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Schiff Bases and Their Transition Metal Complexes: A Review on Biological Facets

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Abstract

Schiff bases forms an important class of organic compounds the azomethine moiety present in these compounds renders them to exhibit a range of biological activities e.g. antimicrobial, antifungal antioxidant, α and β glucosidase and urease inhibition to name a few. The azomethine moiety is rich in electron density which is readily acceptable by electropositive transition metals that potentially opens up the possibility of a diverse array of metal-based candidate drug molecules. A huge number of such metal complexes are reported in the literature, this review presents a review of the literature examples and discussing various results primarily based on the role of azomethine involvement in chelation and the effect of other substitution in the close proximity with the azomethine group and their involvement in the complexation, furthermore the mechanism of biological action and reasons of pre and post complexation biological responses are also discussed. This review can provide a good starting point for people interested in exploring these compounds for any similar biological application in mind. The structural changes in the Schiff bases after chelation, the effect of substitutions, the involvement of azomethine group in the chelation and other important moieties in close proximity to the metal center after chelation can all act in deciding the overall biological activity, if such studies are performed for a series of homologous compounds, the results can become very valuable in identifying possible lead compounds. All examples presented in this review primarily focuses on a new subclass of compounds called bis Schiff bases, and they are so called because of the presence of two azomethine groups in their structures.

Keywords: Bis-schiff bases • Complexes • Antimicrobial • Antioxidant • Enzyme inhibition

Introduction

Schiff bases have a great importance as precursors in synthetic chemistry, due to their synthetic flexibility, selectivity and sensitivity towards transition metals, they are promising "ligands" and therefore many of their metal complexes with diverse biological applications are found in the literature [1-5]. The coordination behavior and related properties of these compounds are frequently attributed to the involvement of azomethine (C=N) moiety and other groups in its close vicinity. The general structure for a Schiff base is shown in Figure 1. These compounds can be synthesized by the one step condensation reaction between a primary amine and a carbonyl compound at ordinary laboratory conditions. Aliphatic Schiff bases have a tendency to polymerize due to their instability while Schiff bases formed from an aromatic aldehyde are more stable because of effective conjugation system.

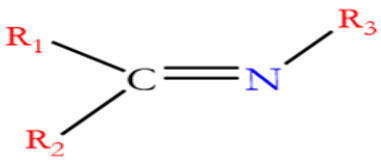

Figure 1. General structure of Schiff base R1-3=Alkyl/Aryl groups.

The azomethine group holds a lone pair of electron and Schiff bases containing two such groups are called "bis Schiff base", a general structure is presented in Figure 2.

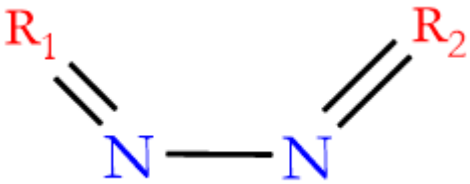

Figure 2. General structure of Bis schiff base R1-2=Alkyl/Aryl groups.

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The remarkable ligational features these compounds exhibits is due to the presence of electron donor atoms such as C, S and N that can readily donate electron pairs to transition metal centers and so enabling them to act in a multi-dentate fashion and offer huge possibilities of coordination complexes as a result. Literature review showed a wealth of such complexes synthesized from bi-dentate, tri-dentate and tetra-dentate Schiff bases with versatile biological applications [1,2,5].

Biological Applications

Schiff bases and their metal complexes have been broadly studied and reported for important contributions in the broad range of biological applications including antibacterial, antifungal, antiviral, antitumor, and enzyme inhibition etc. [6]. They also have got incredible attention over the years to be used in the treatment for diseases like diabetes and HIV-AIDS [7]. They are also involved in the treatment of cancer and often tested as anti-malarial agents and could be used for the immobilization of enzymes [8]. Numerous studies have reported the metal complexes of Schiff bases to be more potent in biological activities than the ligands they are synthesized from. In the next section, some important biological facets with selected examples from literature have been outlined and reviewed followed by a discussion of mechanism of important biological responses.

Antibacterial and antifungal

Multiple resistances to antibiotics of pathogenic bacteria and life-threatening fungal infections have aroused considerable concerns in recent years [9]. The development of new antimicrobial medicines that are effective in combating pathogenic species is markedly a serious contemporary medicinal necessity. In this scenario, Schiff bases and their derivatives have been identified as promising antimicrobial agents and have played significant role in a number of remarkable discoveries of new therapeutics in this arena [10].

Thiazole and benzothiazole Schiff bases possess effective antifungal activity. Presence of methoxy, halogen and napthyl groups enhances fungicidal activity towards Curvularia [11]. Pyrandione Schiff bases show physiological activity against *A. niger*. Some Schiff bases of quinazolinones show antifungal activity against *Candida albicans, Trichophytonrubrum, T. mentagrophytes, A. niger* and Micosporumgypseum. Furfurglidene nictoinamide Schiff base shows antifungal activity against *A. niger, Alternariasolani* and *Collectotricumcapsici* [12-17]. "N-(Salicylidene)-2-hydroxyaniline", (Figure 3), is found to be active against mycobacterium tuberculosis [18].

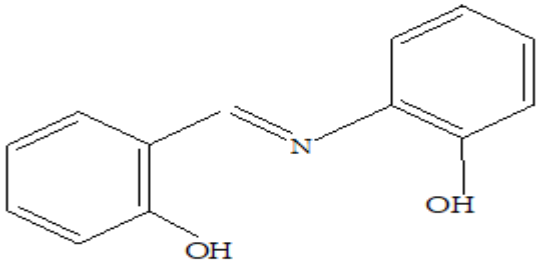


Figure 3. N-(Salicylidene)-2-hydroxyaniline.

Another Schiff base "[(2-hydroxy-1-naphthaldehyde)-3-isatin]-Bishydrazone", Figure 4, has been reported to possess antibacterial potential against *V. cholera, E. coli, B. magaterium* and *S. aureus* [4, 5].

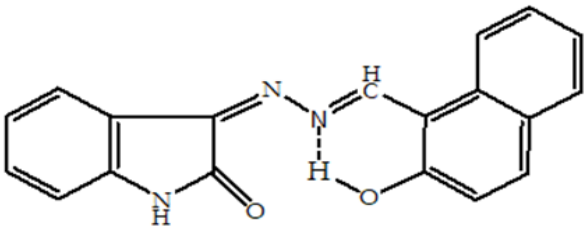
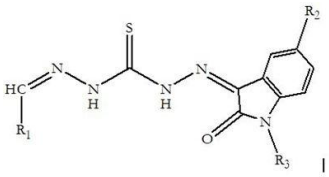


Figure 4. [(2-hydroxy-1-naphthaldehyde)-3-isatin]-bis hydrazine.

M. Saranagapani et al. have reported a series of "β–isatin aldehyde –N,N– thiocarbohydrazone" derivatives shown in Figure 5 , with significant antibacterial activities against various gram positive and gram negative bacteria including *B. subtilis, S. aureus, E. coli* and *P. aeruginosa*. These compounds were also found active against some fungi including *C. albicans, P. notatum* and *A. niger* [19].



No.	R1	R2	R3
1		H	H
2		CH_3	H
3		H	CH_3

Figure 5. β–isatin aldehyde –N,N– thiocarbohydrazone.

A bis Schiff base, "bis(2-aminobenzaldehyde) malonyldihydrazone" Figure 6 , and "5-(benzylidenea mino)-1H-imidazole-4-carboxamide", Figure 6, have been reported as active antibacterial agents against *S. aureus* and some fungi [5,20].

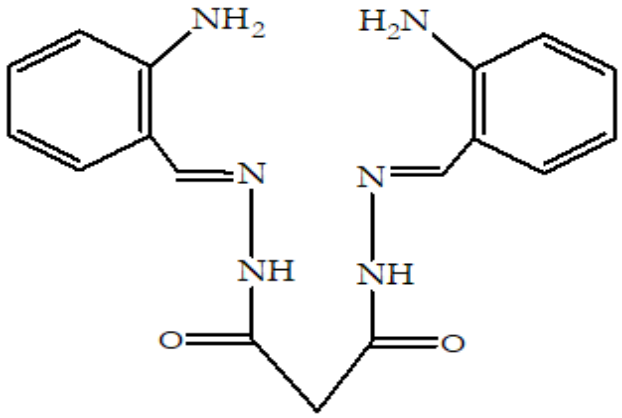


Figure 6. Bis(2-aminobenzaldehyde) malonyldihydrazone.

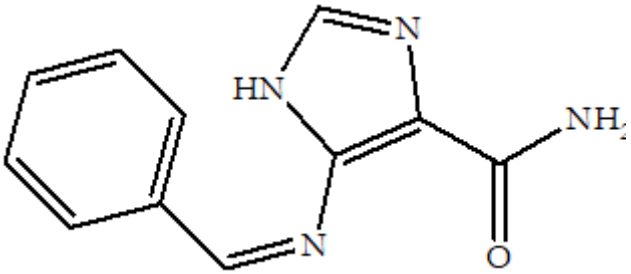


Figure 7. 5-(benzylideneamino)-1H-imidazole-4-carboxamide.

A number of transition metal complexes derived from Schiff bases have also been reported to have promising antibacterial and antifungal activities. It is generally observed that these complexes tend to possess enhanced biological behavior then their parent ligands they are synthesized from. The escalation in the biological response is widely attributed to the reduced metal centers in these complexes that increase the lipophilic nature of the molecule and hence it is able to interfere in the normal cell processes [21]. The Co^{+2}, Ni^{+2}, Cu^{+2} and Mn^{+2} complexes, Figure 8, of a bis Schiff base of isatin have been reported to have activities against bacteria (*P. aeruginosa, E. coli, B. subtilis and S .aureus*) and fungi (*P. Chrysogenum and A. niger*) [1]. Ni^{+2}, Mn^{+2}, Fe^{+2}, Co^{+2}, Zn^{+2} and Cu^{+2} complexes of a Schiff base "[(2-hydroxy-1-naphthaldehyde)-3-isatin]-bishydrazone", Figure 9 have been reported in literature as more strong bactericides than the ligand they are synthesized from [4]. Venkatesh et al. [22,23] reported the excellent antibacterial and antifungal activities of the Cu^{+2} and Zn^{+2} complexes of a Schiff base "(E)- 4-(1-(2, 4-dihydroxyphenyl)ethylidene amino) benzenesulfonamide" shown in Figure10.

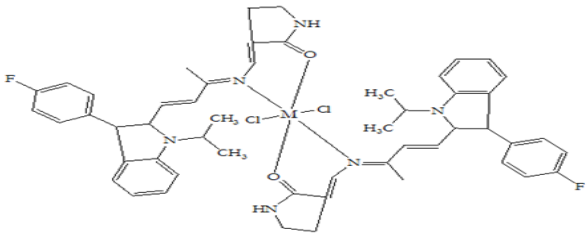


Figure 8. Antimicrobial complexes of Fluvastatin Isatinmonohydrazone.

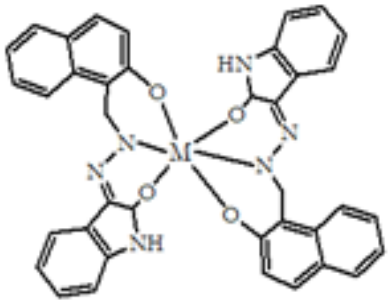


Figure 9. M=Co^{+2}, Ni^{+2}, Cu^{+2} and Mn^{+2} -Antibacterial complexes of [(2-hydroxy-1-naphthaldehyde)-3-isatin]-bishydra zone. M=Ni^{+2}, Mn^{+2}, Fe^{+2}, Co^{+2}, Zn^{+2} and Cu^{+2} (Murukan et al.).

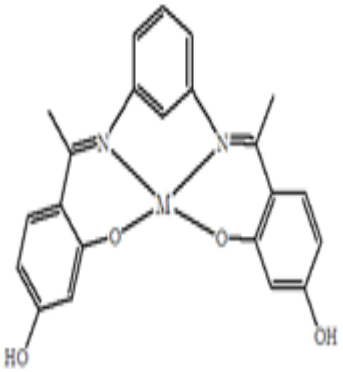


Figure 10. Antifungal complexes of (E)- 4-(1-(2, 4-dihydroxyphenyl)ethylidene amino)benzenesulfonamide, M=Zn^{+2} and Cu^{+2} (Venkatesh et al.).

Kuruba Siddappa et al. have reported Co^{+2}, Ni^{+2}, Zn^{+2}, Cu^{+2}, Cd^{+2} and Hg^{+2} complexes, Figures 11 and 12 of a Schiff base "5-bromo-3-(((8-hydroxy-2-methylquinolin-7 yl)methylene)hydrazono)indolin-2-one". It has been reported that all the complexes were more potent bactericidal and fungicidal agents than the ligand against *S. aureus, B. subtilis, P. aeruginosa, A. niger and C. albicans* [24].

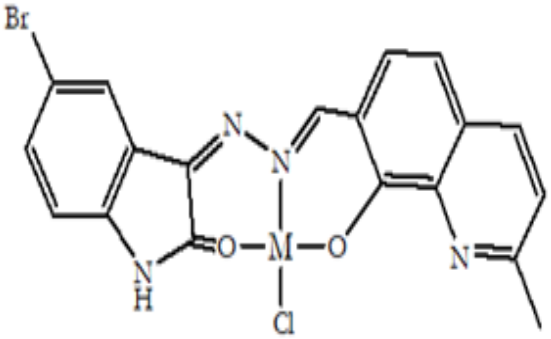


Figure 11. Antimicrobial complexes of 5-bromo-3-(((8-hydroxy-2-methylquinolin-7-yl)methylene)hydrazono)indolin-2-one, M=Zn^{+2}, Cd^{+2} and Hg^{+2} (Kuruba et al.).

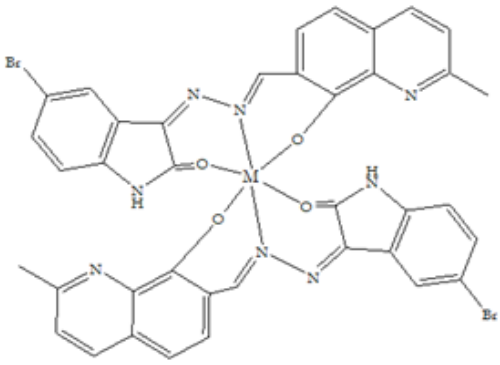
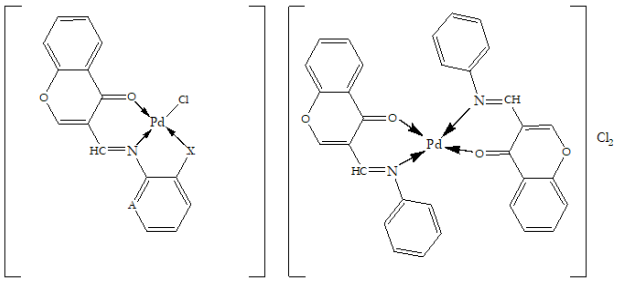


Figure 12. Bivalent Complexes of 5 above ligand with Co^{+2}, Ni^{+2} and Cu^{+2} (Kuruba et al.).

P.Kavitha et al. have reported five Pd^{+2} complexes of "3-formylchromone" Figure 13, to have antibacterial and antifungal activities. They also have reported that the palladium complexes had better microbial inhibition activities than the Schiff base ligands. Antimicrobial potential of complexes was measured against *Proteus vulgaris* and *Klebsiellapnuemoniae* (gram-negative), *S. aureus* and *B. subtilis* (gram-positive) bacteria cultures while *Candida albicans* as fungi culture [25].

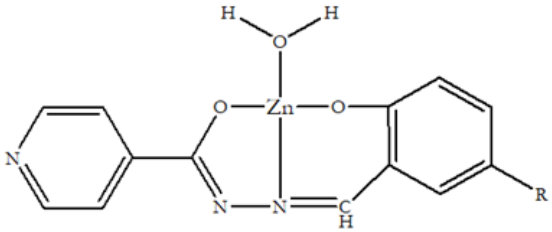
MK. Prasanna et al. have reported two Zn^{+2} complexes, Figure 14, derived from "4- pyridinecarboxylicacid ((2-hydroxyphen yl) methylene) hydrazide" and "4- pyridinecarboxylicacid ((2-hydroxy-5-methoxyphenyl) methylene) hydrazide" Schiff bases active against the *fungus Aspergillus flavus* [26].



1- A=C; X=O
2- A=C; X=COO
3- A=N; X=O
4- A=C; X=S

5

Figure 13. Antimicrobial Pd^{+2} complexes of 3-formyl chromone (Kavitha et al.).



1- R = H
2- R = OCH_3

Figure 14. Zinc complexes of 3-formyl chromone with antifungal activity (Prasanna et al.).

Antioxidant

There are numerous examples available from the literature, which illustrates the antioxidant and free radical scavenging abilities of Schiff bases. Compound "[(3-Bromobenzylidene)-amino]phenol", Figure 15, has been reported in literature as a potent antioxidant agent [27].

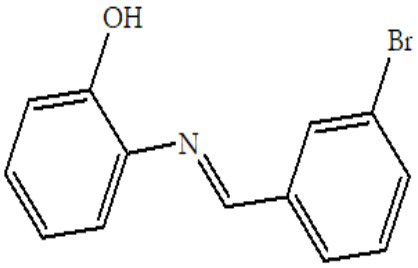


Figure 15. (3-Bromobenzylidene)-amino]phenol, Antioxidant Schiff base.

A bromo substituted Schiff base "(E)-4-(3,4-dihydroxybenzylideneamino)-2,3-dimethyl-1-phenyl-1,2 dihydropyrazol-5-one", Figure 16, has also reported with excellent antioxidant potential [28].

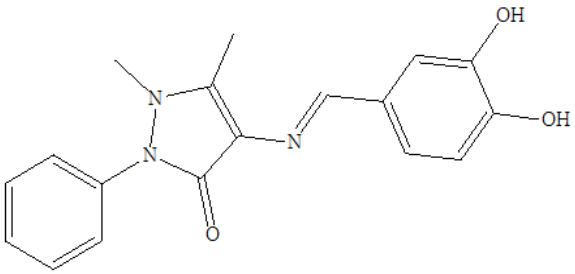


Figure 16. "(E)-4-(3,4-dihydroxybenzylideneamino)-2,3-dimethyl-1-phenyl-1,2-dihydropyrazol-5-one (Alam et al.).

Another Schiff base, "(E)-N'-(4-nitrobenzylidene)-4-chlorobenzohydrazide", Figure 17, is also reported in literature for excellent antioxidant activity [29].

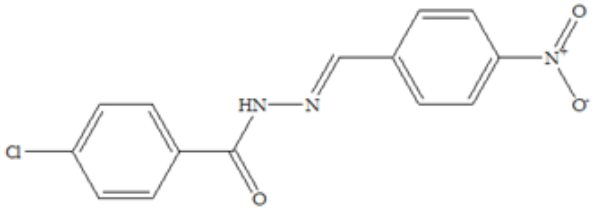


Figure 17. "(E)-N'-(4-nitrobenzylidene)-4-chlorobenzohydrazide" (Bala et al.) .

Kuruba Siddappa et al. have reported Co^{+2}, Ni^{+2}, Zn^{+2}, Cu^{+2}, Cd^{+2} and Hg^{+2} complexes Figure 18, of a Schiff base "5-bromo-3-(((8-hydroxy-2methylquinolin-7yl)methylene)hydrazono)indolin-2one". It has been reported that Co^{+2}, Ni^{+2}, Zn^{+2}, Cu^{+2} complexes were stronger antioxidant agents then the corresponding Schiff base ligand while Cd^{+2} and Hg^{+2} complexes showed moderate DPPH

radical scavenging activity as compared to standard ascorbic acid [24].

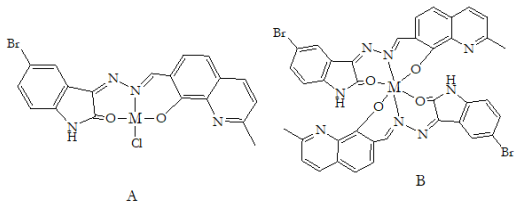


Figure 18. In A; M=Zn^{+2}, Cd^{+2} and Hg^{+2}; In B; M=Co^{+2}, Ni^{+2} and Cu^{+2} - Antioxidant Schiff Base Complexes (Kuruba et al.).

Kumar et al. have reported the antioxidant activity of some M+2 complexes of "8-((2-(2,4-dinitrophenyl)hydrazono)methyl)-7-hydroxy-4-methyl-2H-chromen-2-one" Schiff bas, Figure 19. The antioxidant activity has been reported to be enhanced upon complexation due the increased capacity of the complexes to scavenge free radicals [30].

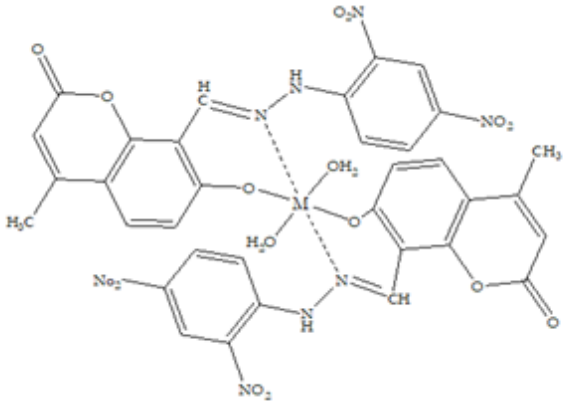
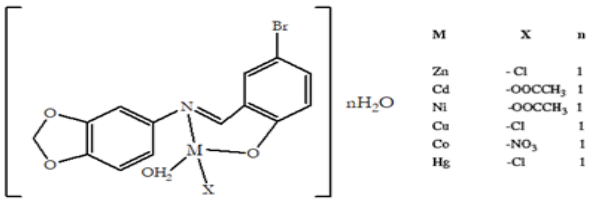


Figure 19. M=Co^{+2}, Ni^{+2}, Mn^{+2} and Cu^{+2} –Antioxidant Schiff Base Complex (Kumar et al.).

M.L. Sundararajan et al. reported some transition metal complexes (Zn^{+2}, Cd^{+2}, Ni^{+2}, Cu^{+2}, Co^{+2}, Hg^{+2}, Mn^{+2}, Fe^{+3}, and Ag^{+1}) of "2-((E)-(benzo(d)(1,3)dioxol-6-ylimino)methyl)-4-bromophenol", Figure 20, with much better antioxidant activity than the free ligand, the Cd^{+2} and Hg^{+2} complexes have been reported to be the most active antioxidant agents among all [31].



M	X	n
Zn	-Cl	1
Cd	$-OOCCH_3$	1
Ni	$-OOCCH_3$	1
Cu	-Cl	1
Co	$-NO_3$	1
Hg	-Cl	1

Figure 20. Series of antioxidant Schiff Base Complexes (Sundararajan et al.).

K. Balan et al have reported a Zn^{+2} complex, Figure 21, of N_2O_2 Schiff base (i.e. bis(3-acetyl-5-methyl-pyran-2,4 dione)ethylenediimine) ligand.

The free radical scavenging potential of the complex have been reported almost comparable to the standards, against both free radicals i.e. hydroxyl and DPPH. In both cases, the activity was found to be dose dependent [32].

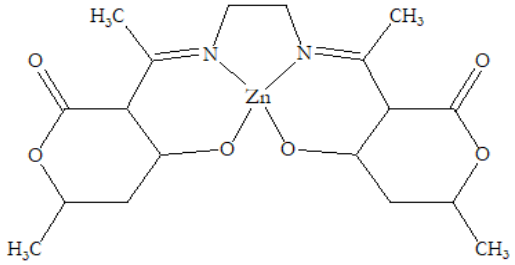


Figure 21. Zn-Complex with Antioxidant activity. (K. Balan et al.).

α-Glucosidase inhibition

Literature evidences shows that Schiff bases also exhibits excellent α–glucosidase inhibition and anti-glycation activities. Compound"4-[(E)-benzylideneamino]-5-(4-chloro-2 methylphenyl)-4H-1,2,4-triazole-3-thiol", Figure 22, represents Schiff bases as α–glucosidase inhibitors [33].

Khalid et al. have reported a series of phenoxyacetohydrazide Schiff base analogs having excellent β-glucuronidase inhibition activity. Two examples are given here: Figures 23 and 24, which showed better β-glucuronidase inhibition activity than the standard i.e. D-saccharic acid-1,4-lactone [34].

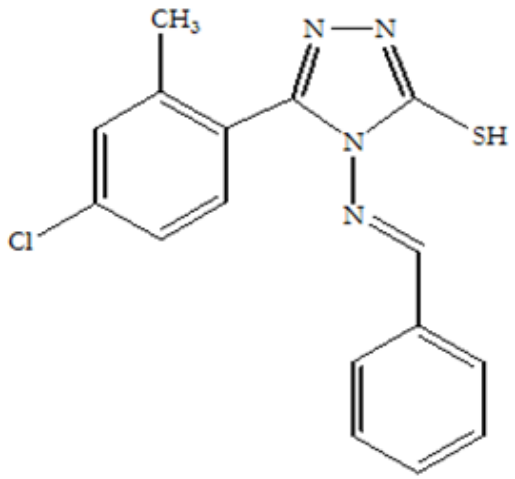


Figure 22. Potent α–Glucosidase Inhibitor Schiff Base (Aswathanarayanappa et al.).

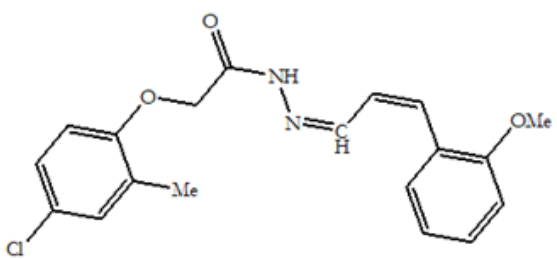


Figure 23. Potent β–Glucosidase Inhibitor Schiff Base (Jamil et al.).

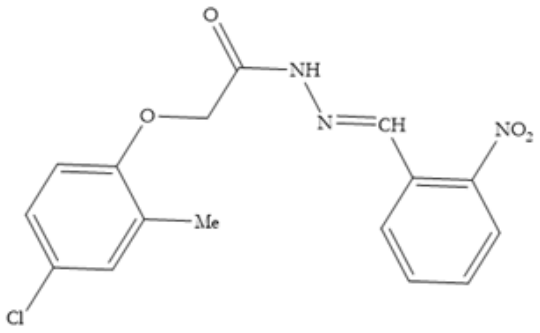


Figure 24. Another potent β–Glucosidase Inhibitor Schiff Base (Jamil et al.).

Mishra et al. have reported some oxo-vanadium IV complexes, Figure 25, with exceptionally stronger α-glucosidase inhibitory activities than the standard acrabose compound. These complexes were found to be capable of lowering the blood glucose level by ~12% while the control could only lower it to about 35% [35].

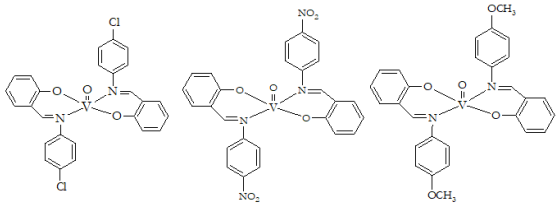


Figure 25. Vanadium Complexes with α-Glucosidase Inhibition Potential (Misra et al.).

K. Balan et al. have reported biological activities of a Zn^{+2} complex Figure 26 of "bis(3-acetyl-5-methyl-pyran-2,4-dione)ethylenediimine", Schiff base ligand. This complex also showed promising α-glucosidase inhibitory activity in a dose dependent manner [32].

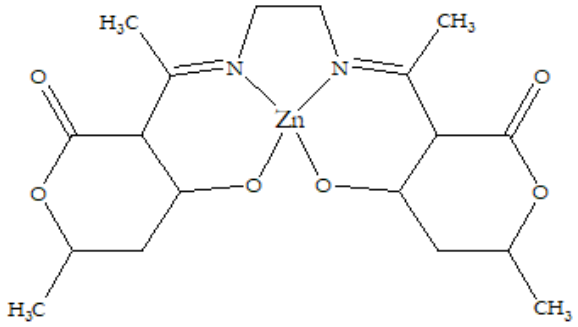


Figure 26. α-Glucosidase Inhibitor Schiff Base Complex (K. Balan et al.).

Urease inhibition

Literature investigations on Schiff bases revealed that they are capable of urease inhibition as well and a number of Schiff bases have been reported for decent urease inhibition activity. We found some examples of Schiff bases as urease inhibitors having adequate inhibition capabilities. Many workers have reported that the activity is significantly enhanced by the complexation [36].

Figures 27-31 shows four Schiff bases that are reported to be promising urease inhibitors [36].

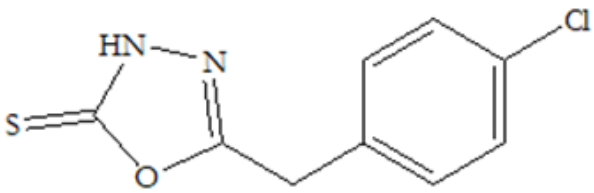


Figure 27. 5-(4-Chlorobenzyl)-1,3,4-oxadiazole-2(3H)-thione (Hanif et al.).

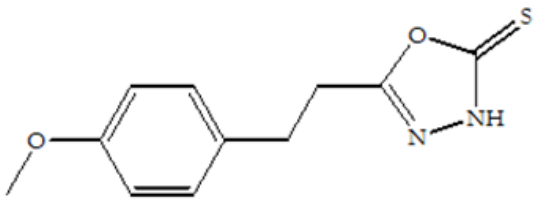


Figure 28. 5-(4-Methoxyphenethyl)-1,3,4-oxadiazole-2(3H)-thione (Hanif et al.).

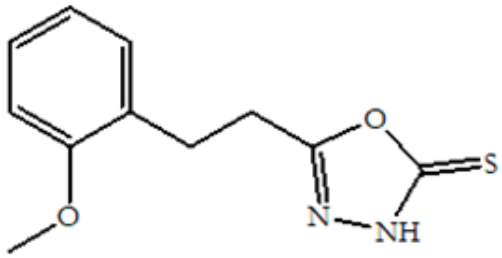


Figure 29. 5-(2-Methoxyphenethyl)-1,3,4 oxadiazole-2(3H)-thione (Hanif et al.).

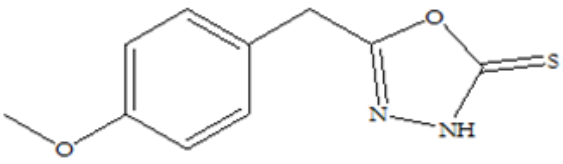


Figure 30. 5-(4-Methoxybenzyl)-1,3,4-oxadiazole-2(3H)-thione (Hanif et al.).

The catalytic activity of urease results in the formation of excess ammonia in the biological systems that can have adverse effects, the urease inhibitor compounds can aid in controlling the activity of urease, and there are a number of such compounds reported in the

literature. Transition metal complexes synthesized from Schiff base ligands are also abundantly reported for their adequate urease inhibitory activities. Some selected examples are presented here.

W. Chen et al. have reported a Cu^{+2} complex of "(E)-2-((2-chlorobenzylimino) methyl)-4,6-dibromophenol") Schiff base, Figure 31, with strong inhibition activity against jack bean urease. They also have reported Co^{+2}, Ni^{+2}, and Zn^{+2} complexes with potent urease inhibition activities [37].

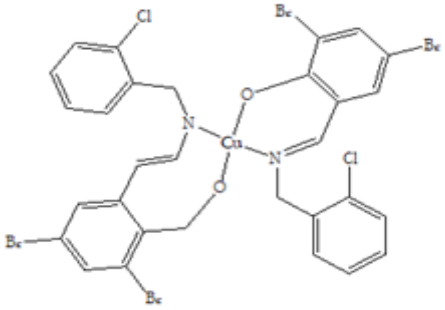


Figure 31. Urease Inhibitor Schiff Base Complex (W. Chen et al.).

Zhong-Lu You et al. have reported some poly-nuclear Cd^{+2} complexes with strong urease inhibitory activities. One of such complex (Cd^{+2} complex of "N-methyl-N_-(1-pyridin-2-ylmethylidene) ethane-1, 2-diamine") is shown in Figure 32 [38].

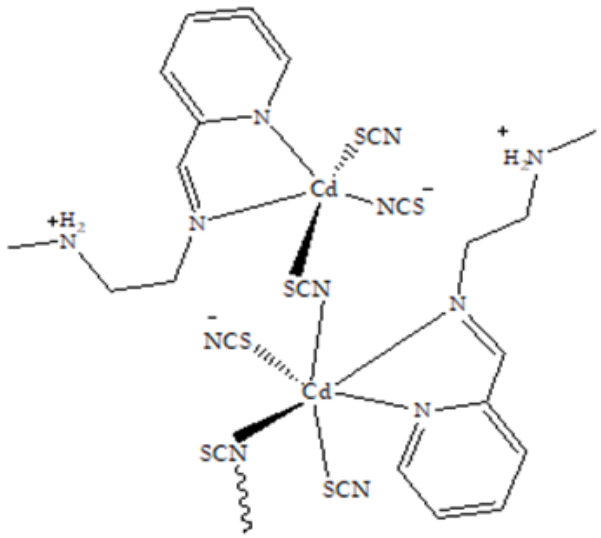


Figure 32. Urease Inhibitor Schiff Base Complex (Zhong-Lu et al.).

Aslam et al. have reported a Cu^{+2} complex of a hydroxyphenyl Schiff base, Figure 33, with potent urease inhibition activity [38].

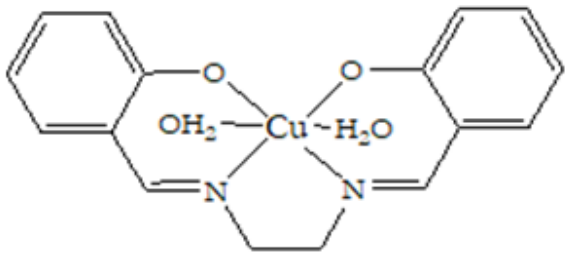


Figure 33. Urease Inhibitor Schiff Base Complex (Aslam et al.).

Mechanism of Action

In almost all the literature we have looked up, the antimicrobial activity has been reported to be increased upon chelation and this escalation of antimicrobial activity has been explained by the increased lipophilic nature of the complexes that is mainly due to the partial sharing of the electron density from metal to ligands. The distinguishing feature of the coordinate bonding is that all sharing electrons are donated by one operand i.e. the ligand, as a result, the polarities of the metal centers reduces and the coordination complexes hence form possesses less polar metal center and delocalized electrons over the entire chelating ring. This favors the lipophilic nature that in turn increase the penetration abilities of the complex to get through the lipid layer of the cell membrane where major constituents of the cell membrane including aminophospholipids and cystienyl ligands are also competing candidates to interact with metal ions. Figure 34 shows the possible metal interaction sites, the sites has generally increased electron density which can readily be accepted by electropositive metal centers leading to the disintegration of plasma membrane and as this interaction of metal ions and lipid is favored, the cell membrane begins to breakdown and the complex come about to affect the normal cell processes and eventually lead to cell death [39-42].

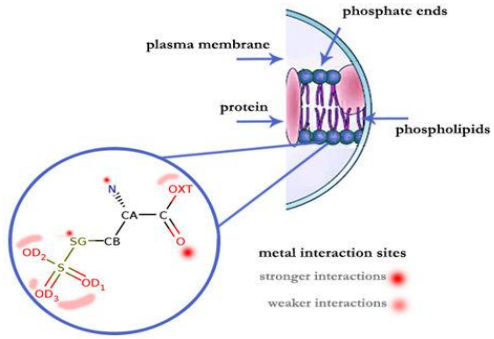


Figure 34. Constituents of plasma membrane with electron rich groups that can interact with metal ions.

Schiff bases are widely reported in literature for having medium to strong free radical scavenging activities specially those having hydroxyl and amino groups [43,44].

Figure 35 shows the general mechanism of quenching free radicals through Schiff bases by donating hydrogen atoms to free radical e.g. DPPH•. Metal complexes of Schiff bases on the other hand have been reported to exhibit reduced antioxidant activity assuming that hydroxyl groups deprotonates on coordination hence are not available to donate hydrogen atom to free radicals, rest of the substitutions on various positions in the ligands come handy that do not participate in complexation and are available to offer hydrogen, hence capable of hunting free radicals. Many reports studied in this review authenticated this assumption and it was evident that Schiff bases having only one OH group with some anti-radical activity showed reduced inhibition when coordinated to metals, while Schiff base have had more than one OH groups managed to stash a decent antioxidant activity even when coordinated to metals. Figure 35 depicts the free-radical quenching process by a Schiff base.

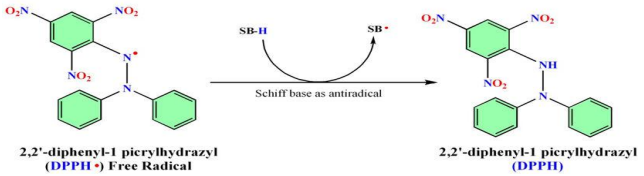


Figure 35. Schiff base acting as anti-radical agent. (SB=Schiff base).

Schiff bases and their metal complexes generally fall into the "non-glycosidic derivative" class of α- glucosidase inhibitors and also behave in the same manner e.g. the compounds having substituent groups enhancing the hydrophobic interactions with the enzyme are more potent. Another reported mechanism of the inhibition is the capability of the inhibitor of forming hydrogen bonds with the catalytic residue of α- glucosidase during the inhibitory action. The hydrogen bonding formed in the inhibitory process between a hydrogen bond donor on the inhibitor and a hydrogen bond acceptor on the enzyme residue or the other way around [45]. The complexes are frequently reported to be better inhibitors than their relevant ligands. The boost in inhibitory potency has been attributed to two reasons either way or presumably more of a combined effect. First being the presence of different substituent groups like chloro, methoxy, hydroxyl, methyl and –N(CH3)2 in the coordinated compounds. The electron withdrawing or donating properties of such substituent groups have a direct influence on the inhibitory potential [46]. Electron withdrawing substituent groups are considerably more potent inhibitors [47,48]. Secondly, chelation causes the polarity of the metal ions to be reduced, resulting in increased lipophilic nature of the complex, which in turn increases the chances of interaction of the inhibitor with the enzyme [42]. It is also reported that α- glucosidase may coordinate to the central metal ions of the complexes if the formation of such a bond is favorable and it can stabilize the inhibitor [49].

Additionally the effect of hydrogen bonding at the enzyme active site is also found beneficial to the inhibition whenever there are chances of such interactions. The substituent groups may have an impact on the hydrogen bond donor or acceptor capabilities of the candidate inhibitor e.g. the chloro and phenyl hydroxyl groups may act as stronger hydrogen bond acceptors than the other groups to the appropriate hydrogen bond donors at the protein side chains of the enzyme [46].

Among the majority of reports on inhibitory mechanism of urease inhibitors, transition metals in general and copper in particular are suggested to be capable of inhibiting the enzyme either by binding to the functional groups in urease or by distorting the active site of the enzyme. Metals other than Cu^{+2} have been reported to have the ability to bind to functional groups in the protein such as thiol groups, N and O containing groups [50-52]. Cu^{+2} on the other hand has been frequently reported to cause the distorted architecture of the enzyme active site when interacted to the enzyme [53-56] hence helps in inhibiting the enzyme to catalyze the hydrolysis of urea.

In metal complexes particularly complexes of Cu^{+2}, functional groups and other substituent moieties on the bound ligand also have the ability to inhibit urease by stabilizing interaction with the enzyme such as binding with nickel ions on the active site etc. [57]. The steric effect also plays a defining role in effective inhibition as less bulky groups in complexes favors the inhibition ability to a great extent [52].

Discussion and Conclusion

During this review it was understood that the azomethine groups in these Schiff bases enables them to exhibit a broad range of biological activities, the electron donor atoms e.g. nitrogen and oxygen are the key elements in these azomethine groups that not only contribute a major part in deciding the biological response of these compounds but also are responsible for the formation of co-ordinate covalent bonds with metal ions and present a number of possibilities of transition metal complexes with significant biological activities, literature review also confirmed that these transition metal complexes show increased biological response than their parent ligands. This increase in biological activity in general and antimicrobial activity in particular is due to the reduced polarities of metal ions upon chelation which enables them to cross the lipid barrier of cell membrane and interrupt in the normal cell functions. For enzyme inhibition, a number of possible mechanisms can contribute, for example, the ability of the complexes to form hydrogen bonding with the receptor where these interactions are favorable, ability of the complex to distort the functional side of the protein and render them inactive, and also the effect of substitutions in the ligands can have an impact on the overall activity of the complex.

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