Bis-Schiff Bases of Isatin Derivatives Synthesis, and their Biological Activities: A Review

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Abstract:

Isatin is a heterocyclic molecule that belongs to one of the most important classes of organic compounds known as indolines. Isatin, isatin analogs, and their Schiff bases have recently attracted a lot of attention in medicinal chemistry. Isatin, itself, shows various biological activities such as antiviral, anticancer, antimicrobial, anti-inflammatory, analgesic, antioxidant, and anticonvulsant. Bis- Schiff bases containing isatin moiety have been known to possess a wide spectrum of pharmacological activities. This review offers up-to-date information on the most active isatin bis-Schiff bases, which would include anticancer, antimicrobial, antiviral, anticonvulsant, anti-inflammatory, and analgesic activities. These observations can lead to new molecular modifications that result in compounds with more desirable pharmacological properties.
Key words: Isatin, Isatin Bis-Schiff bases, biological activities.

قواعد الشيف الثنائية لمشتقات الأيساتين تحضيرها ونشاطها البيولوجي:مقال مراجعة

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الخلاصة:

يعد الأيساتين(Isatin) أحد الفئات المهمة للمركبات الحلقية غير المتجانسة التابعة للأندوليات. وفي الآونة الأخيرة ، أخذ الأيساتين ونظائره وقواعد شيف الخاصة بهذه المركبات اهتمامًا كبيرًا بالكيمياء الطبية أوالصيدلانية. يُظهر الأيساتين كمركب أنشطة بيولوجية مختلفة مثل مضاد للسرطان ومضاد للميكروبات ومضاد للفيروسات ومضاد للالتهابات ومسكن ومضاد للأكسدة ومضاد للاختلاج. ومن المعروف أن قواعد شيف التي تحتوي على جزيئة الأيساتين تمتلك عدد كبير من الأنشطة الدوائية. هذه المراجعة تقدم معلومات حديثة عن قواعد الشيف الثنائية للايساتين وهي الأكثر نشاطًا والتي تم نشرها على أنها تحتوي على مضادات للميكروبات ، ومضادة للسرطان ، ومضادة للفيروسات ، ومضادة للاختلاج ، ومضادة للالتهابات ، وخصائص مسكنة. يمكن أن تؤدي هذه النتائج إلى تعديلات جزيئية جديدة وتؤدي بالتالي إلى مركبات ذات خصائص دوائية فعالة أكثر.

الكلمات المفتاحية: الأيزاتين، قواعد الشيف الثنائية للايساتين، الفعالية البايولوجية.

Introduction

Isatin (2,3-Indolinedione) (Figure 1) is endogenously found and widely distributed in mammalian brain and body tissues.[1] It has also been discovered in the human body as a metabolic byproduct of the adrenaline hormone. [2-4] Isatin, has a building block of an indole, in which a ketone and a γ-lactam moiety are combined with the benzene ring; [4] it has a nitrogen heteroatom at position number 1 and two carbonyl groups at C2 and C3.[5,6] It

has taken a great interest to researchers in the field of organic and pharmaceutical chemistry.[7]

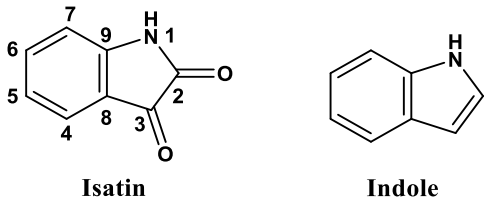


Figure (1): Isatin and Indole chemical structures

The most applicable and classical method to synthesize isatin is Sandmeyer's method (Figure2) which is carried out by cyclization of the condensation product of aniline, chloral hydrate, and hydroxylamine in concentrated sulfuric acid [8,9].

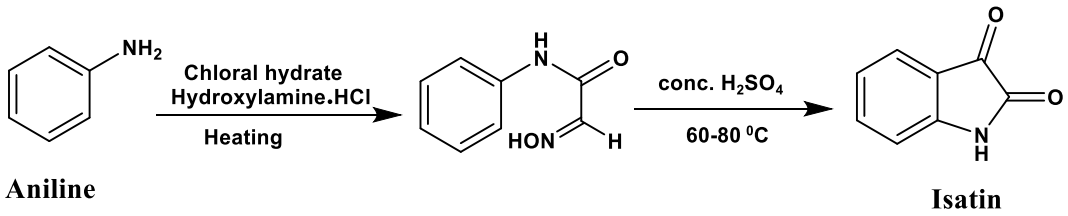


Figure (2): Sandmeyer's Method

Isatin and its analogs are one of the most favorable new classes of heterocyclic molecules which have many considerable activities and are well-tolerated in humans [10, 11]. Isatin can participate in a wide range of chemical synthetic processes, leading to its many uses as a starting molecule in pharmaceutical chemistry [12, 13]. The simple isatin molecule possesses various biological activities like anti-HIV [14], antimicrobial [15], anti-tubercular [16], antiviral [17], antitumor [18], antioxidant [19], anticonvulsant [20], anti-inflammatory [21], and CNS depressant activities [22]. Moreover, structure-activity relationship studies reported that isatin with mono substitution at C5, C6, and C7, as well as, several di- and tri-halogenated isatins, considerably improved the anticancer activity [23].

Schiff bases are compounds with the functional group azomethine (imine; –C=N–) in their chemical structure [24]. Hugo Schiff [25, 26] was the first who prepare these compounds, which are the condensation products of primary amines with carbonyl compounds. Schiff bases have achieved significant values in medical and pharmaceutical fields due to their wide range of biological activities such as analgesic [27], anti-inflammatory [28, 29], antimicrobial [30, 31], anticonvulsant [32], anti-tubercular [33], antioxidant [34], anticancer [35-37], and anthelmintic [38]. The nitrogen atom of the C=N linkage of azomethine is involved in the creation of a hydrogen bond with the active sites of cellular components and interfering with normal cell function [39-42].

In general, isatin Schiff bases can be prepared by combining the keto group at C3 of isatin with various primary amines mainly aromatic amines in the presence of (anhydrous) acetic acid (Figure 3) [43, 44].

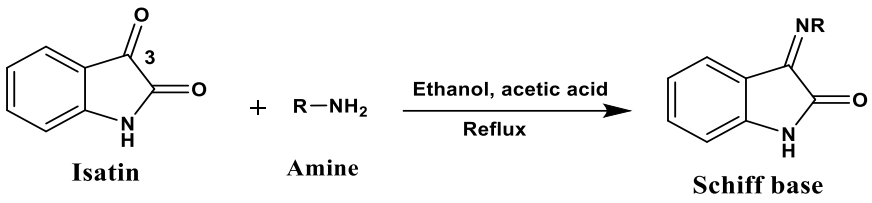


Figure (3): Synthesis of Schiff base of Isatin

Isatin molecules can also be found naturally as bis-isatin compounds (Figure 4). Indigo is a natural blue dye and the oldest and most well-known colorant among them [45]. Indirubin is the active component in traditional Chinese treatment for Chronic Myeloid Leukemia [46]. Indirubin is an isomer of indigo that is found in small amounts in the organic product of Indigo plants. Meisoindigo, another bis-isatin molecule, had greater anti-tumor efficacy than indirubin in laboratory animal models. Indirubin and its analogs (Meisoindigo) were found to be effective inhibitors of cyclin dependent kinases, providing insight into the molecular mechanism of these agents as anti-tumor agents [47]. Azaindirubin, more water-soluble bis-isatin was produced and found to exhibit anti-proliferative properties towards ovarian cystadenoma cell lines [48].

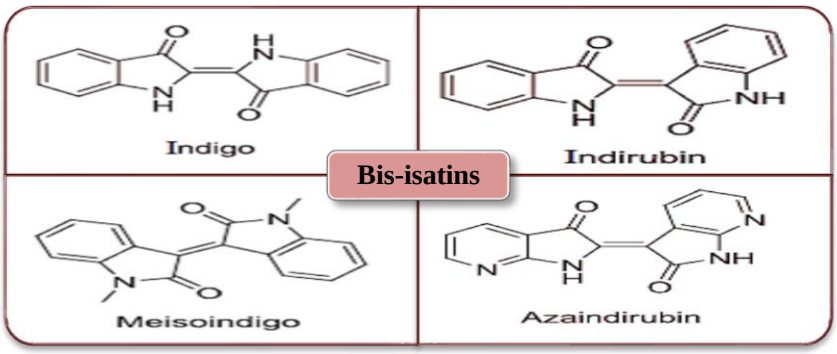


Figure (4): Some Bis-isatins and their chemical structures

Many researchers visualized that if two isatin-containing compounds or isatin with an aldehyde or ketone molecules are directly joined via a different bis-imine-based linkage. These compounds are either symmetrical or asymmetrical, respectively, which will have improved flexibility and water solubility as compared to indirubin and meisoindigo, thereby opening a pathway for enhanced biological activity.

In general, Bis-Schiff bases of isatin can be prepared by reacting 2 moles of isatin with diamine compounds, in the presence of a catalyst, such as glacial acetic acid, [49, 50], or by reacting with an excess amount of hydrazine hydrate in alcohol under reflux conditions [51], (Figure 5).

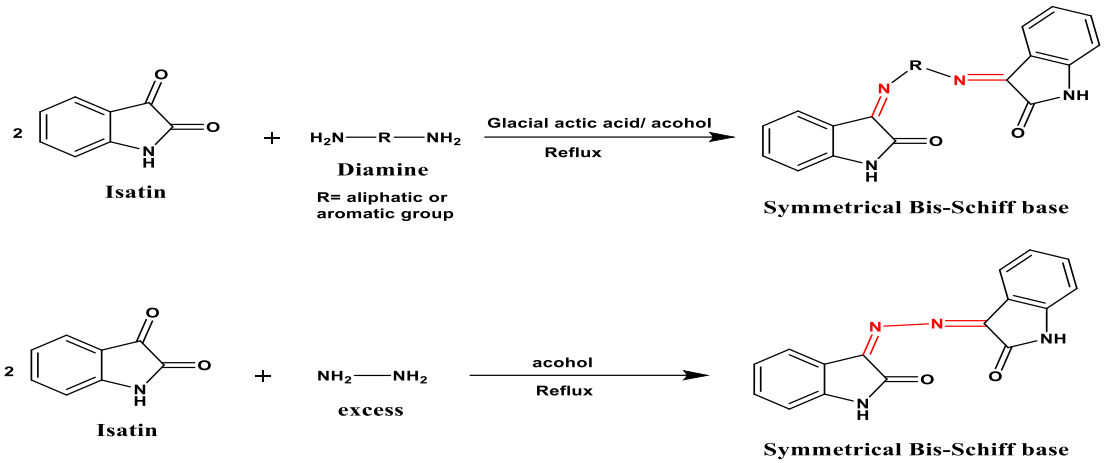


Figure (5): Synthesis of Isatin Bis- Schiff bases

Other isatin' bis-Schiff bases could be prepared from the reaction of 1 mole of isatin and 1mole of other carbonyl compounds (aldehydes or ketones) with hydrazine hydrate, or diamine in ethanol solvent [52], (Figure 6).

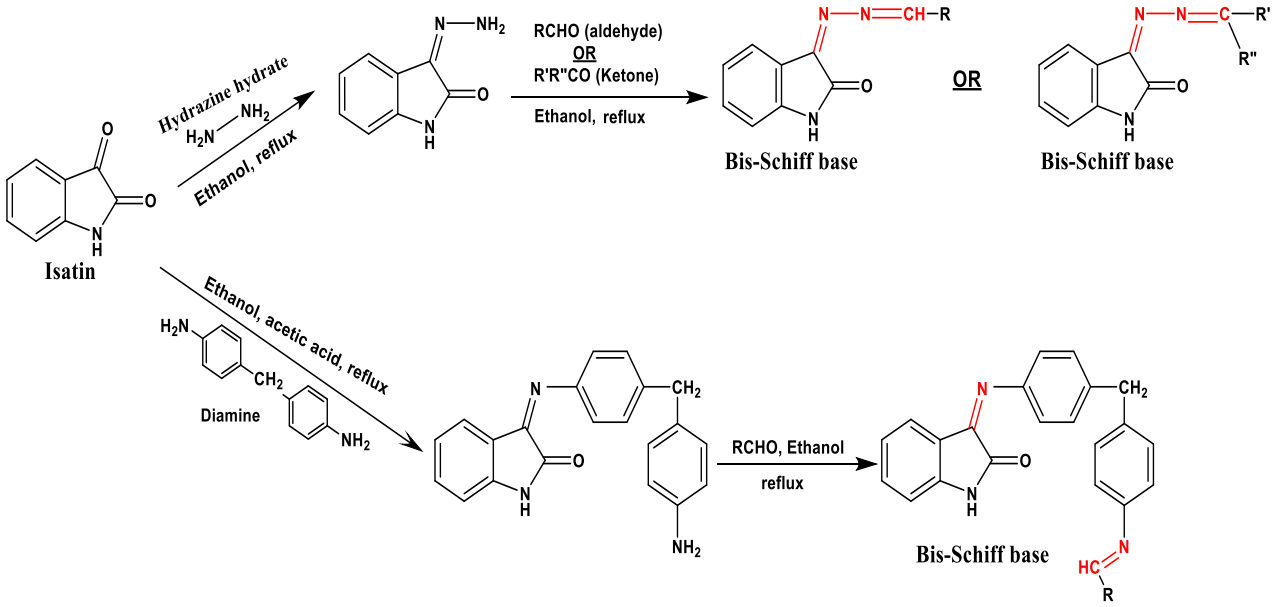


Figure (6): General Bis-Schiff base synthesis of Isatin with carbonyl compounds.

This review covers the recent development of isatin bis-Schiff base as promising antibacterial, antiviral, anticancer, antitubercular, analgesic, anticonvulsant, and anti-inflammatory agents.

Biological activities of Isatin Bis-Schiff bases

Antimicrobial activity

Prakash *et. al.* [53] prepared a series of Ciprofloxacin methylene isatin bis-Schiff base derivatives (**1a-*l***) (Figure 7) and evaluated them spectroscopically. Most of these compounds showed activity against different types of microorganisms. Compound **1c** showed remarkable activity against the tested microorganisms; *Staphylococcus aureus* and *Pseudomonas aeruginosa*, whereas compound **1k** showed potent activity against *Klebsiella pneumoniae* when compared with the reference drug ciprofloxacin.

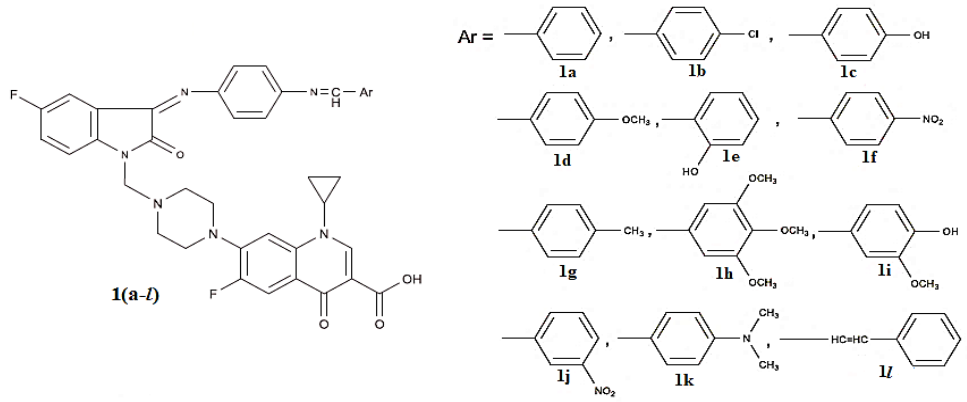


Figure (7): Ciprofloxacin methylene isatin bis-Schiff base derivatives

Nirma *et. al*. [54] synthesized new bis-Schiff bases derivatives of 3-(4-Amino) Phenylimino) 5- fluoroindolin-2-one (Figure 8) and characterized them by IR, ^{1}H-NMR, and mass spectral studies. All the synthesized compounds were active against all examined bacterial strains; *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Micrococcus luteus*, *Bacillus cereus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* and two fungi (*Aspergillus fumigatus* and *Aspergillus niger*). The *in-vitro* antimicrobial activity revealed that compounds **2g** and **2j** exhibited significant anti-microbial activity due to the inclusion of methoxy and phenolic OH groups at the 4th position of benzylideneamino moiety, respectively. While compounds **2f**, **2i**, and **2k** showed moderate activity when compared to standard drugs ciprofloxacin and ketoconazole. Furthermore, the addition of a fluoro group at the 5th position of isatin moiety can increase the lipophilic character of the synthesized derivatives, making them easier to pass through the microorganism's biological membrane and inhibiting its development.

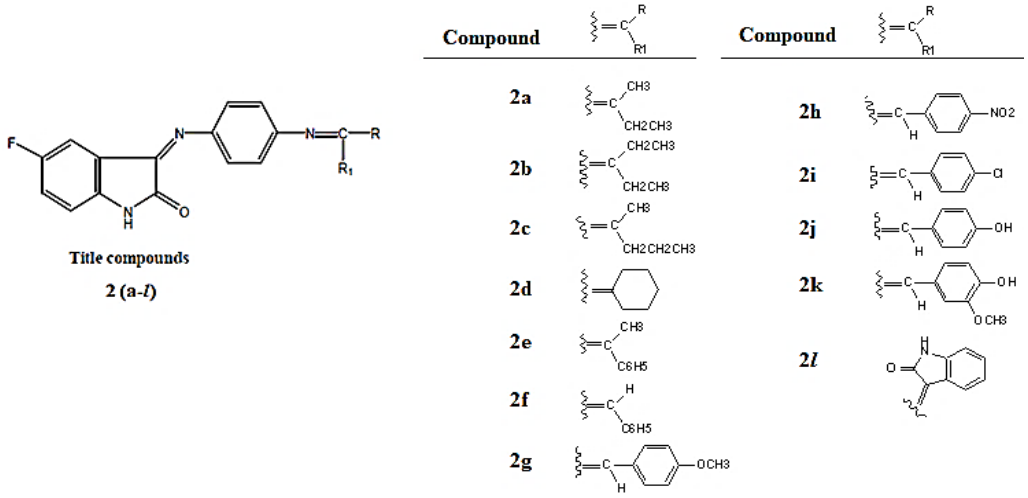


Figure (8): Different bis-Schiff bases of 5-fluoroisatin

Prakash *et. al.*, [55] synthesized new bis-Schiff bases of 5-nitroisatin (**3a-*l***) (Figure 9) by reaction of imesatin with various aromatic aldehydes. The chemical structures of the prepared bis-Schiff bases were established by IR, ^{1}HNMR, ^{13}C-NMR, elemental analysis, and mass spectroscopy. These compounds were evaluated for their antibacterial activity (*Staphylococcus epidermidis*,

Staphylococcus aureus, *Bacillus cereus*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*) and antifungal activity (*Aspergillus niger* and *Aspergillus fumigatus*) by the paper-disc diffusion method. Among the synthesized compounds, **3j** was identified to be the most powerful antimicrobial agent; this is maybe related to the inductive-withdrawal effect of the (NO_2) group in the phenyl ring in the 3rd position, and even in the 5th position of isatin moiety, which might enhance the lipophilic nature of the molecule.

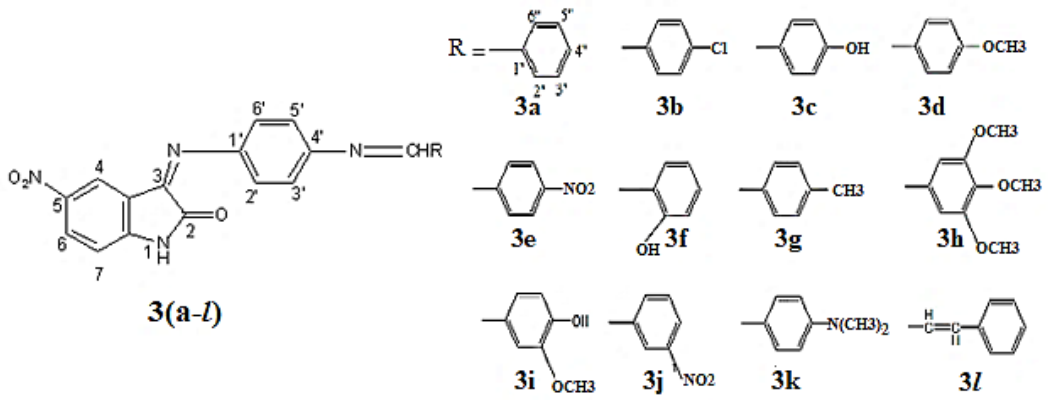
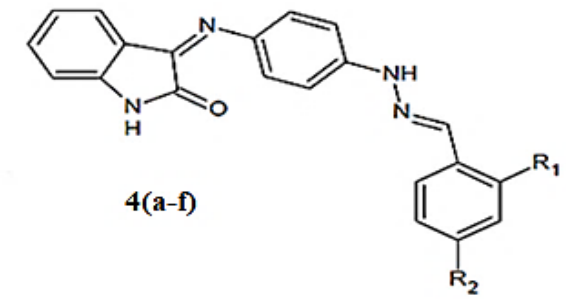


Figure (9): Bis- Schiff bases of 5-Nitroisatin (3a-*l*)

Mishra K. [56] reported the synthesis of **4(a-f)** bis- Schiff bases (Figure 10). All of these new compounds were tested for antibacterial efficacy against a variety of microorganisms (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*). The synthesized compounds exhibited moderate antibacterial activity compared with Ampicillin (standard drug), and compounds **4b** and **4e** were the most potent ones.



Compound	R1	R2
4a	H	H
4b	Cl	H
4c	OCH3	H
4d	OH	OH
4e	H	CH3
4f	H	N(CH3)2

Figure (10): Isatin bis-Schiff base derivatives 4(a-f)

Waddai *et. al.*, [57] revealed the synthesis of bis-imine base (ligand **5**) by the condensation of 2 moles of isatin and 1 mole of 2,3-diaminobutane (Figure 11), and the chemical structure of the ligand was approved by IR, ^{1}HNMR,^{13}CNMR, elemental analysis, UV-visible, mass spectroscopy. The bis-imine base (ligand **5**) coordinates with Co (II), Ni (II), and Cu (II) ions through carbonyl and imino groups resulting in metal ion complexes (**6-8**) (Figure 11). All these compounds were screened with two types of human pathogenic bacteria; *Escherichia coli*, and *Staphylococcus aureus* the most effective one is the bis-Schiff base -Cu complex (**8**).

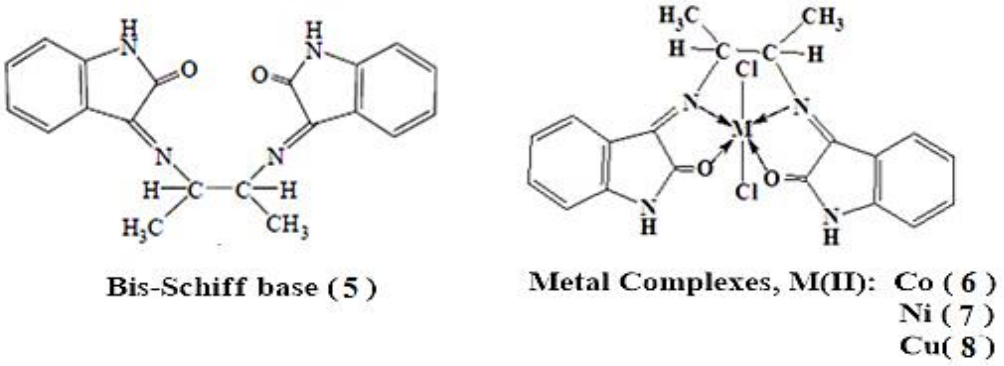
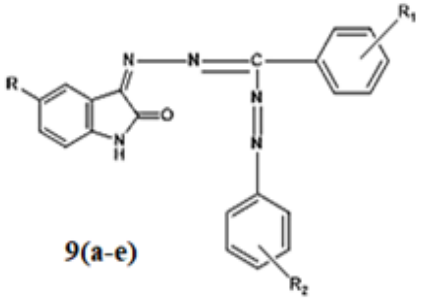


Figure (11): Schiff of Isatin and 2,3-diaminobutane, and its metal complexes.

The synthesis of azo bis-Schiff base derivatives of isatin (**9a-e**) (Figure 12) was established by Katherashala *et. al.* [58] and the chemical structures of the prepared compounds were analyzed by IR, ^{1}HNMR, and mass spectral analysis. All of the new compounds were examined for their antimicrobial potential effects by using the cup–plate technique. The results revealed that compounds **9a** and **9d** exhibited potent efficacy against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* compared with two standard drugs norfloxacin and griseofulvin.



compound	R	R_1	R_2
9a	H	4-Cl	H
9b	H	2-OH	H
9c	H	4N(CH_3)$_2$	H
9d	5-Cl	4-Cl	H
9e	5-Cl	2-OH	H

Figure (12): Derivatives of the azo bis-Schiff base of isatins 9(a-e)

Shukla *et. al*, [59] described the formation of the bis-Schiff base of isatin (ligand **10**) by condensation of isatin with 1,3-diamino propane in a 2:1 molar ratio, the bis-Schiff base (ligand **10)** was coordinated with palladium metal (Pd) through carbonyl group oxygen and azomethine-nitrogen to give the metal complex **(11)** (Figure 13). The Pd-complex showed better antibacterial effects toward *Staphylococcus aureus* and *Escherichia coli* when compared to the reference drug (chloramphenicol).

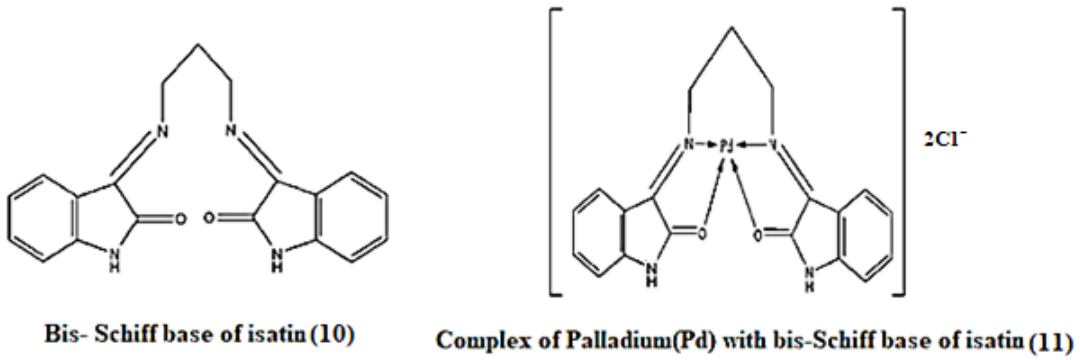


Figure (13): Bis-Schiff base of isatin and its Palladium complex

Kandile *et. al*., [60] synthesized new bis-Schiff base compounds that are built on oxindole moiety formed by condensation of 2 moles of 5-substituted isatins with 1 mole of diamines like 4,4'-diaminobiphenyl and 3,3′-dimethoxybenzidine to give bis N-[(1,3-dihydro)-2H-indol-2-one] 4,4′-diamino-1,1′-biphenyl derivatives (12a-e) and bis N-[(1,3-dihydro)-2H-indol-2-one] 3,3′-dimethoxybenzidine derivatives (13a-e), respectively. As well as bis N-[(1,3-dihydro)-2H-indol-2-one] pyridine 2,6-diamine derivatives(14a-e) by reaction of 5-substituted isatins with 2,6-diaminopyridine. The Mannich bases (15a-d) were prepared by condensation of the bis-Schiff bases (13a and 13b) with formalin and cyclic amines (Figure 14). The chemical structures of the new derivatives were evaluated based on FTIR, GC/MS, ^{1}H NMR, ^{13}C NMR spectral data, as well as CHNS analysis. The *in vitro* antimicrobial activity of the new compounds was estimated by using a broth dilution method for four bacterial species (*S. aureus, S. epidermidis, E. coli, and K. pneumonia*) and two fungal pathogens (*A. flavus* and *C. albicans*) and compared with two reference drugs (sulfamethoxazole and fluconazole). According to the obtained antimicrobial data; compound 12a had moderate activity against all examined microorganisms, while compounds (15a-d) had moderate activity against bacterial strains but were more active against fungus.

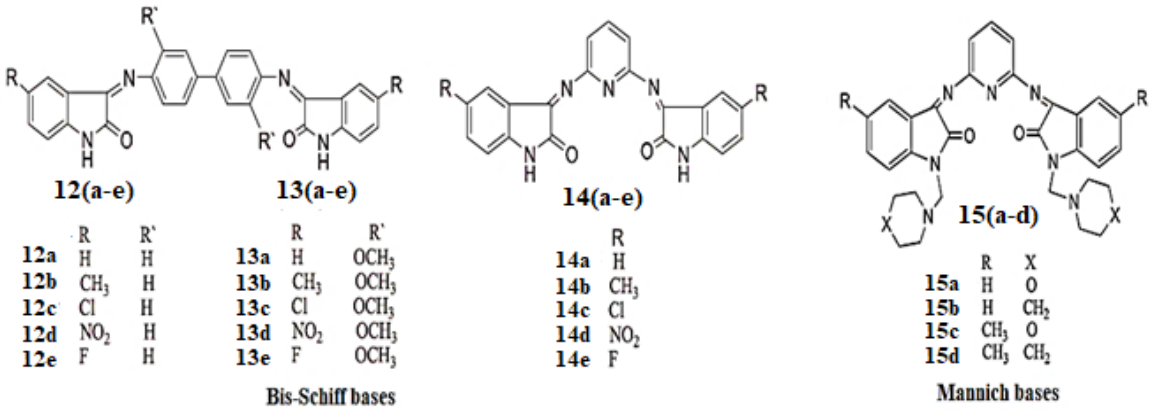


Figure (14): Bis-Schiff bases and Mannich bases of 5-substituted isatins with different aromatic amines

Al-Mudhafar *et. al.* [61] published the synthesis of three different bis-Schiff bases of isatins with thiophene-2-carboxaldehyde (16a-c) and Mannich base derivatives of these Schiff bases (17a-c and 18a-c) (Figure 15). The majority of the synthesized compounds had good antimicrobial activity against *S. aureus, E. coli, K. pneumonitis, P. aeruginosa*, and *Candida albicans*; however, the 5-methoxy isatin derivatives (16c, 17c, and 18c) exhibited significant activity against *S. aureus* when compared to the amoxicillin reference compound. The compounds 17a and 18c are the most active ones against *Candida albicans*.

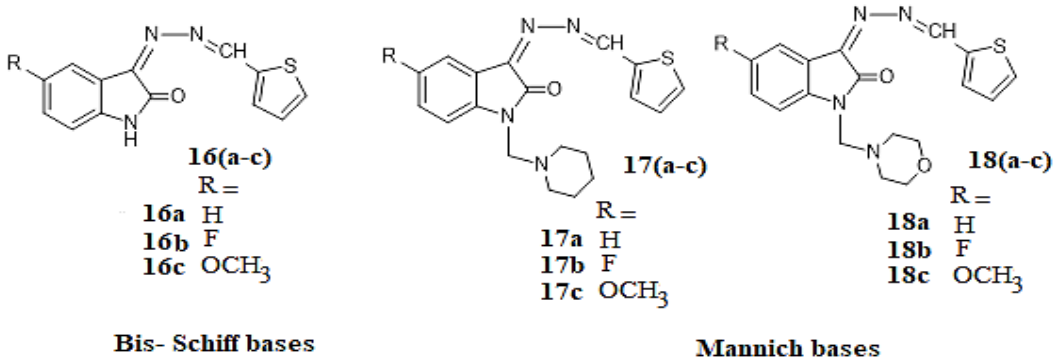


Figure (15): Bis-Schiff bases of isatins with thiophene-2-carboxaldehyde and their Mannich base derivatives

Al-Mudhafar *et. al.*, [62] synthesized four different azo-azomethine derivatives **(19a-d)** (Figure 16) by coupling reaction of diazotized compounds of different sulfonamides (sulfanilamide, sulfacetamide, sulfamethoxazole, and sulfadiazine) with isatin bis-Schiff base chemically named as 3-((4-nitrobenzylidene) hydrazono) indolin-2-one. The data from FT-IR, ^{1}H-NMR and CHNS elemental analysis proved their chemical structures. The antimicrobial activity of the produced azo compounds was tested employing a well-diffusion methodology against a variety of pathogens, including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Candida albicans*. The azo compounds were reported to have moderate activity against *Escherichia coli* and potent activity against *Candida albicans*, and **19b** being the most effective one of these azo compounds.

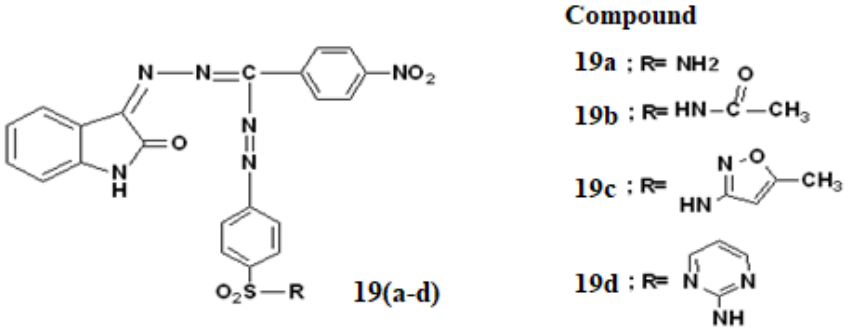


Figure (16): Azo-azomethine derivatives of isatin (19a-d)

Anti-tubercular activity

Sangamesh *et. al.* [63] described the chemical synthesis of the bis-Schiff base of isatin with p-dimethyl amino benzaldehyde **(20)** as well as its coordination complexes of Co (II), Ni (II), Cu (II), and Mn (II) derivatives **(21a-d)** (Figure 17). The chemical structure of the Schiff base and also its coordination complexes were confirmed by IR, magnetic, electronic, and different thermal and electrochemical studies. It was confirmed that the bis-Schiff base is biologically active as well as its metal (II) complexes, but the most active ones are **21c** and **21d** metal complexes which showed good activity compared with standard reference drug streptomycin as anti-tuberculosis against *Mycobacterium tuberculosis*.

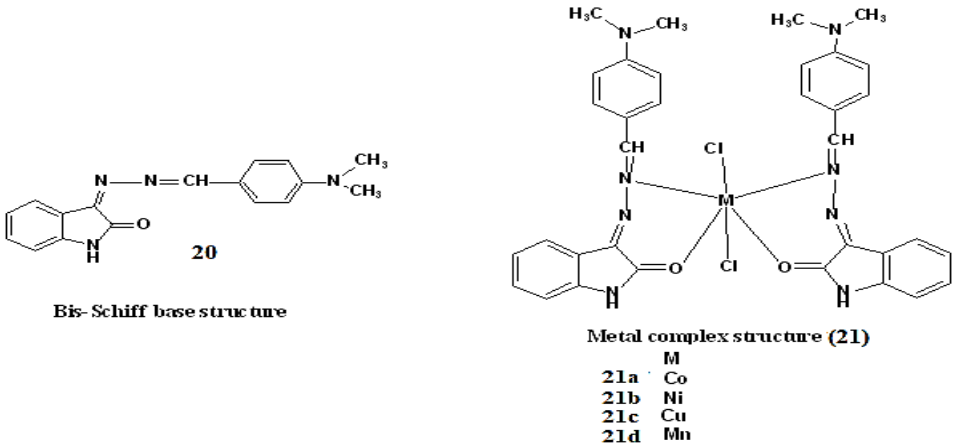


Figure (17): Bis-Schiff base of isatin with *p*-dimethyl amino benzaldehyde and its coordination complexes of Co (II), Ni (II), Cu (II), and Mn (II) derivatives

Rangaraju *et. al*. [64] reported the synthesis N-Benzyl isatin with *p*-phenylenediamine to yield N-benzyl imesatin, the latter compound was subjected to different substituted aromatic aldehydes to give new bis-Schiff bases (**22a-h**) as shown in figure 18. The spectral analysis by IR, ^{1}HNMR, and mass analysis was applied to confirm the structures of the synthesized compounds. All these compounds were evaluated for anti-mycobacterial activity *in vitro* towards *Mycobacterium tuberculosis* using Microplate-Alamar-Blue-Assay (MABA) technique. Most of these bis-Schiff bases have shown promising biological activity. However, compound **22e** showed a minimum inhibitory concentration (MIC) equal to 1.28 µg/mL of 71% inhibition of bacterial growth.

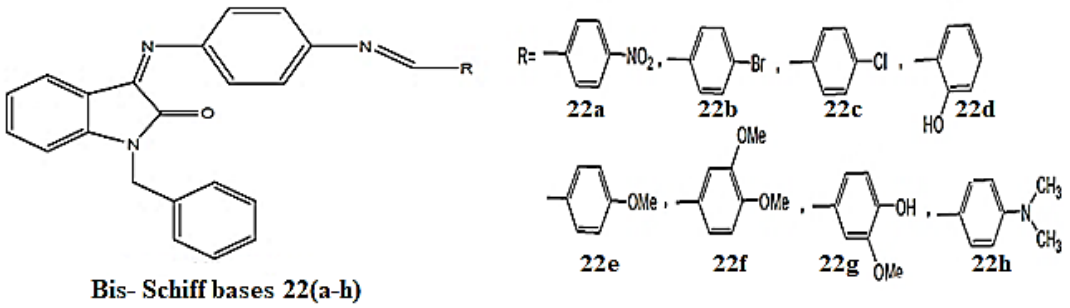
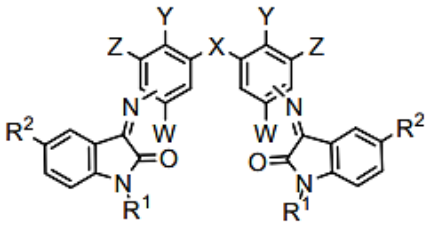


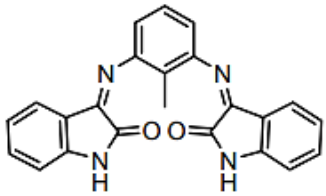
Figure (18): Bis-Schiff bases of N-benzyl isatin with anti-mycobacterial activity

Anticancer activity

The synthesis and characterization of bis-Schiff bases derivatives (23a-k and 24) of isatin, benzylisatin, and 5-fluoroisatin with various primary aromatic amines (Figure 19) were reported by Jarrahpour *et. al.* [65]. The antiviral activity of the synthesized compounds was tested against DNA and RNA panel viruses, and the lowest cytotoxic and viral inhibitory concentrations were identified, it was found that compounds 23c and 24 have the strongest cytotoxic effect in human erythroleukemia cell. There were no antibacterial or antifungal activities found in such bis-Schiff bases.



23(a-k)



24

Compd.	X	Y	Z	W	R^1	R^2
23a	CH_2	H	H	H	H	H
23b	CH_2	H	H	H	H	H
23c	CH_2	H	H	H	H	F
23d	CH_2	H	H	H	H	F
23e	CH_2	Cl	Et	Et	H	H
23f	CH_2	H	H	H	Bn	H
23g	CH_2	H	H	H	Bn	H
23h	O	H	H	H	H	H
23i	O	H	H	H	H	F
23j	O	H	H	H	Bn	H
23k	CO	H	H	H	H	H
24	-	-	-	-	-	-

Figure (19): Isatin, benzylisatin, and 5-fluoroisatin bis-Schiff bases derivatives

Pervez *et. al.* [66] created a variety of new bis-Schiff bases from isatin and 5-substituted isatin with 2,4-diaminotoluene (25a-g) (Figure 20) and their copper (II) complexes (26a-g) and screened them for their urease and cytotoxic inhibitory effect. The urease inhibitory action of compound 25b, which has a Br group at C5 of the isatin molecule, was determined to be the most powerful, with an IC_{50} of 0.04±0.004 µM, while 25f bis-Schiff base having a sulphonic acid group at C5 position was found to be the least potent one with IC_{50} =25.2 ±1.34 µM. *In vitro* cytotoxicity tests indicated that complexation of the bis-Schiff base ligands (25a-g) to Cu (II) showed improvement in their cytotoxic effect and among these copper complexes (26a-g); The complex 26d had a higher level of cytotoxicity against lung carcinoma (H157) cells because it had an electron-withdrawing chlorine group at C5 of the isatin molecule. Vincristine, a well-known anticancer medication, was employed as a standard against the new derivatives that were evaluated. Furthermore, in this analysis, these Schiff bases (25a-g) showed excellent urease inhibitory action, as well as 25(a-e) and 25g, have proven to be extremely potent urease inhibitors, notably better than the conventional inhibitor (thiourea).

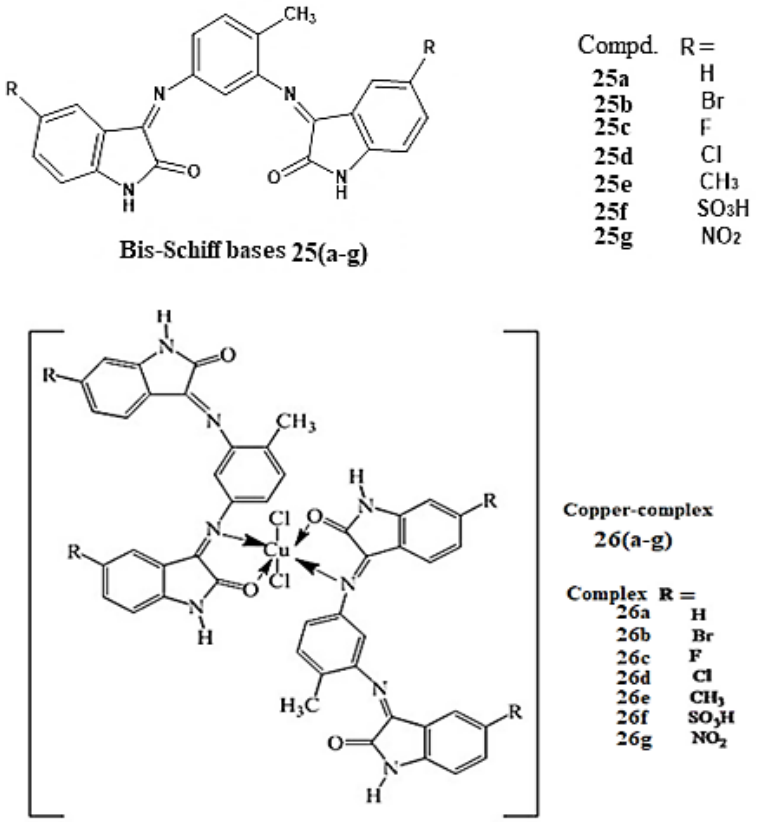


Figure (20): Bis-Schiff bases of isatin and 5-substituted isatin, and their copper (II) complexes

Meenakshi *et al.* [67] successfully synthesized a set of 5-sulfamoyl isatin bis-Schiff bases (27a-j) (Figure 21). IR, ^{1}H-NMR, and mass spectroscopic data were used to characterize all of the synthesized bis-Schiff bases. Moreover, the antitumor efficacy of these derivatives was determined by measuring the tumor size, and the number of viable and non-viable tumor cells. The obtained results were compared with the antitumor medication (5-Fluorouracil) and revealed that the derivatives, 27e, 27f, 27i, and 27j displayed significant antitumor efficacy.

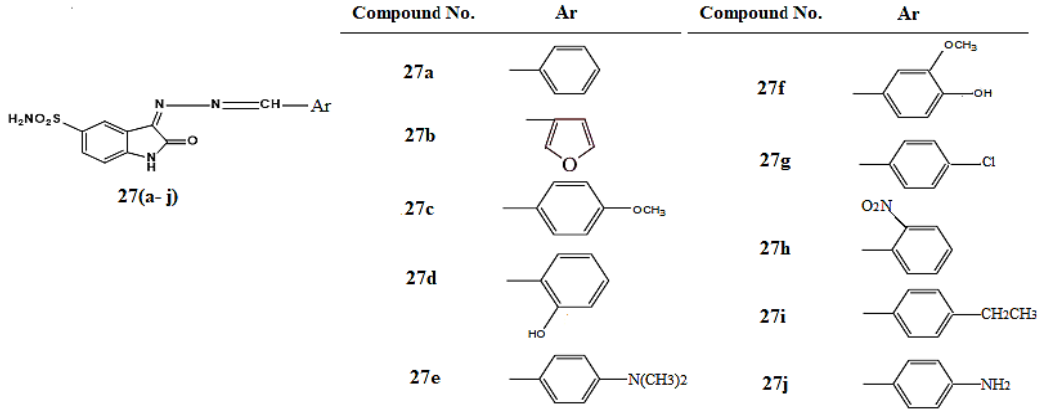
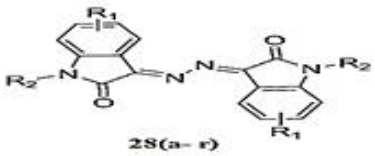


Figure (21): Bis- Schiff bases of 5-sulfamoyl isatin

Liang et. al., 49 described the synthesis of corresponding bis-Schiff base derivatives of several isatin analogs by condensing hydrazine and isatins (Figure 22). These compounds (28a-r) were assessed for anticancer activity in vitro and in vivo. In a

colorimetric MTT analysis on six human cancer cell lines (HeLa, SGC-7901, Hep-G2, U-251, and A-549) more than half of them demonstrated significant cytotoxicity when compared to 5-fluorouracil (5-FU) as a reference drug. In vitro, 28b was found to have more cytotoxic effect than 5-FU, with IC50 values of 4.23 µM for Hep-G2 cells, 12.66 µM for SGC-7901 cells, and 12.78 µM for A-549 cells, respectively. The preliminary SAR suggested that the anticancer activity of unsubstituted bis-isatin molecules at the N1 position and having 5, 5′ two electron-donating groups may be enhanced. Furthermore, 28b showed remarkable in vivo anti-tumor activity; it was revealed that a dose of 40 mg/kg of this compound is able significantly to inhibit tumor growth in HepS-bearing mice, which is more active than 5-FU.



Bis-Schiff bases	R_1	R_2
28a	H	H
28b	5-Me	H
28c	5-Br	H
28d	5-F	H
28e	5-Cl	H
28f	5-MeO	H
28g	7-F	H
28h	6-Cl	H
28i	6-F	H
28j	H	Et
28k	5-Me	Et
28l	5-F	Et
28m	H	Bn
28n	5-Me	Bn
28o	5-F	Bn
28p	H	i-Pr
28q	5-Me	i-Pr
28r	5-F	i-Pr

Figure (22): New bis-Schiff bases of isatin analogs having anti-cancer activity

In 2018, Ammar *et. al.* [68] produced a new morpholinosulfonyl isatin bis-Schiff base (Figure 23), this is done by treating p-phenylenediamine with 5-morpholinosulfonyl isatin to obtain bis (morpholino sulfonyl) 2-indolinone derivative **29**. HCT116, HepG2, MCF7, and CACO cancer cell lines were utilized to evaluate the anticancer activity of compound **29**, which was compared to the standard medicine, Doxorubicin (IC_{50} is equal to 4.5–8.28 µm). Regarding CACO, HepG2, and HCT116 cell lines, this new Schiff base revealed an IC_{50} value of less than 10 µm.

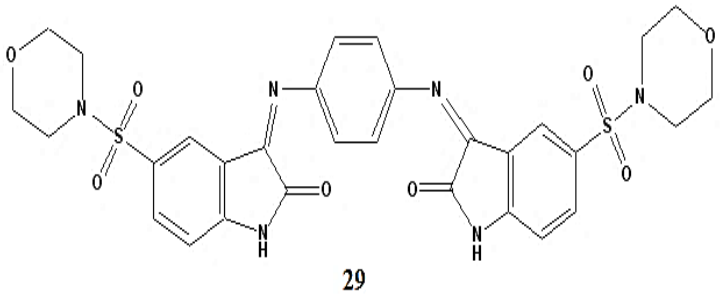


Figure (23): Bis (morpholino sulfonyl) 2-indolinone derivative with anticancer activity

Anti-inflammatory activity

Lingala *et. al.* [69] synthesized and analyzed various new bis-Schiff bases of 5-Sulfamoyl isatin (Figure24) for their anti-inflammatory activity. Compound **30d** exhibited potent anti-inflammatory activity compared to other produced bis-Schiff bases but was less active compared to Diclofenac sodium. Lingala S. *et. al.* observed that compound **30d** has strong

antibacterial action against *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Salmonella typhi*, as well as high antifungal efficacy towards *Fusarium oxysporum*, *Aspergillus flavus*, and *Penicillium notatum.*

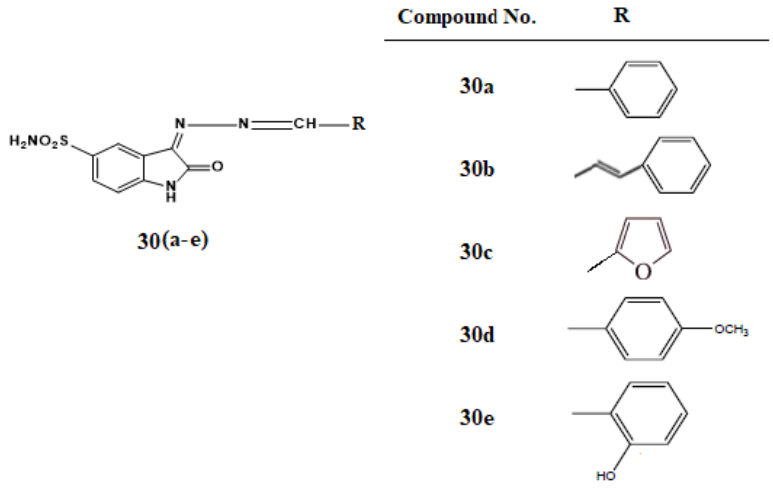


Figure (24): Bis-Schiff bases of 5 -Sulfamoyl isatin

Analgesic activity

The synthesis of new isatin bis-Schiff bases for different aromatic carbonyl compounds (**31a-*l***) (Figure 25) was reported by Chinnasamy *et al.* [70], and their chemical structures were confirmed spectroscopically. The analgesic activity was investigated using the tail-immersion technique at a dosage of 200mg/kg body weight; among the tested compounds (**31i**), was observed to have better analgesic activity in comparison to the reference compound (Pentazocine). It was noted that bis-Schiff bases incorporating electron-releasing substituents had greater analgesic activity than those containing electron-withdrawing substituents.

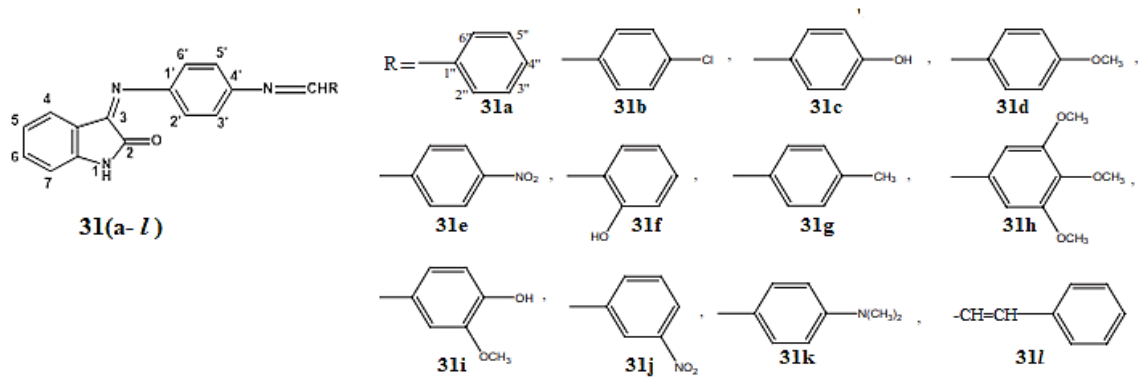


Figure (25): Bis- Schiff bases of isatin (31a-*l*) with analgesic activity

Nirmal *et. al*, [71] synthesized ten new bis-Schiff bases of 5-fluoro-2-oxindole (**32a-j**) (Figure 26). Spectral data (IR, 1H NMR, mass) and elemental analysis were used to characterize these new compounds. The analgesic and anti-inflammatory activities of the produced compounds were investigated, the observed results indicate that compounds **32b** and **32c** had a remarkable analgesic activity that was comparable to that of the reference medicine Diclofenac. Finally, the obtained results revealed that alkyl groups at the N-4 position have superior analgesic and anti-inflammatory properties than aryl groups in compounds (**32f**, **32g**, and **32i**).

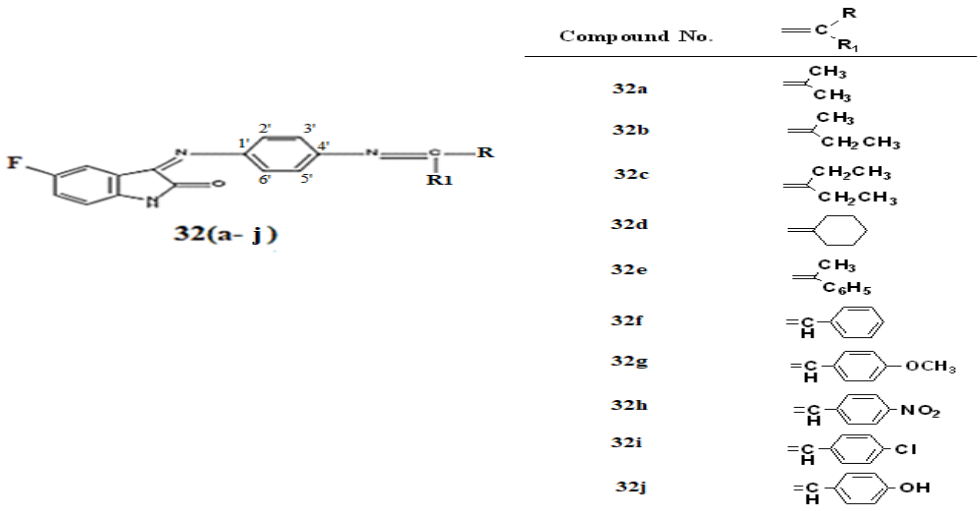


Figure (26): 5-fluoro-2-oxindole bis-Schiff bases (32a-j)

Panneerselvam *et. al,* [72] described the formation of novel bis-Schiff bases (**33 a-i** and **34a-c**) (Figure 27) by the condensation of 5-substituted imesatin derivatives with several substituted aromatic aldehydes. The tail immersion technique and carrageenan-induced paw edema methodology were applied to screen the produced compounds for their analgesic and anti-inflammatory properties, respectively. Among the synthesized bis-Schiff bases **33b**, **33h**, and **33i** were found to exhibit similar analgesic and anti-inflammatory properties, when compared with standard drugs (pentazocine and indomethacin), respectively. However, **33i** showed favorable analgesic and anti-inflammatory activity due to the high lipophilicity of the versatile pharmacophore. Compounds **33a, 33c, 33d,** and **33g** were found to show moderate analgesic activity. It is worth mentioning, Panneerselvam *et. al.* found that **33h** exhibit potent antimicrobial activity compared with two standard drugs (ciprofloxacin and ketoconazole) against different pathogens; *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Bacillus cereus*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Aspergillus niger*, and *Aspergillus fumigatus.*

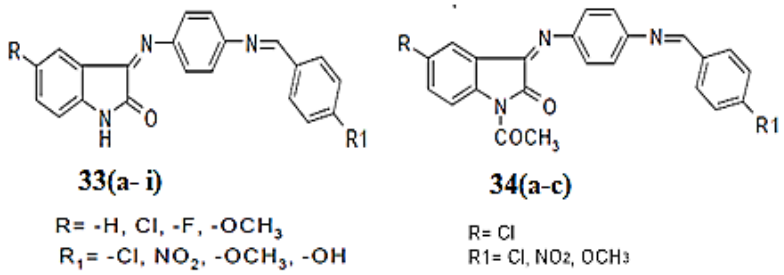


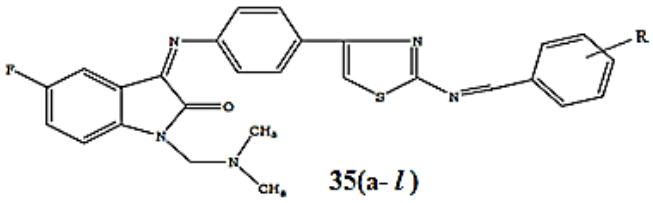
Figure (27): Novel bis-Schiff bases of analgesic activity

Analgesic and anti-inflammatory activity

Prakash *et al.* [73] prepared a series of 5-fluoroindolin-2-one bis- Schiff and Mannich base derivatives using various aromatic aldehydes with 5-fluoroisatin derivatives (Figure 28). By using IR, ^{1}H-NMR, Mass spectra, and elemental analyses, the chemical structures of the synthesized bis-Schiff bases were verified. All the tested derivatives **35a-35*l*** were evaluated for their analgesic activity by tail-flick technique, The compound **35a** of an unsubstituted benzene ring derivative demonstrated modest analgesic and anti-

inflammatory activities when compared to a reference medication (diclofenac).

The substituted derivatives lead to an increase of lipophilicity (35b, 35d, 35g, and 35h) demonstrating the increased activity, with 35b and 35g being stronger than the prescribed medication, on other hand, the addition of a NO_2 or OH group to the phenyl ring reduces its activity, which could explain by its low lipophilicity With improved lipophilicity, the compounds 35d and 35h showed equivalent action compared with the Diclofenac; however, methyl (35b) and chlorine (35g) analogs placed at the *p*-position exhibited superior activity and potency than Diclofenac. The activity was significantly reduced when an OCH_3, NO_2, or OH group was inserted. Moreover, these synthesized compounds were subjected to antimicrobial assessments; both 35b and 35k showed moderated activity, while compounds 35d and 35g showed notable activity compared to ciprofloxacin and ketoconazole as standard drugs.



compd.	R
35a	H
35b	4-CH_3
35c	4-OH, 3-OCH_3
35d	4-$N(CH_3)_2$
35e	4-OCH_3
35f	3,4,5-$(OCH_3)_3$
35g	4-Cl
35h	2-Cl
35i	4-NO_2
35j	3-NO_2
35k	4-OH
35l	2-OH

Figure (28): Series of 5-fluoroisatin bis- Schiff and Mannich base derivatives

Anticonvulsant activity

Prakash, *et al.* [74] developed another new set of bis- Schiff bases of 3-(4-(benzylidene- amino) phenylimino) -2-indolinone derivatives (Figure 29) by reacting isatin and 1,4-benzenediamine with numerous aromatic aldehydes under the influence of anhydrous acetic acid. All the prepared compounds were examined for anticonvulsant activity using the maximal electroshock seizure (MES) test. It was found that the compounds having electron-releasing groups like methyl, methoxy, hydroxy, as well as dimethylamino, demonstrated good anticonvulsant properties, among the prepared of these bis-Schiff bases the compound 36h showed excellent anticonvulsant activity.

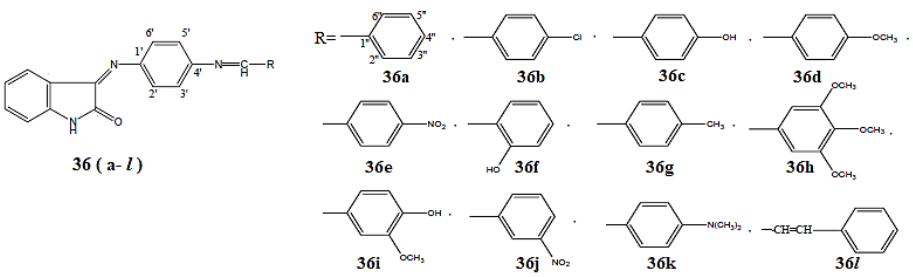


Figure (29): Bis- Schiff bases of 3-(4-(benzylideneamino) phenylimino) -2-indolinone derivatives

Kulkarni *et. al*. [75] synthesized bis-Schiff base derivatives (37a and 37b) of Lamotrigine with isatin and 5-chloroisatin (Figure 30) to get more potent anticonvulsant agents, the new derivatives were spectroscopically evaluated. Anticonvulsant efficacy of these two derivatives was assessed by (Maximal electroshock seizure) MES methodology using Lamotrigine and Phenobarbital as standard medications. The observed results summarized that the synthesized two compounds showed better anticonvulsant activity than Lamotrigine.

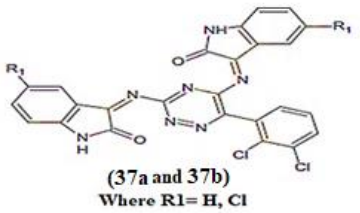


Figure (30): Lamotrigine and isatins' bis-Schiff bases

Antioxidant activity

The reaction of imesatins with various aromatic aldehydes created six bis-Schiff bases (38a-f) (Figure31) was reported by Prakash *et. al.* [20]. The IR, 1H-NMR, mass spectroscopy, and elemental analysis were used to analyze the chemical structures of the new bis-Schiff bases. DPPH radical scavenging activity has been used to evaluate these derivatives for antioxidant activity. It has been found the compound (38c) showed the greatest antioxidant activity due to the presence of the electron-releasing group (–N $(CH_3)_2$).

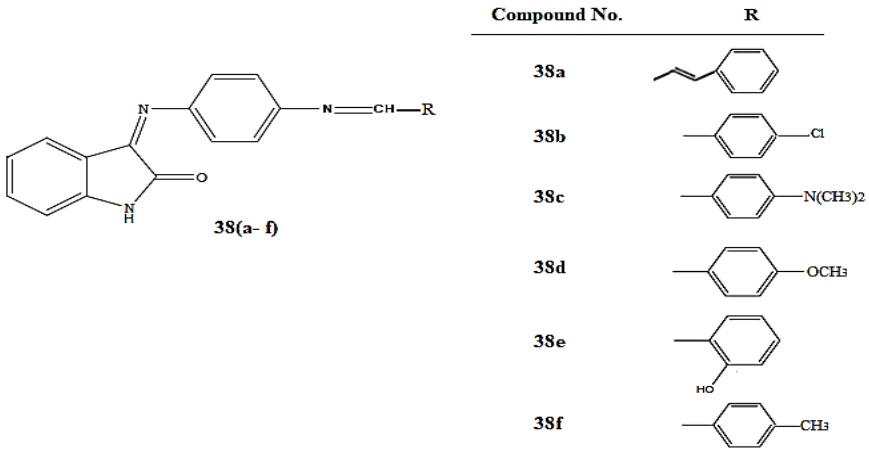
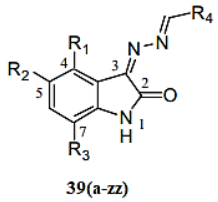


Figure (31): Bis-Schiff bases (38a-f)

Antioxidant and antiglycation activities

Khan *et. al.*, [76,77] synthesized twenty-seven derivatives of bis-Schiff bases of isatins (39a-zz) (Figure 32) and evaluated them *in vitro* for their antioxidant activity and antiglycation potential. It has been found that compounds 39g, 39m, and 39p showed good antioxidant activity when compared to standard compound *n*-propyl gallate, while compounds 39g and 39u showed a potent antiglycation activity better than the standard compound (rutin). Finally, compound 39g was found to have a dual inhibitory potential, both as an antioxidant as well as an antiglycation agent.



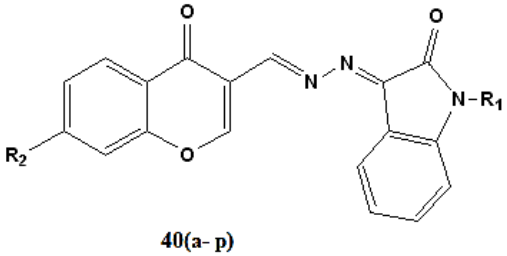
39(a-zz)

Compounds	R_1	R_2	R_3	R_4
39a	H	H	H	
39b	H	H	H	
39c	Cl	H	Cl	
39d	H	H	H	
39e	H	H	H	
39f	H	H	H	
39g	H	H	H	
39h	H	H	H	
39i	H	H	H	
39j	H	H	H	
39k	H	H	H	
39l	Cl	H	Cl	
39m	H	H	H	
39n	H	H	H	
39o	Cl	H	Cl	
39p	H	H	H	
39q	H	H	H	
39r	Cl	H	Cl	
39s	H	H	H	
39t	H	H	H	
39u	H	H	H	
39v	H	H	H	
39w	H	H	H	
39x	H	Cl	H	
39y	H	Cl	H	
39z	H	Cl	H	
39zz	H	Cl	H	

Figure (32): Bis-Schiff's bases of isatin analogs with antioxidant and antiglycation activities

Anti-diabetic activity

Wang *et. al*. [78], developed and synthesized a novel set of chromone-isatin derivatives (40a–p) (Figure33), then evaluated their *in-vitro* α-glucosidase inhibitory efficacy. The inhibitory activity of the synthesized bis-Schiff bases in the range of IC_{50} = 3.18 ± 0.12 to 16.59 ± 0.17 µM of excellent efficacy when compared to the reference medication (acarbose) having IC_{50} equal to 817.38 ± 6.27 µM. The compound 40j (IC_{50} = 3.18 ± 0.12 µM), was reported to be the most active derivative, bearing a 4-bromophenyl group at the N- position of isatin and an OH group at the seventh position of chromone. A molecular docking study was performed to examine the possible binding manner of these derivatives with the active region of the enzyme. The research's findings propose that these new compounds could be employed as lead molecules for the creation of additional α-glucosidase inhibitors.



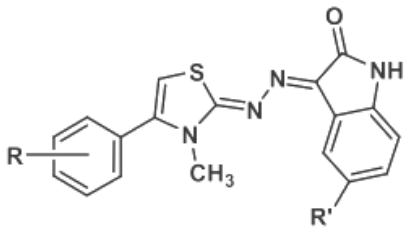
40(a- p)

Compound	R_1	R_2
40a	4-bromobenzyl	H
40b	methyl	H
40c	4-chlorobenzyl	H
40d	H	H
40e	3-fluorobenzyl	H
40f	2-fluorobenzyl	H
40g	4-fluorobenzyl	H
40h	2-chlorobenzyl	H
40i	2,4-dichlorobenzyl	OH
40j	4-bromobenzyl	OH
40k	4-chlorobenzyl	OH
40*l*	3-fluorobenzyl	OH
40m	2-fluorobenzyl	OH
40n	4-fluorobenzyl	OH
40o	2-bromobenzyl	OH
40p	2-chlorobenzyl	OH

Figure (33): Chromone-isatin derivatives with α-glucosidase inhibitory activity

Anti-viral activity

Meleddu *et. al*. [79] designed and prepared a variety of 3- 3- 2- [2- 3-methyl- 4- phenyl - 2, 3-dihydro-1,3 -thiazol-2 -ylidene] hydrazin-1- ylidene - 2, 3 -dihydro-1Hindol-2-one derivatives (Figure34) to evaluate their potency on both (Human Immunodeficiency Virus type 1) HIV-1 and (Reverse Transcriptase) RT-associated functions. The researchers analyzed the effects of introducing a chlorine atom in the 5th position of the isatin moiety as well as a methyl group in the 3rd position of the dihydro-thiazole ring of the newly prepared derivatives would be effective against both ribonuclease H and DNA polymerase within the µM range of concentration. Moreover, the biological activity of these derivatives was determined by the nature of the aromatic ring substitution at the 4th position of thiazole moiety. Finally, this study revealed that the most active compounds are 41g and 42e against both RNase H and RT- associated enzymatic functions RDDP.



41(a- *l*) and 42(a- *l*)
Schiff bases

Compound	R	R'	Compound	R	R'
41a	4-Cl	H	42a	4-Cl	5-Cl
41b	4-F	H	42b	4-F	5-Cl
41c	4-Br	H	42c	4-Br	5-Cl
41d	4-NO2	H	42d	4-NO2	5-Cl
41e	4-C6H5	H	42e	4-C6H5	5-Cl
41f	4-CN	H	42f	4-CN	5-Cl
41g	2,4-F	H	42g	2,4-F	5-Cl
41h	3-NO2	H	42h	3-NO2	5-Cl
41i	3,4-Cl	H	42i	3,4-Cl	5-Cl
41j	4-CH3	H	42j	4-CH3	5-Cl
41k	4-OCH3	H	42k	4-OCH3	5-Cl
41*l*	H	H	42*l*	H	5-Cl

Figure (34): Bis-Schiff bases of isatin-thiazole derivatives with antiviral activity

Discussion:

Finally, in this review, broad spectrums of biological and medicinal properties of isatin bis-Schiff bases compounds were investigated. Many bis-Schiff bases have been created with different substituents at any position of isatin basic structure or the other parts of the bis-Schiff bases to achieve effective and selective pharmaceutical agents. The γ lactam's characteristics were modulated by a variety of substituents at N1, C3, and C5, C6, or C7 in the aromatic moiety of isatin seem to be the most promising, as well as the presence of two imine groups which are bioactive linkers will increase the binding susceptibility to the active components of microorganisms by hydrogen bonding (Figure 35).

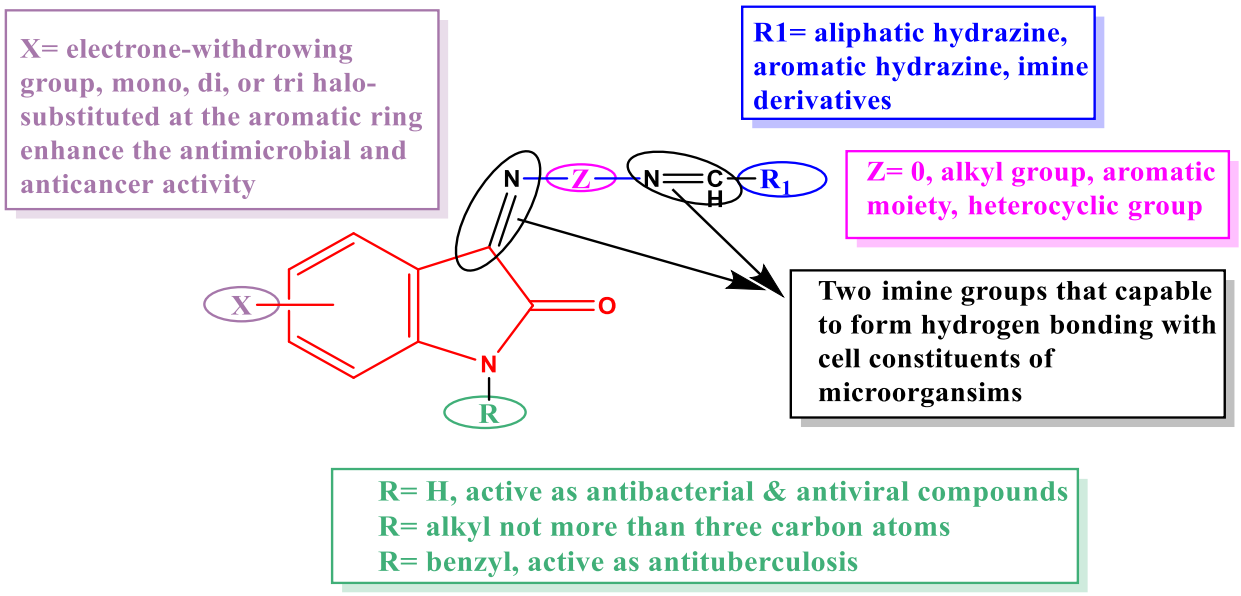


Figure (35): A summary of the biological structure-activity relationship of isatin bis-Schiff bases derivatives.

Conclusion:

Isatin molecule and its derivatives are significant scaffolds in drug development, with a wide spectrum of pharmacological effects. This is due to the ability of the isatin molecule to bind with receptors at several sites and can translate activity through various methods.

To obtain different activities, isatin derivatives rely on substitution at two different positions (N-1 and C-2) and electrophilic substitutions mainly at the fifth position. Several of these derivatives have been shown to have anticancer, antiviral, antibacterial, antifungal, and anti-inflammatory action, indicating that isatin-conjugated molecules have the potential to become therapeutic candidates.

Many mechanisms have been presented to explain the action path of Schiff base on microorganisms, which vary depending on the metabolic process and cell wall structure. The first hypothesis is that the organism's cell wall is disrupted as a result of hydrogen bonding between imine groups and active centers of cell constituents, then interfering with normal cell function. The second hypothesis involves the denaturation of one or more cell proteins, which impairs normal cellular functions. Another mechanism is based on the capacity of imine groups to form complexes with metals like Mg^{2+}, Zn^{2+}, and Ca^{2+}, which are necessary for bacterial metabolic processes and growth.

The bis-Schiff bases of isatin supply the molecule by two imine groups (-C=N-) that can bind more efficiently with the cell wall of bacteria and other proposed mechanisms of action, resulting in enhancement of biological effects will take place. More knowledge about the chemical structure of these molecules and their interactions with certain receptor sites in the biological system is required for the designing of new derivatives that can be used for the treatment of different serious diseases.

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