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Selected Schiff base coordination complexes and their microbial application: A review

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Abstract
Today coordination chemistry comprises a large body of inorganic chemistry research. It is mainly the chemistry of metal complexes has fascinated and inspired the chemists all over the world. There is an ever increasing academic, commercial and biochemical interest on the metal complexes of organic chelating ligands. This has resulted in the emergence of allied fields like organometallic chemistry, homogenous catalysis and bioinorganic chemistry. Among the chelating ligands, Schiff bases have attracted the attention of chemists due to the case of preparation and complexation. In this review we have focused on the synthesis of some selected Schiff base coordination complexes and their biological application such as antibacterial, antifungal, anticancer, DNA interaction, cytotoxicity, Analgesic and anti-inflammatory, Antianxiety activities, ribonucleotide reductage, Anti-HIV activity.

Keywords: Schiff base, coordination complex, antimicrobial, anticancer, DNA-interaction, cytotoxicity, Anti-HIV activity

1. Introduction
Schiff bases containing the azomethine (–RC=N-) and are usually formed by the condensation of primary amine with an active carbonyl compound. This product was first formed by German chemist noble prize winner Huggo Schiff. They are stable and can tune the ligation aspects by varying denticity and basicity. Metal Schiff base complexes have been known since the mid nineteenth century and even before the report of general preparation of the Schiff base ligands. Intensive research on the physicochemical properties and molecular structure of complexes with Schiff bases has provided interesting new results, which need to be surveyed and compared with earlier literature on these types of compounds. Schiff base ligands are essential in the field of coordination chemistry, especially in the development of complexes of Schiff bases because these compounds are potentially capable of forming stable complexes with metal ions [1]. A large number of Schiff base complexes are characterized by an excellent catalytic activity in a variety of reactions at high temperature (>100ºC) and in the presence of moisture. In recent years, there have been numerous reports of their use in homogeneous and heterogeneous catalysis [2, 3]. Schiff bases and their metal complexes are increasingly being used as catalysts in various biological systems, polymers and dyes. Moreover, it is confirmed that these compounds can act as enzyme preparations [4]. Due to the excellent selectivity, sensitivity and stability of Schiff bases for specific metal ions such as Ag(I), Al(III), Co(II), Cu(II), Gd(III), Hg(II), Ni(II), Pb(II), Y(III) and Zn(II), a large number of different Schiff base ligands have been used as cation carriers in potentiometric sensors. Studies in terms of catalytic properties of Schiff bases exhibit the catalytic activity in the hydrogenation of olefins. One of the more interesting applications of these compounds is the possibility to use them as effective corrosion inhibitors. This phenomenon is the spontaneous formation of a monolayer on the surface to be protected [5]. The interest in metal complexes in which the Schiff bases play a role as the ligands are increasing as evidenced by the number of publications appearing annually (approximately 500) [6]. So much interest in imines can be explained by the fact that they are widely distributed in many biological systems and they are used in organic synthesis and chemical catalysis, medicine, pharmacy and chemical analysis, as well as new technologies [7]. Schiff bases form an important class of the most widely used organic compounds and has a wide variety of applications in many fields including analytical, biological and inorganic chemistry. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory

[8-12], analgesic [13-15], antimicrobial [16, 17], anticonvulsant [18], antitubercular [19], anticancer [20, 21], antioxidant [22], anthelmintic [23], and so forth. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centers of cell constituents and interferes in normal cell processes [24, 25]. The chemistry of the transition metal complexes of thiosemicarbazones became largely appealing because of their broad profile of pharmacological activity that provides a diverse variety of compounds with different activities [26–29]. Bis-Schiff base ligands and their coordination compounds having multifunctional groups play an important role in the areas of stereochemistry, structure of science, spectroscopy, magnetic fields [30]. In recent years, sulfur containing ligands such as dithiocarbamates and thiosemicarbazones and their transition metal complexes have received more attention in the area of medicinal chemistry, due to their pharmacological properties, such as antiviral, antibacterial, antifungal, antiparasitic, and antitumor activities [31-36]. Isatin Schiff and Mannich bases were reported to demonstrate a wide range of biological activities such as antibacterial, antifungal, antiviral, anti-HIV, antiprotozoal, and antihelminthic activities [37-39]. Md. Saddam Hossain and Md. Kudrat-E-Zahan have synthesized various Schiff bases and their metal complexes [40-45]. Schiff base of S-methyldithiocarbazate with isatin has been reported to behave as a versatile chelating agent exhibiting variable denticity towards metal ions [46].

2. Chemistry of Schiff base

Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by a German chemist, Nobel Prize winner, Hugo Schiff [48]. Structurally, Schiff base (also known as imine or azomethine) is an analogue of a ketone or aldehyde in which the carbonyl group (C=O) has been replaced by an imine or azomethine group (Fig. 1) [49-52]. A Schiff base or Schiff's base is a type of chemical compounds containing a carbon-nitrogen double bond as functional group, where the nitrogen atom connected to aryl group or alkyl group (R) but not hydrogen. The Schiff base is synonymous with an azomethine. These compounds were named after Hugo Schiff on honor and have the following general structure:

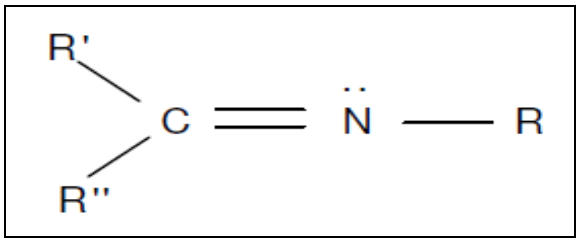


Fig 1: Schiff base

Where R stands for a phenyl or alkyl group which makes the Schiff base a stable imine. This kind of ligands is able to coordinate metal ions through the imine nitrogen and another group, usually linked to the aldehyde. The chemists still prepare Schiff bases and nowadays active and well-designed Schiff base ligands are considered ‘‘privileged ligands’’[53]. The bridged Schiff’s bases have the following structure which contains many functional groups able to change according to the purpose required. Where R′ = H or alkyl group, R" = phenyl or substituted phenyl, X = alkyl or aryl group

In fact, Schiff bases are able to stabilize many different metals in various oxidation states controlling the performance of metals in a large variety of useful catalytic transformations [54] Most commonly Schiff bases have NO or N_2O_2-donor groups but the oxygen atoms can be replaced by sulphur, nitrogen, or selenium atoms [55].

It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme:

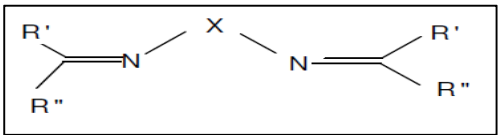


Fig 2: bridged Schiff’s base

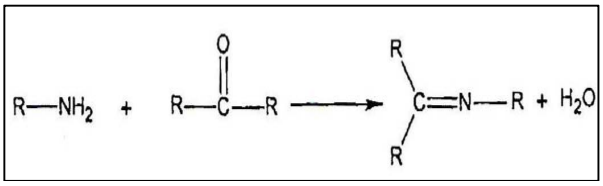


Fig 3: Formation of Schiff base by condensation reaction.

Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituent’s are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable [56, 57]. While those of aromatic aldehydes having effective conjugation are more stable [58-60].

The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating

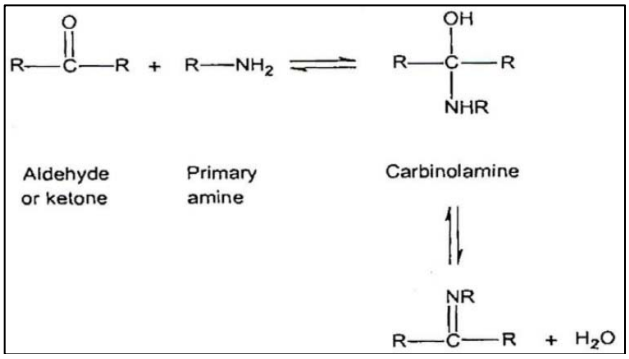


Fig 4: Reversible reaction of a Schiff base formed from an aldehydes or ketones.

The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.

The mechanism of Schiff base formation is another variation on the theme of neucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration.

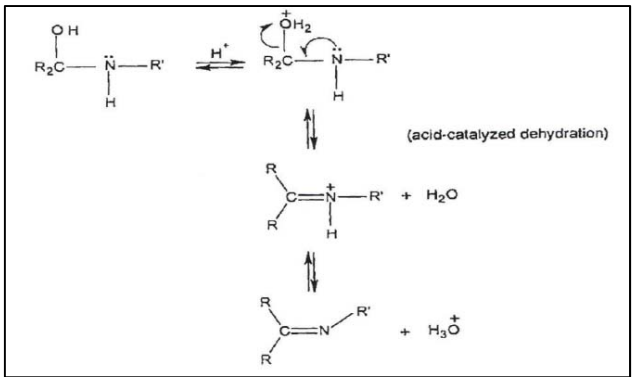


Fig 5: Mechanism of formation Schiff base

Typically the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-neucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff bases synthesis are best carried out at mildly acidic pH. The dehydration of carbinolamines is also catalyzed by base. This reaction is somewhat analogous to the E_2 elimination of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate. The Schiff base formation is really a sequence of two types of reactions, *i.e.* addition followed by elimination [61].

3. Application of Schiff base and their metal complexes

3.1. Antimicrobial activity

One of the most promising areas in which thiosemicarbazone compounds are being developed is their use against microorganism. K. G. O. Casas and coworkers have synthesized the Cu (II) complex with Schiff bases derived from aryl-*S*-benzyildithiocarbazate [62] and was shown good antibacterial activity. M. Emayavaramban and *et al* were synthesized some novel 5-bromo fluoro benzaldehydeoxime and semicarbazone under ultrasonic irradiation and shown antibacterial activity [63]. Salman A. Khan and *et al*. were prepared some Novel Thiosemicarbazone and Its Cu(II), Ni(II), and Co(II) Complexes and determine its *in vitro* antibacterial activity [64]. Fakruddin & co-worker synthesized Schiff base metal complexes of Cr(III), Co(II), Ni(II) and Cu(II) derived from 2, 6-pyridine dicarboxaldehyde-Thiosemicarbazone (PDCTC) by conventional as well as microwave methods. In conventional method the metal complexes was prepared by the mixing of equal moles of metal salts dissolved in the methanol followed by addition of NaOAc (metal: ligand) in 1:1ratio. The precipitated complex was, filtered washed with ether and recrystallized with ethanol and dried under the reduced pressure over anhydrous $CaCl_2$ in a desiccator while in microwave method the ligand and the metal salts was mixed in 1:1 (metal: ligand) ratio in a grinder. The Schiff base and metal complexes displayed good activity against the Gram-positive bacteria *Staphylococcus aureus*, the Gram-negative bacteria *Escherichia coli* and the fungi *Aspergillus niger* & *Candida albicans*. The antimicrobial results also indicated that the metal complexes displayed better antimicrobial activity as compared to the Schiff bases ligand. Chelation tends to make the ligand act as more powerful (Fig. 1) and potent bactericidal agent. Gajendra Kumari & co-workers synthesized and characterized M(III) complexes of Cr, Mn and Fe with a Schiff base derived from 2-amino-4-ethyl-5-hydroxybenzaldehyde and thiocarbohydrazide by several techniques. The Schiff base ligand and the complexes were also tested for their antimicrobial activity (against the bacteria *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Bacillus megaterium*, and the fungi *Kluyveromyces fragilis, Rhodotorula rubra*, *Candida albicans* and *Trichoderma reesei*) to assess their inhibiting potential. S.M.S. Shariar co-workers [66] synthesized Schiff base Benzophenone Thiosemicarbazone derived from thiosemicarbazide and Benzophenone & the compound was used to study their antibacterial activities against some pathogenic bacteria by disc diffusion method. Benzophenone thiosemicarbazone showed significant antibacterial activity as compared with that of Kanamycin. The compounds was found to possess cytotoxic effect. Minimum inhibitory concentration of this compound was also determined. The antibacterial activities of this compound were measured in terms of zone of inhibition. The test compounds showed a good sensitivity against a number of pathogenic bacteria. D. Nasrin & co-workers [67] in view of the antimicrobial activity of a series of nickel, copper and zinc complexes of tridentate Schiff base derived from the condensation reaction of S-benzyl dithiocarbazate with 2-hydroxyl acetophenone have been synthesized and found to be potential antimicrobial agents. An attempt is also made to correlate the biological activities with geometry of the complexes. The synthesized compounds have been evaluated for their antibacterial and antifungal studies. The in-vitro biological screening effects of the investigated compounds were tested against the bacterial species *Shigella dysenteriae*, *Salmonella typhi* and *Bacillus cereus* and fungal species *Fusarium equiseti, Macrophomina phaseolina, Botrydiplodia theobromae* and *Alternaria alternate*. Elena Pahontu and *et al* were synthesized Cu(II), V(V) and Ni(II) complexes with Schiff base ligand derived from 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone and 4-ethyl-thiosemicarbazide and shown Antibacterial, antifungal and *in vitro* antileukaemia activity [68]. Pandeya and coworkers Schiff and Mannich bases derived from isatin derivatives and N-[4-(4'-chlorophenyl) thiazol-2- yl] thiosemicarbazide and was shown antibacterial antifungal and anti-HIV activity. Yidliz. M, Dulger and *et al* were synthesized Schiff base metal complexes derived from thiosemicarbazide with some 2-hydroxyaldehydes and shown their antibacterial property. Prasad. S, Agarwal and his coworkers Cobalt (II) complexes of various thiosemicarbazones of 4-aminoantipyrine and shown its antibacterial property [68]. A K Parekh and K.K Desai were synthesized some thiosemicarbazone Schiff base ligand and shown their antibacterial activity [69]. N. Murthy and his coworkers were prepared copper (II) complexes with phenylglyoxal bis-(thiosemicarbazones) and determine its antibacterial activity [70]. M.B. Ferrari and *et al* were synthesized Ni(II) complexes of P-fluorobenzaldehyde thiosemicarbazones and shown their biological activity [71]. B. L. Latheef and coworkers were synthesized copper (II) complexes of thiosemicarbazones derived from salicylaldehyde and containing ring incorporated at N (4)-position and shown its antimicrobial activity [72]. Kalapala Venkatesh and *et al* were prepared some new thiosemicarbazide derivatives and their transition metal complexes [73]. Urbain C. Kasséhin and his coworkers were shown Trypanocidal activity of a thioacyl-thiosemicarbazide derivative associating both immunostimulating thalidomide and anti-parasitic thiosemicarbazide pharmacophores [74]. K. Alomar and *et al*. were synthesized cobalt(II), nickel(II) and

copper(II) complexes with 3-thiophene aldehyde thiosemicarbazone and investigated their biological activity [75]. M. R. Maurya and *et al* were synthesized Dioxovanadium(V) and *μ*-oxo bis[oxovanadium(V)] complexes containing thiosemicarbazone based ONS donor set and investigate their antimicrobial activity [76]. S. Padhye and *et al*. copper(II) complexes of 4-alkyl/aryl-1,2-naphthoquinones thiosemicarbazones derivatives and determined as potent DNA cleaving agent [77]. R. P. Gupta and *et al.* were synthesized some Mannich bases of 1-cyclohexylidene-N(1,2-dihydro-2-oxo-3H-indol-3-ylidene) thiosemicarbazones and determined their antibacterial activity [78]. T. A. Yousef and *et al.* were synthesized Co(II), Cu(II), Cd(II), Fe(III) and U(VI) complexes containing a NSNO donor ligand and investigated their *in vitro* antibacterial and DNA cleaving property [79]. Moamen S. Refat and *et al.* were synthesized Mn(II), Fe(III), Cr(III) and Zn(II) complexes derived from the ligand resulted by the reaction between 4-Acetyl Pyridine and Thiosemicarbazide and determine their antibacterial property [80]. Xinde Zhu and *et al*. were prepared nickel (II) and iron (II) complexes with Schiff base derived from 3,4-dihydroxybenzaldehyde and thiosemicarbazide [81]. Moamen S. Refat and his coworkers were synthesized new Copper (II) and Manganese (II) Complexes with 1,2,4-Triazines Thiosemicarbazide and determined their biological activity [46]. Wilfredo Hernández and his coworkers were synthesized New Palladium (II) Thiosemicarbazone Complexes and shown their cytotoxic activity against human tumor cell [82]. G. Pelosi and *et al* were shown Antiretroviral activity of thiosemicarbazone metal complexes [83]. A. Karak uc and *et al.* were synthesized Novel platinum (II) and palladium(II) complexes of thiosemicarbazones derived from 5-substitutedthiophene-2- carboxaldehydes and shown their antiviral and cytotoxic activities [84]. P. Genova and *et al* were synthesized palladium (II) complexes with bis (thiosemicarbazone) and shown toxic effect on herpes simplex virus growth [85]. I. Kizilcikh and *et al.* were synthesized a series of thiosemicarbazones and their Zn (II) and Pd (II)complexes and investigated their antibacterial activity [86]. T. Rosu and were synthesized transition metal complexes with thiosemicarbazones and determined their antibacterial activity [87]. M. Er, Y. Unver and *et al* were prepared some new tetra-thiosemicarbazones and their cyclization reactions and shown their biological activity [88]. S. Chandra and M. Tyagi were synthesized Ni (II), Pd(II) and Pt(II) complexes with ligand containing thiosemicarbazone and semicarbazone moiety and investigate their antiviral activity [89]. S. S. Konstantinovi´c and *et al.* were synthesized some isatin-3-thiosemicarbazone complexes and determined their antimicrobial activity [90]. R. V. Singh and *et al* were synthesized palladium (II) and platinum(II) complexes of thiosemicarbazone Schiff base ligand [91].

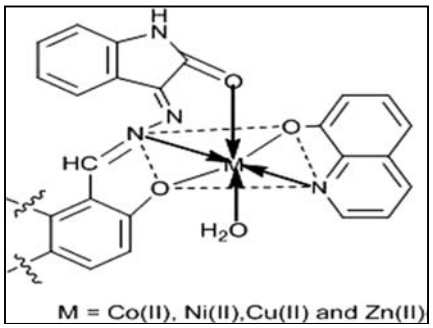
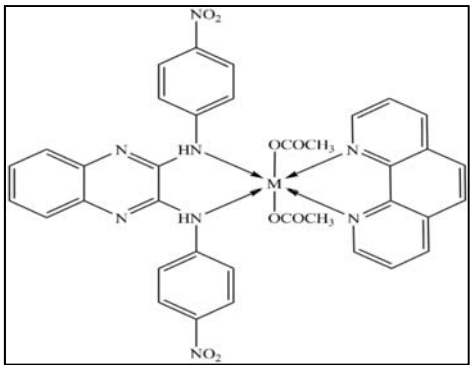


Fig 6: Structure of potent antimicrobial agents.



(M=Co(II), Ni(II), Cu(II) and Zn(II))

Fig 7: Structure of N2, N3-bis(4-nitrophenyl)quinoxaline-2,3-diamine based mixed ligand complexes.

3.2. DNA-Metal complexes interactions

DNA is the storage site of cellular information that is accessed continuously for storing and dispensing information required for existence. Thus, it acts as the main intracellular target for those who thrive to develop a new drug for innumerable diseases, especially cancer. Added to the fact, small molecules that can bind and react with specific DNA sites provide a means to access and manipulate this cellular information creating the desired results. There are many binding modes by which the small molecules bind to the DNA which are covalent and non-covalent binding. Cisplatin binds covalently with the DNA thereby restricting its replication. Among the non-covalent binding modes, intercalation, groove binding and external electrostatic binding, intercalation is the most important one because it invariably leads to cellular degradation [92]. Humungous reports are available throughout the literature regarding the interactions of V(IV), Ni(II), Co(II), Cu(II) and Zn(II) complexes with DNA and still now many research groups have actively involved in this field [99-101]. Among the research groups, most of them are concentrating only copper Schiff-base complexes. For, copper is found in all living organisms and is a vital trace element in redox chemistry, growth and development. It is significant for the function of several enzymes and proteins involved in energy metabolism, respiration and DNA synthesis, particularly cytochrome oxidase, superoxide dismutase (SOD), ascorbate oxidase and tyrosinase. Copper is found to bind DNA with high affinity than any other divalent cation, thus promoting DNA oxidation. Acquaye *et al.* synthesized two new copper Schiff-base complexes and carried out DNA interactions with CT-DNA. The resultant Kb values are 1.52 $\times 10^5$ M^{-1} and 5.00 $\times 10^5$ M^{-1} respectively for the complexes [102]. Yang and his colleagues have synthesized and characterized two novel Schiff base copper(II) complexes derived from kaempferol and polyamines such as ethylenediamine and diethylenetriamine. They evaluated the DNA interactions with CT DNA and predicted the mode of interactions to be intercalation [103]. An extensive DNA-metal complex interaction has been carried out by Lin and his colleagues by synthesizing two new benzimidazole based copper complexes. The studies showed that the complexes exhibited partial intercalation towards the DNA [104]. The novel copper complexes synthesized by Gup and Gokce are found to bind significantly to calf thymus DNA by both groove binding and intercalation modes and effectively cleave pBR322 DNA [105]. Xu *et al.* synthesized three novel structurally associated copper (II) complexes which displayed enhanced intercalation into CT DNA [106].

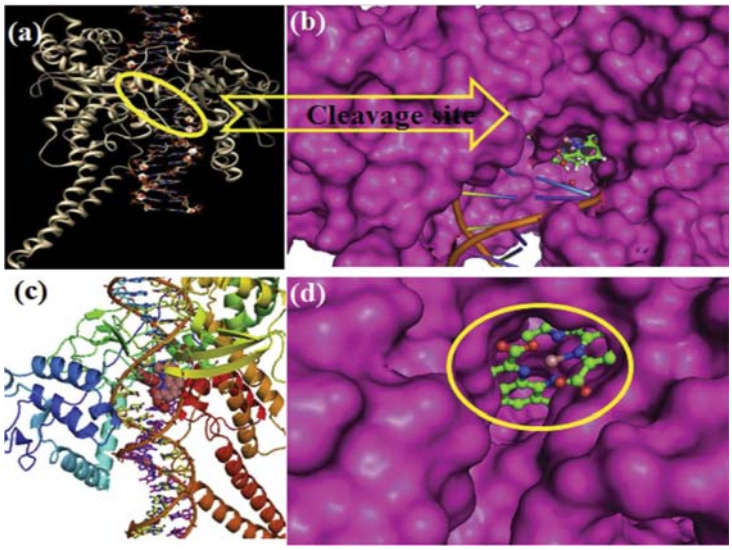


Fig 8: Diagram showing in (a) human-DNA-Topo-I (70 kDa) (PDB ID: 1SC7), (b) docked model of {[Co(mpca)$_2$].H_2O} occupying cleavage active site of Topo-I, DNA is represented by the structure shown as stick representation, (c) docked model {[Co(mpca)$_2$].H_2O} (surface representation) towards the cleavage site of Topo-I (cartoon representation) and (d) binding of {[Co(mpca)2].H_2O} in the Topo-I pocket, preventing the building of the topoisomerase I-DNA complex represented via surface presentation.

Natarajan Raman, Sivasangu Sobha, Liviu Mitu and *et al.* were synthesized isatin-derived tyramine bidentate Schiff base and its metal complexes also evaluated their structural elucidation, DNA interaction, Biological property and molecular docking model [107] as shown in (figure 4, 5).

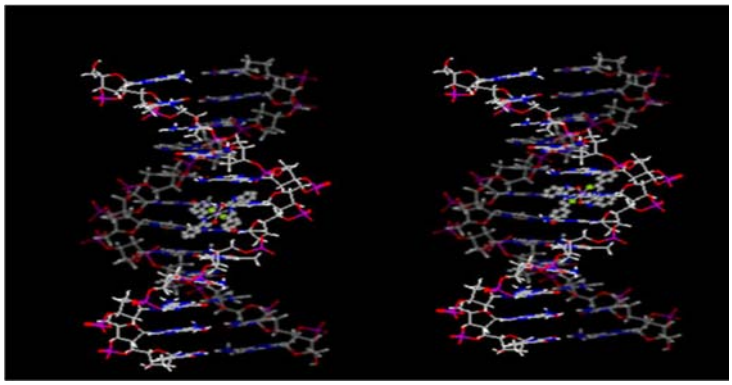


Fig 9: Interaction of the complexes [CuL_2Cl_2] and [ZnL_2Cl_2] with d(CGCGAATTCGCG) strands of DNA by the minor groove binding approach

Mostafa K. Rabia, Ahmad Desoky M and *et al.* synthesized Some Ni(II) Complexes with Isatin-Hydrazones and determined their physiochemical property [108]. Md. Kudrat-E-Zahan *et al.* were synthesized a novel bis imine Schiff base ligand derived from isatin and diethylene triamine and investigate their antimicrobaial activity [109].

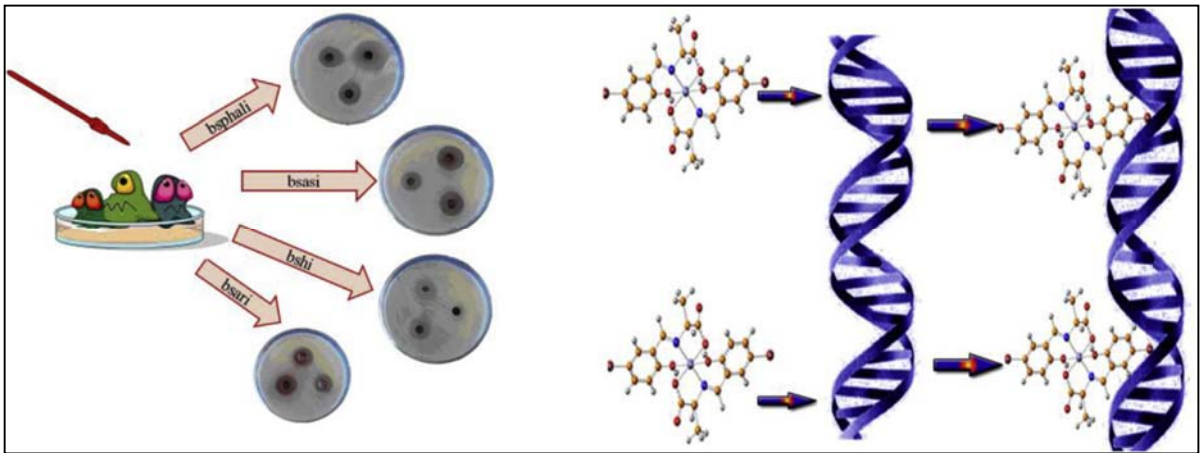


Fig 10: Schematic diagram for antibacterial activity and DNA interaction of the investigated complexes

3.3. Anticancer activity

Chemotherapy using chemical agents is one of the effective methods for the treatment of various cancers. With the increasing number of compounds synthesized as potential anticancer drugs, effective screening methods are needed for classification of these compounds according to their anticancer activities. For preliminary screening, the *in vivo* methods are usually more accurate but rather expensive and time-consuming whereas the *in vitro* methods are simpler and more rapid but with lower accuracy. In general, for large scale preliminary screening, the *in vitro* methods are more effective for refined screening on a smaller scale, naturally, the *in vivo* methods with test animals must be used and the clinical experimental tests are also required. The key advances in the cancer chemotherapy are shown in Figure-6.

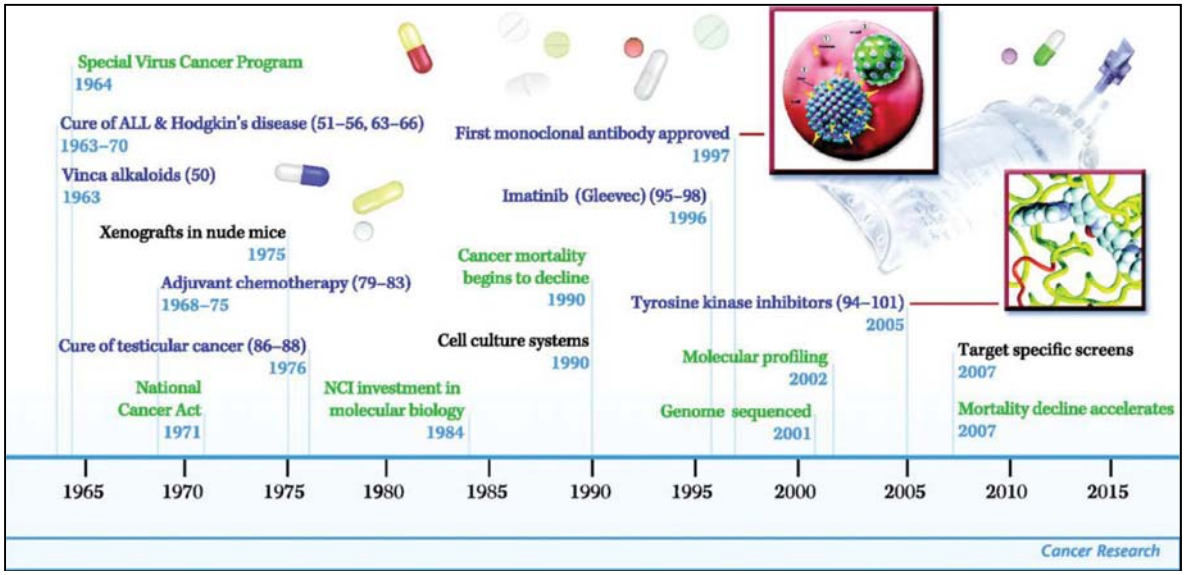


Fig 11: Key advances in the cancer chemotherapy.

3.4. Cytotoxicity

Cancer is a disease characterised by uncontrolled multipication and spread of abnormal forms of the body's own cells [110]. From literature survey it is well known that isatinheterocycles exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent. Bis-diisatin derivatives, Bis-Isatin Thiocarbohydrazone Metal Complexes, 3- o-Nitrophenylhydrazones of isatin possess cytotoxicity activity. Co(II), Ni(II), Cu(II), and Zn(II) complexes of thiocarbohydrazone ligand were formed by reacting with ethanolic solution of metal chloride or aqueous ethanolic solution of metal acetates with specific amount of the ligand. Compound shows antitumour activity [111].

Md. Arifuzzaman [112] *et al.* had been synthesized Bis-diisatin [3, 3] furan (figure 7) on treatment with furan in presence of diethyl amine under intensive stirring. The compounds were evaluated for cytotoxicity study on the brine shrimp as a test organism.

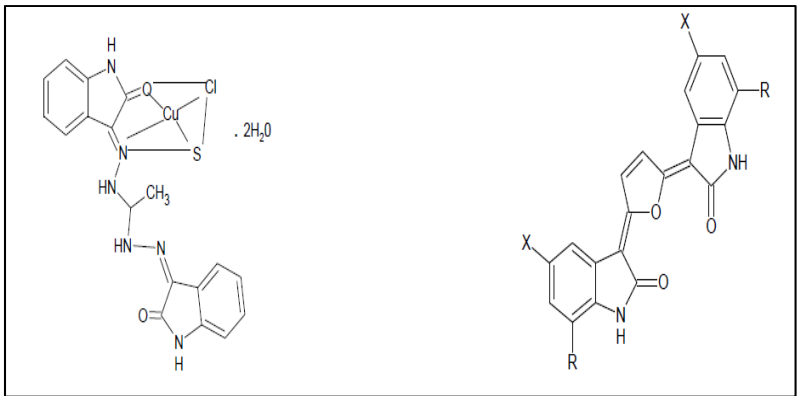


Fig 12: Schiff base of isatin derivatives and its Cu (II) complexes.

3.5. Analgesic and anti-inflammatory

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbial agents. It inhibits Prostaglandin synthesis at the site of injury [113]. Analgesic drug is used to control the pain. Prostaglandin E_2 (PGE2) is thought to sensitize nerve ending to the action of bradykinin, histamine and other chemical mediators released locally by the inflammation process. Thiosemicarbazinoisatin, Isatin-3-p-chlorophenylimine, Azetidinone derivatives of isatin possess analgesic and anti-inflammatory activity. The anti-inflammatory activity was studied by Carrageenan induced pawoedema method and anaglesic activity studied by tail flick and hot plate method. 1-(phenylaminomethyl)3-thiosemicarbazino isatin (fig. 1.16) was formed by 3-thiosemicarbazino isatin and appropriate aromatic amine reacted with formeldehyde. The compound possess analgesic

activity [114]. 3'-(p-chlorophenyl) 6'-Furyl-cis- 5'a, 6'-dihydrospiro [3H-indole 3, 4'-thiazolo(5', 1'-c) isoxazolo-2(1H)-one] (fig. 1.17) was synthesized by the reaction of 3'-p-chlorophenyl 5'-phenyl spiro [3H-indole 3, 2'-thiazolidine]-2-(1H), 4'-(5'H)-dione with hydroxylamine hydrochloride. It possesses analgesic and anti-inflammatory activity [115].

S.K. Srivastav [116] *et al.* had been synthesized a series of compounds from carbazole (figure 8) by condensation with chloroacetyl chloride in the presence of triethylamine afforded azetidinones. The compounds exhibited promising anti-inflammatory activity.

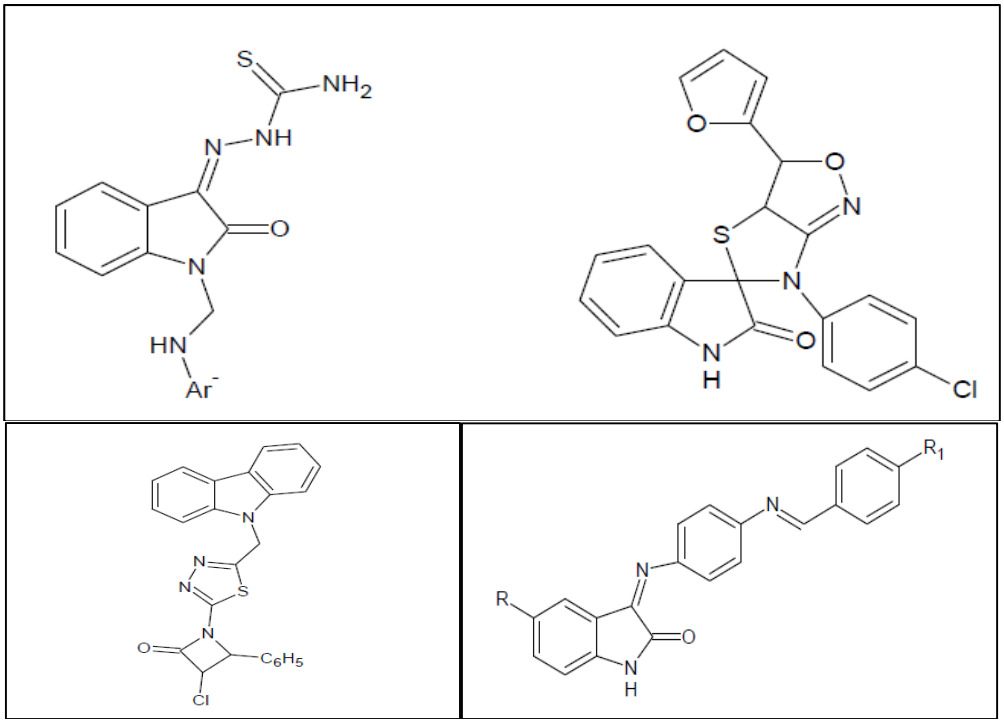


Fig 13: 5- Substituted isatin derivatives

Perumal Panneerselvam [117] *et al.* had been synthesized Novel series of Schiff bases of 5-subsituted Isatin and N-acetyl isatin using different substituted aromatic aldehydes. These synthesized compounds were investigated for analgesic activity by tail immersion method and anti-inflammatory activity by carrageenan-induced paw oedema method. All the synthesized compounds were active against all the tested micro-organisms like Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginos, Klebsiellapneumoni, Aspergillusniger and Aspergillus fumigates.

3.6. Anti-HIV activity

HIV is an RNA retrovirus. Two forms are known HIV-1 is an organism responsible for human AIDS. The HIV-2 organism is similar to the HIV-1 virus in that it also causes immune suppression, but it is less virutent. HIV-1 is distributed around the world, whereas the HIV-2 virus is confined to parts of Africa [110]. In view of the broad spectrum activity of isatin derivatives, discussed here some novel thiosemicarbazides of isatin, Schiff bases of isatin derivatives with sulfodoxine and N-(4, 6- dimethyl-2pyrimidiny) benzene sulphonamide and its derivatives which shows anti-HIV activity.

S.N. Pandey [121] *et al.* had been synthesized 1-[N,N-dimethylaminomethyl]isatin-3-[1'(6"-chloro benzothiazol-2"-yl)] (figure 9) by reacting 3-[-1-(-6-chloro benzothiazol-2 yl) thiosemicarbazone] and formalin with dimethylamine. The synthesized compounds were screened for anti-HIV activity at HIV-1(III B) in MT-4 cells.

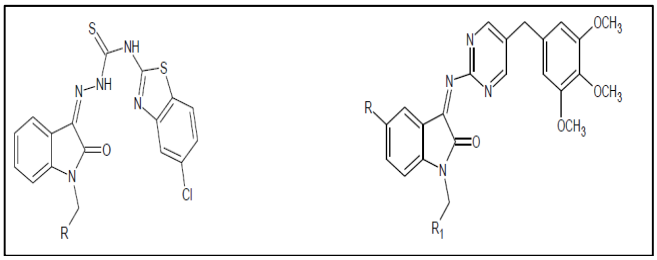


Fig 14: Substituted isatin derivatives

S.N. Pandey [122] *et al.* had been synthesized Schiff bases of isatin derivatives with sulfodoxine. All the compounds showed notable activity when compared to sulphadoxine. The piperidino methyl compounds were found to be the most active ones in the series. Six compounds were active against Candida albicans, Candida neoformis, Histoplasma capsulatum, Microsporumaudounii and Tri chophytonmentagrophytes at a concentration of 100 gml–1. The compound containing piperidino methyl group showed appreciable activity (10%) against the HIV-2 (ROD) strain.

3.7. Antianxiety activities

Anxiety is an unpleasant of tension, apprehension, or uneasiness a fear that seems to arise from a sometimes unknown source. The physological symptoms of severe anxiety are similar to those of fear and involve sympathetic activation [118]. It enhances the response to GABA by facilitating the opening of GABA-activated chloride channel [110]. Isatin derivative like Schiff bases of N-methyl and N-acetyl isatin, Spirobenzodiazepines, 5-Hydroxy isatin and

isatinic acid act as antianxiety agents. G.S. Palit [123] *et al.* had been synthesized Schiff bases of N-methyl and N-acetyl isatin derivatives (figure 10). They studied the behavioral effects of isatin, a putative biological factor in rhesus monkeys. Isatin, one of the constituents of tribulin, a postulated endocoid marker of stress and anxiety, has been shown to induce anxiety in rodents.

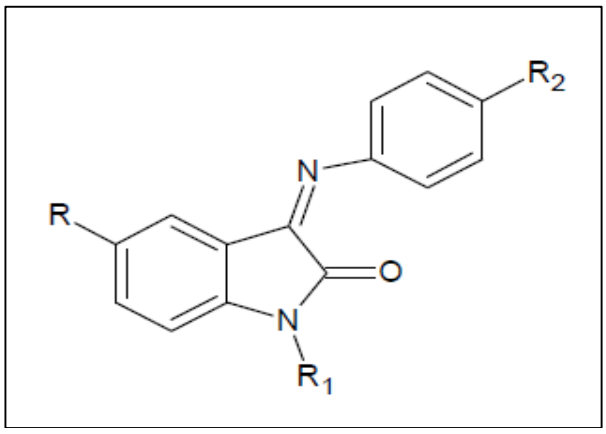


Fig 15: Schiff bases of isatin

3.8. Ribonucleotide reductage

The first breakthrough in the comprehension of the antitumor effect of thiosemicarbazones was obtained in the Sixties and deserves a brief résumé. The anti-leukemic effect of 2-formylpyridine thiosemicarbazone was first reported by Brockman *et al*. [124] in 1956. Almost ten years later, in 1965, French *et al*. [125] formulated hypotheses about the mode of action of the α(N)-heterocyclic thiosemicarbazones Ribonucleotide reductase is an iron-dependent enzyme that promotes the reduction of ribose to deoxyribose through a free radical mechanism that is triggered by a tyrosyl radical. Inhibition of this enzyme leads to a block in the synthesis phase of the cell cycle and eventually to cell death by apoptosis. They also indirectly demonstrated that the active species was the iron(II) complex of 1 formylisoquinoline thiosemicarbazone. In fact, it was later discovered that iron and copper complexes are by far more active than the free ligands [126]. A reasonable mechanism was proposed by Thelander *et al*. [127] who proved, by exposing ribonucleotide reductase to the aforementioned molecules, that it is the tyrosyl free radical of the enzyme that is targeted by the drug and that the thiosemicarbazone complex inhibits the enzyme by destroying the radical. This mechanism requires oxygen and excludes the role of thiosemicarbazones as simple iron chelators. They also report that the reaction is reversible, and this is in agreement with the experimental observations. The fact that 1-formylisoquinoline thiosemicarbazone inhibits more strongly ribonucleotide reductase than 2- formylpyridine thiosemicarbazone gave an indirect hint about the fact that in the enzyme there must be a hydrophobic pocket or patch with which the aromatic system interacts, which could justify the fact that methylation on the aromatic ring of 2-formylpyridine thiosemicarbazone renders this compound more active. In search of an optimum bulk for the aromatic fragment Agrawal *et al*. [128] identified it with 2- formyl-4-(3-amino)phenylpyridine thiosemicarbazone that was the most active of the 3-aminophenyl derivatives. The most active compound found in the isoquinoline series was instead 1-formyl-5-aminoisoquinoline thiosemicarbazone [129]. Two recent interesting papers by Kowol *et al.* [130,131] report the synthesis, characterization and biological assays of complexes of Fe(III) and Ga(III) (this latter is an ion known for inhibiting ribonucleotide reductase and for its antiproliferative properties). L. Otero and *et al* were synthesized Novel antitrypanosomal agents based on palladium nitrofuryl thiosemicarbazone complexes and investigated DNA and redox metabolism as potential therapeutic targets [132]. P. Chellan, T. Stringer, A. Shokar *et al.* were synthesized *in vitro* evaluation of palladium(II) salicylaldiminato thiosemicarbazone complexes against *Trichomonas vaginalis* [133]. N. A. Lewis and *et al.* were synthesized vanadium(IV) complexes with a Schiff base and thiosemicarbazones as mixed ligands and shown its antitumor activity [134]. E. Ramachandran and his coworkers were synthesized Ni(II) and Pd(II) thiosemicarbazone complexes and determined DNA binding, antioxidant and cytotoxicity activity [135]. U. Kulandaivelu, V. G. Padmini, K. Suneetha *et al.* were synthesis novel thiosemicarbazide derivatives and shown their antibacterial and anticancer property [136]. B. Atasever, B. Ulk useven and *et al.* were determined Cytotoxic activities of new iron(III) and nickel(II) chelates of some S-methyl thiosemicarbazones on K562 and ECV304 cells [137]. M. X. Li, C. L. Chen, D. Zhang and *et al.* were synthesized Mn(II), Co(II) and Zn(II) complexes with heterocyclic substituted thiosemicarbazones and determines their antitumor activity [138]. V. Vrdoljak, I. Dilovi´c, M. Rubcic *et al.* were synthesized thiosemicarbazonato molybdenum(VI) complexes and investigated their *in vitro* antitumor activity [139].

4. Conclusion

This review reflects the contribution of Schiff bases to the design and development of novel lead having potential biological activities with fewer side effects. This bioactive core has maintained the interest of researchers in gaining the most suggestive and conclusive access in the field of various Schiff bases of medicinal importance from last decades. The present paper is an attempt to review all the biological activities reported for Schiff bases and their metal complexes in the current literature with an update of recent research findings.

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