SYNTHESIS AND DIVERSE BIOLOGICAL ACTIVITY OF ISATIN DERIVATIVES – A REVIEW

SAYEDA HINA NAAZ
Masters in pharmacy (department of pharmaceutical chemistry)
Sarojini Naidu Vanitha Pharmacy Mahavidyalaya, Tarnaka, Secunderabad, Telangana, 500017

DR. HEMALATHA
SATTU
Professor (department of pharmaceutical chemistry)
Sarojini Naidu Vanitha Pharmacy Mahavidyalaya, Tarnaka, Secunderabad, Telangana 500017

MUGA SAWMYA
Masters in pharmacy (department of pharmaceutical chemistry)
Sarojini Naidu Vanitha Pharmacy Mahavidyalaya, Tarnaka, Secunderabad, Telangana 500017

SHRUTI DESHPANDE
Masters in pharmacy (department of pharmaceutical chemistry)
Sarojini Naidu Vanitha Pharmacy Mahavidyalaya, Tarnaka, Secunderabad, Telangana 500017

ABSTRACT: Heterocyclic moiety serve as perfect framework on which pharmacophore can be effectively attached to produce novel drugs. Isatin (1H-indole-2,3-dione) and its analogues are an important class of heterocyclic compounds and are used in the synthesis of a large number of pharmacologically active compounds. This review comprehend the various synthetic methods for the isatin derivatives, its chemical reactivity, mechanism of action and structural activity relationship. Isatin and its analogues plays a key role in biological applications. Thus, here investigations are made to study the variant developments in the biological activities such as anti-tubercular, antioxidant, anticancer and many more biological evaluation of isatin.

KEY WORDS: Heterocyclic moiety, isatin, anti-tubercular, antioxidant, anticancer.

I. INTRODUCTION

Isatin (1H-indole-2,3-Dione) is an endogenous polyfunctional heterocyclic compound that exist as an indole derivative. It consists of two types of carbonyl groups, one is keto group and the other is lactum group. Isatin has been discovered 150 years ago. In 1841, it was first synthesised in the laboratory as an oxidation product of indigo by chromic and nitric acids [1] by Erdman [2] and Laurent [3] and now it is known as Oxindole and tribulin. It is orange-red in colour and has a freezing point of 200°C.
Naturally, isatin[4] occurs in the plants of genus Italis[5], in couroupitaguaianensis Aubl[6], and in calanthe discolor Lindl[7]. Substituted Isatins are also found in melosatin alkaloids and even from fungi[8]. Additionally, it is an endogenous compound that occurs in human as a metabolic derivative of tryptophan and adrenaline[9].

Isatin covers a wide range of pharmacological activities that include anticancer, anticonvulsant, anti-inflammatory, antimicrobial, antiviral and many other activities. There has been study attempts for different Isatin derivatives for their synthetic aspect[10,11]. This review brings a broad outlook about the chemical reactivity of isatin moiety, its synthesis, mechanism of action of isatin at different sites and various biological activities.

II. SYNTHESIS

Sandmeyer synthesis:

Synthesis of isatin through sandmeyer reaction is one of the most famous synthetic procedure. It is the oldest and the most forward way for the synthesis of isatin derivatives. The synthesis of isatin involves the condensation of trichloroacetylamine, hydroxylamine and primary aryl amine to produce an isonitroacetanilide. This in the presence of strong acid such as concentrated sulphuric acid upon electrophilic cyclization of latter gives isatin derivatives and is generally known as the sandmeyer isatin synthesis[12].

\[
\begin{align*}
\text{R} & \quad \text{NH} \\
\text{NH} & \quad \text{O} \\
\text{OH} & \quad \text{HCl, Na}_2\text{SO}_4 \\
\end{align*}
\]

Figure 1: Synthesis of sandmeyer isatin.

Stolle synthesis:

Stolle synthesis is the most effective procedure for the production of isatin derivatives and is the best alternative to sandmeyer methodology.

Stolle synthesis is a series of chemical reaction in which the first step is an amide coupling and the second step is friedal-crafts reaction.

The first step i.e., the amide coupling involves the condensation of aryl amine with oxalyl chloride to form an chlorooxalylanilide intermediate. This chlorooxalylanilide upon cyclization in the presence of a lewis acid such as titanium tetrachloride or boron trifluoride gives isatin derivatives.

This methodology can be used for the synthesis of both substituted and unsubstituted isatin derivatives[13,14].
Gassman synthesis:

Gassman synthesis is a new approach initiated by gassman for the development of isatin derivatives. This method involves the conversion of aniline to methylthyiooxindol intermediate through characteristic relationship between electrons donating and an electron withdrawing groups. The methyl group of this intermediate is oxidized by N-chlorosucsinamide, which further undergo hydrolysis of chlorinated intermediate for the formation of isatinderivatives[15,16].

MECHANISM OF ACTION

Isatin identified as major constituent of tribulin is a low molecular weight Monoamine oxidase type-B inhibitor[17]. Isatin plays a key role in Acetylcholine in brain by increasing Dopamine level under stress[18,19]. Inspite of tribulin containing isatin[20] metabolites, their physiological and pathological roles are not identified. In humans, tribulin
levels are in higher concentration due to exercise[21] and old age[22]. The excretion level of tribulin is higher in females in comparison to males[23]. Tribulin is enhanced in conditions like stress, agitation or anxiety. Thus, during stress corticotropin releasing factor cells and catecholamine synthesizing cells involved in isatin production[24] plays an important role in stress responses. Tribulin is an anxiety promoting agent[25] which acts on central benzodiazepine receptors. It is selective MAO-B inhibitor and its potency as monoamino oxidase and benzodiazepine receptor binding inhibitors is roughly equal[26]. At higher concentration it even inhibits alkaline phosphatase[27]. Tribulin is extracted from tissues and body fluids with ethyl acetate.

Isatin inhibits acetylcholine esterase (AChE) activity in rat brain[28]. The key role of isatin is to regulate acetylcholine (Ach) levels in rat brain. After 24hrs of administration (50 or 200mg/kg, i.p.) of the levels of Ach, choline (ch), and DA in rat tissues. It was elucidated that Ach and ch levels in the striatum receiving isatin is increased significantly[29]. In other words, isatin induces 93% of MAO inhibition and a 5% of AChE inhibition in the rat brain which states that isatin has a higher affinity for MAO than AChE. Isatin increases Ach levels by affecting central nervous system and not by inhibiting AChE. Isatin inhibits several enzymes in various tissues, like acid and alkaline phosphatase[30], hyaluronidase[31] and Monoaminoxidase. It has been found that isatin enhances antiseizure activity[32] and also acts as benzodiazepine blocker[33]. Isatin attenuates ANP-stimulated guanylatecyclase activity in many regions of rat. It is also found that the anxiogenic effect of isatin is explained by antagonism of ANP.

**CHEMICAL REACTIVITY**

**N-ALKYLATION:**

Many methods were discovered for N-alkylation of isatin in which the most commonly used is the one alkylated by allowing the reaction of isatin sodium salt with alkyl halides[34,35]. Reaction of isatin with sodium hydride in presence of DMF[36] or toluene under reflux[37] gave sodium salt of isatin. Some other methods uses potassium carbonate in acetone or in DMF[38,39] for preparation of sodium salt of isatin.

**N-ARYLATION:**

N-Arylisatin can be synthesised by the reaction of isatin with p3Bi(OAC) and CuO under an inert atmosphere[40] or from arylbromides and cupric oxide[41].

**N-Acylation:**

There are many methods for the preparation of N-acylisatin by using Acyl chlorides or anhydride either alone[42] or by the use of perchloric acid, triethylamine[43], pyridine in benzene[44], or triethylamine in chloroform[45,46] as catalyst. It can also be obtained by the conversion of isatin to sodium isatide by the use of NaH in presence of toluene under reflux followed by the reaction with acyl chlorides[47]. Diacyl chlorides such as nonanedioyl chloride[48], oxalyl chloride[49] and octanediol leads to the formation of a bis-acylisatin.

**N-SULFONYLATION:**

By applying the same methodologies as used for the synthesis of acyl isatin, N-Sulfonylisatin can be synthesised by the reaction of isatin with sulfonyl chlorides[50].
N-HALO DERIVATIVES:

The treatment of isatin with sodium hypochlorite in acetic acid leads to the formation of 1-chloroisatin.

1-chloroisatin is an effective oxidizing agent that converts alcohols to aldehydes and ketones[51] and of insoles to 3-chloroindoles without formation of any by-products[52].

**STRUCTURAL ACTIVITY RELATIONSHIP**

![Chemical Structure](image)

Figure 4: Isatin

NatasaritoVaska et al. Explained that substitution of R1 by electron donating groups yield more active compounds[53].

Thomson et al. Proposed that there is enhanced CNS activity with substitution at 5, 6 and 7[54].

Addition of nitro group at C5 enhances the anticancer activity while addition of a methoxy group increases cytotoxicity.

Halogenation gives more active compounds that parent compounds[55] with 5-bromo-, 5-iodo-, and 5-fluroisatin.

Furthermore, N-Alkylation and Acylation can be carried out on 1sr position.

Substitution of phenyl ring at 3\textsuperscript{rd} position enhances antimicrobial activity[56].

Different degree of biological activity has been found with variation at 3\textsuperscript{rd} position[57].

Prakash et al. Suggested that reaction of aromatic amine with schiff base leads to the formation of a compound with increased anticonvulsant activity[58].

**MEDICINAL IMPORTANCE OF ISATIN DERIVATIVES:**

**ANTIOXIDANT ACTIVITY**

Prakash CR(2011) and his companions synthesised a number of novel schiff bases of isatin by condensation of imesatin with aldehydes. These were synthesised by reaction of isatin with pphenylenediamine. The chemical structures confirmed by IR, HNMR and elemental analysis were screened for antioxidant activity by DPPH radical scavenging activity[59].
Sriram D, Bal TR reported that N-methylisatin-β-4′,4′-diethyl thiosemicarbazone and Nallyl-β-4′,4′-diallyl thiosemicarbazone shows inhibition of HIV by action on reverse transcriptase and viral spectral proteins[60].

Synthesis and evaluation of non-nucleoside HIV-1 reverse transcriptase inhibitors I.e., novel aminopyrimidiniminoisatin derivatives found to be most active against HCV, mycobacterium tuberculosis, HIV and various pathogenic bacteria[61].
Naveen chandral (2015) reported the synthesis of 3, 5-dialkylamino substituted 8H, 10H, 15H, 15b(S)-2,3,6,7-tetrahydro-1,5,3-dioxazepino[3,2-c]pteridine-7-one derivatives potential anticancer agents. They are the growth inhibitors of murine leukemia L1210 cells, comparable to ellipticine[62].

Maryam lelyukh, Dmytro Havrylyuk and Roman lesyk reported the synthesis of 3-hydrazino-5-sulphamoylisatin by the reaction of 5-sulphamoylisatin with hydrazine. By evaluating mean survival time, tumor volume, viable and non-viable tumor cell, the antitumor effect was determined[63].

Javid et al., in 2018 have designed a new class of potent isatin based oxadiazole derivatives and evaluated for anticancer activity against thymidine phosphorylase. It was observed that substitution of -OH and –OCH3 on aryl ring of final product develops into more potent compound[64].
ANTI-MICROBIAL ACTIVITY:

Chaluvaraju kc, Zaranappa(2011) reported the synthesis of novel isatin derivatives using schiff and mannich reaction. The microbial properties was investigated against B.sub, S.typhi and C.albicans using cup plate method. amoxicillin was used as the standard drug. Evaluation showed mild to moderate activity[65].

Anticonvulsant activity:

Kumar et al., suggested that for achieving excellent anticonvulsant activity, variation at para position of phenyl ring consisting of chloro and nitro substituted compound is more preferred when compared to the substitution at any other position[66].
Ragavendran et al., reported the synthesis of N-aryl/alkylidene-4-(1,3-dioxo-1,3-dihydro-2H isoindol-2-yl) butanoyl hydrazides/butanamides which were effective at dose 30mg/kg and was more potent than standard phenytoin and ethosuximide[67].

Sridhar et al., reported the synthesis of 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indole-2-one which was found to be active in MES test and more potent than standard phenytoin and ethosuximide[68].

Lozinskaya et al., suggested that inhibition of glycogen synthase kinase will be a good step towards treatment of cancer and diabetes. Isatin was a starting material for synthesised compounds. Evaluation of the synthesised compounds were done on streptozotocin-treated. The following compound showed improved glucose tolerance at a dose of 50mg/kg of body weight and was found to be more active with an IC50 value of 4.19nM[69].

Gao et al., synthesised a series of Moxifloxacin-acetyl-1,2,3-1H-triazole-methylene-isatin hybrids which were found to have a very good anti-tubercular activity when evaluated against mycobacterium tuberculosis strains[70].
CONCLUSION:

This literature gave a light that isatin moiety has biological activities and can be used for as an intermediate for synthesizing various heterocyclic moieties. Various synthetic methods for the synthesis of Isatin were discussed. Thus, Isatin has a key role in biomedical applications and act as precursor for Synthesis of large number of pharmacologically active compounds.

REFERENCES:

MAO inhibitor, on acetylcholine and dopamine levels in the rat striatum. Biogen Amines 5: 367-377.


52. Tomchin AB, Tumanova IV (1990) Semicarbazonesemiosemicarbazine and
heterocyclic series. LV. Recycling 3-thiosemicarbazone 5 nitroizatina to form 1,2,4- triazine and indazole. Zh Org Khim 26: 1327.


