Isatin-Based Scaffolds

Subjects: Tropical Medicine

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Isatin, chemically an indole-1*H*-2,3-dione, is recognised as one of the most attractive therapeutic fragments in drug design and development. The template has turned out to be exceptionally useful for developing new anticancer scaffolds, as evidenced by the increasing number of isatin-based molecules which are either in clinical use or in trials. Apart from its promising antiproliferative properties, isatin has shown potential in treating Neglected Tropical Diseases (NTDs) not only as a parent core, but also by attenuating the activities of various pharmacophores.

isatin antiproliferatives antiplasmodials antimycobacterials antimicrobials

1. Introduction

Isatin, also known as 1*H*-indol-2,3-dione, is a natural heterocyclic compound extracted as red-orange powder from a variety of plants worldwide, including *Isatis tinctoria*, *Couroupita guianensis Aubl*, *Melochia tomentosa*, and *Boronia koniamboensis* [1]. Moreover, it is also found in the secretion of the parotid gland of Bufo frogs as well as in the Australian mollusc *Dicathais orbita* [2]. In humans, it is identified as a metabolite of tryptophan or epinephrine and is largely distributed in the central nervous system (CNS), peripheral tissues, as well as body fluids. Substituted isatins can also be found in plants such as melosatin alkaloids (methoxy phenyl isatins) isolated from the Caribbean tumourigenic plant *Melochia tomentosa*, as well as in fungi, such as 6-(3-Methylbuten-2'-yl) isatin and 5-(3'-Methylbuten-2'-yl) isatin isolated from *Streptomyces albus* [3]. Among the most important biological activities of isatin derivatives are anticancer, antitubercular, antimalarial, antifungal, antibacterial, anticonvulsant, and antiviral properties. Despite the dominance of biological applications, other areas such as catalysis, dye compounds, nanocomposites, and polymers have merited special attention. Isatin derivatives possess a wide range of applications due to their inherent versatility in structure, which allows for the construction of diverse frameworks suitable for a specific biological or chemical property of interest. A variety of substituents, particularly at N-1, C-3 (C=O) and C5/C6/C7 (aromatic), can be introduced, modulating both the biological and chemical properties of the parent core [4].

2. Anticancer Activities of Functionalized Isatins

In every country on this planet, cancer is the main source of mortality and a key hindrance to extending life expectancy. Cancer is the primary or second largest cause of death among people under the age of seventy, according to the World Health Organization (WHO). Globally, 19.3 million new cancer cases are expected to be diagnosed in 2020, with about 10.0 million cancer deaths [5]. Female breast cancer has superseded lung cancer as the most frequently diagnosed cancer, with an estimated 2.3 million new cases, followed by lung, colorectal,

prostate, and stomach cancers. The unprecedented diversity of cancer continues to provide insights to the underlying factors, but it also perpetuates the need for a global intensification of measures to control the disease [6].

A number of isatin-based compounds have entered into clinical trials, including two compounds, namely Sunitinib and Toceranib, that have been approved for clinical use against tumours (**Figure 1**). Sunitinib suppresses the catalytic activity of kinases in the phosphorylation of proteins by reversibly binding to their ATP binding sites. Toceranib, a Sunitinib-like molecule, acts as a selective inhibitor of specific receptor tyrosine kinases (RTKs), thus triggering tumour cells' apoptosis in vivo. Other derivatives, including Nintedanib, Semaxinib, and Orantinib, are currently undergoing clinical trials for their anticancer potential (**Figure 1**). These promising molecules have demonstrated the capacity to slow or stop the growth of tumours via modulating cell growth, proliferation, survival, and migration. However, some of these anticancer candidates also display side effects, such as limited efficacy, diarrhoea, hypertension, vomiting, hand–foot syndrome, and neutropenia, which provides an impetus for the identification of new candidates with promising activities [7].

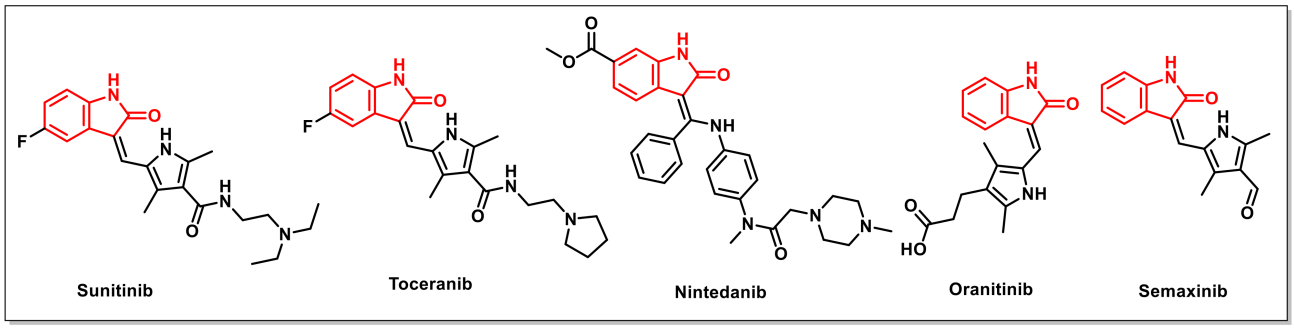

Figure 1. Structures of isatin derivatives approved as drugs or in clinical trials.

3. Antimycobacterial/Tubercular Activities of Isatin-Based Scaffolds

After the outbreak of COVID-19, TB is expected to be the second leading cause of death from a single infectious agent. In 2020, the WHO African and South-East Asia regions accounted for over 84% of HIV-negative TB deaths and 85% of all TB deaths among HIV-negative and HIV-positive adults. [8]. India accounted for 38% of global TB deaths among HIV-negative people and 34% of the total number of TB deaths among HIV-negative and HIV-positive people combined [9]. The rapid emergence of multi drug resistant (MDR) tuberculosis, combined with *Mycobacterium tuberculosis* (*Mtb*)'s prominent ability to enter a dormant state, known as latent TB infection, poses significant challenges for tuberculosis control [10][11]. As a result, the identification of novel targets and the development of new agents capable of combating drug-resistant tuberculosis and latent tuberculosis infection remain urgent priorities [12].

4. Antiplasmodial/Malarial Activities of Isatin-Based Scaffolds

P. falciparum, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* are members of the *Plasmodium* family of protozoan parasites that cause malaria. *P. falciparum* and *P. vivax* are the most virulent and are primarily responsible for the disease's morbidity and mortality [13]. An estimated 241 million malaria cases were reported in 85 malaria-endemic countries in 2020, an increase from 227 million in 2019, with the WHO African Region accounting for the majority of the increase. The WHO African Region accounted for nearly 95 percent of all cases in 2020, with an estimated 228 million cases. India accounted for 83 percent of the cases in the Southeast Asian region. Malaria deaths increased by 11% in 2020 compared to 2019 to an estimated 627,000; of the additional 69,000 deaths, an estimated 47,000 (68%) were caused by service disruptions during the COVID-19 pandemic [14]. The continuous evolving drug resistance to both the conventional (quinolines) as well as contemporary (Artemisinin combination therapy) drugs has exacerbated the need for identifying new entities with promising antiplasmodial activities. A number of reports have shown the potential of isatin-based compounds as promising antiplasmodials [15][16].

5. Antimicrobial Activities of Isatin-Based Scaffolds

Antibiotics are unquestionably a blessing to human civilization, having saved millions of lives by combating infections or microbes. Various antibiotics have been used for therapeutic purposes over the years. In the mid-twentieth century, antibiotics were regarded as the "wonder drug". There was an idealistic belief at the time that communicable disease was on its way out. Antibiotics were thought to be a magic bullet that selectively targeted microbes responsible for disease eradication. Antibiotic resistance progresses rapidly and is therefore a major source of concern. A growing number of infections, such as pneumonia and gonorrhoea, are becoming more difficult and, in some cases, impossible to treat, while antibiotics have become less effective [17].

6. Conclusions

Isatin is a highly promising scaffold in drug discovery due to its ubiquitous presence in biological systems; it is a molecular architecture that can be easily modulated in addition to a plethora of biological activities. Of course, isatin's anticancer potential is overwhelming, as evidenced by the number of isatin-based compounds in use as therapeutics or in various stages of clinical trials. Isatin derivatives have demonstrated promising antiproliferative attributes against various cancer cells, targeting specific biomolecules or organelles as free ligands or those coordinated to metal ions. Adherence to metal ions frequently enhances its bioactivities, indicating a synergistic mechanism comprising the metal and the ligand. They also disclose a variety of modes of action, including the ability to bind DNA, generate reactive species that induce oxidative damage, and suppress specific proteins. Isatin-pharmacophore hybrids have the potential to overcome drug resistance and provide new functional entities with multiple mechanisms of action and good safety profiles. In the case of antimycobacterials, the inclusion of isatin with isoniazid has not only improved the lipophilicity as well as the activity of the hybrids, but also minimized the frequency of the development of resistance. The inclusion of isatin core with quinoline core afforded hybrids better

antiplasmodial profiles than CQ itself against the CQ-resistant species of *P. falciparum*. The current evidence therefore suggests that further exploiting this promising moiety can provide efficient clinical candidates with a reduced incidence of drug resistance. The researchers anticipate that introducing isatin into various drugs/organic moieties will significantly impact the treatment of various diseases in the near future, given the multitude of biological activities and mechanistic pathways provided by isatin-based compounds.

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