

Biological Activities of Schiff Bases and Their Complexes: A Review of Recent Works

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ABSTRACT

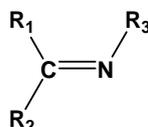
Schiff bases are the most widely used organic compounds. They have been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. This review summarizes the synthesis and biological activities of Schiff bases and their complexes.

Keywords: Schiff Bases; Metal Complexes; Antibacterial; Biological Activities

1. Introduction

Schiff base compounds and their metal complexes have been extensively investigated due to their wide range of applications including catalysts [1,2], medicine [3,4] crystal engineering [5], anti-corrosion agent [6,7]. Schiff bases are studied widely due to their synthetic flexibility, selectivity and sensitivity towards the central metal atom; structural similarities with natural biological compounds and also due to presence of azomethine group(-N=CH-) which imports in elucidating the mechanism of transformation and racemization reaction biologically [8,9]. Schiff bases having chelation with oxygen, nitrogen etc. donors and their complexes have been used as drugs and reported to possess a wide variety of biological activities against bacteria, fungi, and certain type of tumors and also, they have many biochemical, clinical and pharmacological properties [10-14]. Imine or azomethine groups are present in various natural, naturally derived and non-natural compounds (Figure 1). The imine group present in such compounds has been shown to be critical to their biological activities [15-17].

This review concentrates on the synthesis and biologi-



R₁, R₂ and / or R₃=alkyl or aryl

Figure 1. General Structure of a Schiff base.

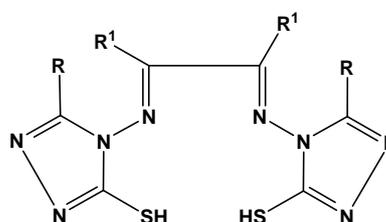
cal activity of Schiff bases and their complexes.

2. Biological Activities of Schiff Bases

Schiff bases are generally bi- or tridentate ligands capable of forming very stable complexes with transition metals. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds.

Complexes of Co(II) and Ni(II) with new Schiff bases (Scheme 1) derived from 4-amino-5-sulfanyl-1,2,4-triazoles and glyoxal, biacetyl or benzil have been prepared. All have the stoichiometry ML(H₂O)₂, with L coordination via the two imine nitrogens and two thiolato sulfurs in an overall octahedral geometry. Some of the complexes were screened for their antibacterial and antifungal activity, and one representative Co(II) complex was evaluated for oxytocic. Furthermore, complex(c) (R; Me, R¹; H) was found to inhibit the oxytocic activity of oxytocin on isolated rat uterus (Table 1) [18].

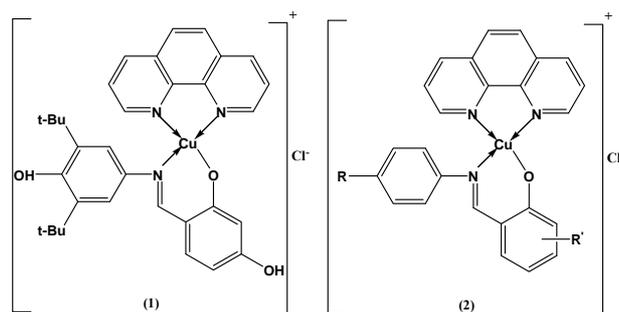
Tumer and coworkers have been prepared and characterized mixed ligand complexes (Scheme 2) of copper(II)



Scheme 1. Complexes of Co (II) and Ni(II) with new Schiff bases.

Table 1. Data showing the oxytotic activity of cobalt(II) complex(c).

Vol. of test solution added (cm ³)	Peak Height (cm)	Oxytotic activity (%)
0.1 (Std. oxytotic)	3.1	88.57
0.2 (Std. oxytotic)	3.5	100.00
0.3 (Std. oxytotic)	3.5	100.00
		(Saturation pt)
(C ₈ H ₈ N ₈ S ₂)Co.2H ₂ O	3.4	97.15
0.3 cm ³ Std. oxytotic		(2.85 Inhibition)

**Scheme 2. Suggested structure for the mononuclear complexes of the ligands HL₃ (1), HL₁-HL₄ and HL₁, HL₄ (2).**

with 1.10-phenanthroline and Schiff bases. Some of the free ligands and their complexes were found to be highly active against both the *Bacillus megaterium* and *Candida tropicalis*. However, the metal complexes were active compared with corresponding ligands as regards to antimicrobial activity of the molecule [19].

Two tridentate Schiff bases (**Scheme 3**) having ONS and NNS donor sequences were prepared by condensing S-benzylthiocarbamate (NH₂NHCSSCH₂Ph) (SBDTC) with pyridine-2-carboxaldehyde and salicylaldehyde, respectively. Complexes of these ligands with Ni(II), Zn(II), Cr(III), Co(II), Cu(II), and Sn(II) were studied and characterized by elemental analyses and various physico-chemical techniques. The ONS Schiff base was moderately active against *leukemia*, while its zinc, antimony and cobalt complexes were strongly active against *leukemic cells* with $DC_{50} = 0.35 - 5.00$ [20].

Paola *et al* have reported the synthesis, characterization and evaluation as antibacterial and antifungal agents of a series of hydrazones (**Scheme 4**) of 1.2-benzisothiazole hydrazides as well as their cyclic and acyclic 1.2-benzisothiazole parent hydrazides. All of the 2-amino-1.2-benzisothiazol-3(2H)-one derivatives, belonging to series I and IV, showed a good antibacterial activity against Gram positive bacteria. Most of them were active against yeasts too. Compounds 1 and 4, together with II, proved to be the most effective compounds [21].

Sevim and coworkers have reported the synthesis and evaluation a series of hydrazide hydrazones and 1.3.4-oxadiazolines of 4-fluorobenzoic and hydrazide (**Scheme 5**) as potential antimicrobial agents and have tested for their antibacterial and antifungal activities against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*. From these compounds, 4-fluorobenzoic acid [(5-nitro-2-furanyl) methylene] hydrazide(1a) showed equal activity with ceftriaxone against *S. aureus* [22].

Two new Schiff base ligands (**Scheme 6**) containing 2,4-disubstituted thiazoles and cyclobutane rings, 4-(1-methyl-1-phenylcyclobutane-3-yl)-2-(2-hydroxy-3-methoxy benzylidene hydrazino)thiazole (L₁H), 4-(1-methyl-1-p-xylylcyclobutane-3-yl)-2-(2-hydroxy-3-methoxybenzylidenehydrazino)thiazole (L₂H) and their mononuclear complexes with a 1:2 metal-ligand ratio have been prepared from acetate salts of Co(II), Cu(II), Ni(II) and Zn(II) in EtOH. Antimicrobial activities of the ligands and their complexes have been tested against six different microorganisms; three are yeast and three are bacteria [23].

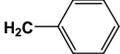
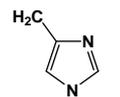
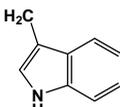
Natarajan and coworkers have reported the synthesis neutral tetradentate chelate complexes of Cu(II), Ni(II), Co(II), Mn(II), Zn(II) and VO(II) in EtOH using Schiff bases (**Scheme 7**) derived from acetoacetanilido-4-aminoantipyrine and 2-aminophenol/2-aminothiophenol. Microanalytical data, magnetic susceptibility, IR., UV-vis., ¹H-NMR. and ESR spectral techniques were used to confirm the structures of the chelates. The *in vitro* antimicrobial activity of the investigated compounds was tested against the microorganisms such as *Salmonella typhi*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Bacillus subtilis*, *Shigella flexneri*, *Pseudomonas aeruginosa*, *Aspergillus niger* and *Rhizoctonia bataicola*. Most of the metal chelates have higher antimicrobial activity than the free ligands [24].

Daniel *et al* have reported the synthesis chiral Schiff base of ruthenium(III) of the type [RuX(LL')(Eph₃)](X=Cl or Br; LL' = chiral Schiff base; E = P or As) (**Scheme 8**) by the reactions of [RuX₃(Eph₃)₃] or [RuBr₃(PPh₃)₂(MeOH)] with appropriate Schiff bases having the donor groups(O,N) viz., bis[3(1-naphthyl) salicylidene cyclohexanediimine](L₁) or bis[(1-naphthyl) salicyli denepropylenediimine] (L₂) or bis[3(1-naphthyl) salicylidene diphenyldiimine](L₃) in 1:1 molar ratio. The catalytic and antibacterial activities have also been carried out for these new complexes [25-29].

The synthesis and *in vitro* antifungal activity of some Schiff bases (**Scheme 9**) and their Sn(IV) complexes has been tested against plant pathogenic fungi and it is found that they possess excellent fungicidal activity [30].

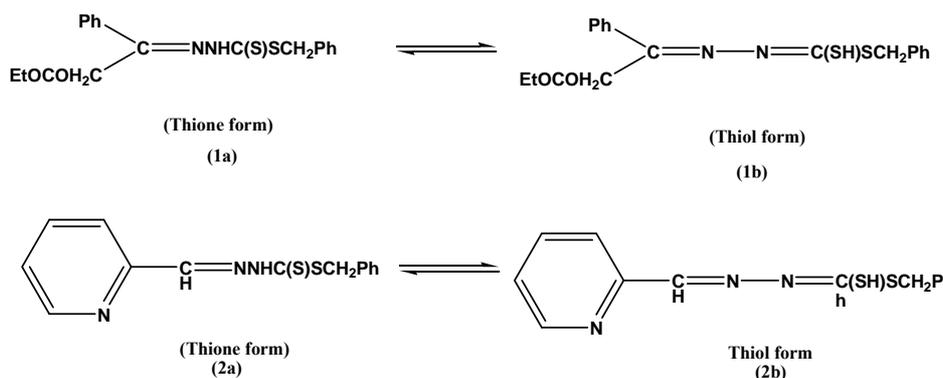
The *in vitro* antibacterial antifungal activities of five different amino acid Schiff bases (**Scheme 10**) derived from

the reaction of 2-hydroxy-1-naphthaldehyde with glycine, L-alanine, L-phenylalanine, L-histidine, L-tryptophane and the manganese(III) complexes of these bases were studied. *In vitro* activities against some Gram-positive (*Staphylococcus aureus* and *Bacillus polymyxa*) and Gram-negative (*Escherichia coli*) bacteria and the fungus *Candida albicans* were determined. The antimicrobial activities tended to decrease with the increasing size of the amino acid residues [31].

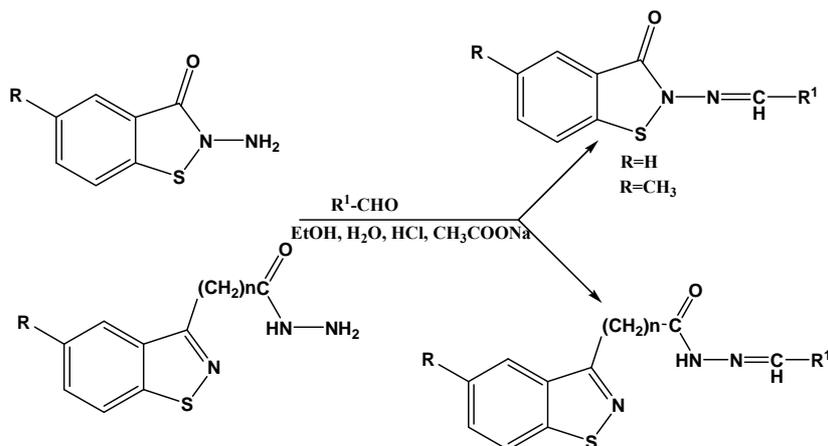
Schiff bases	Complexes	R
1	H ₂ L ¹	6 Na[MnL ₂ ¹] H (Gly)
2	H ₂ L ²	7 Na[MnL ₂ ²] CH ₃ (Ala)
3	H ₂ L ³	8 Na[MnL ₂ ³]  (Phe)
4	H ₂ L ⁴	9 Na[MnL ₂ ⁴]  (His)
5	H ₂ L ⁵	10 Na[MnL ₂ ⁵]  (Trp)

Two small sets of aromatic Schiff bases and 2,3-diaryl-1,3-thiazolidin-4-one (**Scheme 11**) derivatives have been prepared and tested for *anti-inflammatory* and *antinociceptive* activities. The thiazolidinone derivatives have been obtained from the azomethines through the addition of α -mercaptoacetic acid. Both types of compounds displayed good level of activity against *carra-geenan* induced edema in rat hind paw, while only moderate activity was observed in the writhing test in *mice* [32].

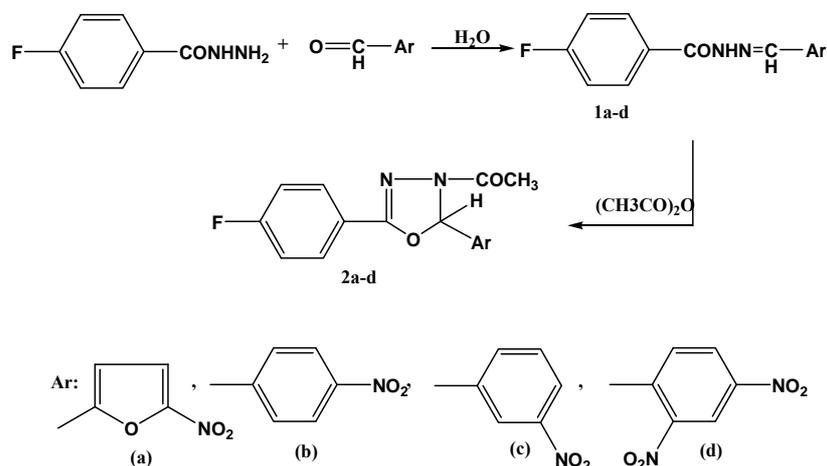
Esin and coworkers have reported the synthesis two new Schiff bases ligands (**Scheme 12**) containing $-\text{SiOCH}_3$ or $-\text{SiOCH}_2\text{CH}_3$ groups, 4-{\{[(3-trimethoxysilanopropyl)imino]methyl}benzene-1,3-diol(1) Hmsb and 4-{\{[(3-triethoxysilanopropyl)imino]methyl}benzene-1,3-diol(5) Hesb by the reaction of 2,4-dihydroxybenzaldehyde with 3-aminopropyltrimethoxysilane and 3-aminopropyltriethoxysilane. Six new transition metal [Cu(II), Ni(II) and Co(II)] complexes of these Schiff base ligands were prepared. The analytical data shows that the metal-to-ligand ratio in the Schiff base complexes contains silane in 1:2. In addition the antimicrobial activity of (1) Hmsb and (5) Hesb Schiff ligands, and their [M(msb)₂] and [M(esb)₂] type coordination compounds, were investi-



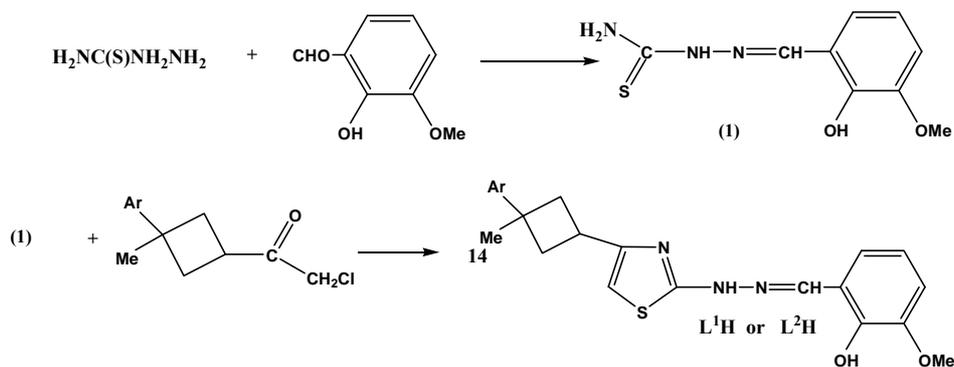
Scheme 3. Synthesis of Tridentate Schiff bases having ONS and NNS.



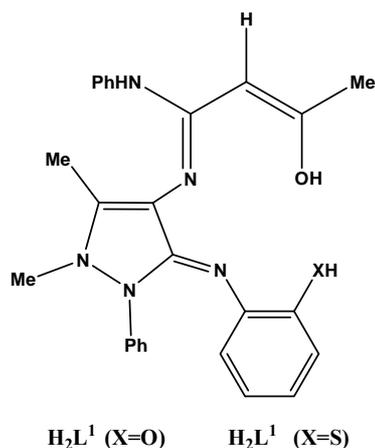
Scheme 4. General Scheme for synthesis of 1,2-benzothiazole hydrazones.



Scheme 5. Scheme of Synthesis a series of hydrazone hydrazones.



Scheme 6. Synthesis of Schiff bases ligands.



Scheme 7. Synthesis Schiff bases derived from acetoacetanilido-4-aminoantipyrine and 2-aminophenol/2-aminothiophenol.

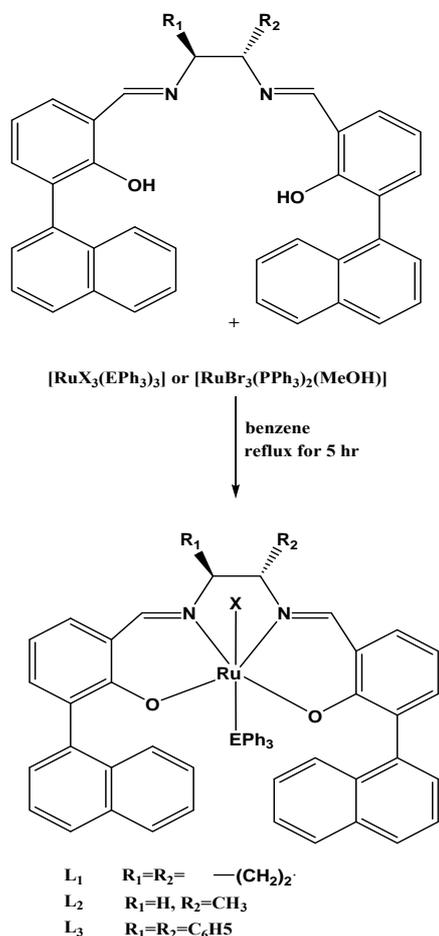
gated [33-35].

Raman and coworkers have reported the synthesis of four copper (II) complexes (Scheme 13) using macrocyclic ligands. The macrocyclic ligands have been synthesized by the condensation reaction of diethyl phthalate with Schiff bases derived from *o*-phenylene diamine and

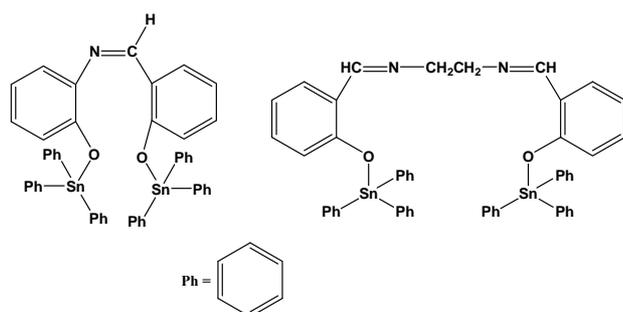
Knoevenagel condensed β -ketoanilides (obtained by the condensation of acetoacetanilide and substituted benzaldehydes). The *in vitro* antifungal activities of the compounds were tested against fungi such as *Aspergillus niger*, *Rhizopus stolonifer*, *Aspergillus flavus*, *Rhizoctonia bataicola* and *Candida albicans*. All the synthesized copper complexes showed stronger antifungal activities than free ligands [36].

Hitesh *et al* have reported the synthesis mixed-ligand complexes (Scheme 14) of Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) with biologically active Schiff bases, viz. potassium salt of *o*-hydroxyacetophenoneglycine [KHL] and bis(benzylidene) ethylenediamine [A¹] or thiophene-*o*-carboxaldene-*p*-toluidine [A²]. The mixed-ligand complexes show higher antifungal activity as compared to the free ligands, metal salts, and the control (dimethylsulfoxide) but moderate activity as compared to the standard fungicides (bavistin and emcarb) [37].

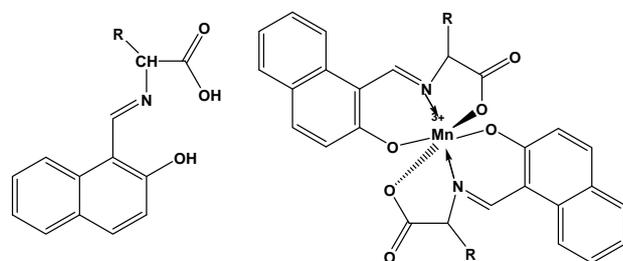
A relationship between antimicrobial activities and the formation constants of amino acid-Schiff bases (Scheme 15) and their Cu(II) and Ni(II) complexes was studied. For this purpose, a series of Schiff bases were prepared from DL-amino acids (DL-glycine, DL-alanine) and haloaldehydes (5-chloro-2-hydroxybenzaldehyde, 5-



Scheme 8. Scheme synthesis of the ruthenium (III) complexes.



Scheme 9. Proposed structure for compounds.



Scheme 10. Structure of the Schiff bases and Mn^{3+} complexes investigated.

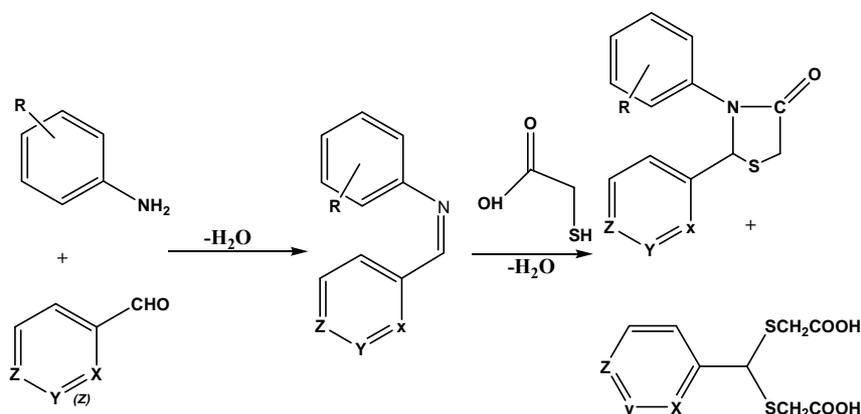
bromo-2-hydroxybenzaldehyde). The complexes were found to have general compositions $[ML(H_2O)]$. The protonation constants of the Schiff bases and stability constants of the complexes were determined potentiometrically in a dioxane–water (1:1) solution at 25°C and 0.1 M KCl ionic strength. Antimicrobial activities of the Schiff bases and their complexes were estimated for six bacteria, such as *Bacillus cereus* RSKK 863, *Staphylococcus aureus* ATCC 259231, *Micrococcus luteus* NRLL B-4375, *Escherichia coli* ATCC 11230, *Aeromonas hydrophila* 106, *Pseudomonas aeruginosa* ATCC 29212, and the yeast *Candida albicans* ATCC 10239. The role of halogen substitution on the ligands, effect of the metal ion, and stabilities of the complexes are discussed on antimicrobial activities [38].

Dharmarajan and coworkers have reported the synthesis and evaluation various diclofenac acid hydrazones and amides (Scheme 16) for *in vitro* and *in vivo* antimycobacterial activities against *Mycobacterium tuberculosis* [39].

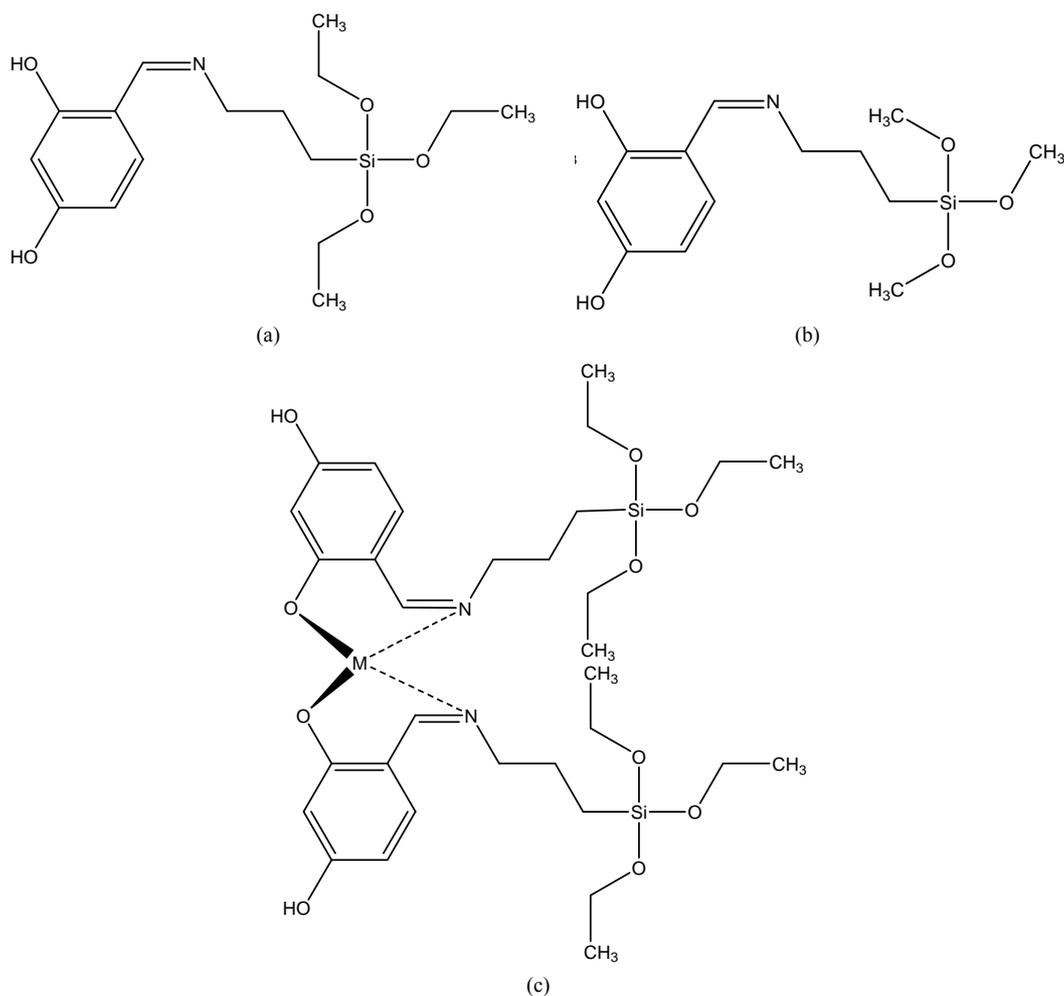
Schiff base tetraazamacrocyclic ligand (Scheme 17), L ($C_{40}H_{28}N_4$) and its complexes of types, $[MLX_2]$ and $[CuL]X_2$ ($M = Co(II), Ni(II), Zn(II)$; $X = Cl^-, NO_3^-$) were synthesized and characterized by elemental analyses, mass, 1H -NMR, IR, UV–vis, magnetic susceptibility and molar conductance data. The ligand (L) and its complexes have also been screened against different fungi and bacteria *in vitro*. The complexes exhibited potential activity at the concentration dose of 5 mg/ml which is comparable to that of tetradentate 12-membered macrocyclic compounds, shown to have antimicrobial activity against various pathogens by disc diffusion technique [40, 41].

Lei and coworkers have reported the synthesis of a series of Schiff bases (Scheme 18) by reacting 5-chlorosalicylaldehyde and primary amines. The compounds were assayed for antibacterial (*Bacillus subtilis*, *Escherichia coli*, *Pseudomonas fluorescens* and *Staphylococcus aureus*) and antifungal (*Aspergillus niger*, *Candida albicans* and *Trichophyton rubrum*) activities. Among the compounds tested, (E)-4-chloro-2-((4-fluorobenzylimino)-methyl)phenol showed the most favorable antimicrobial activity with MIC_s of 45.2, 1.6, 2.8, 3.4, and 47.7 $\mu g/mL$ against *B. Subtilis*, *E. coli*, *P. fluorescens*, *S. aureus* and *A. niger*, respectively. It is also reported that Salicylaldehyde derivatives, with one or more halo-atoms in the aromatic ring, showed variety of biological activities like antibacterial and antifungal activities [42,43].

Samanta and coworkers have reported herein the synthesis three new Cu(II) complexes of tri and tetradentate Schiff base ligands (Scheme 19) containing N_3 or N_4 donor set along with terminal NNN^- or SCN^- ligands: $[L^1Cu(NCS)]ClO_4$ (1), $[L^2Cu(NCS)_2]$ (2) and $[L^3Cu(NNN)]ClO_4$ (3) [$L^1 =$



Scheme 11. Aromatic Schiff Bases and 2,3-diaryl-1,3-thiazolidin-4-one.

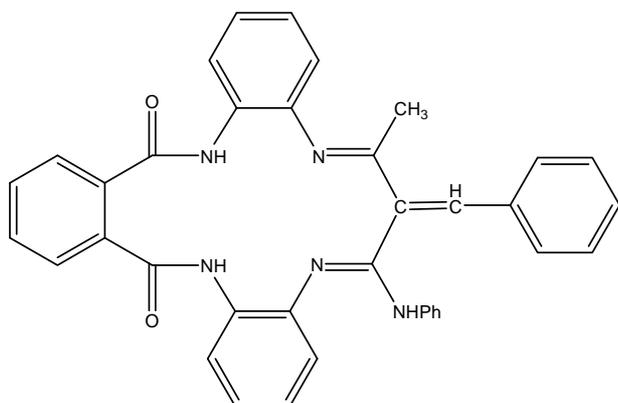


Scheme 12. (a) the proposed structure of Hesb Schiff base Ligand, (b) the proposed structure of Hmb Schiff base Ligand, (c) (a) the proposed structure of the Hesb complexes.

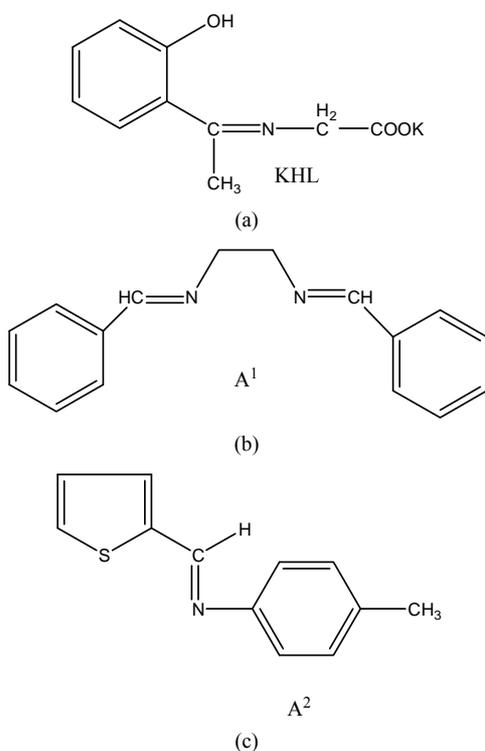
$\text{NC}_5\text{H}_4\text{C}(\text{CH}_3)=\text{N}(\text{CH}_2)_3\text{N}=\text{C}(\text{CH}_3)\text{C}_5\text{H}_4\text{N}$, $\text{L}^2 = \text{Me}_2\text{N}-(\text{CH}_2)_3-\text{N}=\text{C}(\text{CH}_3)\text{C}_5\text{H}_4\text{N}$ and $\text{L}^3 = \text{NC}_5\text{H}_4\text{CH}=\text{N}-(\text{CH}_2)_4-\text{N}=\text{CH}\text{C}_5\text{H}_4\text{N}$. Antimicrobial activities of the Schiff base ligands and their metal complexes have been studied using the disc diffusion method

on the strains of *Candida tropicalis* and *Bacillus megaterium* [44].

Singh have reported the synthesis a new series of complexes (Scheme 20) by template condensation of oxalyldihydrazide and benzil in methanolic medium in



Scheme 13. Structure of macrocyclic ligand.



Scheme 14. Structures of the Schiff bases.

the presence of trivalent chromium, manganese and iron salts complexes. The complexes have been characterized with the help of elemental analyses, conductance measurements, magnetic susceptibility measurements, electronic, NMR, infrared and far infrared spectral studies. On the basis of these studies, a five coordinate square pyramidal geometry has been proposed for all these complexes. The biological activities of the metal complexes have been tested *in vitro* against a number of pathogenic to assess their inhibiting potential. Some of these complexes have been found to exhibit remarkable antibacterial [45].

The complexes (Scheme 21) of Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), dioxouranium(VI), and Th(IV)

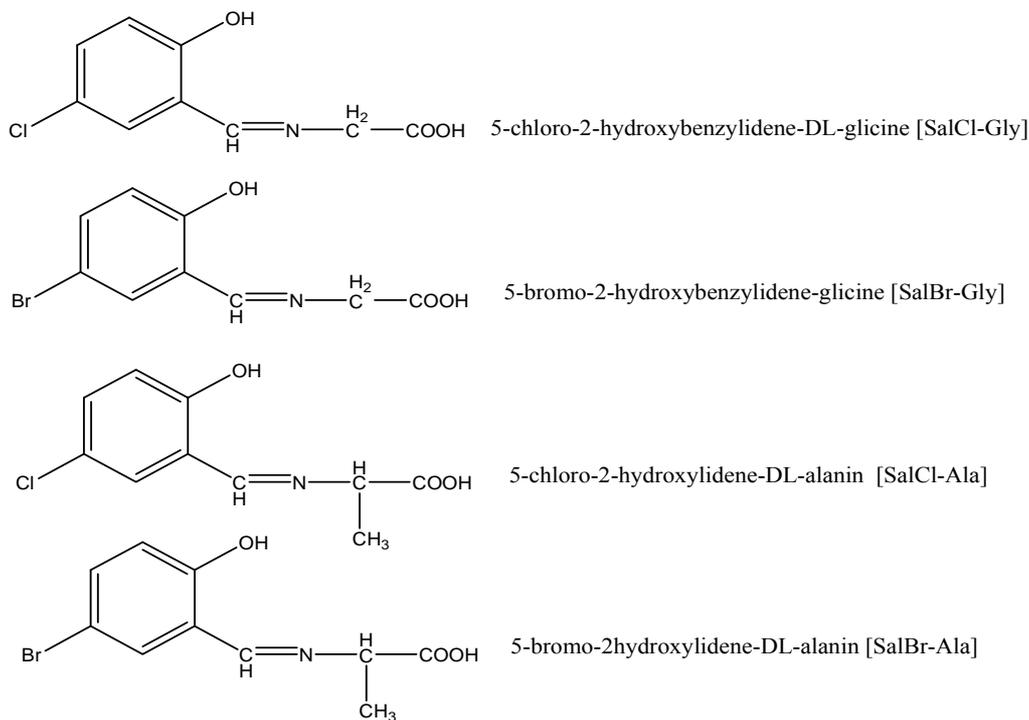
with a new Schiff base, 3-[(z)-5-amino-1.3.3-trimethyl cyclohexylmethylimino]-1.3-dihydroindol-2-one formed by the condensation of isatin (Indol-2.3-dione) with isophoronediamine(5-amino-1.3.3-trimethyl-cyclohexane methylamine)(IPDA) was synthesized and characterized by microanalysis, conductivity, UV-visible, FT-IR, ^1H NMR, TGA, and magnetic susceptibility measurements. All the complexes exhibit 1:1 metal to ligand ratio spectral data revealed that the ligand acts as monobasic bidentate, coordinating to the metal ion through the azomethine nitrogen and carbonyl oxygen of isatin moiety. Both the ligand and the metal complexes were screened for their antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa*, and the complexes are more potent bactericides than the ligand [46].

Complexes of the type $[\text{M}(\text{apash})\text{Cl}]$ and $[\text{M}(\text{Hapash})(\text{H}_2\text{O})\text{SO}_4]$, where $\text{M} = \text{Mn}(\text{II}), \text{Co}(\text{II}), \text{Ni}(\text{II}), \text{Cu}(\text{II})$ and $\text{Zn}(\text{II})$; Hapash = acetone p-amino acetophenone salicyl hydrazone have been synthesized and characterized by elemental analyses, molar conductance, magnetic moments, electronic, ESR and IR spectra, thermal studies (TGA & DTA) and X-ray diffraction studies. The ligand coordinates through two (C=N) and a deprotonated enolate group in all the chloro complexes, whereas through two (C=N) and a (C=O) group in all the sulfato complexes. Most of the complexes show better antifungal activity than the standard miconazole against a number of pathogenic [47].

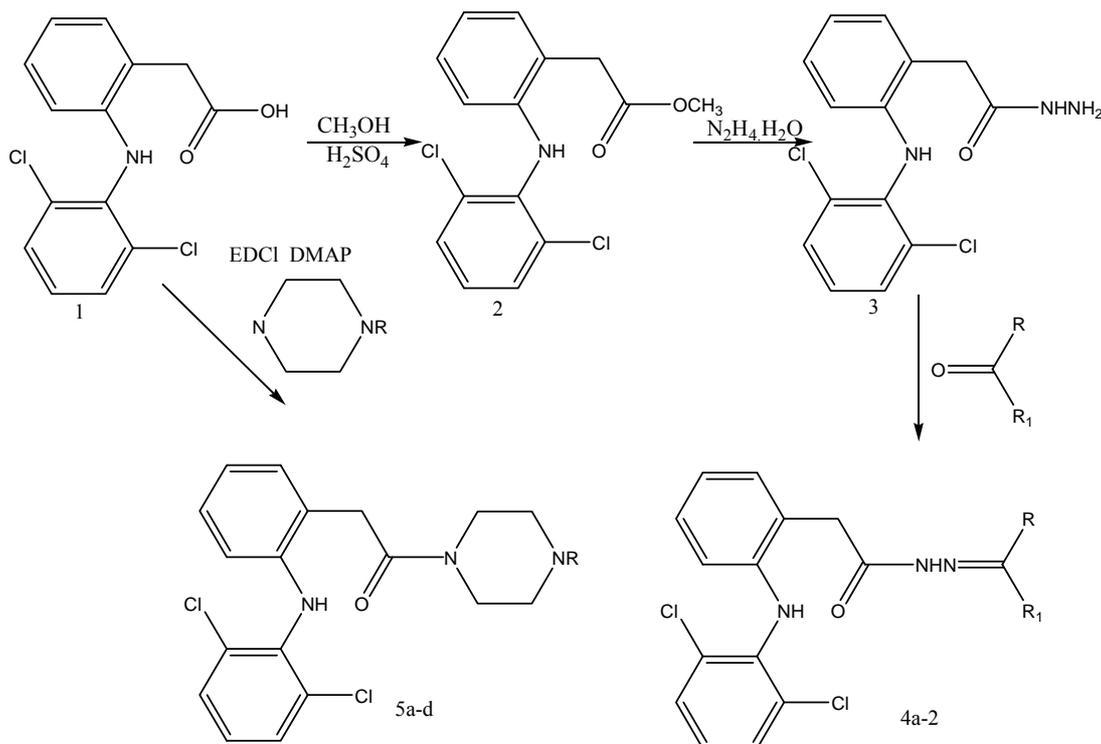
Rehman *et al* have reported the synthesis and characterization of a Schiff base (Scheme 22) derived from aniline and salicylaldehyde and its Co(II), Mn(II), and Zn(II) complexes; several physical, in particular, elemental analysis, infrared and NMR techniques were used to investigate the chemical structure of the complexes. Biological screening of the complexes reveals that the Schiff base transition metal complexes show significant against all microorganisms [48].

A series of new Schiff base hydrazones (Scheme 21) were synthesized by condensation reaction of 4-amino-3-(4-pyridine)-5-mercapto-1,2,4-triazole with various aldehydes and/or dialdehydes. The all prepared compounds were assayed for antibacterial (*Escherichia coli* and *Staphylococcus aureus*) and antifungal (*Candida albicans*) activities by disc diffusion method. The results indicate that all tested compounds did not show any antibacterial activity against *E. coli*, as gram negative bacteria, and antifungal activity against *C. albicans*. But the compounds containing 4-Cl, 4-Me, 4-MeO, 2,4-di-Cl and 2-OH substituted phenyl moiety, respectively, showed good inhibition against *S. aureus* as compare to standard drugs [49].

A series of oxovanadium complexes with mixed ligands, a tridentate ONO-donor Schiff base ligand (Scheme 22)



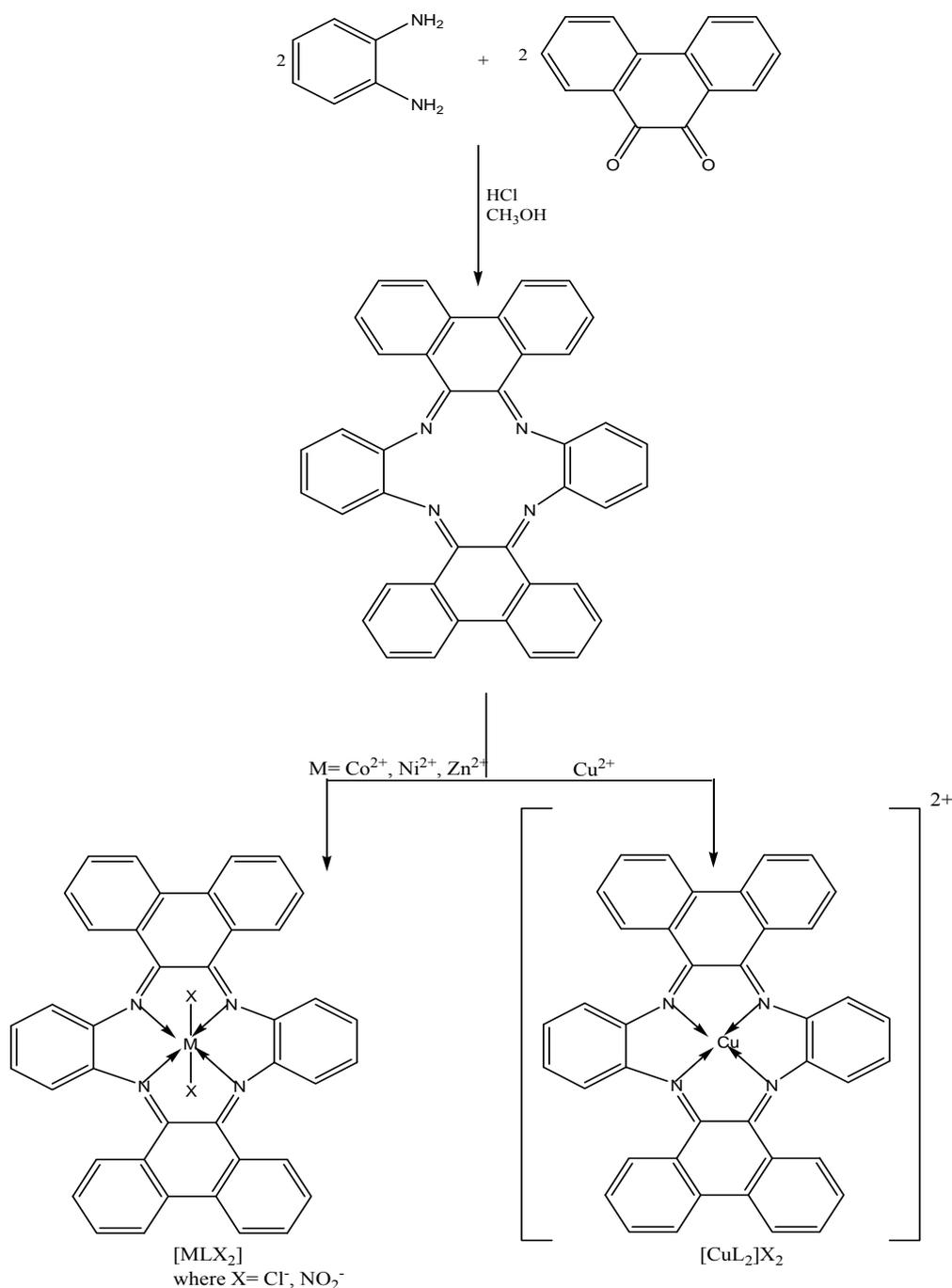
Scheme 15. Amino Acid-Schiff Bases.



Scheme 16. Synthesis protocol of dicofenac acid hydrazones and amides.

[viz., salicylidene anthranilic acid (SAA)], and a bidentate NN ligands [viz., 2,2'-bipyridine (bpy), 1,10-phenanthroline (phen), dipyrido[3.2-d:2'.3'-f] quinoxaline (dpq), dipyrido[3.2-a:2'.3'-c] phenazine (dppz), or 7-

methyldipyrido[3.2-a:2'.3'-c] phenazine (dppm)], have been synthesized and characterized by elemental analysis, electrospray ionization mass spectrometry, UV-vis spectroscopy, Fourier transform IR spectroscopy, EPR spec-

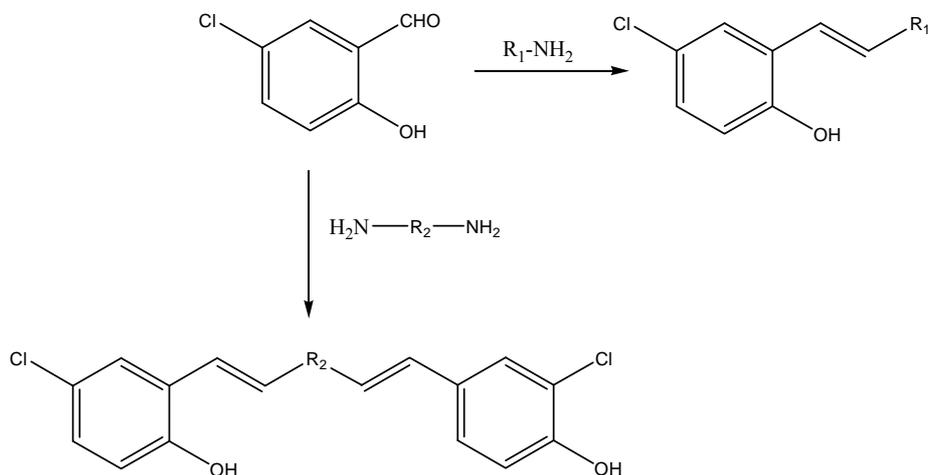


Scheme 17. Synthetic Scheme of the macrocyclic ligand(L) and its complexes (where X = Cl⁻, NO₃⁻).

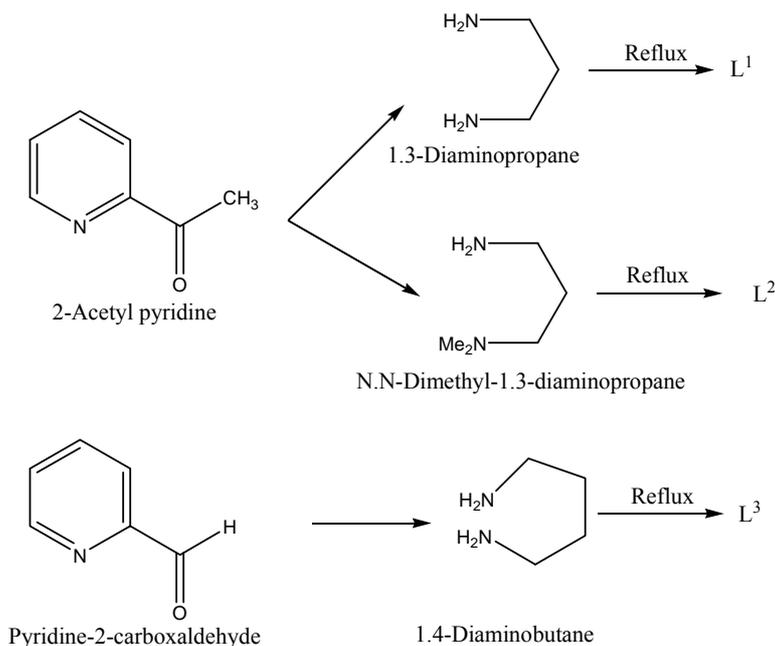
trosopy, and X-ray crystallography. The complexes have been found to be potent inhibitors against human protein tyrosine phosphatase 1B (PTP1B) (IC_{50} approximately 30 - 61 nM), T-cell protein tyrosine phosphatase (TCPTP), and Src homology phosphatase 1 (SHP-1) *in vitro*. Interestingly, the $[\text{V}^{\text{IV}}\text{O}(\text{SAA})(\text{bpy})]$ complex selectively inhibits PTP1B over the other two phosphatases (approximate ninefold selectivity against SHP-1 and about twofold selectivity against TCPTP). Kinetics as-

says suggest that the complexes inhibit PTP1B in a competitive and reversible manner. These suggest that the complexes may be promising candidates as novel antidiabetic agents [50].

New complexes of a Schiff (**Scheme 25**) derived from 2-hydroxy-5-chloroaceto phenone and glycine with Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and UO₂(VI) have been synthesized. Antibacterial activities of the ligand and its metal complexes have been determined



Scheme 18. Syntheses of the Schiff bases.



Scheme 19. Syntheses of Schiff base ligands.

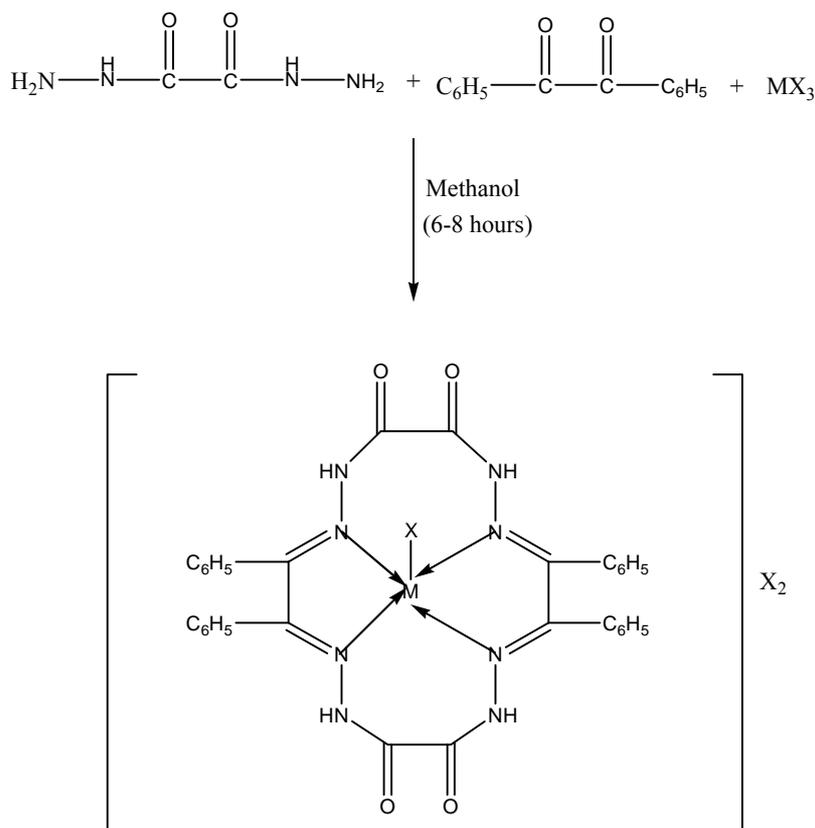
by screening the compounds against various Gram(+) and Gram(-) bacterial strains. The solid state d. c. electrical conductivity of the ligand and its complexes has been measured over 313 - 398 K and the complexes were found to be of semiconducting nature [51].

The synthesis and characterization were reported of four iron(III) complexes (Scheme 26) of general formula $[Fe(pythsalX)-(H_2O)_2]Cl_2$, derived from the NSNO-donor tetradentate Schiff base ligands pythsalHX ([5-X-N-(2-pyridylethylsul-fanylethyl) salicylideneimine] ($X=OMe$, N_2PH , I , NO_2). The free Schiff bases and their complexes have been screened for antimicrobial activities and the results show that the free Schiff bases are more potent antibacterial than the complexes [52].

Singh and coworkers have reported the synthesis a

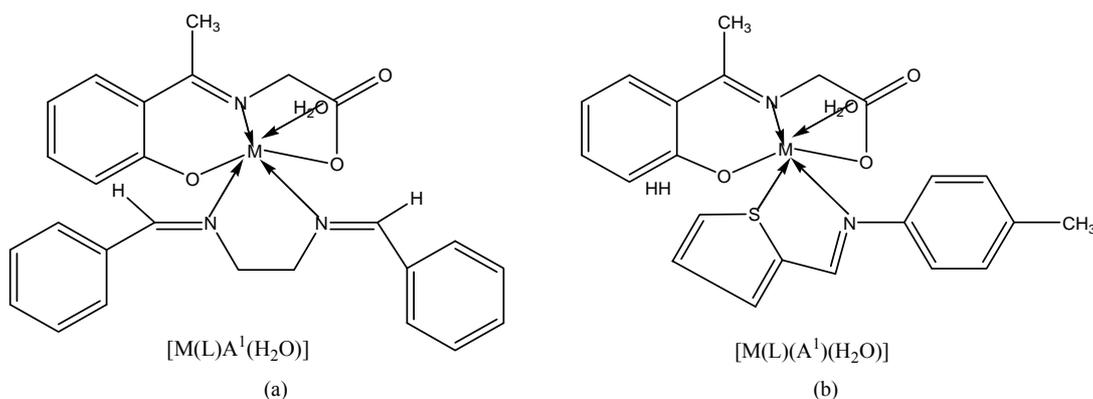
novel series of macrocyclic complexes (Scheme 27) by template condensation of 1,8-diamino naphthalene and benzil in the presence of trivalent metal salts in methanolic medium. These metal complexes were also tested for their *in vitro* antimicrobial activities to assess their inhibiting potential [53].

Reactions of $[RuCl_2(DMSO)_4]$ with some of the biologically active macrocyclic Schiff base ligands (Scheme 28) containing N_4 and N_2O_2 donor group yielded a number of stable complexes, effecting complete displacement of DMSO groups from the complex. The interaction of tetradentate ligand with $[RuCl_2(DMSO)_4]$ gave neutral complexes of the type $[RuCl_2(L)]$ [where L = tetradentate macrocyclic ligand]. All the macrocycles and macrocyclic Ru(II) complexes along with existing antibacterial



where $M = \text{Cr(III)}, \text{Mn(III)}, \text{Fe(III)}$,
 $X = \text{Cl}^-, \text{NO}_3^-, \text{CH}_3\text{COO}^-$

Scheme 20. Synthesis a new series of Complexes.



Scheme 21. Suggested structure of the mixed complexes.

drugs were screened for antibacterial activity against Gram(+) (*Bacillus subtilis*, *Staphylococcus aureus*) and Gram(-) (*Escherichia coli*, *Klebsiella pneumonia*) bacteria. All these compounds were found to be more active when compared to streptomycin and ampicillin. The representative macrocyclic Schiff bases and their complexes were also tested *in vitro* to evaluate their activity against fungi, namely, *Aspergillus flavus* and *Fusarium species* [54].

A novel Schiff base ligand (**Scheme 29**) derived from 5-bromo salicylaldehyde and 4-substituted amines and its transition complexes with Co(II), Ni(II) and Cu(II) have been synthesized. The antimicrobial activity properties of the ligands and their metal complexes have been studied [55].

4-Phenyl-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (**Scheme 30**) was obtained in basic media via the formation of 2-isonicotinoyl-N-phenylhydrazinecar bothioamide

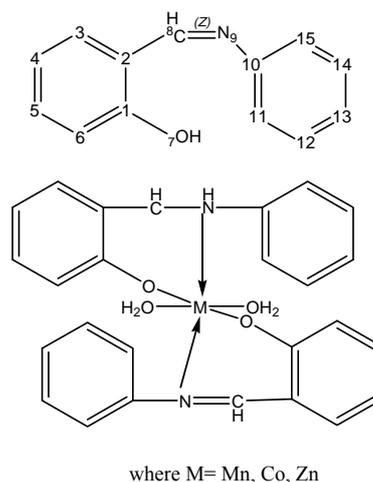
(2), and converted to some alkylated derivatives and Mannich base derivatives. 2-[(4-Phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio]acetohydrazide (7) that was obtained by using compound 3 as precursor in two steps was converted to thiosemicarbazide derivative (8), Schiff base derivatives (9) and 5-{[(4-phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio]methyl}-1,3,4-oxadiazole-2-thiol(10). Moreover, (Scheme 30) 5-{[(4-phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio] methyl}-3-{(2-morpholin-4-ylethyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione (11) was synthesized via reaction of compound 10 with 2-(4-morpholino)ethylamine. The treatment of compound 8 with NaOH gave 4-(4-methylphenyl)-5-{[(4-phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio]methyl}-4H-1,2,4-triazole-3-thiol (12), while the acidic treatment of compound 8 afforded 5-{[(4-phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio]methyl}-2(4-methylphenyl)-amino-1,3,4-thiadiazole. All newly synthesized compounds were screened for their antimicrobial activities. The antimicrobial activity study revealed that all the compounds screened showed good or moderate activity except compounds 3, 5, 7, 9, 9, and 11 [56].

Microwave-assisted synthesis and characterization of the organotin (IV) complexes (Scheme 31) are reported. Trigonal bipyramidal and octahedral complexes of tin (IV) have been synthesized by the reaction of dimethyltin (IV) dichloride with 4-nitrobenzylidene-S-benzylthio-carbazate (L_1H), 4-chlorobenzylidene-S-benzylthio-carbazate (L_2H), 4-nitrobenzylidenebenzothiazoline (L_3H) and 4-chlorobenzylidenebenzothiazoline (L_4H). The antimicrobial activities of the ligands and their correspond-

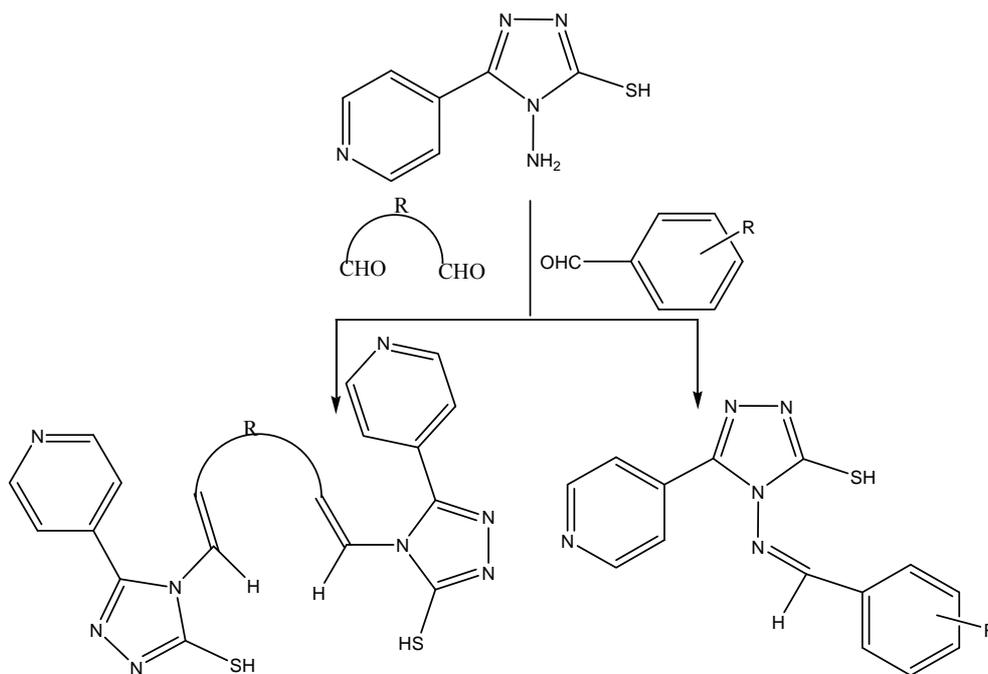
ing organotin (IV) complexes have been screened against various strains of bacteria and fungi. Antifertility activity against male albino rats has also been reported [57].

A media consisting of isatin-Schiff bases (Scheme 32) (isatin-3-thiosemicarbazone, isatin-3-semicarbazone, and isatin-3-phenylhydrazone) was developed to maximize the production of antibiotics Hexaene H-85Azalomycine B by *Streptomyces hygroscopicus*. The media isatin-3-thiosemicarbazone resulted in the maximum antibiotics concentration of $372 \mu\text{g}\cdot\text{cm}^{-3}$ for Hexaene H-85 and $118 \mu\text{g}\cdot\text{cm}^{-3}$ for Azalomycine B [58].

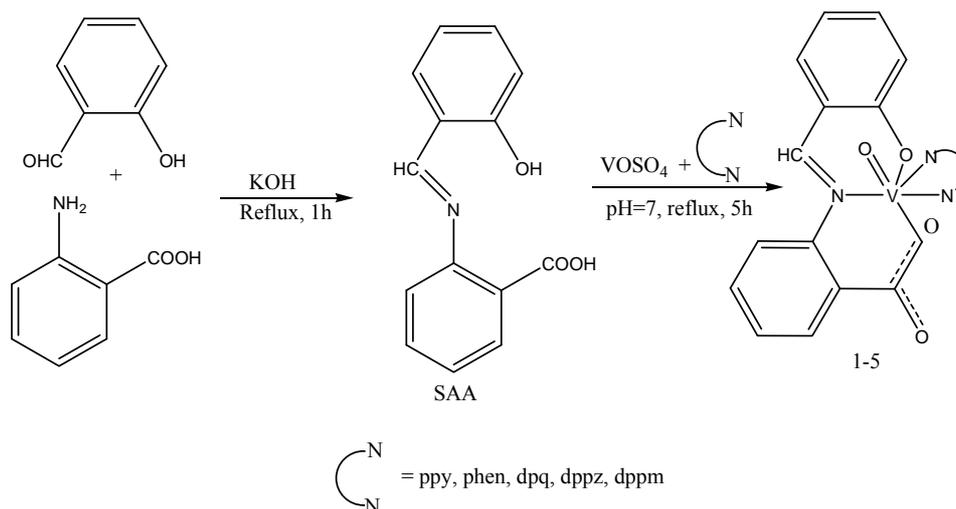
Two end-on azido-bridged Co(III) complexes $[\text{Co}_3(\text{L}1)(\mu_{1,1}\text{-N}_3)_4(\text{N}_3)_2(\text{OH}_2)(\text{OCH}_2\text{CH}_3)]\cdot 0.5 \text{H}_2\text{O}$ (1)



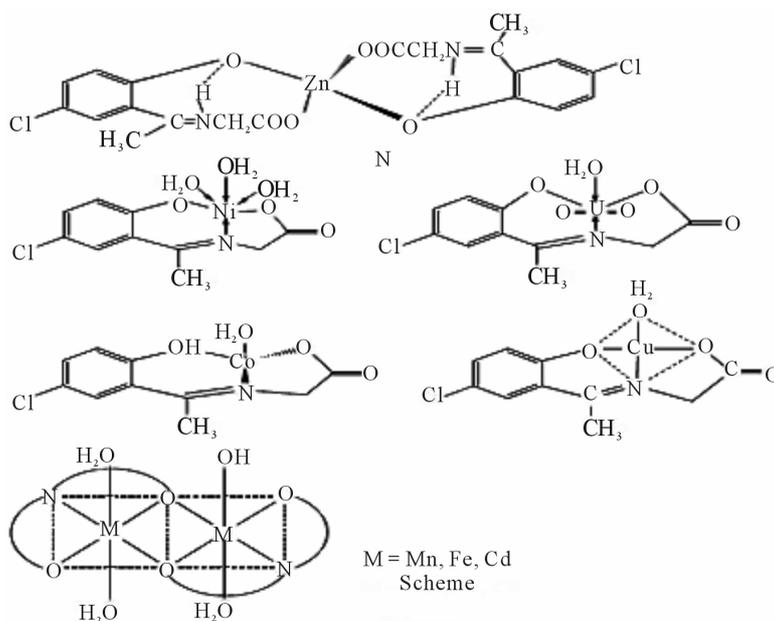
Scheme 22. Complexes of the type $[\text{M}(\text{apash})\text{Cl}]$ and $[\text{M}(\text{Hapash})(\text{H}_2\text{O})\text{SO}_4]$.



Scheme 23. The synthesized hydrazones.



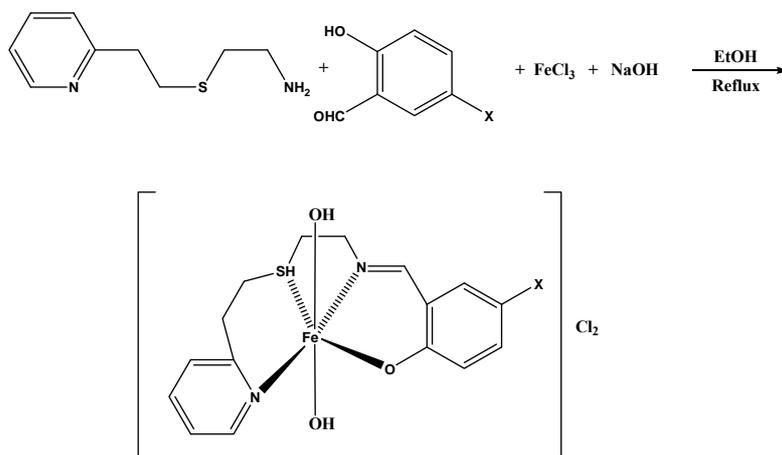
Scheme 24. The synthesis of the complexes, SAA Salicylidene anthranilic acid, bpy 2,2'-bipyridine, phen 1,10-phenanthroline dpq dipyrido[3.2-d; 2'.3'-f] quinoxaline, dppz dipyrido[3.2-a;2'.3'-c] phenazine, dppm 7-methyldipyrido[3.2-a; 2',3'-c] phenazine.



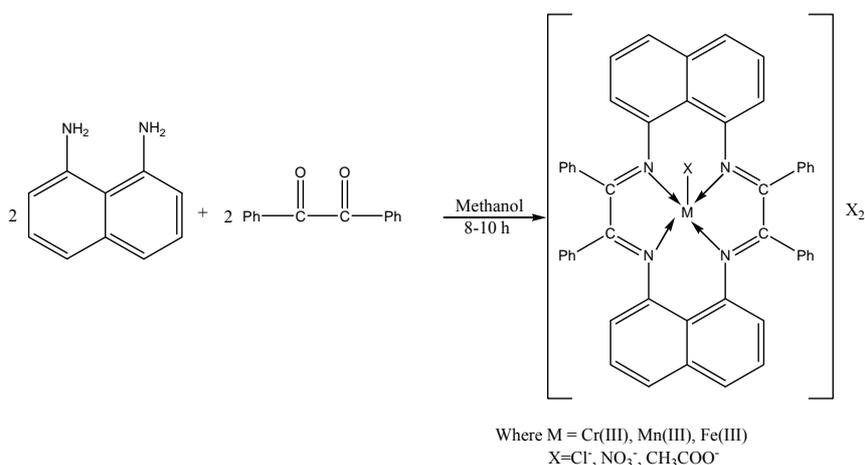
Scheme 25. Synthesis New complexes of a Schiff Bases derived from 2-hydroxy-5-chloroaceto phenone and glycine with M(II).

and $[\text{Co}_2(\text{L}2)_2(\mu_{1,1}\text{-N}_3)_2(\text{N}_3)_2]$ (2), where L1 and L2 are the deprotonated form of 5-methoxy-2-[2-morpholin-4-ylethy-limino) methyl]phenol and 2-ethoxy-6-[2-morpholin-4-ylethy-limino)methyl] phenol, respectively, were prepared and structurally characterized by physicochemical and spectroscopic methods and single crystal X-ray determination. Complex (1) is a trinuclear Co compound, while complex (2) is a centrosymmetric dinuclear Co compound. In both complexes, the Co atoms are in octahedral coordination. The preliminary biological tests show that the complexes have excellent antibacterial activity [59].

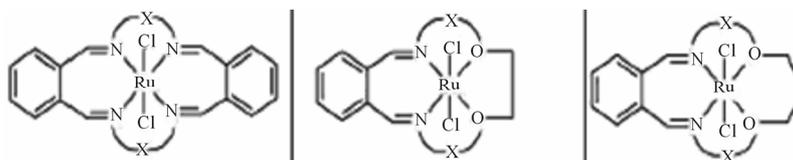
Singh *et al* have reported the synthesis new Zn(II) complexes (**Scheme 33**) by the reactions of zinc(II) acetate with Schiff bases derived from 3-substituted phenyl-4-amino-5-hydrazino-1,2,4-triazole and benzaldehyde, 2-hydroxyacetophenone or indoline-2,3-dione. All these complexes are soluble in DMF and DMSO; low molar conductance values indicate that they are non-electrolytes. All these Schiff bases and their complexes have also been screened for their antibacterial activities against *Bacillus subtilis*, *Escherichia coli* and antifungal activities against *Colletotrichum falcatum*, *Aspergillus niger*, *Fusarium oxysporium* and *Carvularia pallescens*



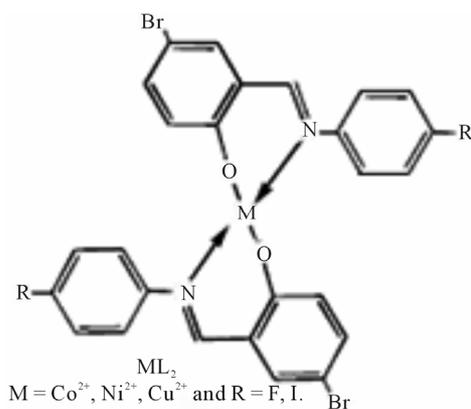
Scheme 26. Preparation of complexes X = I, NO₂, OMe, N₂Ph.



Scheme 27. Synthesis of Novel series of Macrocyclic Complexes.



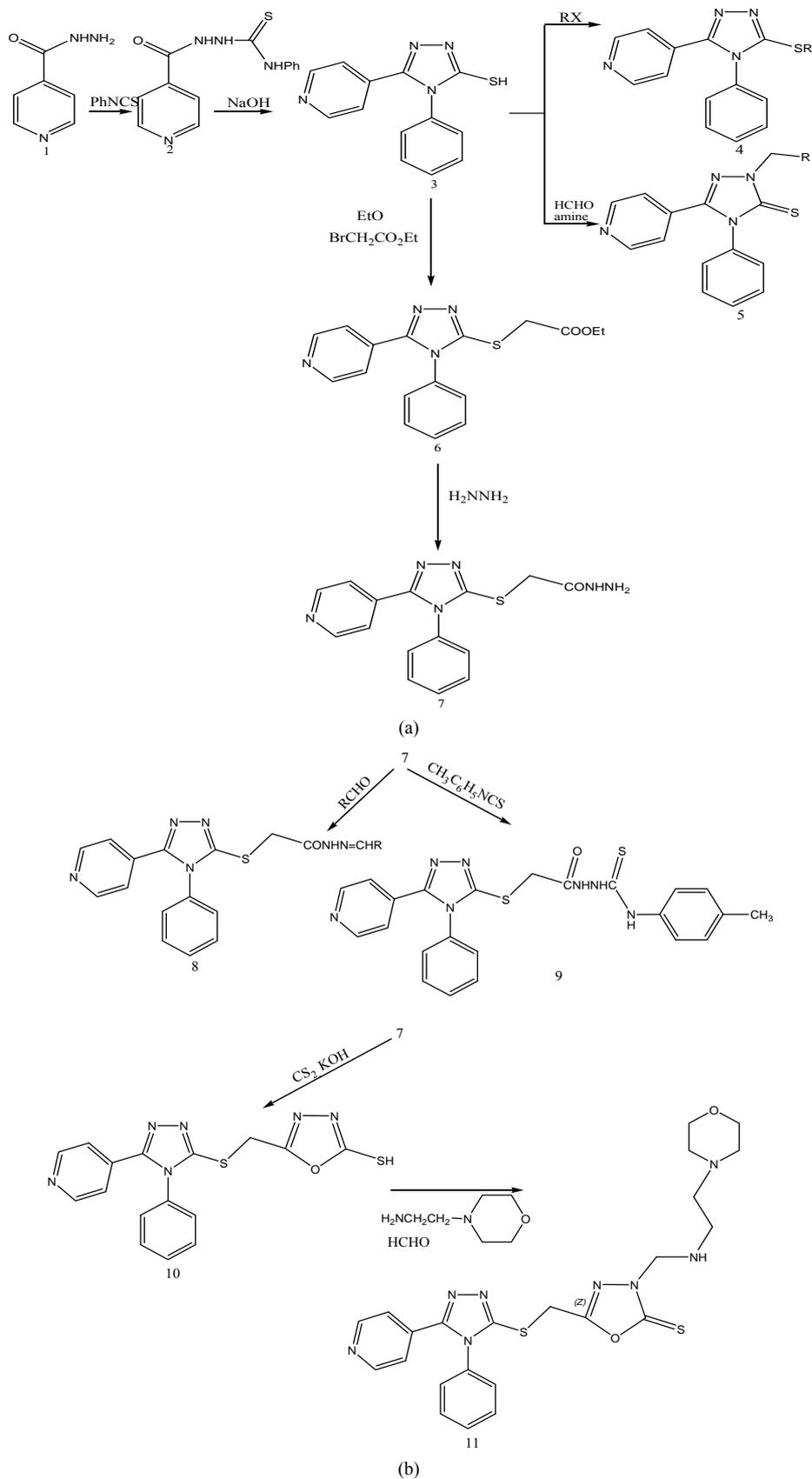
Scheme 28. Structure of macrocyclic Ru(II) compounds.



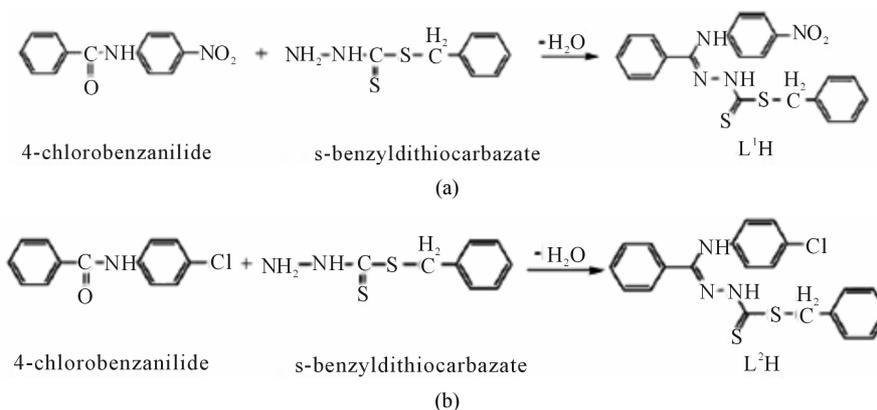
Scheme 29. General structure of metal complex.

by petriplates methods [60].

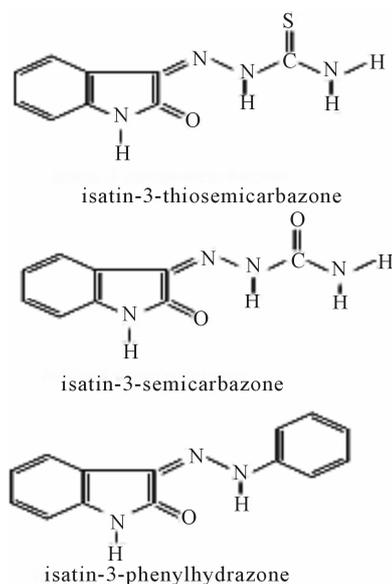
Schiff base; N,N'-bis(2-hydroxy-1-naphthaldimine)-1,3-diaminopropanol (napdapOH) reacts with metal chlorides to form dinuclear complexes of the type [M₂L₂]_nCl₂ where M = Ni, Cu, Fe and n = 0.1 Schiff base complexes were characterized by using FT-IR, LC-MS, magnetic moments and conductance measurements. Coordination was found to be through the phenolic oxygen atoms and azomethine nitrogen atoms. The electronic properties of the compounds were investigated theoretically by performing semi-empirical molecular orbital theory PM3 method in Hyperchem 7 (Release). The antibacterial activities of the compounds were investigated against Escherichia coli ATCC 11230, Bacillus subtilis RSKK 244,



Scheme 30. Synthesis pathway for the preparation of compounds 2 - 11.



Scheme 31. Synthesis of L¹H and L²H.



Scheme 32. Structures of Schiff bases.

Bacillus megaterium RSKK 5117, *Salmonella enteritidis* ATCC 13076, *Staphylococcus aureus* ATCC 25923 by using microdilution method [61].

Plech *et al* have proved that chemical character of the C-5 substituent significantly determines the antibacterial activity of the Mannich bases (**Scheme 34**) derived from 4,5-disubstituted 1,2,4-triazole-3-thiones. This activity was considerably increased by an introduction of a bromine atom to the phenyl ring. The obtained compounds were particularly active against opportunistic bacteria (*Bacillus subtilis* and *Bacillus cereus*). The antibacterial activity of some Mannich bases was similar or higher than the activity of commonly used antibiotics such as ampicillin and cefuroxime [62].

Schiff base ligand (H₃L) was prepared from the condensation reaction of protochatechualdehyde (3,4-dihydroxybenzaldehyde) with 2-amino phenol. From the direct reaction of the ligand (H₃L) with Co(II), Ni(II) and Cu(II) chlorides, and Fe(III) and Zn(II) nitrates in 2:1 L molar

ratio, the five new neutral complexes were prepared. The characterization of the newly formed compounds was done by ¹H-NMR, UV-Vis, and IR spectroscopy and elemental analysis. The *in vitro* antibacterial activity of the metal complexes was studied and compared with that of free ligand [63].

Kalanithi *et al* have reported the synthesis tridentate chelate complexes (**Scheme 35**) of Co(II), Ni(II), Cu(II) and Zn(II) from the chalcone based ligands 2-[1-(3-(1H-imidazol-1-yl)propylimino)-3-(phenylallyl)]phenol (HL₁), 2-[1-(3-(1H-imidazol-1-yl)propylimino)-3-p-tolylallyl] phenol (HL₂), 2-[1-(3-(1H-imidazol-1-yl) propylimino)-3-4-nitrophenylallyl] phenol (HL₃). The anti-microbial activity of the ligands and metal(II) complexes against the species *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans* and *Aspergillus niger* has been carried out and compared [64].

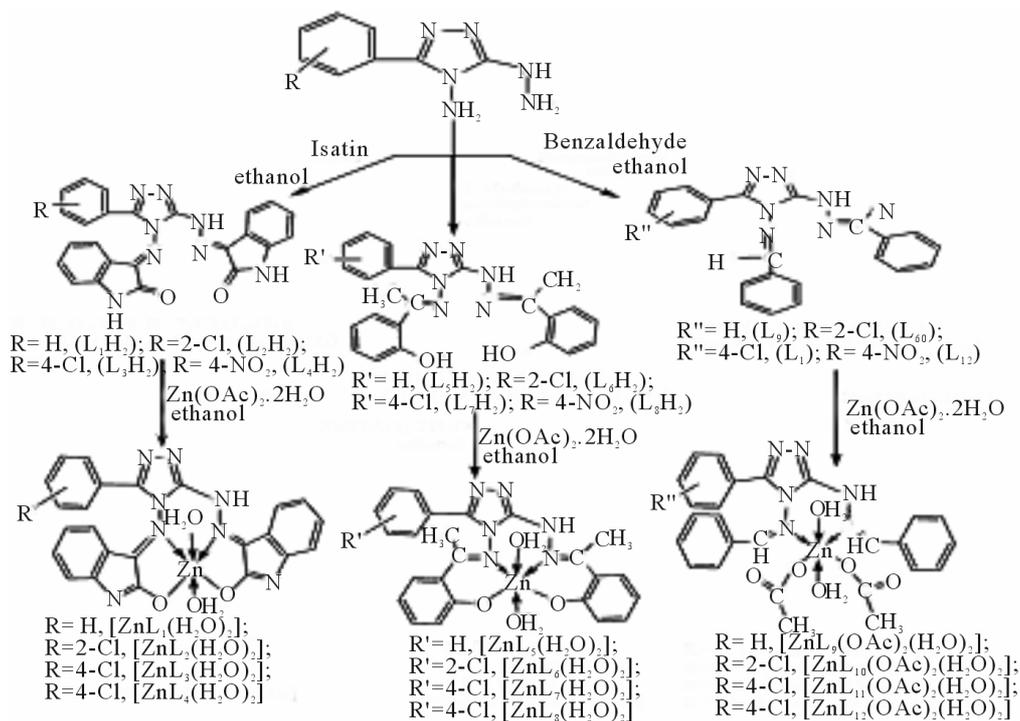
Ugras *et al* have reported the synthesis, complexation, antifungal and antibacterial activity studied of a new macro cyclic Schiff base (**Scheme 36**) [65].

Preparation, physical characterization and antibacterial activity of Ni(II) Schiff base complex was reported by Morad *et al*. [65].

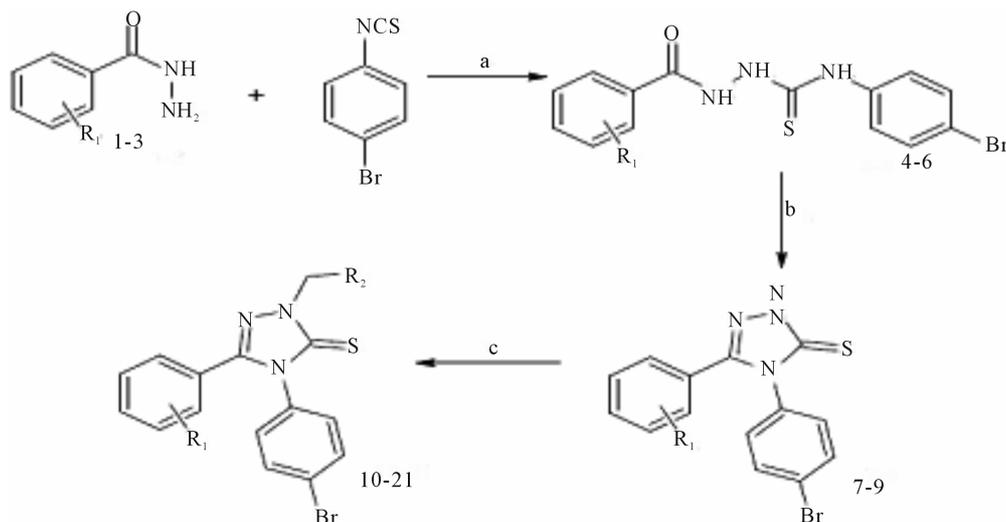
Synthesis and pharmacological studies of novel Schiff bases of 4-Hydroxy 6-carboxyhydrazino benzofuran (**Scheme 37**) was reported by Gopal Krishna Rao *et al*. [65].

4-Chloro-2-oxo-2H-chromene-3-carbaldehyde was made to react with different anilines in rectified spirit to yield a series of Schiff bases (**Scheme 38**) of type 4-chloro-3-(substituted-phenylimino)methyl)-2H-chromen-2-one. These compounds were characterized in the basis of their spectral (IR, ¹H NMR) data and evaluated for antimicrobial activity *in vitro* against fungi, gram positive and gram negative bacteria [65].

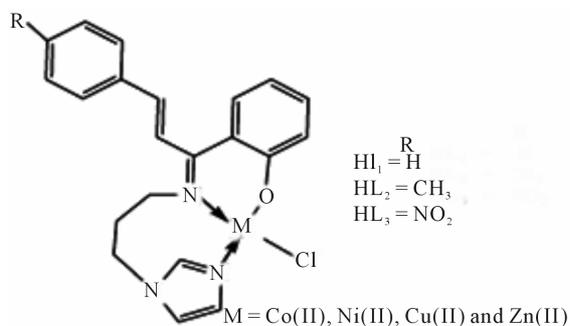
Vijey *et al* have reported the synthesis of a series of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted-pyridin-2-yl)thiosemicarbazide (**Scheme 39**) derivatives.



Scheme 33. Reaction scheme for the preparation of Schiff bases and their zinc(II) complexes.



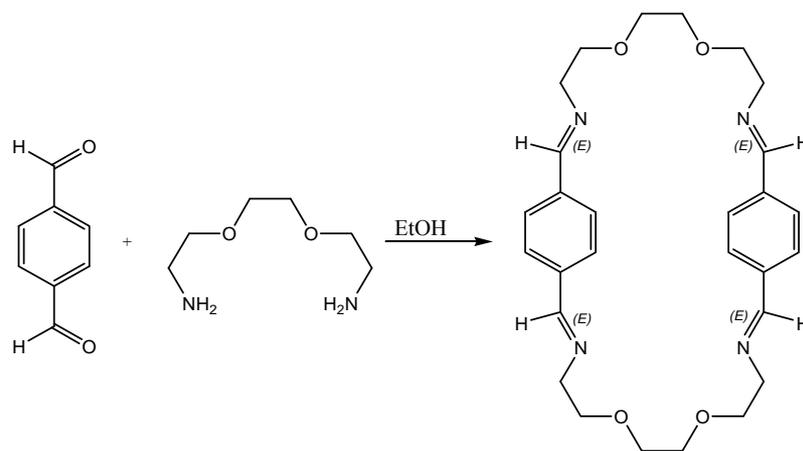
Scheme 34. Synthetic route to target compounds.



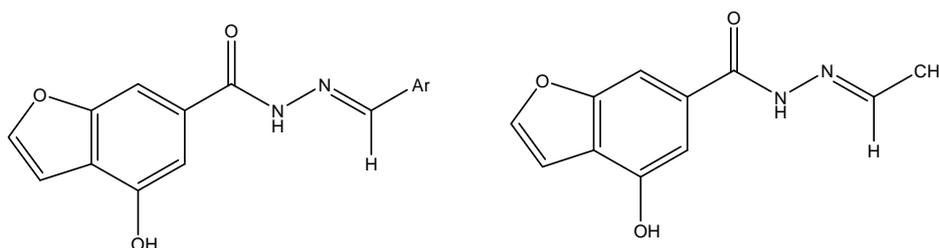
Scheme 35. Proposed structure of the metal(II) complexes.

These compounds were screened for *in vitro* antibacterial and antifungal activity against *B. subtilis*, *S. aureus*, *E. Coli*, *P. aeruginosa*, *C. albicans*, and *A. niger*. All the compounds were reported to exhibit moderate to good antibacterial and antifungal activity [65].

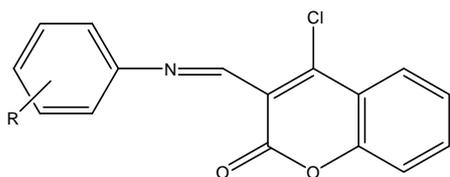
A series of biologically active pyrazine-derived Schiff base ligands (**Scheme 40**) have been synthesized by the condensation reaction of 2-aminopyrazine with salicylaldehyde and acetamidobenzylaldehyde. Then their Co(II), Ni(II) & Zn(II) complexes have been prepared. The biological evaluation of the simple uncomplexed



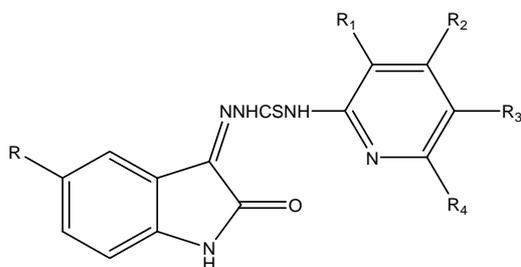
Scheme 36. Synthesis of Macrocyclic.



Scheme 37. Novel Schiff bases of 4-Hydroxy 6-carboxyhydrazino benzofuran.



Scheme 38. 4-Chloro-2-oxo-2H-chromene-3-carbaldehyde.



Scheme 39. 1-(5-substituted-2-oxindolin-3-ylidene)-4-(substituted-pyridin-2-yl)thiosemicarbazide.

ligand in comparison to their complexes have been determined to their complexes have been determined against bacterial strains namely *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [65].

Baluja *et al* have studied the biological activities of the following Schiff base (Scheme 41) and metal complexes [65]

Raman *et al* have reported the synthesis of the following Schiff ligands (Scheme 42). These authors have also

studied the DNA cleavage and antimicrobial activity of the Schiff base transition metal complexes [65].

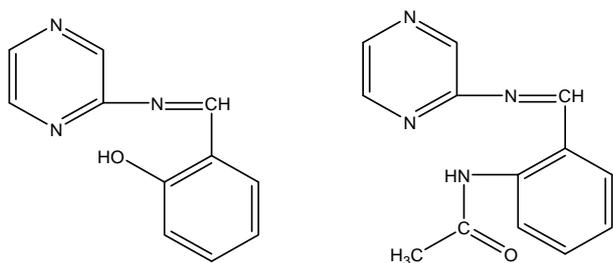
Synthesis of Schiff bases (Scheme 43) of the naphtha [1,2-d] thiazol-amine and metal complexes of 2-(2'-hydroxy)benzylideneaminonaphthathiazole as potential antimicrobial agent was reported by Faizul and co-workers [65].

Rajendran and Karvembu have reported the synthesis of Schiff bases (Scheme 44) derived from 3-amino-2H-pyrano[2.3-b]quinolin-2-ones. The synthesized Schiff base compounds were screened against the fungal strain as *Aspergillus niger* and *Fusarium sp* [65].

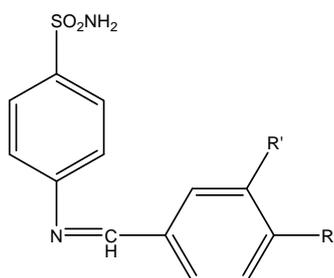
Raman *et al* have reported the synthesis of a novel 14-membered macrocyclic Schiff base (Scheme 45) derived from 3-cinnamalideneacetanalide and *o*-phenylenediamine which acts as a tetradentate and strongly conjugated ligand to form a cationic solid complex with Cu(II)/Ni(II)/Co(II) and/Zn(II). The ligand complexes were characterized by the usual spectral and analytical techniques. The antimicrobial tests were also recorded and gave good results in the presence of metal ions in the ligands system [65].

A series of 4-substituted-emoni-methyltetrazole [1.5-a] quinoline with appropriate amine by refluxing in dioxane (Scheme 46). They have been evaluated for their anti-inflammatory and antimicrobial activities [66].

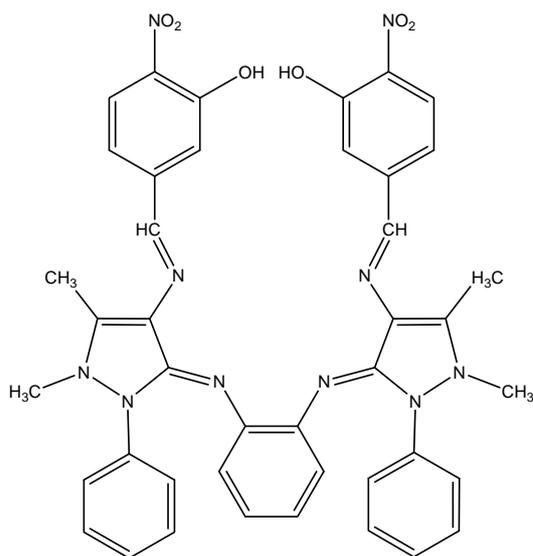
Raman *et al* have reported the synthesis of Schiff bases (Scheme 47) of 4-aminoantipyrene neutral com-



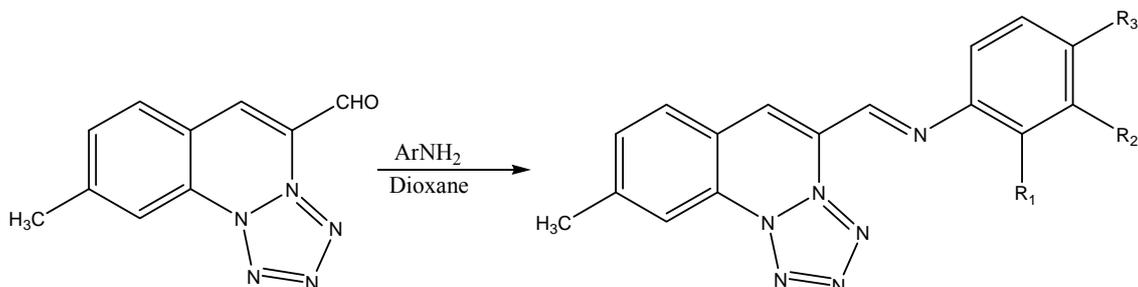
Scheme 40. Pyrazine-derived Schiff base ligands.



Scheme 41. Schiff base ligand.

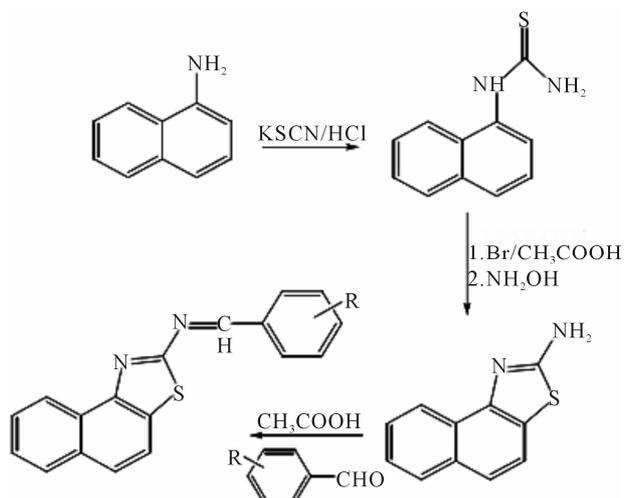


Scheme 42. Schiff base ligand.

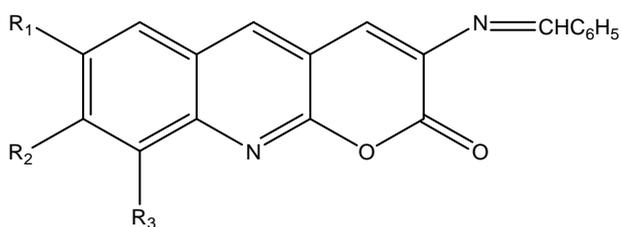


Scheme 46. Schiff bases from 4-substituted-4-methyl-1H-tetrazolo[5,1-a]quinoline and appropriate amines.

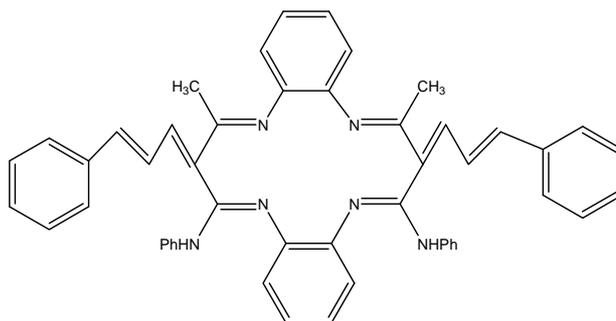
plexes of Cu (II) from salicylidine-4-aminoantipyrine and PhNH₂/substituted anilines. These authors con-



Scheme 43. Synthesis of Schiff bases.

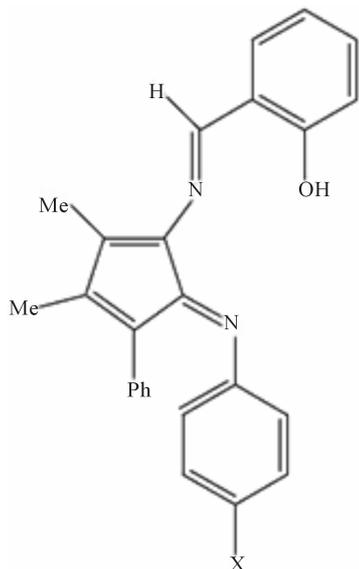


Scheme 44. Schiff bases derived from 3-amino-2H-pyrano[2,3-b]quinolin-2-ones.



Scheme 45. Macrocyclic Schiff base derived from cinnamalideneacetanalide and o-phenylenediamine.

firmed their structure using IR, UV-visible, ¹H-NMR and ¹³C-NMR spectra [67].



Scheme 47. Schiff bases of 4-aminoantipyrine neutral complexes of Cu(II).

3. Conclusions

The Chemistry of Schiff bases is a field that is being noticed. Schiff base ligands are considered privileged ligands because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines.

In this review, the biological activities of Schiff base and their complexes are summarized from 1996-2012.

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