

Effect of Substituents on the Biological Activity of Isatin Hybrids – A SAR Study

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ABSTRACT: Isatin (2,3-dioxindole) is a benzopyrrole derivative that belongs to a large class of heterocyclic chemicals. Isatin derivatives are essential synthetic substrates that can be utilized as starting materials to build a wide range of heterocycles with diverse applications in pharmaceutical sciences. Isatin derivatives therefore have recently gained a lot of attention. This review emphasizes on the Schiff base derivatives from isatin, isatin quinoline/flouroquinone, isatin -thiazole, isatin–azole hybrids, all possessing potential biological activity. The structure–activity relationships of these potential leads are also discussed.

KEYWORDS: 2,3-Dioxindole, Isatin hybrids, Benzopyrrole, Structure-activity relationship.

INTRODUCTION

Isatin was first isolated from the plants of *Isatis tinctoria*, *Couroupita guianensis* and *Calanthe discolor*, in 1840. It also occurs in the leaves and roots of the plant *Strobilanthes cusia*, commonly known as Nees [1, 2]. Linne Erdman and Auguste Laurent first discovered Isatin from an indigo dye in the year 1941. It was first synthesized by the oxidation of indigo with nitric acid and chromic acid [3]. Isatin or 1H-Indole-2,3-dione is also known as indole quinine or indanedione. It is a fusion of a six membered ring, benzene, with a five membered ring containing nitrogen, both being on the same plane. Baeyer in 1882 disclosed that isatin can be represented in two tautomeric forms, the lactum or the lactim structure [4, 5].

Isatin derivatives possess varied pharmacological properties [6]. It also acts as a building block for a number of complex heterocyclic molecules [7] and is able to participate in a broad range of reactions particularly in synthetic medicinal chemistry [8] owing to the presence of several reaction centers. The keto group at position 2 as well as at position 3 can undergoes addition as well as condensation reactions. Isatins have also been found in mammalian tissues where their role comprises of a modulator of biochemical processes [9]. It is also found as a core component in a variety of dyes, agricultural products and pharmaceuticals [4].

Literature survey reveals that various derivatives of isatin possess diverse biological activities such as antibacterial, antifungal, antiviral, anti-HIV, anti-mycobacterial, anticancer, anti-inflammatory and anticonvulsant activities [10, 11]. Isatin has been the focal point for developing antibacterial agents [12] through chemical modifications involving Schiff base formation [13], N-alkylation/acylation [14, 15], Mannich base synthesis [16] and metal complexations [17, 18]. The broad spectrum of biological activities exhibited by isatin and its derivatives combined with the potential for structural modifications have inspired the study of this class of compounds to help create a large pool of structurally diverse moieties.

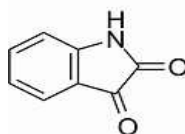


Figure 1: General Structure of Isatin



Figure 2: Lactum structure Lactim structure

The most common synthesis of isatin (or substituted isatin) is by the Sandmeyer isatin synthesis which consists of reacting aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form isonitrosoacetanilide. The latter after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield. The method also applies to anilines with electron-withdrawing substituents, such as 2-fluoroaniline, and to some heterocyclic amines, such as 2-aminophenoxathine [9].

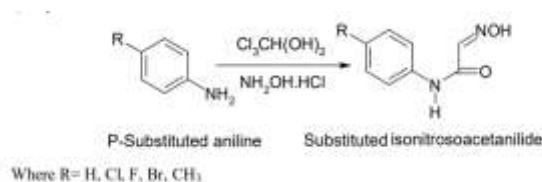


Figure 3: Synthesis of Substituted isonitroso acetanilide from substituted aniline

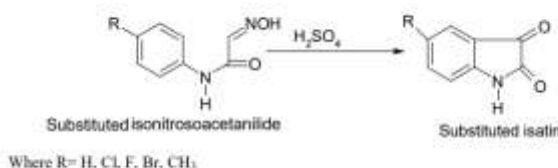


Figure 4: Synthesis of 5-substituted isatin from substituted isonitrosoacetanilide

In this review we shall focus on the SAR of isatin hybrids with respect to their pharmacological activity.

RESULTS AND DISCUSSION

1. Schiff bases of isatin

Schiff bases of isatin possess anti-HIV, anticonvulsant, antibacterial, antianxiety, anthelmintic, antiprotozoal, antifungal, antiviral, and anthelmintic activities [4-19]. Bis-Schiff base derivatives of isatin were evaluated both in vitro and in vivo and were reported to show cytotoxic and antitumor activities especially against human lymphoma cells [19]. Based on the hypothesis that by directly connecting two isatin-containing molecules via a bis-Schiff base linker, the resulting compounds by virtue of bearing a symmetrical structure will have greater flexibility and aqueous solubility [20] than indirubin or meisoindigo [10], a number of symmetrical Schiff base compounds were synthesized and tested for biological activity. The synthesized compounds had improved bioavailability [10, 19, 16] and had comparable if not enhanced pharmacological activity.

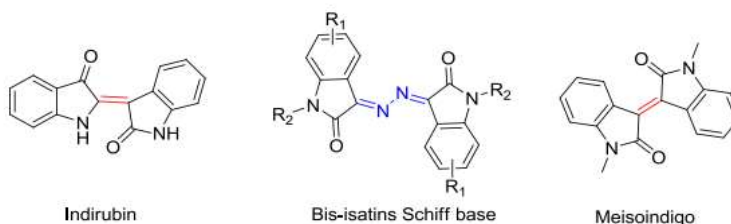


Figure 5: A structural comparison of the designed symmetrical Schiff base derivatives of isatin with Indirubin and Meisoindigo

2. Isatin-Quinolone/Fluoroquinolone hybrids

Fluoroquinolones or FQs have prominent antibacterial activity, and the World Health Organization has recommended several of them as second-line of treatment for bacterial infections [21]. Furthermore, the lipophilicity of FQs plays a crucial role in their entry into the bacterial cells [22]. The addition of lipophilic groups at the C-7 position helps boost anti-TB activity. Four different series of isatin clubbed quinazoline [23], phthalazine, and quinoxaline [24] derivatives were synthesized and tested for their anticancer efficacy against the HT-29 (colon), ZR-75 (breast), and A-549 (lung) cancer cell lines.

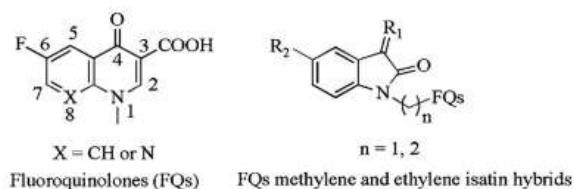


Figure 6: Chemical structures of FQs and FQs methylene and ethylene isatin derivatives

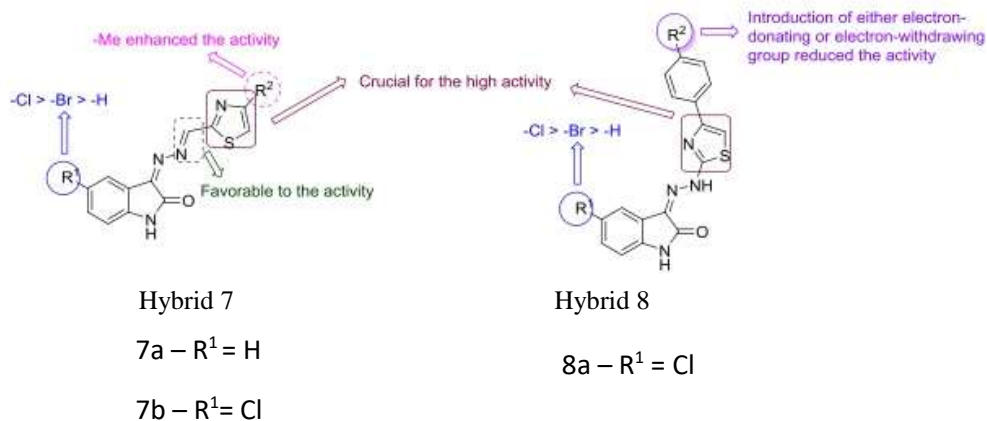
3. Isatin-thiazole/thiazolidinone derivatives

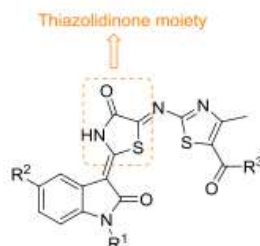
Anticancer activity is one of the pharmacological features shown by isatin-thiazole/thiazolidinone derivatives and several anticancer drugs such as tiazofurin and bleomycin have this moiety [25]. This class of compounds have therefore been explored as potential anticancer leads [23, 26].

The isatin-thiazole hybrids (7) and (8) showed promising action against A-549, ZR-75, and HT-29 cancer cells [27]. SAR studies showed that the thiazole moiety was responsible for the increase in activity. Substitution of thiazole by the phenyl ring brought about a loss of activity. Introduction of halogen atoms at the C-5 position of the isatin moiety proved favorable, the relative increasing order in activity being Cl > Br > H. For the molecule (7), electron-donating groups such as methyl on the thiazole skeleton showed higher activity as compared to unsubstituted analogs [26].

For the hybrid molecule (8), the introduction of either electron-donating or electron-withdrawing groups at para-position of the phenyl ring in the thiazole moiety decreased the activity. Compound (7b) [28] was 1.3–7.1-fold more powerful than Sunitinib against all the three tried cancer cell lines, while hybrid (6a) seemed to decrease the cell development of the multidrug-resistant lung cancer NCI-H69AR cell line.

The thiazolidinone tethered isatin-thiazole hybrids (9) exhibited promising antibacterial, antitubercular, and antifungal activity but none were active against a panel of 60 cancer cell lines [28] indicating that the thiazolidinone tether was irrelevant for anti-cancer activity.





Hybrid 9

Figure 7: Chemical structures of isatin–thiazole/thiazolidinone hybrids 7-9

4. Isatin -1,2,3 –Triazole hybrids

1,2,3-Triazole, a moiety commonly associated with biodiversity and hence a potential lead for new drugs [29] has the capability to enhance the pharmacological, pharmacokinetic and physiochemical profiles of molecules as they are able to modify the lipophilicity, polarity and hydrogen bonding capacity of molecules [30]. Moreover drugs containing the 1,2,3-triazole moiety such as Cefatrizine [31] and Carboxyamidotriazole [32] can be used to treat various cancers. Therefore, such hybrids act as leads for the development of new anticancer agents [10, 26, 33].

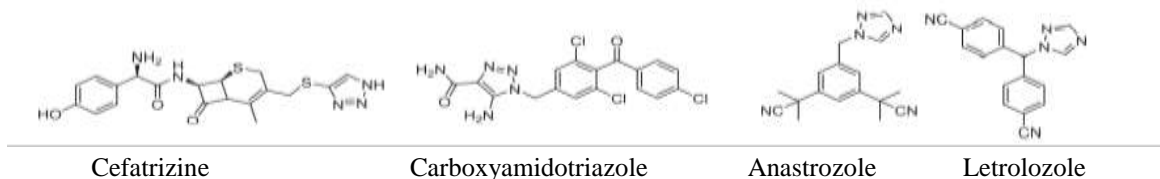


Figure 8: Chemical structures of the azole-based anticancer agents

The SAR study of isatin–1,2,3-triazole hybrids, Figure 9, against DU145 (prostate), PC-3 (prostate), MDA-MB-231 (breast), BT549 (breast), A549 (lung), and HeLa (cervical) cancer cell lines indicated that the configuration of the molecule had a bearing on the activity. The Z- configuration were in general more potent than the corresponding E- isomers [34]. The electron-donating bulky aryl groups at C-5 position (R1) of the isatin moiety were more favorable than electron- withdrawing groups, whereas hybrids with methoxy at phenyl ring (R2) could not improve the activity when compared with their unsubstituted analogs [26, 35].

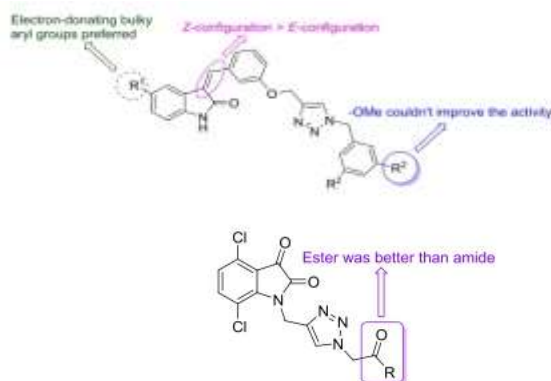


Figure 9: Isatin–1,2,3-triazole hybrids 10-11

Fluoroquinolone-1,2,3-triazole-isatin hybrids including moxifloxacin-1,2,3-triazole-isatin 1, Fig. 10 having alkyl substituents showed fair antimicrobial activity [36, 37]. The structure-activity relationship and the structure-cytotoxicity relationship proved that the linker between the fluoroquinolone and 1,2,3-triazole fragments as well as substituents on the isatin moiety affected the activity significantly for fluoroquinolone-1,2,3-triazole isatin hybrids [32]. Substituents at C-3 position controls the lipophilicity while substituents on the phenyl ring affected the biological activity [38]. Amide functional group at the C-7 position of fluoroquinolone framework had greater biological activity as compared to the unsubstituted analogs. A series of new moxifloxacin-amide-1,2,3-triazoleisatin hybrids were designed, synthesized and evaluated for their in vitro antibacterial activity against Gram-positive and Gram-negative bacteria including drug-resistant pathogens as shown in Fig. 11 [36, 39].



Figure 10: Alkyl tethered moxifloxacin-1,2,3-triazole-isatin hybrids

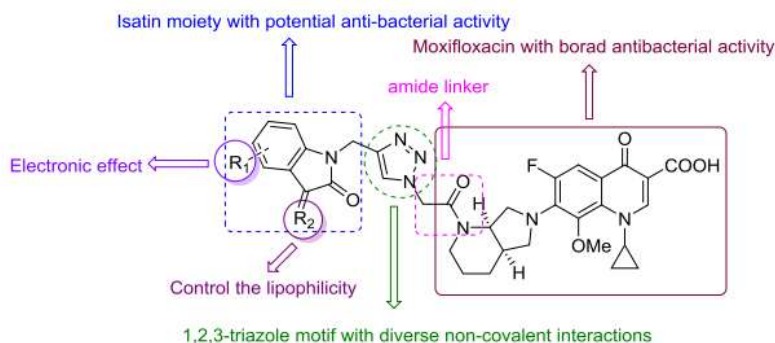


Figure 11: Moxifloxacin-amide-1,2,3-triazole-isatin hybrids

5) Isatin-Imidazole/Benzimidazole/Imidazolone hybrids

Imidazole / benzimidazole / imidazolone derivatives such as Pretomanid [40], Delamanid [41] showed significant efficacy against both sensitive drugs and drug-resistant pathogens making them a viable lead for the discovery of new anticancer candidate [42, 43].

Introduction of halogen atoms at the C-5 position of the isatin moiety could improve the activity of hybrids against cancer cells [44].

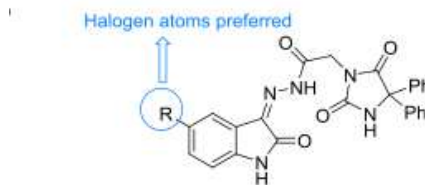


Figure 12

6) Isatin-Pyrazole/Pyrazolidine/Pyrazolone Hybrids

Pyrazole/pyrazolidine/pyrazolone derivatives are potential inhibitors of epidermal growth factor receptor [45]. SAR studies revealed that addition of substituents at C-4 or C-5 position of the isatin moiety did not improve the activity, while halogen atoms at the C-6 position helped increase the activity, implying that the C-6 position was the most suitable position for the introduction of substituent [46].

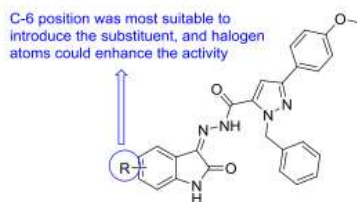


Figure 13: Isatin–thiazolidinone–pyrazoline hybrids

CONCLUSION

Isatin scaffold is found in a broad range of natural and synthetic products of medicinal value, the hybrid derivatives of isatin have the capability to improve the dosage compliance, biological activity, solubility, enhanced antimicrobial activity. The Schiff bases of isatin showed great flexibility and solubility. The addition of lipophilic character at C-7 position in the isatin quinone/flouroquinone derivative showed increase in antibacterial activity. The C-3 and C-5 positions are favorable for modification in isatin azole derivatives. Incorporation of halogen at the C-5 position of isatin moiety showed increase in activity for the isatin thiazole hybrid. Thus, hybrid molecules of isatin have the ability to improve the pharmacological effects of drug, minimize toxicity, reduce the risk of drug-drug interactions and overcome the problem of drug resistance.

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