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REVIEW ARTICLE

The Development of Biologically Important Spirooxindoles as New Antimicrobial Agents

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Abstract: ***Background*:** Antibiotic resistance is one of the biggest threats to global health today, leading to higher medical costs and increased mortality. Because of the emergence and rapid spread of new resistance mechanisms globally, a growing number of infections are becoming harder to treat as the antibiotics used to treat them become less effective. Therefore, the development of new effective antimicrobial agents is still urgently needed. In last decades, a large number of structurally novel spirooxindoles have been synthesized mainly based on the ylide intermediates generated *in situ* and further assessed for their antimicrobial activity against different types of bacteria, leading to the discovery of some potent lead compounds with antimicrobial potentials.

***Objective*:** The aim of this review to submarize recent advances on the synthesis, structure-activity relationship studies (SARs) and antimicrobial activity of spirooxindoles.

***Methods*:** Peer-reviewed research work on spirooxindoles with antimicrobial activity were downloaded from bibliographic databases and analyzed based on their chemoptypes.

***Results*:** 50 papers were retrieved from the literature databases, of which 20 papers described the synthesis and antimicrobial activity of spirooxindoles.

***Conclusion*:** This review highlights the importance of spirooxindoles as potential antimicrobial agents. The antimicrobial activity of spirooxindoles against different types of bacteria is less studied, mainly centering on primary antimicrobial assessment, some of these compounds have showed interesting antimicrobial activity. However, the current study is only limited to primary antimicrobial assessment, no detailed modes of action are investigated.

Keywords: Spiro compounds, spirooxindoles, oxindoles, chemical synthesis, antimicrobial activity, antifungal activity.

1. INTRODUCTION

Antibiotic resistance is one of the biggest threats to global health today, leading to higher medical costs and increased mortality [1]. Because of the emergence and rapid spread of new resistance mechanisms globally, a growing number of infections are becoming harder to treat as the antibiotics used to treat them become less effective. The US Centers for Disease Control and Prevention (CDC) estimates that there are about 23,000 people who die every year from antibiotic-resistant infections in the US. There is currently a shortage of effective therapies, lack of successful prevention measures, and only a few new antibiotics, which require

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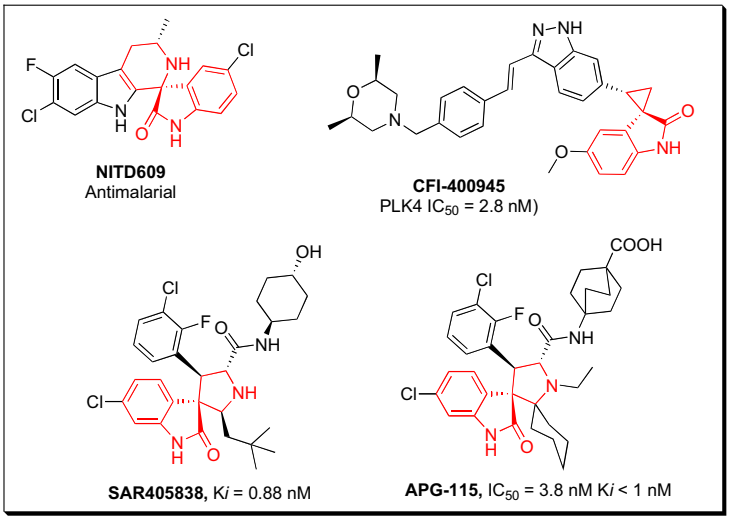


Fig. (1). Spirooxindole-based drug candidates in clinical trials.

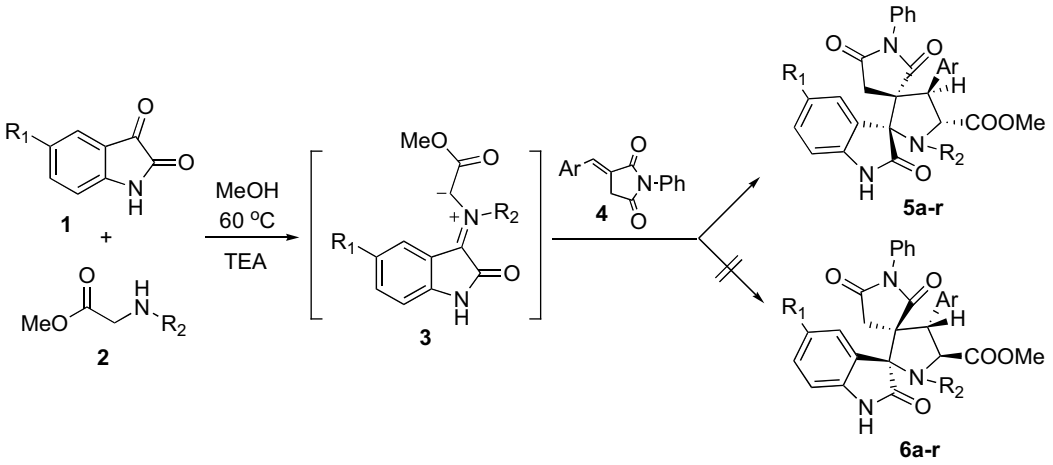
development of novel treatment options and alternative antimicrobial therapies [2]. Therefore, the development of new effective antimicrobial agents is still urgently needed although these new therapeutic agents could not completely overcome the antimicrobial resistance. Great efforts have been devoted to the discovery of new antibiotics in last decades. Recently developed vancomycin 3.0 being about 25,000 times more potent than its predecessor-vancomycin 1.0 has a unique three-pronged approach to killing drug-resistant bacteria and offers a potent weapon against antibiotic-resistant infections [3].

The discovery of new structural scaffolds has recently been recognized as an efficient strategy to find biologically promising molecules that can target some biological sites and explore more chemical space [4, 5] as some already known scaffolds have failed to target biologically relevant sites, especially the undruggable targets [6]. Of particular interest are spiro compounds, which have attracted ever increasing attention due to their highly pronounced biological properties [7, 8], interesting conformational features and unique 3D structural features. It is well recognized that spirocyclic compounds have a reduced conformational entropy upon binding to a protein target and conformational restriction, which make them the promising scaffolds in drug discovery [9]. In particular, spirooxindoles have emerged as attractive synthetic targets because of their prevalence in a large number of biologically validated natural alkaloids and pharmaceutically relevant molecules [10-15]. The key structural characteristic of these compounds is the spiro ring fused at the C3 position of the oxindole core with varied heterocyclic motifs. These spirooxindoles seem to be promising candidates for drug discovery, since they incorporate both oxindoles and other heterocyclic moieties simultaneously. Spirooxindole is a privileged heterocyclic motif that exists in pharmaceutical candidates and naturally occurring compounds. Spirooxindole (Highlighted in red in Fig. **1**) containing compounds have exhibited diverse biological properties, such as anticancer [16-21], antimicrobial [22, 23], antivirus [24], *etc.* Representative examples are NITD609 (also known as Cipargamin) [25], CFI-400945 (the first PLK4 inhibitor) [26, 27], SAR405838 (MDM2 inhibitor) [28, 29] and APG-115 (MDM2 inhibitor) (Fig. **1**) [30], which are currently being evaluated in clinic for the treatment of malaria and human cancers, respectively. In last decades, much efforts have been devoted to the development of new spirooxindole-based antimicrobial agents [31]. In this review, we first summarized the advances of antimicrobial spirooxindoles from the chemistry and biology perspectives with a hope of providing an overview of spirooxindoles with antimicrobial potentials and possible directions for designing more potent antimicrobial agents. This review is organized based on the spiro rings attached to the C3 position of the oxindole scaffold.

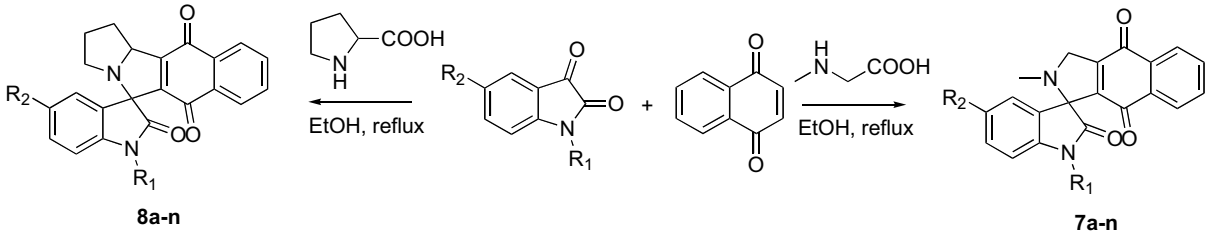
2. THE DEVELOPMENT OF NEW SPIROOXINDOLES AS ANTIMICROBIAL AGENTS

2.1. Spiropyrrolidine Oxindoles

In 2014, Askri *et al.* synthesized a series of spiro[pyrrolidin-2,3-oxindoles] **5a-r** through the exo-selective 1,3-dipolar cycloaddition reaction of the stabilized azomethine ylides **3** with various (*E*)-3-arylidene-



Scheme 1. Synthesis of bis-spirooxindoles **5a-r** with antimicrobial activity.

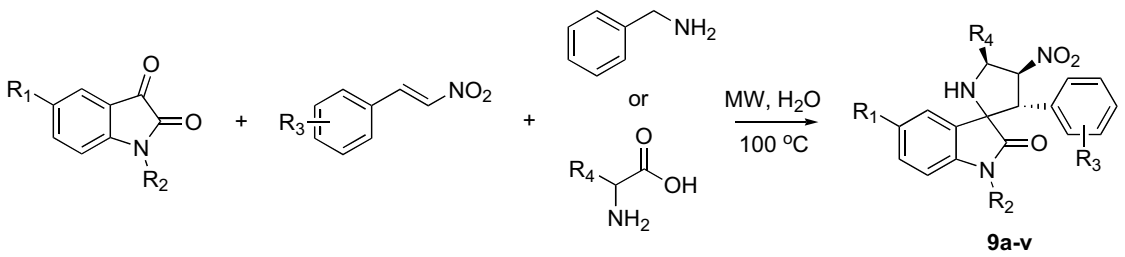


Scheme 2. Synthesis of new spirooxindoles as antibacterial and anti-fungal agents.

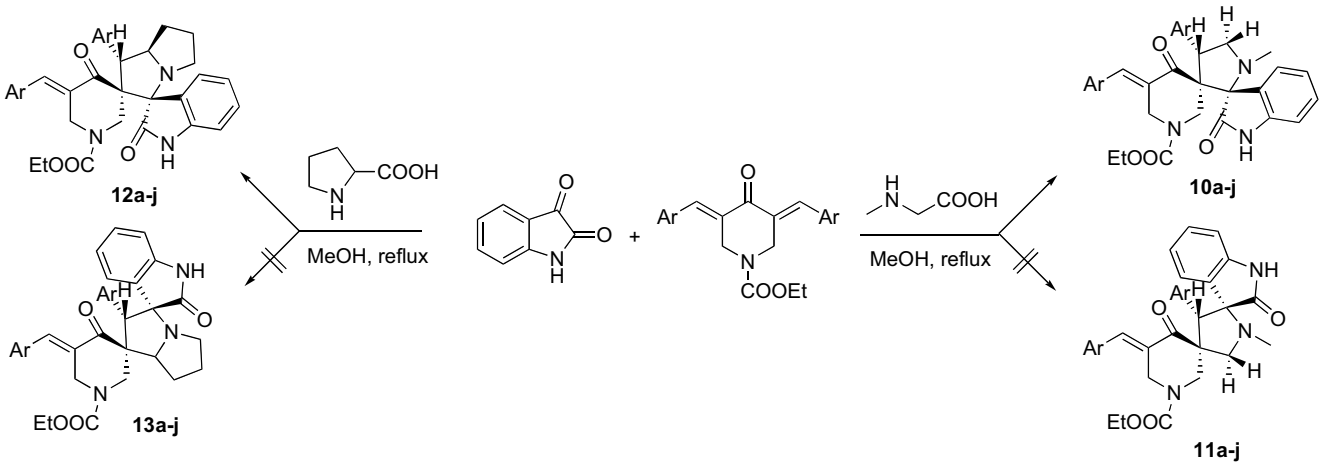
1-phenyl-pyrrolidine-2,5-diones **4**. The ylides **3** were generated *in situ* by thermal prototropy of the corresponding iminoesters **2** with (*E*)-3-arylidene-1-phenyl-pyrrolidine-2,5-diones **4** as dipolarophiles (Scheme **1**) [32]. Interestingly, other possible diastereoisomers **6a-r** were not observed. All products were obtained in good yields (63-95%) and with high regio- and stereoselectivity regardless of the electronic properties of the substituents at the *para*-position of the aryl groups. Among these series, compounds **5i** (R_1 = Br, R_2 = H, Ar = p-ClPh) and **5p** (R1 = H, R2 = Me, Ar = Ph) showed comparable activity with ampicillin against *Escherichia coli* with the MIC value of 62.5 µg/mL. In the case of *Pseudomonas aeruginosa*, compound **5r** (R_1 = H, R_2 = Me, Ar = 4-ClPh) was found to be the most active *in vitro* with the MIC of 62.5 µg/mL against MTCC 1688. Compound **5f** (R_1 = Br, R_2 = H, Ar = Ph) was found to be the most active derivative *in vitro* against *Staphylococcus aureus* MTCC 96 (MIC = 62.5 µg/mL). The *in vitro* antifungal activity was also evaluated, showing that compounds **5n** ((R_1 = NO_2, R_2 = H, Ar = 4-ClPh)) and **5p** displayed the highest activity against Griseofulvin with the MIC value of 200 µg/mL against *Candida albicans* (MTCC 227).

The Perumal group synthesized a series of novel spirooxindoles using the 1,3-dipolar cycloaddition of an azomethine ylide generated from isatin and sarcosine or *L*-proline with the dipolarophile 1,4-naphthoquinone as the key step (Scheme **2**) [33]. The antimicrobial activities of synthesized compounds were screened against eight bacteria and three fungi using *in vitro* disc diffusion method. Among these compounds, compound **7n** (R_1 = acetyl, R_2 = H) was 1.6 times more active against *S. aureus* (MIC = 31.25 µg/mL) than streptomycin and ciprofloxacin, 6.4 times more active against *M. luteus* (MIC = 15.62 µg/mL) and *S. typhimurium* (MIC = 15.62 µg/mL) than ciprofloxacin, and more than 3.2 times more active against *C. albicans* fungi (MIC = 31.25 µg/mL) than fluconazole. The authors claimed that compound **7n** could be potentially used to develop potent antibacterial and anti-fungal agents.

Meshram *et al.* developed a simple one-pot three-component aqueous phase protocol for the synthesis of functionalized spirooxindole derivatives by the reaction of isatin, β-nitrostyrene and benzyl amine/α-amino acids in water under microwave irradiation. The protocol allows facile construction of a library of spirooxindoles **9a-v** in moderate to good yields (up to 92%) with good diastereoselectivity (Scheme **3**) [34]. The antimicrobial activity was assessed against *Escherichia coli* ATCC 10536, *Candida tropicalis* ATCC 750, *Staphylococcus aureus* ATCC 25923 and *Pseudomonas aeruginasa* ATCC 15442 with reference standard ciprofloxacin



Scheme 3. Synthesis of the pyrrolidine containing spirooxindoles.

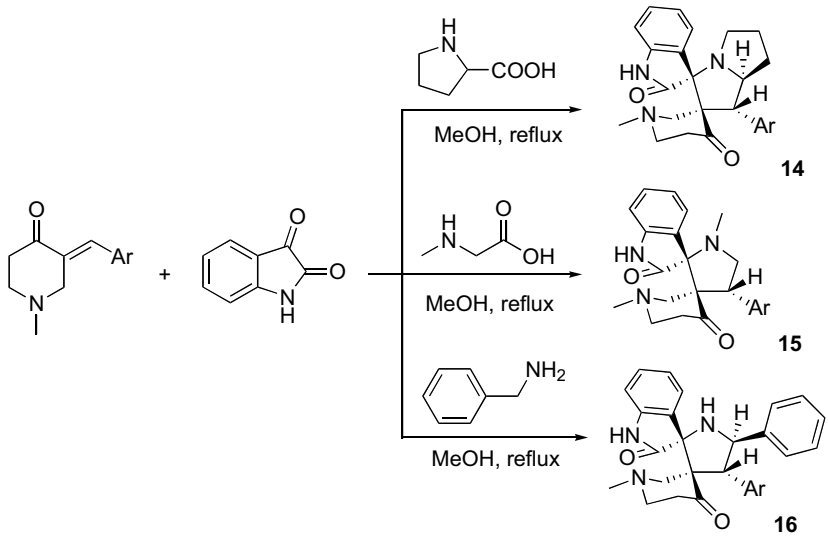


Scheme 4. Regioselective synthesis of spiropyrrolidine/pyrrolizine-oxindoles.

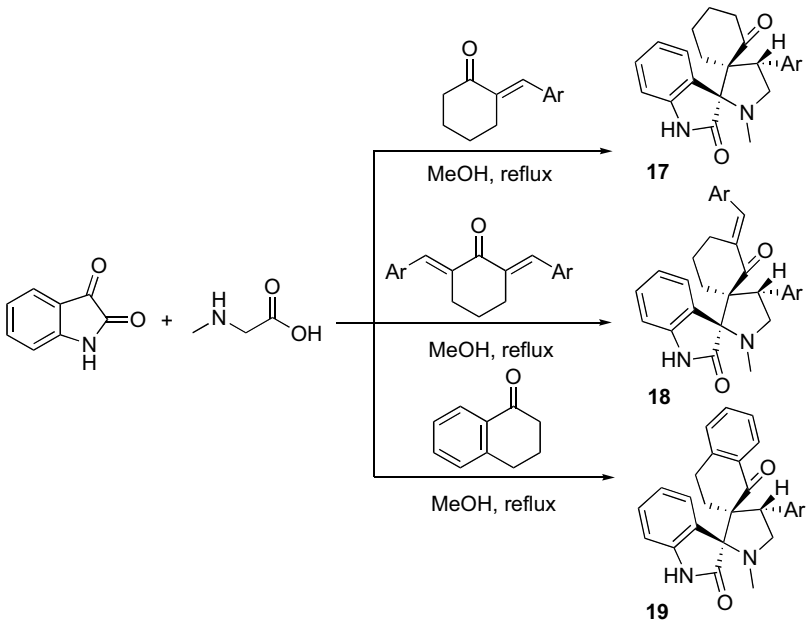
using the agar well diffusion method. Interestingly, the majority of the synthesized compounds showed good to excellent activity, comparable to that of ciprofloxacin (MIC = 0.3 μg/mL). The pyrrolidine NH and attached NO_2 groups provide functional synthetic handles which can be utilized to construct compound library of pharmaceutically and medicinally significant.

Mabkhot *et al.* reported the highly regioselective synthesis of new derivatives **10a–j** and **12a–j** through a 1,3-dipolar cycloaddition reaction of azomethine ylides generated *in situ* from isatin, sarcosine, and *L*-proline through the decarboxylative route with dipolarophile (Scheme **4**) [35]. However, the corresponding bis-adducts were not formed possibly due to the steric hindrance and fixing of the geometry of the spiropyrrolidine ring. All of the newly synthesized compounds were evaluated for their antimicrobial activities. Compounds **12b** (Ar = 4-NO_2Ph), **12e** (Ar = 4-MeOPh), **12g** (Ar = 2,4-diFPh) and **10c** (Ar = 4-ClPh) exhibited the best inhibitory effect against *Bacillis subtilis* (RCMB 010067) with the IC_{50} values of 2.92, 1.34, 1.36, and 1.24 μg/mL, respectively. SARs studies showed that the electron-withdrawing groups attached to the aryl rings were preferred over the electron-donating groups for the antimicrobial effects.

Similarly, the Perumal group also achieved the efficient synthesis of structurally novel 1-methyl-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **14-16** by the reaction of 3-substituted 1-methyl-4-piperidones, isatin and *L*-proline, sarcosine or benzyl amine under reflux (Scheme **5**) [36]. The products were obtained in excellent yields and with high regio- and stereoselectivities. The compounds were screened for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *M. tuberculosis* (MDR-TB) and *Mycobacterium smegmatis* (MC^2) using the agar dilution method. Compound **15e** (Ar = 2,4-diClPh) showed the best potency with the MIC values of 1.76 and 0.88 μM, respectively against MTB and MDR-TB, more potent than control anti-TB drugs Isoniazid, Ethambutol and Pyrazinamide. For MDR-TB, compounds **14c** (Ar = 2-ClPh) and **14e** (Ar = 2,4-diClPh) were also active with the IC_{50} values of 3.58 and 1.66 μM, respectively, possibly suggesting the importance of the 2-Cl group of the phenyl ring for the observed activity against MDR-TB. Interestingly, all these compounds **14-16** showed good to excellent inhibition against MTB, most of them were much more potent than reference drug pyrazinamide, underscoring the importance of such scaffolds for the activity against MTB. In contrast, compounds **14-16** exerted weak inhibition toward MC^2.



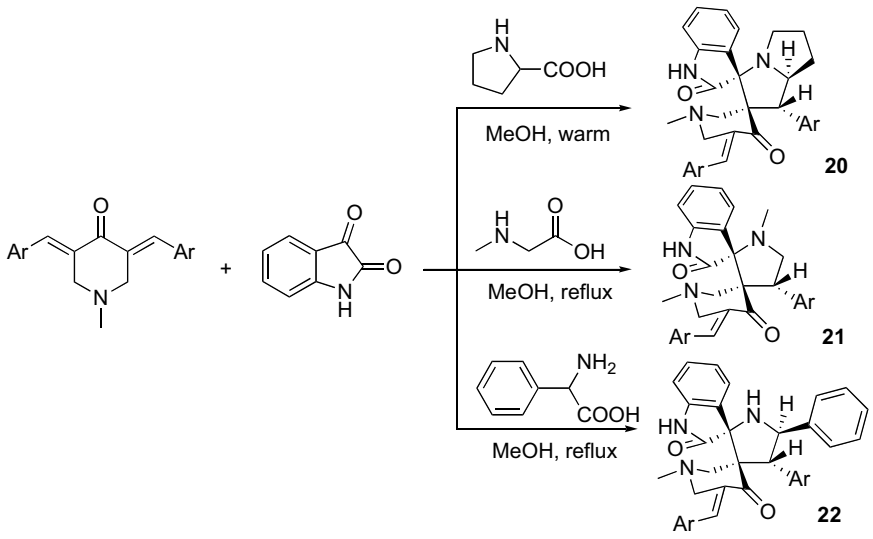
Scheme 5. Synthesis of structurally new spiropyrrolidyl oxindoles **14-16.**



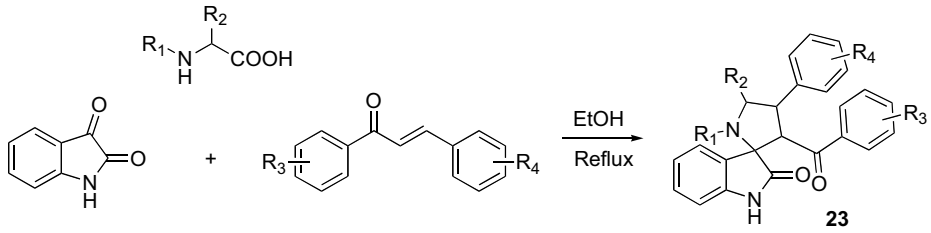
Scheme 6. Regioselective synthesis of new spirooxindoles **17-19.**

Similar to above work, Raghunathan *et al.* synthesized three series of spirooxindoles **17-19** from isatin, sarcosine, and the corresponding cyclohexanone-based dipolarophiles via the regioselective 1,3-dipolar cycloaddition reactions (Scheme **6**) [37]. Some of the compounds showed certain antibacterial and antifungal activity.

Following their previous work on the identification of new antimycobacterial agents [36], Perumal *et al.* reported an atom economic and stereoselective synthesis of several spiro-piperidin-4-ones **20-22** through the 1,3-dipolar cycloaddition of azomethine ylides generated in situ from isatin and amino acids (*L*-proline, phenylglycine, and sarcosine) (Scheme **7**) [38]. The compounds were screened for their *in vitro* and *in vivo* activity against MTB, MDR-TB and MC^2. All compounds showed moderate to excellent *in vitro* activity against MTB with MIC ranging from 0.07-53.30 μg/mL. Compound **22e** (Ar = 4-FPh) was found to be the most active *in vitro* with the MIC value of 0.07 μg/mL against MTB and showed 5.1 and 67.2 times potency than isoniazid and ciprofloxacin, respectively. Compound **22e** also potently inhibited MDR-TB with the MIC value of 0.16 μg/mL. Collectively, for MTB, MDR-TB and MC^2, compound **22e** was the most potent compound, suggesting the importance of the core structure and



Scheme 7. Stereoselective synthesis of new spiro-piperidin-4-ones **20-22**.



Scheme 8. Synthesis of spiro-oxindole derivatives **23.**

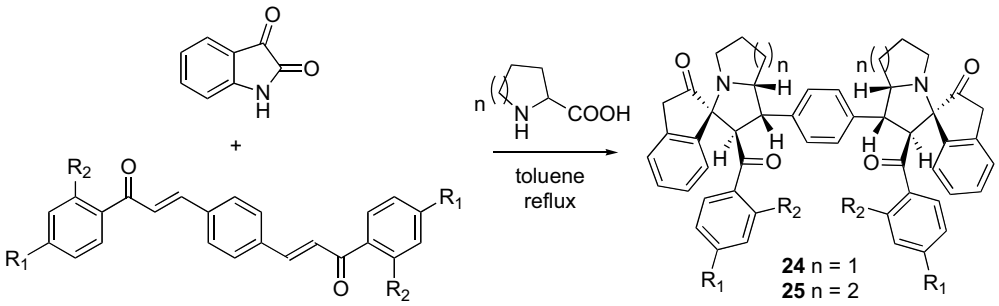
substituents attached to the phenyl ring. Further *in vivo* studies indicated that compound **22e** decreased the bacterial load in lung and spleen tissues with 1.30 and 3.73-log 10 protections, respectively, but was less potent than isoniazid at the same dose level. Besides, compound **22e** was nontoxic up to 62.5 μg/mL (111.41 μM) and showed good selectivity index (IC_{50}/MIC) of 1634. Additionally, compound **21f** (Ar = 2-ClPh) displayed the best potency against MTB, MDR-TB and MC^2 with the IC_{50} values of 0.17, 0.08 and 1.47 μg/mL, respectively, significantly more potent than other compounds of this series. Taken above data into consideration, the substituents attached to the pyrrolidinyl ring played an essential role in the antimicrobial activity.

Narayana *et al*. identified a new series of spiro-oxindoles that could inhibit methionine tRNA synthase (PDB ID: 1PFV) and glucosamine-6-phosphate synthase (PDB ID: 1JXA) enzymes through the virtual screening (Scheme **8**). The compounds were efficiently synthesized from isatin, amino acids, and dipolarophile chalcones by a three-component 1,3-dipolar cycloaddition reaction [22]. These compounds were then then found to be active against *Staphylococcus aureus, Escherichia coli, Aspergillus niger* and *Aspergillus flavus.* Compounds **23a** (R_1, R_2, and R_4 = H, R_3 = 4-F), **23e** (R_1 = H, R_2 = CH_2OH, and R_4 = Br, R_3 = 4-F), **23g** (R_1 = H, R_2 = *i*-butyl, and R_4 = Cl, R_3 = 4-F) showed the MIC value of 0.8 μg/mL for their antitubercular activity.

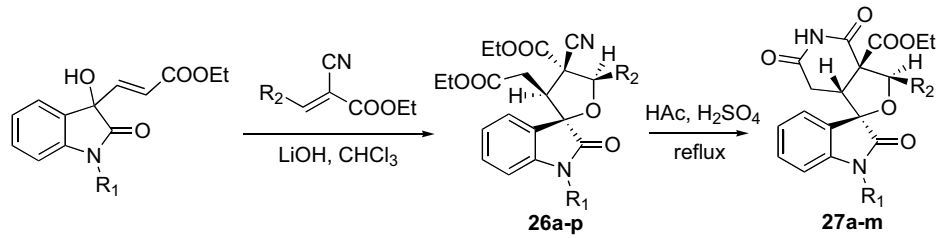
Raghunathan *et al.* described the synthesis of a series of structurally novel and complex dispiro pyrrolizidines **24** and **25** through the 1,3-dipolar cycloaddition reaction of azomethine ylides generated in situ from secondary amino acids and isatin with bischalcones (Scheme **9**) [39]. These compounds were evaluated for their antibacterial activity, and some of them exhibited good antibacterial activity against *Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Salmonella typhi*, Proteus vulgaris, and Proteusmirabilis. Compounds **24c** and **25c** (R_1 = H, R_2 = OH) showed good antibacterial activity against the tested pathogens, more potent than Tetracycline.

2.2. Spirooxindole Tetrahydrofurans and 4*H*-pyrans

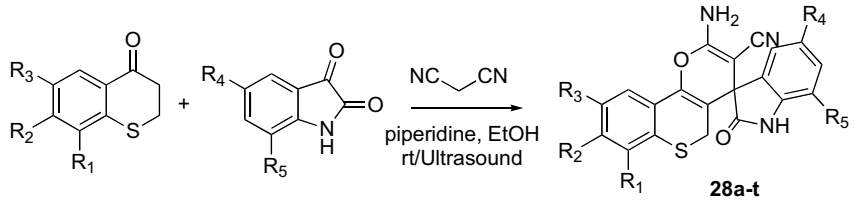
3-Hydroxyoxindole scaffolds exist in natural products and have proven to possess promising biological activities. 3-Hydroxyoxindoles as versatile precursors have also been used in the total synthesis of natural products and for constructing structurally novel scaffolds [40]. Based on the 3-hydroxyoxindoles, Xie *et al.*



Scheme 9. Synthesis of structurally novel and complex dispiro pyrrolizidines.



Scheme 10. Diastereoselective synthesis of new spirooxindole tetrahydrofurans and octahydrofuro[3,4-*c*]pyridines.

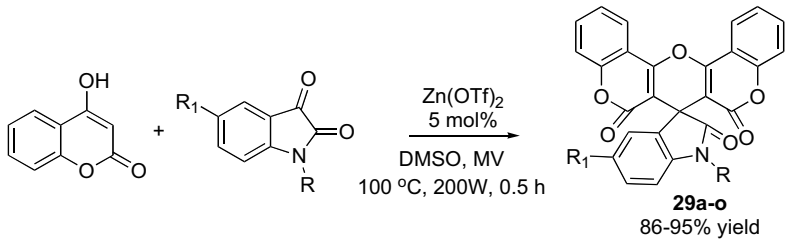


Scheme 11. Ultrasound-promoted synthesis of spirooxindole 4*H*-pyrans.

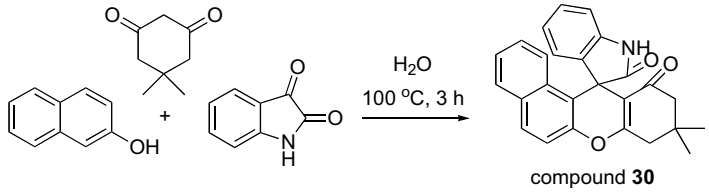
[41] synthesized a series of new spirooxindole tetrahydrofuran derivatives **26a-p** from oxindole derivatives and *β*-arylacrylonitrile derivatives in moderate to good yields (up to 88% yield) and with high diastereoselectivity (up to 98: 2 dr) via the base-mediated cascade [3+2] double Michael reactions (Scheme **10**). Spirooxindole tetrahydrofuran derivatives were then transformed to functionalized spirooxindole octahydrofuro[3,4-c]pyridine derivatives **27a-m** under acidic conditions, which contain two new heterocyclic rings and two quaternary carbon centers. The antifungal activities of all of the synthesized compounds were evaluated against *Rhizoctonia solani, Fusarium semitectum, Alternaria solani, Valsa mali* and *Fusarium graminearum* using the mycelium growth rate method. In general, compounds **26a-p** were much more potent than compounds **27a-m** against *Valsa mali* and *Fusarium graminearum*, unveiling that the incorporation of the piperidine-2,6-dione into the core scaffold was unbeneficial for the activity. Among these compounds, compound **27a** (R_1 = Me, R_2 = Ph) exhibited the best potency against *F. g.* with an IC_{50} value of 3.31 μg/mL, comparable to that of the control cycloheximide (IC_{50} = 3.3 μg/mL).

Song *et al.* developed an efficient ultrasound-promoted one-pot three-component synthesis of polycyclic spirooxindole 4*H*-pyrans (Scheme **11**) [42]. The antifungal activity was then determined by micro dilution method. Compound **28f** (R_1, R_2, R_5 = H, R_3, R_4 = Me) exhibited good inhibitory activity against *Cryptococcus neoformans, Epidermophyton floccosum* and *Mucor racemosus* with the MIC values of 16, 8, 16 μg/mL, much more potent than the positive control drug fluconazole.

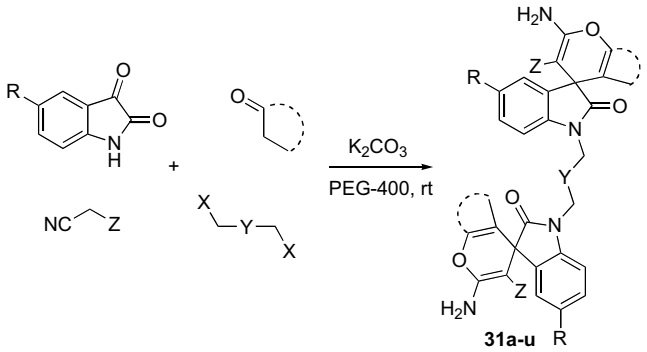
4-hydroxycoumarin is a structural motif present in various pharmaceuticals and clinical drugs like warfarin, *etc.* [43, 44]. Based on their unique pharmacological properties, Praveen *et al.* speculated that combining the structural characteristics of both spirooxindole and 4-hydroxycoumarin moieties by a hybrid pharmacophore approach could remarkably enhance the biological activity. Based on the hypothesis, these two interesting heterocycles were utilized in the presence of $Zn(OTf)_2$ for the synthesis of new spirooxindole 4*H*-pyrans containing the bis-coumarin motif (Scheme **12**) [45]. All compounds were obtained in 86-95% yields. Interestingly, the *in vitro* antibacterial



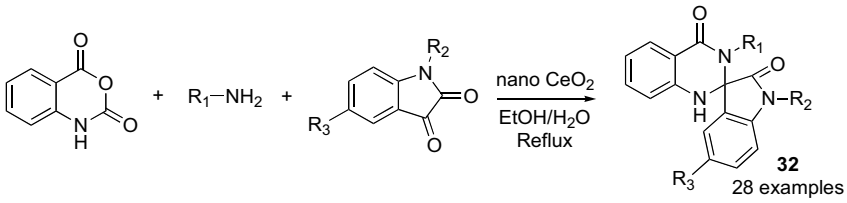
Scheme 12. $Zn(OTf)_2$ catalyzed synthesis of bis-coumarin containing spirooxindole 4*H*-pyrans.



Scheme 13. On-water synthesis of spirooxindole **30.**



Scheme 14. Green synthesis of bis-spirooxindole containing compounds **31a-u.**



Scheme 15. Nano CeO_2-catalyzed synthesis of spiro-oxindole dihydroquinazolinones.

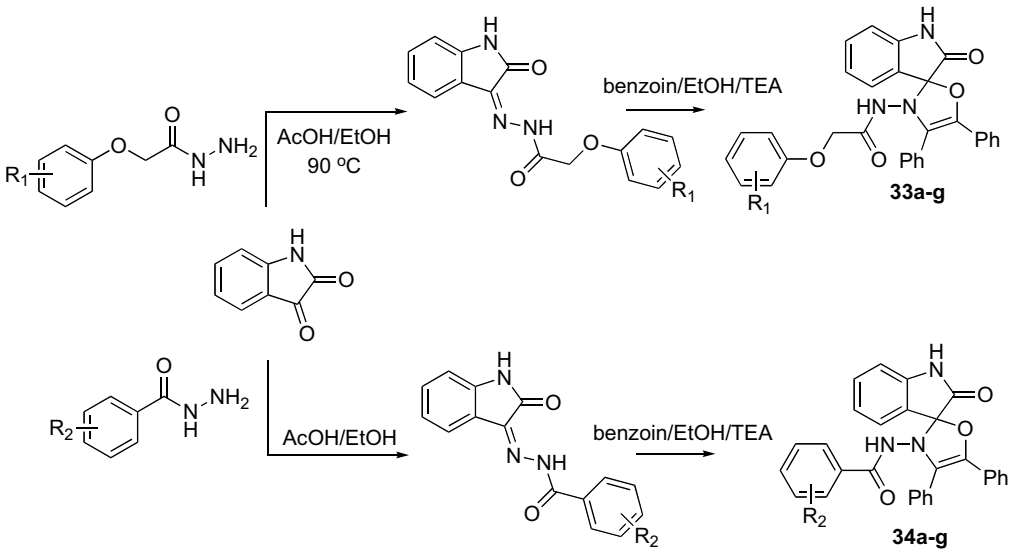
and antifungal evaluation showed that the compounds **29a** (R, R' = H), **29j** (R = Bn, R' = H), and **29m** (R = H, R' = Br) exerted promising antimicrobial activity with the MIC value of 62.5 μM. Docking studies showed that compound **29a** was well fitted into the pocket of AmpC-*β*-lactamase receptor (PDB ID: 3OT3).

Similar to above work, the Wu group developed an efficient on-water synthesis of spirooxindole 4*H*-pyran **30** (Scheme **13**), which showed good activities against *Micrococcus tetragenus, Bacillus cereus, Bacillus subtilis, Staphylococcus aureus, S. albus* and *Escherichia coli*. with the MIC values of 10, 8, 10, 7, 10 and 10 μg/mL [46].

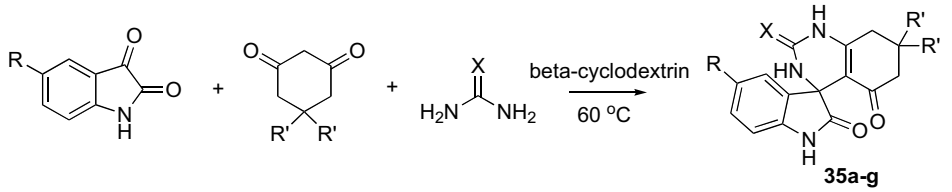
Hasaninejad *et al.* developed a highly efficient, one-pot multi-component synthesis of novel bisspirooxindoles **31a-u** featuring bis-spirooxindole scaffold with excellent yields (up to 95% yield) (Scheme **14**) [23]. PEG-400 was used as a biodegradable polymeric solvent in the reaction.

2.3. Other Spirocyclic Oxindoles

Ma *et al.* developed the nano CeO_2-catalyzed synthesis of two series of new spiro-oxindole dihydroquinazolinone derivatives (Scheme **15**) [47]. The synthesized compounds were evaluated for their *in vitro* antibacterial activity, and compounds **32i-p** showed



Scheme 16. Synthesis of 2,3-dihydrooxazole-spirooxindole derivatives.



Scheme 17. β-Cyclodextrin-catalyzed synthesis of new spirooxindoles.

considerable antibacterial activities against *E. coli.* with the MIC values between 62.5 and 15.6 μg/mL. Further molecular docking studies were performed to predict the interactions of the synthesized compounds in the active site of Biotin Carboxylase (EcBC) enzyme (PDB ID: 2W6O).

Tiwari *et al.* efficiently synthesized two series of new 2,3-dihydrooxazole-spirooxindole derivatives (Scheme **16**) and then evaluated their antibacterial and antifungal activity against *Bacillus subtilis, Enterobacter* and *Klebsiella pneumoniae* using Ciprofloxacin as positive control [48]. Among these compounds, compound **33g** (R_1 = 2,4-diCl) was found to be active against *K. pneumoniae* and *S. fuliginea* at 25 and 14 μg/ml, respectively.

Singh *et al.* developed a new eco-friendly strategy for the synthesis of novel spiro-oxindole derivatives by one-pot multicomponent reaction using isatins, urea and 1,3-dicarbonyls (Scheme **17**) [49, 50]. β-Cyclodextrin was used as the catalyst and can be reused for further reaction after recovery. The synthesized compounds were evaluated for their antimicrobial activities against *Escherichia coli, Staphylococcus aureus, Aspergillus niger* and *Candida albicans*, showing that all the synthesized spiro-oxindoles exhibited significant antimicrobial activity, equal to that of standard drug streptomycin.

CONCLUSION AND OUTLOOK

Spiro scaffolds have been recognized as privileged scaffolds in drug design due to their highly pronounced biological properties, interesting conformational features and unique 3D structural features. In particular, spirooxindoles have emerged as attractive synthetic targets because of their prevalence in numerous biologically validated natural alkaloids and pharmaceutically relevant molecules. The key structural characteristic of these compounds is the spiro ring fused at the C3 position of the oxindole core with varied heterocyclic motifs. Spirooxindole is a privileged heterocyclic motif that exists in pharmaceutical candidates and naturally occurring compounds. Spirooxindole containing compounds have exhibited diverse biological properties. Antimalarial agent NITD609, PLK4 inhibitor CFI-400945, MDM2 inhibitors SAR405838 and APG-115 have advanced into clinical trials for the treatment of malaria and human cancers. In last decades, a large number of structurally novel spirooxindoles have been synthesized mainly based on the ylide intermediates generated in situ and further assessed for their antimicrobial activity against different types of bacteria, lead-

ing to the discovery of some potent lead compounds with antimicrobial potentials. The structural complexity and diversity of spirooxindoles could be achieved by using diverse dipolarophiles and ylides generated from isatin and amino acid derivatives. However, the current study is only limited to primary antimicrobial assessment, no detailed modes of action are investigated.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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