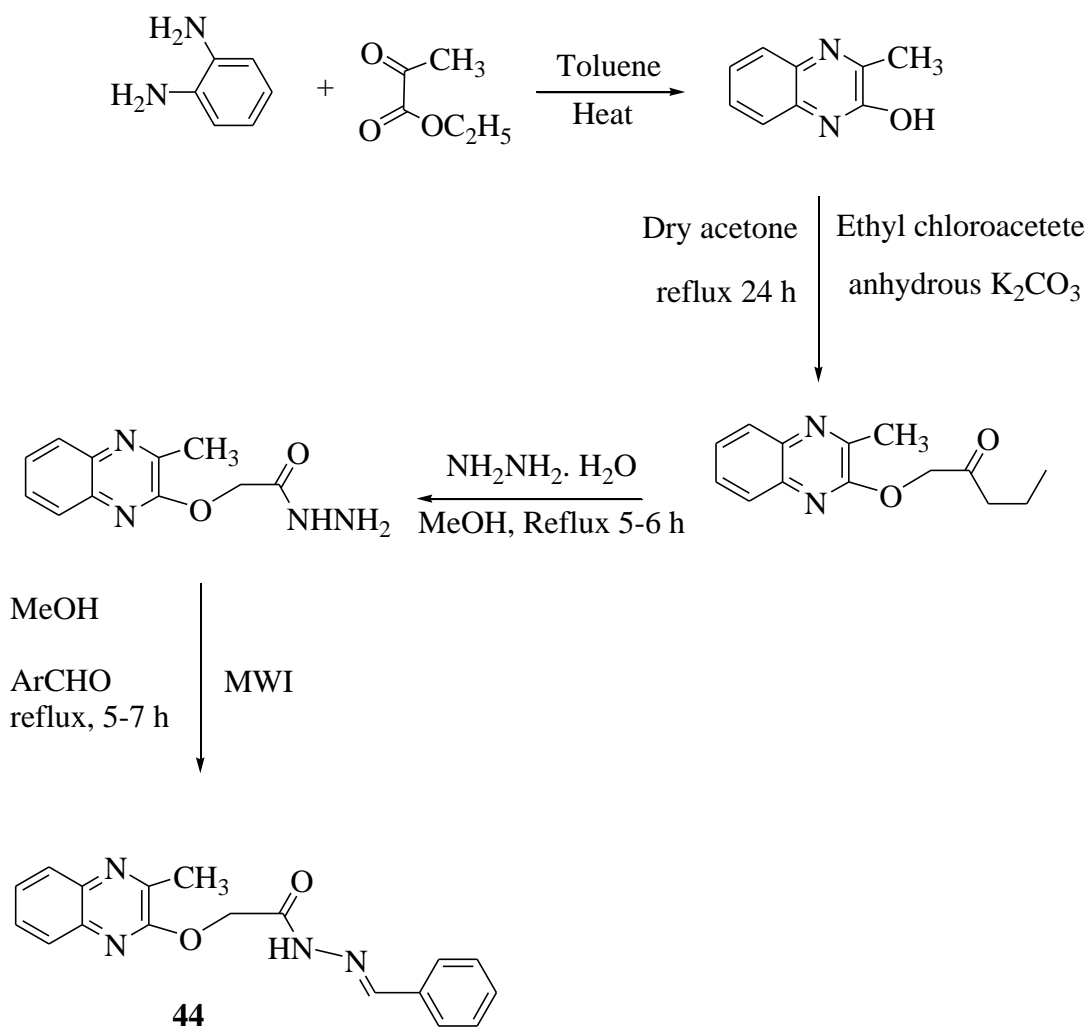
**M. Sebastian *et al.***, reported the synthesis and spectral characterization of Schiff base derived from quinoxaline-2-carboxaldehyde and L-histidine and its complexes obtained by template method. The physico-chemical and spectrochemical measurements revealed square planar geometry for Cu(II) complex, tetrahedral geometry for Mn(II) and Zn(II) complexes (**41**), octahedral geometry for Ni(II) complexes (**42**) and Fe(III) (**43**) complexes<sup>48</sup>.



**P. M. V. Kumar *et al.***, synthesized a novel heterocyclic NO donor Schiff base 4-isopropylbenzaldehyde[*N*-(3-oxo-3,4-dihydro-2-quinoxaliny)hydrazone]. A series of Ni(II) complexes has been synthesized where the ligand acts as a bidentate ligand coordinating through the imine nitrogen and quinoxaline oxygen. The single crystal X-ray diffraction analysis of the ligand and the Ni(II) complex revealed that both crystallized in the monoclinic  $P2_1/c$  space group giving rise to 1D and 2D architecture, respectively<sup>49</sup>.

**L. Achutha *et al.***, have synthesized quinoxaline-incorporated Schiff bases (**52**) by the condensation of 2-[(3-methylquinoxalin-2yl)oxy]acetohydrazide with indole-3-carboxaldehyde, furfuraldehyde, 5-(4-nitrophenyl)-2-furfuraldehyde and substituted benzaldehydes under conventional and microwave irradiation methods. The microwave method was remarkably successful with higher yields and less reaction time compared to conventional heating method. All the synthesized compounds were characterized by IR, <sup>1</sup>H NMR, and mass spectral data; the compounds were evaluated for anti-tubercular and anti-inflammatory activities<sup>50</sup>.





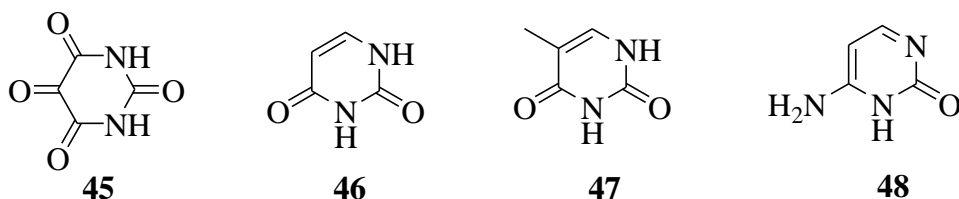
**N. V. Kulkarni *et al.***, synthesized new transition metal complexes of quinoxaline–thiosemicarbazone ligands and characterized by spectro-analytical techniques. The ligands were obtained by condensation of quinoxaline-2,3(1,4*H*)-dione with methyl and phenylthiosemicarbazide. Some of the synthesized compounds exhibited antidiabetic activity<sup>51</sup>.

**Q. Guo *et al.***, synthesized novel 2,3-bis(1*H*-pyrrol-2-yl)quinoxaline-functionalized hydrazones and characterized as new chemosensors for Cu(II)<sup>52</sup>.

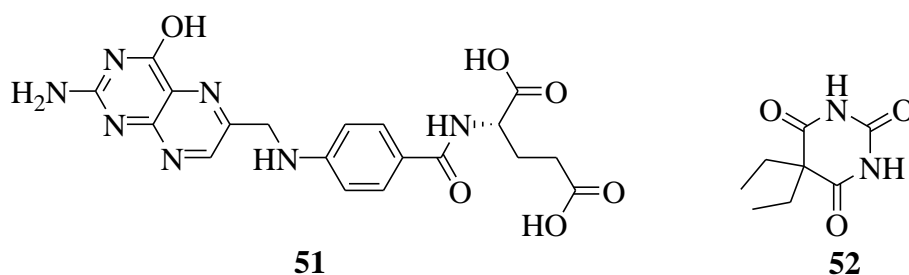
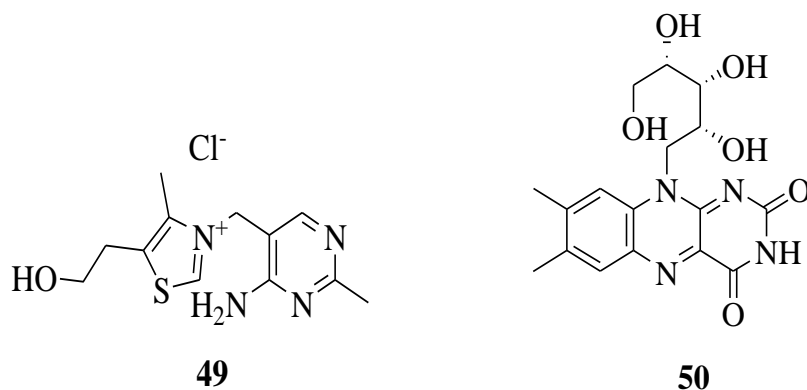
**P. V. A. Lakshmi *et al.***, synthesized VO(IV) complexes and characterized on the basis of analytical, molar conductance, magnetic moment, IR, NMR, ESR and electronic spectral data. The ligands were monobasic tridentate ONN donors and co-ordinated to the metal through phenolic oxygen and azomethine nitrogens<sup>53</sup>.

## 2.2. Pyrimidines

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS.

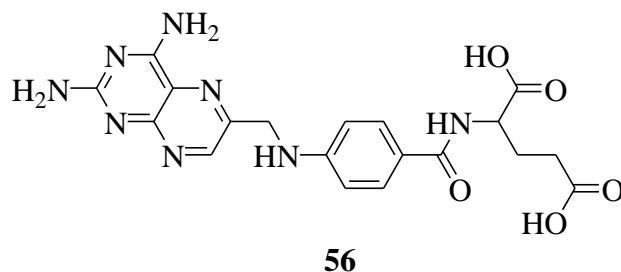
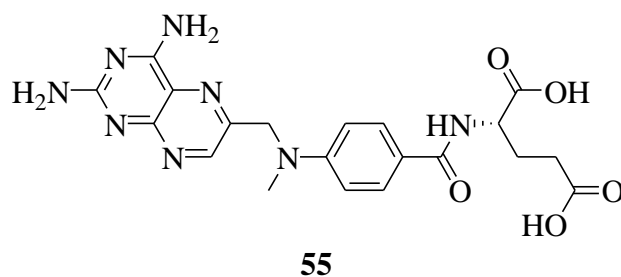
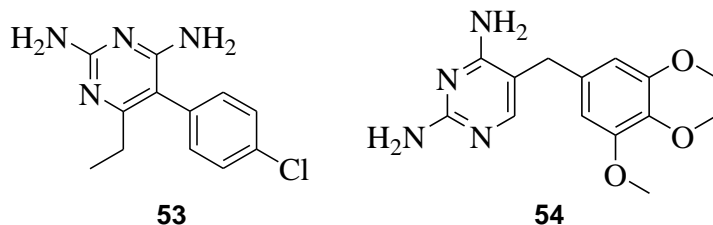


Alloxan (**45**) is known for its diabetogenic action in a number of animals. Uracil (**46**), thymine (**47**) and cytosine (**48**) are the three important constituents of nucleic acids. The pyrimidine ring is found in vitamins like thiamine (**49**), riboflavin (**50**) and folic acid (**51**). Barbitone (**52**), the first barbiturate hypnotic sedative and anticonvulsant is a pyrimidine derivative<sup>54-57</sup>.



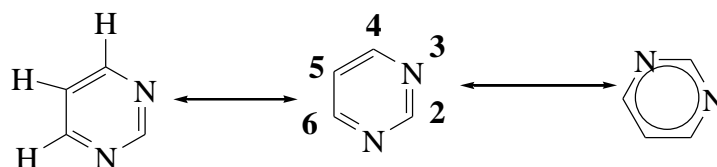
In 1948, **Hitchings** made an important observation that a large number of 2,4-diaminopyrimidines and some 2-amino-4-hydroxypyrimidines are antagonists of folic acid. Since then, a large number of 2,4-diaminopyrimidines have been synthesized as antifolates. It was eventually proved that these pyrimidines are

inhibitors of the enzyme dihydrofolate reductase (DHFR). Notable amongst the 2, 4-diaminopyrimidine drugs are pyrimethamine (**53**), a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim (**54**), an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non selective DHFR inhibitors, methotrexate (**55**) and aminopterin (**56**), both used in cancer chemotherapy<sup>58</sup>.



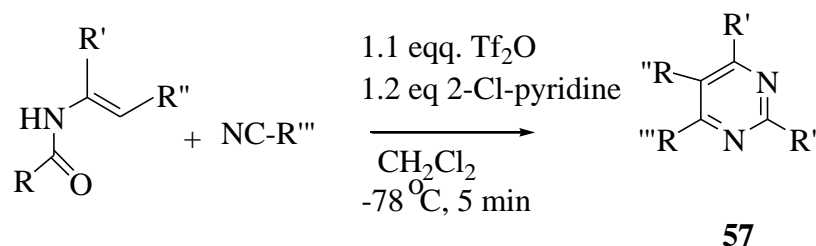
### 2.2.1. Review on various pyrimidine derivatives and its transition metal complexes

Pyrimidinetriazines commonly known as barbituric acids play an important role in the biological field. 5-alkylated pyrimidine triazines have been reported to show antispasmodic, muscle relaxant and anticonvulsant activity. The metabolism of these pyrimidines is unique and important to understand both biochemical utilization of these compounds and drug metabolism of pyrimidine derivatives<sup>59,60</sup>. Pyrimidine is considered to be a resonance hybrid of the charged and uncharged canonical structures,

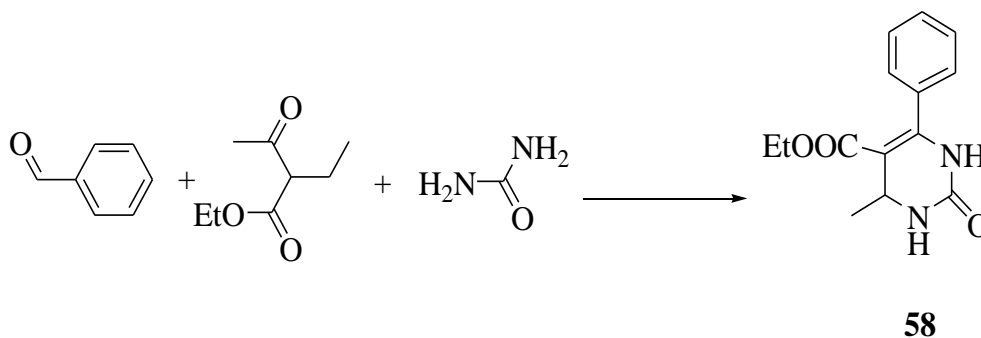


Various methods for synthesis of pyrimidine derivatives are available in literature. The naturally occurring pyrimidine derivative was first isolated by **Gabrial** and **Colman** in 1870, and its structure was confirmed in 1953 as 5- $\beta$ -D-glucopyranoside. Some pyrimidines of physiological as well as pharmacological importance are as under: *e.g.*, cytosine, bedmethrin and trimethoprim.

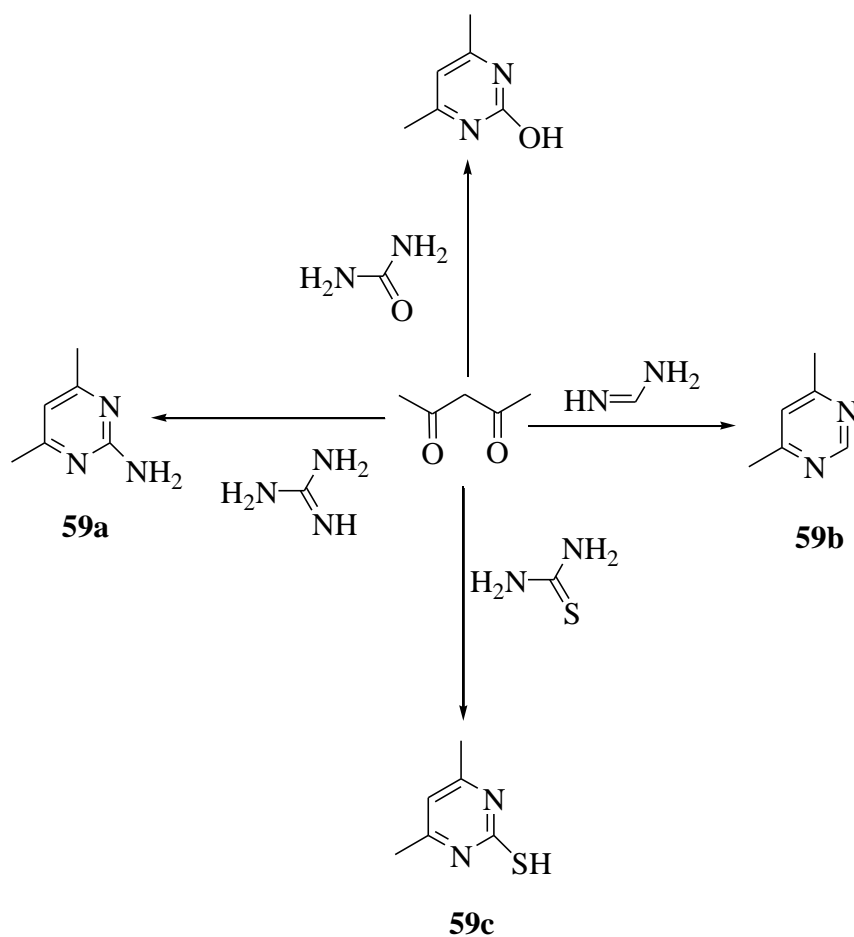
**M. Movassaghi *et al.***, have synthesized (**57**) by the direct condensation of cyanic acid derivatives with *N*-vinyl/aryl amides which affords the corresponding C4-heteroatom substituted pyrimidines. The use of cyanic bromide and thiocyanatomethane in this chemistry provides versatile azaheterocycles poised for further derivatization<sup>61</sup>.



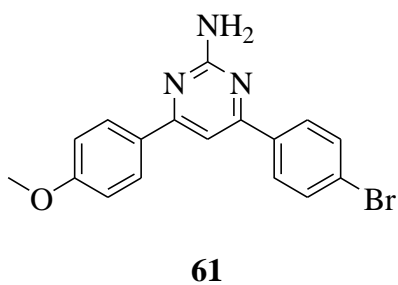
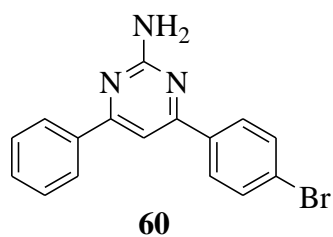
**R. R. Hunt *et al.***, have synthesized pyrimidines using Biginelli reaction which involved the reaction between an aldehyde, a 1,3-dicarbonyl and urea under acidic conditions, proceeding through a sequence of reactions. The product of this novel one-pot, three-component synthesis was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one (**58**)<sup>62</sup>.

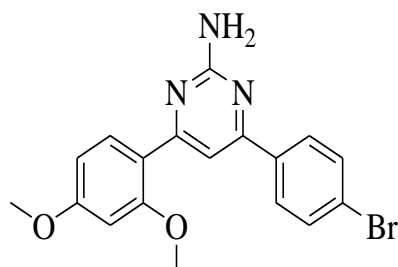


The nitrogen containing fragment may be an amidine, urea, thiourea or guanidine and acetyl acetone serves as an excellent illustrative example, it readily undergoes reaction with formamidine, guanidine, urea or thiourea to produce 4,6-dimethyl pyrimidines (**59a-c**).



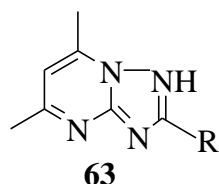
D. T. Nguyen *et al.*, have synthesized and characterized a series of 4-(4-bromophenyl)-6-phenylpyrimidin-2-amine (**60**), 4-(4-bromophenyl)-6-(4-methoxy phenyl)pyrimidin-2-amine (**61**), and 4-(4-bromophenyl)-6-(2,4-dimethoxyphenyl) pyrimidin-2-amine<sup>63</sup> (**62**).



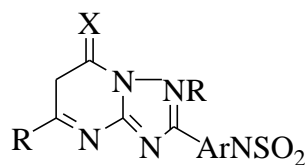


**62**

V. Ram *et al.*, have synthesized triazole substituted triazolo-pyrimidine (**63**) derivatives and characterized using various spectral techniques. The compounds were screened for the biological activities and found them to exhibit anti-inflammatory activity. They also prepared 6,7-dihydro-1,3,4-triazolo-pyrimidine [1,5-*a*]-1,3,5-triazin-2-sulfonamides (**64**) and found them as agents with herbicidal and plant growth regulating activity<sup>64</sup>.



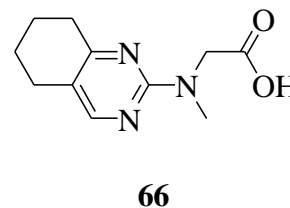
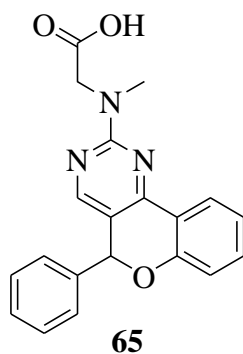
**63**



**64**

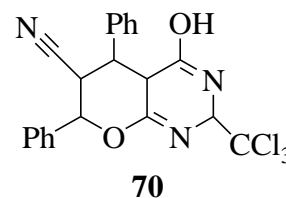
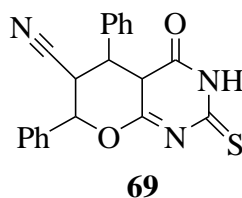
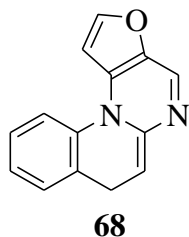
B. A Olga *et al.*, have prepared a series of N-methyl-N-pyrimidin-2-yl glycines, having the pyrimidine ring fused with a cyclohexane, [N-methyl-N-(5,6,7,8-tetrahydroquinazolin-2-yl)glycine], cyclohexene[N-methyl-N-(5,6-dihydroquinazolin-2-yl)glycine], 1,2,3,4-tetrahydronaphthalene[N-methyl-N-(5,6-dihydrobenzo[e]quinazolin-2-yl)glycine] and benzopyrane[N-methyl-N-(5-phenyl-5H-[1]benzopyrano[4,3-*d*]pyrimidin-2-yl)glycine] have been prepared and tested for anti-inflammatory activity (**65**, **66**)<sup>65</sup>.

A. Nagaraj *et al.*, have prepared amino pyrimidine derivatives and characterized using various spectral techniques. These synthesized pyrimidine derivatives possess a broad spectrum of biological effectiveness such as antimicrobial and anti-inflammatory activity(**67**)<sup>66</sup>.



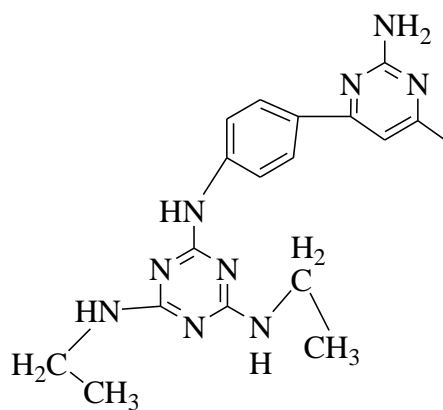
**B. Padamashale *et al.***, have reported the naphtho[2,1-*b*]furo[3,2-*d*]pyrimidine(**68**) and induced rat paw edema method was employed for evaluating the anti-inflammatory activity. Novel angularly fused pentacyclic heterocycles *viz.*, tetrazolo[1,5-*c*]pyrimido[5,4-*b*]naphtha[2,1-*b*]furan derivatives and triazolo[4,3-*c*]pyrimido[5,4-*b*]naphtha[2,1-*b*]furan derivatives were synthesized by reacting with appropriate reagents. All the newly synthesized compounds have been characterized by elemental analysis and spectroscopic data and have been evaluated for antimicrobial, anthelmintic, anticonvulsant and antipyretic activities<sup>67</sup>.

**M. Favre *et al.***, have synthesized some substituted thieno pyrimidine-4-one and screened them for analgesic and anti-inflammatory activity<sup>68</sup>.

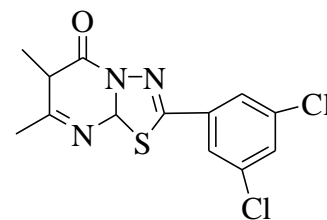


**M. S. El-Hossini *et al.***, have carried out the reaction of ethyl cyanoacetate with  $\alpha$ -cyanochalcone, which lead to the formation of a  $\beta$ -enaminoester *via.*, Michael addition. This was reacted with ethyl cyanoacetate, phenyl isothiocyanate and trichloroacetonitrile to yield the pyranopyrimidines (**69**, **70**) which were evaluated for their antibacterial activity<sup>69</sup>.

**S. Anjani *et al.***, have synthesized 2,4-bis(ethylamino)-6[4-{ 3-(substituted phenyl 2-propenone-1-yl-3-phenyl-amino)-5-triazine (**71**) by treating a ketone with different substituted aromatic and heterocyclic aldehyde in the presence of alkali<sup>70</sup>. All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method.



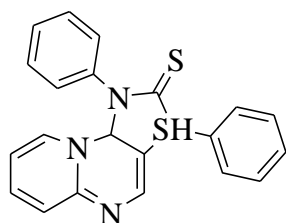
71



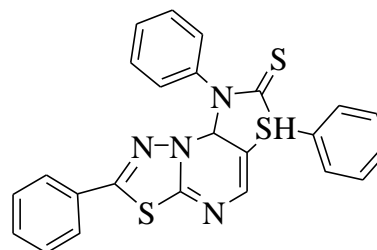
72

**P. Gogia *et al.***, have synthesized 1,3,4- thiadiazolo-(3,2-a)pyrimidin-5-one (72) which exhibited antifungal activity<sup>71</sup>.

**J. S. Singh *et al.***, synthesized a number of 3,10-diaryl-2-thiothiazolo[4,5-*d*]pyrido[2,1-*b*] pyrimidines and 3,6,9-triaryl-2-thiothiazolo[4,5-*d*][1,3,4]thiadiazolo[2,3-*b*] pyrimidines from the Michael adducts which in turn have been prepared by the reaction of arylidenorhodanines with 2-aminopyridine and 2-amino-5-aryl-1,3,4-thiadiazoles<sup>72</sup>. The antifungal activity of the compounds (73, 74) have been screened and found positive.



73



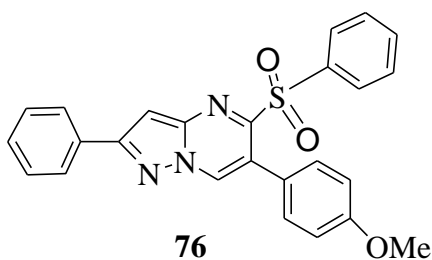
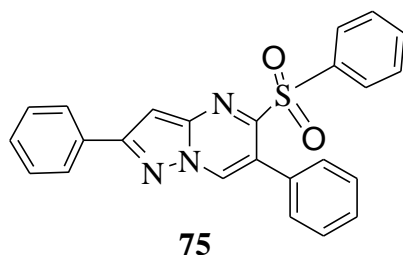
74

**O. A. Fathalla, *et al.***, have synthesized a series of pyrimidine derivatives and examined them for their anticancer activity. The five thiouracil derivatives were subjected to a screening system for evaluation of their antitumor activity against liver cancer (HEPG2) tumor cell line in comparison to the known anticancer drugs: 5-Fluorouracil and Doxorubicin. These selected thiouracil derivatives showed antitumor activity with varying intensities in comparison to the known anticancer drugs<sup>73</sup>.

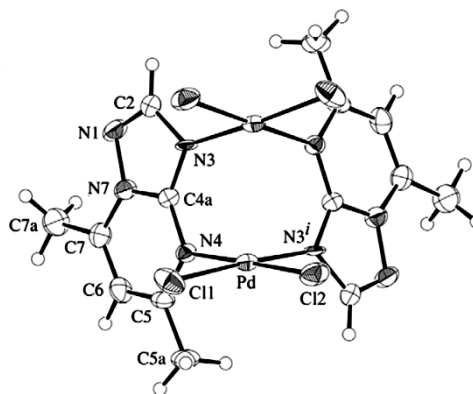
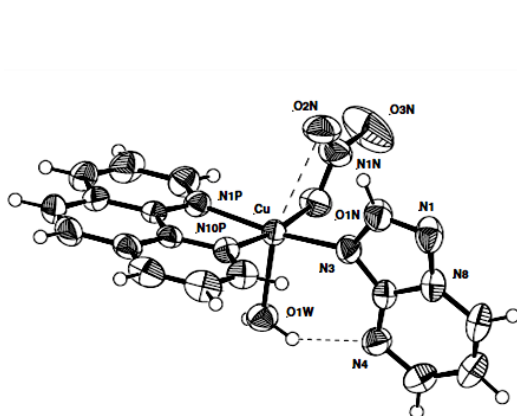
**R. S. Mohamed *et al.***, have reported the synthesis of 2,7-diphenyl-6-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidine and its *p*-methoxy analogue (75, 76) and



evaluated them as Aurora-A kinase inhibitors<sup>74</sup>. The cytotoxic activity of the newly synthesized compounds against HST116 colon tumor cell line was investigated.



**R. M. Carmen *et al.***, have isolated and structurally characterised several Cu(II) complexes with 1,2,4-triazolo[1,5-*a*]pyrimidine (tp) and its 5,7-dimethyl derivative (dmtp)<sup>75</sup>. Five of them were mononuclear and contained, 10-phenanthroline (phen) or ethylenediamine (en) as auxiliary ligands, their formula being [Cu(H<sub>2</sub>O)(phen)(tp)<sub>2</sub>](ClO<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O, Cu(H<sub>2</sub>O)(phen)(dmtp)<sub>2</sub>](ClO<sub>4</sub>)<sub>2</sub>, [Cu(NO<sub>3</sub>)(H<sub>2</sub>O)phen (tp)](NO<sub>3</sub>), [Cu(H<sub>2</sub>O)<sub>2</sub>(en)(tp)<sub>2</sub>](ClO<sub>4</sub>)<sub>2</sub> and [Cu(H<sub>2</sub>O)<sub>2</sub>(en)(dmtp)<sub>2</sub>](ClO<sub>4</sub>)<sub>2</sub>. A dinuclear compound with tp was also isolated, its formula being [Cu<sub>2</sub>(OH)(H<sub>2</sub>O)2.5(tp)<sub>5</sub>](ClO<sub>4</sub>)<sub>3</sub>(H<sub>2</sub>O)1.5, with both metal atoms linked by an hydroxyl group and by a tp bridging ligand, coordinated to one of the copper atoms *via* N3 and to the other *via* N4.



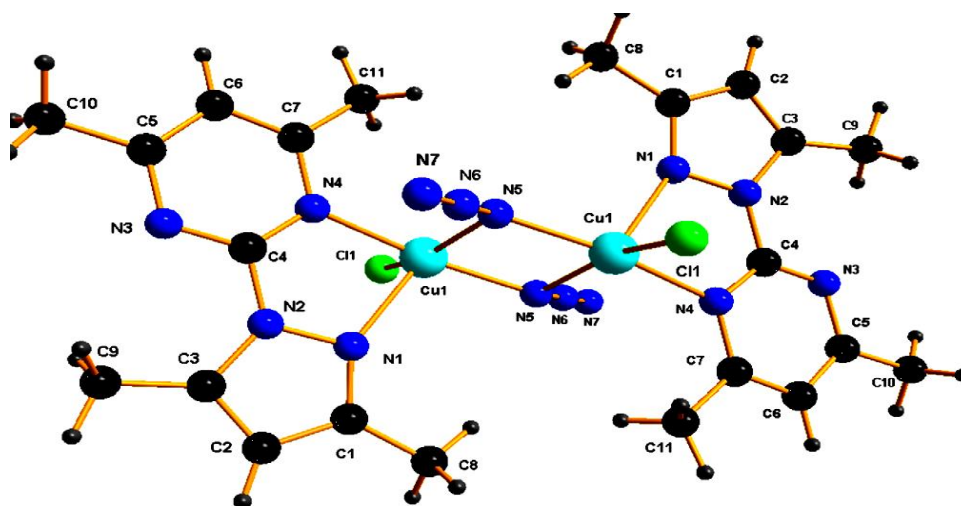
This compound had several unusual features among the metal complexes with triazolopyrimidine derivatives: the presence of two different kinds of bridging moieties, the coexistence of bridging and terminal ligands and the formation of a N3–N4 bridge for a Cu(II) dinuclear compound (**77**) for a derivative without exocyclic oxygen atoms.

**N. Saha *et al.***, have reported some tris complexes of Co(II), Ni(II), Cu(II) fluoroborates, perchlorates and iodides with the pyrimidine ligand. Physico-chemical characterization of the complex species have been made from electronic and vibrational spectra, magnetic susceptibility measurements in the solid state and conductivity measurements in solution. Electronic spectral features together with the corresponding ligand field parameters suggested an overall octahedral environment for all the metallic complexes<sup>76</sup>.

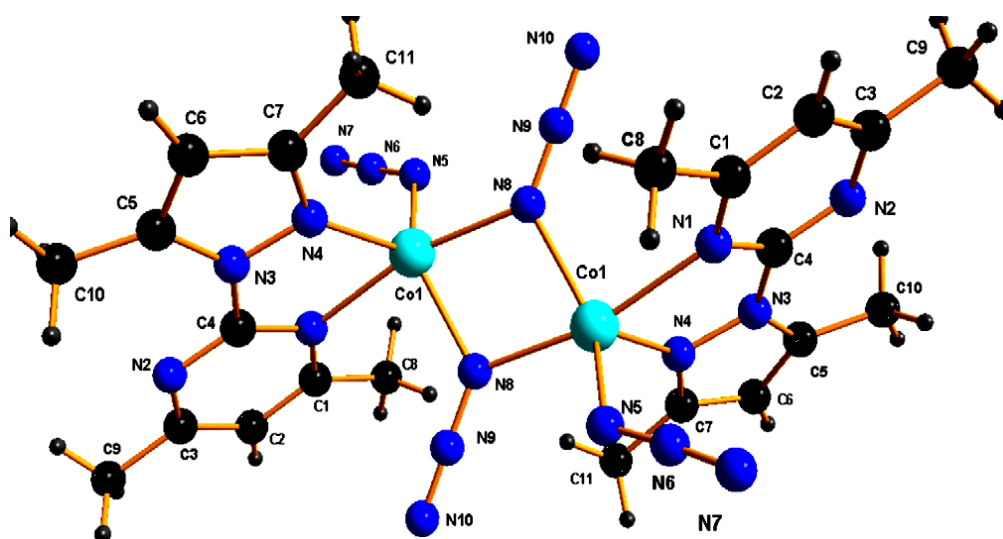
**L. Nikos *et al.***, synthesized Pd(II) and Pt(II) complexes with triazolopyrimidine C-nucleosides and characterized by elemental analysis and NMR spectroscopy. The structure of the palladium complex (**78**) was established by X-ray crystallography. The Pd(II) coordination to the ligand did not affect the sugar conformation probably due to the high stability of the C–C glycoside bond<sup>77</sup>.

**P. D. Raksha *et al.***, synthesized 2-oxo-4-phenyl-6-styryl-1, 2, 3, 4-tetrahydropyrimidine-5- carboxylic acid (ADP) and complexed with acetates of Mn(II), Ni(II), Cu(II) and Zn(II)<sup>78</sup>. The structures of the ligand and its metal complexes were characterized by microanalysis, IR, NMR, UV–vis spectroscopy, magnetic susceptibility and TGA–DTA analyses. Octahedral and square planar geometries were suggested for the complexes in which the central metal ion coordinated with O donors of the ligand and acetate ions. The ligand and complexes were evaluated for their antimicrobial activities against different species of pathogenic bacteria and fungi.

**J. Atanu *et al.***, synthesized two new dinuclear copper(II) (**79**) and cobalt(II) complexes (**80**) and characterized them crystallographically and spectroscopically. The exchange pathway parameters for all the complexes have also been evaluated from density functional theoretical calculations to corroborate the bridging signatures with experimental findings<sup>79</sup>.

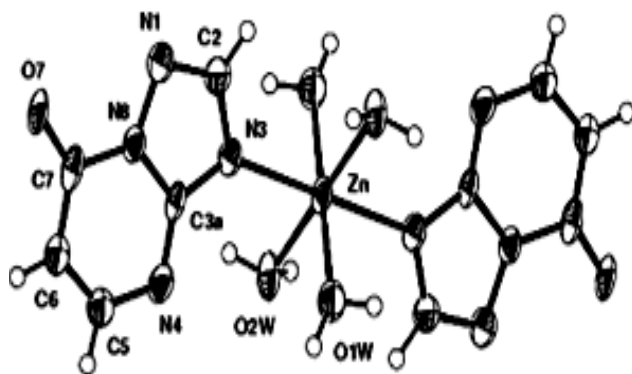


79



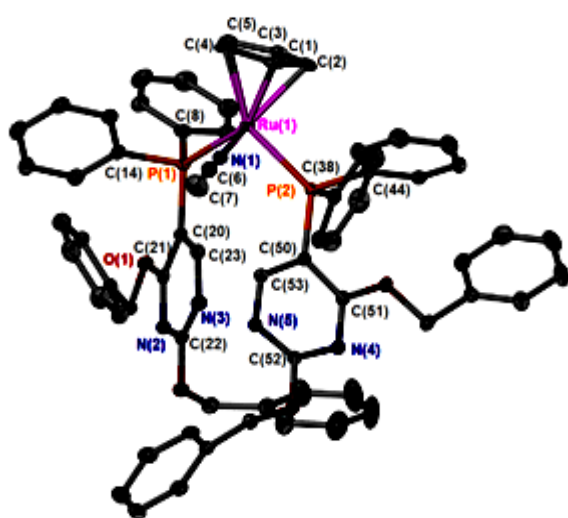
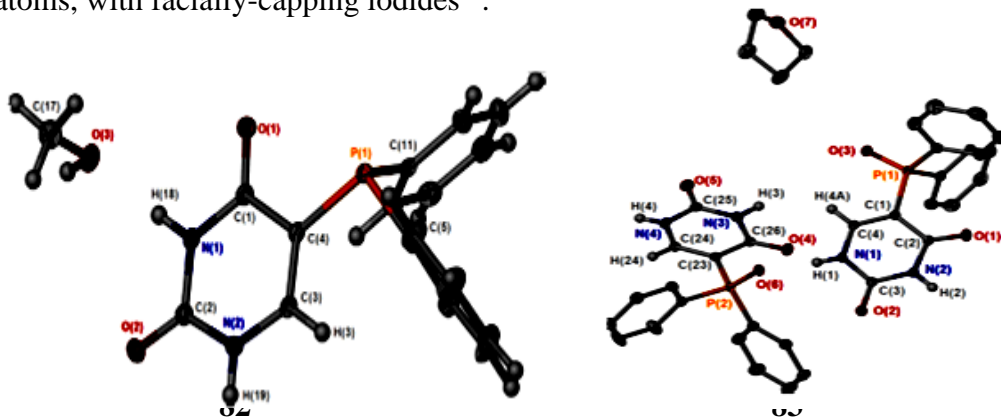
80

A. Mohammed *et al.*, synthesized several complexes of the ligand 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine-7-one in its anionic form with divalent metals and characterized them by analytical techniques (elemental analysis, thermogravimetry and differential scanning calorimetry), spectral methods (IR and electronic spectroscopy), and magnetic measurements (77–290 K)<sup>80</sup>. The crystal structure of Zn(II) complex (**81**) has been solved by single crystal X-ray diffraction. In this compound, the ligand binds the metal ion through the N atom in position 3 and four water molecules complete the slightly distorted octahedral environment with the Zn atom occupying an inversion center.

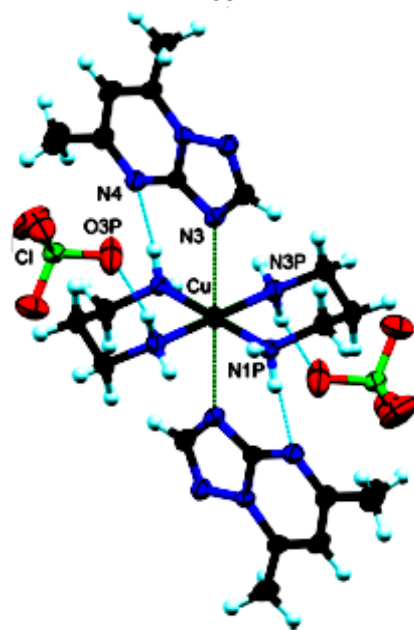


81

D. N. Tracy *et al.*, studied the reaction of  $\text{PPh}_2\text{H}$  with  $\text{UrI}$  ( $\text{Ur}$  = uracil) in the presence of  $\text{Pd}(\text{OAc})_2$  to yield  $\text{PPh}_2\text{Ur}$ . In the solid state,  $\text{PPh}_2\text{Ur}$  (**82**) crystallized as a methanol solvate in the monoclinic space group  $\text{P}21/c$ . A single crystal X-ray diffraction study demonstrated that this species contains a distorted tetrahedral core of copper atoms, with facially-capping iodides<sup>81</sup>.



84



85

The uracil groups in the clusters are engaged in hydrogen bonding to groups on neighbouring molecules to form an extended array. A similar reaction between PPh<sub>2</sub>Ur and CuI in unpurified THF resulted in the phosphine oxide P(O)PPh<sub>2</sub>Ur (**83**). The synthesis of the benzyl-protected phosphine PPh<sub>2</sub>UrP was also described [UrP = 2,4-bis(benzyloxy)pyrimidine]. Reaction of PPh<sub>2</sub>UrP with [Ru(η<sup>5</sup>-C<sub>5</sub>H<sub>5</sub>)(NCMe)<sub>3</sub>]PF<sub>6</sub> resulted in the isolation of [Ru(η<sup>5</sup>-C<sub>5</sub>H<sub>5</sub>)(NCMe)(PPh<sub>2</sub>UrP)<sub>2</sub>]PF<sub>6</sub> (**84**).

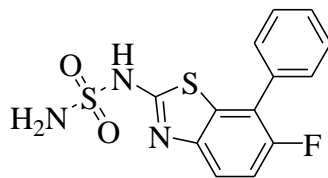
**B. C. Ana *et al.***, synthesized five new metal complexes with the metal ions Cu(II), Ni(II) and Zn(II) containing 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives and 1,3-propanediamine<sup>82</sup>. The structural morphology of these coordination compounds depends on the triazolopyrimidine derivative used, being mononuclear for 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine and 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one, and 1D-polymeric for 7-amine-1,2,4-triazolo[1,5-*a*]pyrimidine. All isolated metal complexes have been characterized by single-crystal X-ray diffraction, IR and UV–Vis spectroscopies, and EPR measurements. Moreover, luminescence measurements have been carried out for ligand and its polynuclear complex with Cu(II)(**85**).

### 2.3. Benzothiazoles

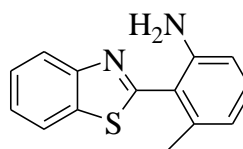
Benzothiazole consists of thiazole ring fused with benzene ring and possess multiple applications. In 1950s, a number of 2-aminobenzothiazoles were intensively studied as central muscle relaxants. Since then, biologist's attention was drawn to this series when pharmacological profile of Riluzole (6-trifluoromethoxy-2-benzothiazolamines, Rilutek), as a Glutamate neurotransmission inhibitor was discovered. After that benzothiazole derivatives have been extensively studied and found to have diverse chemical reactivity and broad spectrum of activity. Benzothiazole derivatives possess a wide spectrum of biological applications such as anticonvulsants, antimicrobial, schistosomicidal, anti-inflammatory, antidiabetic, antitumor, antipsychotic, and diuretic *etc.*,

Benzothiazoles show chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles. 2-(substituted arylsulfonamido)-6-substituted benzothiazoles have reported for their anti-bacterial activity against *Bacillus subtilis*, *Salmonella typhi* and

*S. dysentery*. Another derivative *i.e.*, N-(2-amino-6-fluorobenzo[*d*]thiazol-7-yl)benzene sulfonamide (**86**) was synthesized and studied for their antibacterial and anti-fungal activities and it showed moderate activity against *S. aureus*, *S. albus* and *C.ablicans*.



**86**

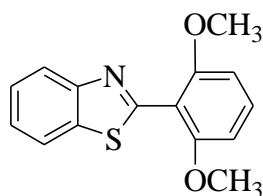


**87**

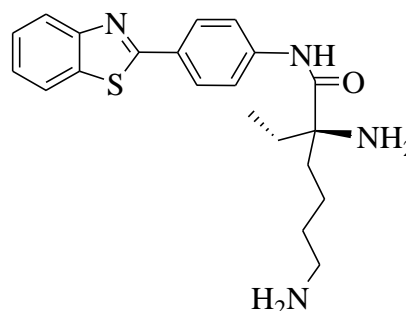
Pyrimido benzothiazole and benzothiazolo quinoline derivatives, imidazo benzothiazoles and polymerized benzothiazoles have anti-tumour activity. Some fluorinated analogues of 2-(4-aminophenyl)benzothiazoles (**87**) were reported to block the C-oxidation. The 2-cyano derivatives of benzothiazole exhibited interesting *in-vitro* anti-tumour activity.

### 2.3.1. Review on benzothiazole derivatives and its transition metal complexes

M. Stevens *et al.*, reported the *in-vitro* antitumor activity of a new series of alkyl-, halo-, cyano-, alkoxy- and hydroxy- substituted 2-(4-aminophenyl) benzothiazoles. The compound showed the most potent growth inhibition against the ER+ (MCF-7 and BO) and ER- (MT-1 and MT-3) tumors. Further aryl substituted 2-phenyl benzothiazoles(**88**) and L-lysyl and L-alanyl amide prodrugs of 2-(4-aminophenyl) benzothiazole (**89**) were found to possess exquisitely potent anti-proliferative activity<sup>83-87</sup>.



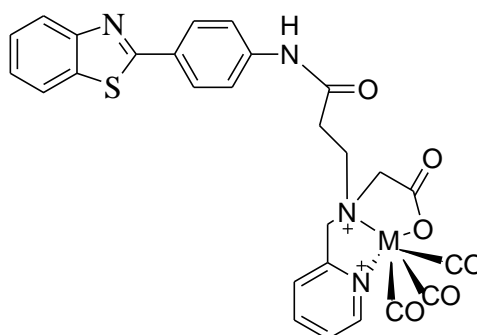
**88**



**89**

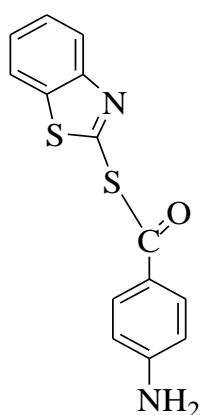
M. Pelecanou *et al.*, prepared a series of Rhenium (<sup>185/187</sup>Re) and Technetium-99m (<sup>99m</sup>Tc) complexes of 2-(4'-aminophenyl)benzothiazole. The *in-vitro* evaluation

of complexes (**90**) and *in-vivo* application of the  $^{99m}\text{Tc}$  complexes in MCF-7 tumor bearing SCID mice established the potential of these labeled 2-(4'-aminophenyl) benzothiazole derivatives for radiopharmaceutical applications<sup>88</sup>.

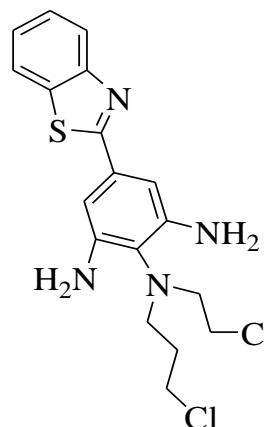


**90**

V. P. Devmurari *et al.*, prepared a series of seven substituted 2-phenylbenzothiazoles and substituted 1,3-benzothiazole-2-yl-4-carbothioate derivatives. All the synthesized novel compounds were screened for anticancer activity and compounds (**91**) and (**92**) showed very good anticancer activity.

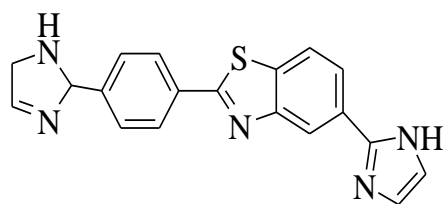


**91**

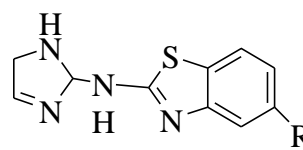


**92**

M. Kralj *et al.*, synthesized many benzothiazole derivatives and carried out antitumor evaluation of some novel benzothiazole derivatives (**93**) and (**94**). Almost all amidino derivatives showed noticeable anti-proliferative effect on several tumor cell lines while cyano derivatives showed considerably less pronounced activity due to poor solubility in aqueous cell culture<sup>89,90</sup>.

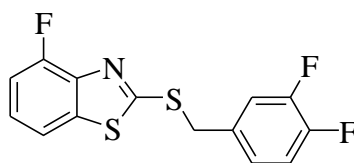


93



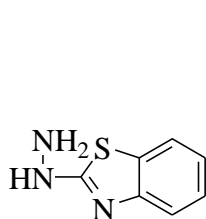
94

W. Yang *et al.*, 2-(3, 4-Difluoro-benzylsulfanyl)-4-fluoro benzothiazole (95) exhibited most interesting antifungal activity against *R. solani*, *B. cinereapers* and *D. gregaria* among a series of polyfluorinated 2-benzylthiobenzothiazoles. Further thiazole, thiophene and pyrazole derivatives of benzothiazole were prepared and examined for antibacterial and antifungal activities<sup>91</sup>.

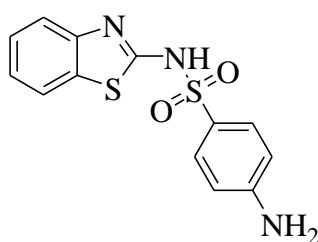


95

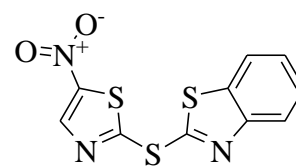
L. Katz *et al.*, synthesized some derivatives of 2-hydrazinobenzothiazole (96) and evaluated them for anti-tuberculosis activity. Some 4-amino-*N*-(1,3-benzothiazol-2-yl) benzenesulphonamide (97) derivatives were prepared and found to have good *in-vitro* antimycobacterial activity against *H37Rv* strain of *mycobacterium tuberculosis* and other derivatives were also found active as antibacterial and antifungal agents<sup>92</sup>.



96



97

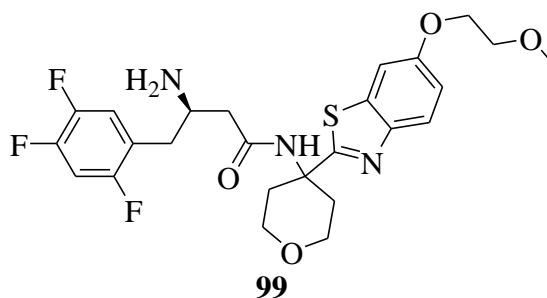


98

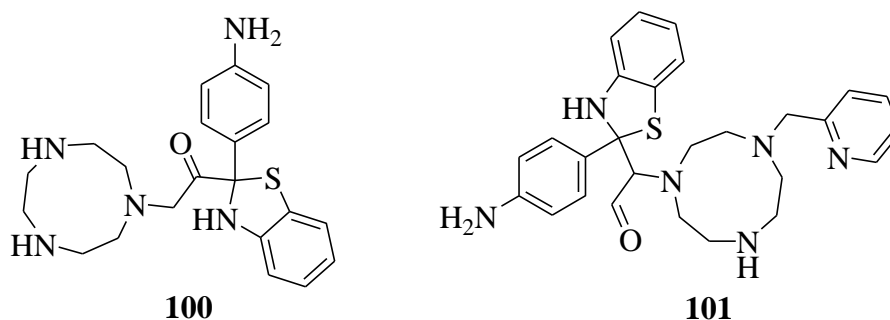
K. D. Surya *et al.*, synthesized some novel 2-(5-nitrothiazol-2-ylthio) benzo [d] thiazole derivatives (98) and screened for their ability to inhibit *c-Jun-N-terminal kinase*. The compounds demonstrated good *in-vivo* activity in a diabetic model of insulin resistance. A series of dipeptidyl peptidase inhibitors IV for the treatment of type 2 diabetes was synthesized and evaluated. The compound (3R)-3-amino-4-(2,4,5-trifluorophenyl)-*N*-{4-[6-(2-methoxyethoxy)-benzothiazol-2-yl]tetrahydropyran-4-yl}

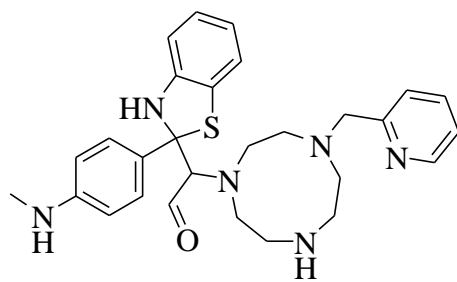


butanamide (**99**) was found to reduce the blood glucose level to a significant extent in an oral glucose tolerance test<sup>93</sup>.

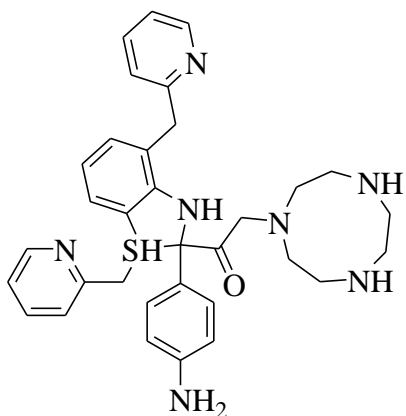


**B. Jose *et al.***, studied the spectroscopic characterization of four new 2-(4-aminophenyl)benzothiazole substituted 1,4,7-triazacyclononane derivatives with and without appended pyridyl groups on the macrocycle. 1-(2-(4-aminophenyl)benzothiazolyl)-2-oxoethyl)-1,4,7-triazacyclononane (**100**), 1-(2-(4-aminophenyl)benzothiazolyl)-2-oxoethyl)-4-(2-pyridylmethyl)-1,4,7-triazacyclononane (**101**), 1-(2-(4-N-methylaminophenyl)benzothiazolyl)-2-oxoethyl)-4-(2-pyridylmethyl)-1,4,7-triazacyclononane (**102**), 1,4-bis(2-pyridylmethyl)-7-(2-(4-aminophenyl)benzothiazolyl)-2-oxoethyl)-1,4,7-triazacyclononane (**103**). The ligands have been applied in the synthesis of a series of copper (II) complexes, whose structures have been determined by X-ray crystallography. As commonly observed for Cu(II) complexes (**104**, **105**) of 1,4,7-triazacyclononane derivatives, the geometry of the metal centre ranged from distorted square pyramidal to pseudo-octahedral. Notably, the amide carbonyl coordinates to the copper(II) centre in C1 and C2 but not in C4 where the presence of an additional pyridyl group results in an N5 coordination sphere<sup>94</sup>.

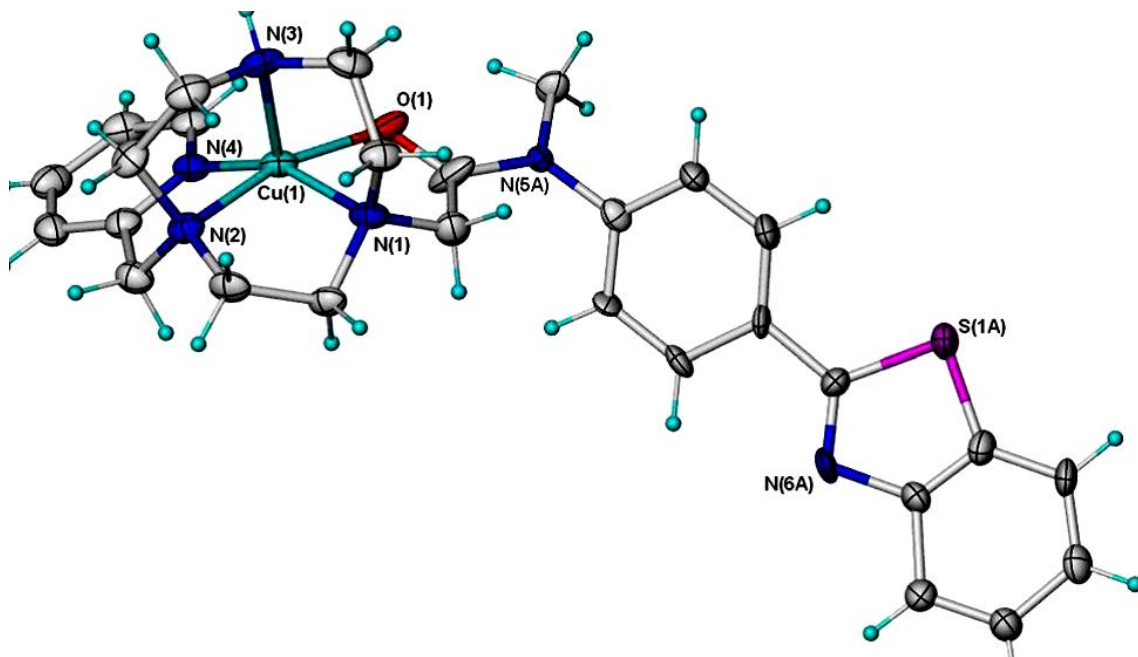




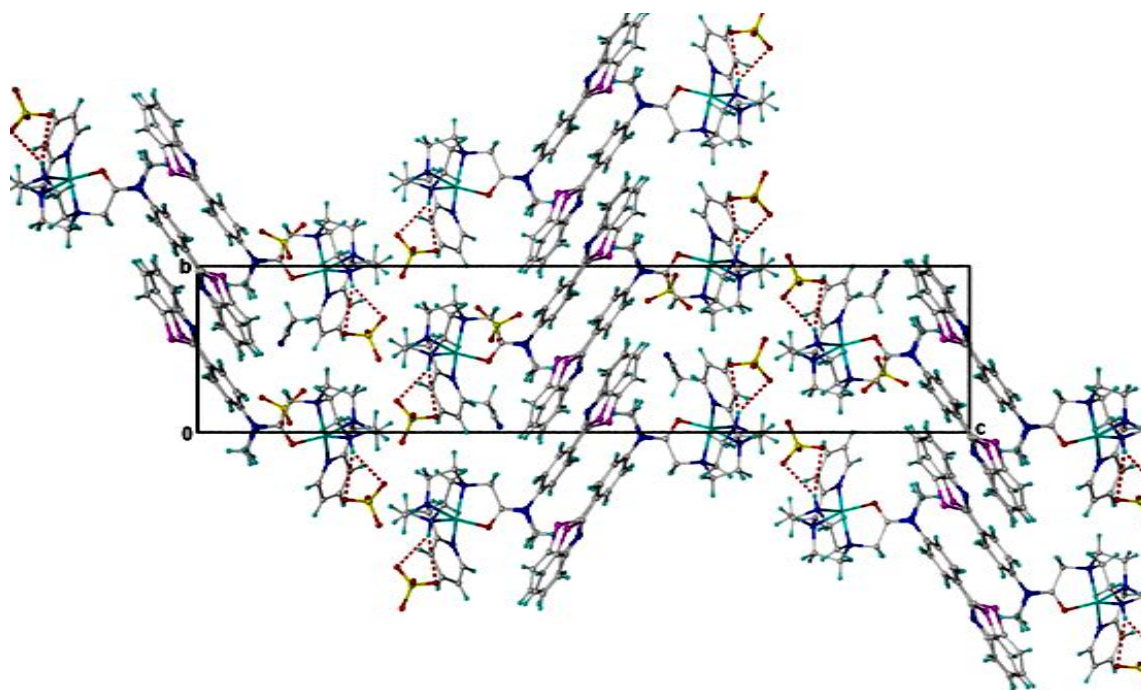
**102**



**103**

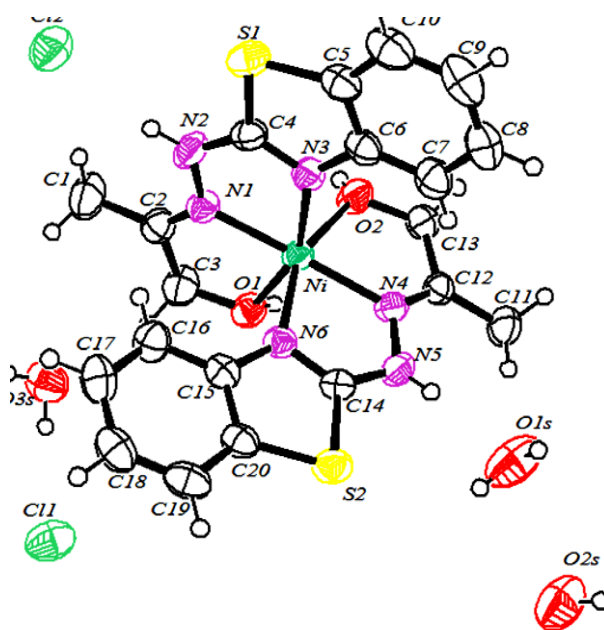


**104**



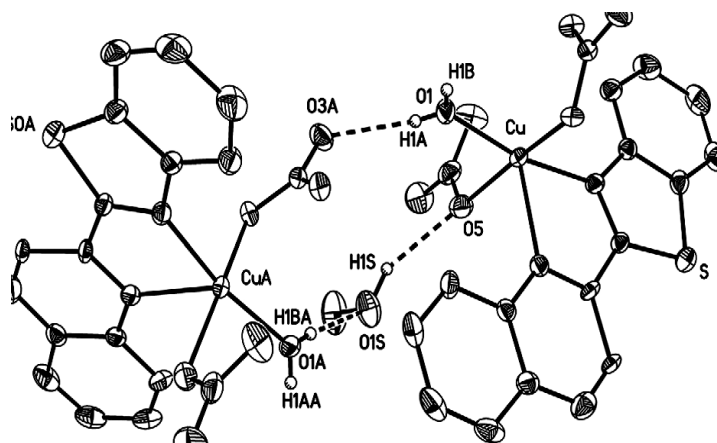
105

P. N. Priya *et al.*, studied the air and moisture stable coordination compounds of late first row transition metals, *viz.*, Co(II), Ni(II), Cu(II) and Zn(II), with a newly designed ligand, 2-(2-benzo[d]thiazol-2-yl)hydrazono)propan-1-ol and successfully characterized using various spectro-analytical techniques. The molecular structures of the ligand and nickel complex(**106**) were unambiguously determined by single-crystal X-ray diffraction. All the complexes revealed an MIC value of 0.8 mg/mL, which is almost 8 times active than the standard used (Streptomycin, 6.25 mg/mL)<sup>95</sup>.



**H. E. Safaa *et al.***, synthesized N-(thiophen-2-ylmethylene)benzo[d]thiazol-2-amine Schiff base derived from 2-aminobenzothiazole and 2-thiophenecarboxaldehyde was synthesized and characterized using elemental analysis, IR, mass spectra,  $^1\text{H}$  NMR and UV-vis spectra. Its complexes with Cu(II), Fe(III), Ni(II) and Zn(II) were prepared and isolated as solid products and characterized by elemental and thermal analyses, spectral techniques as well as magnetic susceptibility. The IR spectral data revealed that the Schiff base under investigation behaved as bidentate ligand. The UV-vis spectra and magnetic moment data suggested octahedral geometry around Cu(II) and Fe(III) and tetrahedral geometry around Ni(II) and Zn(II). In view of the biological activity of the Schiff base and its complexes, it has been observed that the antimicrobial activity of the Schiff base increased on complexation with the metal ion. In vitro antitumor activity assayed against five human tumor cell lines furnished the significant toxicities of the Schiff base and its complexes<sup>96</sup>.

**A. S. Ramsey *et al.***, synthesized and characterized a series of Cu(II) complexes (**107**) with ligand frames based on quinoline derivatives appended with a benzothiazole substituent<sup>97</sup>.

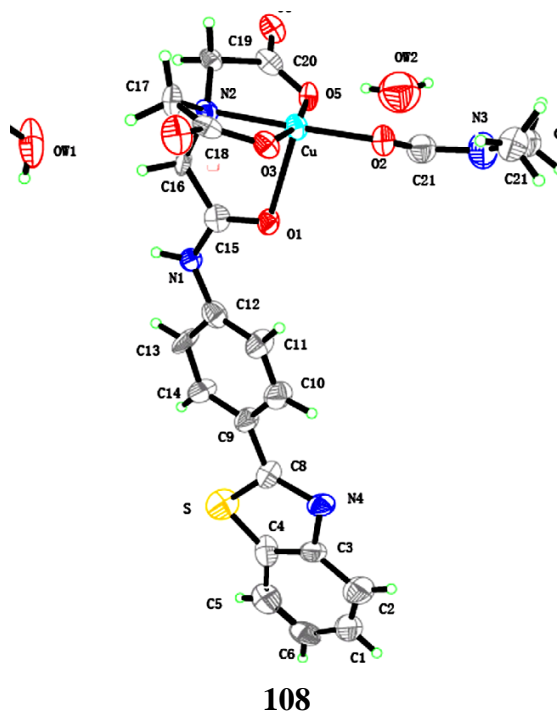


107

**F. Xia Bing *et al.***, synthesized a new copper(II) complex,  $[\text{Cu}(\text{glygly})(\text{pbt})(\text{H}_2\text{O})]\text{ClO}_4$  (glygly=glycylglycine anion and pbt=2-(2-pyridyl)benzothiazole) and characterized by elemental analysis, molar conductivity, mass spectra, IR spectra, UV-vis spectra and thermogravimetric analysis (TGA). Spectroscopic titration, viscosity and electrophoresis measurements revealed that the complex intercalated to calf thymus (CT)-DNA with moderate binding affinity ( $K_b =$

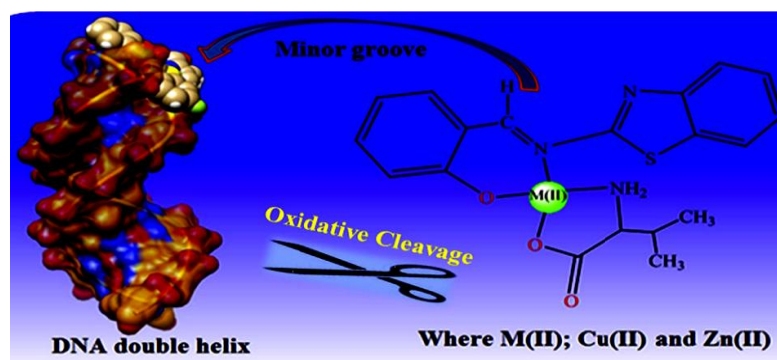
$5.64 \times 10^4 M^{-1}$ ), and cleaved pBR322 DNA at a low concentration in the presence of ascorbic acid, presumably *via.*, an oxidative mechanism. Further, the protein-binding ability was monitored by various spectroscopic techniques (UV–vis, fluorescence and CD) using human serum albumin (HSA) as a model protein. The complex displayed desired affinity to HSA in which hydrophobic interaction played a major role. In addition, the complex was subjected to cytotoxicity tests *in vitro* using three human cancer cells lines (HepG2, HeLa and A549) and showed prominent and selective cytotoxicity against HepG2 cell lines<sup>98</sup>.

**L. Guo-Wu Lin *et al.***, synthesized and characterized (2-(4-(benzothiazole)phenyl)carbamoylmethyl)iminodiacetic acid and its three metal complexes (**108**). The structures were determined by <sup>1</sup>H NMR and X-ray analysis<sup>99</sup>.



**A. Rahman *et al.***, synthesized and designed chiral antitumor chemotherapeutic agents of Cu(II) (**109**) and Zn(II), L- and -D benzothiazole Schiff base-valine complexes have been reported. Interaction of the complexes was studied with CT DNA by employing UV–vis, fluorescence, circular dichroic methods and cleavage studies of the complexes with pBR322 plasmid DNA. Molecular docking was done in order to demonstrate their enantiomeric disposition toward the molecular drug target DNA. Interestingly, these studies unambiguously demonstrated the greater potency of L-enantiomer in comparison to D-enantiomer. The cleavage study

demonstrated that the complex preferred the minor groove of the DNA helix; these results were supported by molecular docking experiments<sup>100</sup>.



In view of the interesting pharmacological activities of quinoxaline, pyrimidine and benzothiazoles. An attempt was made to synthesize some novel transition metal complexes of the above heterocycles and evaluate them for their pharmacological activity.

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## Chapter-III

### Quinoxaline Schiff base Complexes

#### 3.1. Introduction