



## Review Article

### A COMPREHENSIVE REVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITY OF SCHIFF BASES

Divya Gupta \*, Dharam Pal Pathak, Garima Kapoor, Rubina Bhutani

Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research, MB Road, New Delhi, India

\*Corresponding Author Email: dg8930962628@gmail.com

Article Received on: 26/02/19 Approved for publication: 07/04/19

DOI: 10.7897/2230-8407.1005153

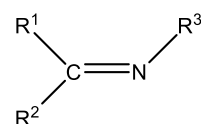
#### ABSTRACT

The chemistry of Schiff base containing compounds has been an interesting field of study from ancient years. Subsequently, Schiff base constitutes a significant class of compounds for new drug development. Schiff bases are the most widely used organic compounds. They are broadly utilized for industrial purposes and also exhibit a broad range of biological activities. The basic mechanism involved is a two step addition elimination mechanism. In the first step, the nitrogen base adds to the carbonyl compound to give a carbinolamine intermediate, followed by elimination of water to form the carbon-nitrogen double bond. Schiff bases are synthetically accessible and structurally diverse compounds, typically obtained by facile condensation between an aldehyde or a ketone with primary amines. These compounds along with their metal complexes are considered to be an important as catalysts in various biological processes. The search for Schiff base containing compounds with more selective activity and lower side effects continues to be an active area of argument examination in medicinal chemistry. This review summarizes the synthesis and biological activities of Schiff bases and their complexes.

**Keywords:** Antimicrobial, Anti-inflammatory, Anticancer, Schiff base, Synthesis

#### INTRODUCTION

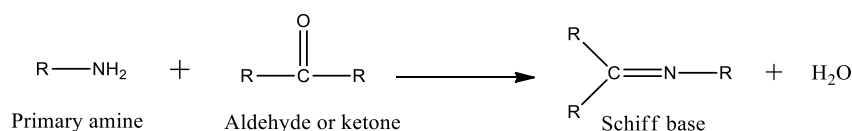
Schiff base (have been reported by Hugo Schiff) is a compound with the common structure  $R_2C=NR'$  ( $R' \neq H$ ). Schiff base can be considered a sub-class of imines, being either secondary ketimines or secondary aldimines depending on their structure. The word is often synonymous with azomethine which refers purposely to secondary aldimines (i.e.  $R-CH=NR'$  where  $R' \neq H$ ).<sup>1</sup> The significance of Schiff bases and their metal complexes are significant as analgesic<sup>2-3</sup>, anti-inflammatory<sup>4-8</sup>, anticancer<sup>9-13</sup>, anticonvulsant<sup>14</sup> and antimicrobial activities<sup>15-24</sup>.



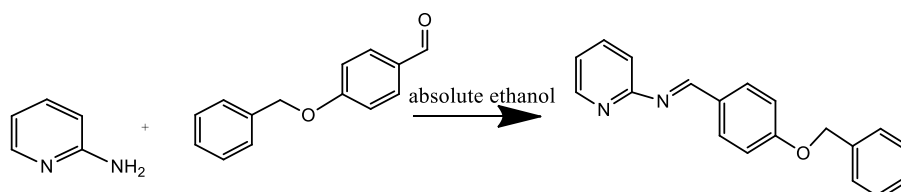
$R^1, R^2$ , and/or  $R^3$ =alkyl or aryl

#### General structure of a Schiff base

It is generally formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme<sup>25</sup>.

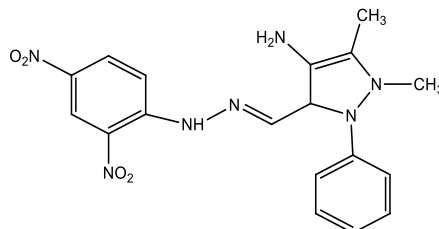


Aysen *et al* have reported the synthesis, characterization and investigation of antibacterial activities on five bacteria of Schiff base ligands. By the elemental analysis, FT-IR, <sup>1</sup>H NMR was used to characterize Schiff base ligands. From 4-benzyloxy-benzaldehyde and 2-aminopyridine (4-benzyloxy-benzylidene) pyridine-2-yl-amine was derived<sup>26</sup>.



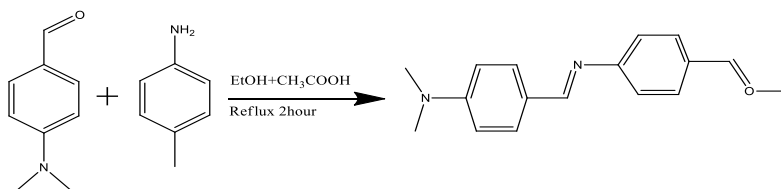
## Scheme-1

Ak Kaura *et al* reported the synthesis of some novel Schiff bases of biological importance. With the help of agarwell diffusion method all the compounds have been screened for their *in vitro* antibacterial activity against two Gram +ve and two Gram –ve bacterial strains. It has been found that amongst all the test compounds taken for antibacterial evaluation, Compound 1 has shown maximum activity against *Bacillus subtilis*<sup>27</sup>.



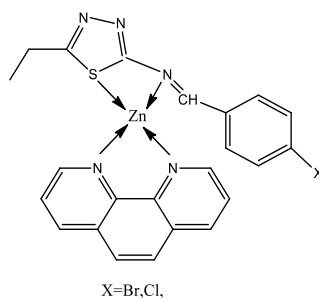
1

Ibrahim Razzaq *et al* reported transition metal complexes of Mn(II), Co(II) and Ni(II) which is derived from 4-aminoantipyrine, p-dimethyl amino benzaldehyde, p-amino benzaldehyde to give the following ligand 4-(4-(4-dimethyl aminobenzylideneamino) benzylideneamino)-1,5-dimethyl-2-phenyl-pyrazol-3 one<sup>28</sup>.



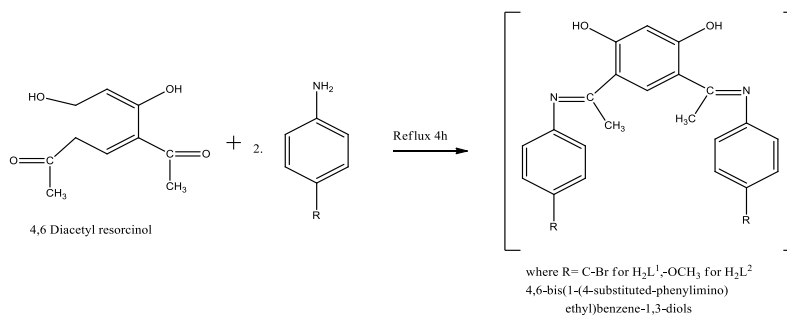
## Scheme-2

The synthesis of three zinc (II) complexes of thiadiazole derived Schiff base ligand describes by the KRM Naveen *et al.* The antibacterial investigations disclosed that the tested zinc (II) complexes illustrated potent microbial growth inhibition than their relevant thiadiazole Schiff base ligands<sup>29</sup>.



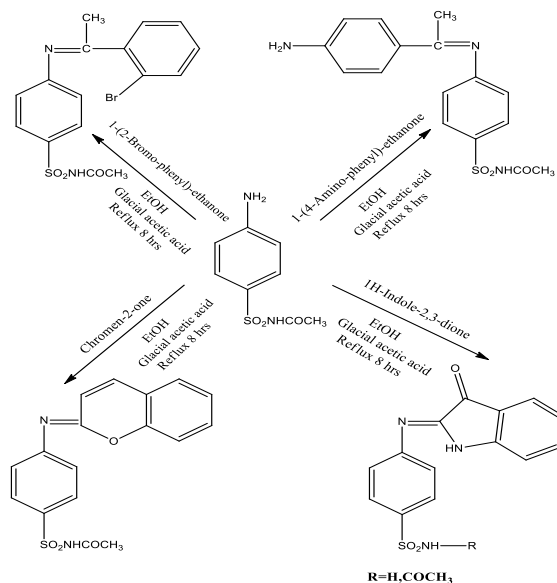
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Pandya H. Jignesh *et al* prepared two new series of Copper (II), Nickel (II) and Cobalt (II) complexes with two newly synthesized Schiff base ligands H2L1, H2L2. Through the condensation of 4, 6-diacetyl resorcinol with 4-bromo aniline and 4-methoxy aniline, H2L1 and H2L2 ligands of Schiff bases were synthesized. The outcomes of the biological screening disclose that the antimicrobial activities of the chelated ligands are superior as evaluated to the free ligands<sup>30</sup>.

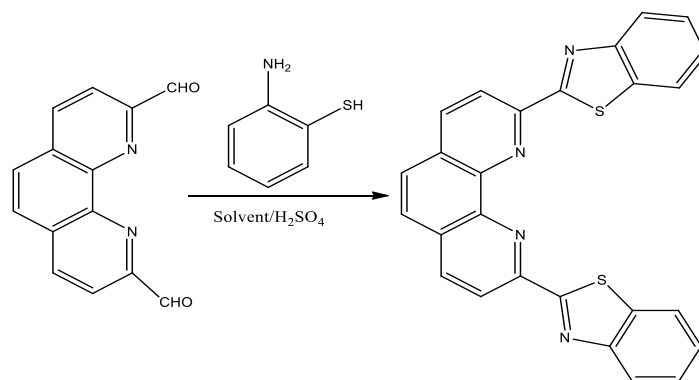


**Scheme-3**

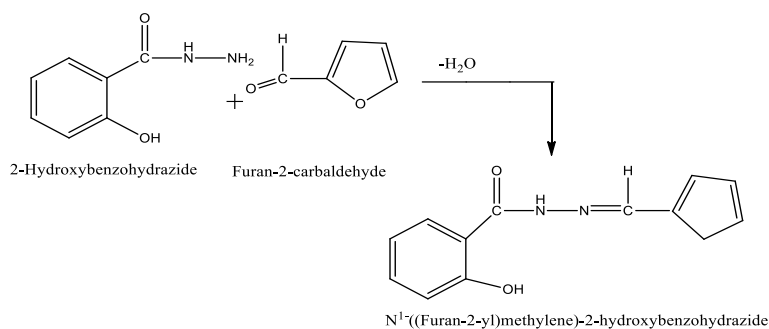
Sonu *et al* have synthesized the superior antimicrobial compounds with Different substituted aromatic aldehydes / acetophenone are selected as the starting material for the synthesis of Schiff Bases by means of sulphonamide assists to formation of Schiff bases in presences of alcohol and acidic reagent. All the synthesized Schiff bases of sulphacetamide have revealed excellent antimicrobial activity<sup>31</sup>.

**Scheme-4**

Arifuzzaman Md. *et al* have synthesized four new Schiff bases with sulfur-containing amines such as 2-mercapto aniline, S-alkyl/aryl dithiocarbazates and thiosemicarbazide of 1,10-phenanthroline-2,9-dicarboxaldehyde<sup>32</sup>.

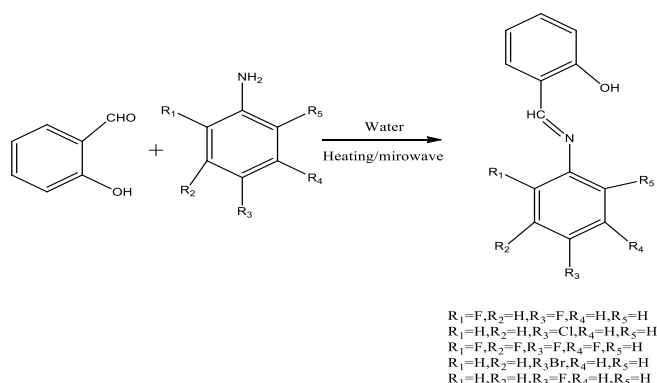
**Scheme-5**

Mangamamba T. *et al* have prepared Coordination complexes through metal ions Cu (II), Ni (II), Co (II), Fe (III), Mn (II), Cr (III), and VO (II) with six ligands formed through condensation products with azides and aldehydes or ketones are characterized. When compared to the activity of the commercial standard, the VO (II) complexes are found to be more potent<sup>33</sup>.

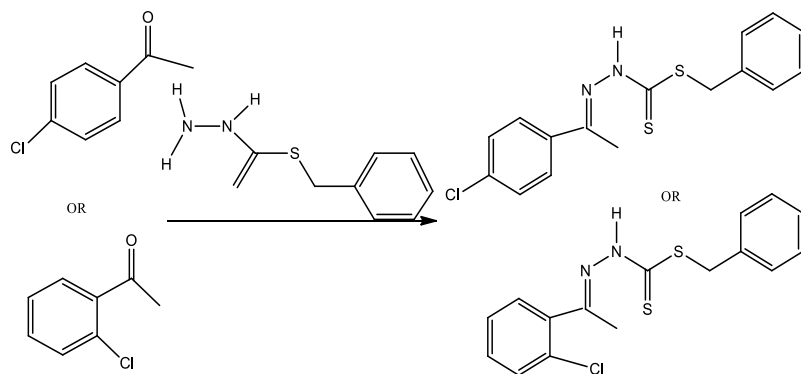


**Scheme-6**

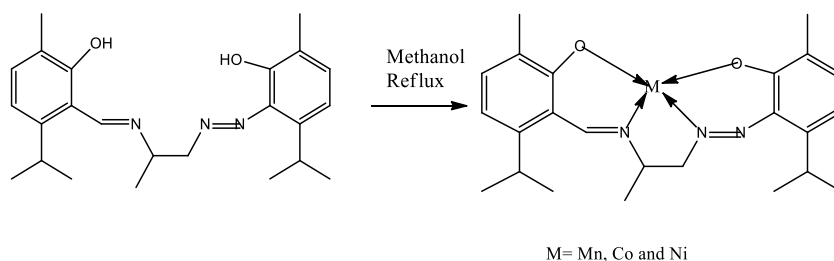
Bhagat Sunita *et al* have synthesized a series of Salicylaldehyde-based Schiff bases under microwave irradiation. It involves the condensation of Salicylaldehyde with various aromatic amines within water in microwave irradiation<sup>34</sup>.

**Scheme-7**

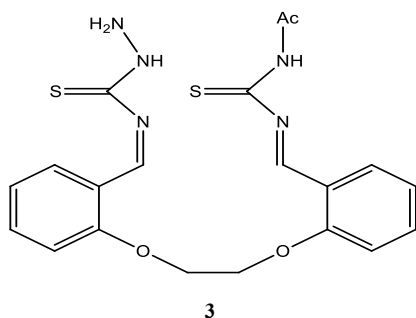
From the condensation of S-benzylthiocarbamate (SBDTC) with 2-chloroacetophenone and 4-chloroacetophenone to give S-benzyl- $\beta$ -N-(2-chlorophenyl)methylenedithiocarbamate (NS2) and S-benzyl- $\beta$ -N-(4-chlorophenyl)methylenedithiocarbamate (NS4) isomer, two bidentate Schiff base ligands having nitrogen sulphur donor sequence were reported by Khaled Mohammed *et al.* Anti microbial assay established the potential of NS2 and its complexes as well-built antimicrobial agents and the generally higher biological activity possessed by NS2 when compared to NS4<sup>35</sup>.

**Scheme-8**

Tadavi K. Samina *et al* prepared [MnL], [CoL] and [NiL]<sub>2</sub> complexes from a novel schiff base H2L which derived from the simple condensation of 2-hydroxy-6-isopropyl-3-methyl benzaldehyde and 1,2-diaminopropane in 2:1 M ratio<sup>36</sup>.

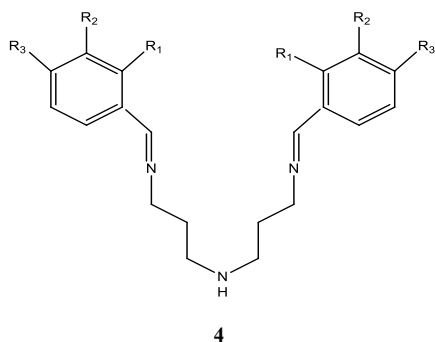
**Scheme-9**

Ehab M Zayed *et al* reported novel Schiff bases (Figure 8). Their biological activities have been checked *in vitro* against *Escherichia coli*, *Proteus vulgaris*, *Bacillus subtilis* and *Staphylococcus aureus* bacteria in order to evaluate their antimicrobial potential<sup>37</sup>.



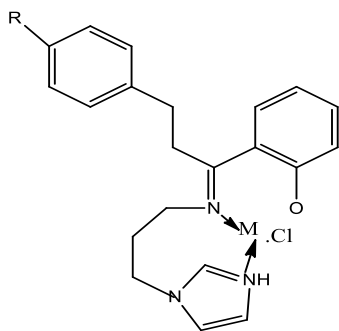
3

Six Schiff bases Synthesized by SA Matar *et al* through reacting 3, 3' -diaminodipropylamine with different benzaldehyde derivatives. The synthesized compounds were evaluated for *in vitro* antimicrobial activity against a number of Gram-positive and Gram-negative bacteria. These compounds confirmed bacteriostatic rather than bactericidal activities against Gram positive and Gram-negative bacteria<sup>38</sup>.



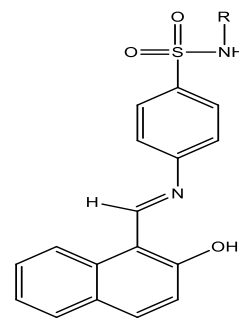
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Kalanithi M *et al* reported tridentate Co (II), Ni (II), Cu (II) and Zn (II) complexes of chalcone based ligands of schiff bases 2-[1-(3-(1H-imidazol-1-yl) propylimino)-3-(phenylallyl)]phenol, 2-[1-(3-(1H-imidazol-1-yl)propylimino)-3-p-tolylallyl]phenol, and 2-[1-(3-(1H-imidazol-1-yl)propylimino)-3-4-nitrophenylallyl]phenol (Figure 5)<sup>39</sup>.



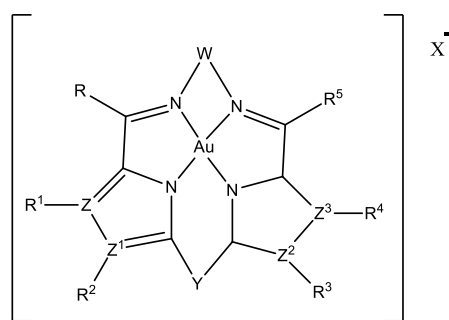
5

S Mondal *et al* synthesized schiff bases with the help of condensation of sulfonamides (sulfathiazole, sulfa pyridine, sulfadiazine, sulfamerazine and sulfa-guanidine) and 2-hydroxyl naphthaldehyde<sup>40</sup>.



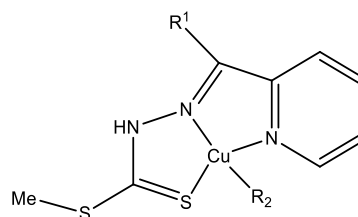
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Munro *et al* synthesized gold (III) complexes, resultant from Schiff bases, as potent cytotoxic agents, by reacting two equal amount of 1 H-pyrrole-2-carbaldehyde or 5-methyl-1 H imidazole- 4-carbaldehyde with diamines (1,2 or 1,3-diaminoalkanes). *In vitro* evaluation of these complexes showing cytotoxicity against the cancer cell<sup>41</sup>.



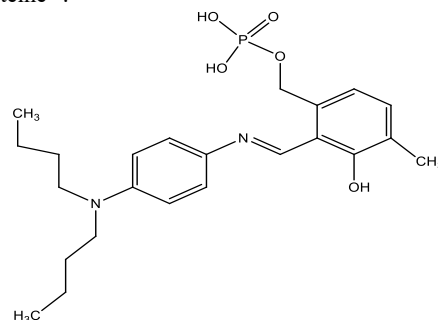
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Djaballah H *et al* reported Schiff base copper complexes as reversible allosteric inhibitors of the enzyme caspase (typically caspase 9 and caspase 3) that are also capable of disrupting tumor necrosis factor- $\alpha$  (TNF $\alpha$ )<sup>42</sup>.



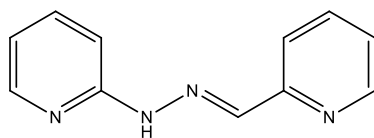
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Tan Y *et al* synthesized schiff bases by reacting pyridoxal-5'-phosphate with N, N- dibutyl-p-phenyldiamine for purpose of homocysteine<sup>43</sup>.



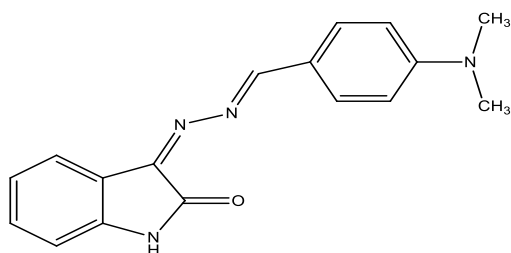
9

Al-Nuri MA *et al* synthesized six heterocyclic Schiff bases as novel anti glycation agents Schiff base was established as the most potent anti glycation agent surrounded by all the compounds<sup>44</sup>.



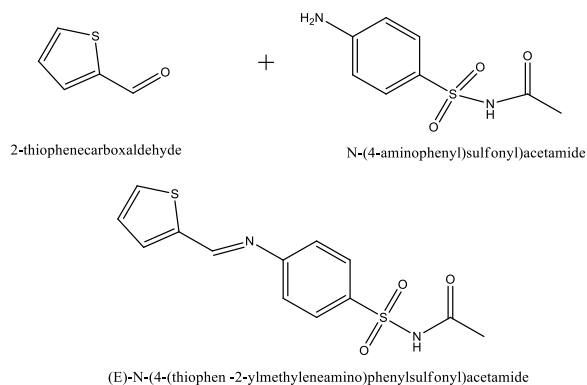
10

Sangamesh A. Patil *et al* reported the preparation of Co (II), Ni (II) and Mn (II) metal complexes of new is a tin schiff base ligand and the complexes show activity against *Mycobacterium tuberculosis* strain (H37Rv)<sup>45</sup>.



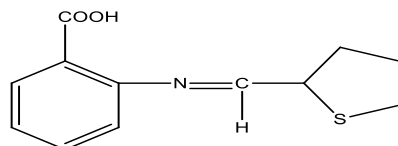
11

Ahmad S. Abu-Khadra *et al* synthesized the Metal complexes of (*E*)-*N*-(4-(thiophen-2-ylmethyleneamino) phenylsulfonyl) acetamide (S.TH) Schiff bases resulting from sulfacetamide (*N*-[4-(amino-phenyl) sulfonyl] acetamide) and 2-thiophenecarboxaldehyde. Complexes have shows potential activity upon screening for the antifungal and antibacterial characteristics<sup>46</sup>.



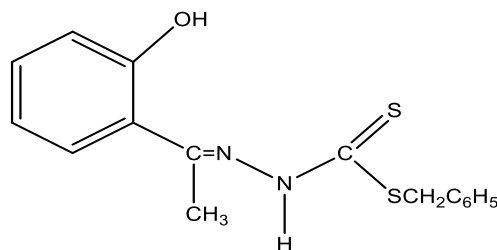
Scheme-10

A.V.G.S. Prasad *et al* reported the Schiff base from 2-thiophenecarboxy- aldehyde and 2- nitro benzoic acid. By various spectroscopic studies, the chemical structures of the Schiff-base ligand and its metal complexes were confirmed. The experimental results recommended that Schiff base derivatives are much potent in antibacterial and antifungal activities<sup>47</sup>.



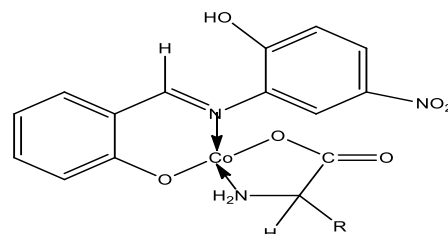
12

D. Nasrin *et al* synthesized the Schiff base ligand through the condensation reaction of S-benzylthiocarbamate with 2-hydroxyacetophenone. The produced compounds have been checked for their antibacterial and antifungal studies<sup>48</sup>.



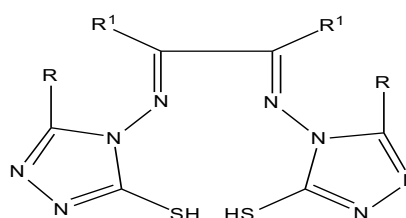
13

Ajay R. Patil *et al* prepared Co (II) complexes of Schiff base 2-amino-4-nitrophenol-N-salicylidene with amino acids<sup>49</sup>.



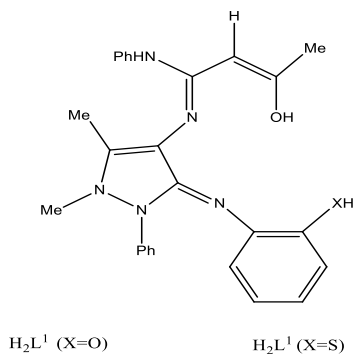
14

M. S. Yadawe *et al* synthesized Complexes of Co (II) and Ni (II) with new Schiff bases through the 4-amino-5-sulfany-1.2.4-triazoles and glyoxal, biacetyl or benzil. Various of the complexes were screened for their antibacterial and antifungal activity, and one of the Co (II) complex was evaluated for oxytocic Moreover, complex(c) (R; Me, R1; H) was establish to inhibit the oxytocic activity of oxytocin on isolated rat uterus<sup>50</sup>.



15

Natarajan *et al* synthesized neutral tetradentate chelate complexes of Cu (II), Ni (II), Co (II), Mn (II), Zn (II) and VO (II) in EtOH using Schiff bases resultant from acetoacetanilido-4-aminoantipyrine and 2-aminophenol/2-aminothiophenol. The *in vitro* antimicrobial activity of the investigated compounds was tested against the microorganisms, a large amount of the metal chelates have higher antimicrobial activity than the free ligands<sup>51</sup>.



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## CONCLUSION

The impact of Schiff bases in medicinal chemistry is deep rooted. Schiff base ligands are believed advantageous ligands because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines. These compounds and their metal complexes had a diversity of applications including clinical, analytical, industrial they also play significant roles in catalysts. In this review, the biological activities of Schiff base and its complexes have been summarized. Thus Schiff bases derivative can be further explored for development of potent medicinal agents.

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**Cite this article as:**

Divya gupta *et al* . A Comprehensive Review on Synthesis and Biological Activity of Schiff Bases. Int. Res. J. Pharm. 2019; 10(5):1-8 <http://dx.doi.org/10.7897/2230-8407.1005153>