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Review Article

REVIEW ON ANTI-MICROBIAL ACTIVITY OF SOME MANNICH BASE AND SCHIFF BASE OF ISATIN DERIVATIVES

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ABSTRACT

Isatin has display moderate antimicrobial effect in a wide variety of preclinical antimicrobial models. Isatin is also exerting other biological activities such as anticonvulsant activity, cytotoxic activity, antifungal activity etc. Isatin and its analogs are versatile substrates, which can be used for the synthesis of numerous heterocyclic compounds. Investigation of antimicrobial properties were done against microbes such as *S.aureus, B.subtilis, S.typhi E.coli, A.niger* , *C.albicans* etc by paper-disk-plate technique (disk diffusion methods) and/or tube dilution technique using antibiotics such as amoxicillin, fluconazole etc as standard drugs. Substitution of isatin at 3-position with substituted phenyl ring is conductive for anti-microbial activity compaired to an unsubstituted phenyl group or no substitution at the same position of isatin. Isatin derivatives are used in evaluating new product that possesses different biological activities.

Key words: Isatin derivatives, Mannich base, Schiff base, Structure activity relationship, Antimicrobial activity

INTRODUCTION

Isatin (1H-indole-2,3-dione) is a synthetically versatile substrate and member of an indole derivative family. The compound was first obtained by Erdmann [1] and Laurent [2] in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids. It is found in the brain, peripheral tissues and other body fluids of human beings and animals, display a wide range of biological as well as pharmacological functions. The biological activities of isatin are anti-microbial activity, anti-convulsant activity, anti-pyretic activity, anti-fungal activity, cytotoxic activity etc.

Isatin is believed to be a component of tribulin [3] and a selective inhibitor of MAO-B (Monoamine oxidase-B enzyme). In humans tribulin levels increase as a result of exercise and old age. Tribulin excretion is significantly higher in females than males.

Naturally, Isatin is found in plants of the genus Isatits [4], in *Calanthe discolor* [5], in *Courouptia guianensis* Aubl [6], has also been found as a component of the secretion from the parotid gland of *Bufo frogs* [7] and in humans as it is a metabolic derivative of adrenaline [8].

Isatin has a wide spectrum of biological properties [9]

- A marker of stress and anxiety
- An inhibitor of a number of enzymes
- An anti-seizure agent
- An inhibitor of ANP binding to its receptors
- An agonist at the 5-HT3 receptors and
- An inhibitor of benzodiazepine receptors

The method developed by Sandmeyer is the oldest and the most frequently used for the synthesis of isatin. Isatin is prepared from cyclicizing the condensation product of chloral hydrate, aniline and hydroxilaamine in sulphuric acid [10, 11]. This reaction is called the Sandmeyer isonitrosoacetanilide isatin synthesis and discovered in 1919.

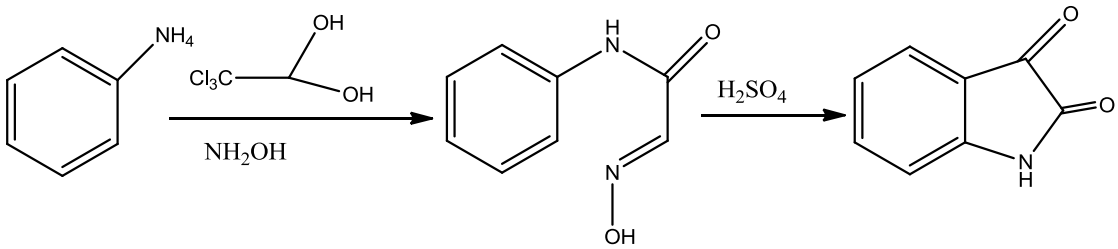


Fig.1. Synthesis of Isatin

Table.1.Chemical Properties [9] of Isatin

Properties	
Molecular formula	$C_8H_5NO_2$
Molar mass	147.1308 g/mol
Apperance	Orange-red solid
Melting point	200^{0}C, 473K
Solubility	Soluble in warm water, ethanol, methanol, acetone, DMF, benzene

Structure activity relationship

Isatin is a heterocyclic molecule and it is identified in human being and rat tissues. Thus, keto group at position 2 and particularly, at position 3 can enter into addition at the c-o bond and into condensation with release of water. Through the NH group compounds of the Isatin series are capable of entering into N-alkylation and N-acylation and into the Mannich and Michael reactions. Substitution of Isatin at 3-position with substituted phenyl ring is conductive for anti-microbial activity compared to an unsubstituted phenyl group or no substitution at the same position of Isatin [12, 13].

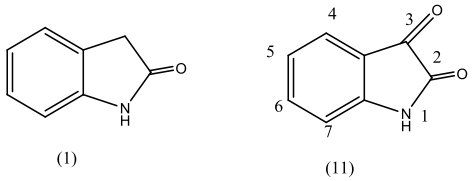


Fig.2. 2 -Indolinone (1) and 2, 3-indolindione (11)

Thomson et al. [14] were found that a little variation at position 3 of 2-indoline (I) and 2,3-indolindione (II) produce different degree of biological activity.

- C3 substitution generally enhanced anti-microbial activity
- C5, C6 and C7 substitution generally enhanced CNS activity with some di and tri halogenated Isatin

Bond donor (1)

Bond acceptor at the position (3)

Free rotation bond O#H

Polar surface area-37.38

Anti-microbial agents [15, 16] are effective against microbes such as bacteria, fungi and virus. Anti-microbial agents are of two types-

Bactericidal

Bacteriostatic

Bactericidal- These are the substances that can kill the susceptible micro-organism.

e.g.- β-lactums- Penicillin

Amino glycosides- Gentamicin, Streptomycin

Quinolones

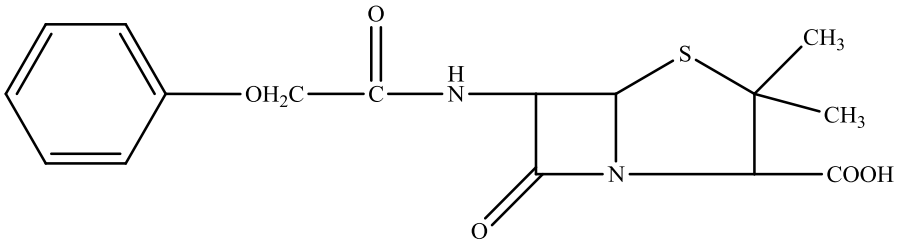


Fig.3. Structure of Penicillin V

Bacteriostatic- These are the substances that can inhibit the growth of the susceptible micro-organisms.

E.g.- Tetracycline, Chloramphenicol, Erythromycin, Sulfonamide

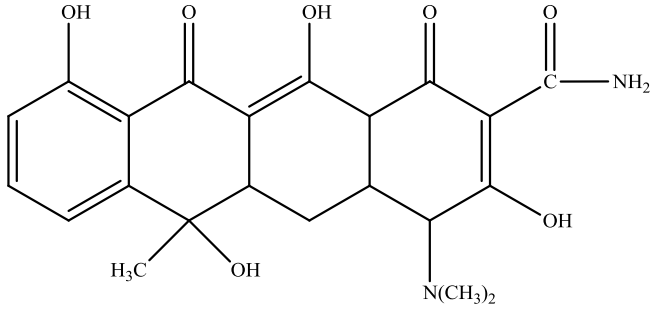


Fig.4. Structure of Tetracycline

Anti-microbial spectrum is divided into narrow spectrum and broad spectrum. Mechanistically, anti-microbial agents inhibit the cell wall synthesis (e.g.- Penicillin), inhibit the protein synthesis (tetracycline), and inhibit the nucleic acid synthesis (eg-rifampicin). Anti-microbial activity are depends on the factors such as size of the inoculums, metabolic state of organisms, PH, temperature, duration of interaction, concentration of the inhibitor and presence of interfering substances. Anti-microbial activities of synthesized compound are determined by two official methods- (a) Paper-disk-plate technique

(disk diffusion methods) and (b) Tube dilution technique.

Procedure for Zone of Inhibition Test

A microbial suspension is spread by a sterile swab, evenly, over the face of a sterile agar plate.

The antimicrobial agent is applied to the center of the agar plate (in a fashion such that the antimicrobial doesn't spread out from the center) and incubated.

If substantial antimicrobial activity is present, then a zone of inhibition appears around the test product. The zone of inhibition is simply the area on the agar plate that remains free from microbial growth.

The size of the zone of inhibition is usually related to the level of antimicrobial activity present in the sample or product - a larger zone of inhibition usually means that the antimicrobial is more potent [17].

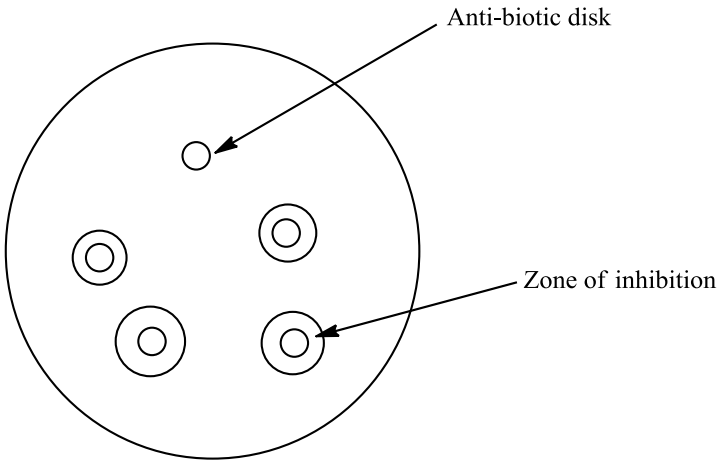


Fig.5. Schematic Diagram of Zone of Inhibition for Anti-Microbial Activity

Advantages of Zone of Inhibition Testing

Zone of inhibition testing is fast and inexpensive relative to other laboratory tests for antimicrobial activity.

Zone of inhibition testing is especially well suited for determining (albeit qualitatively) the ability of water-soluble antimicrobials to inhibit the growth of microorganisms.

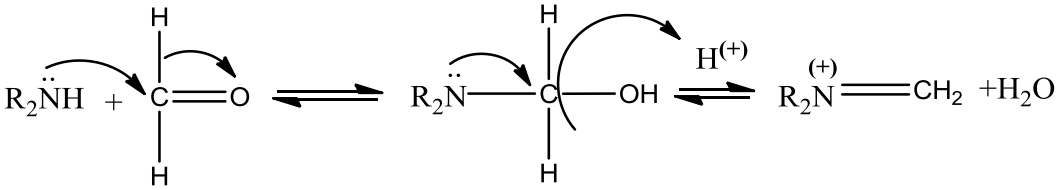
A number of samples can be screened for antimicrobial properties quickly using this test method. A variety of antimicrobial product types can be tested using this method. Liquids, coated antimicrobial

surfaces, and antimicrobial-impregnated solid products can all be tested for their ability to produce a "zone of inhibition" [17, 18].

Mannich Base Reaction: Mechanism of Action [19]

Mannich bases are generally formed by the reaction between a compound containing a reactive hydrogen atom, formaldehyde and a secondary amine. On occasions, Aldehydes other than formaldehyde may be employed and the secondary amine may be replaced by ammonia and primary amines. The process whereby these compounds are formed is known as Mannich reaction. It is a condensation reaction and the base, called Mannich base, is usually isolated as its hydrochloride.

In step-I, the amine and HCHO in the presence of $H^{(+)}$ condense to form imminium cation.



It is then attacked by the enolate anion of the active hydrogen compound in the step-II to form the Mannich base.

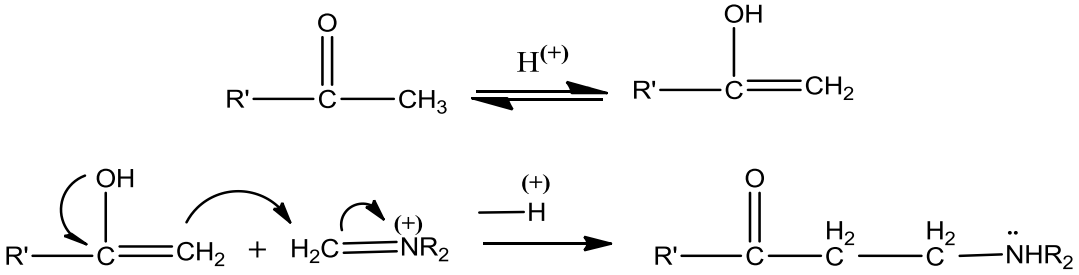


Fig.6. Mechanism of Mannich Base Reaction

Schiff Base Reaction: Mechanism of Action [20]

Schiff base was first reported by Hugo Schiff in 1864. In recent years, there has been an increased interest in the chemistry of Schiff bases because of their biological significances. Schiff base can be prepared by condensing carbonyl compounds and amines in different conditions and in different solvents with the elimination of water molecules. In Schiff base reactions

the C=O double bond is replaced by a C=N double bond.

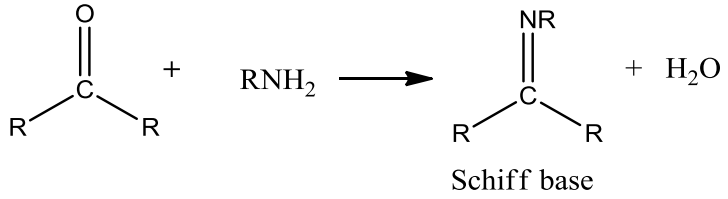
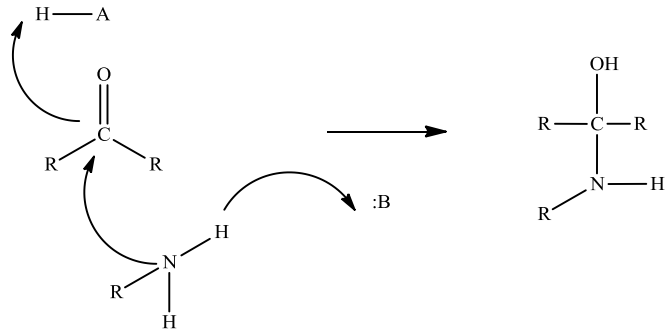


Fig.7. Formation of Schiff Base

Mechanistically, the formation of an imine involves two steps. First, the amine nitrogen acts as a nucleophile, attacking the carbonyl carbon. This is closely analogous to hemiacetal and hemiketal formation.



Based on your knowledge of the mechanism of acetal and ketal formation, you might expect that the next step would be attack by a second amine to form a compound with a carbon bound to two amine groups – the nitrogen version of a ketal. Instead, what happens next is that the nitrogen is deprotonated, and the electrons from this N-H bond 'push' the oxygen off of the carbon, leaving us with a C=N double bond (an imine) and a displaced water molecule.

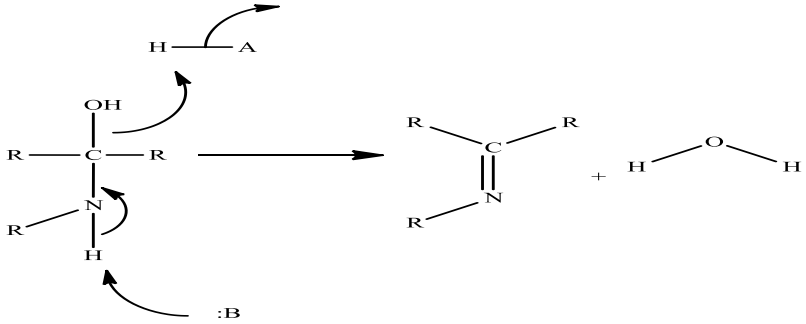
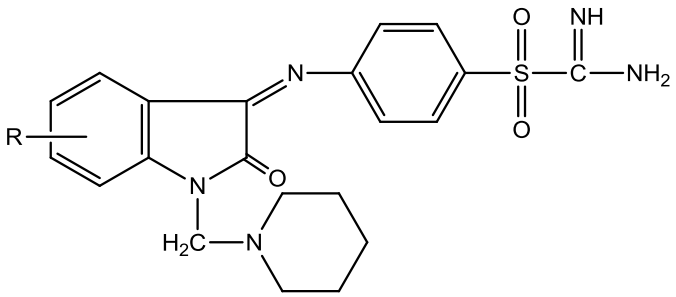


Fig.8. Mechanism of Schiff Base Formation

The conversion of an imine back to an aldehyde or Ketone is a hydrolysis, and mechanistically is simply the reverse of imine formation.

ANTI-MICROBIAL ACTIVITY OF SOME MANNICH BASE REACTIONS OF SOME ISATIN DERIVATIVES

Singh U K et al. [21] have been reported synthesis and antimicrobial activity of N-Mannich Bases of Isatin and its Derivatives with 4-Amino-N-Carbamimidoyl Benzene Sulfonamide. These compounds were obtained by the reaction of Schiff base containing the acidic imino group of Isatin, tetrahydrofuran, piperidine in presence of formaldehyde. All the newly synthesized compounds were screened for their anti-microbial activity using paper-disk-plate method taking sulphaguanidine as standard drug. The test strains such as S. aureus, B. Pumulis, B. Subtilis, E.Coli, S. abony, K. Pneumoniae are used for anti-microbial activity of this synthesized compound.



R= H, NO_2, Cl, Br, CH_3

Fig.9.(Z)-((2-Oxo-1-(piperidine-1-ylmethyl)indolin-3-ylidene)amino)phenyl)sulphonyl) Methannimidamide Derivatives

Chhajed S.S et al. [22] have been reported antimicrobial evaluation of some novel mannich bases of Isatin and its derivatives with quinolin. Evaluation of anti-microbial activity is done by the agar dilution method. The anti-microbial activity was tested against various bacteria such as B.subtilis, S.aureus, S.faecelis, E.coli, P.aerouginosa, C.albicans, A.niger with standard drug (sulphamethaxole and ketoconazole) using solvent control.

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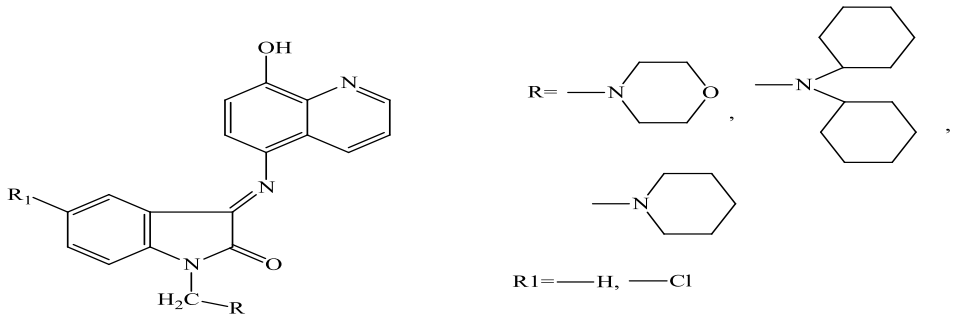


Fig.10. (E)-3-((8-hydroxyquinolin-5-yl)imino)indolin-2-one Derivatives

Ravichandran V et al. [23] have been reported synthesis and antimicrobial activity of mannich bases of isatin and its derivatives with 2[(2,6 dichlorophenyl) amino] phenyl acetic acid. All the synthesized compounds were tested for invitro anti-microbial activity. All the compounds have shown moderate activity because of the bulky phenyl acetic group present at nitrogen atom of isatin nucleus.

Substitution of isatin at 3-position with substituted phenyl ring is conductive for anti-bacterial activity compared to an unsubstituted phenyl group or no substitution at the same position of isatin. This bulky phenyl acetic acid group may sterically hinder the compounds binding with bacteria. The test strains E. Coli, P. aeruginosa, S.aureus, P.notatum, C albicans, A. Niger are used for anti-microbial activity. Ciprofloxacin, fluconazol are used as standard drug for this activity.

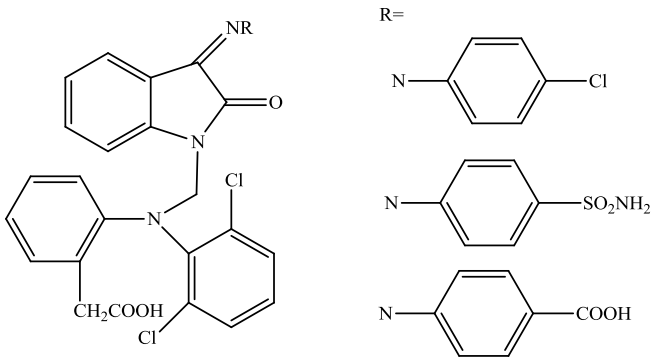
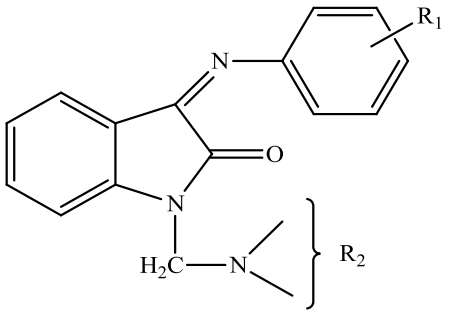


Fig.11. 2-(2-((2,6-dichlorophenyl)((3-imino-2-oxoindolin-1-yl)amino)phenyl) Acetic acid Derivatives

Chaluvaraju KC et al. [24] have been reported synthesis and biological evaluation of mannich base reaction of some isatin derivatives for antimicrobial properties.

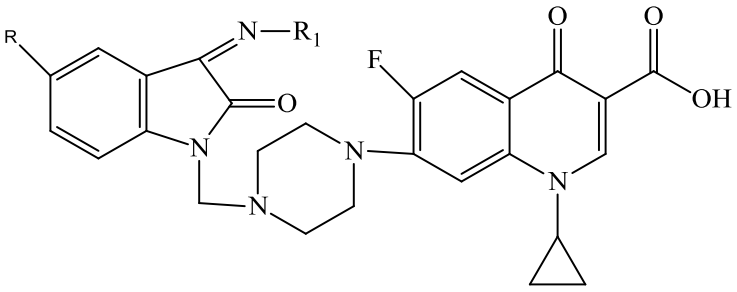


where,
R_1= p-Br, p-NO_2, p-CH_3, p-Cl, o-NO_2

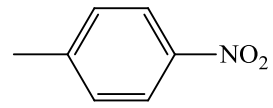
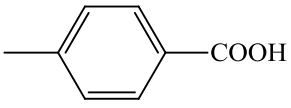
R_2= Diethyl amine, Morpholine, Piperidine, NMP

Fig.12. Mannich Base of Isatin Derivatives

Ramachandran S [25] has been reported synthesis and anti-microbial evaluation of some novel Schiff and mannich bases of isatin derivatives.



R= NO_2, Cl, H

R_1=  , 

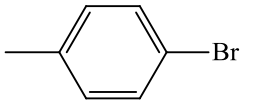
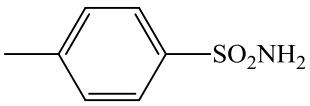
 , 

Fig.13. 1-cyclopropyl-6-fluro-7-(4-imino-2-oxoindolin-1-yl)methyl)piperazin-1-yl)-4-oxo-1,4-oxo-1,4-dihydroquinolin-3-carboxilic Acid Derivatives

ANTI-MICROBIAL ACTIVITY OF SOME SCHIFF BASE REACTIONS OF SOME ISATIN DERIVATIVES

Ramachandran S [25] has been reported synthesis and anti-microbial evaluation of some novel Schiff bases of isatin derivatives. The antimicrobial activity of the synthesized compounds was determined by cup-plate method. The organisms selected for antibacterial activity were gram positive organisms like *Staphylococcus aureus*, *Streptococcus pyogenes*, gram negative organisms like *Escherichia coli*, *Klebsiella aero genes*. Similarly the antifungal activity was carried out by using *Candida albicans*. The concentrations of sample compounds was 30 mcg/ml. Ciprofloxacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activity respectively.

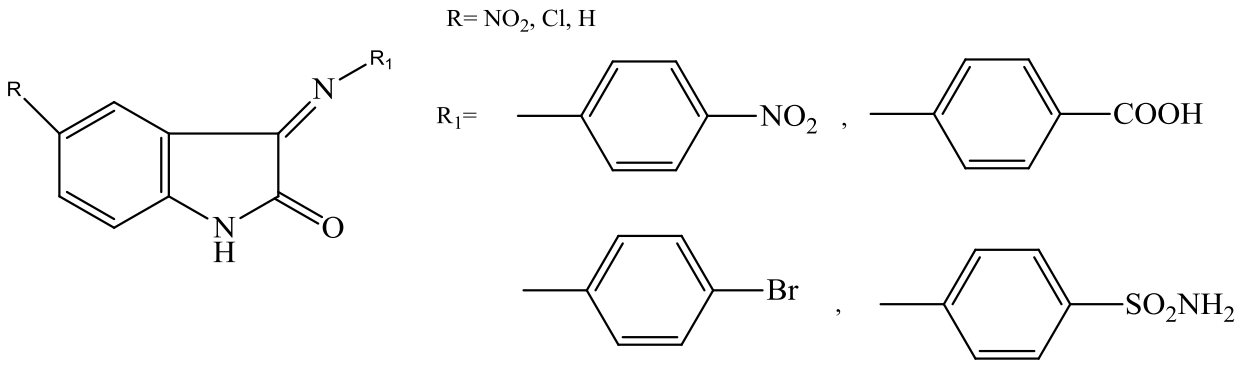


Fig.14. Schiff Base of Isatin Derivatives

Jarrahpour A et al. [26] have been reported synthesis, anti-bacterial evaluation of some new bis-schiff bases of isatin and their derivatives.

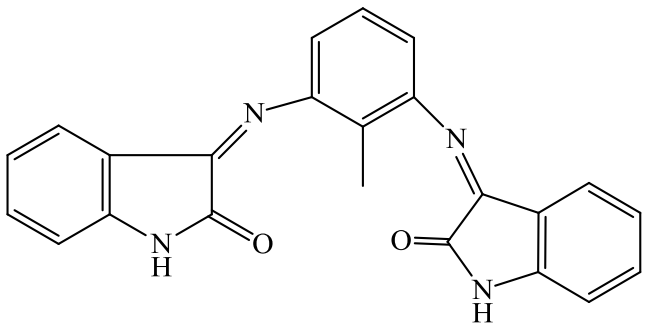


Fig.15.(3Z,3'Z)-3,3'-((2-methyl-1,3-phenylene)bis(azanylylidene)bis(indolin-2-one) Derivatives

Aditya J et al. [27] have been reported synthesis, characterization and anti-microbial activity of novel Schiff base of isatin.

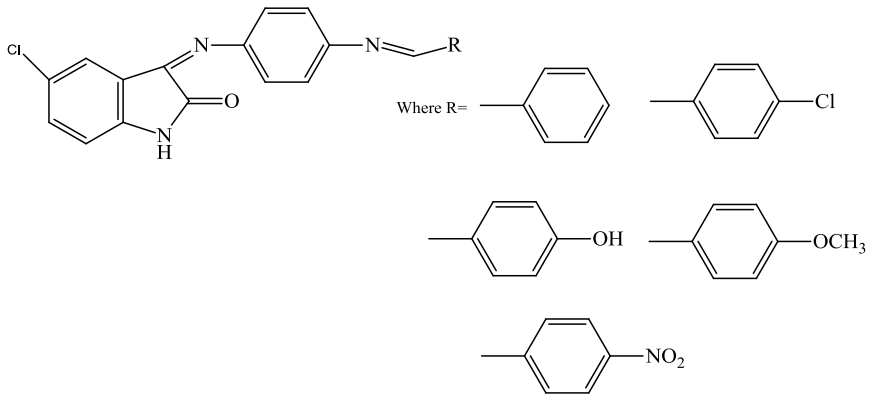
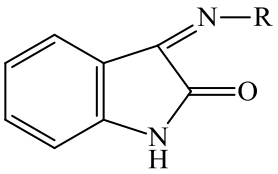


Fig.16.(Z)-5-chloro-3-((4-(methyleneamino)phenyl)imino)indolin-2-one Derivatives

Panda J et al. [28] have been reported green chemistry approach for efficient synthesis of Schiff bases of isatin derivatives and evaluation of their anti-bacterial activities.



Where R= Phenyl,
2-nitrophenyl,
3-nitrophenyl,
4-nitrophenyl,
3-chlorophenyl,
4-chlorophenyl,
4-bromophenyl,
4-fluorophenyl,
3-Cl-4-F phenyl,
2,6-dichlorophenyl

Fig.17. Schiff Base of Isatin Derivatives

Chhajed S.S et al. [22] have been reported antimicrobial evaluation of some novel Schiff base of isatin and its derivatives with quinolin [21].

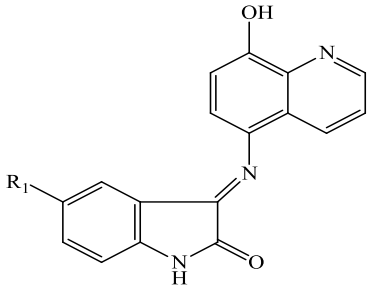


Fig.18. (E)-3-((8-hydroxyquinolon-5-yl) imino)-5-methylindolin-2-one derivatives

CONCLUSIONS

Isatin can be used for the synthesis of a large variety of heterocyclic compounds, and as raw material for drug synthesis. Isatin shows potent biological and pharmacological activities. So isatin are synthetically versatile substrates. The survey of the literature revealed that, Isatin is a versatile lead molecule for designing potential bioactive agents, and its derivatives were reported to possess anti-microbial and other biological activity.

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