



- A REVIEW

## RECENT PHARMACOLOGICAL ADVANCEMENTS IN ISATIN CHEMISTRY

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### ABSTRACT

Isatin (1*H*-indole-2,3-dione) is a heterocyclic compound, involved in many pharmacological activities. Significant amount of data has been published about its pharmaceutical importance; therefore, a comprehensive overview of recent developments is required. This review will provide a brief account on the recent advancements and future perspectives in the pharmacological aspects of isatin and its derivatives reported in last six years. Besides many other pharmacological activities, isatin and its derivatives have been found to show promising results against various cancer cell lines and a large range of pathogenic microbes. Isatin is a versatile precursor for many biological active molecules. Most of the work done reported in literature is about *in vitro* studies and only few examples are *in vivo* studies in rats. Therefore, a more systematic and targeted scientific research is required to use these therapeutically potent molecules as drugs.

**Key words:** Isatin, Anticancer, Antioxidant, Antimicrobial, Monoamine oxidase, Pharmacology.

### INTRODUCTION

Isatin occurs in roots and leaves of the *Strobilanthes cusia* (Nees) and was first isolated from plants of the *isatistinctoria*, *couroupitaguianesis* and *calanthe discolor* in 1840<sup>1</sup>. These plants are abundant in northern and central China and are of ethnic importance in traditional therapeutics. Isatin can also be found in secretion from the parotid glands of Bufo frogs and other biotic like; Caribbean tumorigenic plant, *Melocitomentosa*, fungi and

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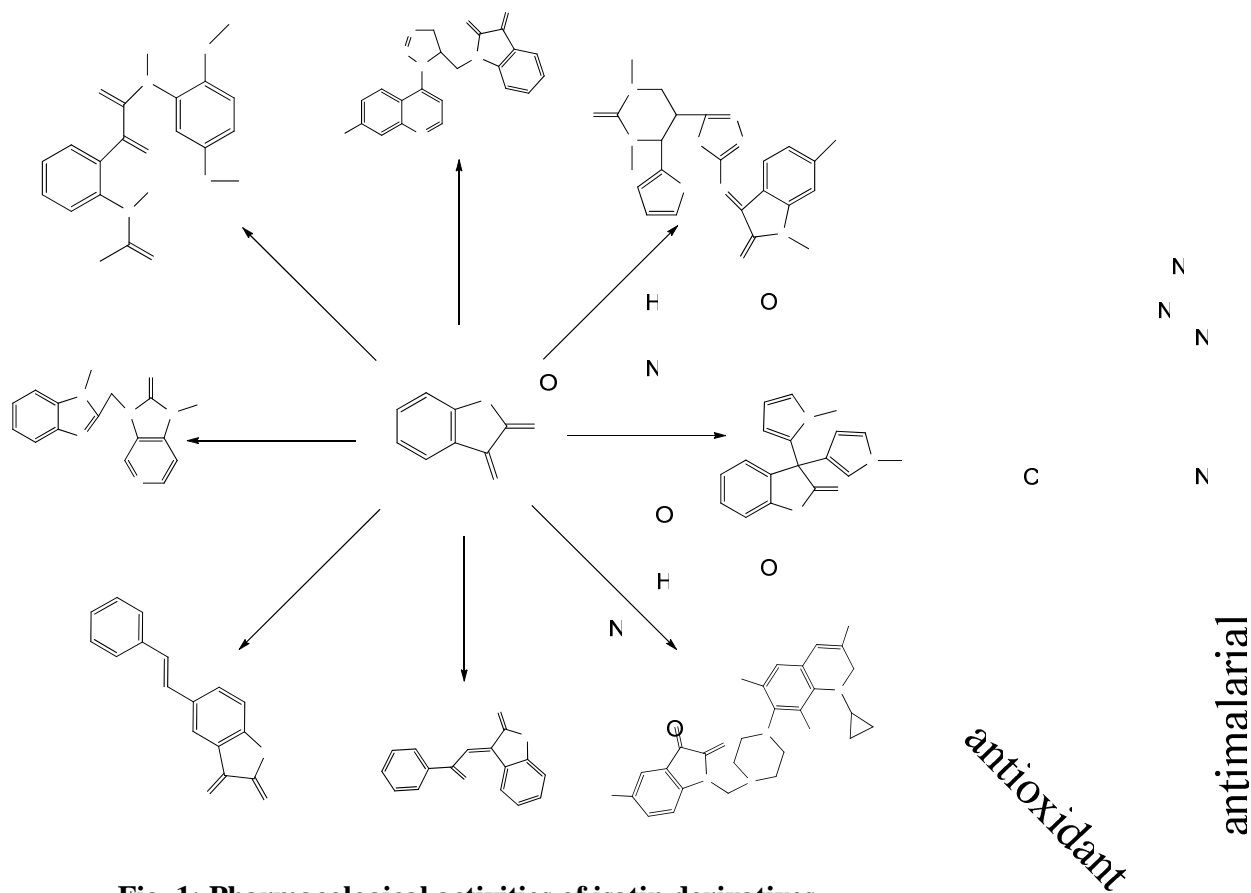
marine mollusks. Isatin was first synthesized by Erdmann and Laurent in 1840<sup>2</sup>. Isatin and triazole containing heterocyclic compounds are reported as a cure of lethal diseases<sup>3</sup>. Extensive literature has been published regarding the chemistry of this medically important compound including few reviews<sup>4</sup> i.e. Sumpter, Popp and Dasilva. However, in the literature synthesis, reactivity and pharmacology of isatin has been extensively discussed but a brief account on pharmacological developments of isatin in recent past is required. Current work is an effort to summarize the published pharmacological data of isatin and its derivatives in last five years.

### Pharmacological properties of medically important isatin

Isatin can also be found in rat brain, mainly in hippocampus, cerebellum and in other mammalian tissues, where it functions as modulator of biochemical processes<sup>5</sup>. Isatin and its derivatives have been reported highly efficient during *in vitro* studies against genotoxic and mutagenic diseases but during *in vivo*, the genotoxic and mutagenic potentials of isatin is not well established and reported. Isatin was first reported as “Tribulin” and was identified as a selective inhibitor of monoamine oxidase (MAO)<sup>6</sup>. Isatin shows a wide range of pharmacological activities reported in the literature including antiviral<sup>7</sup>, anticancer<sup>8-10</sup>, spermicidal<sup>11</sup>, anti-corrosive<sup>12</sup>, analgesic<sup>13</sup>, anti-convulsant<sup>14-16</sup>, antioxidant<sup>17</sup>, transthyretin fibrillogenesis inhibitory activity<sup>18</sup>, anti-depressant<sup>19</sup> and anti-epileptic<sup>20</sup>. List of pharmacological activities of isatin is long but only few of them are selected and summarized in this review (Table 1).

**Table 1:**

Pharmacological activities	References
Anticancer	21-31
Antiallergic	18-20
Antimalarial	32-34
MAO inhibitor	32-34
Antiviral	35-37
Antimicrobial	38-48



**Fig. 1: Pharmacological activities of isatin derivatives**

### Antiallergic

Asthma is characterized by heavy production of sputum leading to a chronic cough, decreased lung function, increase susceptibility to exacerbation and obstruction of air flow and claims 300 million people worldwide and still number is increasing every year<sup>21</sup>. Traditionally, asthma is treated by inhalation of drugs containing corticosteroids and long-acting beta agonists; which reduce swelling and body immune response but these drugs can contribute to serious side effects. However, encapsulated isatin in chitosan nanoparticles have been reported effective against allergic asthma<sup>22</sup>. Respiratory syncytial viral infection can be the reason of asthma in infants. Moreover, asthma is currently cured with prophylactic treatment, which is expensive and tedious. However, benzimidazole derivatives of isatin have been reported effective against respiratory syncytial viral infection<sup>23</sup>. Therefore, a more comprehensive and targeted research is required to find out potential drug candidates against asthma from the isatin derivatives.

## Anticancer

Isatin and its derivatives have been found effective against a variety of cancer cell lines<sup>24-28</sup> and possess cytotoxic activities<sup>29,30</sup>. Cancer is a fast growing threat in the current century; therefore, new therapeutics are required to counter it<sup>31</sup>. Derivatives of isatin are recently reported for antineoplastic activity<sup>32</sup> and are even found effective to inhibit tyrosin kinase, serine kinase, cyclic-dependent kinase, carbonic anhydrase isozyme and caspase 3, which is involved in apoptosis<sup>33,34,49</sup>. Diversified nature of isatin makes it a versatile substrate for further modifications. Therefore, many derivatives of isatin have been synthesized and evaluated both for *in vitro* and *in vivo* studies and reported for cytotoxic and antitumor activities especially against human lymphoma cells<sup>50,51</sup>. Moreover, various derivatives of isatin have been reported effective against breast cancer cells, lung cancer and prostate cancer and neuroblastoma cell line<sup>35-39</sup>. Some modifications like a halogen at position C-5 can enhance the anticancer activity<sup>40,41</sup>. Isatin is important as an anticancer moiety as evident from literature; therefore, more extensive and scientific approach is required to get the new therapeutic molecules against cancers.

## Antimalarial

Malaria, an epidemic disease of recent past claims almost 500 million affected people with a death toll of one to three millions every year. *Plasmodium falciparum*, main cause of malaria has developed resistance against traditional treatment of chloroquine, cycloguanil and pyrimethamine due to gene mutation. In the quest of new and effective drugs, some derivatives of isatin have been recently evaluated and found to be effective during *in vitro* studies against *Plasmodium falciparum* W2 strain<sup>42</sup>. Carbodithioate 2,3-dioxindoline derivatives of isatin have been reported to show antimalarial activity against *Plasmodium falciparum*<sup>33</sup>. Schiff base derivatives of isatin are also known to exhibit good *in vitro* activity against four species of Plasmodium (*Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium falciparum* and *Plasmodium vivax*)<sup>43</sup>. The literature shows that current focus of antimalarial activity of isatin derivatives has been converged in the recent years and it will help to explore new drug candidates for chloroquine resistant variety of Plasmodium.

## Monoamine oxidase inhibitor

Monoamine oxidase (MAO) is a flavine adenine dinucleotide containing enzymes involved in the catalysis of oxidation of serotonin and norepinephrine by utilizing dopamine as substrate. MAO activity in brain increases with age and cause neurodegenerative disorders such as Parkinson disease<sup>44</sup>. Synthesis and evaluation of MAO inhibitors are an

active area of research and isatin has been reported as reversible inhibitor of MAO isozyme<sup>45,46</sup>. Recently, isatin derivatives styrylisatin with substitution at five and six position have been reported to exhibit more inhibiting affinity than isatin itself alone<sup>47</sup>. Chlorostyrylcaffeine, synthesized from caffeine and isatin, has been found 40,000 fold more potent inhibitor of MAO-B than is caffeine itself<sup>48</sup>. Phthalimide is an isomer of isatin, substituted analogues of which has been evaluated as inhibitor of MAO-A and B. Phthalimide with benzyloxy side chain has been reported to possess good binding affinity to MAO-B<sup>52</sup>.

### **Antiviral**

Isatinoxime ether derivatives have been reported for their *in vitro* cytotoxicity and inhibitory activity against respiratory sanctial virus, which produces infection in children before 2 years of age and cause death. Isatin and its derivatives have been reported to exhibit inhibitory effect against the replication of a variety of viruses such as harps simplex virus, adenovirus, poxvirus, herpesvirus, picornavirus, reovirus, orbovirus, myxo and paramyxovirus and retrovirus, influenza virus and human immune virus<sup>53</sup>. Isatin sulfamidine derivatives are reported as the potential inhibitors of swine influenza virus<sup>54</sup>. *N*-Mannich base derivatives of thiosemicarbazoneisatin with substituent at C-5 have been reported with activity against sars virus, pox virus, viccinia, rhino virus and meloneyleukemia virus<sup>55</sup>.

### **Antimicrobial**

Isatin analogues are important due to their therapeutic potential against a variety of pathogenic microbes. Isatin derivatives have been effectively evaluated against a variety of microbes, an example is thiadiazole derivatives and dispiropyrrolidine derivatives of isatin, are reported to show anti-tubercular activity against *Mycobacterium tuberculosis*<sup>56,57</sup>. Moreover, isatin substituted ciprofloxacin derivatives have been reported to exhibit *in vitro* activity against a variety of bacteria including gram positive, gram negative and anaerobic bacteria<sup>58</sup>. In addition, balofloxacin, ofloxacin and levofloxacin isatin derivatives have also been optimized for their anti-mycobacterial activities<sup>59,60</sup>. Moreover, metal complexes of Schiff bases, thiophenecarbonyl, isonicotinoylhydrazones, thiocarbohydrazide and rare earth metals like lanthanide derivatives of isatin have also been found active against microbes like *Escrishia coli*, *Staphylococcus aurous*, *Bacillus subtilis*, *Pseudomonas aeroginosa* and *Aspergillusniger* and some fungi. The results have been reported comparable to that of ciprofloxacin and amphotericin-B<sup>61-65</sup>. During *in vitro* studies of Schiff bases, isatinoisoxalin, spiroxindole and other derivatives of isatin have been reported to show antibacterial as well as antifungal activity against *Candida albicans* and *Aspergillus flaves*<sup>66-68</sup>.

## CONCLUSION

Isatin plays a significant role in pharmaceutical industry due to its usefulness as a substrate for various life saving medicines. Therefore, isatin and its derivatives are one of the developing area of interest for the synthetic chemists and pharmacists.

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