REVIEW ARTICLE

A Comprehensive Review on Isatin Hybrid: Opportunities in Medicinal Chemistry

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ABSTRACT

The fused heterocyclic compounds with effective medicinal chemistry applications include isatin hybrids, IUPAC Name 1H-indole-2,3-dione. The isatin hybrid, its many biological features, and its possible medicinal uses are all thoroughly examined in this review. Isatin has tremendous biological promise as a hybrid structural component with benzimidaole, coumarin, and indole. Comprehensive investigation is carried out into the processes that underlie their antibacterial, anticancer, anti-inflammatory, anti-oxidant, and antiviral actions. This review also includes molecular docking experiments that explain how isatin hybrid binds to certain biological targets. They are even more important in drug development and discovery because of the computational methods used to forecast structure-activity relationships.

KEYWORDS: Isatin, Hybrid, Molecular Docking, Drug Discovery

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INTRODUCTION

Essential to the fight against many illnesses across the globe, chemists find new and improved medications. Scientists specialising in medicinal chemistry find promising new chemicals, refine them into effective medications, and study the molecular interactions between these molecules and their biological targets (1). Research into the development of more efficient chemotherapeutic drugs is continuing, as are the worldwide concerns of cancer and parasite infections (1-3). An important heterocyclic molecule, indole has six carbon atoms in its benzene ring and five members in its pyrrole ring, with nitrogen and oxygen rounding out the ring. Tryptophan, serotonin, and melatonin are indole-based compounds that have important biological functions (4-6). Isatin and other indole derivatives have been the subject of much research into their chemical reactivity because of the promising medicinal uses for these compounds.(3). The indole derivative issatin (1H-indole-2,3-dione), which was first produced in 1841 by Erdmann and Laurent by oxidising indigo. It occurs naturally in the secretions of the parotid glands of Bufo frogs and in a number of plant species, including Isatis, Calanthe discolour, and Couroupita guianensis. Additionally, it is a metabolic consequence of adrenaline in humans. It is well-known that compounds produced from isatin exhibit a diverse array of pharmacological effects.(7), such as anticancer, anti-HIV, anti-mycobacterial, antifungal, antiviral, antiviral, and antibacterial characteristics. To modify their pharmacological effects, these chemicals interact with a wide variety of biological targets (5). Recent developments in the pharmaceutical uses and computational molecular docking investigations of isatin hybrids, with a focus on structure-activity relationship (SAR) research, are the primary topics of this review (11.12).

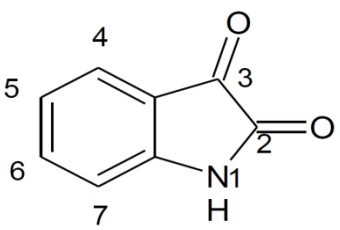
METHODS FOR SYNTHESIS

Several synthetic methodologies have been developed to produce isatin and its derivatives, including:

Sandmeyer Synthesis

An aqueous sodium sulphate solution is used to facilitate the reaction of aniline, chloral hydrate, and hydroxylamine hydrochloride in the Sandmeyer process. Isatin is produced by first forming the intermediate isonitrosoacetanilide, and then by cyclisation with concentrated sulphuric acid. Isatin derivatives with high yield and purity may be produced using this procedure.(11–15).

Stolle Synthesis



Isatin

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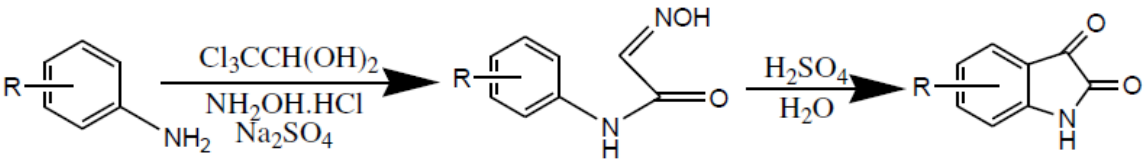

Figure 1: Sandmeyer method

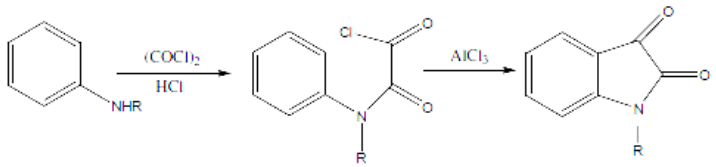

Figure 2: Stolle synthesis

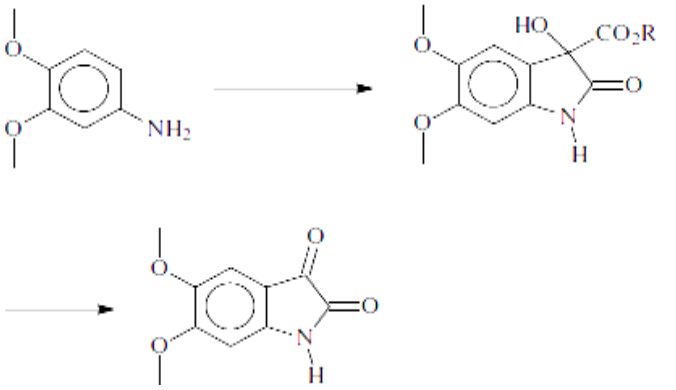

Figure 3: Martinet approach

Another well-established approach is the Stolle synthesis, which involves cyclisation after the use of substituted anilines and oxalyl chloride. In the presence of Lewis acids like BF_3 or $AlCl_3$. Many N-alkylated or N-arylated derivatives, as well as polycyclic isatins, can be efficiently produced using this method.(11–17,17).

The Martinet Isatin Synthesis

An aromatic amine and an oxomalonate ester or its hydrate are combined with an acid catalyst in the Martinet reaction to produce 1H-indole-2,3-diones. "The desired isatin derivative is derived by oxidative decarboxylation of an intermediate 3-(3-hydroxy-2-oxindole)carboxylic acid, which is formed in this procedure. The use of this method to produce 5,6-dimethoxyisatin from 4-aminoveratrole has been successful; however, the yield of 2,4-dimethoxyaniline is reduced.(18–22).

ACTIVITY

Antimicrobial Activity

Antimicrobial potency is enhanced in isatin derivatives by structural modifications, such as the addition of electron-withdrawing groups (e.g., nitro, halogens)(23-25), which also give these compounds their antifungal and antibacterial characteristics. Isatin derivatives have been shown to block bacterial DNA gyrase and topoisomerase enzymes, according to molecular docking studies. This has shed light on how these compounds work. This chemical has possible antibacterial characteristics (i)(6,26,27) due to the incorporation of an isatin moiety into a thiazolidinone ring, a 5-membered ring including sulphur and nitrogen. This hybrid has been investigated for its potential anticancer effects due to its coumarin ring structure, which is a 6-membered oxygen-containing heterocycle, coupled with isatin (ii)(24,25). This derivative possesses potential as an anti-inflammatory agent due to the incorporation of a 1,2,4-triazole ring onto the isatin core. This ring consists of five members, three of which contain nitrogen atoms (iii). Produced by click chemistry, this molecule combines an isatin structure with a 1,2,3-triazole ring, which is a ring with five members and three nitrogen atoms. It shows significant antifungal activity (iv)(6,26,27). The compound's antioxidant capabilities have been studied due to its isatin-chromone ring structure, which is a 6-membered oxygen-containing heterocycle (13,14,21). It has been shown that this hybrid, which contains isatin and a quinazolinone ring—a fused bicyclic system containing nitrogen atoms—may have anticonvulsant properties (vi). (vii) This compound has antibacterial properties because it is based on an isatin scaffold that integrates a 1,3,4-oxadiazole ring, a 5-membered ring with two nitrogen atoms and one oxygen atom (13,14,21,28-30).

Anticancer Activity

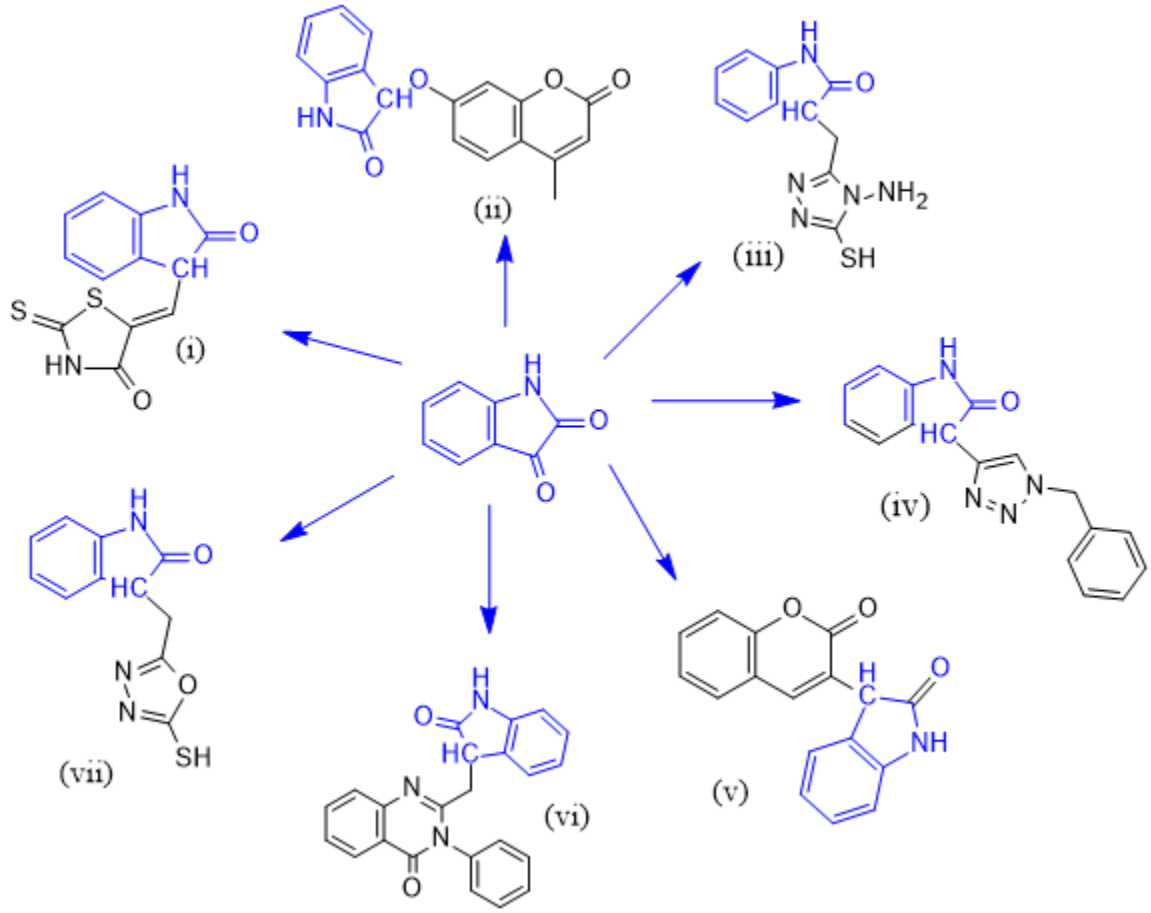

Figure 4: Antimicrobial Isatin Hybrid

The ability of isatin derivatives to inhibit many proteins associated with cancer has led to great hope for their use as a cancer therapy. By interfering with tubulin polymerisation and, by extension, cell division, 5-[(1H-Indol-2,3-dione)-3-ylmethylene]-2-thioxo-4-thiazolidinone has shown promise in the fight against breast cancer (31–33). In a similar vein, 3-(4-Methyl-2-oxo-2H-chromen-7-yloxy)-1H-indole-2,3-dione inhibits the proliferation of lung cancer cells by blocking the signalling pathways of the epidermal growth factor receptor (EGFR). By inhibiting the enzyme histone deacetylase (HDAC), 3-(4-Pyrrolidin-1-yl-phenyl)-1H-indole-2,3-dione promotes cell death in colon cancer. The compound 3-[(2,3-Dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)methylene] is used to treat pancreatic cancer.-1H-indole-2,3-dione causes DNA damage and cell death by inhibiting topoisomerase II (16,34). The last one is 5-fluoro-3-(4-morpholinophenyl)By lowering tumour growth, -1H-indole-2,3-dione has been discovered to be an effective treatment for prostate cancer by targeting androgen receptor pathways.(17,17).

Antiviral Activity

The antiviral characteristics of isatin derivatives have attracted considerable interest due to their ability to combat various pathogens, such as influenza, SARS-CoV, and HIV. Methisazone, which stands out as an example, was one of the first synthetic antiviral agents to be used in clinical practice (19,35). In addition, inhibitory activity against HIV-1 and HIV-2 in MT-4 cells has been demonstrated by Schiff bases formed from isatin and sulfadimidine, with EC_{50} values ranging from 8 to 15.3 µg/mL for HIV-1 and from 41.5 to 125 µg/mL for HIV-2 (18,20,22). In addition, the SARS coronavirus 3CL protease is an essential enzyme in viral replication; several isatin derivatives have been shown to block this enzyme well. These findings demonstrate the potential of molecules produced from isatin as antiviral therapeutic options. (13,14,21).

Anti-inflammatory and Antioxidant Properties

By focussing on and blocking key enzymes such as cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS), isatin derivatives have shown promising promise in modifying inflammatory pathways. Evidence suggests that these chemicals inhibit iNOS and COX-2 protein expression, which in turn reduces the synthesis of prostaglandin E_2 (PGE_2) and nitric oxide (NO) and other pro-inflammatory mediators (15,23,24). Isatin compounds show promise as potential novel anti-inflammatory and anticancer medicines due to their dual inhibition (25,26).

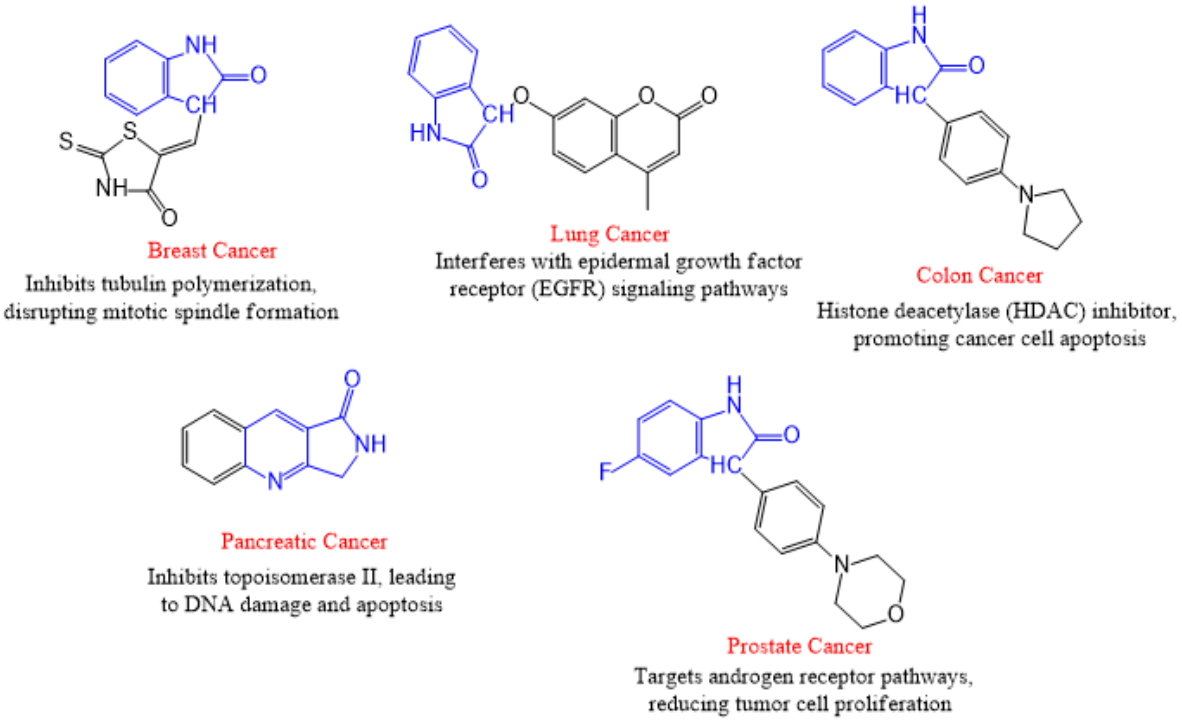

Figure 5: Anticancer hybrids

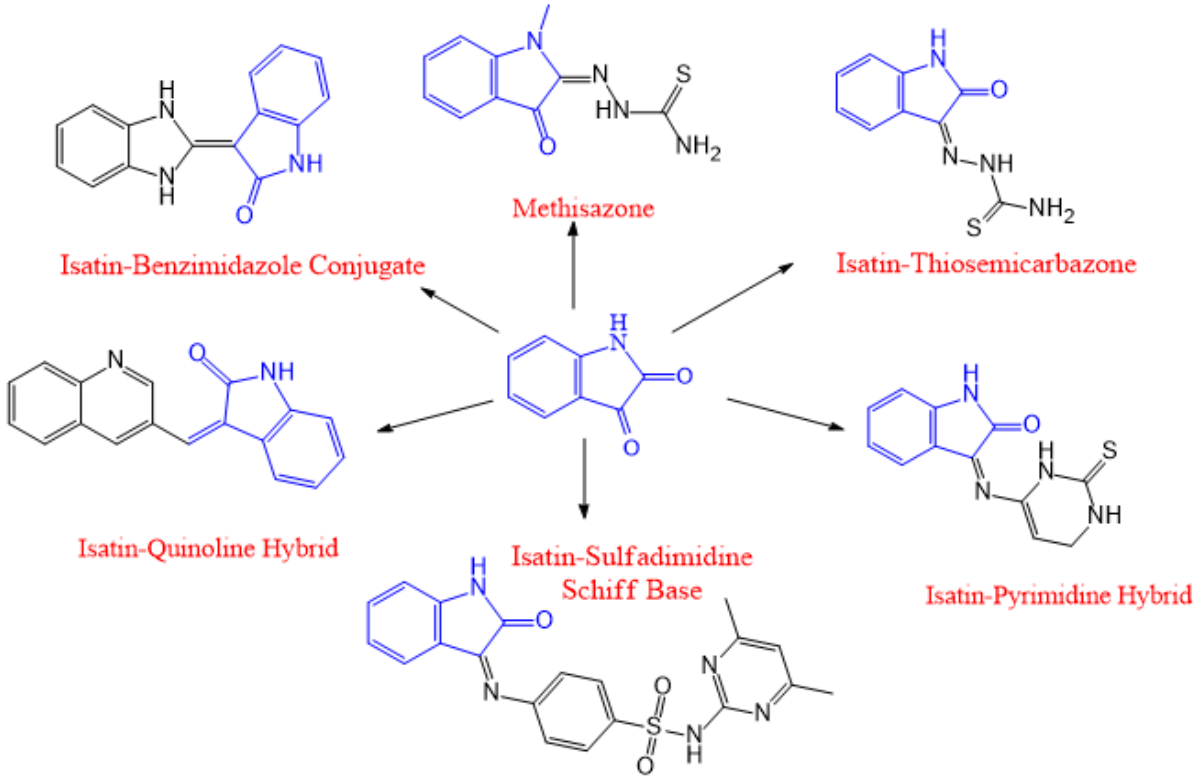

Figure 6: Antiviral Hybrids of Isatin

Isatin compounds have shown remarkable antioxidant capabilities in addition to their anti-inflammatory actions. As an example, several Schiff bases based on isatin are developed, synthesised, and tested for their antioxidant properties; these compounds have promising future use in lowering oxidative stress and free radical scavenging.(2,4). Isatin derivatives have antioxidant properties that make them a promising therapeutic agent for oxidative stress-related

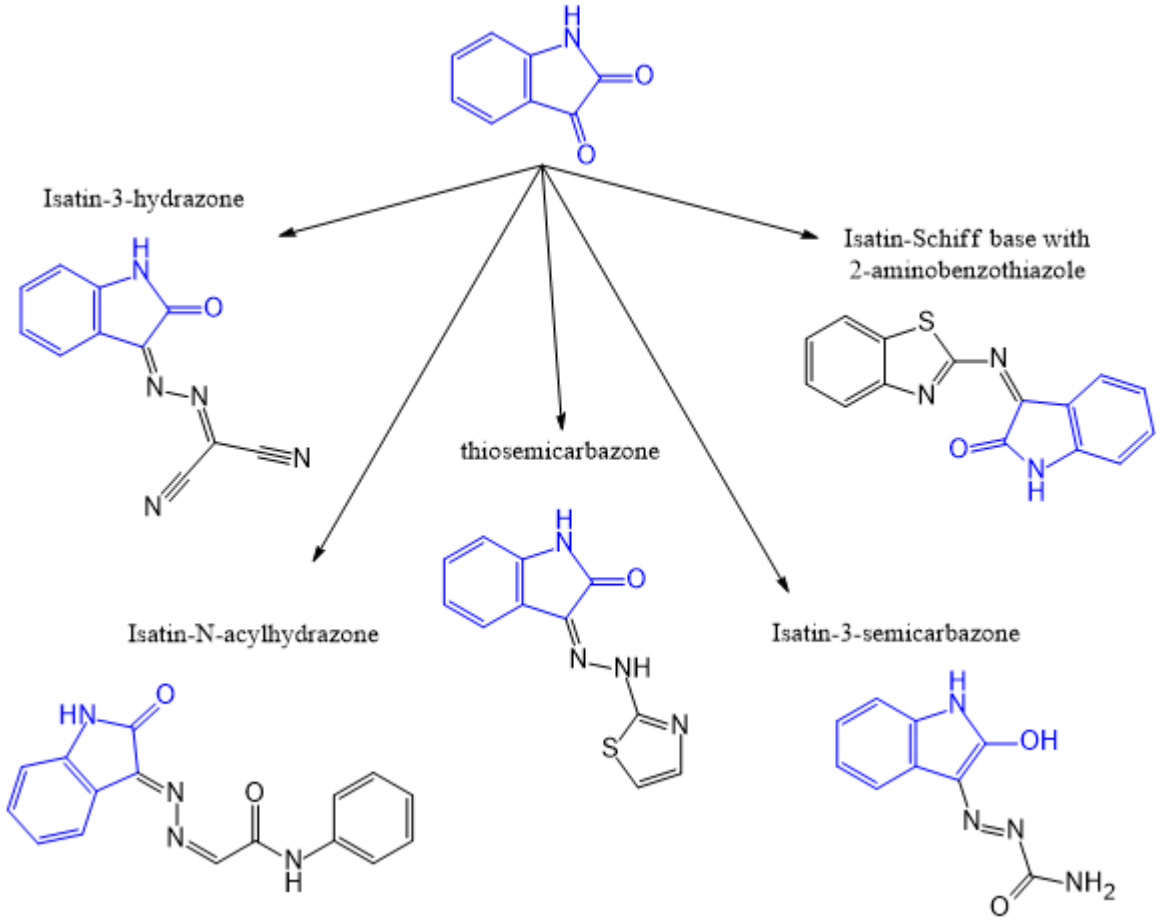

Figure 7: Anti-inflammatory and Antioxidant Isatin Hybrid

diseases. Molecular docking studies have shown that isatin analogues interact with inflammatory mediators by forming stable complexes with COX-2 and iNOS enzymes, blocking their active sites and inhibiting their catalytic functions. These findings highlight the potential of using isatin-based compounds to rationally develop new anti-inflammatory drugs that are more effective and selective. (7–9).

Molecular Docking Studies of Isatin Derivatives

Molecular docking studies have played a crucial role in understanding the therapeutic potential of isatin hybrids by revealing their interactions with various biological targets (10). A number of illnesses, including as inflammation, cancer, viral infections, and bacterial resistance, are impacted by isatin hybrids, which have shown high binding affinities to important enzymes and receptors (5). As an example, compounds derived from isatin have been investigated for their potential to inhibit cyclooxygenase (COX) enzymes, Promising inhibitory effect against COX-1 (PDB ID: 3N8Y) and COX-2 (PDB ID: 3LN1) was shown by 2-Hydroxy-N'-(2-oxoindolin-3-ylidene)benzohydrazide (i), in that order, with docking scores of −26.79 kcal/mol and −68.73 kcal/mol, respectively. Its potential applications as an anti-inflammatory agent is suggested by these findings (6).

A derivative of isatin, indolinacetate (ii), was shown to have a substantial binding score with the major protease, Mpro, with a docking score of -14.694 kcal/mol, in antiviral research. This highlights the potential of isatin derivatives as intriguing options for the development of antiviral drugs (25-27). The epidermal growth factor receptor (EGFR) is an important target in cancer therapy, and docking simulations have shown that isatin derivatives have strong interactions with this receptor". Promising action against EGFR-related malignancies has been shown by oxoindolin-methanesulfonamide(iii), an EGFR inhibitor (23,24).

Isatin derivatives like oxoindolin-benzenesulfonamide (iv) have also shown promise as a potential target for the cancer-related enzyme phosphoinositide 3-kinase (PI3K) (28,29). It has been discovered that isatin hybrids can inhibit the enzyme enoyl-acetyl carrier protein reductase (InhA), which is important in tuberculosis treatment. An important enzyme in mycolic acid biosynthesis is located in Mycobacterium tuberculosis. One of its derivatives, cinnoline-3-carboxamide (v), has a high docking score of 92.9384 and shows great promise as an anti-tubercular agent (30-32).

Molecular docking studies have helped to rationalise the drug development possibilities of isatin derivatives, and these results highlight their broad-spectrum therapeutic

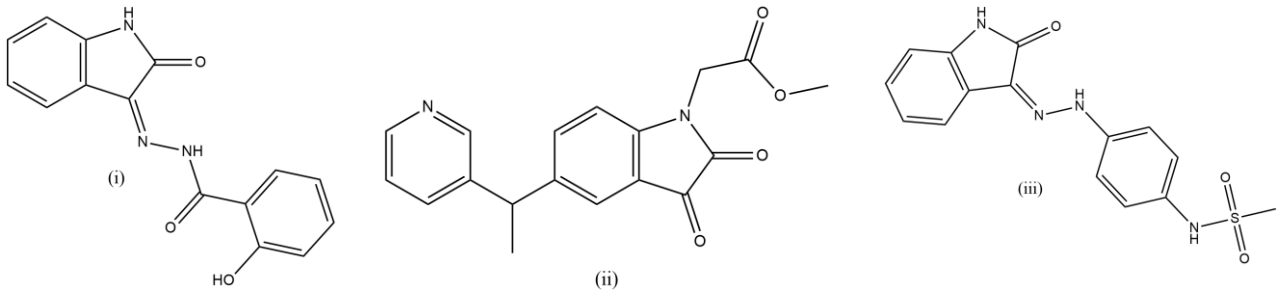

Figure 8: Anti-inflammatory agents

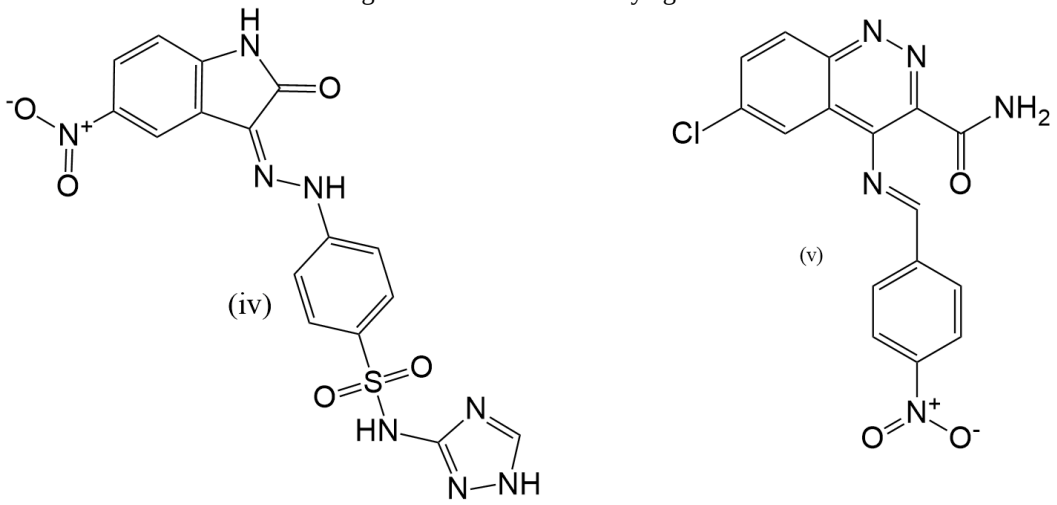

Figure 9: Isatin derivatives like oxoindolin-benzenesulfonamide

potential. Additional optimisation of these derivatives for the treatment of cancer, viral infections, inflammation, and bacterial infections can be achieved by identifying strong binding interactions with important biological targets.(16,17,33,34).

CONCLUSION

Isatin hybrids are a class of bioactive molecules that have many different pharmacological uses. Their utility has grown thanks to synthetic methodology advancements, and their molecular action has been explained by computational docking studies. The incorporation of molecular docking techniques has improved our understanding of how they interact with biological targets, which has led to the creation of new isatin-based medicines. To help bring these drugs from the lab to the clinic, future studies should concentrate on improving their pharmacokinetic and toxicity profiles.

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