



Review on Isatin- A Remarkable Scaffold for Designing Potential Therapeutic Complexes and Its Macrocyclic Complexes with Transition Metals

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Received: 7 February 2023 / Accepted: 18 April 2023 / Published online: 7 May 2023

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Abstract

Role of synthetic coordination chemistry in pharmaceutical science is expeditiously increased due to its sundry relevances in this field. The present review endows the synthesized macrocyclic complexes of transition metal ions containing isatin and its derivatives as ligand precursors, their characterization and their copious pharmaceutical applications. Isatin (1*H*-Indole-2,3-dione) is a protean compound (presence of lactam and keto moiety permits to change its molecular framework) that can be obtained from marine animals, plants, and is also found in mammalian tissues and in human fluids as a metabolite of amino acids. It can be used for the synthesis of miscellaneous organic and inorganic complexes and for designing of drugs since it has remarkable utility in pharmaceutical industry due to its wide range of biological and pharmacological activities, for instance anti-microbial, anti-HIV, anti-tubercular, anti-cancer, anti-viral, anti-oxidant, anti-inflammatory, anti-angiogenic, analgesic activity, anti-Parkinson's disease, anti-convulsant etc. This review provides extensive information about the latest methods for the synthesis of isatin or its substituted derivatives based macrocyclic complexes of transition metals and their plentiful applications in medicinal chemistry.

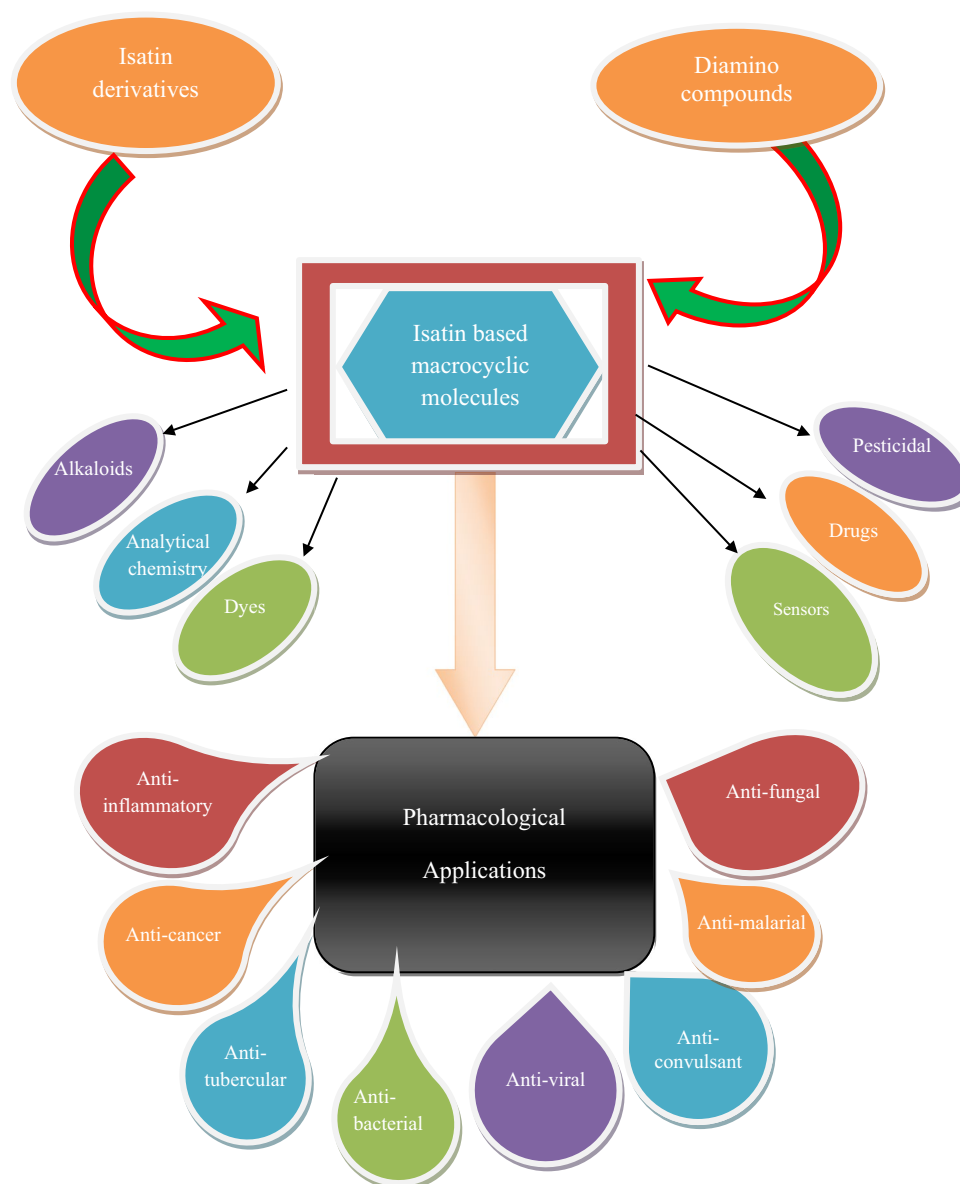
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Graphical Abstract



Keywords Isatin · Macrocyclic complexes · Antimicrobial activity · Antibacterial studies

1 Introduction

Isatin is a popular natural product that is present as an interior compound in plants, marine animals and human beings as it was found in tissues, blood and urine by the use of GCMS (gas chromatography mass spectrometry) and HPLC technique [1, 2]. It is an orange-red coloured organic heterocyclic compound with $C_8H_5NO_2$ formula and also known as tribulin, obtained by Erdman and Laurent [3, 4]. It is a well known precursor for copious compounds due to its versatile applications as alkaloids, dyes, pesticides, catalysts, drugs,

analytical reagents and in numerous pharmacological applications as anti-HIV, anti-cancer, anti-viral, anti-tubercular, anti-fungal, anti-microbial, anti-malarial, anti-convulsant, anti-oxidant, anti-inflammatory, anti-tubercular, anti-asthmatic, anti-bacterial, potent SARS-CoV-2 3C-like protease inhibitors etc., which developed tremendous research interest among researchers on it [5–12].

Due to these extraordinary marvellous features and presence of transformations (Fig. 1a–c) development of macrocyclic complexes containing isatin or its derivatives is exploring progressively. Here two active carbonyl groups at

Fig. 1 Keto-enol tautomerism in isatin/tribulin

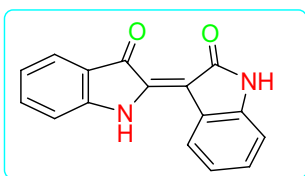
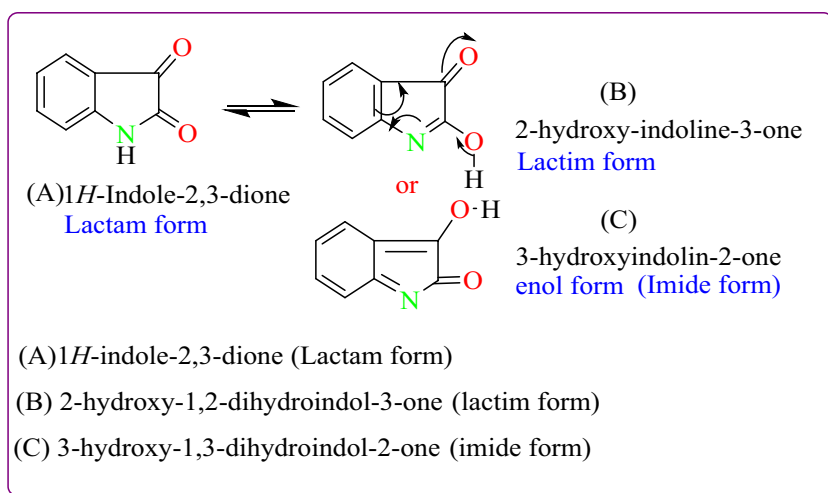


Fig. 2 Indirubin [14]

2nd and 3rd position in keto form of isatin are available to coordinate with different moieties and form imine, hydrazone, oximes, semicarbazone, thiosemicarbazone etc. which are commonly known as effective kinase inhibitors and thus increases the anticancer activity of the formed complexes. It was also found that halogenation at four to seventh position of isatin also boosted the antitumor activity of the respective complex. It was also noticed that after complex formation with transition metal ions biological properties of such kind of molecules and their derivatives were increased which created enormous province research for researchers on these compounds. In 2017, Vandana et al. [13] reviewed diverse biological activity shown by isatin and its derivatives viz., anti-HIV, antimicrobial, anticancer, anti-inflammatory, analgesic, antipyretic, CNS activity, anti-convulsant, sedative activity and anti-oxidant activity. In 2019, Guo [14], summarized anti-bacterial potential of isatin and its various derivatives likely isatin dimmers (Fig. 2- Indirubin), isatin-azole, isatin-indole, isatin-furan, isatin-semicarbazone, isatin-quinoline, etc. hybrids and their structure–activity relationship was also given to understand further rational designs of active candidates. Table 1 shows some reported isatin-based compounds along with their biological activities.

In 2022, Varshney et al. [15] designed and synthesized Mannich bases of isatin by the reaction of secondary amines with 37% aqueous solution of formaldehyde firstly and there after reacted with aromatic primary amines in the presence

of glacial acetic acid. The compounds were characterized by physical, chromatographic and spectroscopic methods and reports suggested that these compounds showed good activity against MCF-7 cell lines. Doxorubicin drug was used as standard for comparison and found that these analogues were effective against breast cancer, and therefore the isatin moiety could serve as the lead molecule to the development of new anti-breast cancer agents.

Islam et al. synthesized a series of spiro-oxindole analogs (≈ 19) (Fig. 3) embedded with pyrazole scaffolds via [3 + 2] cycloaddition reaction in 2022, and screening of these synthesized analogs was also carried out to check their biological property against several targets like Acetylcholinesterase (AChE), Butylcholinesterase (BChE) for anti-choline activity and DPPH for anti-oxidant activity. Among these compounds, some showed excellent potential against Alzheimer's disease due to AChE and BChE inhibition, antioxidant potential against DPPH, enzyme inhibitory and molecular docking potential [16].

Some newly synthesized isatin-based oxadiazole derivatives (1–30) as potential inhibitors of thymidine phosphorylase enzyme involved in pyrimidine salvage route, were studied by Javid et al. [17] (Fig. 4). Further these synthesized compounds evaluated by molecular docking study and SAR elucidation. Results showed that all analogs performed potent inhibition against thymidine phosphorylase compared with standard 7DX (7-Deazaxanthine).

Further investigation by Lahari and Sundararajan in 2019 on isatin-based compounds indicated their antimicrobial potential against a variety of pathogenic bacteria and fungi [18]. Likewise, various biological properties such as antioxidant, antimicrobial, CNS depressant, diuretic, anti-tubercular, anti-anxiety, anti-HIV, anti-cancer and anti-inflammatory of isatin-based compounds were reviewed by Shukla et al. in 2018 [19]. Furthermore antibacterial activity of Mannich base derivatives of isatin was consolidated by

Table 1 Reported Isatin-based compounds and their reported activities [115–127]

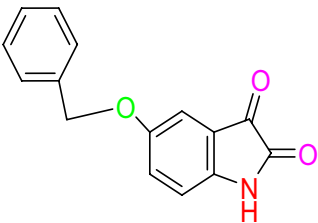
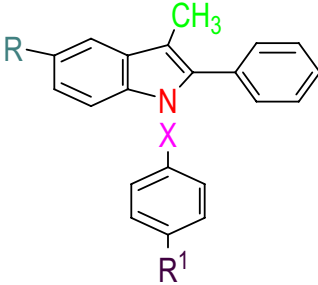
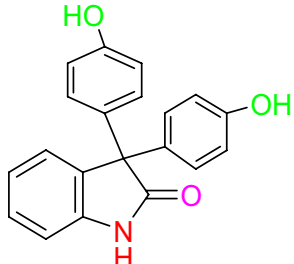
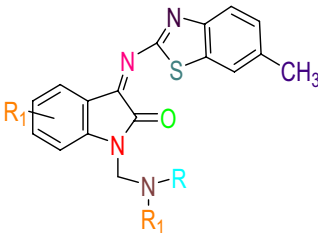
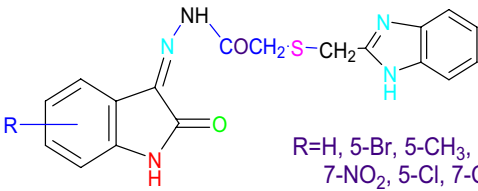
S. No	Reported compound	Reported activity with reference number
1	 <p>5-(benzoxy)-indoline-2,3-dione</p>	MAO inhibitor [115]
2	 <p>R = H, SO₃Me; R₁ = H, Cl X = CO, CH₂</p>	Anti-inflammatory and Analgesic agents, [116]
3	 <p>3,3-Bis(4-hydroxyphenyl)indolin-2-one</p>	Anticancer activity [117]
4		Anti-breast cancer activity [118]
5	 <p>R = H, 5-Br, 5-CH₃, 7-CH₃, 5-NO₂, 7-NO₂, 5-Cl, 7-Cl, 5-COOH</p> <p>2-[1<i>H</i>-benzimidazol-2-ylmethyl] sulfanyl]-N'- [(3<i>Z</i>)-2-oxo-1,2-dihydro-3<i>H</i>-indol-3- ylidene]aceto hydrazides</p>	Anti-inflammatory activity [119]

Table 1 (continued)

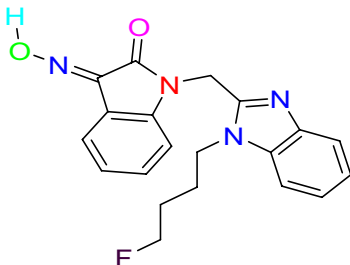
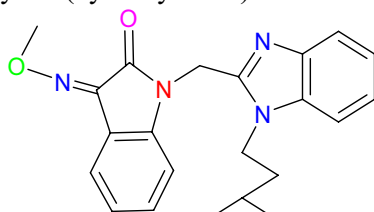
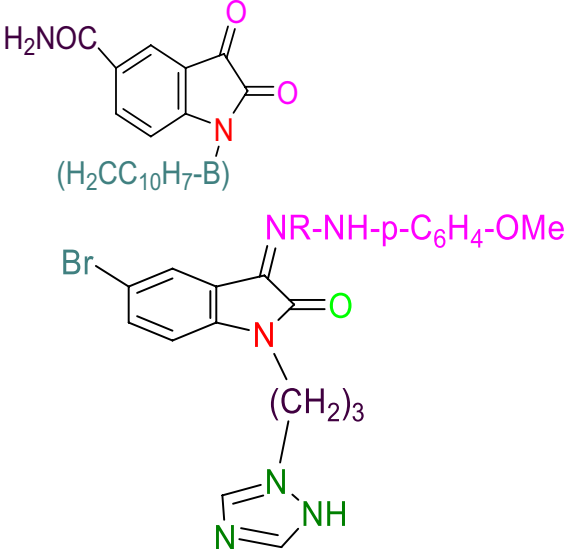
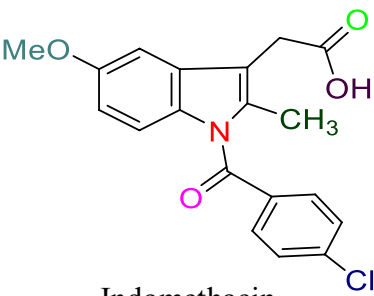
S. No	Reported compound	Reported activity with reference number
6	 <p>E-1-((1-(4-fluorobutyl)-1H-benzo[d]imidazol-2-yl)methyl)-3-(hydroxyimino)indolin-2-one</p>	Antiasthamatic activity [120]
7	 <p>Z-1-((1-Isopentyl-1H-benzo[d]imidazol-2-yl)methyl)-3-(methoxyimino)indolin-2-one</p>	Potent SARS-CoV-2 3C-like protease inhibitors [121]
8	 <p>Z-1-[3-(1H-1,2,4-Triazol-1-yl)propyl]-5-bromo-3-[2-(4-methoxyphenyl)-hydrazono]indolin-2-one</p>	Anti-inflammatory [122]
9	 <p>Indomethacin</p>	Nonsteroidal Anti-inflammatory drug, indomethacin, as selective cyclooxygenase-2 inhibitors [123]

Table 1 (continued)

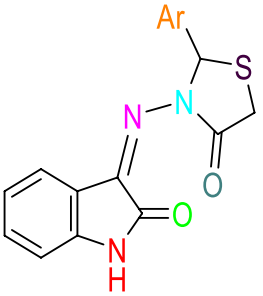

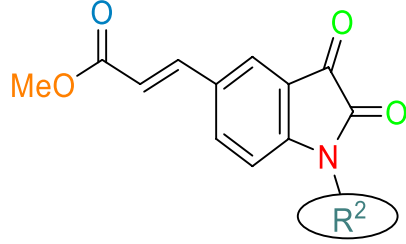
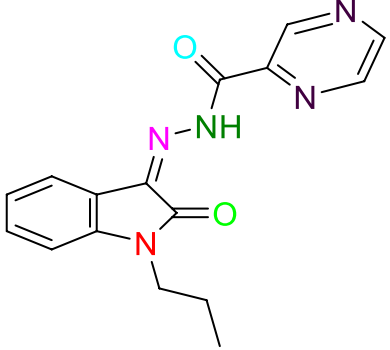
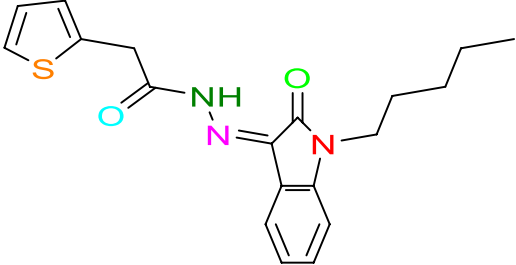
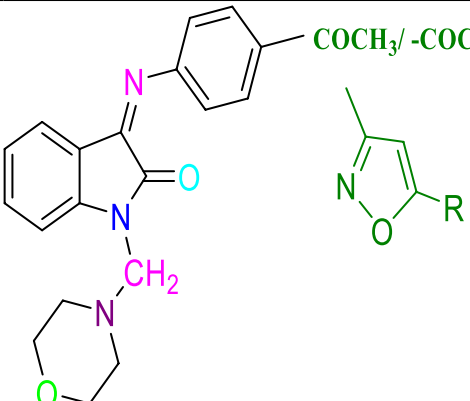
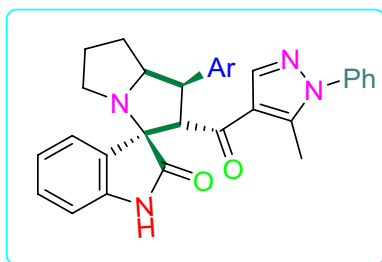
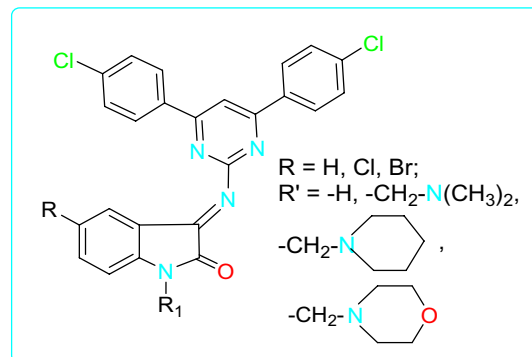
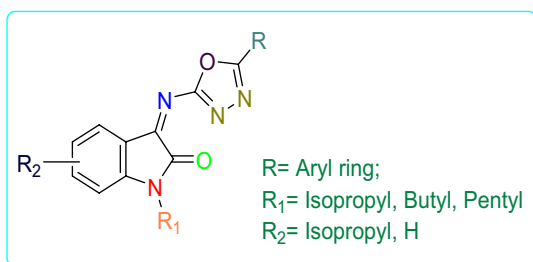
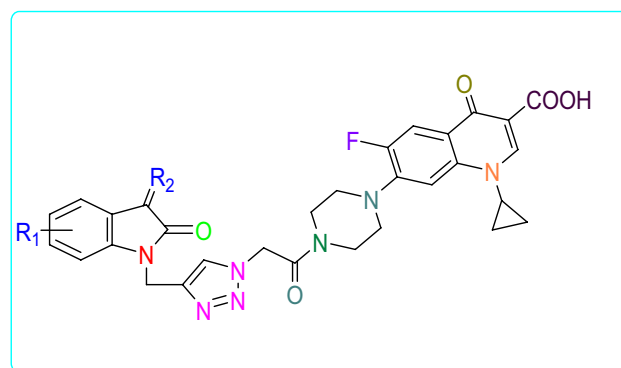
S. No	Reported compound	Reported activity with reference number
10	 <p>where, Ar = </p> <p>R = Cl, OH, CH₃, OCH₃</p>	Anticonvulsants [124]
11		Anticancer agents [125]
12	 <p>N-pyrazoloyl hydrazone of isatin (PHI),</p>  <p>N-thiopheneacetyl hydrazone of isatin(THI)</p>	Anti-inflammatory and anti-nociceptive [126]

Table 1 (continued)

S. No	Reported compound	Reported activity with reference number
13		Anticonvulsant activity [127]

**Fig. 3** Spiro-oxindole analogs [16]**Fig. 5** Synthesized Mannich base derivatives of isatin [20]**Fig. 4** Oxadiazole derivatives [17]**Fig. 6** Reported Ciprofloxacin-1,2,3-triazole-isatin hybrids [21]

Pandeya et al. [20] (Fig. 5). It was observed that these compounds were found to be active against *S. typhimurium*, *S. aureus*, *E. faecalis*, *P. aeruginosa*, *K. pneumoniae*, *S. albus*, *A. hydrophila*, *B. subtilis*, *P. rettgeri* and *vibrio cholerae-01*. All these compounds were also tested for their inhibitory potential against HIV-1 in human MT-4 cells.

Chen et al. [21] in 2019, prepared some new ciprofloxacin-1,2,3-triazole-isatin hybrids (Fig. 6) tethered via amide and evaluated them for their in vitro anti-mycobacterial activity against MTBH37Rv and MDR-MTB strains and

cytotoxicity activity in VERO cells. Similarly, Gao [22] also designed moxifloxacin-acetyl-1,2,3-1*H*-triazole-methylene-isatin hybrids (Fig. 7) and their biological studies results showed that these compounds act as potential anti-tubercular agents against both drug-susceptible

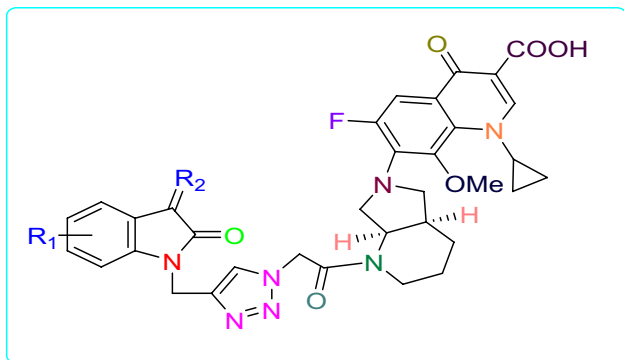


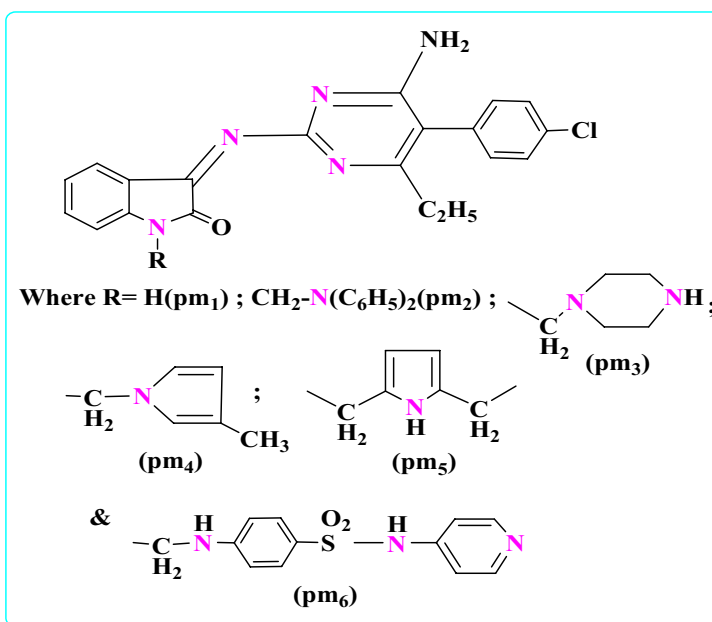
Fig. 7 Reported Moxifloxacin-acetyl-1,2,3-1H-triazole-methylene-isatin hybrids [22]

and drug-resistant strains of *Mycobacterium tuberculosis*. Excellent cytotoxicity results towards VERO cells and inhibitory activity against MTB DNA gyrase were also reported in that article.

In 2020, Almutairi et al. [23] studied certain isatin-based compounds as anti-proliferative agents in rat liver microsomes using LCMS (liquid chromatography-mass spectrometry) technique and one of the seven isatin indole conjugate compounds was metabolized into three (hydroxylated, reduced and *O*-demethylated) metabolites in RLMs in the presence of NADPH which will really be useful for providing information related to the effect of different substituents on the ionization/fragmentation processes and can also be used in the characterization of isatin derivatives.

Moreover, Senthilraja and Anand synthesized and characterised a series of N-mannich bases of isatin derivatives

Fig. 8 N-mannich base of isatin derivatives [24]



(Fig. 8) and their antimicrobial performance was investigated against pathogenic bacteria, pathogenic fungi and results indicated that these compounds showed greater activity compared to the standard drug [24].

Similarly, some compounds are also reported as antifungal agents. In this context, Richman reported that isatin-thiosemicarbazone can be used as prophylactic agent against various viral diseases [25]. Moreover, in 2013, Abbas et al. [26] synthesized some 5-fluoroisatin derivatives and evaluated them for their antiviral property, replication of vesicular stomatitis virus (VSV) and cytotoxicity evaluation in Vero clone CCL-81 cell. Reports indicated that out of all compounds (–C₁₀H₉N₄OFS–) and (–C₁₃H₁₅N₄OFS–) showed good inhibitory activity against these viral species (Fig. 9 from a–f).

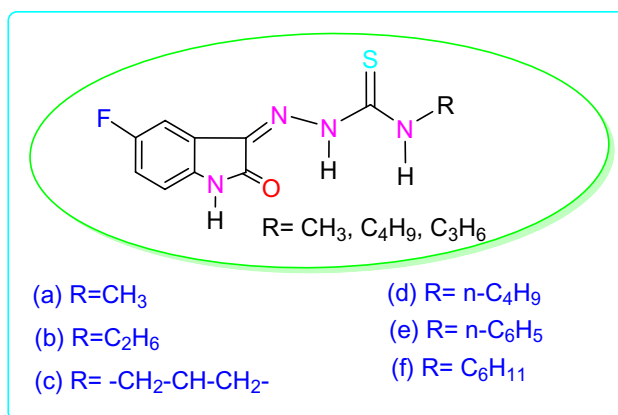


Fig. 9 Reported 5-fluoroisatin derivatives compounds [26]

In recent years, interest on macrocycles and their complexes is gaining attention due to their vast applications in diverse fields. Macrocycles are demarcated as cyclic molecules having more than nine atoms with 3 or more donor atoms (N, O, S, P etc.). Chemistry of synthetic macrocyclic complexes is burgeoning branch of coordination chemistry because of structural and functional properties of naturally occurring macrocyclic moieties such as metalloporphyrin (haemoglobin, chlorophyll, myoglobin, cytochrome), corrins (vitamin-B₁₂), and antibiotics (valinomycin, nonactin) [27–30]. Crown ether or macrocyclic polyether was firstly discovered macrocycle having ethylene-bridge separated through oxygen atoms by Pederson [31]. By the inclusion of metal ions into their cavity they form complexes, having greater stability than their noncyclic analogues. Various factors like macrocyclic effect (chelate effect) that increases stability constant, their capabilities to differentiate two metal ions based on their ionic radii are responsible for increased stability. Macrocyclic complexes have multiple applications because of their versatility in coordination behavior, combined hard-soft donor characters and their biomedical qualities [32]. Derivatives of macrocyclic complexes embrace by nature for rudimentary biological processes such as conversion of CO₂ into carbohydrate and transportation of O₂ in plants and human being's cells respectively. Macrocycles act as molecular baskets for binding the guest like neutral molecules, metal anions and organic cation [33]. Host–guest complexation can be affected by cavity size, macrocyclic structure, functional group's nature and the type of substituent in ligand. Macrocyclic complexes are extremely used in diverse areas viz., as a chemical sensitizer for photographic AgX emulsions (generally Cu, Ni, Fe, Rh and Th metal ions used), extraction of various metals for analytical separation, for transportation of metals (alkali and alkaline earth metals) through natural and artificial membranes, for determination of dissolved oxygen concentration in water (basically cobalt^{II}-macrocyclic complexes), as clinical or therapeutic agents for various disinfections, as electrical conductivity material, as powerful oxidizing agent (Ni–macrocyclic complex), and as single electron oxidizing agents ('Cyclam' containing macrocyclic complexes of Ni and its derivatives [34]). These are used as effective imaging agent or contrast enhancing agent for magnetic resonance or NMRI (which provides notable increase in proton relaxation rate of water, non-toxic in nature and thermodynamic more stable for example Gd³⁺, Fe³⁺, Mn²⁺ and Cr³⁺ are most commonly used as imaging agent), as catalyst (Ni(II) and Co(I) macrocyclic complexes, e.g., transfer of phosphoryl group by the poly ammonium macrocycles), in radio-immune therapy e.g., dodecane tetra acetic acid (DOTA) chelating agents with lanthanides can be used in radio-immune therapy, as

conjugated antibodies, as shifting reagent in NMR e.g., macrocyclic complexes of lanthanides (Dy³⁺ or Tm³⁺ with 1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetra-yl-tetrakis(methyl-phosphoric acid) (C₁₂H₃₂N₄O₁₂P₄).

Heme corrin, chlorophyll, natural products, coenzyme B₁₂ (cobalt III) are examples of naturally occurring macrocycles. Along with naturally occurring macrocycles a large number of synthesized macrocycles have also been reported having utilities in numerous fields like catalytic, selective ion transportation, therapeutic agents and many more. Generally, macrocycles can be designed by two methods:-

1.1 Non template/Direct Synthesis

In this method macrocyclic ligands are synthesized by the reaction of ligand precursors followed by the addition of metal ions for the generation of macrocyclic complexes. However, this is the simple method to synthesize the macrocyclic ligands that can be isolated, purified and characterized before the complex synthesis, but low yield of desired product is obtained due to side reactions like polymerisation are some demerits of this method. To increase the yield and decrease the side reactions stepwise cyclisation is frequently carried out under high dilution conditions or by the introduction of rigid groups which retard the open chain rotation of precursors. In 2017, Gull *et al* synthesized a ligand (L) by [2+2] condensation reaction of *O*-phthalaldehyde and 1,4-dicarbonyl-phenyl-dihydrazone and its complexes with Ni(II), Cu(II) & Co(II) metals (Figure 10) *via* conventional synthesis method [35] (Scheme 1).

Recently in 2022, Kanaoujiya *et al.* consolidated novel Ru(III) macrocyclic complex (Fig. 11) by using cyclam macrocyclic ligand i.e. 1,4,8,11-tetraazacyclotetradecane *via* non-template route and complexation properties of cyclam ligand (L') with Ru(III) ion were checked by molar conductance, XPS, FTIR and elemental analysis. An octahedral

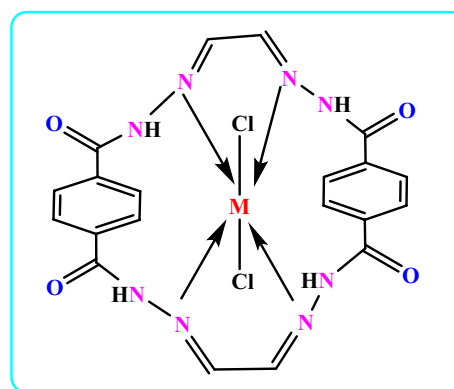


Fig. 10 Synthesized metal complex of (L) [35]

Scheme 1 Synthesis of macrocyclic Schiff base ligand (L) [35]

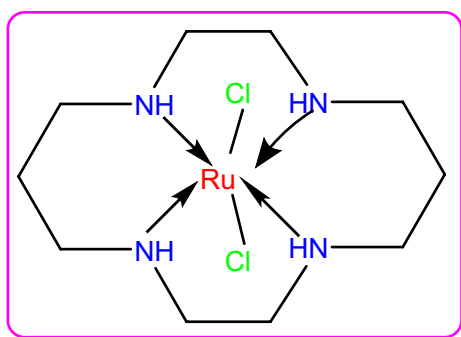
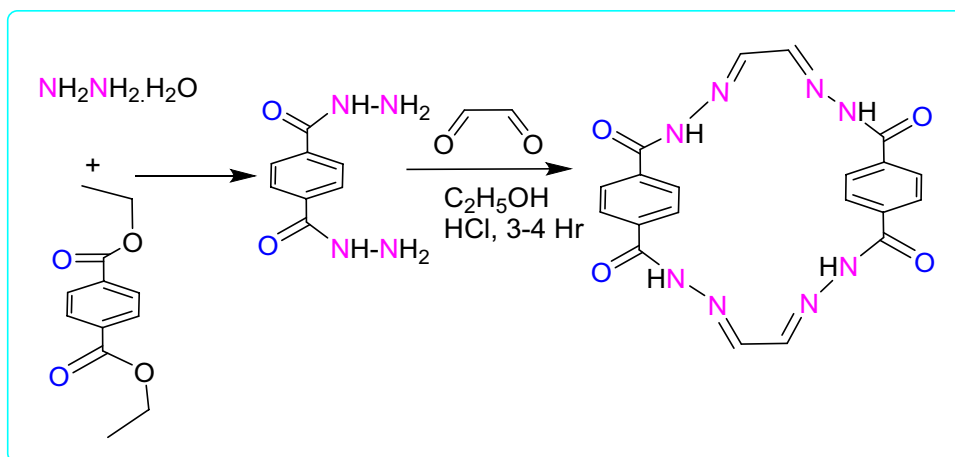
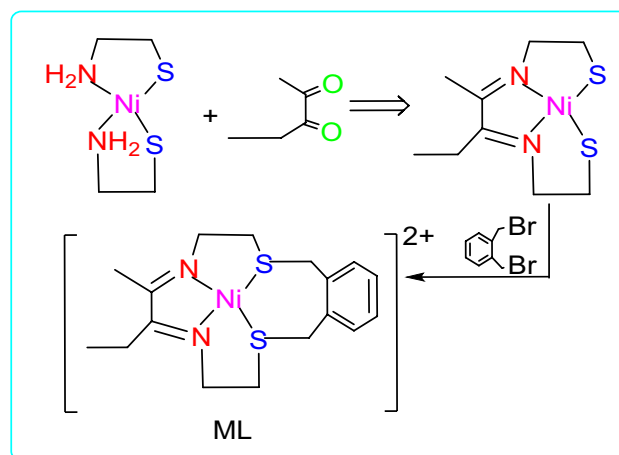


Fig. 11 Novel Ru(III) macrocyclic complex derived from cyclam macrocyclic ligand [36]

geometry of the complex had been reported on the basis of above mentioned studies. The hirshfeld analysis was performed for the determination of three dimensional and two dimensional intermolecular interactions of surfaces of the ligand & crystal [36]. Based on drug likeness studies they disclosed that cyclam ligand could be used for enlargement of different type of drugs. Cell viability assessment, cell imaging and DBPI staining were also performed to study the cytotoxic potential of ruthenium metal-based complex in cervical cancer cells, the morphological changes with the effect of drug and the morphological changes in the nucleus after treatment with the drug respectively. It was found that the proliferation of SiHa cells was suppressed. With increasing concentration of drug the viability of cells, were decreased. Authors demonstrated that complex exhibited significant anticancer attribute in the pathogenesis of cervical cancer [37].

1.2 Metals Ion Promoted Synthesis/Template Method

In 1960s, it was acknowledged that the company of metal ion encouraged the synthesis of macrocyclic complex during



Scheme 2 First knowingly synthesized macrocyclic complex by Thompson and Busch via metal template method [38]

the course of reaction. Since reaction is controlled by the metal template or *in situ* process named as template reaction. Busch introduced this term by synthesizing Ni(II) macrocyclic complex by [1+1] cyclo-condensation (Scheme 2). Before that, Curtis synthesized tetraaza-macrocyclic chelate of Ni(II) by the reaction of ethanediamine-1,2- acetone and Ni perchlorate [38] (Figure 12).

This method gives greater yield than conventional methods so hugely used by researchers but removal of the metal from the synthesized complex may always not be possible and provide thermodynamic and kinetic stabilities to the complex.

First row transition metals are widely used for the synthesis of macrocyclic complex showing amazing applications in material synthesis, photochemistry, bioinorganic, analytical, supramolecular, agriculture, industrial, gelatin matrix, electrochemistry, catalysis and most evidently in designing new drugs for biological systems [39–52]. It well established that addition of transition metals to the macrocyclic ligand increases the biological activity of these molecules [53, 54]. Aza and oxo-macrocyclic metal complexes have remained a

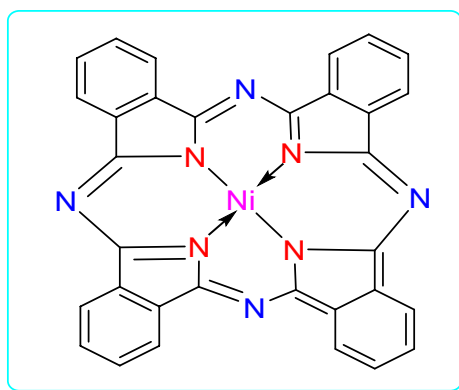


Fig. 12 Ni(II) tetraaza-macrocyclic chelate synthesized by Curtis 1960 [38]

focus of scientific attention because these complexes exhibit potent antibacterial, antifungal [55], anti-HIV [56–58], antiviral, anti-tumor [59–61], anti-carcinogenic, anti-fertility [62, 63], anti-inflammatory [64], etc. activities. These complexes act as MRI contrast agent [65–67], enzyme mimic [68–71] and catalytic agent [72–74]. These complexes have significance in many directions including inorganic synthesis, dyes, catalysts, analytical, polymer, metal extraction, anion receptors, drug discovery, molecular recognition, nanoscience and serve as therapeutic agent for the treatment of various diseases [75–78]. They have also received special attention as DNA binding agents, industrial and laboratory homogenous and heterogeneous catalysts [79, 80], for accelerating the photo-degradation of hazardous pollutants [81] and as radio therapeutic agent [82]. Chemistry of macrocycles is also being used as a nuclear waste cleanup. Macrocyclic complexes are used to design, synthesize and evaluate new drugs to degrade drug resistance problems [83], used as dyes and pigments [84], NMR shift reagents [85] that's why macrocycles have great potential in applied and fundamental science [86].

Soroceanu and Bargan reported a comprehensive review on Schiff base ligand and their metal complexes with the addition of antioxidant, redox and catalytic activities of Schiff base complexes. They also reported the recent advancement of these ligand base chemistry domain and its future prospect as a potential bioactive core [87]. In 2022, Kanaoujiya et al. also reported a review exploring the role of ruthenium-based complexes for the treatment of malignant tumors [88]. Mikhailov reviewed the role of aza, oxa-aza and thia-aza macrocyclic transition metal complexes in gelatin matrix [89]. Moreover, Bacchi et al. [90] reported a new ligand 1,5-bis(isatin) thiocarboxohydrazone along with its derivatives and also synthesized their complexes with Sn(IV). Satisha et al. [91] also synthesized Co(II), Ni(II), Cu(II) and Zn(II) TCH complexes by the use of upper ligand. Antimicrobial screening of these TCH complexes were also explored against a number of fungi and bacteria. Results indicated that isatin and

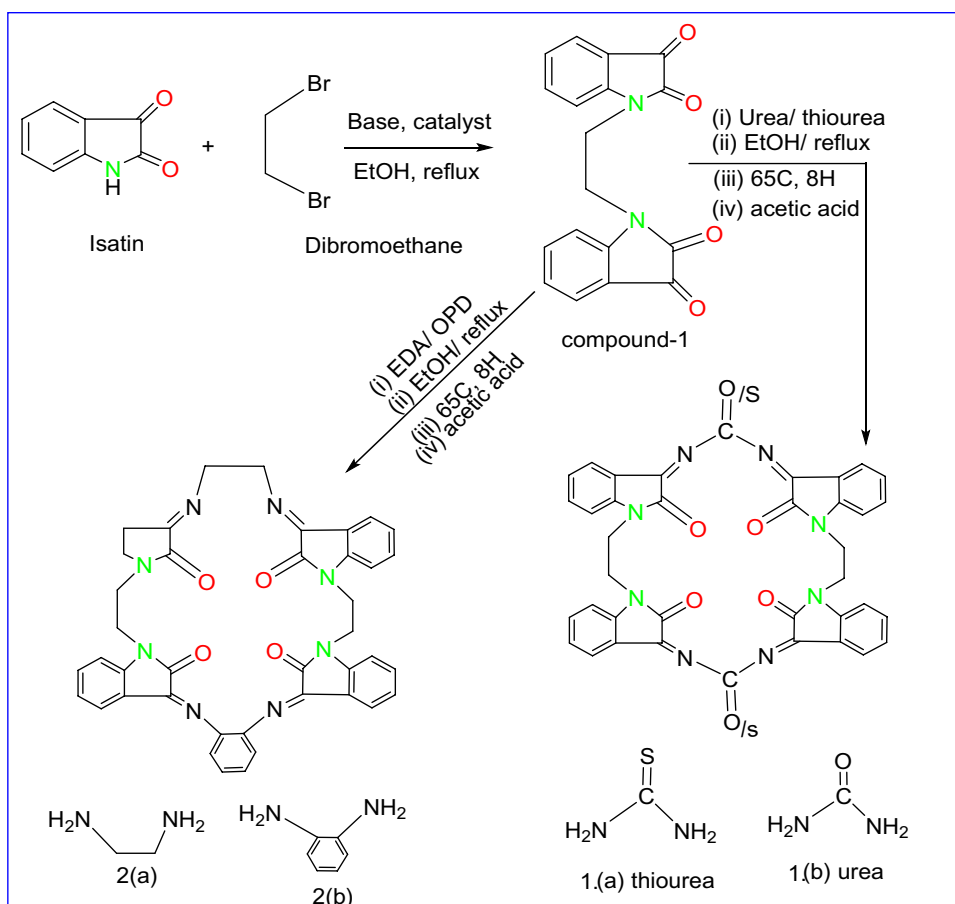
n-methyl-isatin-organotin(IV) complexes exhibited highest activity against Gram positive bacteria. Co(II) metal complexes showed best results against fungi than the others and reported that TCH drug common precursors can be used for drug designing. Owing to versatile applications of macrocyclic complexes of transition metal ions, researchers are enormously attracted towards these complexes.

Although bunch of studies have been published related to isatin or transition metal ion containing macrocyclic complexes with possible uses in diverse fields such as material science, catalysis, pharmaceuticals etc. [92–105], herein this concise review, we have focused on recently reported macrocyclic complexes of transition metal ions containing isatin or its derivatives as ligand precursors and their potential applications. This will help expedite the exploration of supramolecular and macrocyclic chemistry class in diversified applied fields especially in medicinal chemistry. These collective informations help readers to validate the great potential of isatin based macrocyclic complexes of transition metal ions as a class of effective medicinal agent.

Herein this concise review, a short introduction to isatin and its compounds with viable applications are highlighted then after macrocyclic complexes of transition metal ions containing isatin or its derivatives as ligand precursors with possible applications are mentioned. Transition metal complexes containing imine bond (C=N) have shown to be an excellent precursor for several metal based inorganic syntheses, nanochemistry or organic synthesis. So to provide a relevant literature on the synthetic approaches and applications of transition metal complexes containing isatin and its derivatives based macrocyclic ligands in various fields, like in pharmaceutical chemistry, as anticancer, anti HIV, anti-tumor, antioxidant, etc. agents, we target this to construct an informative review article to researchers. Moreover, to focus on comprehensive collection of the informations about the transition metal complexes along with their potent medicinal values.

2 Review of Literature

This review article provides comprehensive review about the designing and synthesis of macrocyclic complexes of transition metal ions containing isatin-based derivatives as precursors and their potential applications. In 2018, Bharathi dileepan et al. [106] introduced a novel class of isatin based macrocyclic ligands that can be used for drug designing. Both antimicrobial and anti-oxidant activities and *ex-vivo* DNA binding properties were also studied. Reaction of dibromomethane with isatin afforded Compound 1 (C₁₈N₁₂N₂O₄) which on treatment with urea or thiourea and EDA or OPD, produced compounds 1(a)(C₃₈H₂₄N₈O₆) or 1(b)(C₃₈H₂₄N₈O₄S₂) and compound 2(a)(C₄₀H₃₂N₈O₄) or 2(b)(C₄₈H₃₂N₈O₄) respectively (Scheme 3).

Scheme 3 Synthesized isatin based macrocyclic ligands [106]

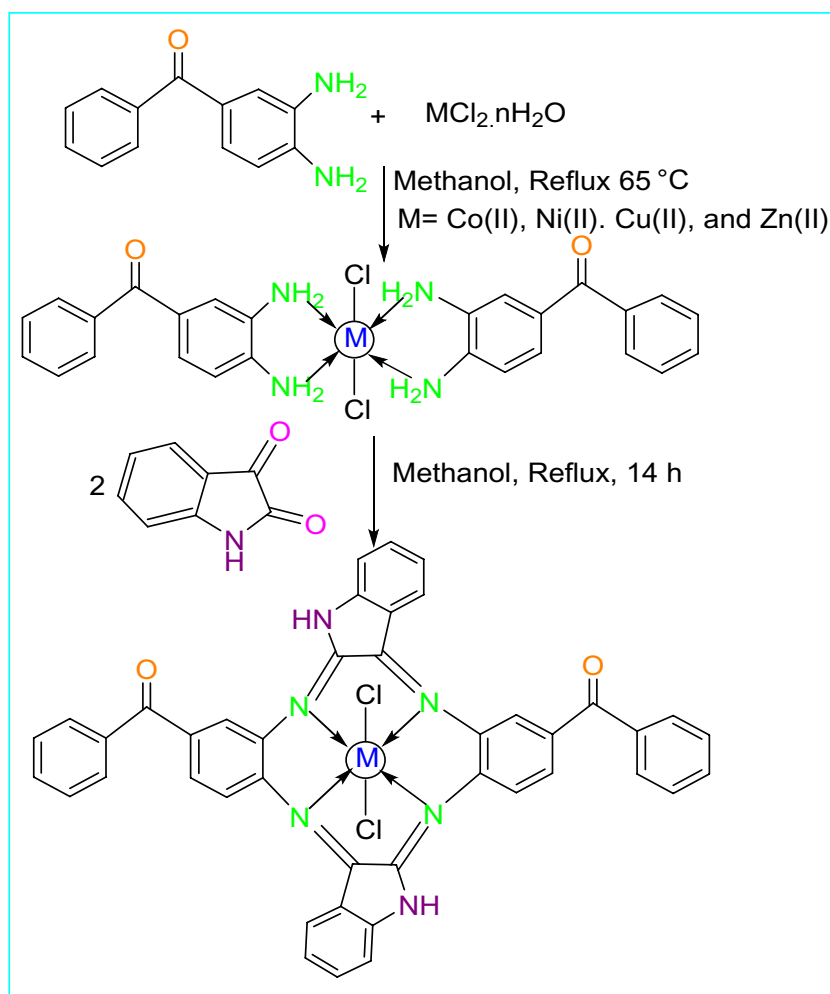
Reported compounds were characterized by FT-IR, 1D and 2D NMR, elemental analyses and electron spin ionisation mass spectral studies and *ex-vivo* DNA binding ability of these compounds were analysed by UV-visible, fluorescence, circular dichroism spectroscopy and viscosity measurement. Resulted data indicated that the order of DNA binding affinity for these five ligands as follows: 2b ($1.52 \pm 0.06 \times 10^5 \text{ M}^{-1}$) > 2a ($1.12 \pm 0.11 \times 10^5 \text{ M}^{-1}$) > 1b ($1.05 \pm 0.04 \times 10^5 \text{ M}^{-1}$) > 1a ($0.97 \pm 0.14 \times 10^4 \text{ M}^{-1}$) > 1 ($0.75 \pm 0.21 \times 10^4 \text{ M}^{-1}$) favours that the presence of electron donor group in the compound is main governing factor for their best DNA binding ability. Antioxidant property was explored against DPPH and OH & NO radicals and results indicated that all compounds show enough scavenging action against DPPH and OH rather than NO radical. In vitro antimicrobial activity and in silico molecular docking stimulation result favours that these compounds adequately seize the growth of microorganisms. These resulted data supports that in upcoming future, this work will really be beneficial for the synthesis of new macrocyclic complexes (with various metal containing the given framework/Skeleton) that can be used for designing new antimicrobial drug with efficient capacity. Among the entire compounds 1a compound showed best results against all biological tests and authors suggested that it can be further used for clinical purpose.

In 2017, a series of 12-membered complexes with Co(II), Ni(II), Cu(II) and Zn(II) were prepared by using isatin and 3,4-diaminobenzophenone as primary ligands (Scheme 4). Reaction was carried out in methanol solvent and template condensation pathway was adopted for the synthetic purpose [107]. FTIR, Mass, NMR, UV-Vis, EPR, SEM, TGA/DTA and elemental analyses techniques were used to characterize the newly synthesized complexes $[\text{M}(\text{C}_{21}\text{H}_{13}\text{N}_3\text{O})_2\text{Cl}_2]$ {M=Co(II), Ni(II), Cu(II) or Zn(II)}. Among these four complexes, $[\text{Cu}(\text{C}_{21}\text{H}_{13}\text{N}_3\text{O})_2\text{Cl}_2]$ complex was reported with highest DNA binding ability based on circular dichroism and docking studies results. 2,2-diphenyl-1-picrylhydrazyl method was adopted to check antioxidant properties in DMSO solvent with different concentrations (50-450 $\mu\text{g}/\text{ml}$) of testing complexes and % of free radical scavenging activity was calculated by

$$\%RSA = \left[\frac{(A_o - A_c)}{A_o} \right] \times 100$$

Here, RSA Radical scavenging activity; A_o Reference absorbance (ascorbic acid); A_c Absorbance of complex at C concentration.

Scheme 4 Synthesized 12-membered complexes of Co(II), Ni(II), Cu(II) and Zn(II) [107]



% RSA results indicated that out of all complexes Cu(II) macrocyclic complexes showed best antioxidant activity with 64% and the reason for increased free radical scavenging activity of this complex was explained by the fact that large fraction of O_2^- reacts with Cu(II) as compared to the ligand and causes reduction of Cu(II) to Cu(I). Additionally, further oxidation results in the formation of Cu(II) complex with another O_2^- molecule. Through scanning electron microscopic micrograph, various morphological, structural and void fractions in between the atoms of the complexes aspects were explained. *E. Coli* (Gram -ve) & *S. aureus* (Gram + ve) bacterial and *C. albicans* fungal strain were used for antimicrobial screening of all the complexes via disc diffusion method. Standard antibiotic Gentamicin and Amphotericin B (antifungal screening) were used as reference. % Activity was calculated by the following equations.

$$\% \text{ Activity index} = \frac{\text{zone of inhibition by sample (diameter)}}{\text{zone of inhibition by reference (diameter)}} \times 100$$

Additionally, minimum inhibitory concentration of these complexes was also determined by incubating the test solution (1 mg/ml of 5% DMSO). Comparative antimicrobial results indicated that Cu(II) complexes $[Cu(C_{21}H_{13}N_3O)_2Cl_2]$ performed best activity and that was certified by checking its capacity to form a biofilm against *E. Coli*, *S. aureus* and *C. albicans*. Out of these microbes, this complex exhibited more inhibition against *S. aureus* biofilm.

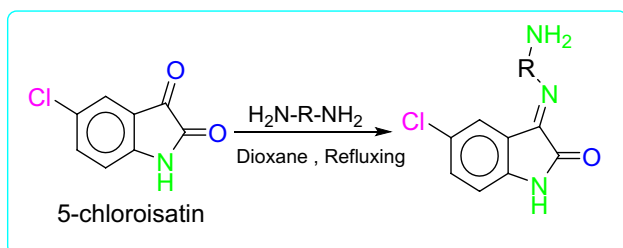
In 2020, Khalid et al. [108] designed a series of macrocyclic complexes containing Co(II), Ni(II), Cu(II) and Zn(II) metals as central moiety by the reaction of 5-chloroisatin with a variety of diamines namely ethane 1,2-diamine, propane-1,3-diamine, butane-1,4-diamine or benzene 1,2-diamine. It was reported that these complexes showed more antifungal and antibacterial activity than the free ligands (Schemes 5 and 6).

Complexes containing Co(II), Ni(II), and Cu(II) metals exhibited DNA binding, cleavage and cytotoxic activity with calf thymus DNA and AGS cell lines, respectively. Gomathi et al. [109] designed these complexes through condensation

reaction of 1-phenylindoline-2,3-dione with iso-nicotinohydrazide followed by the addition of metal ions [Co(II), Ni(II) or Cu(II)]. Both Ni(II) and Cu(II) complexes showed stronger binding ability and satisfactory cytotoxic activity against AGS cell line that can be formulated into an efficient drug against cancer treatment as reported by the author.

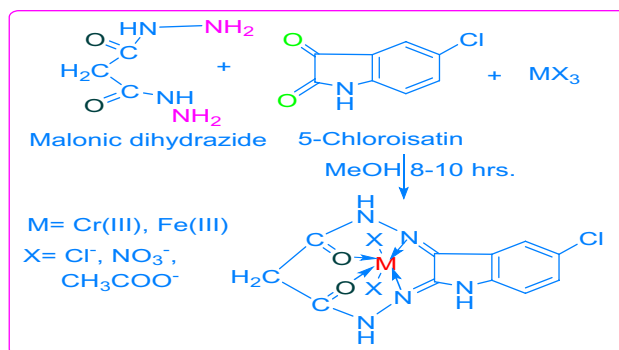
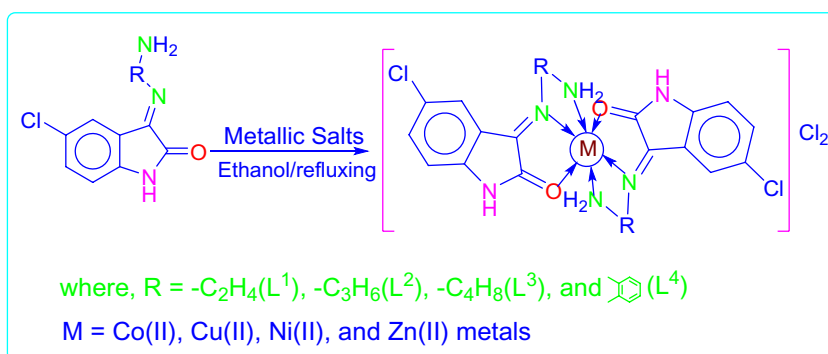
In 2015, a macrocyclic ligand $C_{11}H_8N_5O_2Cl$ (synthesized by the reaction between 5-chloroisatin and malonic dihydrazide in CH_3OH solvent) and its series of complexes with Cr(III) and Fe(III) metal chlorides, acetate or nitrates was consolidated by Singh and Ali via template condensation methodology [110]. Magnetic susceptibility, Infra-red, analyses of elements, molar conductance, and electronic spectral results favoured a six coordinated geometry of these complexes as represented in Scheme 7.

Absence of two bands at $\sim 3275\text{ cm}^{-1}$ & $\sim 3215\text{ cm}^{-1}$ (due to presence of $-NH_2$ group in malonic dihydrazide ligand precursor) and a band at $\sim 1735\text{ cm}^{-1}$ (due to presence of $>C=O$ group in 5-chloroisatin ligand precursor) indicated that both groups got condensed during course of reaction and a new strong band attributed at $\sim 1590\text{--}1610\text{ cm}^{-1}$ (due to $>C=N$ -group) also supported the condensation reaction results. Magnetic moment results for $[Cr(C_{11}H_8N_5O_2Cl)Cl]Cl_2$ observed 3.9 to 4.5 BM indicated presence of three free electrons in metal ion. Similarly, for Fe(III) complexes it was observed 5.85 to 5.90 BM indicated presence of five free electrons in Iron metal. Ex vivo antimicrobial screening of the reported complexes and their individual ligand were also



Scheme 5 Synthesis of ligand [108]

Scheme 6 Synthesized macrocyclic complexes of metals using ligand [108]



Scheme 7 Proposed route for the synthesis of macrocyclic complexes [110]

performed by determining MIC via spot-on-lawn on Muller Hinton Agar method against *B. cerus*, *S. typhi*, *E. coli*, *S. aureus* pathogens and compared with Linazolid cofactor standard drugs. Results indicated that $[\text{Fe}(C_{11}H_8N_5O_2Cl)Cl]Cl_2$ complex showed better results instead of other complexes and satisfactory results of antimicrobial activities explained on the basis of chelate ring effect that causes the increased permeability of the complex into microbial cell was also reported.

Sharma et al. [111] adopted template method for synthesizing biological active macrocyclic complexes of Co(II), Ni(II), Cu(II), Zn(II) metal ions by the reaction of oxal-dihydrazide with isatin and reported $[M(C_{20}H_{14}N_{10}O_4)X_2]$ typed complex {where $X = \text{Cl}^-$, NO_3^- , CH_3COO^- }. Elemental analyses, conductance measurements, magnetic susceptibility measurements, electronic, infrared, EPR and NMR spectral studies were employed for the characterization and based on studies a distorted octahedral geometry of synthesized complexes was reported. Ex vivo antibacterial studies evaluated against some bacterial species and results favoured their satisfactory antibacterial power. Alkam et al. [112] composited Cu(II) and Hg(II) complexes from the Schiff base ligands (L1) [2,2-(biphenyl-4,4-diylbis(azan-1-yl-1-ylidene))bis(1,2-diphenylethanol)] obtained by benzidine and benzoine ligand precursors condensation reaction

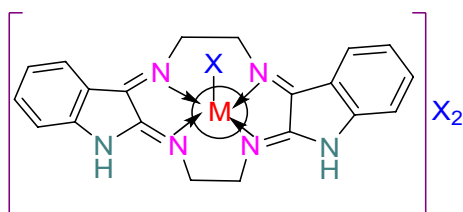


Fig. 13 Proposed macrocyclic complex [113]

and (L2) [3,3-(biphenyl)-4,4-diylbis(azan-1-yl-1-ylidene) diindolin-2-one] was acquired via the condensation of the benzidine and isatin. Characterization of these ligands and their complexes were done by molar conductance (transmitting their ionic nature), NMR, IR, electronic spectral studies. Additionally, antifungal and antibacterial activities were also performed to find out their potential as antimicrobial drug by employing disc diffusion method and reports indicated their significant role in this context.

Complexes having formulae $[M(\text{TML})\text{X}]\text{X}_2$ (Fig. 13); {where X may be Cl^- , NO_3^- or acetate} were obtained, via both conventional and microwave methods by condensation reaction of tribulin and 1,2-diaminoethane [113]. By considering various physico-chemical analysis techniques viz., analyses of elements, measurement of conductance, magnetic susceptibility measurement, IR, FAR IR, UV/Vis spectral studies etc., a square pyramidal geometry having five coordination numbers were proposed for these complexes. Spot on lawn on Miller Hinton Agar method was adopted for ex vivo antibacterial screening of these complexes and were performed against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *salmonella typhi* bacterial strains and results indicated that all complexes showed minimum inhibitory concentration greater than the standard antibiotics, viz., Linezolid and Cefactor. Formation of a ring around the metal increases the penetration power of the complex into the microbial cell membrane, which may lead to the activity of the complexes.

A novel series of complexes having formulae $[M(\text{C}_{36}\text{H}_{22}\text{N}_6)\text{X}]\text{X}_2$ (Fig. 14); {where X may be Cl^- , NO_3^- or acetate} were manufactured by Singh et al. by the cyclocondensation reaction of naphthalene-1,8-diamine and 2,3-Indolinedione in methanol solvent [114]. Various physico-chemical analysis techniques namely elemental analyses, conductance, UV/Vis, IR, mass spectrometry, etc. favoured a square pyramidal geometry with coordination number five for these complexes. Agar well diffusion method and poisoned food technique were used for the ex vivo assessment of all these complexes against antimicrobial and antifungal strains respectively. The complexes were screened against *S. aureus* and *B. subtilis* (Gram positive) and *P. aeruginosa* and *E. coli* (Gram negative) bacterial strains. *Aspergillus flavus* and *Aspergillus niger* fungal strains were chosen for

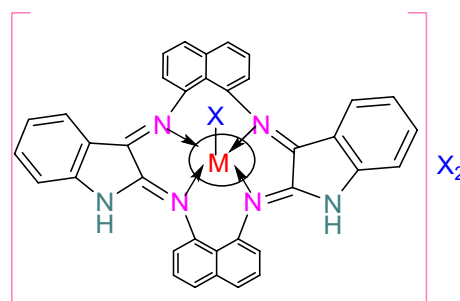


Fig. 14 Proposed macrocyclic complex [114]

antifungal assessment. For the comparison of the resulted minimum inhibiting concentrations of these complexes, standard antifungal Amphotericin-B & antibacterial Ciprofloxacin were applied. All complexes showed remarkable but in consistent results for both of the activities.

3 Challenges and Opportunities

No doubt in the present scenario, macrocyclic chemistry has gained more and more attention from researchers due to its chemical diversity and occupies a distinctive portion of chemical space through advancements in bioinformatics and synthetic methodology. Cyclization in macrocycles improves oral bioavailability due to more conformationally restriction that imparts higher target binding and selectivity than their acyclic analogues. Isatin, a magical molecule, or its derivatives based macrocyclic complexes, gained more interest in medicinal chemistry because of its remarkable pharmacological properties, such as anti cancer, anti tumor, anti HIV, insulin resistance, antioxidant, SARS-CoV-protease inhibitor are few of them. Entrapment of a transition metal ion within a macrocyclic ligand increases the therapeutic potential of ligand e.g. ruthenium, platinum and palladium complexes are found more active against malignancy disease and vanadium complexes in overcoming insulin resistance. Indeed, the synthesis of these complexes containing isatin or its derivatives constitutes an opportunity for novel avenues expanding the processing toolbox for medical science to provide bioactive molecules with several other metal ions.

With these opportunities, the synthesis of these molecules is still challenging due to structural complexity and synthetic intractability limitations. Beside it, the ring closing reaction also depends upon the size and geometry of the bridging linker and the size of the ring. Moreover, during the course of macrocyclization, conformational pre-organization is important for the reaction to occur and often requires high dilution conditions to counter balance entropic loss. In our opinion, scientists must focus on the synthetic route that will provide higher yield of complexes

without harming the environment (green synthesis), by keeping in their minds the marvelous roles of these complexes against prominent diseases such as tumor, HIV, cancer, diabetes, obesity, Parkinson's disease etc.

4 Conclusion

In essence, it can be concluded that isatin is employed as a precursor for synthesis of numerous organic compounds e.g. alkaloids, dyes, pesticides, catalysts, drugs, analytical reagents etc. due to presence of two carbonyl groups (at 2nd and 3rd position of keto form of isatin) which can coordinate with different moieties and cast new organic functionalities like imine, hydrazone, oximes, semicarbazone, thiosemicarbazone are few of them. Presently, in the contemporary drug discovery process, macrocyclic complexes of transition metal ions containing isatin and its substituted derivatives as a ligand have emerged as an essential pharmacophore due to their wide pharmacological applications. This review summarizes the latest published isatin or its derivative based macrocyclic complexes of transition metal ions, such as Ni(II), Cu(II), Zn(II), Fe(II/III), Co(II), Hg(II), Cr(III), Ru(III) etc. with their synthetic routes and provides comprehensive literature about diverse and potent biological applications like antioxidant, anticancer, antitubercular, antiasthmatic, antiinflammatory, potent SARS-CoV-2 3C-like protease inhibitors, antiviral, and antimicrobial and many other activities. Therefore, we hope this review is expected to serve as a reference guide for the development of the new macrocyclic complexes of transition metals from isatin or its derivatives and their potential role for diverse pharmacological applications. Hence, the summary of these complexes with their miscellaneous applications will definitely provide their opportunities in pharma-science and material science for researchers who are working with these ligands or who are just starting out in this interesting field. Finally, we wish this review will be useful and helpful for readers and young researchers to work in this field.

Acknowledgements Authors are thankful to the Department of Chemistry, University of Rajasthan, Jaipur, (India), for providing all kinds of facilities and support related to this work.

Author contributions For this manuscript all authors reviewed all papers from valuable scientific literature as they summarize the findings of existing literature. So readers can get an idea about the existing knowledge on the topic without having to read all the published work in the field.

Funding During the course of this research work, no specific grant was received from any of the funding agencies.

Declarations

Conflict of interest Authors declare there is no conflict of interest.

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