STRUCTURAL MODIFICATION OF ANTIMICROBIAL TO PRODUCE HIGH THERAPEUTIC INDEX:ANTIMICROBIAL ACTIVITY OF SOME INDOLE DERIVATIVES

Kashif Hussain[1]
Gyani inder singh institute of Professional studies[1] ,Dehradun[1] India[1]
Dr.Nadeem Ahmad Siddique[2]
Associate Professor[2], School of Pharmacy[2] ,Glocal University Saharanpur[2] , India[2]
Dr.Asif Husain[3]
Deptt of Pharmaceutical Chemistry[3],SPER
Jamia Hamdard University N.Delhi [3] India[3]

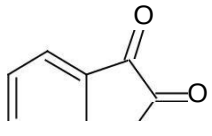
ABSTRACT

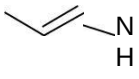
Antimicrobial are an essential part of innate immunity that evolved in most living organisms over 2.6 billion years to combat microbial challenge. These small cationic peptides are multifunctional as effectors of innate immunity on skin and mucosal surfaces and have demonstrated direct antimicrobial activity against various bacteria, viruses, fungi, and parasites. This review summarizes their progress to date as commercial antimicrobial drugs for topical and systemic indications. The biological, chemical, and socioeconomic environments of antibacterial research are dealt with in context. Natural products, many from soil organisms, have provided the majority of lead structures for marketed anti-infectives. Surprisingly, numerous classes of antibacterial natural products has never been intensively traverse, through medicinal chemists. Research on antibacterial natural products is flagging. Apparently, the "old fashioned" natural products no longer fit into modern drug discovery. The handling of natural products is cumbersome, requiring nonstandardized workflows and extended timelines. Revisiting natural products with modern chemistry and target-finding tools from biology is one option for their revival.

KEYWORDS: *Antimicrobial, Erythromycin, Bacteria, antibacterial natural products.*

INTRODUCTION

Isatin is the indole derivative containing keto group at position 2 & 3 of the ring. Isatin ring system consists of pyrrole ring fused with benzene ring. Isatin was first synthesized by Erdman and Laurent in 1841 by the oxidation of indigo with ni-tric acid and chromic acids . his compound is found in many plants, such as *Isatis tinctoria*, *Calanthe discolor* and in *Couroupita guianensis*. Substituted isa-tins are also found in plants. Example the melosatin alkaloids (methoxy phenylpentyl isatins) in *Melochia tomentosa.* Isatin has also found in humans beings as it is a met-abolic derivative of adrenaline .





1*H*-indole-2,3-dione

Isatin is a versatile chemical building block which able to form a large number of heterocyclic molecules. Isatin is able to participate in a wide range of synthetic reactions, leading to its large-scale use as a precursor molecule in medicinal chemistry. In the presence of manyl reaction centers in isatin and its most of derivatives render them capable of participating in a large number of reactions Before the evolution of adaptive immunity in higher vertebrates added complexity, specificity, and memory to fight microbial challenge, a simpler, non-specific ancient system of innate immunity evolved 2.6 billion years ago and continues to

function as the principal defense for almost all living organisms.Biopharmaceutical activity of 2-oxo-indolyl derivatives is well established in the field of pharmaceutical chemistry. Now we will describe the synthesis of isatin derivatives as potential antimicrobial agent.Enter into addition reactions at the C-O bond and into condensation reactions. Literature surveys shows that various derivatives of isatin possess change activities such as anti-mycobacterial, anti-inflammatory ,antibacterial, antifungal, anti-HIV, and anticonvulsant activities .

MATERIALS AND METHOD

Organisms

Standard cultures of five bacteria Bacillus pumilus, Bacillus subtilis, Escherichia coli, Proteus vulgaris and Staphylococcus aureus were obtained and maintained on nutrient agar medium at 37^0C.

Test Compounds

Using Erythromycin and Polymyxin for comparison, the antimicrobial activity of 2- oxo-3- indolyl derivatives was studied.

Testing Procedure

Since erythromycin and Polymyxin both are insoluble in water so DMSO is used as solublising agent. To check the antimicrobial activity of synthetic compounds along with control drugs in given bacterial cultures their suspensions were prepared by suspending a loopful of pure culture in 10ml of sterile distilled water. One ml of bacterial suspension were separately mixed with 15ml of sterile molten nutrient agar in previously labeled different sterile petri dishes. After solidification the media of each petri dish were divided into four equal parts and with cork borer uniform holes of 8mm were made. Each hole was filled with 0.08 ml of sol of test compound and forth was kept as control. Zone of inhibition was measured using vernier caliper after incubating the dishes at 37^0C for 24hrs.

Synthesis of 2- oxo-3- indolyl derivatives

Following derivatives were prepared and their Infra red spectra were run as KBr discs, NMR spectra were recorded using tetramethyl silane as internal standard and Mass spectra was also measured. The different compounds prepared were (1.) N-chloroacetyl isatin (2.)Isatin -3-isonicotinylhydrazone (3.) t-Acetyl isatin-3-isonicotinylhydrazone (4.) 1 Benzoyl isatin-3-isonicotinylhydrazone (5.) Isatinazine (6.) 1- Morpholinomethyl isatinazine (7.) 1,1` Morpholinomethyl isatinazine (8.) 3'-Acyl-5'-(acetylamino)-1-acetyl-spiro(indoline-3,2'-thiadiazoline)-2-one (9.) 5-Amino-spiro(indoline-3,2'-thiadiazoline)-2-one (10.) 2-Acylamino-5-methyl-1,3,4-thiadiazoline

RESULT AND DISCUSSION

Synthesis of compounds

Isatin-3-isonicotinylhydrazones-2, 3 and 4 were prepared by condensation of isoniazide hydrochloride with appropriate N-substituted isatin. The compound isatinazine 5 and its Mannich bases 6 and 7 were prepared. Isatin-3- thiosemicarbazone was treated with acetic anhydride to formulate 3'-acyl-5' (acetylamino) - t-acetyl- spiro (indoline-3,2'-thiadiazoline)-2-one i.e. 8.

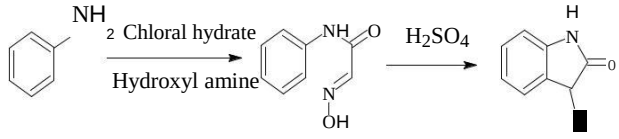
Antibacterial activity

The compound synthesized exhibited antibacterial activity in both Gram positive and Gram negative Bacteria. They indicated a structure activity relationship of the test compound. Most effective were compound no. 2, 3 and 4 They exhibited maximum zone of inhibition against bacteria and were so effective that zone could not be measured and need further dilution. Control group of Erythromycin and Polymyxin indicated 22-30mm and 13-18mm zone of inhibition respectively. Compound 5 and their Mannich bases 6 and 7 exhibited broad spectrum activity probably because of their 2-oxo-3-indolinylidene system present. Further, compound 8 exibited more antibacterial activity as compared to its deacylated analogue compound 9. Compound 1 and 10 showed minimum activity.

GENERAL METHODS FOR SYNTHESIS OF ISATINS

Sandmeyer synthesis

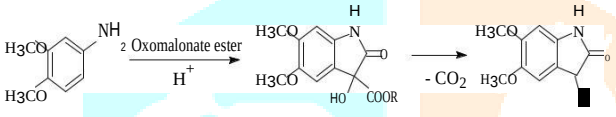
The synthesis of isatin derivative involving the reaction of chloral hydrate, hydroxylamine, and a primary aryl amine to give α-isonitrosoacetanilide and subsequent electrophilic cyclization in the presence of a strong acid such as concentrated sulfuric acid is generally known as the Sandmeyer isatin synthesis. This method is suitable for anilines with electron-withdrawing substituents, such as 2-fluoroaniline .



Scheme 1: Sandmeyer isatin synthesis

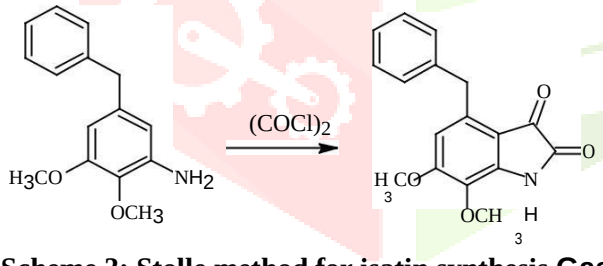
Martinet isatin synthesis

The Martinet method (Scheme 2) for the synthesis of isatins involves the reaction of an aminoaromatic com-pound and either an oxomalonate ester or its hydrate in the presence of an acid to yield a 3-(3-hydroxy-2-oxindole) carboxylic acid derivative which after oxidative decarboxylation yields the respective isatin .



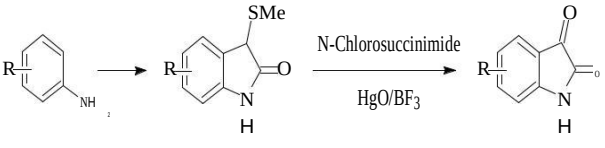
Scheme 2: Martinet isatin synthesis Stolle method

The most important alternative to Sandmeyer synthesis is the method of Stolle (Scheme 3). In this method ani-lines are reacted with oxalyl chloride to form an inter-mediate chlorooxalylanilide which can be cyclized in the presence of a Lewis acid, usually aluminium chloride to give the corresponding isatin .



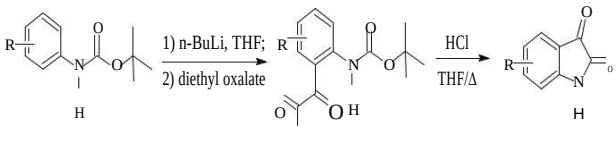
Scheme 3: Stolle method for isatin synthesis Gassman method

This method involves the formation and subsequent oxidation of an intermediate 3-methylthio-2-oxindole to give the corresponding substituted isatins . Two complementary methods for the synthesis of the 3-methylthio-2-oxindoles were developed. When electron-withdrawing groups are present, the oxindole derivative can be synthesized via an N-chloroaniline intermediate, which further reacts with a methylthioacetate ester to furnish an azasulfonium salt. In the case of electron-donating groups that destabilize the N-chloro intermedi-ate, by reaction of the chlorosulfonium salt with appro-priate aniline gives better yields of the 3-methylthio-2-oxindoles .



Scheme 4: Gassman method for isatin synthesis Metalation of anilide derivatives

A more recent method for the synthesis of isatins is based upon the directed ortho-metalation of N-pivaloyl-and N-(t-butoxycarbonyl)-anilines (Scheme 5). The cor-responding dianions are treated with diethyl oxalate and the isatins are obtained after deprotection and cyclisa-tion of the intermediate α-ketoesters .

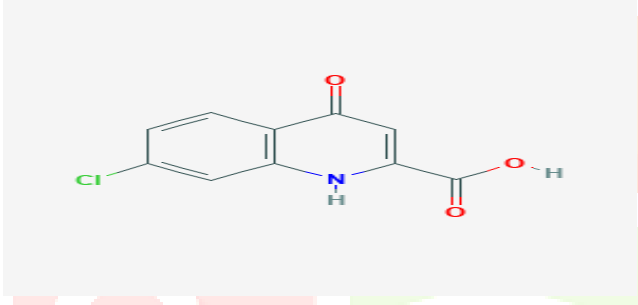


Zone of inhibition (mm)obtained by various derivatives of indole against bacteria Concentration of($400_{\mu g/ml}$) as compared to test compounds take as 5µg/ml

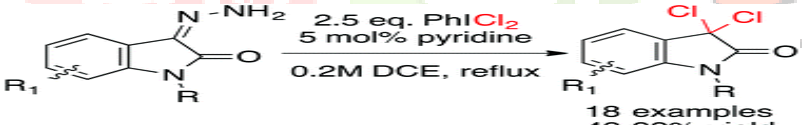
	1	2	3	4	5	6	7	8	9	10
Bacillus Pumilus	14	17	26	13	14	17	14	30	26	19
Bacillus Sublitus	-	12	11	14	16	20	-	-	-	-
E.Coli	-	12	13	17	16	-	-	21	-	-
Proteus vulgaris	15	12	25	18	12	15	18	16	19	13
Staphylococcus aureus	-	17	12	15	13	16	20	24	11	12

N-Chloroacetyl Isatin

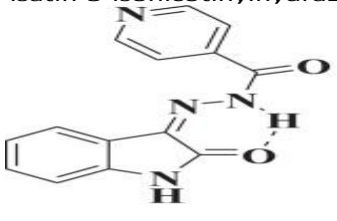
$C_{10}H_6ClNO_3$



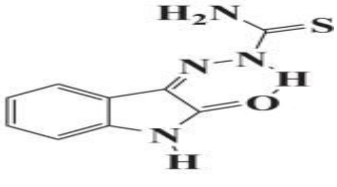
Synthesis of 3,3-dichloroindolin-2-ones from isatin-3-hydrazones and (dichloroiodo)benzene



isatin-3-isonicotinylhydrazone (INH) 100 and isatin-β-thiosemicarbazone (IBT) 101



100



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ISATIN DERIVATIVES WITH ANTHELMINTIC ACTIVITY

A new series of tetradentate Schiff bases was synthe-sized and screened for anthelmintic activity against earthworm (*Peretima posthuma*) using 5 µg/ml concen-tration . A series of novel isatin derivatives were synthesized from different substituted chalconised in-dole-2,3-dione prepared from the different chalconised isatin. Some compounds reported anthelmintic activity against *Pheretima posthuma* . Various 3-(2-hydrazino benzothiazoles)-substituted Indole-2-one de-rivatives were synthesized, and all the synthesized compounds were screened for anthelmintic activity by using Indian adult earthwarms (*Pheretima postuma*) .

ISATIN DERIVATIVES WITH ANTIANXIETY ACTIVITY

Isatin derivative like Schiff bases of N-methyl and N-acetyl isatin, spirobenzodiazepines, 5-hydroxy isatin and isatinic acid act as antianxiety agents. A new series of 5-hydroxy isatin derivatives was synthesized by the hydroxylation of the aromatic ring in isatin and showed mild antianxiety effect

CONCLUSION

Isatin is a versatile chemical building block which able to form a large number of heterocyclic molecules. Isatin is able to participate in a wide range of synthetic reactions, leading to its large-scale use as a precursor molecule in medicinal chemistry.The isatin scaffold can be found in a wide range of natural & synthetic compounds of medicinal importance. Isatin and its derivatives showed diverse pharmacological activities including anticonvulsant, anti-HIV, anticancer, antiviral, antibacterial, antifungal, anti-tubercular, antiglycation, anti-inflammatory, anal-gesic, antimalarial, antioxidant, anthelmintic and anti-anxiety activity.

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