Review

A Survey of Isatin Hybrids and their Biological Properties

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A Survey of Isatin Hybrids and Their Biological Properties

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Abstract: The emergence of diverse infections worldwide, which is a serious global threat to human existence, necessitate the urgent development of novel therapeutic candidates that can combat these diseases with efficacy. Isatin, a secondary metabolite from tryptophan is considered a privileged scaffold and favorable pharmacophore with a unique structural moiety and varied chemical and biological properties resulting in its widespread applications by medicinal chemists. Molecular hybridization is one of the most common and important techniques use in the synthesis of their bioactive hybrids in drug discovery. This review containing published articles from 2005 to 2022 focuses on isatin hybrids which have been synthesized and reported in the literature alongside a discussion on their biological properties. The purpose of this review is to set up the direction for the design and development of isatin-hybrids with tailored biological properties as effective therapeutic candidates inspired by nature.

Keywords: isatin; hybrids; biological properties; pharmacophore; molecular hybridization

1. Introduction

Isatin **1** (indol-2,3-dione; Figure 1), a secondary metabolite of tryptophan has been found to be widely distributed in the central nervous system, mammalian tissues, and body fluids of humans [1,2,3]. This oxidized indole has been used as the core structure in the formulation of several compounds which have been tested and identified as potent inhibitors of apoptosis [4–9], anticonvulsants [10,11], antiviral [5,12–16], Antitubercular [17–19], Antifungal [20,21], Antimicrobial [22,23], Antioxidant [24,25], antimalarial [26,27], anti-inflammatory [28,29], Anticonvulsant [10]. Isatin, therefore, is considered a versatile and favorable precursor for pharmacophore development as a privileged scaffold [9] because the moiety can be modified at various positions (N-1, C-3, C-4, C-5, and C-7 positions) as illustrated in Figure 1, resulting in different derivatives with diverse biological properties [30,31].

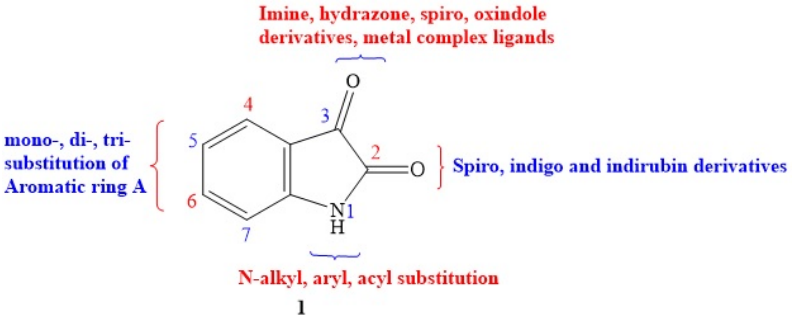

Figure 1. The various possible modification position on the isatin scaffold [12].

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Recently, some isatin-containing compounds have been approved for clinical trials (Sunitinib and Toceranib) [17] used in the treatment of tumors, while others (Nintedanib, Semaxinib, and Orantinib) are currently undergoing clinical trials for the evaluation of their therapeutic activities as anti-cancer agents [2]. The development of a single hybrid compound by combining two or more pharmacophores has been proven to be a promising approach in the development of new drugs which have the potential of overcoming drug resistance and possess improved activity when compared to parent drugs [32]. It is therefore plausible that the molecular hybridization of the isatin moiety with other pharmacophores has the potential to generate new and more effective therapeutic candidates [8]. There exist several isatin hybrid molecules generated by the combination of isatin moiety with other useful pharmacophores that have outstanding biological activities. Some of these hybrids include; Isatin-Azole hybrids [8–10,14,23,33–38], Isatin-furan hybrids [9,18,33,35,39], Isatin-thiophene hybrids [8,40], Isatin-indole hybrids [9,41], Isatin-fluoroquinolone hybrids[9,17,42], Isatin-Imine hybrids[9], Isatin-sulfonamide hybrids [2,9,21,43,44], Isatin-pyridine hybrids [45–48], Isatin-chalcone hybrids [49], Isatin-quinazoline hybrids [50,51], Isatin-pthalazine hybrids [50], Isatin-hydrazide hybrids [9,33,35,48], Isatin-naphthalene hybrids [14], isatin-thiosemicarbazone hybrid[9,20], Isatin-oxime hybrids [52], Isatin-nitrone hybrids [52], Isatin-ketone hybrids [53], Isatin-piperazine hybrids [54], Isatin-uracil hybrids [55], Isatin-coumarin hybrids [56], Isatin-thiolactone hybrids[57], and Isatin-pyrimidine hybrids [17]. The purpose of this review is to set up the direction for the design and development of isatin-hybrids with tailored biological properties as effective therapeutic candidates inspired by nature.

2. Isatin-Azole Hybrids

Azole, a privileged scaffold of choice when designing novel therapeutic agents are mainly found as core structures in several natural products and synthesized compounds which are used by pharmaceutical or agrochemical industries [58]. Most azole compounds are used as antifungal drugs [59,60] and some of its derivatives possess a variety of biological properties such as anticancer [7,59], antibacterial [60,61], and antitubercular properties [17,62]. Several isatin-azole hybrids have been synthesized [4,17,28,63–68] and reported to possess diverse pharmacological properties. The chemical structures of these isatin-azole hybrids are presented in Figure 2. Eldehna et al., in 2018 [69] reported the synthesis of the isatin-pyrazole hybrids **2a-c** and evaluated their anti-proliferative properties. The hybrid **2b** was identified as the most active analogue portraying broad spectrum activity against breast, colon, and lung human cancer cell lines with an IC_{50} value of 2.14 μM.

With the outbreak of SARS-CoV-2 and the urgent need for the development of bioactive molecules, Badavath et al., in 2020 [14] conducted in silico studies, by making use of computer-aided drug design approaches to screen over 118 compounds. The molecular docking studies against M^{pro} protein revealed that the isatin-oxidiazole hybrids **3** and **4** possessed excessive interactions to M^{pro} with best docking scores -11.22 kcal/ mol and -11.15 kcal/mol respectively. Thus, these compounds could serve as starting points for the development of potential SARS-CoV-2 M^{pro} inhibitors. Özil et al., in 2011 [70] synthesized a series of isatin-1,2,4-triazole hybrids **5a-h** and evaluated their anti-microbial properties against four bacterial strains: Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Bacillus subtilis. The hybrid **5g** emerged with quite interesting antibacterial activity against Staphylococcus aureus and Bacillus subtilis bearing an MIC value of 8 and 16 μg mL^{-1} respectively. Neglected tropical diseases remain a global threat to health and thus the need for the development of new approaches and therapies to fight against these infections. Freitas et al., in 2021 [36] reported the synthesis and evaluation of the anti-parasitic properties of some isatin-thiazolyl **6a-j** hybrids. The hybrid **6e,h,i,j** were found to be the most potent compounds with anti-*Trypanosoma cruzi* activity for trypomastigote form having IC50 values of 4.43 μM, 2.05 μM, 4.12 μM and 1.72 μM respectively. Nikalje et al., 2015 [10] reported a microwave-assisted synthesis of a series of novel isatin-thiazolidin-4-one hybrids **7a-e** and analysed their anti-convulsant activities in mice using maximal electroshock seizure (MES) and subcutaneouspentylenetetrazole (sc-PTZ) induced seizure tests. Hybrids **7d,e** exhibited potent protection against MES test cells thus indicating interesting anticonvulsant properties [28].

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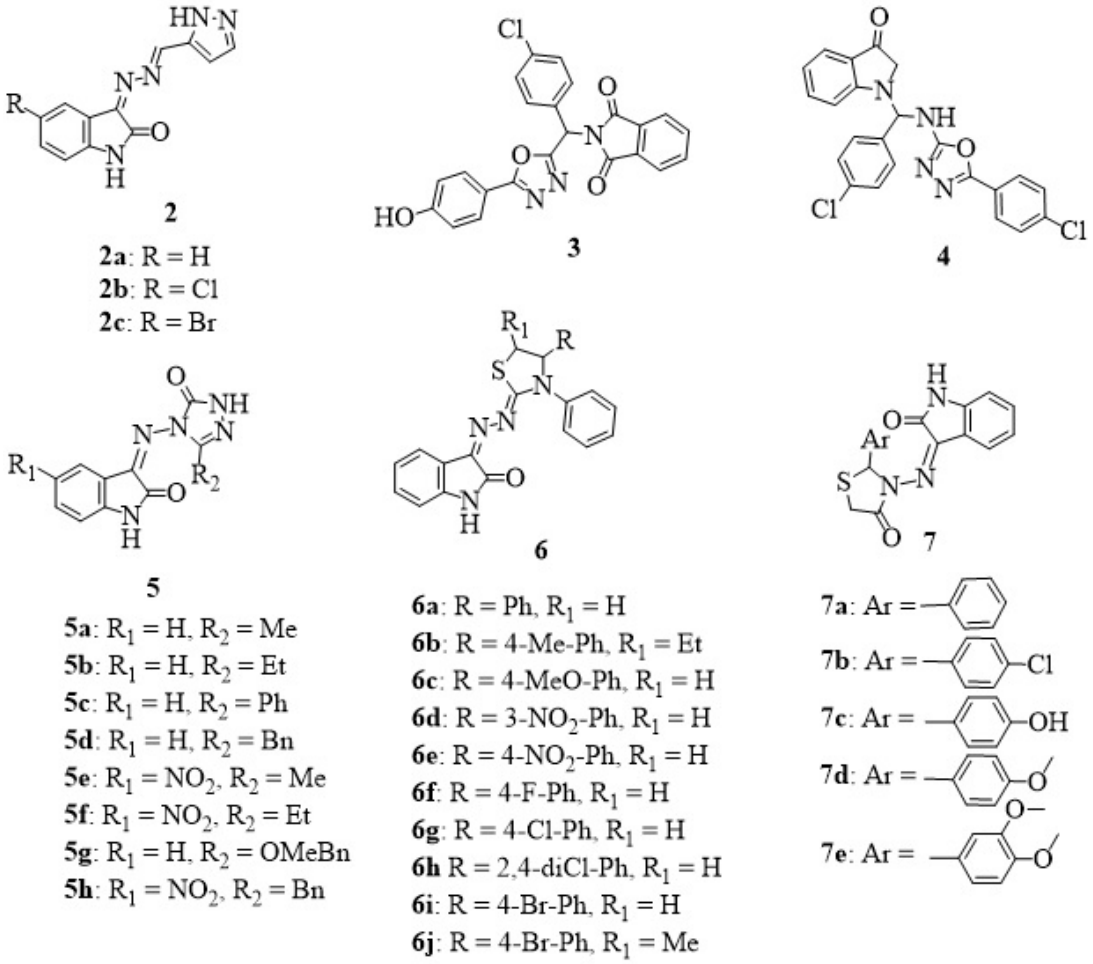

Figure 2. Chemical structures of isatin-azole hybrids.

3. Isatin-Furan Hybrids

Furan is an important pharmacophore of natural origin with several biological properties (anticancer, antimalarial, antibacterial, and antifungal). It has been used as a starting material in the production of several industrial chemicals such as catalysts, resins, agrochemicals and pharmaceuticals [71,72]. The chemical structures of isatin-furan hybrids are presented in Figure 3. The synthesis and anti-bacterial evaluation of a series of isatin-benzofuran hybrids **8a-e** were reported by Gao et al., in 2019 [18]. The synthesized compounds were tested on a panel of gram-negative and gram-positive bacteria and the minimal inhibition concentration (MIC) values obtained. The hybrid **8e** was identified as the most promising compound with interesting antibacterial activity against majority of the tested pathogens *(Staphylococcus epidermidis, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter aerogenes, Proteus mirabilis*) with MIC values of ≤1 μg/mL. In 2018, Gao et al., [73] reported the synthesis of some isatin-benzofuran hybrids **9a-d** and evaluated their anti-mycobacterial activity against MTB H37Rv and MDB TR strains. Among the synthesized compounds, the hybrid **9d** was found to be the most active with over 128 folds effectiveness when compared to Rifampicin, a well-known antibiotic used in the treatment of tuberculosis having MIC values of 0.25 and 0.5 μg/mL against MTB H37Rv and MDR-TB strains respectively [35].

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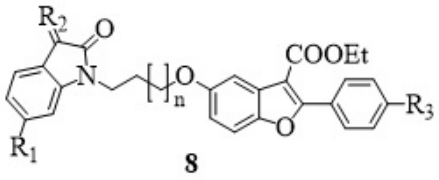
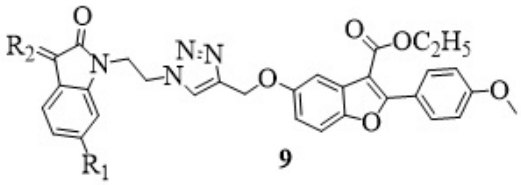


8

8a: n = 1, R_1 = F, R_2 = NOMe, R_3 = H
8a: n = 1, R_1 = F, R_2 = NOMe, R_3 = OMe
8a: n = 1, R_1 = F, R_2 = NOEt, R_3 = OMe
8a: n = 1, R_1 = OMe, R_2 = NOMe, R_3 = H
8a: n = 2, R_1 = H, R_2 = NOMe, R_3 = OMe



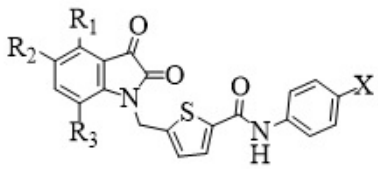
9

9a: R_1 = Br, R_2 = NOH
9b: R_1 = Br, R_2 = NOEt
9c: R_1 = H, R_2 = NOMe
9d: R_1 = OMe, R_2 = $NNHCSNH_2$

Figure 3. Chemical structures of isatin-furan hybrids.

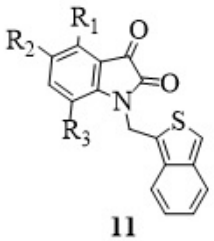
4. Isatin-Thiophene Hybrids

Thiophene, one of the most abundantly found heterocyclic rings present in biological systems has emerged as a potent scaffold in drug discovery. This moiety and its derivatives have found widespread applications in different fields of life such as the pharmaceutical and dye industries. Several pharmacological properties have been reported to be associated with this scaffold some of which include; anticancer, antimicrobial and anti-inflammatory properties [74,75]. Figure 4 presents some of the chemical structures of isatin-thiophene hybrids. Chen et al., in 2005 [76] synthesized some isatin derivatives **10a-b** and **11a-f**. The synthesized compounds were evaluated in vitro for their inhibitory activity against SARS coronavirus 3CL protease. Notably, some of the synthesized compounds exhibited potent inhibitory activity against the virus with hybrids **11a** and **11e** being the most active hybrids amongst the compounds having IC_{50} values of 0.98 μM and 0.95 μM respectively [14,40].



10

10a: R_1 = H, R_2 = I, R_3 =H, X = Cl
10b: R_1 = H, R_2 = I, R_3 = H, X = F



11

11a: R_1 = H, R_2 = H, R_3 = Br
11b: R_1 = H, R_2 = CH_3, R_3 = NO_2
11c: R_1 = H, R_2 = CH_3OH, R_3 = H
11d: R_1 = H, R_2 = F, R_3 = H
11e: R_1 = H, R_2 = I, R_3 = H
11f: R_1 = Cl, R_2 = H, R_3 = H

Figure 4. Chemical structures of isatin-thiophene hybrids.

5. Isatin-Indole Hybrids

Indoles constitute an important subunit for the discovery of new drug candidates. It is widely distributed in natural products and bioactive molecules and is responsible for the faecal smell in human faeces, scents of flowers and the flowery smell of perfumes [77–79]. The indole moiety is a versatile molecule with several biological properties such as: Anti-fungal, antimicrobial, antiviral, and antitubercular properties [80]. Figure 5 presents some of the chemical structures of isatin-indole hybrids.

Al-wabli et al., in 2020 [41] reported the synthesis of some isatin-indole molecular hybrids **12a-g** and evaluated their potentials as anti-proliferative agents against human breast (ZR-75), colon (HT-29) and lung (A-549) tumor cell line. The hybrid **12c** showed potent antiproliferative activity which

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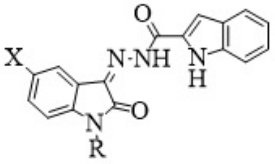
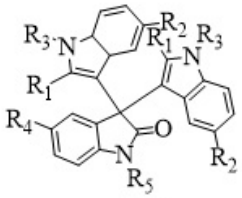
was approximately seven-folds greater than sunitinib, a well-known anti-cancer medication. Some bis-isatin-indole hybrids **13a-c** were synthesized and reported by Praveen in 2011 [81]. The anticonvulsant and antibacterial properties of the synthesized compounds were evaluated against Maxima Electroshock seizure (MES) model and two bacterial strains (*Staphylococcus aureus and Escherichia coli*) respectively. The hybrids **13a** and **13c** demonstrated excellent anticonvulsant activity and in addition, hybrid **13c** revealed excellent antibacterial activity against *Escherichia coli* [9].



12

12a: X = H, R = H
12b: X = Br, R = H
12c: X = Cl, R = C_6H_5-CH_2
12d: X = F, R = H
12e: X = OMe, R = H
12f: X = H, R = CH_3
12g: X = Br, R = CH_3



13

13a: R_1 = H, R_2 = OMe, R_3 = allyl, R_4 = OMe, R_5 = CH_2CO_2Et
13b: R_1 = H, R_2 = H, R_3 = propargyl, R_4 = H, R_5 = Bn
13c: R_1 = H, R_2 = Me, R_3 = propargyl, R_4 = H, R_5 = H

Figure 5. Chemical structures of isatin-indole hybrids.

6. Isatin-Fluoroquinolone Hybrids

Quinolone is an essential class of nitrogen-containing heterocycles widely used as a building block for medicinal agents. Fluoroquinolones possess broad-spectrum activity and very good oral bioavailability, and as such often used as antibacterial agents. Some fluoroquinolones which are currently available include; ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin [19,82–84]. Figure 6 presents some of the chemical structures of isatin-fluoroquinolone hybrids.

In 2013, with the aim of developing potential antimicrobials, Prakash et al., [85] reported the synthesis of a series of novel ciprofloxacin-isatin hybrids **14a-k**. Most of the compounds showed interesting in vitro antibacterial and antifungal activity against the investigated microbes. The hybrid **14c** was identified as the most potent hybrid with better antibacterial activity against *Staphylococcus. aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* when compared to the parent drug ciprofloxacin, and similar antifungal activity against *Aspergillus fumigatus* and *Aspergillus niger* when compared to ketoconazole [9].

Over one-third of the world's population are potentially infected with tuberculosis (TB), a common infectious disease. In the quest for novel, effective, and fast acting anti-TB drugs with low toxicity, Sriram et al., in 2006 [86] synthesized a series of Gatifloxacin-isatin **15a-g** hybrids and evaluated their antimycobacterial activity. Hybrid **15d** was shown to be the most potent with improved activity when compared to the parent drug gatifloxacin [17].

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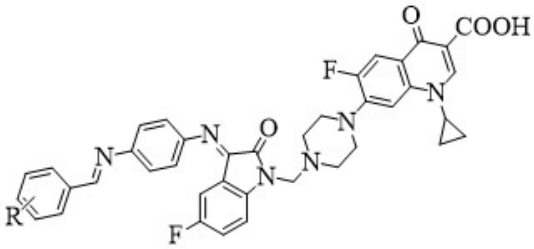
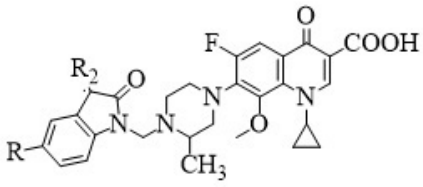


14

14a: R = H
14b: R = 4-Cl
14c: R = 4-OH
14d: R = 4-OMe
14e: R = 2-OH
14f: R = 4-NO_2
14g: R = 4-Me
14h: R = 3-NO_2
14i: R = 3,4,5-OMe
14j: R = 3-OMe, 4-OH
14k: R = 4-$N(CH_3)_2$



15

15a: R = F, R_1 = $NNHCONH_2$
15b: R = CH_3, R_1 = $NNHCONH_2$
15c: R = Cl, R_1 = $NNHCONH_2$
15d: R = H, R_1 = =$NNHCONH_2$
15e: R = F, R_1 = =$NNHCSNH_2$
15f: R = CH_3, R_1 = =$NNHCSNH_2$
15g: R = Cl, R_1 = =$NNHCSNH_2$

Figure 6. Chemical structures of isatin-fluoroquinolone hybrids.

7. Isatin-Sulfonamide Hybrids

Sulfonamides are naturally occurring structural motifs in medicinal chemistry with leading roles in novel drug design and development against complex infections [84]. They are highly versatile organo-sulphur compounds containing the -SO_2NH_2 and/or -SO_2NH- groups and small chemical modifications often result in improved activity. Sulfonamides are generally used in the treatment of bacterial infections and also possess several biological activities such as antifungal, anti-inflammatory, antioxidant, diuretic, anticancer [87,88]. The chemical structures of these isatin-sulfonamide hybrids are presented in Figure 7.

In 2014, Farag [89] reported the synthesis and evaluation of antimicrobial activity of a series of 5-(morpholinosulfonyl)isatin hybrids **16** and **17a-h**. The synthesized compounds were evaluated for their activity against gram +ve (*Staphylococcus aureus, Staphylococcus epidermidis* and *Bacillus subtilis*), gram –ve (*Proteus vulgaris*, *Klebsiella pneumonia*, *Shigella flexneri*) bacterial and fungi. The hybrid **16** revealed better antibacterial activity against all tested bacteria strains when compared to ampicillin B and fourfold antifungal potency against Aspergillus fumigatus when compared to amphotricin B.

Abo-Ashour et al., [90] with main goal to develop novel isatin-based anticancer candidates targeting the tumor-associated hCA isoforms IX and XII, synthesized two series of isatin-sulfonamide hybrids **18** and **19a-h** followed by the evaluation of their *in vitro* biological activity. All the synthesized compounds revealed potent inhibitory activities against the tested hCA isoforms and thus were further investigated for their anti-proliferative activity against several cancer cell lines. Notably, the hybrids **19f** and **19h** were the most active against the various cell lines inhibiting the cancer cells in a concentration dependent manner [43].

Eldehna et al., 2018 [91] synthesized and evaluated the anticancer activity of a series of isatin-sulfonamide hybrids **20a-f** against colorectal cancer HCT-116 and breast cancer MCF-7 cell lines. The most promising hybrid amongst the series **20e** exhibited potent anticancer activity against HCT-116 cell lines with an IC_{50} value of 3.67 ± 0.33 μM.

Selvam and collaborators in 2010 [92] reported the synthesis of a series of isatin-sulfadimidine hybrids **21a-e** and determination of their antiviral activity against swine influenza A/California/07/2009 (H1N1) virus. The synthesized compounds revealed quite potent activity against the virus by blocking its adsorption to cells with the hybrid **21e** being the most active amongst the synthesized compounds.

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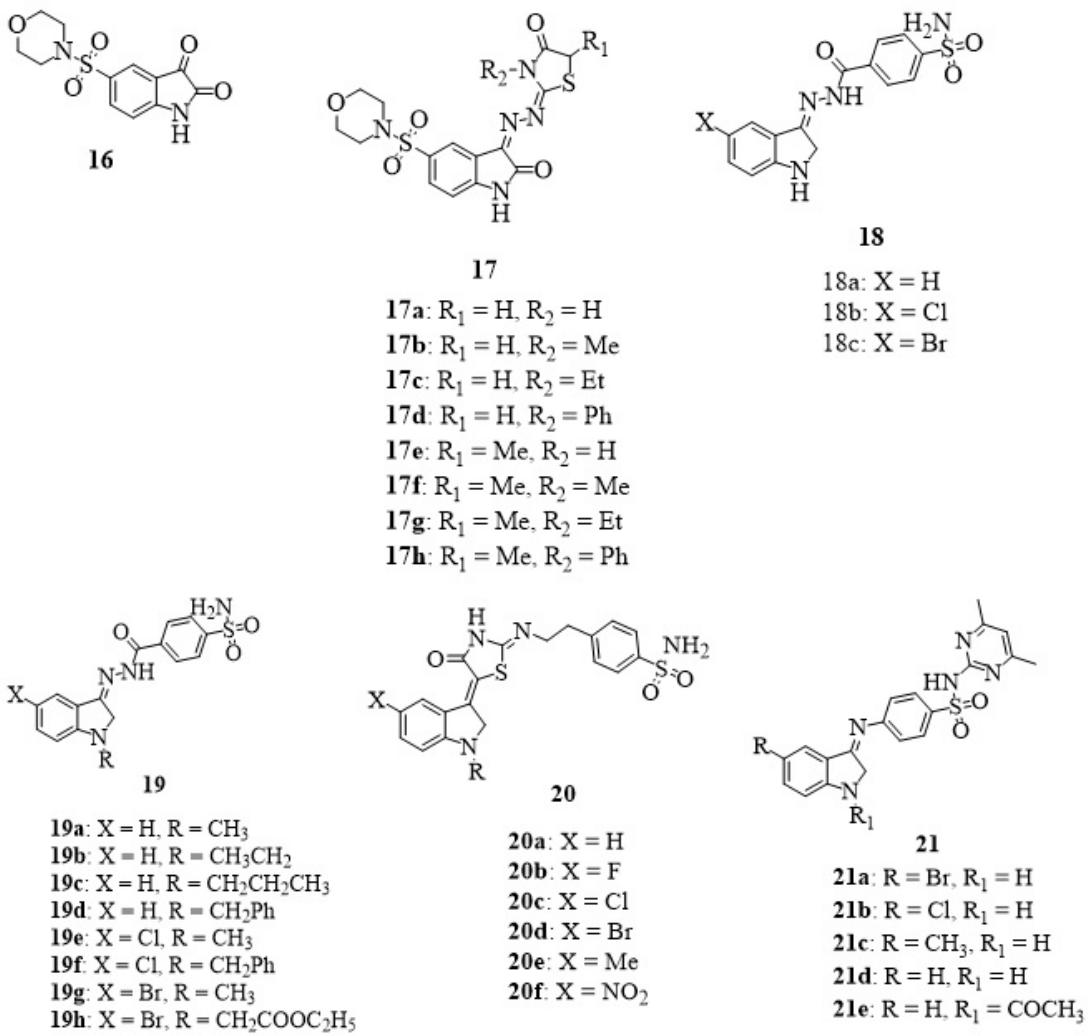

Figure 7. Chemical structures of isatin-sulfonamide hybrids.

8. Isatin-Pyridine Hybrids

Pyridines are a class of heterocyclic nitrogenous compounds with tremendous applications in diverse fields of life. This moiety and its derivatives are naturally present in different molecules such as vitamins, co-enzymes and alkaloids. Due to their wide range of pharmacological properties, pyridine-based compounds have found widespread applications in the field of drug design and discovery. It is widely used as a solvent for organic reactions, paints and pharmaceuticals as well as intermediates in the manufacture of agrochemicals and pharmaceuticals [93]. The chemical structures of these isatin-pyridine hybrids are presented in Figure 8.

Adopting a hybrid pharmacophore approach, Eldehna et al., in 2014 [45] designed, synthesised and evaluated the anti-proliferative activity of a series of isatin-pyridine hybrids **22-24** against HepG2, A549 and MCF-7 cancer cell lines. Notably, the hybrid **23** was identified as the most active compound with over 2.7 fold increase in activity against HepG2 cell line when compared to doxorubicin, a known anticancer medication. Quantitative structure activity relationship studies revealed that the introduction of a more lipophilic and bulky chlorine atom, resulted in a tremendous increase in activity thus making hybrid **24c** the most active against A549 and MCF-7 cancer cell lines.

Kitagawa et al., in 2021 [46] in an attempt to combat organophosphorus poisoning caused by some pesticides and nerve agents, designed and synthesised a series of isatin-pyridine oxime hybrids **25a-e** and analyzed their properties as acetylcholinesterase reactivators. All the synthesized compounds demonstrated reactivation properties with hybrids **25c** and **25e** showing the highest percentage of reactivation even at low concentrations thus making them potential lead compounds.

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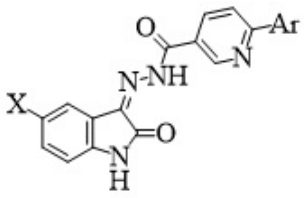
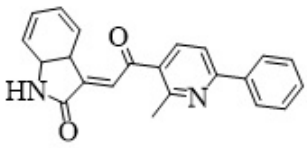


22

22a: X = H, Ar = 4-FC_6H_4
22b: X = Cl, Ar = 4-FC_6H_4
22c: X = Br, Ar = 4-FC_6H_4
22d: X = F, Ar = 4-FC_6H_4
22e: X = H, Ar = 4-$MeOC_6H_4$
22f: X = Cl, Ar = 4-$MeOC_6H_4$



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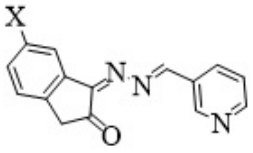
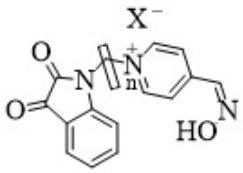


24

24a: X = H
24b: X = F
24c: X = Cl
24d: X = Br



25

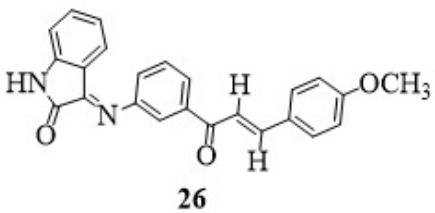
25a: n = 3, X^- = Br^-
25b: n = 4, X^- = Cl^-
25c: n = 5, X^- = Br^-
25d: n = 6, X^- = Cl^-
25e: n = CH_2-O-$(CH_2)_2$, X = Cl^-

Figure 8. Chemical structures of isatin-pyridine hybrids.

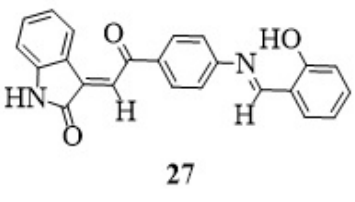
9. Isatin-Chalcone Hybrids

Chalcones are one of the most important classes of natural products derived from plants with widespread distribution in vegetables, teas, fruits, and many others [94,95]. They are a group of plant-derived polyphenolic compounds, known to be biogenetic precursors of flavonoids and isoflavonoids with several medicinal and pharmaceutical applications some of which include; antihypertensive, anti-bacterial, ant-obesity, anti-malarial, anti-retroviral, anticancer, fungicidal, germicidal, herbicidal and insecticidal [96,97]. Figure 9 presents some of the chemical structures of isatin-chalcone hybrids.

Fayed et al., in 2021 [49] reported the synthesis and screening of a series of isatin-chalcone hybrids **26-28** for their anticancer activities against MCF-7, HepG-2, and HCT-116 human cell lines. All the synthesized compounds demonstrated quite interesting anti-tumour properties with the hybrid **27** showing very high anti-cancer activity against HepG-2 cell line with an IC50 value of 5.33 μM/mL when compared to imatinib.



26



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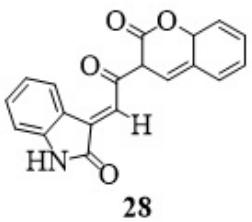

28

Figure 9. Chemical structures of isatin-chalcone hybrids.

10. Isatin-Quinazoline Hybrids

Quinazoline scaffold is a vital class of biologically active nitrogen-containing heterocycles with unique properties such as ease of synthetic accessibility and flexible structural modification, which have motivated the exploitation of their biological activities [98]. This scaffold has attracted

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significant attention over the past years due to its diverse pharmacological activities such as anti-malarial, anti-cancer, anti-convulsant and anti-inflammatory properties [99]. The chemical structures of these isatin-quinazoline hybrids are presented in Figure 10.

Implementing a molecular hybridization approach, Fares et al., 2015 [51] designed and synthesised a series of isatin-quinazoline hybrids **29a-f**. The synthesised compounds were tested for their in vitro anticancer activity against liver, breast and colon cancer cell lines. It is worth noting that, the hybrids **29a**, **29c** and **29f** were the most active with the ability to induce apoptosis in liver HepG2 cells.

Eldehna et al., 2017 [50] with primary goal to develop potent anti-proliferative agents capable of targeting triple-negative breast cancer (TNBC) MDA-MB-231 cell lines, synthesized a series of isatin-pthalazine hybrids **30a-e**. The hybrid **30e** was found to be the most potent against MDA-MB-231 cell lines with over 2.37 fold increase in activity when compared to 5-fluorouracil, the reference drug.

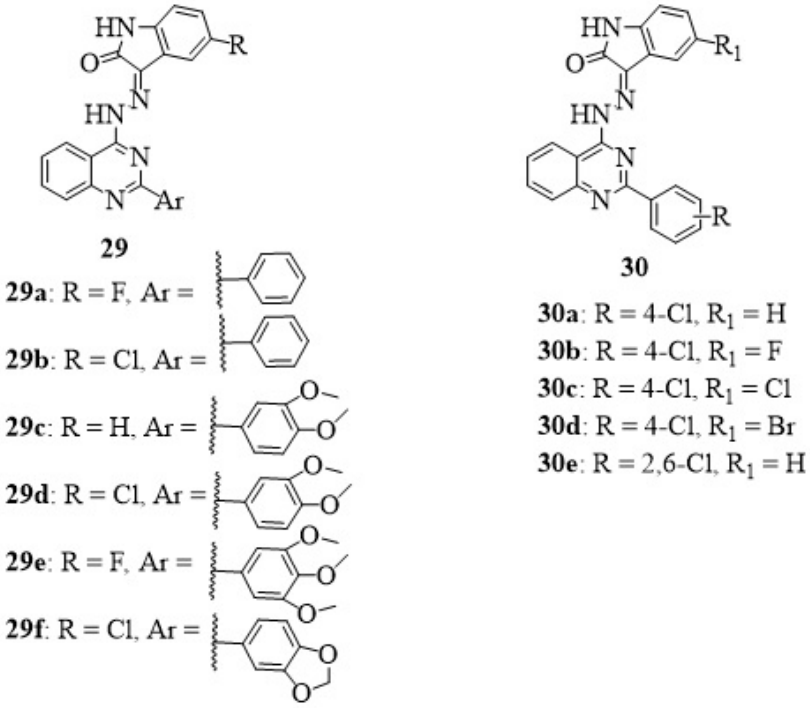

Figure 10. Chemical structures of isatin-quinazoline hybrids.

11. Isatin-Pthalazine Hybrids

Pthalazines are essential nitrogen-containing heterocyclic compounds with interesting chemical, industrial and pharmacological properties such as; anticancer, anticonvulsant, anti-inflammatory, antifungal, and antibacterial properties. Different drug molecules are presently available in the market which contain the phthalazine pharmacophore some of which include; hydralazine, budralazine, vatalanib, olaparib and azelastine. Owing to its broad application in the treatment of diverse infections, the phthalazine scaffold has received much attention in the area of drug discovery. Pthalazines are used as starting materials for the development of new medications and as an intermediary in the synthesis of chemicals [100]. Figure 11 presents some of the chemical structures of isatin-pthalazine hybrids.

Exploring the potentials in hybrid-pharmacophore approach, Eldehna et al., 2017 [50] reported the synthesis of a series of isatin-pthalazine hybrids **31a-g** and evaluated their activity as anti-proliferative agents against triple-negative breast cancer (TNBC) MDA-MB-231 cell lines. Notably, the hybrid **31g** showed improved activity against MDA-MB-231 cell lines with over 2.44 fold increase in activity when compared to 5-fluorouracil, the reference drug.

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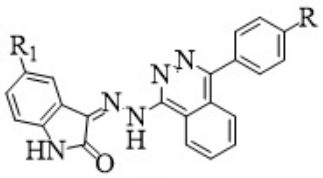

31

31a: R = H, R_1 = H
31b: R = H, R_1 = F
31c: R = H, R_1 = Cl
31d: R = H, R_1 = Br
31e: R = Cl, R_1 = H
31f: R = Cl, R_1 = F
31g: R = Cl, R_1 = Cl

Figure 11. Chemical structures of isatin-pthalazine hybrids.

12. Isatin-Hydrazide Hybrids

Hydrazides represent an important class of organic compounds that contain the azomethine functional group connected to a carbonyl group. These functionalities accord pharmacophore its unique pharmacological properties thus making it a key intermediate and vital starting material for the development of novel bioactive compounds. Several drugs are currently in use which contain the hydrazide moiety some of which include; isoniazide (anti-tuberculosis), nifuroxazide (antibiotic), isocarbazide (antidepressant), iproniazide (anti-tuberculosis), and galavit (anti-inflammatory) [101,102]. The chemical structures of these isatin-hydrazide hybrids are presented in Figure 12.

In 2020, Salem et al., [103] reported the synthesis of some isatin-carbohydrazide hybrids **32a-b** and the evaluated their in vitro antimicrobial activity. The compounds were tested on some strains of both gram positive and gram negative bacterial and the hybrid **32b** was found to possess the most potent antibacterial activity amongst the synthesised compounds with its activity comparable to that of Norfloxacin and Tetracycline.

Elsayed et al., 2021 [48] reported the synthesis of a series of isatin-nicotinohydrazide hybrids **33a-c** and **34a-h** followed by the evaluation of their activities as anti-tubercular and antibacterial agents. Amongst the synthesized compounds, the hybrids **34g** and **34h** were found to be the most potent anti-tubercular agents demonstrating broad spectrum antibacterial activity against the tested strains [35].

Rawat et al., 2016 [104] reported the synthesis of a series of isatin-carbohydrazide hybrids **35a-g** and evaluation of their antimicrobial activity against different bacterial and fungal strains. Most of the synthesized compounds revealed interesting antimicrobial activities with the hybrids **35c** and **35d** being the most potent against the bacterial strain *Escherichia coli* while hybrids **35a** and **35b** revealed very potent antifungal activity against *Candida albicans*.

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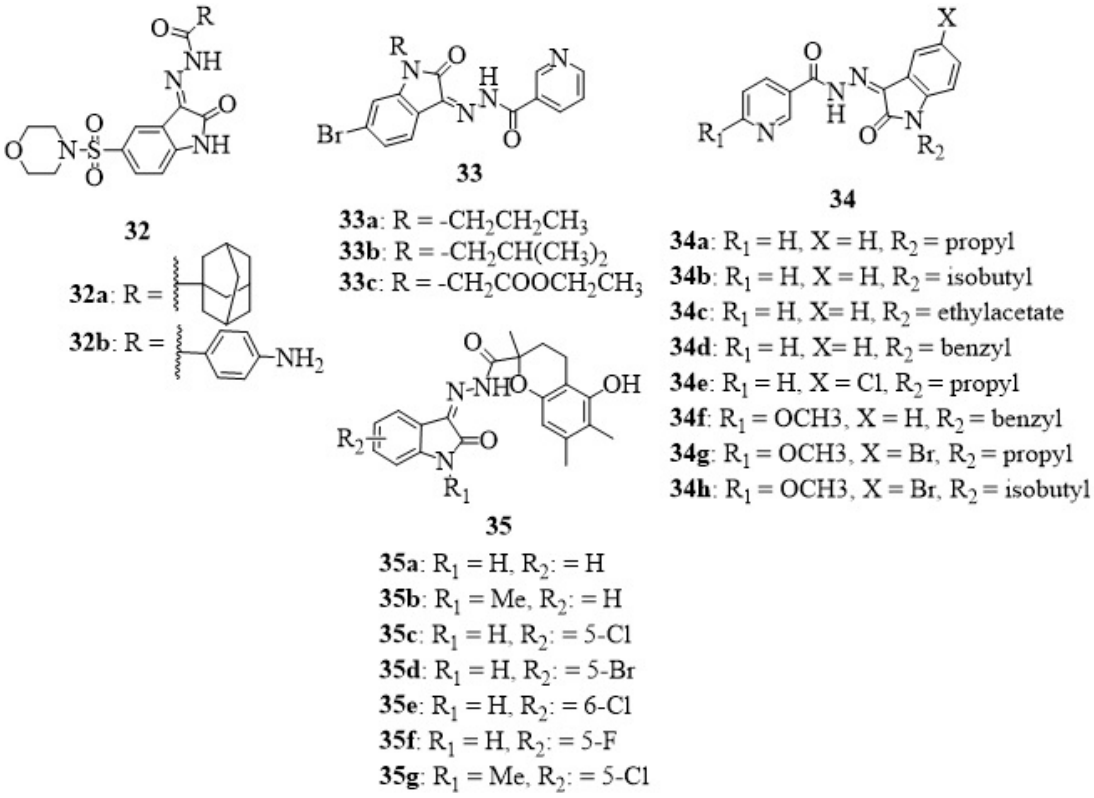

Figure 12. Chemical structures of isatin-hydrazide hybrids.

13. Isatin-Thiosemicarbazone Hybrids

Thiosemicarbazones are an important class of ligands generally obtained as condensation products from the reaction of thiosemicarbazide with aldehydes and ketones. Over the years, thiosemicarbazones have gained so much interest owing their metal-chelating properties, wide range of biological properties and structural flexibility [105]. Figure 13 presents some of the chemical structures of isatin-thiosemicarbazone hybrids.

In an attempt to discover novel anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents, Zhang et al., 2015 [106] synthesized a series of isatin-β-thiosemicarbazones hybrids **36a-i**. The synthesized compounds were evaluated for their antibacterial activity against gram-positive bacterial strains: *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (ATCC 6633). All tested compounds exhibited interesting antibacterial activity with **36b** being the most active with a minimum inhibitory concentration (MIC) value of 0.78 mg/L.

Thanh et al., 2016 [20] reported the synthesis and evaluation of the *in vivo* antioxidant/ *in vitro* antimicrobial activity of a series of isatin-thiosemicarbazone hybrids **37a-f**. The *in vitro* antimicrobial activity was conducted against different bacterial (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Enterobacter aerogenes*) and fungal strains (*Aspergillus niger*, *Candida albicans*, *Fusarium oxysporum*, *Saccharomyces cerevisiae*) while *in vivo* antioxidant activity was determined by evaluating the superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities of the compounds. The synthesized compounds revealed quite promising activities and the hybrid **37d** was identified as the most potent antioxidant, antibacterial and antifungal agent.

Conducting pharmacophoric modelling studies on non-nucleoside reverse transcriptase inhibitors (NNRTIs), a series of isatin-β-thiosemicarbazone hybrids **38-40** were synthesized and evaluated for their anti-HIV activity. The synthesized hybrids were found to possess interesting anti-HIV activity with hybrid **39** being the most active amongst the synthesized compounds [15].

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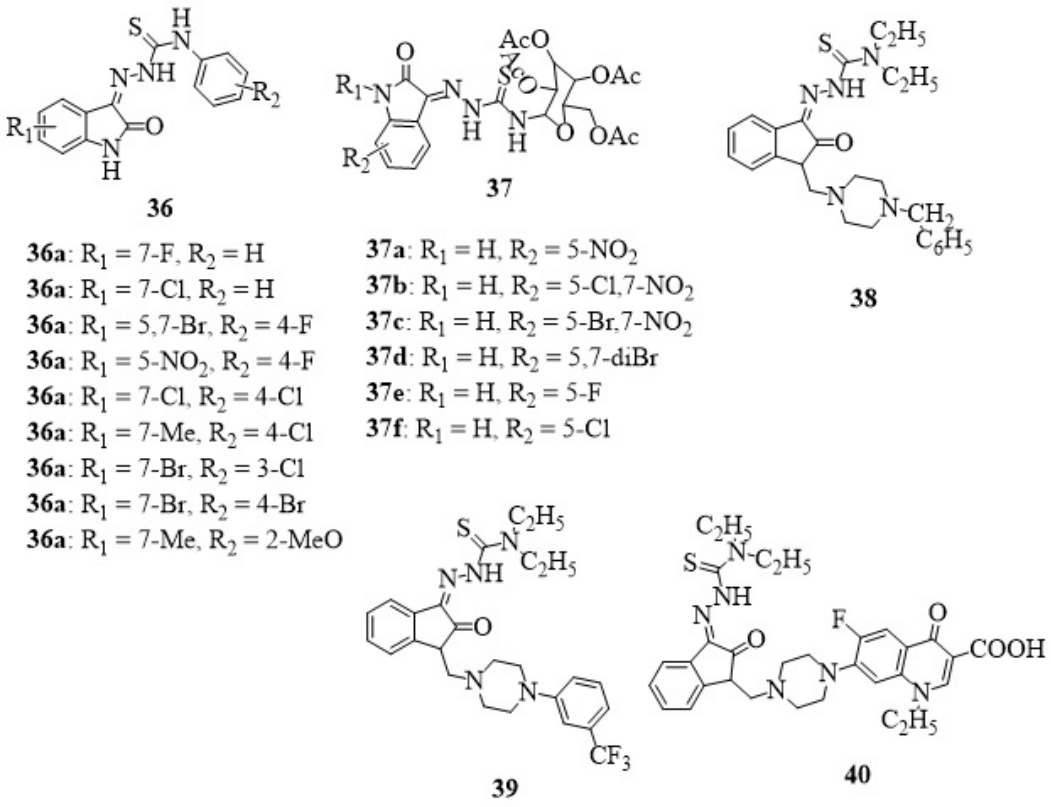

Figure 13. Chemical structures of isatin-thiosemicarbazone hybrids.

14. Isatin-Oxime Hybrids

Oximes are an essential class of nitrogen-containing compounds usually obtained as condensation products from the reaction of hydroxyl amines with aldehydes or ketones. This pharmacophore has found widespread use in different fields of life such as in industries, some oxime-containing compounds are used as artificial sweeteners. A good number of marketed drugs contain the oxime moiety some of which include; pyraloxime methiodine: a cholinesterase inhibitor and ceftobiprole [107,108]. Furthermore, oxime-containing chemicals have been reported to possess antiviral properties against influenza virus A and HIV-1 virus as well as anticancer properties against human breast and colon adenocarcinoma cell lines [109,110]. The chemical structures of these isatin-oxime hybrids are presented in Figure 14.

In an attempt to meet the demand for orally active inhibitors of respiratory syncytial virus (RSV) replication, Sin et al., 2009 [52] synthesized a series of isatin hybrids **41a-i**. The tested compounds revealed potent antiviral activities with the hybrids **41b-g** bearing methyl, ethyl and fluoroethyl substituents being the most active hybrids.

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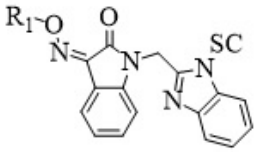


41

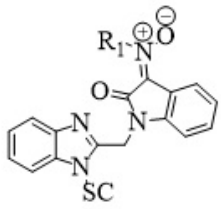
41a: SC = $(CH_2)_2CH(Me)_2$, R_1 = H
41b: SC = $(CH_2)_2CH(Me)_2$, R_1 = Me
41c: SC = $(CH_2)_4OH$, R_1 = Me
41d: SC = $(CH_2)_4OAc$, R_1 = Me
41e: SC = $(CH_2)_3OMe$, R_1 = Me
41f: SC = $(CH_2)_3OMe$, R_1 = Et
41g: SC = $(CH_2)_3OMe$, R_1 = CH_2CH_2F
41h: SC = $(CH_2)_3OMe$, R_1 = CH_2CF_3
41i: SC = $(CH_2)_3CN$, R_1 = CH_2CF_3

Figure 14. Chemical structures of isatin-oxime hybrids.

15. Isatin-Nitrone Hybrids

Nitrones are organic species that react with, "trap" and stabilize free radicals for identification and characterization purposes [111]. They are potent antioxidant molecules capable of reducing oxidative stress as well as suppressing signal transduction processes suggesting potential anti-inflammatory and anti-apoptotic activities [112–114]. The chemical structures of these isatin-nitrone hybrids are presented in Figure 15.

Sin et al., 2009 [52] reported the synthesis of a series of isatin-nitrone hybrids **42a-c** and evaluation of their inhibitory activity against respiratory syncytial virus (RSV). The synthesized compounds revealed moderate antiviral activity with the hybrid **42c** being the most potent.



42

42a: SC = -$(CH_2)_3OMe$, R = *i-pr*
42b: SC = -$(CH_2)_3OMe$, R = -$CH(CH_2CH_3)_2$
42c: SC = -$(CH_2)_3OMe$, R = -cHex

Figure 15. Chemical structures of isatin-nitrone hybrids.

16. Isatin-Piperazine Hybrids

Piperazine is a vital heterocyclic scaffold found in several biologically active compounds. This scaffold is present in some antiviral agents such as Delavirdine and Indinavir, which are used in HIV treatment. It is considered a privileged scaffold for drug design and widely used due to its unique properties some of which include; solubility, basicity, chemical reactivity and conformational properties [115,116]. This ring is present in several commercially available drugs and its derivatives are known to possess a broad spectrum of therapeutic properties such as; antidepressant, anticancer, antimalarial, anticonvulsant, antifungal, and antitubercular properties [117]. The chemical structure of an isatin-piperazine hybrid is presented in Figure 16.

In 2021, Omar et al., [54] in the quest for possible SARS-CoV-2 Protease Enzyme inhibitors, synthesized the isatin-piperazine hybrid **43** and evaluated its physicochemical, bioactivity scores and

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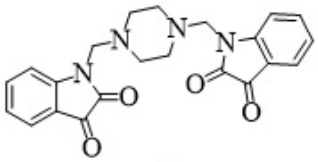
pharmacokinetic properties using in silico computational tools. Molecular docking studies were conducted to predict the inhibitory activity of the ligand against SARS-CoV-2 Protease Enzyme. Based on the study, the piperazine ligand made strong hydrogen bonding interactions with the SARS-CoV-2 Protease with a negative dock energy thus suggesting it could be a good lead for the design of new drug candidates.



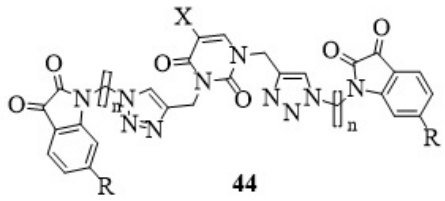
43

Figure 16. Chemical structure of an isatin-piperazine hybrid.

17. Isatin-Uracil Hybrids

Uracil, a naturally occurring pyrimidine nucleobase, is a major component of nucleic acid. Oxidative degradation of uracil yields urea and maleic acid in the presence of hydrogen peroxide and ferrous ions. It has widespread applications in different fields of life such as; medicine, pesticide and chemical synthesis. Uracil is used as starting material for the synthesis of many pyrimidine-based herbicides and in the design and application of medicine [55]. The chemical structure of some isatin-uracil hybrids are presented in Figure 17.

Kumar et al., 2012 [55] reported the synthesis of a series of isatin-uracil hybrids **44a-l** and evaluation of their cytotoxic activity against three human cancer cell lines; HeLa (cervix), MCF-7 (breast) and DU145 (prostate). Amongst the synthesized compounds, the hybrids **44g** and **44k** were found to be active against DU145 (prostate) cancer cell lines at low concentrations. Notably, most of the compounds were inactive against the HeLa (cervix) cell line except for hybrids 44d and h bearing electron withdrawing substituents.



44

44a: n = 2, R = H, X = H
44a: n = 2, R = F, X = F
44a: n = 2, R = Cl, X = H
44a: n = 2, R = Me, X = H
44a: n = 2, R = H, X = F
44a: n = 2, R = Cl, X = F
44a: n = 2, R = H, X = Cl
44a: n = 2, R = Cl, X = Cl
44a: n = 3, R = H, X = H
44a: n = 3, R = F, X = H
44a: n = 3, R = Cl, X = H
44a: n = 3, R = Me, X = H

Figure 17. Chemical structures of isatin-uracil hybrids.

18. Isatin-Coumarin Hybrids

Coumarin represents a privileged scaffold for medicinal chemists with unique physicochemical properties which undergo easy synthetic transformations [118,119]. It is found extensively in nature and its derivatives have been found to demonstrate interesting pharmacological activities (antibacterial, antifungal, antimalarial, and anticancer activities). Coumarins are widely used in

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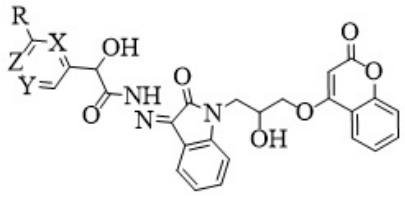
perfumes, hand soap, detergents and lotions where they function as fragrance enhancers or stabilizers [120,121]. Figure 18 presents some of the chemical structures of isatin-coumarin hybrids.

Considering the availability of limited and unsatisfactory antileishmanial chemotherapeutics, Khatoon et al., in 2021 [56] synthesized a series of isatin-coumarin hybrids **45a-i**. The synthesized compounds were evaluated for their in silico and in vitro activities against Leishmaniasis. Notably, hybrids **45f**, **45h** and **45i** were found to be the most active at macro molar concentrations against Leishmania tropica promastigotes and amastigotes.

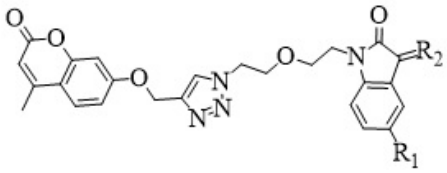
In 2019, Diao et al., [122] reported the design and synthesis of a series of isatin-coumarin hybrids **46a-l**, and evaluation of their in vitro anticancer activities against; HepG2 (liver carcinoma), Hela (cervical cancer), A549 (lung adenocarcinoma), DU145 (prostatic cancer), SKOV3 (ovarian carcinoma), MCF-7 (breast cancer), and drug-resistant MCF-7/DOX (doxorubicin-resistant MCF-7) human cancer cell lines. The compounds revealed weak to moderate anticancer activities and such can be considered as starting points for further research.

Huang et al., 2019 [123] reported the design, synthesis and evaluation of the *in vitro* anti-tubercular activity of a series of isatin-coumarin hybrids **47a-d** against Mycobacterium tuberculosis (MTB) H37Rv. The compounds, however, were inactive but could serve as good starting points for the development of anti-TB molecules.



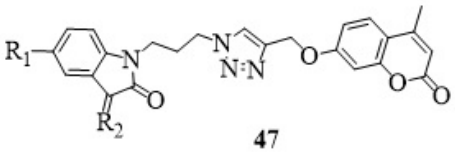
45

45a: X = CH, Y = CH, Z = CH, R = H
45b: X = C-Cl, Y = CH, Z = CH, R = H
45c: X = CH, Y = CH, Z = CH, R = Cl
45d: X = CH, Y = CH, Z = C-Cl, R = H
45e: X = CH, Y = CH, Z = C-Me, R = H
45f: X = CH, Y = CH, Z = CH, R = Me
45g: X = N, Y = N, Z = CH, R = H
45h: X = CH, Y = CH, Z = C-NH_2, R = H
45i: X = CH, Y = CH, Z = N, R = H



46

46a: R_1 = H, R_2 = O
46b: R_1 = Me, R_2 = O
46c: R_1 = Cl, R_2 = O
46d: R_1 = F, R_2 = O
46e: R_1 = H, R_2 = NOH
46f: R_1 = Me, R_2 = NOH
46g: R_1 = Cl, R_2 = NOH
46h: R_1 = F, R_2 = NOH
46i: R_1 = H, R_2 = NOMe
46j: R_1 = Me, R_2 = NOMe



47

47a: R_1 = H, R_2 = O
47b: R_1 = Me, R_2 = O
47c: R_1 = Cl, R_2 = O
47d: R_1 = F, R_2 = O

Figure 18. Chemical structures of isatin-coumarin hybrids.

19. Isatin-Thiolactone Hybrids

Thiolactone is an essential class of heterocyclic scaffold with the extensive use of their cores as synthetic intermediates for the generation of ligands required for applications in catalysis and medicinal chemistry. They are often referred to as latent thiols and have been reported to possess anticancer, antibacterial, and anti-Alzheimer activity[124]. Figure 19 presents some of the chemical structures of isatin-thiolactone hybrids.

Hans et al., 2011 [57] synthesized and evaluated the antiplasmodial activity of a series of isatin-thiolactone hybrids **48a-f** against chloroquine-resistant (W2) strain of *Plasmodium falciparum*. Notably, none of the compounds revealed potent antimalarial activity. However, it was observed that activity

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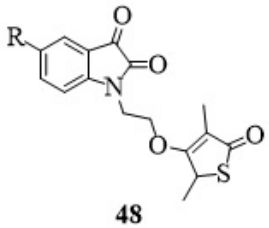
of some of the compounds were enhanced as a result of hybridization and could be a starting point for further investigation.



48

48a: R = Br
48b: R = Cl
48c: R = F
48d: R = I
48e: R = Me
48f: R = H

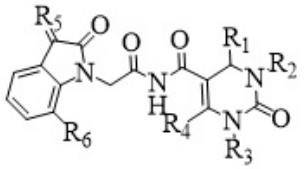
Figure 19. Chemical structures of isatin-thiolactone hybrids.

20. Isatin-Pyrimidine Hybrids

Pyrimidines represent one of the most active classes of compounds with a wide spectrum of biological activities which can be exploited for drug discovery [125]. Substituted pyrimidines are widely distributed in nature and are of the first compounds which were studied by organic chemists. They can be found in both natural products (vitamin B1) and synthetic compounds (barbituric acid and veranal) used as hypnotics [126]. The chemical structure of some isatin-pyrimidine hybrids are presented in Figure 20.

In 2016, Devale et al., [47] reported the synthesis of a series of isatin-pyrimidine hybrids **49a-e**. These compounds were screened for their **in vitro** Reverse Transcriptase (RT) inhibitory activity against HIV-1 virus, resulting in the identification of two hybrids **49c** and **49d** with higher RT inhibitory activity when compared to rilpivirine, a reference drug.

Akhaja et al., 2012 [127] reported the synthesis and in vitro evaluation of some isatin-pyrimidine hybrids **50-53** as anti-tubercular agents. Most of the synthesized compounds revealed moderate activity with hybrids **50** and **51** being the most active against MTB H37Rv. Notably, the hybrids **52** and **53** were found to completely inhibit MTB H37Rv by 99% at an MIC of 3.10– 3.12 mg/mL.



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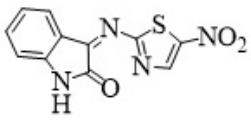
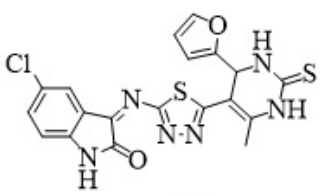
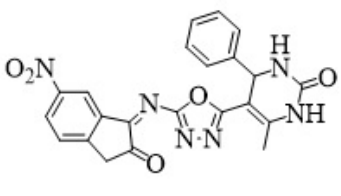


50

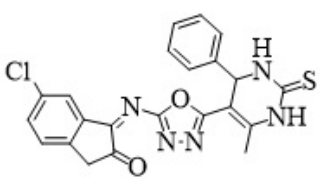
49a: R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = O
49b: R_1 = H, R_2 = H, R_3 = H, R_4 = Me, R_5 = O
49c: R_1 = Me, R_2 = H, R_3 = H, R_4 = Me, R_5 = O
49d: R_1 = Et, R_2 = H, R_3 = H, R_4 = Me, R_5 = O
49e: R_1 = pr, R_2 = H, R_3 = H, R_4 = Me, R_5 = O



51



52



53

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Figure 20. Chemical structures of isatin-pyrimidine hybrids.

21. Isatin-Quinoline Hybrids

The quinoline moiety, a nitrogen-containing heterocyclic compound, can be found in several natural compounds. It is one of the most recognized fragments in bioactive compounds and is found in different pharmaceutically important alkaloids such as quinine and cinchonine. Pharmacological studies of quinoline have reported a broad spectrum of activities associated with this moiety [118,119]. Figure 21 presents some of the chemical structures of isatin-quinoline hybrids.

Raj et al., 2014 [128] reported the synthesis and evaluation of antimalarial activity of two isatin-chloroquinoline hybrids **54** and **55** against chloroquine-resistant W2 strain of *Plasmodium falciparum*. The synthesized compounds were not as potent as standard antimalarial drugs. However, the most potent compound revealed activity which is comparable to that of chloroquine thus suggesting these compounds could be a starting point for further research.

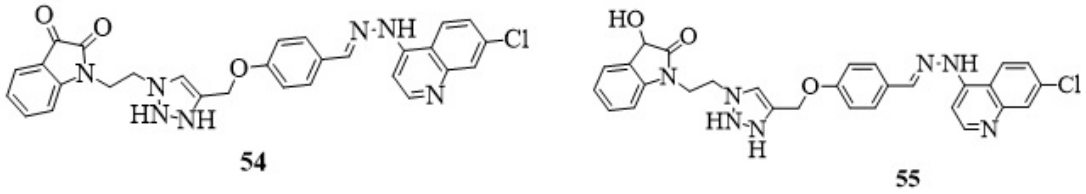

Figure 21. Chemical structures of isatin-quinoline hybrids.

22. Isatin-Thioacetazone Hybrids

Thioacetazone is a bacteriostatic drug used in combination with other antimycobacterial agents to treat tuberculosis. However, the dermatological side effects associated with its use by AIDS patients have limited its exploitation. Thioacetazone has weak activity against mycobacterium tuberculosis and is never used on its own. It is useful in preventing resistance to more powerful drugs like isoniazid and rifampicin [129]. The chemical structure of some isatin-thioacetazone hybrids are presented in Figure 22.

In an attempt to develop new and more potent anti-tubercular agents, a series of thioacetone-isatin hybrids **56-59** were synthesized. The hybrid **57** revealed quite interesting inhibitory activity against MTB H37 Rv while hybrid **58** was found to be the least potent [17].

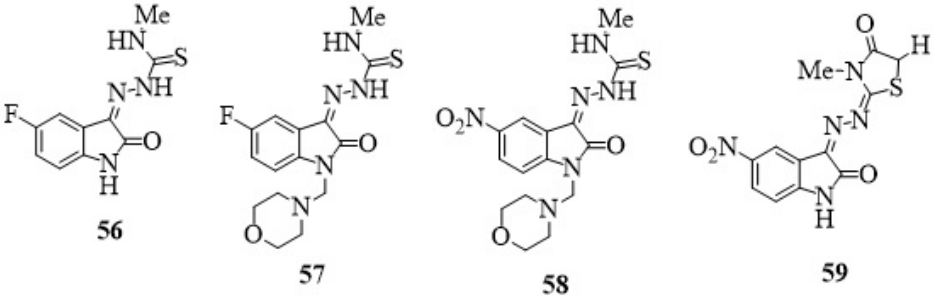

Figure 22. Chemical structures of isatin-thioacetazone hybrids.

23. Other Isatin Hybrids

A series of isatin-imine **60a-e** analogues were successfully synthesized and evaluated for their antibacterial and antifungal activities against certain microbes by Debnath et al., 2015. Some of the compounds portrayed quite interesting properties with **60d** being the most potent against the investigated microbes having the highest docking score. Structure activity relationship studies revealed that the introduction of 2,5-dimethyl substituent at position R2 improved the activity of the compound [130]. Figure 23 presents some of the chemical structures of other isatin hybrids.

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In 2018, Xu et al., [131] reported the synthesis of a series of ethylene tethered bis isatin-derivatives **61a-i**. The synthesized compounds were evaluated for their in vitro anti-mycobacterial activities against MTB H37Rv and MDR-TB. All tested compounds revealed interesting anti-mycobacterial properties with **61i** being the most potent.

Teng et al., 2015 [132] reported the design and synthesis of a series of di- and tri-subtituted isatin derivative **62a-g** and **63a-d**, as well as the evaluation of their in vitro anticancer properties against human T-lymphocyte Jurkat cells. The compound **63a** was found to be the most potent compound capable of inhibiting the proliferation of Jurkat cells by inducing apoptosis.

Wang et al., 2018 [53] while attempting to exploit the potentials in molecular hybridization for the development of anticancer drugs, synthesized some novel isatin-α,β-unsaturated ketone hybrids **64a-k** and **65a-d**. Majority of the synthesized compounds revealed potent antiproliferative properties in the tested cell line. The hybrid **65a** was identified as the most potent hybrid which can be a promising lead compound for the development of anticancer agents.

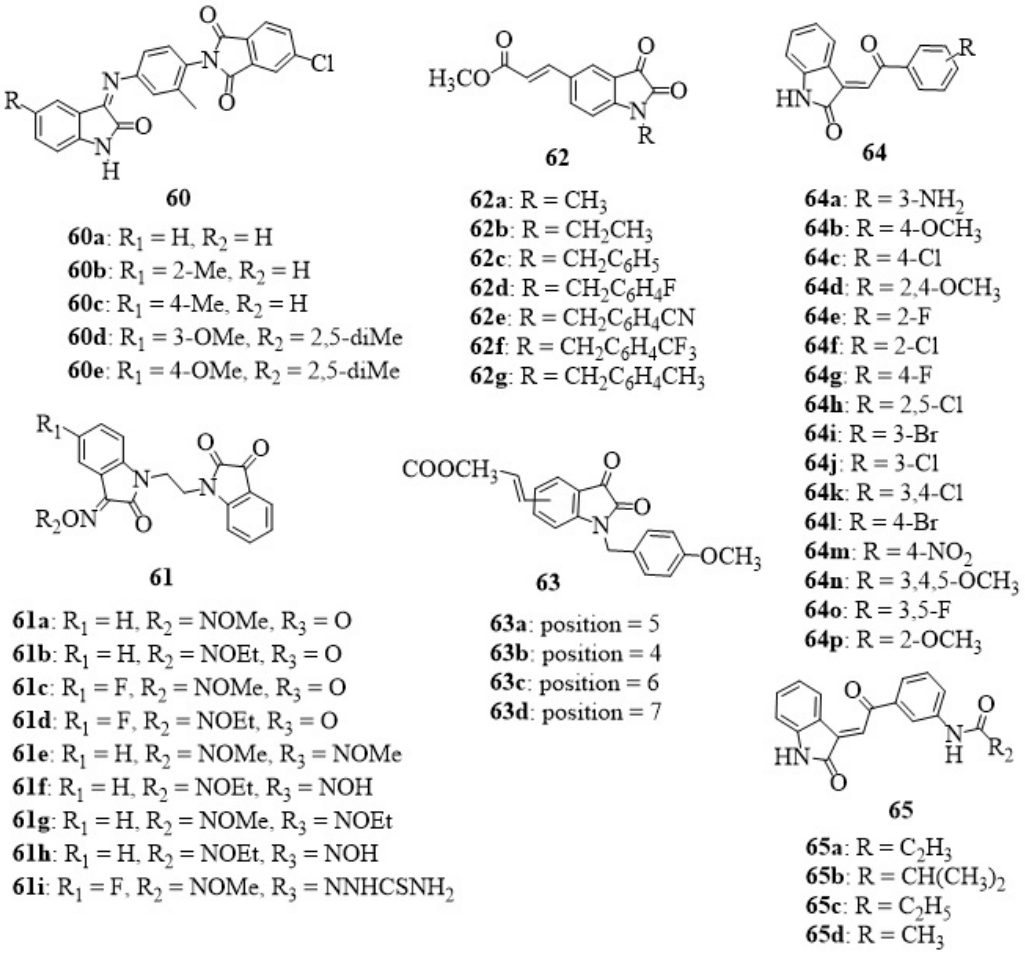

Figure 23. Chemical structures of other isatin hybrids.

5. Conclusions

The concept of molecular hybridization has been established as a pivotal technique in drug discovery with tremendous contributions towards the designing and synthesizing of bioactive molecules [133–137]. The isatin moiety and its hybrids have proven to possess widespread pharmacological properties and as such generating hybrid molecules of isatin with other pharmacophores has the potential of yielding novel compounds with improved potency and new biological activities. Over the past years, several hybrid molecules of isatin and different privileged pharmacophores have been designed and synthesized. In this review, we have outlined some hybrids of isatin which have been successfully synthesized and their biological properties evaluated. Most of

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the compounds reported in the literature have demonstrated very interesting biological activities. For example, hybrid **36b** exhibited potent antibacterial activity with a minimum inhibitory concentration (MIC) value of 0.78 mg/L and could serve the purpose of a lead compound for further research. The isatin-pyrimidine hybrids **49c** and **49d** exhibited excellent in vitro Reverse Transcriptase (RT) inhibitory activity against HIV-1 virus bearing IC_{50} values in the nanomolar level, which were more potent when compared to the reference drug. The compounds discussed in this review could serve as starting points for further research on promising therapeutic drug candidates.

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