A mini Review of Complexes of Schiff Base and their Biological Activities

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Abstract:
The present paper deals with recent work carried out with reference to the complexation of Schiff's bases with transition and inner transition metals. These complexes were found to be biological active and shows varied properties. Schiff Base is organic compound formation by condensation of a primary amine with an active carbonyl due to that condensation an imine or azomethine group (-RC=N-) appears, due to this group formation stable complexes with metals takes. The ligands and their complexes play an important role in variety of field, in inorganic, organic and biochemistry. Therefore extensively studied by the researchers, this review focuses around some Schiff base ligand, their metal complexes and biological activities of them.

Keywords: Schiff bases, metal complexes, biological activities, Amoxicillin Drug, cefotaxime antibiotic.

Introduction:
Product in condensation reaction between primary amine with carbonyls compounds is nothing but Schiff base ligand. Schiff base may obtained by either aliphatic or aromatic aldehyde. Synthesis of Schiff base from aromatic aldehyde is more facile due to conjugation system than aliphatic aldehyde which readily get polymerized \(^{(1,2)}\). Schiff bases with general formula RHC=N-R\(_1\) where R & R\(_1\) are alkyl, aryl, cyclo alkyl or heterocyclic called as Imines or azomethine or anils where Schiff base or imine are compound containing azomethine group-(HC=N)-, which forms when (O) atom of
aldehyde or ketone has been replaced by (N) atom of primary amine in condensation reaction between primary amine with carbonyls compounds. Schiff bases shows considerable chemical and biological importance due to the lone pair of electrons in sp² hybridized orbital of nitrogen atom of azomethines (3-4), not just that but the activities increase when the Schiff base ligand involve heterocyclic molecules beside in azomethine so Schiff base are excellent chelating agents. They may be bi-tri tetra- multidentate ligands, but bi-tri dentate ligands forms very stable complexes with transition metal. Schiff bases derived from amino acid are important ligand (5). Schiff base has variety of application specially biological system such as antibacterial, antifungal, anticancer, antitumor etc. They are also used in organic synthesis, medicine and pharmacy, dyes for solar collector, solar filters, catalyst, anti-corrosion agents (6-8).

1-Amoxicillin Drug:
Amoxicillin antibiotic drug is derivative of ampicillin drug which has activity against bacteria (gram positive, gram negative) the activity of this drug related to lactam ring. 4-[(E)-(3,4-dihydroxybenzylidene) amino]-N-(1,3-thiazol-2yl) benzenesulfonamide is nothing but novel Schiff base derived from amoxicillin drug which prepared by condensation reaction of Amoxicillin tri hydrate with 2-hydroxy-1-naphthaledyne in methanol as solvent.

This Schiff base biological activity against some bacteria with high activities against *Salmonella sp* and *Klebsella sp* and moderate activities against *Bacillus cereus* and *Staphylococcus aureus* and no active against *Streptococcus sp, Pseudomonas sp* and *Escherichia coli*. It also shows antifungal activity and exhibit moderate activities towards *Candida albicans* and *Aspergillus multi* but does not show activities towards *Candida trobicalis, Cadida krusi* and *Aspergillus niger* as compared with drug (9). AMXPC (Amoxicillin pyrrole-2-carbaldehyde) is nothing but novel Schiff base which synthesized by refluxing AMX (Amoxicillin tri hydrate) in aqueous methanol solution in weak acidic medium with Pyrrole-2-carbaldehyde.
and metal complexes of AMXPC prepared by condensation reaction of AMXPC with chloride salts of Copper, Cobalt and Zinc in metabolic solution as solvent in general complexes.

Where Schiff base ligand and its complexes exhibit highest biological activities than drug as well as metal complexes having higher activities than ligand against (E. coli, B. subtilis & S. aureus) various pathogenic bacteria (10)

2-Schiff bases of salicylidenebenzylamine,2-hydroxy-1-naphthylidenebenzylamine families:
Eighteen Schiff base which derivative from salicylaldehyde and 2-hydroxynaphthaldehyde with ArNH2 in ethanol as solvent.
Where the Schiff base contain Cl group which belong to salicylidenebenzylamine exhibit activities only on gram-negative (Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa and Serratiamarcescens), but Schiff base of salicylidenebenzylamine contain-CH3, -Br group doesn’t possess any activities.
Schiff base which, belong to 2-hydroxy-1-naphthlidenebenzylaminidedoesn't enhance antibacterial and antifungal, but –SH, -OH group at Para or ortho position on aniline site found increase the activities of the drug\(^{11}\)

3-pyrazole Schiff bases:
4-[(3-substituted-1H-pyrazol-3-yl) methylene amino]-5-substituted-4H-1,2,4-triazole-3-thiols is Schiff base derived from 4-amino-5-substituted-4H-1,2,4-triazole-3-thiol and 3-(4-substitutedphenyl)-1H-pyrazole-4-carbaldehyde by refluxing them in ethanol-dioxane mixture as solvent and synthesized derivatives for this Schiff base to get series of pyrazole Schiff bases.

All new Schiff bases show antibacterial activities against \textit{S. aureus, B. subtilis, E. coli} and \textit{P. aeruginosa} microorganisms as compared to Ceftriaxone (standard drug).\(^{12}\)

4-Schiff base derived from cefotaxime antibiotic (CFX):

\[
\begin{align*}
3a: & R=C_2H_5 R^1=H, \\
3b: & R=C_2H_5 R^1=4-OCH_3, \\
3c: & R=C_2H_5 R^1=4-F, \\
3d: & R=C_2H_5 R^1=4-CL, \\
3e: & R=C_2H_5 R^1=2-CL, \\
3f: & R=H R^1=H, \\
3g: & R=H R^1=4-OCH_3, \\
3h: & R=H R^1=4-F, \\
3i: & R=H R^1=4-CL, \\
3j: & R=C_3H_7 R^1=4-F
\end{align*}
\]
Cefotaxime is antibiotic against bacteria (gram positive, gram negative) which third generation of cephalosporin. Two Schiff base synthesized from (CFX) and 1H-Indole-2, 3-dione (isatin) and -N, N-dimethyl amino benzaldehyde in methanol as solvent and glacial acetic acid.

The complexes of these ligands has been reported with Co(II), Ni(II), Cu(II), Cd(II), Pd(II) and Pt(IV) . Where ligand act as tri dentate with Metal to ligand 1:1 ratio and exhibit octahedral geometries except Pd(II) complexes which shows square planar structures. The biological activities are reported for this ligands are negative against E. coli, Staphylococcus aureus, Pseudomonas aeruginosa and Streptococcus pneumonia, but all the complexes show positive activities. Compared to plain drug CFX the Pt complexes and its Schiff’s bases was found to be more active against Streptococcus pneumonia and Pseudomonas. Other metal complexes are also exhibits good biological activities with these organism.

5- Schiff base Sulfacetamide:
The Schiff base (E)-N-(4-(2-hydroxybenzylideneamino) phenylsulfonyl) {S,S} derived from Salicylaldehyde and sulfacetamide by refluxed them in hot ethanolic solution. The complexation study of Schiff base with Ag(I), Ce(II), Cr(III), Fe(III), Ni(II), Pd(II) is reported in the literature.
The metal complexes of Schiff’s base derived from 2-hydroxy benzaldehyde shows activities against Gram positive bacteria (Bacillus subtilis and Sterptococcus pneumoniae), Gram negative bacteria (Escherichiacoli and Pseudomonas aeruginosa) and also exhibits antifungal (Aspergillus fumigates and Candida albicans).\(^{(14)}\)

6- Schiff base derived from 2-amino-4-phenyl-5-methyl thiazole:
2-amino-4-phenyl-5-methyl thiazole forms Schiff’s base with salicyaldehyde in ethanol and glacial acetic acid. The Schiff’s base so obtained was by refluxed with metal chloride to produce complexes. The complexes as well as Schiff’s base was found to be exhibit anticancer activities particularly complexes with Zn (II) was show higher activity.\(^{(15)}\)

7- Novel Schiff bases derived from Sulfa drug:
Sulfa drug is sulfonamides compound has sulfur atom in its structure which control growth bacteria. Sulfathiazole, a sulfa drug used to synthesized novel Schiff bases, when condensed with pyridine-2-carbaldehyde 3-ethoxysalicylaldehyde respectively gives Schiff bases. These Schiff’s bases was found to be active against bacteria and fungus\(^{(16)}\)

\[\text{Sulfathiazole} \quad \text{Pyridine-2-carbaldehyde} \quad 3\text{-ethoxysalicylaldehyde} \]

8- **Pyrazolone-based sulfa drug Schiff bases:**

The Schiff base derivative from sulfa drug had more important due to activity of sulfa drug. When 3-methyl-1-phenyl-4-valeryl-2-pyrazolin-5-one condensed with sulphadiazine, sulfaguanidine, sulfamethoxazolin and sulphanilamide gives Schiff bases.\(^{(17)}\)

9- **Gemifloxacin drug:**

Salicylidene gemifloxacin is Schiff base derived from Gemifloxacin drug and Salicylaldehyde in methanol at 7-8 pH. It forms complexes with different transition ions when treated with metal acetate or chloride.
All the complexes hydrate are investigated for the biological activities, it was observed that ligands and its complexes exhibit higher antibacterial than original drug (18).

**10-Turmeric curcumin schiff base derived from bioactive ingredients presence in medicinal plants:**

Turmeric has yellow color and using in food and as pigment from long time but recent year investigated the medicinal properties. Curcuminaniline is derived from ingredients presence in medicinal plants i.e the curcumin extracted from the Turmeric plant. The curcumin was condensed with aniline to get Curcuminaniline Schiff base.

It is found that the Curcuminaniline have more activities against *C.albicans, C.lunata* (19).
11- Anti-mycobacterium Schiff bases of quinolone and their metal complexes:
When 6-fluoro-2-hydroxyquinoline-3-carbaldehyde is condensed with substituted aniline in ethanol it gives a Schiff base. The Schiff's base so obtained was used as ligand to form complexes.

All compound investigated of biological activities and found that anti-tubercular activities of Schiff base complexes of Zn(II) more active than Cu(II), and Schiff base ligand of Quinolone more potent than original drug as antimycobacterial agents.\(^{(20)}\)

12-Sulfamethoxazole drug and their complexes:
Sulfamethoxazole–salicylaldimine Schiff base was synthesized by condensation salicylaldehyde and sulfamethoxazole in methanol.

Schiff base sulfamethoxazole–salicylaldimine forms complexes in water-acetone mixture with metal salt FeSO\(_4\).7H\(_2\)O and CoC\(_{12}\).6H\(_2\)O in ratio 1:2.
Biological activities exhibit that complexes of the ligand more active than ligand against \textit{Staphylococcus aureus} and \textit{bacteria Escherichia coli}.\(^{(21)}\)
13-New Schiff Base Transition Metal Complexes Derived from sulphadizinedrug:
Sulphadizine and 2-carboxybenzaldehyde in the basic media and ethanol form Schiff base Schiff base form complexes with metal salt copper (II), cobalt (II), zinc (II), nickel (II), manganese (II), iron (II) in ratio 2:1 in the ethanol. These show the activities against *Bacillus pumilus, Klebsiella oxytoca, Staphylococcus aureus, Escherichia coli* and *Enterobacter*. The report shows that antibacterial activity more with complexes than ligand.(22)

14-Amino acid:
From condensation between amino acid (histidine, glutamic acid, aspartic acid, leucine, valine) and indole 3-carboxaldehyde, in ethanol Schiff’s bases are obtained. These Schiff bases exhibit antibacterial activity and antifungal activity against *Staphylococcus aureus, Pseudomonas fluorescense, Bacillus subtilis* and *Candida albicans, Aspergillus niger, Trichophyton rubrum* respectively.(23)

15-Isonocotinyl hydrazine:
N-[(1Z)-(substituted aryl) methylidene] pyridine-4-carboxyhydrazides is Schiff base synthesized by irradiated under microwave using appropriate aromatic aldehydes with Isoniazid. Schiff bases are
formed by reaction the Schiff base chloroacetyl chloride and triethyl amine using dichloro methane and stirring at low temperature.

(2,5-dimethoxyphenyl)-4-oxoazetidin-1-yl] pyridine-4-carboxamide &N-[(1Z)-(2,5-dimethoxyphenyl) methylidene] pyridine-4-carbohydrazide possess highest antidepressant activity, where as N-[3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl] pyridine-4-carboxamide &N-[(1Z)-(4-nitrophenyl) methylidene] pyridine-4-carbohydrazide possess highest nootropic activity\(^{(24)}\)

16- Thiadiazoles:

When substituted aromatic acids and aryl/alkyl isothiocyanates condensed with 4-amino-5-substituted-3-mercapto-(4H)-1,2,4-triazoles gives 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazolesis compounds.

Some of Schiff base from this category exhibit anti-inflammatory activity, ulcerogenic, lipid peroxidation, analgesic, antibacterial and antifungal activities as compared to that original drugs ibuprofen and flurbiprofen has been observed\(^{(25)}\)

17- 1, 2, 4-Triazole-3-thione:

4-amino-5-benzyl-4H-1,2,4-triazoles-3-thione and pyridine-2-carboxyaldehyde, pyridine-3-carboxyaldehyde and pyridine-4-carboxyaldehyde, when refluxed in the glacial acetic acid gives Schiff bases as 4-(3-pyridylmethelenamino)-3-mercapto-5-benzayl-1,2,4-triazole,4-(2-
pyridylmethelenamino)-3-mercapto-5-benzyl-1,2,4-triazole and 4-(4-pyridylmethelenamino)-3-mercapto-5-benzyl-1,2,4-triazol respectively. Co(II), Ni(II), Cu(II) and Cd(II) complexes with 1,2,4-triazole-3-thione in ethanol.

All three Schiff bases and their metal complexes exhibit antibacterial activity against (*Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus cereus, Micrococcus luteus, Escherichia coli, Serratia marcescens*) and antifungal (*Candida albicans, Geotrichum candidum, Fusarium oxysporum, Scopulariopsis brevicaulis, Aspergillus flavus, Trichophyton rubrum*) but in the different level (26).

18- Potassium 2-N (4-N, N-dimethylaminobenzyliden)-4-trithiocarbonate 1,3,4-thiadiazole and their complexes:
Potassium 2-N (4-N, N-dimethylaminobenzyliden)-4-trithiocarbonate 1,3,4-thiadiazole is synthesized from condensation reaction of 2-amino-5-mercapto1,3,4-thiadiazole with 4-N, N-dimethylaminobenzyliden in ethanol and glacial acetic acid mixture, complexes are prepared by treating this ligand with various metal ions.

The ligand and their complexes exhibit various biological activity against *P. aeruginosa* and *S. aureus* where the ligand doesn't exhibit any activity against them but the Ni(II) complex exhibit
highest activity than Cu(II) complex which has moderate activity and Co(II) which has slight activity as compared to drug (ampicillin).\(^{(27)}\)

19- Schiff bases derived from 3, 3-diaminodipropylamine:
By condensation reaction of 3, 3-diaminodipropylamine and different benzaldehyde & Derivatives in ethanol six Schiff bases were obtained.

![Schiff base structure](image)

These Schiff bases exhibit bacteriostatic activity instead of bactericidal activities.\(^{(28)}\)

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