A Comprehensive Review on Isatin Derivatives: Antimycobacterial Potential and Antifungal Applications

Corresponding Author: Ms. Manju kher[1],

Co Author: Dr. Kratika Daniel[2], Dr. Sudha Vengurlekar[3], Dr. Sachin K. Jain[4]

1, Department of Pharmaceutical Chemistry, Scholar of Pharmacy, Oriental University, Indore

2, Department of Pharmaceutical Chemistry, Professor, Oriental college of Pharmacy & Research, Faculty of Pharmacy, Oriental University, Indore

3, Department of Pharmaceutical Chemistry, Professor of Medicinal Chemistry, Faculty of Pharmacy, Oriental University, Indore

4 Department of Pharmacy, Professor & Principal, Faculty of Pharmacy, Oriental University, Indore

ABSTRACT

Isatin derivatives have emerged as a versatile class of compounds in medicinal chemistry due to their remarkable pharmacological activities. This review highlights the significant role of isatin derivatives as potent antimycobacterial and antifungal agents. The structural framework of isatin allows for extensive modifications, enabling the development of compounds with enhanced biological efficacy. In the context of antimycobacterial activity, isatin derivatives have demonstrated promising results against *Mycobacterium tuberculosis* and other pathogenic mycobacteria. Structural-activity relationship (SAR) studies identify crucial functional groups responsible for their antimycobacterial properties, providing valuable insights for designing new therapeutics to combat drug-resistant strains. Similarly, isatin derivatives exhibit potent antifungal activity, making them effective against a range of fungal pathogens, including *Candida* and *Aspergillus* species. These derivatives act by targeting critical fungal pathways, such as enzyme inhibition and disruption of membrane integrity. Their broad-spectrum activity offers a viable alternative for treating fungal infections, particularly in cases where resistance to existing drugs poses a challenge. This review consolidates recent advancements in the synthesis and biological evaluation of isatin derivatives, emphasizing their dual potential as antimycobacterial and antifungal agents. The insights provided aim to guide future research toward the rational design of novel derivatives with improved pharmacological profiles.

Keywords: Isatin derivatives**,** Antimycobacterial agents**,** Antifungal compounds**,** Drug resistance**,** Medicinal chemistry

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BACKGROUND

Isatin (1H-indole-2,3-dione) and its derivatives have captivated the interest of medicinal chemists and pharmaceutical researchers for decades due to their remarkable pharmacological properties and structural versatility (figure 1). This small heterocyclic compound, initially identified as a product of the oxidation of indigo dye, serves as a versatile scaffold for designing novel bioactive molecules.[1] Its unique structure, comprising an indole core with adjacent keto and imine functionalities, allows extensive modifications, enabling the synthesis of derivatives with diverse biological activities.[2]

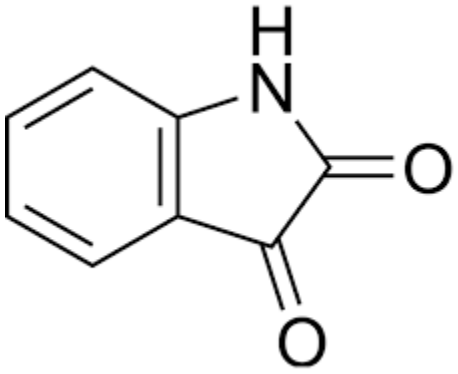

Figure 1: Isatin (1H-indole-2,3-dione) [3]

Among the numerous therapeutic applications of isatin derivatives, their roles as antimycobacterial and antifungal agents have emerged as particularly noteworthy. These applications address two significant global health challenges: tuberculosis (TB) and fungal infections.[4]

Tuberculosis, caused by *Mycobacterium tuberculosis* (M.tb), remains one of the top infectious killers worldwide, with drug-resistant strains posing a major challenge to public health. The World Health Organization (WHO) has reported alarming rates of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, emphasizing the urgent need for novel therapeutic agents. Isatin derivatives have demonstrated promising antimycobacterial activity, often displaying enhanced efficacy compared to conventional drugs. Structure-activity relationship (SAR) studies have provided valuable insights into the key substituents that optimize antimycobacterial properties, guiding the rational design of more potent derivatives.[5]

Similarly, fungal infections, particularly invasive mycoses caused by *Candida*, *Aspergillus*, and other opportunistic pathogens, represent a growing concern in both immunocompromised and healthy populations. The increasing prevalence of drug-resistant fungal strains, coupled with limited treatment options, underscores the need for new antifungal agents. Isatin derivatives have

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exhibited potent antifungal activity, acting through diverse mechanisms such as enzyme inhibition and membrane disruption. Their broad-spectrum activity and structural flexibility make them promising candidates for overcoming antifungal resistance.[6, 7]

This comprehensive review aims to provide a detailed overview of the advancements in the synthesis and biological evaluation of isatin derivatives as antimycobacterial and antifungal agents. Key topics include the exploration of SAR trends, mechanistic insights, and the potential of these derivatives in drug development. Furthermore, the review highlights the dual therapeutic potential of isatin derivatives, underscoring their relevance in addressing the dual burden of TB and fungal infections. Through an analysis of recent studies and a discussion of challenges and future directions, this review seeks to inform and inspire continued research in the field of isatin-based drug discovery. The synthesis of multifunctional derivatives that target both mycobacterial and fungal pathogens represents a promising avenue for addressing unmet medical needs and combating the global health threats posed by infectious diseases.

ANTIMYCOBACTERIAL PROPERTIES OF ISATIN DERIVATIVES

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (M.tb), remains a critical global health issue, ranking as one of the leading causes of death from infectious diseases. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB has necessitated the development of novel therapeutic agents with improved efficacy and safety profiles. In this context, isatin derivatives have gained considerable attention as promising candidates for antimycobacterial therapy. Their unique structural features and diverse chemical modifications enable the design of potent compounds with enhanced activity against *M.tb*.[8]

Structural Basis of Antimycobacterial Activity

Isatin (1H-indole-2,3-dione) contains an indole nucleus, which is an essential pharmacophore in many biologically active compounds. The presence of keto and imine groups in isatin allows for the synthesis of various derivatives through substitutions at the C-3, C-5, C-7, and N-1 positions. These modifications can significantly influence antimycobacterial activity. For instance, the introduction of lipophilic groups, halogens, or heterocyclic moieties has been shown to enhance cell wall penetration and binding affinity to target enzymes in *M.tb*.[9]

Mechanism of Action [10, 11]

Isatin derivatives exert their antimycobacterial effects through multiple mechanisms, often targeting essential bacterial enzymes and pathways:

1. **Enzyme Inhibition**: Many derivatives inhibit InhA, a key enzyme in the fatty acid synthesis pathway critical for mycobacterial cell wall biosynthesis.

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2. **DNA Intercalation**: Some isatin derivatives intercalate with mycobacterial DNA, disrupting replication and transcription processes.
3. **Reactive Oxygen Species (ROS) Generation**: Certain derivatives induce oxidative stress in *M.tb*, leading to bacterial cell death.

Structure Activity Relationship (SAR) studies [12]

SAR studies of isatin derivatives reveal critical insights into their antimycobacterial efficacy:

- **C-3 Substituents**: Substitution at the C-3 position with hydrazones, thiosemicarbazones, or Schiff bases often enhances antimycobacterial potency. These groups increase molecular interactions with key bacterial enzymes, such as enoyl-acyl carrier protein reductase (InhA).
- **Halogenated Derivatives**: Halogen substitution at C-5 or C-7 improves lipophilicity and cell membrane permeability, leading to better activity against mycobacteria.
- **Aromatic and Heterocyclic Moieties**: Incorporation of aromatic rings or heterocycles at various positions enhances π-π stacking interactions with bacterial targets.

REVIEW OF LITERATUR

Selvam *et al.*, (2001) synthesized 4-[(1,2-dihydro-2-oxo-3H-indol-3-ylidene) amino]- *N*(4,6-dimethyl-2-pyrimidinyl)-benzene sulphonamide and its derivatives by reaction of isatin and its derivatives with sulphadimidine. Their chemical structures have been confirmed by IR, H NMR data and elemental analysis. Investigation of anti-HIV activity of compounds were tested against replication of HIV-1 (IIIB) and HIV-2 (ROD) strains in acutely infected MT-4 cells and the activity compared with standard azidothymidine. Among the compounds tested, 4-[(1,2-dihydro-2oxo-3H-indol-3-ylidene)amino]-*N*(4,6-dimethyl-2-pyrimidinyl)-benzene sulphonamide and its *N*-acetyl derivative were the most active compounds.[13]

Shakir *et al.*, (2016) synthesized novel bioactive 5-chloro isatin based Schiff base ligands, (N,N'E,N,N'Z)-N,N'- (5-chloroindoline-2,3-diylidene)bis(5-nitrobenzo [d]thiazol-2-amine), L1 and (N,N'E,N,N'Z)-N,N'-(5-chloroindoline-2,3-diylidene) bis(5-nitrothiazol-2-amine), L2 derived from 2-amino 5-nitrobenzothiazole and 2- amino 5-nitrothiazole and their metal complexes,[Cu(L1)2]Cl2;1,[Zn(L1)2(H2O)2]Cl2;2,[Cu(L2)2]Cl2;3and [Zn(L2)2(H2O)2]Cl2;4. The composition, stoichiometry and geometry of the proposed ligands and their complexes have been studied by the results of elemental analysis and spectroscopic data. They also reported their thermal stability by TGA/DTA studies while the crystalline nature has been demonstrated by XRD. A comparative study of in vitro antibacterial study against different bacterial strains with respect to standard antibiotic and scavenging activity against standard control of the metal complexes as compared to free ligands. [14]

Shimazawa *et al.*, (2008) synthesized N-alkyl oxindolylidene acetic acids as a new class of

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potent Cdc25A inhibitors. These have long N-alkyl chains exhibited strong inhibitory activity toward dual specificity phosphatase Cdc25A.[15]

Shmidt *et al., (*2016) presented two new methods based on rearrangement reactions to obtain novel 2-substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines, an important family of heterocycles with potential applications. Alkyl 3-hydroxy-4-oxo-1,4- dihydroquinoline-2-carboxylates were obtained by alkoxide promoted rearrangement of alkyl isatin acetates. A second synthetic route involves the alkoxide promoted reaction of both isatin and N-methylisatin, with alkylating agents having acidic methylenes. This reaction leads to the formation of spiroepoxyoxindoles via Darzens' condensation. When phenacyl bromides are used, the initially obtained benzoyl substituted spiroepoxyoxindoles were smoothly transformed into the corresponding 2- benzoyl-3-hydroxy-4-quinolinones with good to excellent yields.[16]

Singh *et al.,* (2009) described the synthesis of new 1-alkyl/cyclohexyl-3,3-diaryl-10 methylspiro[azetidine-2,30-indoline]-20,4-diones from the reactions of the 2-diazo- 1,2-diarylethanones with 1-methyl-3-(alkyl/cyclohexylimino)indolin-2-ones under thermal condition. The compounds, characterized by satisfactory analytical and spectral (IR, 1H NMR and 13C NMR) data, have been screened for their antibacterial and antifungal activities.[17]

Sridhar *et al., (*2001) carried out studies on synthesis and pharmacological activities of Schiff bases and hydrazones of isatin derivatives. The compounds were screened for analgesic, anti-inflammatory and antipyretic activity.[18]

Sriram *et al.,* (2005) synthesized and evaluated Various 7-substituted ciprofloxacin derivatives for antimycobacterial activity in vitro and in vivo against Mycobacterium tuberculosis and for inhibition of the supercoiling activity of DNA gyrase from Mycobacterium smegmatis. Preliminary results indicated that most of the compounds demonstrated better in vitro antimycobacterial activity against M. tuberculosis than ciprofloxacin. Compound 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[[N4-[10-(5-methylisatinylsemicarbazo)]methyl]N1-piperazinyl]-3-quinoline carboxylic acid (3h) decreased the bacterial load in spleen tissue with 0.76-log10 protections and was considered to be moderately active in reducing bacterial count in spleen. The results demonstrated the potential and importance of developing new quinolone derivatives against mycobacterial infections.[19]

Sriram *et al.,* (2007) prepared N-hydroxythiosemicarbazide by two methods starting from 2,4-dimethoxy benzyl amine and hydroxylamine hydrochloride, which in turn was reacted with various aldehydes and ketones to obtain the titled compounds. Eighteen compounds were tested for their in vitro activity against Mycobacterium tuberculosis H37Rv using the agar dilution method. Compound 10p was found to be the most potent compound (MIC: 0.28 lM) and was 2.5 times more active than standard isoniazid.[20]

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Pandeya *et al.*, *(*2000) reported synthesis, antibacterial, antifungal and anti HIV evaluation of Schiff and Mannich bases of isatin and its derivatives with triazole. The ompounds were tested for anti-HIV activity against replication of HIV-1 (III B) in MT-4 cells and found inactive.[21]

Bergman *et al*., 1985. In man, isatin has been found to function as an endogenous monoamine oxidase inhibitor (figure 2). Isatin **1** (indole-2, 3-dione) **[Sumpter, 1944]** has been known since 1841 when Erdmann and Laurent prepared it by oxidation of indigo **2** by nitric and chromic acids. Although known as a synthetic molecule for almost 140 years, isatin was later found in nature, for instance in the fruits of the cannon ball tree, *Couroupita quianensis* Aub.[22]

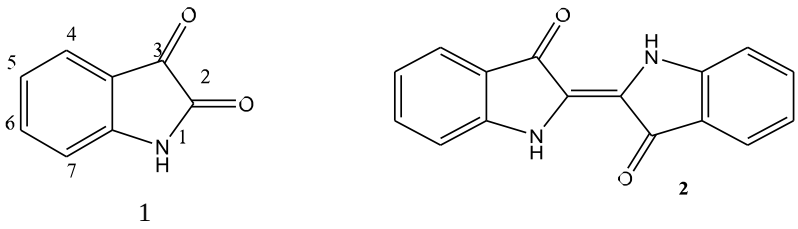

Figure 2: Isatin (1) and Indigo (2) [23]

SYNTHESIS AND FUNCTIONALIZATION OF ISATIN DERIVATIVES

Isatin (1H-indole-2,3-dione) serves as a versatile scaffold in medicinal chemistry, offering opportunities for structural modifications that enhance its biological activities. The synthesis and functionalization of isatin derivatives are crucial for developing potent therapeutic agents, particularly in the context of their antimycobacterial and antifungal applications. This section provides an overview of the strategies employed for the synthesis of isatin and its derivatives, with an emphasis on functionalization approaches that improve pharmacological properties.[24]

Synthesis of Isatin [25]

Isatin is traditionally synthesized through the oxidation of indigo, a process that dates back to its discovery in the 19th century. Modern methods for isatin synthesis typically involve more precise and efficient techniques:

1. **Sandmeyer Method**: This classical approach involves the reaction of aniline derivatives with chloral hydrate and hydroxylamine hydrochloride under acidic conditions, forming isatin through cyclization.

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2. **Modified Stollé Synthesis**: Aniline is reacted with oxalyl chloride, followed by cyclization and hydrolysis to yield isatin. This method allows for structural variations by using substituted anilines.
3. **Green Chemistry Approaches**: Recent advancements emphasize eco-friendly synthesis, employing catalysts such as ionic liquids, microwave-assisted heating, and bio-based reagents to reduce environmental impact.

Functionalization Strategies [26]

The biological activity of isatin is significantly influenced by substitutions at the N-1, C-3, C-5, and C-7 positions. Functionalization strategies are designed to introduce pharmacophoric groups that enhance binding affinity, selectivity, and overall pharmacological activity.

1. **C-3 Substitution**
   - **Hydrazones and Thiosemicarbazones**: Substituents like hydrazones and thiosemicarbazones at the C-3 position enhance antimicrobial activity by facilitating interactions with microbial enzymes. These derivatives have shown potent activity against *Mycobacterium tuberculosis* and fungal pathogens.
   - **Schiff Bases**: Schiff bases derived from isatin exhibit improved lipophilicity, enabling better cell membrane penetration and enhanced therapeutic effects.
2. **N-1 Functionalization**
   - Alkylation and acylation at the N-1 position improve the pharmacokinetics of isatin derivatives, including solubility and metabolic stability.
   - The introduction of aromatic or heterocyclic groups at N-1 increases π-π interactions with target biomolecules, enhancing bioactivity.
3. **C-5 and C-7 Substitution**
   - **Halogens**: Substituting chlorine, fluorine, or bromine at the C-5 and C-7 positions enhances lipophilicity and membrane permeability, leading to improved antimycobacterial and antifungal activity.
   - **Electron-Withdrawing Groups**: Functional groups like nitro ($-NO_2$) or cyano (-CN) at these positions contribute to higher binding affinity with microbial enzymes.
4. **Multifunctional Derivatives**
   - Combining different functional groups in a single isatin derivative often results in dual-action compounds effective against both mycobacterial and fungal pathogens.
   - Hybrid molecules, where isatin is linked with other active pharmacophores, have shown promise in overcoming drug resistance.

Synthetic Techniques for Isatin Derivatives [27]

To achieve targeted functionalization, various synthetic techniques are employed:

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1. **Microwave-Assisted Synthesis**: This method accelerates reaction times and improves yields, particularly for C-3 hydrazones and Schiff bases.
2. **Catalytic Approaches**: Transition metal catalysts, such as palladium or copper, are used in cross-coupling reactions to introduce complex functional groups.
3. **One-Pot Reactions**: These methods streamline the synthesis of isatin derivatives, combining multiple reaction steps in a single process to reduce waste and improve efficiency.

FUTURE PERSPECTIVES AND CHALLENGES

Isatin derivatives have shown remarkable promise as potential antimycobacterial and antifungal agents, making them a valuable subject of research in the field of drug discovery. While their therapeutic potential is significant, several challenges remain in optimizing their efficacy, safety, and clinical applicability. Addressing these challenges will require innovative approaches in synthetic chemistry, pharmacology, and drug development. The following sections explore the future directions and challenges in the development of isatin derivatives as antimicrobial agents. [28]

Future Perspectives [29]

1. **Development of Dual-Action Compounds**: One promising direction is the design of multifunctional isatin derivatives that simultaneously target both mycobacterial and fungal pathogens. This approach could be particularly beneficial in treating co-infections, which are common in immunocompromised individuals. By targeting multiple microbial pathways, dual-action compounds may also reduce the risk of developing resistance, a growing concern in both TB and fungal infections.
2. **Target-Specific Modifications**: Advances in computational techniques, such as molecular docking and quantitative structure-activity relationship (QSAR) modeling, provide valuable insights into the specific binding interactions between isatin derivatives and microbial targets. These tools can guide the design of derivatives with higher selectivity and potency, improving their therapeutic profiles. Targeting specific enzymes or bacterial pathways critical to *Mycobacterium tuberculosis* or fungal pathogens will enhance the clinical efficacy of these compounds.
3. **Optimization of Pharmacokinetics and Toxicity**: While isatin derivatives show potent activity in vitro, optimizing their pharmacokinetic properties remains crucial. Modifications aimed at improving solubility, bioavailability, and metabolic stability can enhance the clinical relevance of these compounds. Furthermore, minimizing toxicity to host cells and organs, which can be a concern with certain derivatives, is essential for their safe use in humans.
4. **Sustainable Synthesis and Green Chemistry**: The growing emphasis on environmental sustainability is prompting the development of greener synthetic routes for isatin

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derivatives. New methods that utilize renewable reagents, reduce waste, and employ catalytic processes could make the synthesis of isatin derivatives more efficient and eco-friendly. Green chemistry approaches, such as enzymatic catalysis, are particularly promising for large-scale production.

5. **Combination Therapies**: To combat the development of drug resistance, combination therapies involving isatin derivatives and existing antimycobacterial or antifungal drugs could be a highly effective strategy. This approach may enhance the therapeutic efficacy by exploiting synergistic effects, reducing the required dosage of individual drugs, and potentially circumventing the emergence of resistance.

Challenges [30]

1. **Resistance Development**: Despite the promising activity of isatin derivatives, the potential for microbial resistance remains a significant concern. Resistance could arise due to mutations in microbial targets or efflux mechanisms. To address this, ongoing research must focus on understanding the mechanisms of resistance and developing derivatives with novel modes of action or those that can overcome existing resistance mechanisms.
2. **Clinical Translation**: Moving from promising in vitro results to clinical applications is often a lengthy and complex process. While isatin derivatives have shown efficacy in preclinical models, further studies are required to assess their safety, toxicity, and effectiveness in human trials. Overcoming regulatory hurdles and ensuring that these compounds meet clinical standards are major steps before they can be widely used.
3. **Manufacturing and Scalability**: The synthesis of isatin derivatives on an industrial scale presents challenges related to cost, efficiency, and reproducibility. Large-scale production methods need to be developed that are both economically viable and capable of producing compounds with consistent quality. This is especially important when considering the need for widespread distribution in resource-limited settings, particularly for TB treatment.

CONCLUSION

In conclusion, isatin derivatives represent a promising class of compounds with significant antimycobacterial and antifungal potential. Their structural versatility enables the development of novel agents targeting drug-resistant pathogens. While challenges remain in optimizing pharmacokinetics, overcoming resistance, and ensuring clinical applicability, continued research and innovative approaches in synthesis, functionalization, and combination therapies hold great promise for the future use of isatin derivatives in combating global infectious diseases.

 https://doi.org/10.5281/zenodo.14600567

REFERENCES

1. Ding, K., Lu, Y., Nikolovska-Coleska, Z., Wang, G., Qiu, S., Shangary, S., Gao, W., Qin, D., Stuckey, J., Krajewski, K., Structure-based design of spiro-oxindoles as potent, specific small-molecule inhibitors of the MDM2-p53 interaction, Journal of medicinal chemistry, 49, 3432-3435, 2006.
2. dos Santos, E. L., Gomes Jr, W. A., Ribeiro, N. M., Andrade, H. M. C., Ecofriendly ketalization of isatin using heteropolycompounds as catalysts, Journal of Molecular Catalysis A: Chemical, 295, 18-23, 2008.
3. https://file.medchemexpress.com/product_pic/hy-y0265.gif
4. Elinson, M. N., Merkulova, V. M., Ilovaisky, A. I., Chizhov, A. O., Belyakov, P. A., Barba, F., Batanero, B., Electrochemically induced aldol reaction of cyclic 1, 3-diketones with isatins, Electrochimica Acta, 55, 2129-2133, 2010.
5. Erdmann, O. L., Untersuchungen über den Indigo, Archiv der Pharmazie, 72, 253- 285, 1840.
6. Esmaeili, A. A., Amini-Ghalandarabad, S., Mesbah, F., Tasmimi, M., Izadyar, M., Fakhari, A. R., Salimi, A. R., Efficient synthesis of novel spiro [indole-3, 6′- pyrano [2, 3-d][1, 3] thiazolo [3, 2-a] pyrimidine derivatives through an organobase-catalyzed, three-component reaction, Tetrahedron, 71, 2458-2462,
7. 2015.
8. Feng, J., Yan, W., Wang, D., Li, P., Sun, Q., Wang, R., The highly enantioselective addition of indoles and pyrroles to isatins-derived N-Boc ketimines catalyzed by chiral phosphoric acids, Chemical Communications, 48, 8003-8005, 2012.
9. Fensome, A., Adams, W. R., Adams, A. L., Berrodin, T. J., Cohen, J., Huselton, C., Illenberger, A., Kern, J. C., Hudak, V. A., Marella, M. A., Design, synthesis, and SAR of new pyrrole-oxindole progesterone receptor modulators leading to 5- (7-fluoro-3, 3-dimethyl-2-oxo-2, 3-dihydro-1 H-indol-5-yl)-1-methyl-1 H-pyrrole- 2-carbonitrile (WAY-255348), Journal of medicinal chemistry, 51, 1861-1873, 2008.
10. Flores, M., Pena, J., Garcia-Garcia, P., M Garrido, N., Diez, D., Enantioselective Organocatalytic Reactions with Isatin, Current Organic Chemistry, 17, 1957-1985, 2013.
11. Fukuda, Y., Itoh, Y., Nakatani, K., Shiro, T., Synthetic studies on duocarmycin. 1. Total synthesis of dl-duocarmycin A and its 2-epimer, Tetrahedron, 50, 2793- 2808, 1994.
12. Gao, H., Sun, J., Yan, C.-G., Molecular diversity of acid-catalyzed one-pot reaction of arylamines, methyl propiolate, and isatins, Molecular diversity, 18, 511-519, 2014a.
13. Gao, H., Sun, J., Yan, C.-G., Povarov Reaction of β-Enamino Esters and Isatin-3-imines for Diastereoselective Synthesis of Spiro [indoline-3, 2′-quinolines], Synthesis,

 https://doi.org/10.5281/zenodo.14600567

46, 489-495, 2014b.

14. Gao, H., Sun, J., Yan, C.-G., Selective synthesis of functionalized spiro [indoline- 3, 2′-pyridines] and spiro [indoline-3, 4′-pyridines] by lewis acid catalyzed reactions of acetylenedicarboxylate, arylamines, and isatins, The Journal of organic chemistry, 79, 4131-4136, 2014c.
15. Garden, S. J., Skakle, J. M., Isatin derivatives are reactive electrophilic components for the Baylis–Hillman reaction, Tetrahedron Letters, 43, 1969-1972, 2002.
16. Gassman, P. G., Cue Jr, B. W., Luh, T.-Y., A general method for the synthesis of isatins, The Journal of organic chemistry, 42, 1344-1348, 1977.
17. Gassman, P. G., Van Bergen, T., Oxindoles. New, general method of synthesis, Journal of the American Chemical Society, 96, 5508-5512, 1974.
18. Ghahremanzadeh, R., Ahadi, S., Shakibaei, G. I., Bazgir, A., Grindstone
19. Ghahremanzadeh, R., Rashid, Z., Zarnani, A. H., Naeimi, H., Synthesis of novel spirooxindoles in water by using MnFe 2 O 4 nanoparticles as an efficient magnetically recoverable and reusable catalyst, Applied Catalysis A: General, 467, 270-278, 2013.
20. Guo, Q.-X., Liu, Y.-W., Li, X.-C., Zhong, L.-Z., Peng, Y.-G., Enantioselective and solvent-controlled diastereoselective Mannich reaction of isatin imines with hydroxyacetone: Synthesis of 3-substituted 3-aminooxindoles, The Journal of organic chemistry, 77, 3589-3594, 2012.
21. Gupta, R., Narayana, N., Synthesis of some Mannich bases of 1-cyclohexylidene- N (1, 2-dihydro-2-oxo-3H-indol-3-ylidene) thiosemicarbazones and their antibacterial activity, Pharmaceutica Acta Helvetiae, 72, 43-45, 1997.
22. Hamama, W. S., Gouda, M. A., Badr, M. H., Zoorob, H. H., Synthesis of Some New Fused and Binary 1, 3, 4-Thiadiazoles as Potential Antitumor and Antioxidant Agents, Journal of Heterocyclic Chemistry, 50, 787-794, 2013.
23. Han, Y.-Y., Chen, W.-B., Han, W.-Y., Wu, Z.-J., Zhang, X.-M., Yuan, W.-C.,
24. Highly Efficient and Stereoselective Construction of Dispiro-[oxazolidine-2- thione] bisoxindoles and Dispiro [imidazolidine-2-thione] bisoxindoles, Organic letters, 14, 490-493, 2012a.
25. Han, Y., Wu, Q., Sun, J., Yan, C.-G., Synthesis of the functionalized spiro [indoline-3, 5′-pyrroline]-2, 2′-diones via three-component reactions of arylamines, acetylenedicarboxylates, and isatins, Tetrahedron, 68, 8539-8544, 2012b.
26. Hashiba, I., Ando, Y., Kawakami, I., Sakota, R., Nagano, K., Mori, T., Jpn. Kokai Tokkyo Koho 79 73,771 1979, CA 91: P193174v,
27. Hewawasam, P., Meanwell, N. A., A general method for the synthesis of isatins: preparation of regiospecifically functionalized isatins from anilines, Tetrahedron

Letters, 35, 7303-7306, 1994.

28. Hu, Y., Wang, M.-M., Chen, H., Shi, D.-Q., Efficient and convenient synthesis of spiroindolinone-quinazolines induced by stannous chloride, Tetrahedron, 67, 9342-9346, 2011.
29. Huang, H., Xu, Y., Mao, F., Zhu, J., Jiang, H., Li, J., A highly efficient approach to unnatural amino-acids containing 3-hydroxyoxindole skeleton via a one-pot, three-component procedure, Tetrahedron Letters, 56, 586-589, 2015.
30. Itoh, J., Han, S. B., Krische, M. J., Enantioselective Allylation, Crotylation, and Reverse Prenylation of Substituted Isatins: Iridium-Catalyzed C C Bond-Forming Transfer Hydrogenation, Angewandte Chemie International Edition, 48, 6313-6316, 2009.

 https://doi.org/10.5281/zenodo.14600567