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AN OVERVIEW ON ISATINS AND ITS DERIVATIVES

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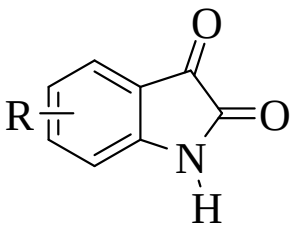
ABSTRACT

The present review article offers a detailed account on the synthesis of isatin and its derivatives. The isatin moiety displays wide range of biological and pharmacological activities such as anti-tumor, anti-HIV, antiviral, anti-angiogenic, antifungal, anti-Parkinson's disease, anticonvulsants, etc. It contains the synthesis of substituted isatins, conversion of aniline to isatins, synthesis of new 3-[(5-benzylidene-2-phenyl)-3,5-dihydro-4-*H*-imidazol-4-one-3-(4-bezoylhydra zono)]-indole-2-ones, etc.

KEYWORDS: Isatin, synthesis, Isatin derivatives.

1. INTRODUCTION

Isatin (1) (Also known as 1H-indole-2,3-dione) was first obtained by Laurent[1] and Erdman[2], from the oxidation of indigo dye by nitric acid and chromic acids in 1841. It is also found in many plants and has been investigated for their Pharmaceutical properties.[3]



1

Where R= Cl, NO_2, Br.

It was observed that 1H-indole-2,3-dione forms a blue dye if it is mixed with sulphuric acid and crude benzene. The reaction with benzene was believed to be completed by the formation of the blue indophenin. Victor Meyer isolated the substance responsible for this reaction from

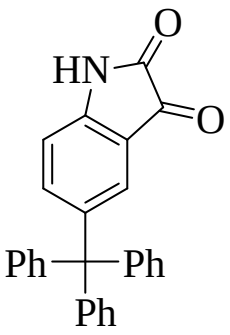
benzene. This new heterocyclic compound was "thiophene".[4] Isatin may also be isolated from urine of rabbits that fed o-nitrophenyl glyoxylic acid. Isatin is an endogenous compound identified in human and rat tissues. It was first identified by Glover and Halket in 1988.[5]

Isatin (1H-indole-2,3-dione) is a versatile heterocyclic scaffold with vast possibility of chemical modifications at C-3, C-5 and at N- 1 position.[6] The endogenous molecule displays a wide range of biological and pharmacological activities such as anti-tumor[7,8], anti-HIV, antiviral[9], anti-angiogenic[10], antifungal[11], anti-Parkinson's disease therapeutic[12], anticonvulsants, and effective SARs coronavirus 3CL protease inhibitor[13] along with excellent tolerance in humans.

2. Review

a. Synthesis of substituted isatins

Isatins are valuable intermediates for heterocyclic chemistry. Most of the common methods for their production are less than adequate when the number and lipophilicity of substituents on the targeted Isatin are increased. The group desired such molecules and identified an alternative method for their production. The 5-tritylisatin (2) was produced in 67% yield.[14]



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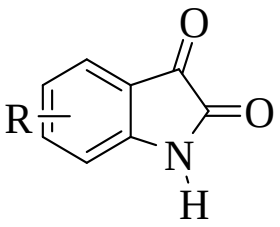
b. Conversion of aniline to isatins

A new method has been developed for the conversion of anilines into isatins. The general process utilizes our efficient method for the conversion of anilines into 3-methylthiooxindoles, which in turn serve as key intermediates. To synthesise Isatins (3), firstly the oxidation of methane carbon of 3-methylthiooxindoles is done with N-chlorosuccinimide, which is further followed by the hydrolysis of chlorinated intermediate. This method requires the strong electron-withdrawing or strong electron-donating group on the aniline.[15]

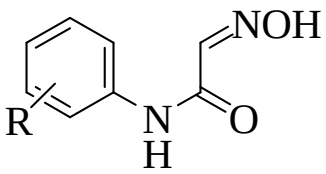


3

Where R = H, CH_3, OCH_3, Cl, $CO_2C_2H_5$, CN, NO_2, CF_3

c. Synthesis of Isonitrosoacetanilide

The synthesis of Isonitrosoacetanilide can be done by the two step process involving the acetylation of aniline derivatives, and then reaction with Hydroxylamine HCl. Various aniline derivatives are used for the synthesis of these Isonitrosoacetanilides (4) and thus, Isatins.[16]

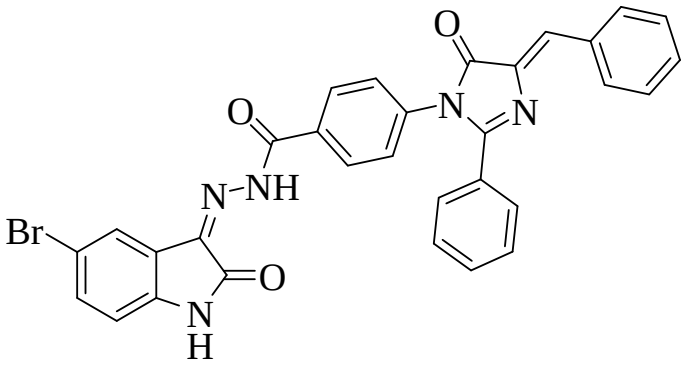


4

Where R= H, 2-OCH_3, 2-NO_2, 2-Cl, 2-I, etc.

d. Synthesis of new 3-[(5-benzylidene-2-phenyl)-3,5-dihydro-4-*H*-imidazol-4-one-3-(4-bezoylhydra zono)]-indole-2-ones

Different Isatin Hydrazones are used for the synthesis of novel 3-[(5-benzylidene-2-phenyl)-3,5-dihydro-4-*H*-imidazol-4-one-3-(4-bezoylhydra zono)]-indole-2-ones. The process involved condensation of Isatin Hydrazones with 2-phenyl-5-benzylidene- 3-N (4-acetyl phenyl)-1, 5-dihydro-imidazol- 4-one. The confirmation of structures are done by IR, ^{1}H NMR, MS and elemental analysis. From the number of synthesized compounds, the 5-Br substituted compounds 5 showed best antimicrobial activity.[17]



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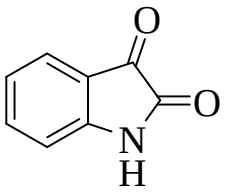
e. Microwave assisted synthesis of Isatins

A mixture of aromatic amines, chloral hydrate and hydroxylamine HCl was exposed to microwave irradiation in a domestic microwave oven. The careful analysis of reaction mixture indicated the formation of isonitrosoacetanilide derivatives (6-12) in two to three minutes in most cases. This intermediate was smoothly cyclised to the isatin with 86% H_2S0_4 under microwave conditions or by heating the reaction mixture.[18]



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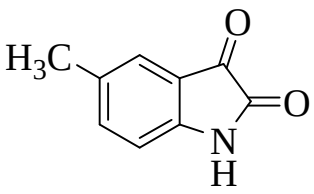

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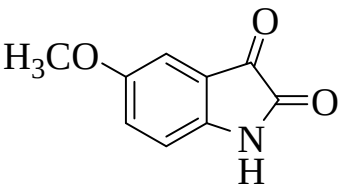

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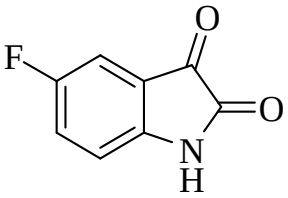

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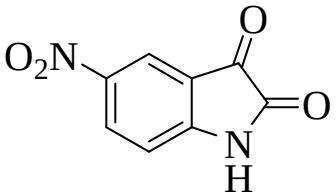

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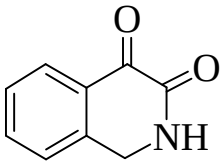

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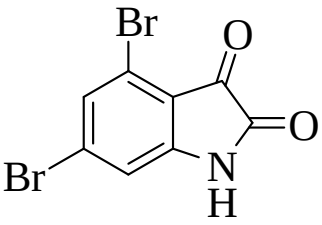
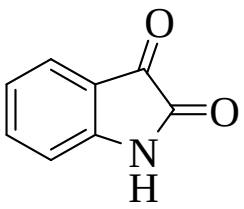


12

f. Recent advances in synthesis of Isatin

Isatin (13) and its analogs, act as the precursor for various pharmacologically active compounds. Due to this reason it is used for synthesis of different heterocyclic compounds. Its activities range from the antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic.[19]



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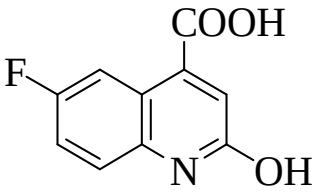
g. Synthesis of Fluorinated isatins

The Sandmeyer isatin synthesis can be performed by the use of 4-fluoro-, 3,4-difluoro-, and 4bromo-3-fluoroanilines. But, donot involve the 2-duoro- and 2,4-difluoroaniline. These fluorinated Istains (14) were used for the synthesis of various fluorine-containing quinolines, acridines, and indophenazines required for testing as potential carcinogens.[20]



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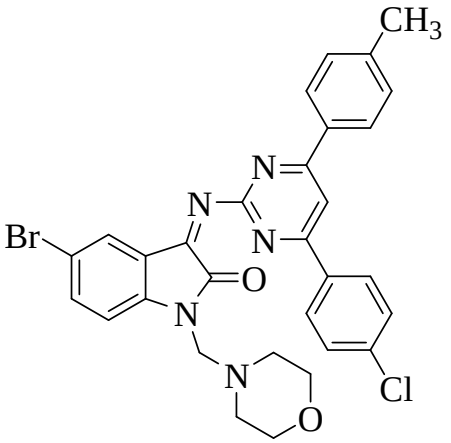
h. Synthesis of Schiff bases and Mannich bases of Isatin

To synthesise the Schiff bases from the Isatin, it is treated with 4-(4%-chlorophenyl)-6-(4¦-methyl phenyl)-2-aminopyrimidine and the *N*-Mannich bases are prepared in the presence of formaldehyde and several secondary amines. The investigation of the antimicrobial activity of the compounds synthesized is done by the agar dilution method against 8 pathogenic fungi,

28 pathogenic bacteria. Also, the anti-HIV activity is investigated against the replication of HIV-1 (III B) in MT-4 cells. The compounds were found to be significantly active against both, fungi and bacteria. The compound 15 was most active antibacterial agent and compound 16 was most active antifungal agent.[21]



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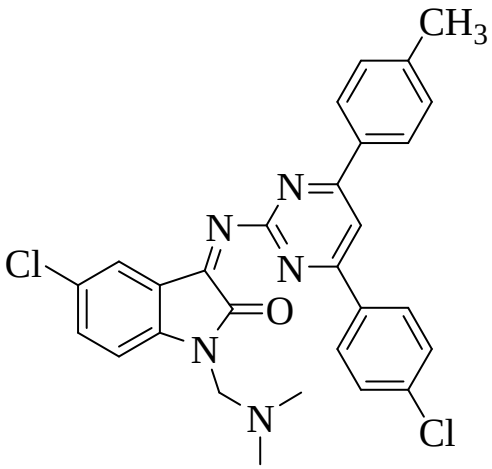

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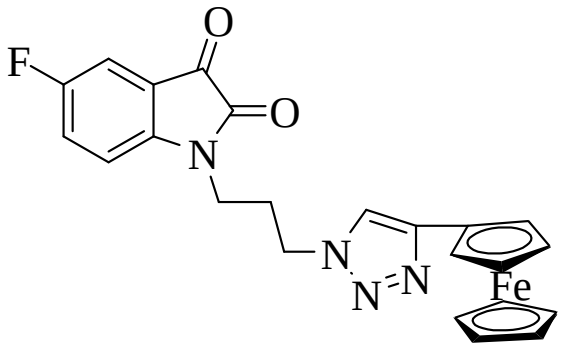
i. Synthesis of 1H-1,2,3-triazole tethered isatin-ferrocene conjugates

The synthesis and evaluation of isatin-ferrocene conjugates was performed against chloroquine-resistant and chloroquine-susceptible strains of *Plasmodium falciparum*. The isatin-ferrocene conjugates 17 and 18 were found to be most potent and non-cytotoxic from all synthesized conjugates. They have both electron-withdrawing halogen substituent at C-5 position of Isatin moiety and a propyl chain in optimum range.[23]



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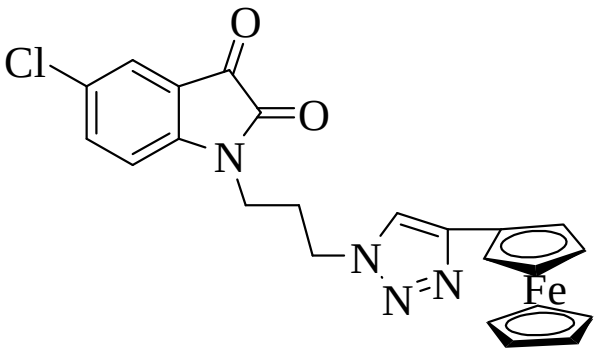
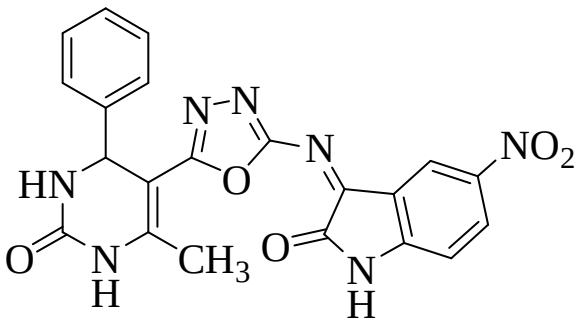


18

j. Synthesis of Tetrahydropyrimidine–isatin hybrids

A series of 5-substituted-3-[{5-(6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-oxadiazol-2-yl}-imino]- 1,3-dihydro-2H-indol-2-one were synthesized, characterized and screened for their anti-tubercular and antimalarial activity. The compounds 19 and 20 displayed excellent antimalarial potency.[23]



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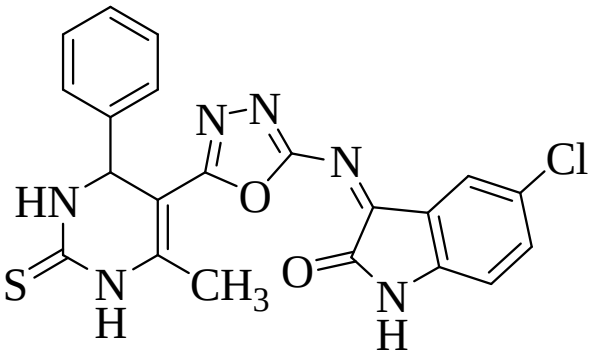
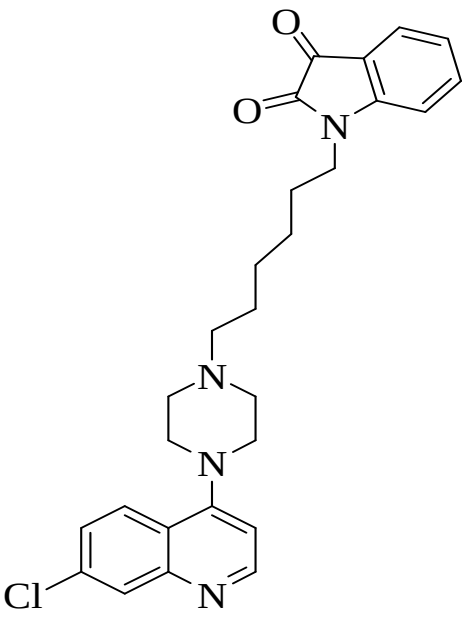


20

k. Synthesis of 7-Chloroquinoline–isatin Conjugates

A number of piperazine-tethered 7-chloroquinoline-isatin hybrids were synthesized. The synthesis can be either done by using the Cu()Cl-mediated Mannich reaction or by the direct nucleophilic substitution. The antimalarial and antitubercular activity was evaluated against chloroquine-resistant strain of *Plasmodium falciparum* and *Mycobacterium tuberculosis*, respectively. Also, the cytotoxicity is tested against 3T6 cell line, a permanent mouse embryonic fibroblast cell line. The most potent of the test compound 21 displayed a high selective index of 143.73.[24]

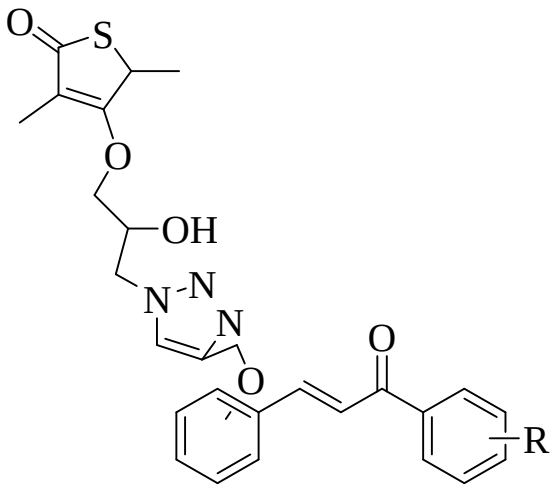


21

l. Synthesis of hybrids of chalcone, thiolactone and isatin moieties

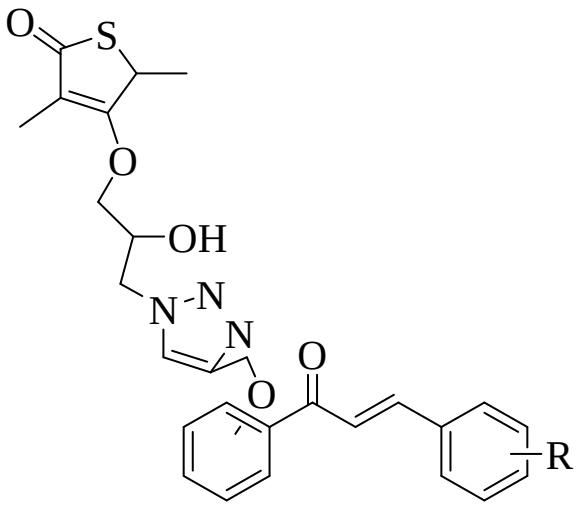
A series of hybrids of chalcone, thiolactone and isatin moieties are synthesized and evaluated. It was suggested from the biological evaluation that the thiolactone-chalcones (22, 23) were

most potent against W2 strain of *Plasmodium falciparum* than isatin-chalcones (24, 25), with IC50s ranging from 0.68 to 6.08 lM. But, isatin-chalcones displayed good falcipain-2 inhibitory activity, as compared to thiolactone-chalcones.[25]



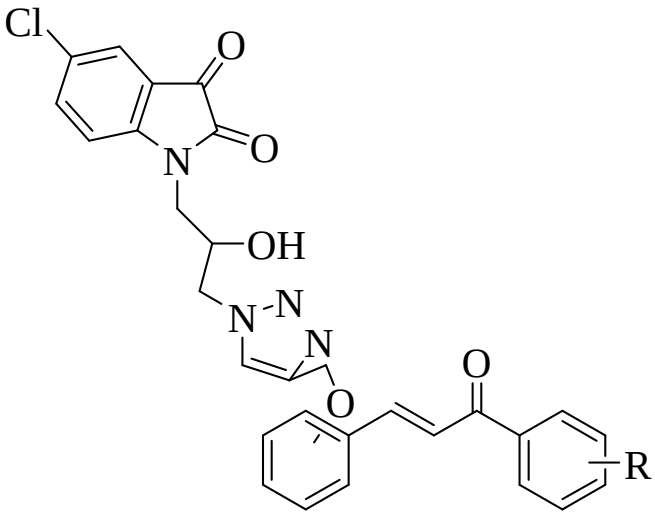
22

Where R = 4-methoxy; 2,4-dimethoxy; 2,3,4-trimethoxy.



23

Where R = 4-methoxy; 2,4-dimethoxy; 2,3,4-trimethoxy.



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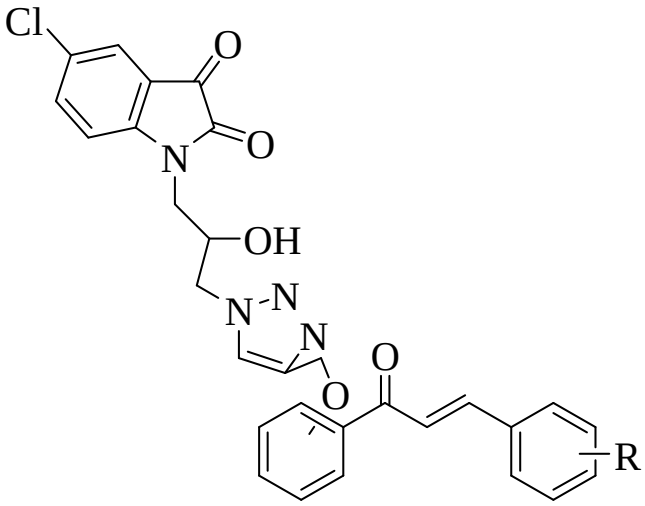
Where R = 4-methoxy; 2,4-dimethoxy; 2,3,4-trimethoxy.



25

Where R = 4-methoxy; 2,4-dimethoxy; 2,3,4-trimethoxy.

3. CONCLUSION

The isatin moiety displays wide range of biological and pharmacological activities such as anti-tumor, anti-HIV, antiviral, anti-angiogenic, antifungal, anti-Parkinson's disease, anticonvulsants, etc. Here, we presented the synthesis of substituted isatins, conversion of aniline to isatins, synthesis of new 3-[(5-benzylidene-2-phenyl)-3,5-dihydro-4-*H*-imidazol-4-one-3-(4-bezoylhydra zono)]-indole-2-ones, synthesis of hybrids of chalcone, thiolactone and isatin moieties, synthesis of 7-Chloroquinoline–isatin Conjugates, etc. The knowledge of the synthesis of Isatins may help in the further synthesis of various drugs as it itself show many biological activities.

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