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## Exploration of Isatin as Anti-cancer and Anti-tubercular Modern Armamentarium. A Comprehensive Review on Isatin Congeners and its Promising Biological Activities

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### Keywords:

Cancer; tuberculosis; morbidity; mortality; WHO; anti TB agents

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### ABSTRACT:

In recent eras, cancer, and tuberculosis have become the leading causes of not only morbidity but also mortality. Around 10 million cancer-related fatalities are reported annually worldwide, but 10.4 million new cases are also discovered each year. According to World Health Organization data, 10.4 million cases were in 2016 worldwide, whereas 360,565 cases in Indonesia was reported. Some clinically approved anticancer and anti-TB drugs demonstrate a most promising role in their treatment. Still, the need for new, powerful, and secure candidates as anticancer and Anti TB agents with a variety of modes of action is constantly present due to the serious growth of drug resistance, side effects, multidrug-resistant malignancies, and tuberculosis as a result of mutations. Over the last decade, various heterocyclic compounds in medicinal chemistry were explored and reported frequently in the literature; these derivatives have received substantial attention as anticancer and anti-TB agents. In which nitrogen-containing heterocyclic moiety, isatin emerged as a significant and versatile heterocyclic for developing novel anticancer and anti-TB candidates.

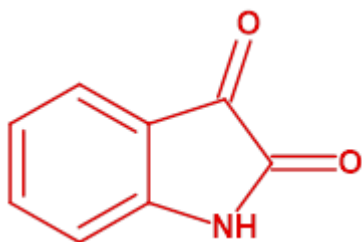
### Introduction:

Isatin (indole 2, 3-dione, Figure 1) is a heterocyclic compound that is present in all body fluids in mammalian cells.<sup>1</sup> It is also extracted from plants as an alkaloid.<sup>2</sup> Many pharmacological properties of the isatin nucleus have been reported, notably Anti-tubercular,

anti-inflammatory, anti-histaminic, anti-viral, anti-cancer, anti-convulsant, Anti-depressant, and some other biological activities strong inhibitor of various enzymes and receptors, including histone deacetylase, carbonic anhydrase, tyrosine kinase, natriuretic peptide receptor guanylate cyclase, and tubulin.<sup>3,4,5,6</sup> It

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precipitates as orange-red monoclinic prism crystals from water, alcohol, or acetic acid.<sup>7</sup> These enzymes and receptors are the leading cause of apoptosis in variety of cells including malignant tumor cells, and can affect the expression of genes related to apoptosis.<sup>8</sup>



Isatin nucleus is chemically benzene fused pyrrolidine 3 one and found biologically active heterocycle.<sup>7,9</sup> Firstly, in 1841, Erdman and Laurent discovered the isatin nucleus by oxidizing indigo with nitric acid (Fig: 2).<sup>10</sup>

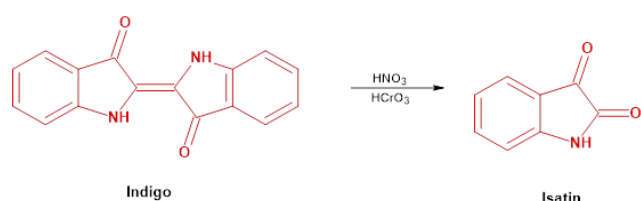


Figure 2: Formation of Isatin by oxidation of dye Indigo

It is crystallized with water, alcohol, or acetic acid as orange-red monoclinic prisms. Moreover, Isatin shown variety of chemical reactions, such as Friedel-Crafts, ring expansion, oxidation, and Aldol-condensation. Isatin widely used for the preparation of biologically active molecules like, tryptanthrin, indirubin, and 2-oxindoles.<sup>8</sup> It represent essential building block in organic synthesis and act as not only electrophile but also nucleophile in many cases. Indole, quinoline, pyrrolidine, 2-oxindoles, and lactam are few examples of biologically significant heterocyclic compounds that are produced by utilizing Isatin starting material.<sup>9</sup>

### Reactivity of Isatin:

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Isatin primarily interacts at three positions: C-5 aromatic substitution, which stimulates biological activity; C-3 N-alkylation; and C-3 chemo-selective carbonyl reactions. Ring-expansions, reductions, oxidation, and spiro-annulation occurs at C-2.

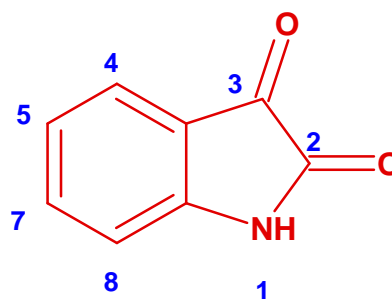
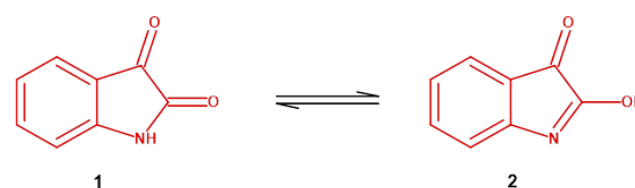


Figure 3: Spatial position in Isatin scaffold.

### Structural Characteristics:

Isatin exist as two tautomeric forms as lactam(1) and lactim(2), in which proton transfer takes place between the nitrogen atom and the oxygen atom positioned at the second carbon, this discovery were first identified by Baeyer in 1882. Most isatin is present in solid form as the lactam structure.

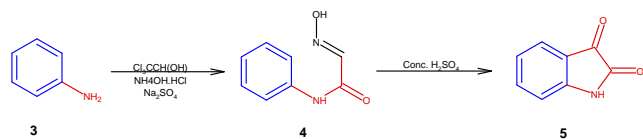


### Methods for Synthesis of Isatin:

These are the three procedures for synthesizing isatin derivatives from aniline

#### i. Sandmeyer method:

In this method aniline (3) was condense with chloral hydrate in the presence of hydroxyl amine and sodium sulphate to form an intermediate 2-(hydroxyimino)-N-phenylacetamide(4). Indoline-2,3-dione (5) was obtained after cyclization of formed intermediate by using strong acid (H<sub>2</sub>SO<sub>4</sub>).<sup>11</sup>

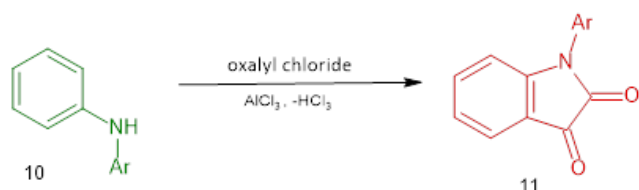


### ii. Grassman method:

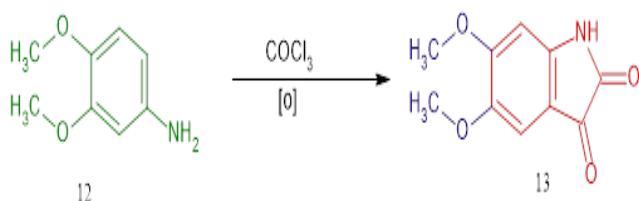
First, anilines (6) were converted into 3-(methylthio) oxindoles (8), followed by oxidative elimination of the methylthio group by chlorination and subsequent hydrolysis and finally Isatin (9) was formed.

### iii. Stole method:-

In this method, Isatin is formed by using primary and secondary aryl-amine (10) along with oxalyl chloride to form an intermediate product like chlorooxalyl anilide that further reacts with aluminium tri-chloride or other Lewis bases that help to cyclize the intermediate and form 1-aryl-indole-2,3-dione (11).<sup>12</sup>



In this method, Isatin derivatives (13) were formed from aminoaromatics (12) or oxamalonate esters.



## Chemical Reaction

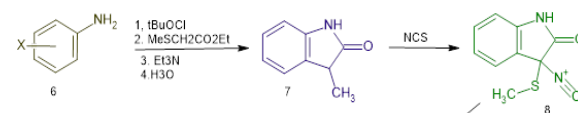
After the literature survey found that there were many Isatin-based derivatives produced from Isatin (14) through different chemical reactions.

### a) N-Alkylation of Isatin:

Alkylated Isatin (15) can be easily prepared by the reaction of alkyl, allyl-, benzyl-, and propargyl halides with isatin at 40 to 100°C.

### b) Pfitzinger Reaction:

In this reaction, Isatin reacts in a very alkaline solution with ketones that have a



methylene group next to the carbonyl group. This reaction produced quinoline-4-carboxylic acid (16) as the final product.

### c) Reduction of Isatin:

Oxindole derivatives (17) were formed on the reduction of Isatin in the presence of sodium hydro sulfite or zinc-copper catalyst.

### d) Friedel-Crafts Reaction:

The asymmetric Friedel-Crafts alkylation of Isatin with electron-rich aromatic compounds yields the clinically intriguing and optically active 3-aryl-3-hydroxy-2-oxindoles (18).

### e) N-Arylation:

N-Arylation can take place when Isatin reacts with aryl bromide in the presence of  $\text{Ph}_3\text{Bi}(\text{OAc})_2$  and  $\text{Cu}^0$  in an inert atmosphere and N-arylated isatin is formed (19).

## f) Oxidation:

Conversion of Isatin to isatoic anhydride (20) through oxidation in the presence of chromium trioxide.

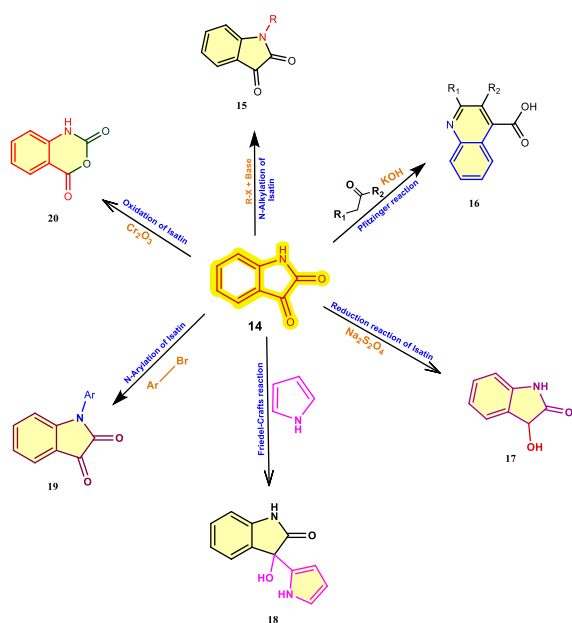
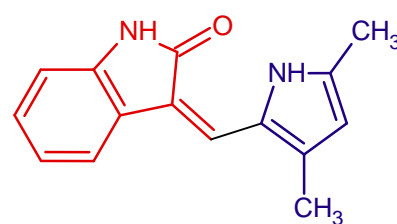


Figure 4: Chemical reaction exerted by isatin motif.

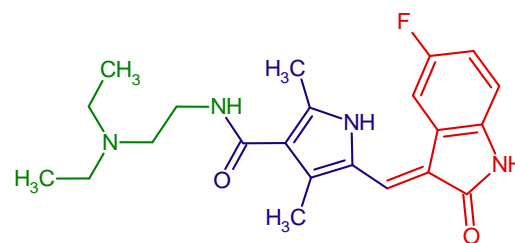
### Role of Isatin in Cancer Chemotherapy:

One in every eight deaths globally is caused by cancer, which is the second biggest cause of death after heart disease.<sup>13</sup> According to the International Organization for Research on Cancer, approximately 18.1 million people will be diagnosed with cancer in 2018 and 9.6 million will face death from it.<sup>14</sup> The prostate, lungs, bronchus, colon, rectum, and urinary bladder cancer are more reported in males whereas women are commonly suffer with the breast, lung and bronchus, colon, rectum, uterine corpus and thyroid. Additionally, blood cancer, and cancers related to the brain and lymph nodes found in children.<sup>15</sup> The widely used method to treat disease is the incorporation of chemotherapeutic agent along with surgery on latent stages. Radiation, hormonal therapy, and immunological therapy are some of the advance methodologies used to combat the disease.<sup>16</sup>

More than 100 medications have been approved for the treatment of cancer, but the vast bulk of them have led to drug resistance and fatal side effects necessitating the urgent need for the establishment of novel anticancer agents. Isatin is a versatile pharmacophore in the development of new anticancer drugs, and many of them, such Semaxanib,<sup>14,17</sup> sunitinib,<sup>14,17</sup> Nintedanib<sup>14,17</sup> and Hesperadin<sup>14</sup> (Figure. 4), have been approved for clinical use to treat variety of malignancies, including some that are resistant to therapy with conventional regimen.<sup>17</sup>



Semaxanib



Sunitinib

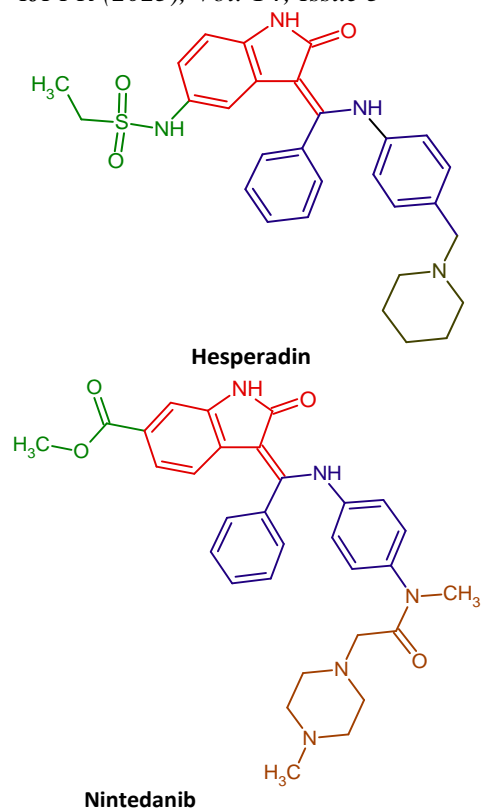


Figure 5: Recently discovered isatin bearing potent Anti-cancer moieties.

### Role of Isatin in the Treatment of Tuberculosis:

A life-threatening illness tuberculosis (TB) is caused by *Mycobacterium tuberculosis*. The infectious agent transmitted through the air. TB strike 5 position in top 10 diseases that lead to mortality. According to the World Health Organization data 10.4 million cases in 2016 worldwide and whereas 360,565 cases in Indonesia have been reported.<sup>18</sup> *Mycobacterium* predominantly affected the lungs (pulmonary TB), but also can affect other body areas such as (extra pulmonary TB).<sup>19</sup> One of the major challenges to treating the global TB epidemic is drug-resistant TB (DR-TB), particularly multi-drug resistant TB (MDR-TB).<sup>20</sup> First-line anti-TB agents such as isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) are used for treatment of drug-susceptible MTB infected patients.<sup>21</sup> Second lines drug like levofloxacin, Bedaquiline and delamanid are two recently developed anti-TB drugs that play a

significant role in the treatment of individuals with DR-TB and MDR-TB, however they are typically less successful than first-line anti-TB drugs.<sup>22</sup> Various isatin hybrids have been developed and examined as potential anti-TB agents and their potency was tested against both drug-susceptible and drug-resistant strains of MTB.<sup>23</sup>

Yu-Ou Teng *et al.* have designed a series of novel di- or trisubstituted isatin analogues as anti-cancer agents. All compounds were characterized using <sup>1</sup>H NMR, <sup>13</sup>C NMR, and LC-MS, and their anticancer activity against the human T lymphocyte Jurkat cell line was assessed using the MTT assay in vitro. When compared to the other compounds in the series, Compound 21a demonstrated the most potent anti-cancer effect with an IC<sub>50</sub> value of 0.03 M.<sup>24</sup>

Adel S. El-Azab *et al.* have synthesized a series of compounds and tested their anti-cancer activity against the MDA-MB-231 and LOVO cells. The structures are all confirmed by <sup>1</sup>H and <sup>13</sup>C NMR. Among them, compound 22a was found to be most potent as an EGFR-TK inhibitor with a value of (IC<sub>50</sub> = 38 0.22, 9.91 0.12) and compared with two standard 5-fluorouracil and erlotinib (IC<sub>50</sub> = 70.28 0.2, 15.23 0.09, 22.24, 0.22, 25.31, 0.12). A docking study was performed using MOE 2008.10 software.<sup>25</sup>

Mohamed El-Naggar *et al.* proposed two novel anti-cancer series of thiazolidinedione-isatin conjugates and thiazolo[3,2-a] benzimidazolone-isatin conjugates. In-vitro cytotoxic activity was performed against the two breast cancer cell lines MDA-MB-231 and MCF-7. After the in-vitro cytotoxic screening, it was found that compounds 23a (7.6 ± 0.5, 8.4 ± 0.5) and 23b (13.2 ± 1.2, 21.2 ± 1.5) possess the most potent anti-cancer activity but less than the standard doxorubicin (IC<sub>50</sub> 4.7 ± 0.4, 3.8 ± 0.4) and sunitinib (IC<sub>50</sub> 5.5 ± 0.5, 3.4 ± 0.3). On the other

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hand, two non-tumorigenic cell lines were used to assess the cytotoxic efficacy of the active conjugates (breast MCF-10A and lung WI-38).<sup>26</sup>

Wagdy M. Eldehna *et al.* has proposed various compounds of carbonylhydrazone-linked benzofuran-isatin conjugates. The MTT assay was used to identify the most active anti-cancer compound against all tested cancer subpanels, and compound 24b demonstrated the most potent anti-proliferative activity. In addition, all compounds were tested against the colorectal cancer SW-620 and HT-29 cell lines, and it was found that compounds 24a and 24b were more effective, with (IC<sub>50</sub> = 8.7 and 9.4 mM (5a), and 6.5 and 9.8 mM for (5d). Both compounds exhibited favorable safety profiles and selective cytotoxicity. Moreover, both compounds triggered apoptosis in SW-620 cells in a dose-dependent manner. They dramatically enhanced the level of cleaved PARP, which caused SW-620 cells to undergo apoptosis, and decreased the expression of the anti-apoptotic Bcl2 protein.<sup>27</sup>

Pardeep Singh *et al.* Have been designed a series of 1H-1,2,3-triazole tethered isatin. IR, NMR, and mass spectral analysis confirmed the structures of all hybrids. Anti-cancer activity of all synthesized assessed against the four different cancer cell lines, and compounds 25a and 25c exhibited the most potent anti-cancer activity. IC<sub>50</sub> value of compound 5a (<1 μm against A-549, PC-3, and THP-1 cell lines) and compound 25b with the value of IC<sub>50</sub> 0.03, 0.48, 32.6 and 44.9 mM against A-549, THP-1, PC-3 and Caco-2 cell lines respectively, Paclitaxel has been employed as a standard treatment for lung (A-549), 5-fluorouracil for leukemia (THP-1), Caco-2 for colon cancer, and mitomycin for PC-3 (prostate). SAR activity revealed that a strong electron-withdrawing fluoro as well as nitro substituents on isatin either ring decreased the anticancer activity.<sup>28</sup>

Mahmoud F. Abo-Ashour *et al.* Have been synthesized two series of N-substituted isatin

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moieties clubbed with benzenesulfonamide moieties via a hydrazine linker. Once all newly synthesized compounds were subjected to in-vitro anti-cancer screening, compounds 26a and 26b showed the most optimistic broad-range anti-proliferative activity towards a wide range of cell lines. % growth inhibition of several cancer cells by compounds 26a and 26b at a concentration of 10 mM Compound 26b effectively halted the growth of CNS cancer (SF-539). Non-small cell lung cancer A549/ATCC, NCI-H460, colon cancer HCT-116, COLO 205, renal cancer RXF 393, ovarian cancer OVCAR-4, OVCAR-8, and leukemia CCRF-CEM were all inhibited to varying degrees (84%, 69%, 56%, 86%, 42%, 57%, 69%, 44%, and 47%, respectively). Whereas compound 26a had a strong growth inhibitory impact against ovarian cancer, OVCAR-4, Non-Small Cell Lung Cancer NCI-H226, CNS Cancer SNB-19, Renal Cancer RXF 393, 786-0, and Breast Cancer HS 578T with inhibition percent of 71%, 66%, 59%, 55%, 52%, and 55% respectively. However, both compounds had little suppressive activity towards CDK2 and CDK9 (IC<sub>50</sub> > 10 m).<sup>29</sup>

Kailin Hanet *et al.* Have reported di- or trisubstituted novel isatin hybrids, and their structures were estimated by 1H NMR and 13C NMR as well as LC-MS spectral methods. Anti-cancer activity of all compounds was assessed against the three cancer cell lines viz K562, HepG2, and HT-29 by using an in-vitro MTT assay. Compounds 27h (IC<sub>50</sub> = 3 nM) and 27b (IC<sub>50</sub> = 6 nM) show the most effectiveness against human leukemia K562 cells, with Camptothecin (CPT) as the positive control.<sup>30</sup>

Sharma *et al.* has proposed a series of isatin-based new 3-tetrazolyl methyl-3-hydroxy-oxindole hybrids. While, all compounds were examined for their in vitro anticancer activity on five human cancer cell lines, including breast (BT549 and MDA MB-231), prostate (PC-3 and DU-145), ovarian (PA-1), and prostate (PC-3

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and DU-145). The compounds 28a and 28b selectively demonstrate potent anticancer activity against the DU-145 cell line, with IC<sub>50</sub> values in the range of 7.01±0.91 and 4.26±0.09 μM respectively. Compound 6r altered the morphology and long-term clonogenic survival of DU-145 cells. Cell cycle analysis exhibited that all molecules arrest the cells in G<sub>2</sub>/M phase. All compounds induced anti-proliferation activity in cells, which was validated by DAPI staining, annexin-V binding assay, AO/EB staining, and DNA fragmentation analysis.<sup>31</sup>

Dmytro Havrylyuk *et al.* has suggested a series of satins-based conjugates with thiazolidine and pyrazoline molecules. All compounds were tested against the NCI-60 cancer cell lines. Among them, only compound 29 had the most encouraging anti-proliferative activity against all leukemia subpanel tumor cell lines, with GI<sub>50</sub> values ranging from 0.69 to 3.35 mM and the strongest activity against the CCRF-CEM and RPMI-8226 cell lines (GI<sub>50</sub> = 0.75 mM and 0.69 mM, respectively) cell lines. The SAR study exhibited that antitumor action may show as a result of the hybridization of the pyrazoline ring system with the isatin ring system.<sup>32</sup>

Zainab M. Elsayed *et al.* has synthesized a series of novel isatin-nicotinohydrazides. All compounds were tested for biological activity against two different strains of anti-tubercular. Drug-susceptible *M. tuberculosis* strain (ATCC 27294) was allowed to be all molecules as a *Mycobacterium tuberculosis*, and it was found that compounds 30a, 30b, and 30c showed excellent activity (MIC = 2.4 mg/mL) that is similar to standard INZ with (MIC = 2.4 mg/mL) whereas compounds 30b and 30c showed excellent activity against isoniazid/streptomycin resistant *M. tuberculosis* (ATCC 35823) with (MIC = 3.9 mg/mL). AutoDock Vina was used to determining the protein-ligand interaction.<sup>33</sup>

Feng Gao *et al.* Were defined A series of novel benzofuran-isatin hybrids were evaluated as anti-

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mycobacterial, and all hybrids were assessed against drug-susceptible and multi-drug resistant (MDR) *Mycobacterium tuberculosis* (MTB) and their cytotoxicity towards VERO cells. Compound 31a exhibited excellent anti-mycobacterial activities against MTB H37Rv and MDR-MTB strains with the value of (MIC: 0.125 and 0.125 μg/mL) which was comparable to or better than RIF (MIC: 0.5 & 64 μg/mL) and INH (MIC: 0.06 & >128 μg/mL) but less than TAM16 (MIC: <0.06 & <0.06). moreover, compound 6 also showed the most promising cytotoxic activity towards VERO cells (CC<sub>50</sub>: 128 μg/mL).<sup>34</sup>

Vinay Pogaku *et al.* has proposed a series of 1,2,4-triazol-1-yl-pyrazole-based spirooxindolopyrrolizidines as anti-tuberculosis and ultrasonication and ionic liquid were used as green synthesis to synthesized all hits in this series. All compounds were established by <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectrometry, and single-crystal X-ray diffraction. The in vitro anti-tuberculosis screening revealed that various compounds showed similar activity to standard ethambutol (MIC: 1.56 μg/mL) but compound 32a was found to be more potent (MIC: 0.78 μg/mL) than the standard. The anti-proliferative activity was also performed against RAW 264.7 cells.<sup>35</sup>

Yaohuan Zhang *et al.* Were suggested that a series of benzofuran-isatin-hydroxyimine/thiosemicarbazide hybrid isanti-TB activities against drug-sensitive MTB H37Rv and MDR-TB as well as cytotoxicity in-vitro model were used to determine the biological activity of all synthesized compounds. Compound 33a show outstanding anti-TB effect (MIC: <0.06, 0.22 and 0.86 μg/mL, respectively) which were more than from the standard first-line anti-TB agents INH and RIF (MIC: 0.078 μg/mL). All compounds also showed significant cytotoxicity activity.<sup>36</sup>

Zhi Xu *et al.* designed a series of novel 1H-1,2,3-triazole-tethered gatifloxacin (GTFX)

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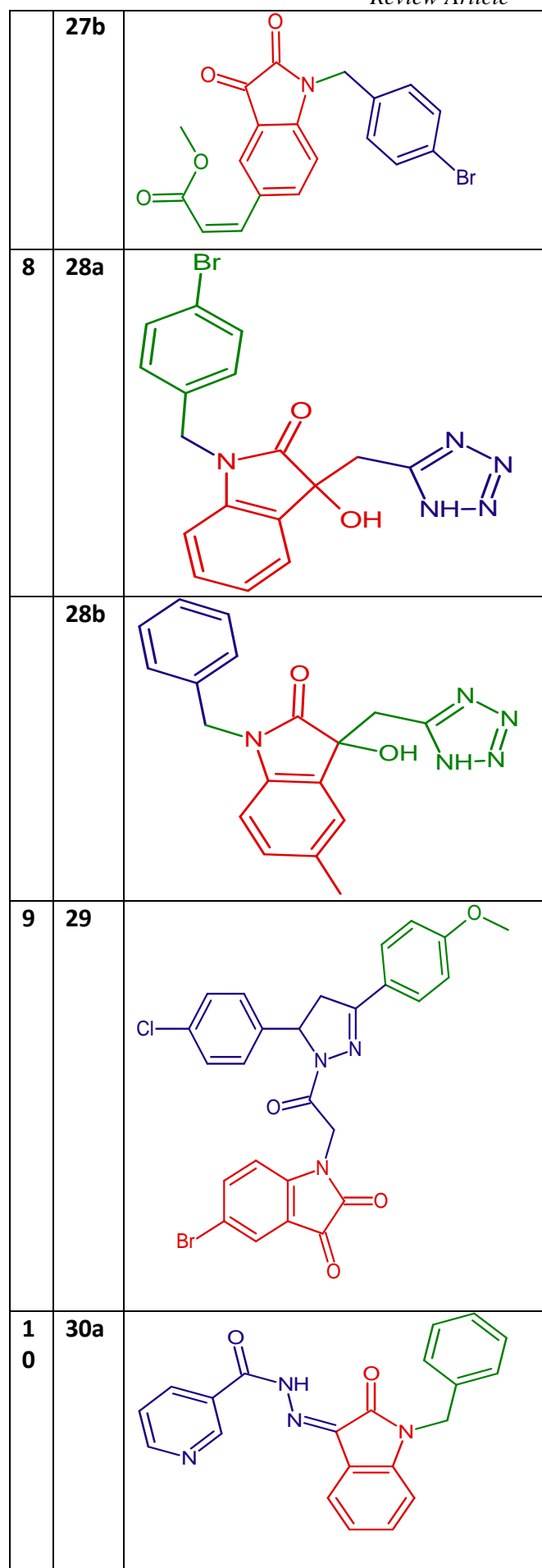
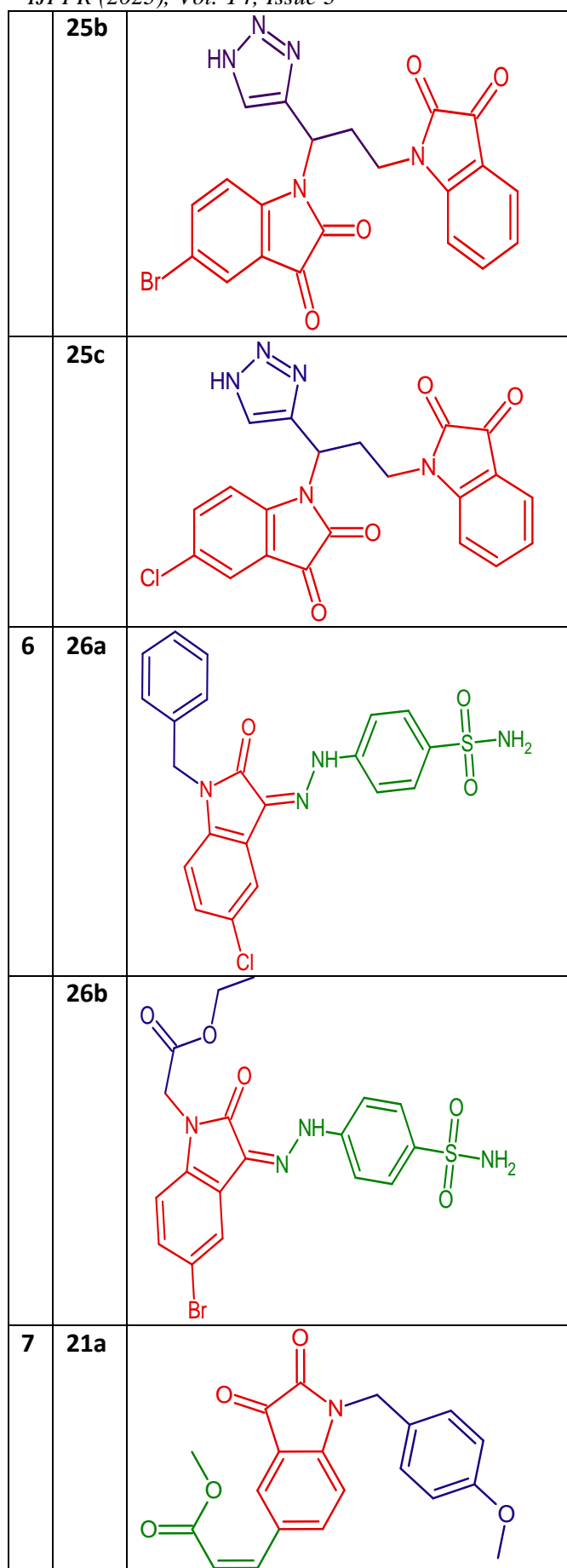
isatin All compounds are characterized by CNMR, HNMR, MASS, and other spectral analyses. M. tuberculosis (MTB) H37Rv, and MDR-TB, as well as cytotoxicity, were used to evaluate the biological activity of all compounds. Among them, compound 34a (MIC: 0.10 µg/mL) had 4-8 times more potent in vitro anti-TB activity against MTB H37Rv than the references GTFX (MIC: 0.78 µg/mL) and RIF (MIC: 0.39 µg/mL) but less effective than INH (MIC: 0.05 µg/mL). In the case of MDR-TB, compounds 34a and 34b (MIC: 0.25 g/mL) showed the most promising activity compared to the three references (MIC: 1.0->128 g/mL). Moreover, compounds 34a and 34b also displayed the most promising anti-proliferative activities with the value of CC50: 7.8 µg/mL which was more effective than the other hits and references.<sup>37</sup>

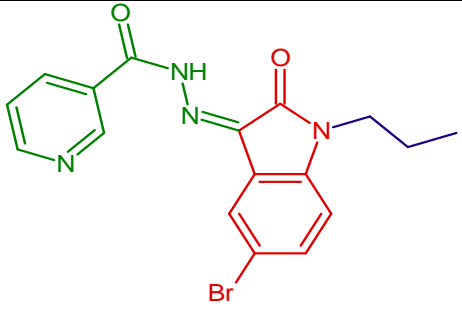
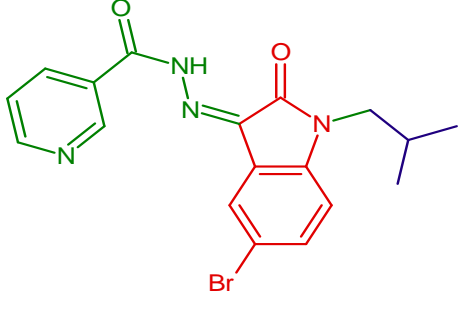
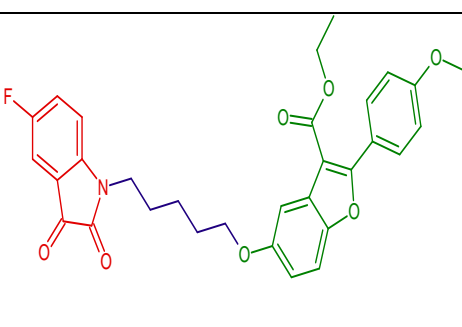
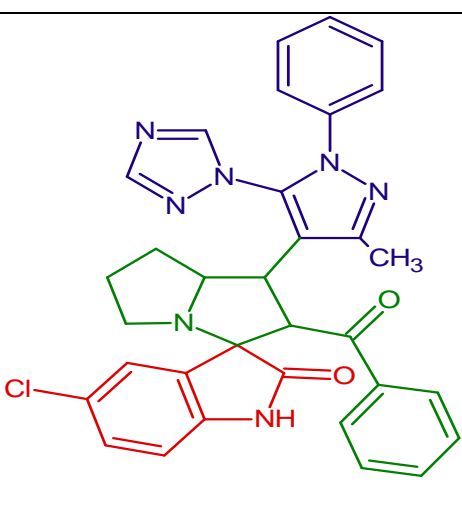
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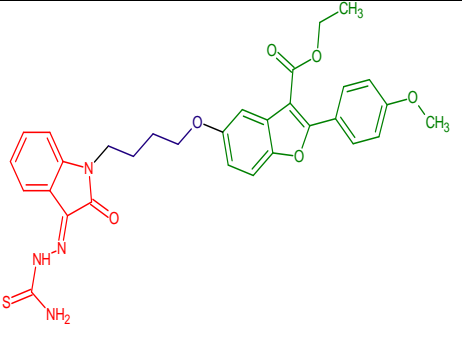
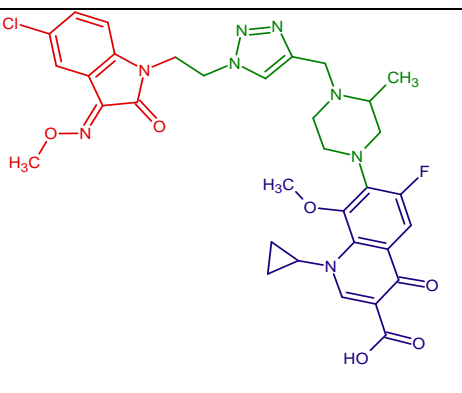
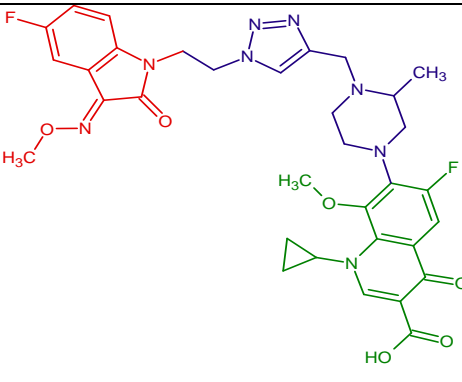
S. No.	Compound	Structure
1	21a	
2	22a	

3	23a	
	23b	
4	24a	
	24b	
5	25a	





	<b>30b</b>	
	<b>30c</b>	
<b>1</b> <b>1</b> <b>.</b>	<b>31a</b>	
<b>1</b> <b>2</b>	<b>32a</b>	

<b>1</b> <b>3</b>	<b>33a</b>	
<b>1</b> <b>4</b>	<b>34a</b>	
	<b>34b</b>	

### Conclusion and Future Direction:

Generally, it is observed that the development of drug moieties with the help of heterocyclic skeleton is moving gradually for the treatment of critical diseases. The heterocyclic compounds and their analogs illustrated in this review article is still represent great value and important contributions to the field of novel drug discovery. As it is well known that the drugs from natural resources found to be useful in the treatment of life-threatening diseases including Cancer and Diabetes mellitus. Contemporary, synthetic heterocyclic scaffolds exhibit versatile intrinsic biological actions which is also utmost important for the disease treatment. In this review we mainly emphasis on Isatin of natural

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and synthetic origin used in multifactorial disorders influenced by cancer TB and. This review also illustrates their synthetic strategies, structural activity relationship, *in-vitro* inhibition potency, and cytotoxicity. No matter which direction the future takes us, the heterocyclic chemistry finds its way and definitely help us in the development of potent, safe, and effective future drugs which can be employed for the treatment of all kinds of diseases

### Acknowledgments:

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