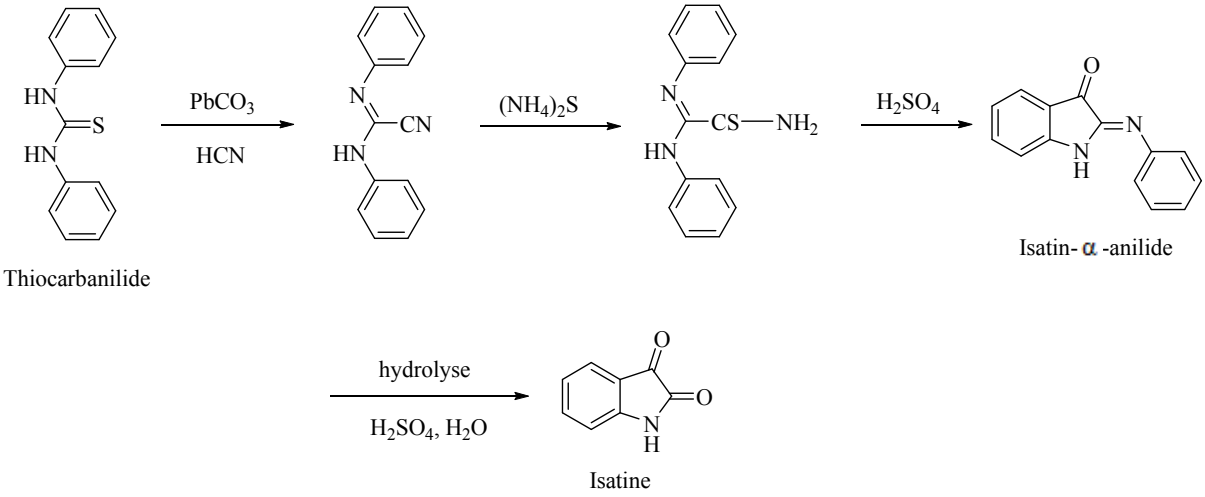
Chapter I: Bibliography

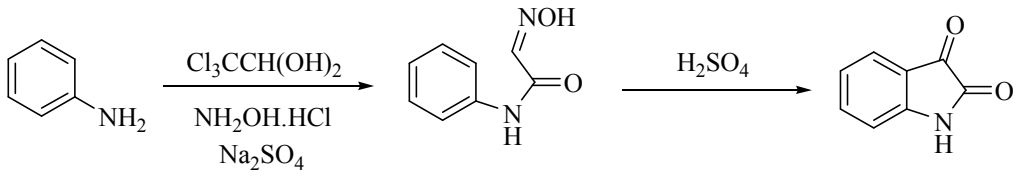
I. Synthesis of isatin

Isatin is generally synthesized from aniline and its derivatives. Although isatin was previously prepared by different authors,[10] the two procedures developed by **Sandmeyer** (1903-1919) were the most accomplished. The first method involves a thiocarbanilide which, by reacting with lead carbonate and hydrogen cyanide gives anilil nitrile, the latter treated with ammonium sulphide and cyclized with sulfuric acid leads to isatin-α-anilide hydrolyzed directly to isatin as depicted in Scheme 1.[10]



Scheme 1. Synthesis of isatin by the 1st method of Sandmeyer.

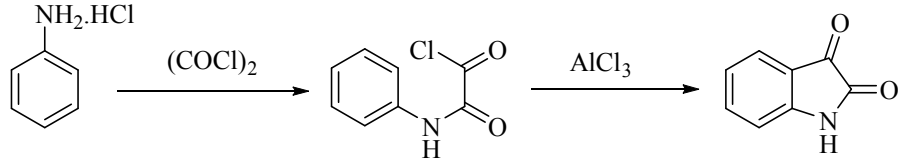
The second and most widely used method involves the formation of an isonitrosoacetanilide from aniline, chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate.[1,11] After isolation, the isonitrosoacetanilide is cyclized to isatin by treatment with concentrated sulfuric acid, or, less frequently, by treatment with polyphosphoric acid,[12,13] or by heating in $BF_3.Et_2O$ at 90°C, and then adding water to give the corresponding isatin[14] (Scheme 2). This method also applies to anilines with electron withdrawing groups such as fluoroanilines.[1]



Scheme 2. Synthesis of isatin by Sandmeyer's 2nd method.

Several isatin derivatives have been prepared according to the Sandmeyer protocol because the starting materials are inexpensive, safe to handle, stable and the yields are usually high.[15-23] This method has undergone some modifications such as the introduction of ethanol as a co-solvent in the preparation stage of isonitrosoacetanilides,[24,25] the use of microwave irradiation,[26] the use of 2,2,2-trichloro-1-ethoxyethanol in place of chloral hydrate[27] or a two-step synthesis of isonitrosoacetanilides which involves the acylation of the anilines with 2,2-diacetoxyacetyl chloride, followed by a reaction of the resulting 2,2-diacetoxy acetanilide with hydroxylamine hydrochloride in aqueous ethanol.[28]

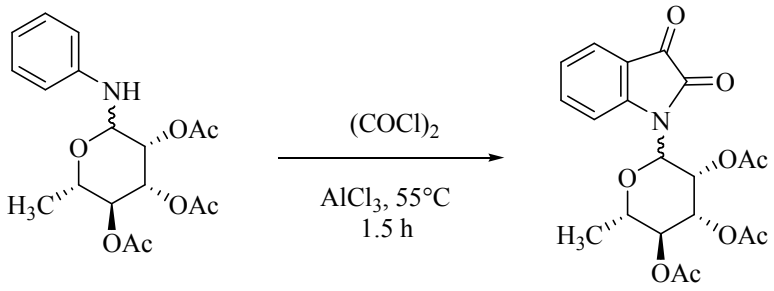
Another method, the most used after the Sandmeyer synthesis, is the **Stolle** method.[29,30] In this method an aniline, generally in its hydrochloride form, reacts with oxalyl chloride to give a chlorooxalylanilide intermediate, which, by cyclization in the presence of a Lewis acid, such as aluminum chloride, $BF_3.Et_2O$[31] or $TiCl_4$[32] gives the corresponding isatin (Scheme 3).



Scheme 3. Synthesis of isatin by the Stolle method.

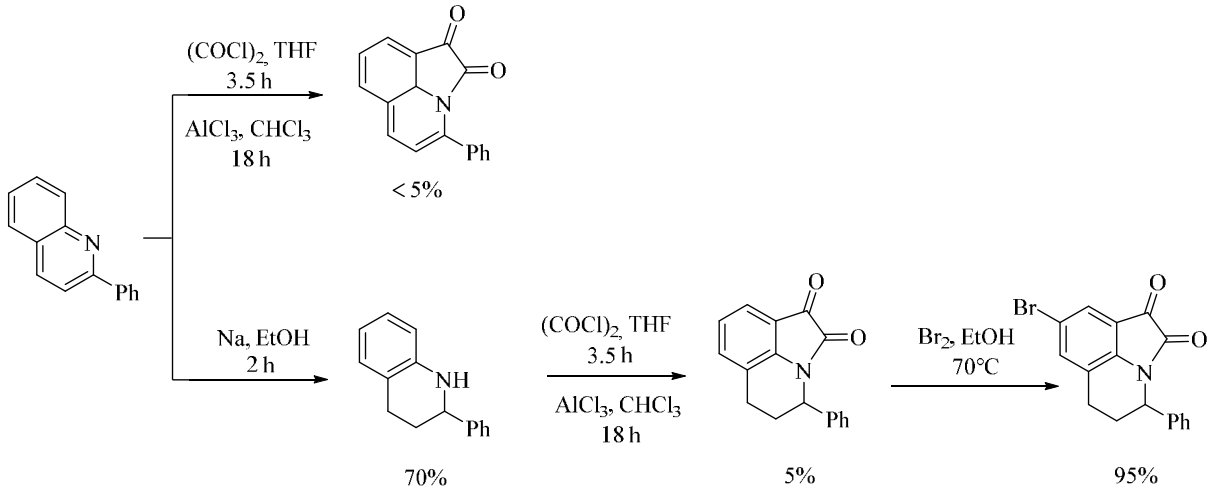
Dimethoxyanilines went through cyclization spontaneously to give dimethoxyisatines in the absence of Lewis acids, which is probably due to the activation of the ring towards electrophilic attack by the presence of methoxy groups.[33-35] This method (Stolle's synthesis) has been used for the preparation of several heterocyclic compounds *via* 1-arylisatin[36] and polycyclic isatins.[37,38]

A step in the synthesis of the first indirubin-*N*'-glycosides, which exhibits significant antiproliferative activity against various human cancer cells, is based on the Stolle procedure (Scheme 4).[39]



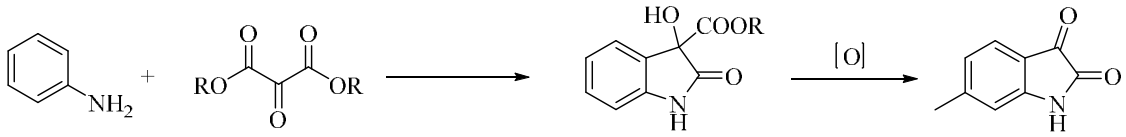
Scheme 4. A step in the synthesis of indirubin-*N'*-glycosides based on the Stolle reaction.

Matesic et al. used the Stolle synthesis for the preparation of some polycyclic derivatives of isatin, albeit, the compounds were obtained with low yields (Scheme 5).[40]



Scheme 5. Preparation of polycyclic derivatives by the Stolle synthesis.

The **Martinet** synthesis of 1*H*-indol-2,3-dione is a reaction between a substituted aromatic amine and the ethyl or methyl ester of mesoxalic acid to form a dioxindole, followed by an oxidation reaction to yield isatin (Scheme 6).[41]

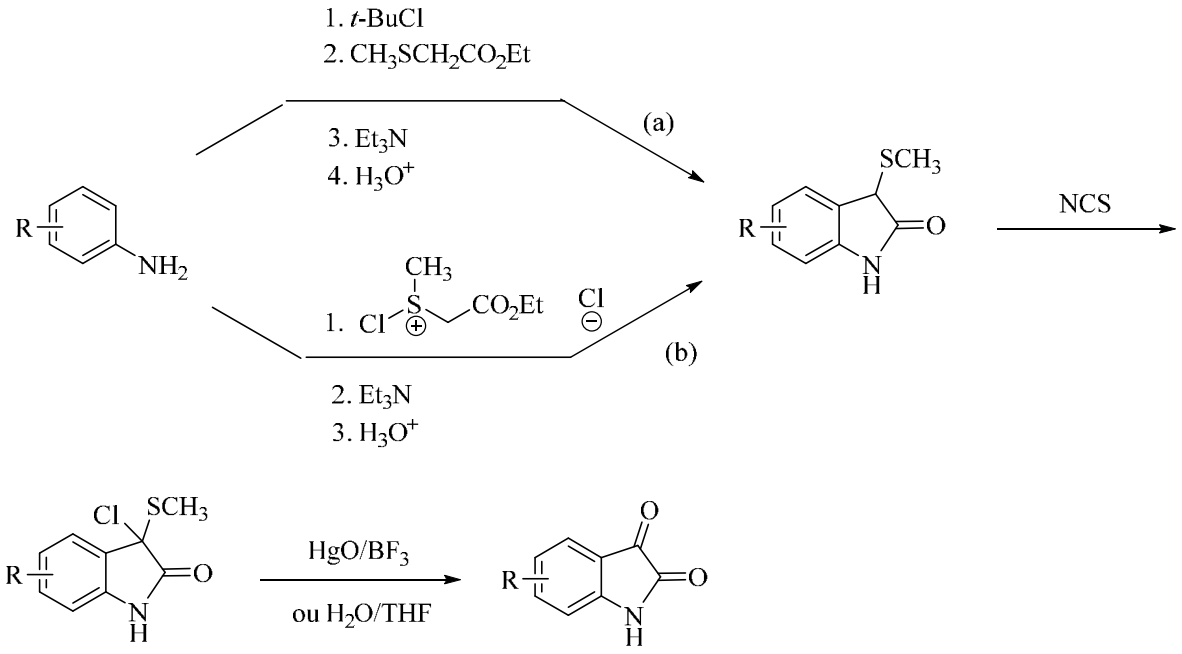


Scheme 6. Synthesis of Martinet of isatin.

This method was applied to the synthesis of various substituted isatins,[42] benzoisatins,[43] and analogs of (*E*)-styrylisatin.[44]

In the **Gassman** method, the anilines are first converted to 3-methylthiooxindoles. The oxidation of the methine carbon in the third position of 3-methylthiooxindoles with *N*-

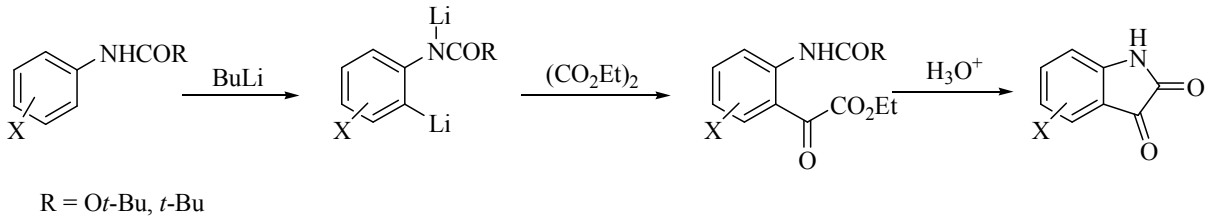
chlorosuccinimide, followed by hydrolysis of the chlorinated intermediate, provides the corresponding isatins.[45] Two methods for the conversion of anilines to 3-methylthiooxindoles have been reported. When electron withdrawing groups are present in the starting aniline, these derivatives may be synthesized *via* an intermediate *N*-chloroaniline, the latter is further reacted with a methylthioacetate ester to provide an azasulfonium salt (method (a), Scheme 7). For electron donating groups, the chlorosulfonium salt was prepared and then treated with the appropriate aniline (Method (b), Scheme 7).[46,47]



Scheme 7. Synthesis of isatin according to Gassman.

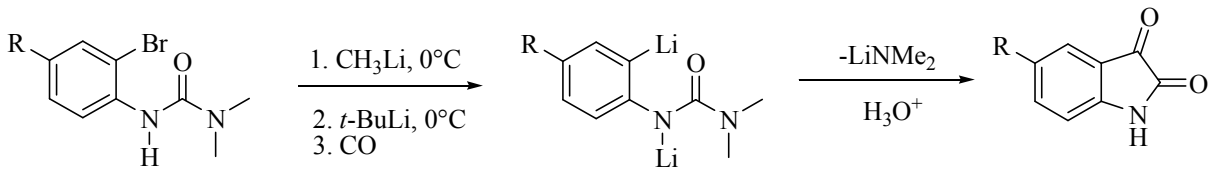
This method (Gassman) is compatible with the presence of electron donating or electron withdrawing substituents on the starting aniline.

The foregoing methods suffer from a lack of regioselectivity, particularly in the case of *meta*-substituted anilines, in which a mixture of 4 and 6 substituted isatins is obtained. A method has been developed by Hewawasam and Meanwell[48] for the regiospecific conversion of substituted anilines into isatin. The method utilizes the reaction of an *ortho*-lithiated protected aniline derivative (when the amino group of aniline is protected, it can direct the metallization to the *ortho* position) with diethyl oxalate to provide an α-ketoester. Deprotection of the amino group is accompanied by cyclization to provide isatin (Scheme 8).



Scheme 8. Synthesis of isatin by Hewawasam and Meanwell.

Smith et al. have also synthesized isatin and its 5-substituted derivatives with very good yields (71-79%) from *N*'-(2-bromoaryl)-*N*,*N*-dimethylureas by a bromine-lithium exchange, followed by treatment with carbon monoxide (Scheme 9).[49]



Scheme 9. Synthesis of isatin by Smith et al.

II. Schiff bases of isatin as antimicrobial agents

Schiff bases of isatin have drawn a lot of attention due to their diverse biological activities. Here some publications focusing on the antimicrobial activity are described.

Chhajed and Padwal prepared Schiff bases by reacting isatin and 5-chloroisatin with 5-amino-8-hydroxyquinoline.[3] The *N*-Mannich bases of these compounds were synthesized by a condensation reaction with formaldehyde and several secondary amines (Fig. 1). The compounds were screened for their antibacterial and antifungal activities by cup-plate method. Sulfamethaxozole and Ketoconazole were used as standards. The compounds showed moderate activities.

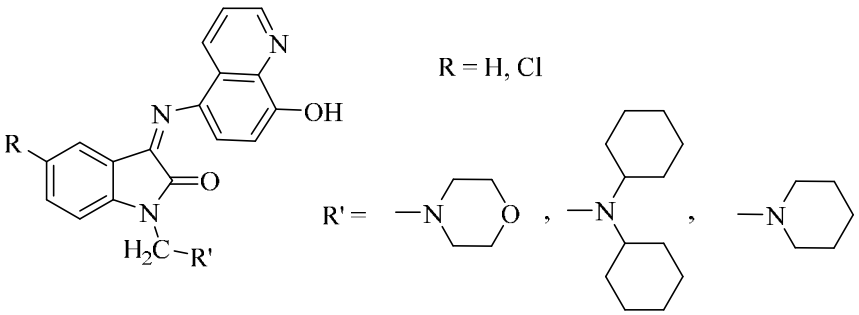
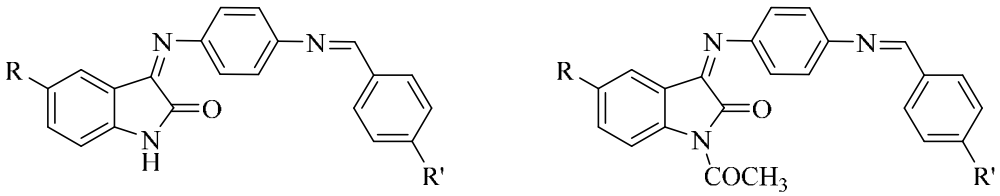


Fig. 1

In another study, new Schiff bases were synthesized by a condensation between substituted isatin and *N*-acetylisatin with different aromatic aldehydes (Fig. 2).[4] The compounds were studied for their analgesic, anti-inflammatory and antibacterial activities by paper disk diffusion technique. The minimum inhibitory concentrations (MICs) of the compounds were also determined by the dilution method. Most of the synthesized compounds exhibited significant antibacterial and antifungal activities. Among the compounds synthesized, the compound prepared from 5-fluoroisatin exhibited good analgesic and anti-inflammatory activities.

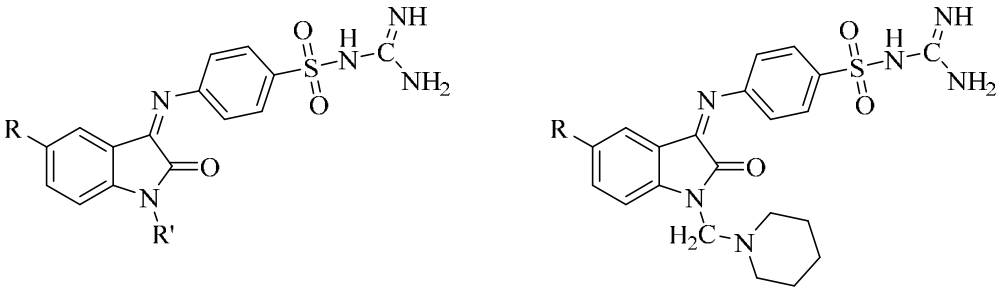


R = H, Cl, F, OCH_3

R' = Cl, NO_2, OCH_3, OH

Fig. 2

Singh et al. reacted simple and substituted isatin with 4-amino-*N*-carbamimidoylbenzenesulfonamide to form a series of Schiff bases.[5] The Mannich bases of these compounds were synthesized by reacting them with formaldehyde and piperidine (Fig. 3). The antimicrobial activity was evaluated by tube dilution method. The compounds showed better antibacterial activity than the reference drug (4-amino-*N*-carbamimidoylbenzenesulfonamide). None of the compounds showed significant antifungal activity comparable to that of the conventional drug Clotrimazole against *Saccharomyces cerevisiae* and *Candida albicans*.



R = H, 5-Br, 5-NO_2, 5-Me, 5-Cl

R' = H, Me, COMe

R = H, 5-Br, 5-NO_2, 5-Me, 5-Cl

Fig. 3

Chaluvaraju and Zaranappa prepared a series of isatin derivatives using Schiff and Mannich reactions (Fig. 4).[6] Antimicrobial properties were investigated against *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhi*, *Escherichia coli*, *Aspergillus niger* and *Candida albicans* by cup plate method using amoxicillin and fluconazole as references. All the compounds tested showed moderate activity.

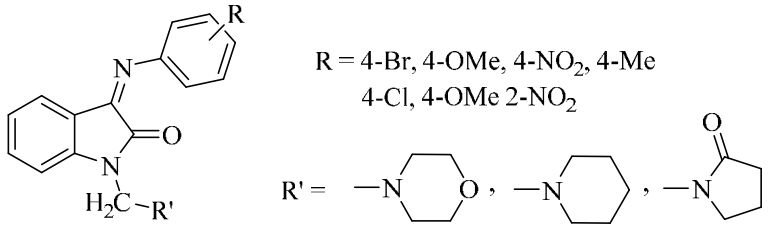


Fig. 4

A new series of Schiff bases of *N*-nitrosoisatin was prepared by Kumar and Parthiban (Fig. 5).[7] The compounds were tested for their antibacterial activity and as antifungal agents. The minimal inhibitory concentrations of the compounds were also determined by the dilution method. *N*-nitroso-5-bromo-3-(4-bromophenylimino)-indolin-2-one was found to be the most potent antimicrobial agent with a MIC of 18, 19, 17, 20 and 24 μg/mL against *E. coli*, *S. typhi*, *B. subtilis*, *S. aureus* and *A. niger*, respectively.

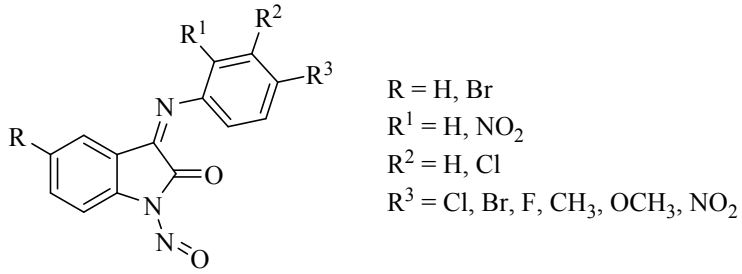
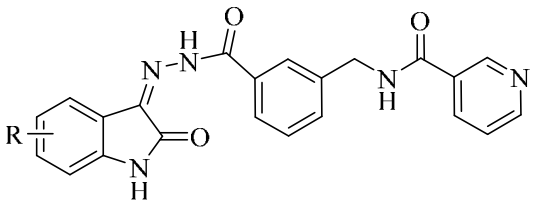


Fig. 5

In another study, a new *N*-[3-(2-oxo-1,2-dihydro-indol-3-ylidene-hydrazinocarbonyl)-benzyl]nicotinamide was synthesized by the condensation of different isatin derivatives with *N*-(3-hydrazinocarbonylbenzyl)nicotinamide (Fig. 6).[50] The study of the antimicrobial activity of the compounds was carried out by the disk diffusion technique. Of all the compounds tested, the compound with 5-F and 5-CH_3 gave the best results.



R = H, 5-Cl, 5-Br, 5-CH_3, 5-F, 5-NO_2, 5-I, 7-Cl

Fig. 6

Prakash and Raja prepared a series of new Ciprofloxacin methylene isatin derivatives incorporating different aromatic aldehydes (Fig. 7).[51] Antibacterial and antifungal properties were tested *in vitro* against seven bacteria (including four gram positive and three gram negative) and two fungal strains using the disk diffusion technique. Most of the synthesized derivatives showed significant antimicrobial activity, and the electron-donating-substituted derivatives showed more remarkable antimicrobial properties than compounds containing electron withdrawing groups.

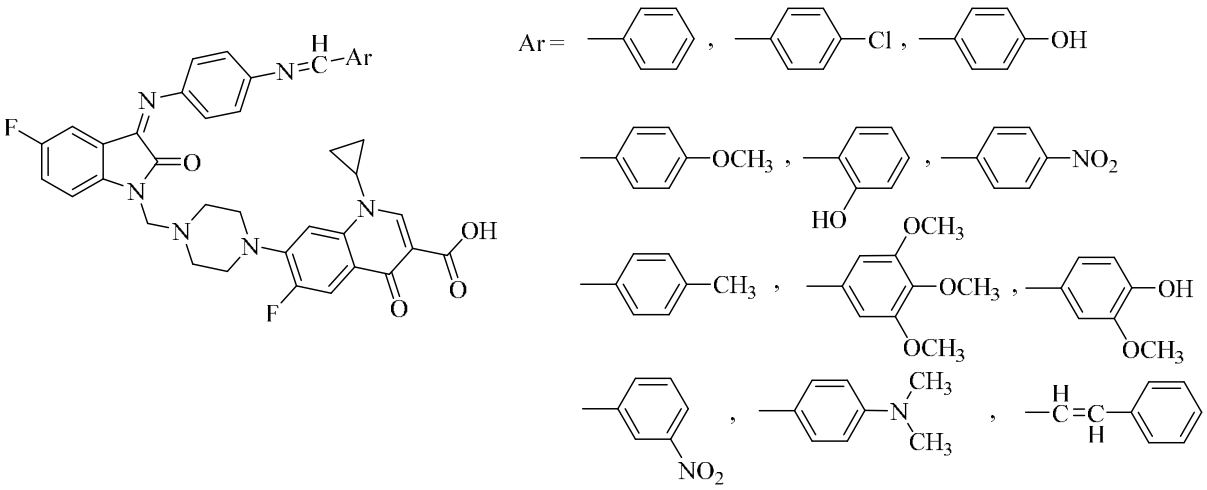


Fig. 7

In the same way, isatin was reacted with different substituted anilines. The corresponding Mannich bases were prepared by reacting the Schiff bases with diphenylamine in the presence of formaldehyde (Fig. 8).[52] The synthesized compounds have been tested for their antibacterial, analgesic and anti-inflammatory activities. Among the compounds tested, the compound containing the 4-chloro-2-nitro groups showed the most favorable activity.

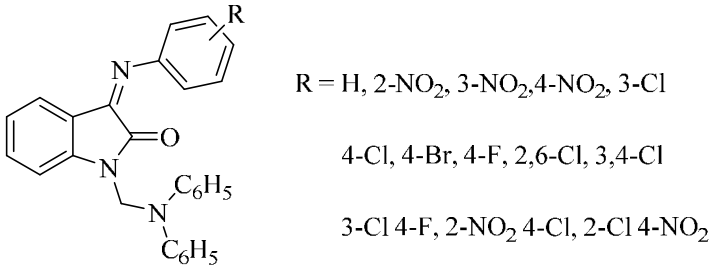
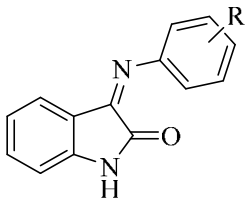


Fig. 8

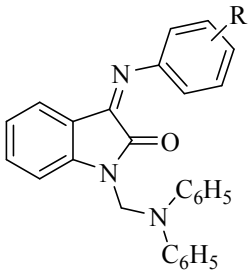
The same group prepared some Schiff bases of isatin using conventional and microwave methods (Fig. 9).[53] The antibacterial activity of the compounds was evaluated against Gram-positive and Gram-negative bacteria. Compounds with electron withdrawing substituents at *para* position exhibited good antibacterial activity against all the studied micro organisms.



R = H, 2-NO_2, 3-NO_2,
4-NO_2, 3-Cl, 4-Cl, 4-Br,
4-F, 3-Cl-4F, 2,6-Cl

Fig. 9

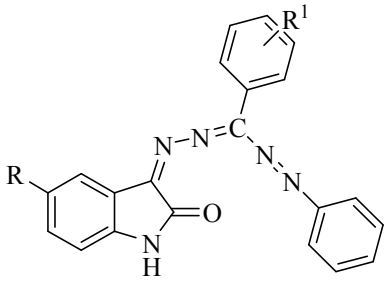
Panda prepared Mannich bases of isatin and evaluated them for their antibacterial, analgesic and anti-inflammatory activities.[54] The Schiff bases were first synthesized by reacting isatin with different aromatic amines. The compounds were then reacted with formaldehyde and diphenylamine to obtain the *N*-Mannich bases (Fig. 10).



R = H, 2-NO_2, 3-NO_2,
4-NO_2, 3-Cl, 4-Cl, 4-Br,
4-F, 3-Cl-4F, 2,6-Cl, 2,4-NO_2,
4-Cl, 2-NO_2, 2-Cl, 4-NO_2

Fig. 10

Another group prepared 3-((phenyl [phenyldiazenyl]methylidene)hydrazinylidene)-1,3-dihydro-2*H*-indol-2-ones by treatment of 3-(benzylidenehydrazinylidene)-1,3-dihydro-2*H*-indol-2-one with hydrochloric acid, sodium nitrite and aniline (Fig. 11). All compounds were tested for their antibacterial and antifungal activities using a cup plate method. The compounds exhibited mild to moderate antibacterial and antifungal activities.[55]

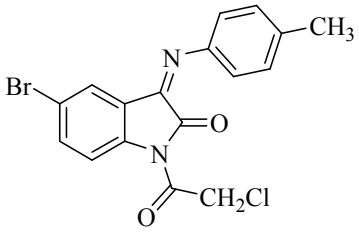


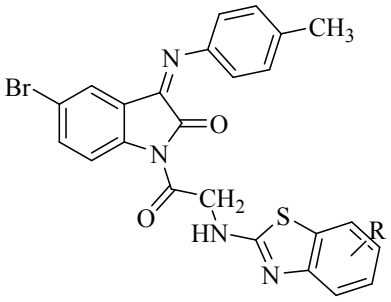
R = H, Cl, CH_3

R_1 = 4-Cl, 2-OH, 4-$(CH_3)_2$

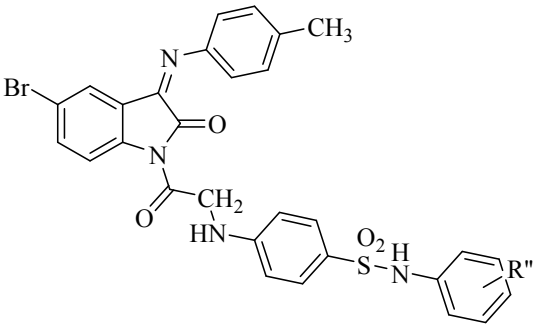
Fig. 11

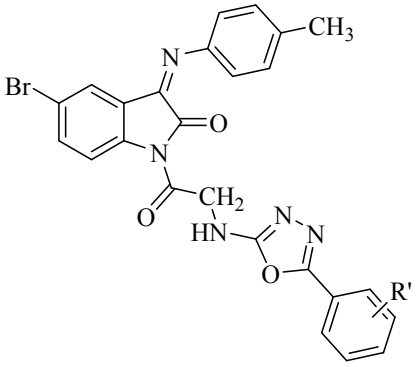
New 2-amino thiazole, oxodiazole, sulfonilamide and diazine of *N*-(α-chloroaceto)-3-(tolylimino)-5-bromo-2-oxo-indole have been synthesized and screened for their antimicrobial activity (Fig. 12).[56] The results obtained showed that all the compounds have a moderate activity against certain types of bacteria.





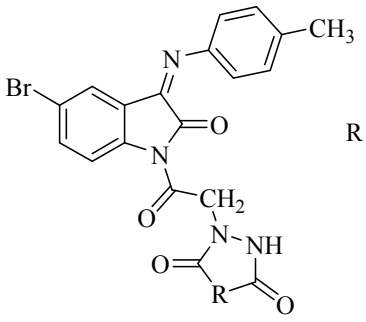
R = H, 6-NO_2, 6-CH_3, 5,7-Cl, 5-NO_2, 6-Cl



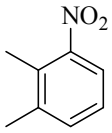


R'' = H, 2,3-NO_2, 4-OCH_3, 4-Cl, 2-Cl, 6-CH_3

R' = 2-OCH_3, 4-OH, 3,4-OH, 3-COOH, 4-OH



R = -CH_2-CH_2-CH_2-, -CH_2-CH_2-,



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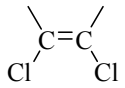

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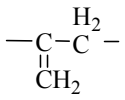

Fig. 12

A number of Schiff bases was prepared by reacting 5-substituted and *N*-benzyl isatins with amines/hydrazides (Fig. 13).[57] The antibacterial activity of the synthesized derivatives was evaluated using a microtiter plate method on a series of Gram-positive and Gram-negative bacterial strains. Analysis of the structure/activity relationship showed that the presence of a thiourea in Schiff bases leads to more potent derivatives with a broader spectrum of antibacterial activity.

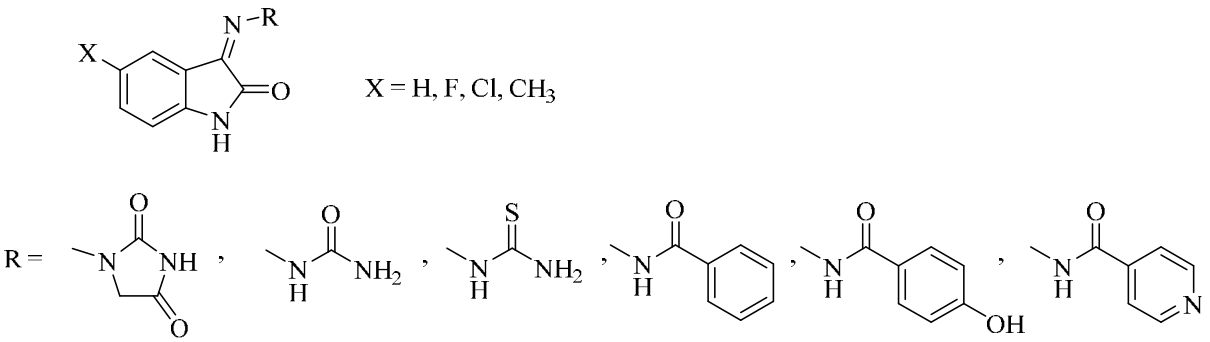

Fig. 13

Shakir et al. prepared Cu(II)/Zn(II) complexes of two 5-chloroisatin Schiff bases.[58] The *in vitro* antibacterial activity was conducted for the complexes as well as for the free ligands. The results suggest that the metal complexes are more potent candidates than the free ligands.