Spirooxindole Derivatives as Anticancer Agents: A Comprehensive Review on Synthetic Strategies (2019–2025)

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Abstract

Spirooxindole derivatives have emerged as a vital class of heterocyclic compounds with significant relevance in modern medicinal chemistry, particularly in the discovery of anticancer drugs. The spirooxindole core, defined by a unique spiro-fusion at the C-3 position of the oxindole nucleus, first gained attention through natural products such as spirotryprostatins, horsfiline, and rhynchophylline, which exhibited potent bioactivity. Their rigid, three-dimensional architecture offers improved metabolic stability and target selectivity, making them valuable in therapeutic design. This review summarizes recent synthetic advancements (2019–2025) in regio- and stereoselective approaches, including green, metal-free, and enantioselective methods. It highlights strategies for scaffold diversification through the incorporation of pharmacophores and heterocyclic motifs, contributing to the development of bioactive hybrids targeting cancer-related proteins such as MDM2, tubulin, CDKs, and EGFR. By integrating foundational chemistry with modern innovations, this review provides a concise reference for researchers in synthetic and medicinal chemistry.

Keywords: Spirooxindole derivatives; Heterocyclic compounds; Medicinal Chemistry; Pharmacophores; Anticancer drugs; Therapeutic design.

INTRODUCTION

Spirocyclic scaffolds have attracted considerable attention in synthetic organic chemistry owing to their conformational rigidity and their ability to spatially orient functional groups in a well-defined three-dimensional framework, thereby enhancing molecular complexity and biological relevance. Among them, spirooxindole compounds, where an oxindole ring is spiro-fused to a carbocyclic or heterocyclic moiety, represent a privileged class of heterocycles. The oxindole nucleus, featuring a lactam (2-oxoindoline) fused to a benzene ring, offers multiple sites for functionalization and diverse chemical reactivity. The spiro-fusion at the C-3 position generates a quaternary stereocenter, presenting both a synthetic challenge and an opportunity for complex scaffold construction.

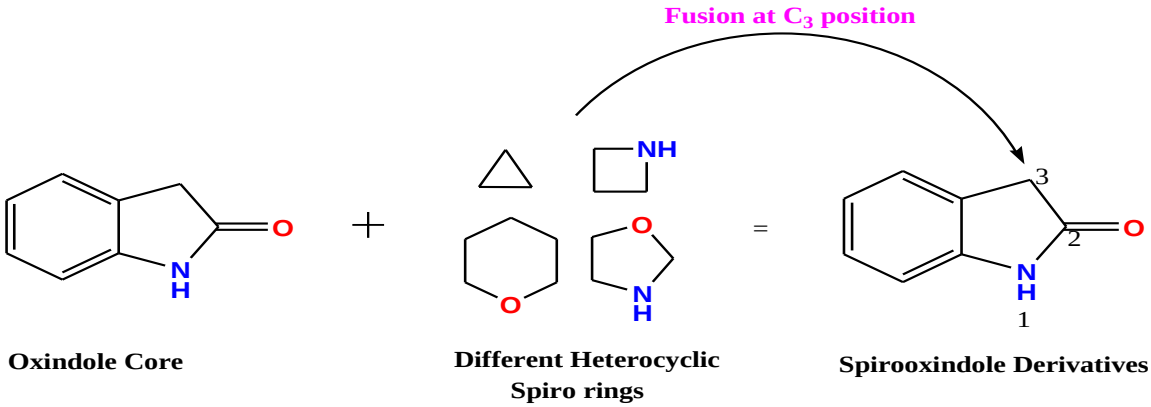


Fig. 1. Basic composition of Spirooxindoles.

Spirooxindoles possess distinctive structural characteristics and exhibit a broad spectrum of biological activities, positioning them as valuable candidates in the development of novel therapeutic agents. Over the past decade, they have significantly expanded the chemical space of oxindole-based and related heterocyclic scaffolds, garnering considerable attention from both synthetic and medicinal chemists due to their notable chemopreventive and anticancer potential. Spirooxindoles represent a pivotal class of heterocyclic frameworks featured in a diverse range of pharmacologically active compounds, maintaining a central role in modern medicinal chemistry. **Figure 02** illustrates representative spirooxindole-based drug candidates currently under investigation or development.

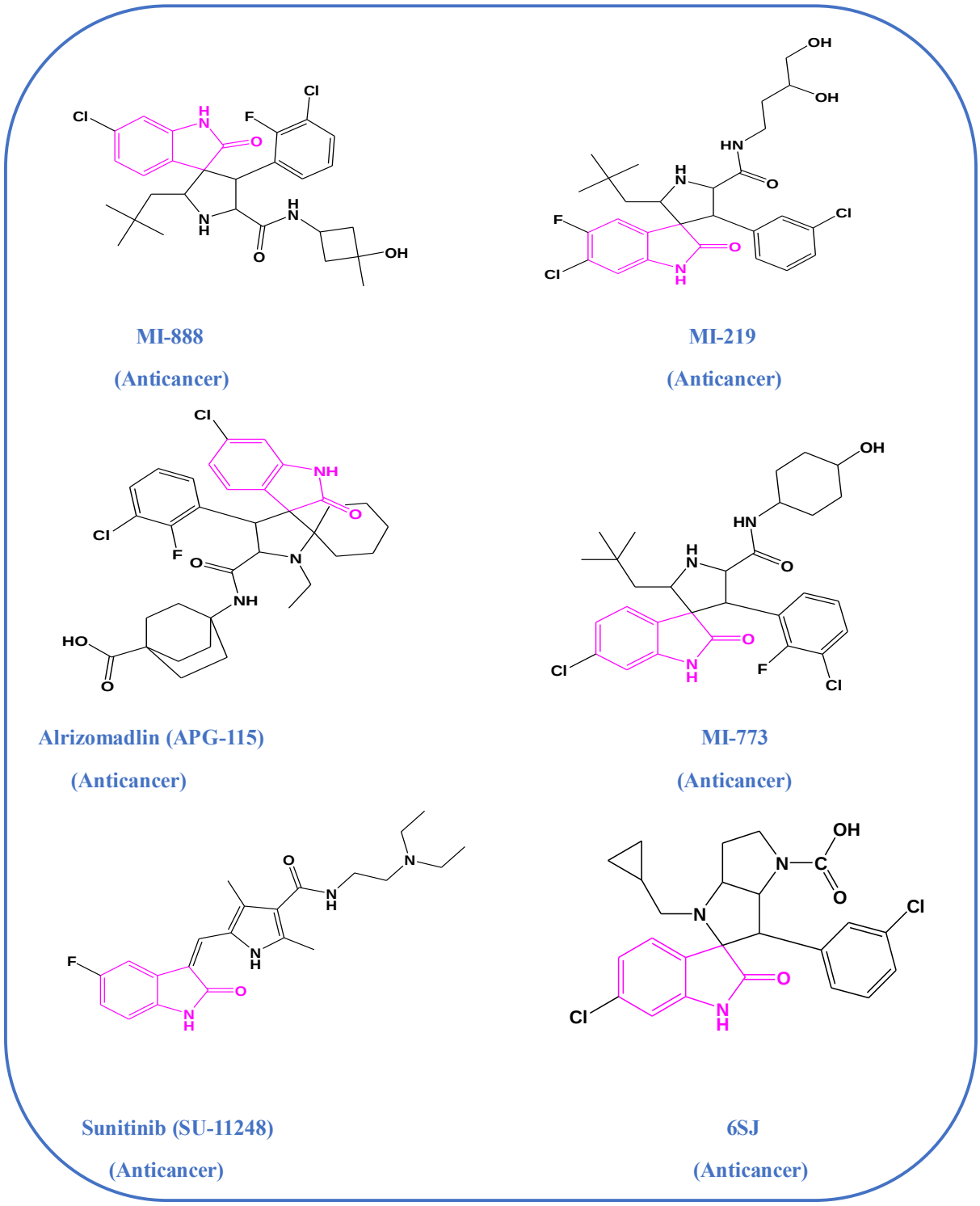


Fig. 2. Structural depiction of Spirooxindole derivatives with approved or investigational status.

TAUTOMERIC FORMS OF OXINDOLES

Oxindole tautomers are important in medicinal chemistry, particularly in drug design and reaction mechanisms, as tautomerism affects binding, reactivity, and bioavailability. Tautomeric forms of oxindoles involve the migration of a proton and a shift of a double bond, typically between a lactam (keto) form and an enol form.

1. **Keto (Lactam) Form** – Major and More Stable
2. **Enol Form (Tautomer)** – Less Stable

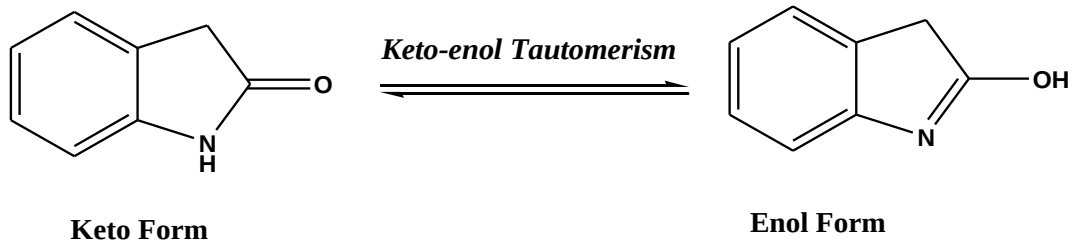
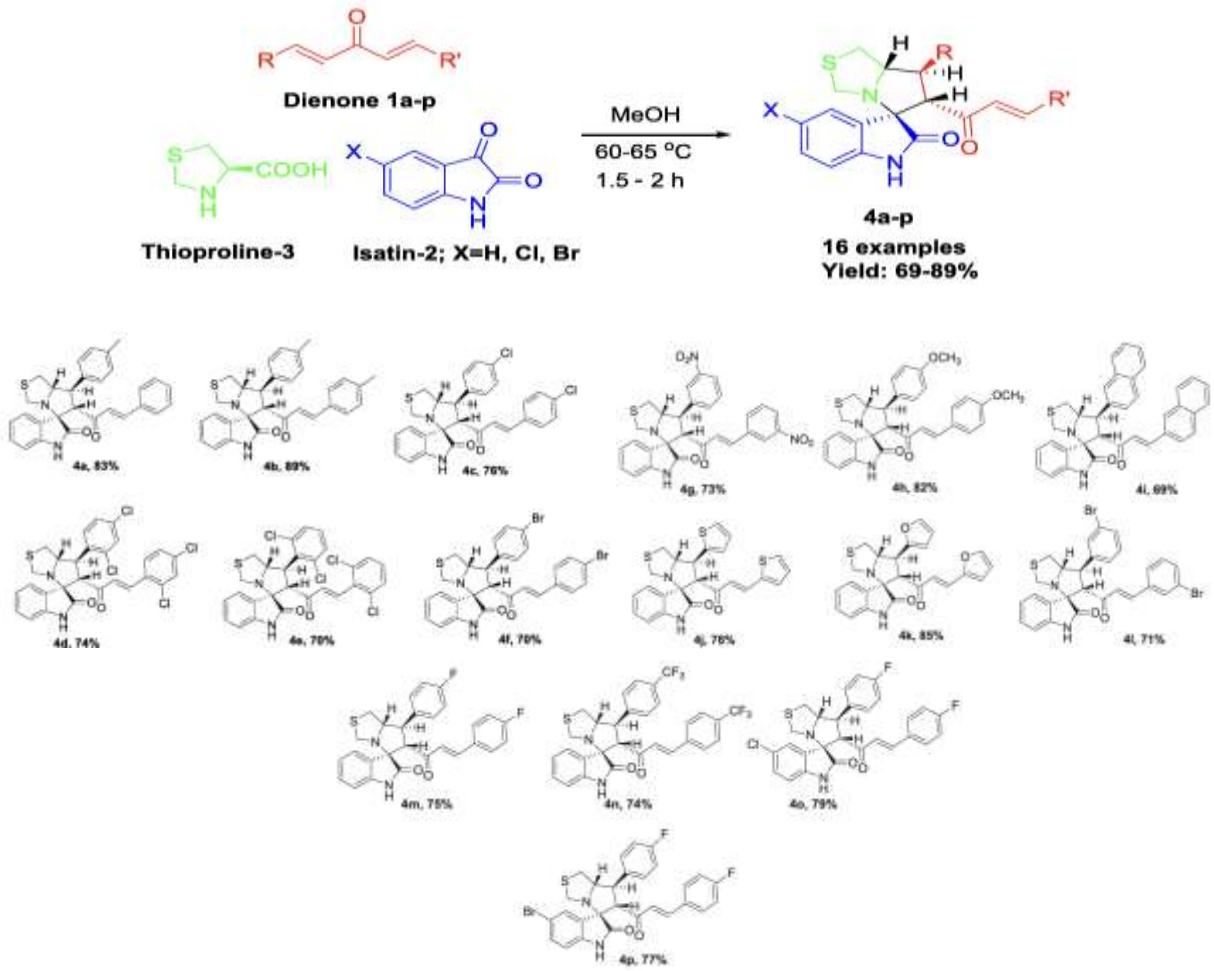


Fig. 3. Keto-Enol tautomeric forms of the Oxindole scaffold.

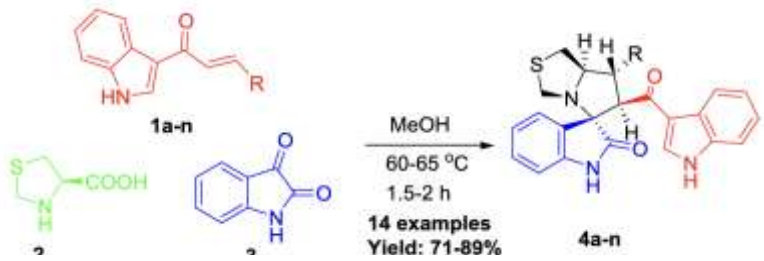
SYNTHETIC STRATEGIES

Barakat A *et al.* reported the design and synthesis of substituted spirooxindoles as potent MDM2 inhibitors, using an efficient 1,3-dipolar cycloaddition reaction. The one-pot multi component reaction of α, β-unsaturated dienone derivative 1, with the dicarbonyl compound 2 (substituted isatin), and amino acid derivative 3 (L-4 thiazolidinecarboxylic acid), was heated up in MeOH at 60°C for 1.5–2.0 h to generate the focused cycloadduct library, 4a-p, having 4 stereogeneric centers, in good to excellent yield (69–89%) (**Scheme 1**).[1]



Scheme 1. Structures of the synthesized compounds, 4a–p.

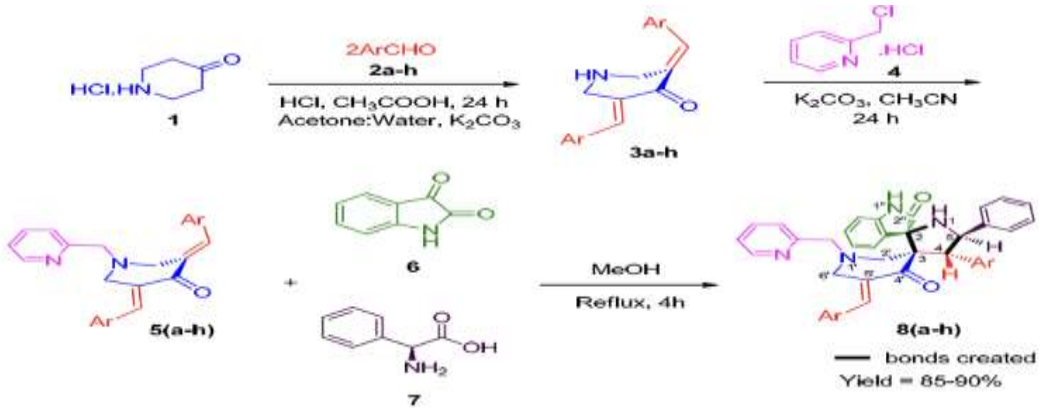
M.S. Islam *et al.* reported the synthesis of 14 new thiazolo-pyrrolidine–(spirooxindole) tethered to 3 acylindole as anticancer agents. One-pot reaction of chalcone derivative 1a–n, active carbonyl compounds (isatin,3), and secondary amino acid (L-4-thiazolidinecarboxylic acid, 2) in high yield (71–89%) in boiling MeOH for 1.5–2.0h (**Scheme 2**).[2]



Entry	4a–n	R	Yield (%)
1.	4a	C_6H_5	88
2.	4b	*p*-MeC_6H_4	87
3.	4c	*p*-ClC_6H_4	81
4.	4d	2,4-$Cl_2C_6H_3$	80
5.	4e	*p*-$MeOC_6H_4$	85
6.	4f	*p*-BrC_6H_4	79
7.	4g	*p*-FC_6H_4	81
8.	4h	*m*-FC_6H_4	77
9.	4i	*m*-MeC_6H_4	83
10.	4j	*m*-BrC_6H_4	71
11.	4k	*p*-$CF_3C_6H_4$	83
12.	4l	2-Thiophene	88
13.	4m	2-Furan	89
14.	4n	3,4,5-tri-$MeOC_6H_2$	83

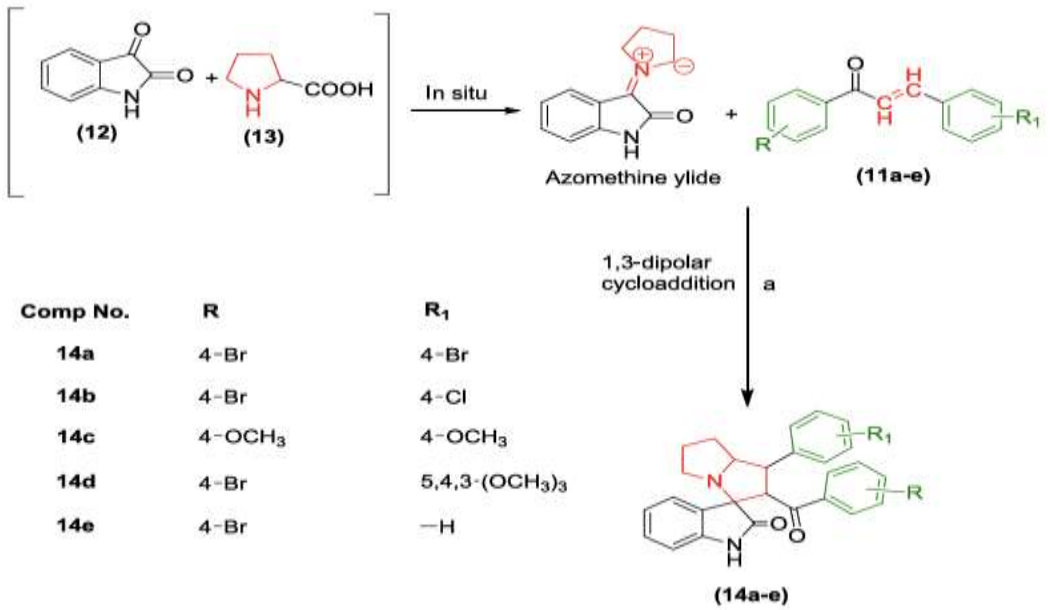
Scheme 2. The synthesis of the target thiazolo-pyrrolidine/spirooxoindole derivative 4a-n.

Kumar *et al.* reported the one-pot three-component synthesis and investigation of the in vitro mechanistic anticancer activity of highly functionalized spirooxindole-pyrrolidine heterocyclic hybrids. With the compound 3 (a–h) in hand, the dipolarophiles and N-substituted bisarylmethylidene-tetrahydropyridinones 5 (a–h) required for the present study were synthesized in an 85–90% yield range through the alkylation of 3 (a–h) with 2-(chloromethyl) pyridine hydrochloride in the presence of K2CO3. The synthesis of spirooxindole molecular scaffold employing isatin 6 and (L)-Phenylglycine 7 was based on a multicomponent reaction strategy involving the 1,3-dipolar cycloaddition reaction between N-pyridinylmethyl-bisarylmethylidenepyridinones 5 (a–h) and azomethine ylide generated in situ from 6 and 7. AnequimolarmixtureofN-substituted bisarylmethylidene-tetrahydropyridinones 5(a–h) (0.100 g, 0.27 mmol), isatin 6 (0.040 g, 0.27 mmol), and phenylglycine 7 (0.041 g, 0.27 mmol) were dissolved in methanol (5 mL) and heated under reflux with constant stirring for 4 h. After completing the reaction an equimolar mixture of N-substituted bisarylmethylidene-tetrahydropyridinones 5(a–h) (0.100 g, 0.27 mmol), isatin 6 (0.040 g, 0.27 mmol), and phenylglycine 7 (0.041 g, 0.27 mmol) were dissolved in methanol (5 mL) and heated under reflux with dissolved in methanol (5 mL) and heated under reflux with constant stirring for 4 h. After completing the reaction as evident from TLC, the reaction mixture was transferred into 50 mL of ice-cold water to form a precipitate which was separated by filtration and washed with water to obtain the product 8(a–h) in good yields (**Scheme 3**).[3]



Scheme 3. Synthesis of spirooxindole-pyrrolidine molecular scaffolds 8(a–h).

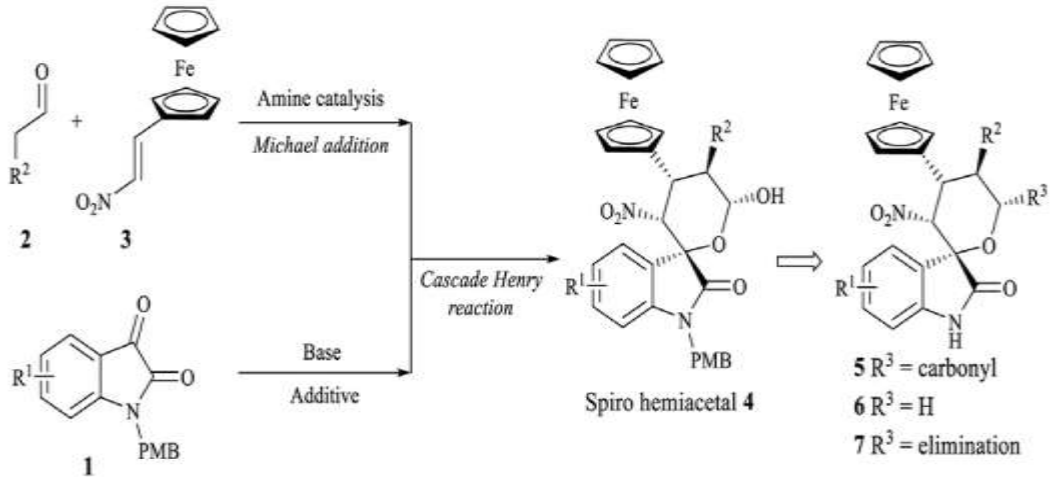
Ghosh *et al.* reported stereoselective synthesis of spirooxindole derivatives using one-pot multicomponent cycloaddition reaction and evaluation of their antiproliferative efficacy. A mixture of appropriate α,β-unsaturated carbonyl compounds 11a−e (0.003 mol), isatin (12) (0.004 mol), and L-proline (13) (0.004 mol) was refluxed together in absolute ethanol (10 mL) for 5 h. After completion of the reaction, as indicated by TLC (chloroform/n-hexane = 4:1), the reaction mixture was filtered hot, and the filtrate was concentrated under vacuum to obtain the crude product. The crude was then dried and recrystallized from ether to obtain Pyrrolizidine Spirooxindole Derivatives 14a−e (**Scheme 4**).[4]



Comp No.	R	R_1
14a	4-Br	4-Br
14b	4-Br	4-Cl
14c	4-OCH_3	4-OCH_3
14d	4-Br	5,4,3-$(OCH_3)_3$
14e	4-Br	−H

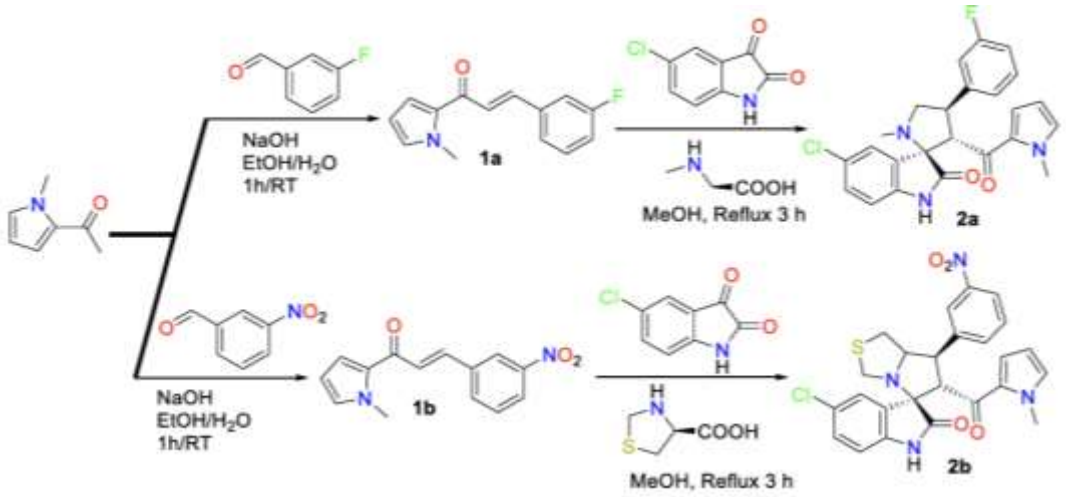
Scheme 4. Reaction and Reagents for the Pyrrolizidine Spirooxindoles 14a-e:(a) Ethanol, Reflux with Stirring,5h.

Jun Mu *et al.* reported the synthesis of spirooxindole–ferrocene hybrids as novel MDM2 inhibitors. Reactions were performed with 2 (0.4 mmol), 3 (0.36 mmol), Hayashi-Jørgensen secondary amine catalyst (0.04 mmol), and AcOH (0.04 mmol) in 2 mL CH2Cl2at r.t. for 3 h, after which 1 (0.2 mmol) and TABA (0.02 mmol) were added. Oxidation of 4 with DMP generated spirooxindole d-lactone 5. Reduction of 4 with Et3SiH and BF3Et2O at 20 °C generated spirooxindole tetrahydropyran 6. Protonation of 4 with para-toluenesulfonic acid at 40 °C generated spirooxindole 3,4-dihydropyran 7 (**Scheme 5**).[5]



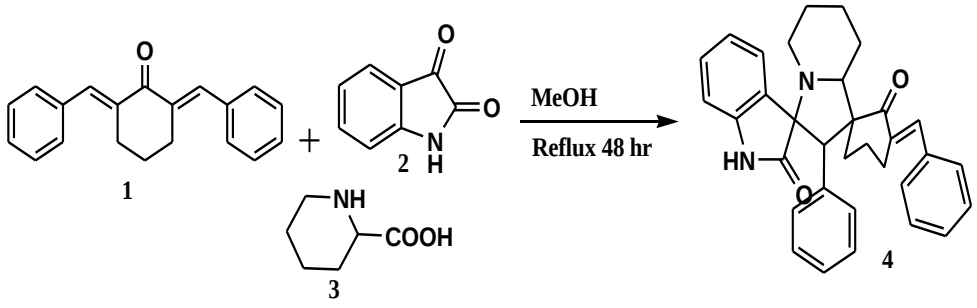
Scheme 5. Asymmetric synthesis of chiral spirocyclic oxindole-ferrocene hybrids.

Abdel Aziz *et al.* reported design, synthesis, chemical, and biochemical insights into novel hybrid spirooxindole-based p53-mdm2 inhibitors with potential Bcl2 signaling attenuation. The starting material required for the synthesis of the substituted spirooxindole scaffold is the N-methyl pyrrole-based chalcone. The later chalcone1a, bissynthesized by aldol condensation of N-methyl-2-acetylpyrrole with the appropriate aldehydes (3 fluorobenzaldehyde/3-nitrobenzaldehyde) in the presence of aqueous NaOH, by employing a multicomponent one-pot reaction approach to furnish the requisite compound in high purity as well as regioselective and diastereoselective fashion (**Scheme 6**).[6]



Scheme 6. Synthesis of the spirooxindole derivatives 2a, b.

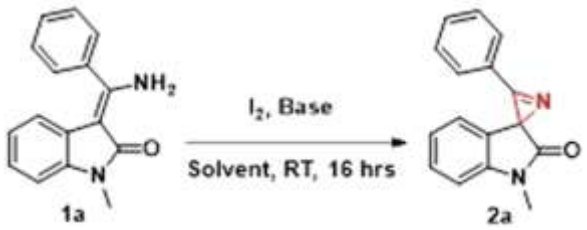
Abdel Aziz *et al.* reported the synthesis and characterization of a new spirooxindole grafted pyrrolidino/piperidine moiety. A mixture of 2,6-di((E)-benzylidene) cyclohexan-1-one 1 (137mg, 0.5mmol), isatin 2 (73.5mg, 0.5 mmol), and (R)-piperidine-2-carboxylic acid 3 (64.5mg, 0.5 mmol) in methanol (10 mL) was refluxed on an oil bath for 1h. After completion of the reaction, as evident from TLC, the mixture was kept for slow evaporation. The resulting solid was filtered and recrystallized from ethanol to yield a faint yellow powdered product 4 (**Scheme 7**).[7]



Scheme 7. Synthesis of the spiroxindole derivative 4.

Bisht *et al.* reported the synthesis of quaternary spirooxindole2h-azirines and continuous flow conditions and metal-assisted umpolung reactivity for the ring-opening reaction. A control experiment was performed in 1,2-dichloroethane (DCE) by taking a reaction mixture containing 3-(amino(phenyl) methylene)-1-methylindolin-2-one 1a and Cs_2CO_3 in the absence of iodine, resulting in no reaction. In another control experiment using 3-(amino(phenyl)methylene) 1-methylindolin-2-one1a and molecular iodine in the absence of base was failed to give 2a. Thus, the reaction was performed in conjunction with base and molecular iodine afforded 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2' one 2a. Poor yield was obtained when the action was performed with organic

base such as DBU. Further, this reaction was screened with different bases derived from carbonate salts such as $NaHCO_3$, Na_2CO_3, and K_2CO_3, resulting in an improved yield of product 2a. Interestingly, while using Cs_2CO_3 as a base in the reaction, 75% yield of the product 2a was observed. After having a base screening, solvent optimization was studied. Polar solvents such as DMF, ACN, and ethyl acetate were found to be good for this transformation. Interestingly, excellent yield was observed when the most commonly available, inexpensive, less-toxic, and green ethyl acetate was used as a solvent. However, this reaction with a catalytic amount of iodine decreases the yield of the product 2a. A best optimized condition for the product 2a 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one (90%) wasachievedbyusingI2 (1.2eq.) and Cs2CO3 (2.2eq.) in ethyl acetate as solvent. In addition, the compound 2a was optically inactive from polarimetry analysis and indicated that compound 2a was obtained as a racemic mixture (**Scheme 8**).[8]

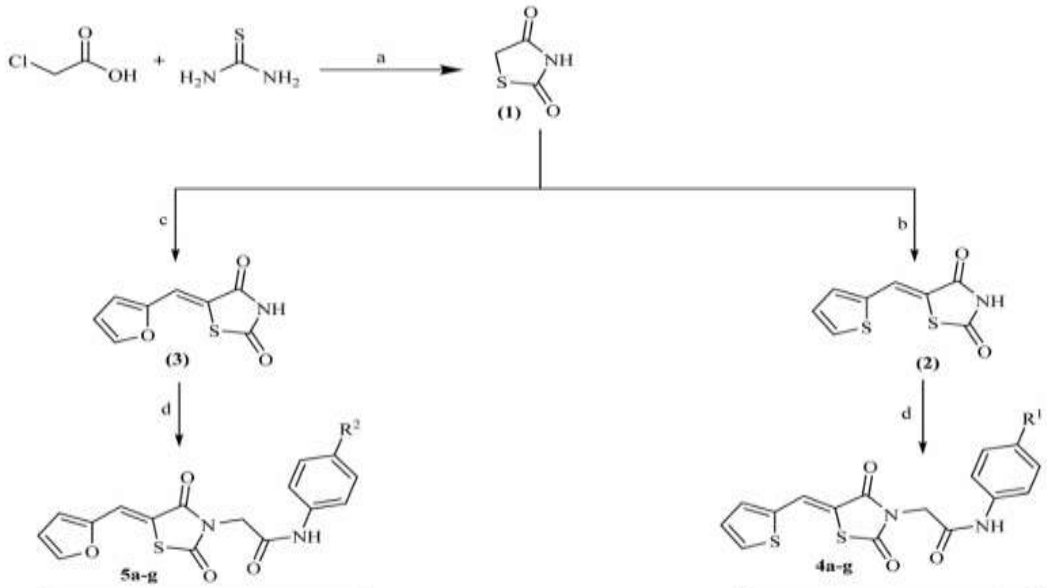


Entry	Base	Solvent	Yield of 2a [%]
1	Cs_2CO_3 (2.5)	DCE (No iodine)	–
2	–	DCE (I_2 1.2 eq)	–
3	DBU (2.5)	DCE	15
4	$NaHCO_3$ (2.5)	DCE	35
5	Na_2CO_3 (2.5)	DCE	45
6	K_2CO_3	DCE	50
7	Cs_2CO_3 (2.5)	DCE	75
8	Cs_2CO_3 (2.2)	ACN	68
9	Cs_2CO_3 (2.2)	DMF	85
10	**Cs_2CO_3 (2.2)**	**EtOAc**	**90**
11	Cs_2CO_3 (1)	EtOAc	40
12	Cs_2CO_3 (1.5)	EtOAc	80
13	Cs_2CO_3 (2.2)	EtOAc	15
14	Cs_2CO_3 (2.2)	EtOAc	40

Reaction Conditions: [a] 3-(amino(phenyl)methylene)-indolin-2-ones **1a** (0.25 mmol), iodine (1.2 eq.), base (see table) and solvent 4 mL (see table) were stirred at room temperature in a round-bottom flask for 16 hrs. [b] 30 mol% of iodine has been used. [c] 50 mol% of iodine has been used.

Scheme 8. Synthesis of Spirooxindole 2H-azirines.

Aziz *et al*. reported the design, synthesis, in silico docking, ADMET, and anticancer evaluations of thiazolidine-2,4-diones bearing heterocyclic rings as dual VEGFR-2/ EGFRT790M tyrosine kinase inhibitors. Synthesis was initiated by cyclocondensation of thiourea with chloroacetic acid to afford thiazolidine-2,4-dione (1) which underwent further condensation reaction with thiophene-2-carbaldehyde and/or furan-2-carbaldehyde via Knoevenagel condensation 27 to afford 5-(thiophen-2-ylmethylene) thiazolidine-2,4-dione 2 and 5-(furan-2-ylmethylene) thiazolidine-2,4-dione 3, respectively. Subsequent heating of 2 and 3 under reflux with the appropriate chloroacetamide derivative in acetone in the presence of potassium carbonate afforded the corresponding amide derivatives 4a–g and 5a–g respectively (**Scheme 9**).[9]



	R^2		R^2
5a	H	5e	$CH(CH_3)_2$
5b	Cl	5f	OCH_3
5c	F	5g	COOH
5d	CH_3		

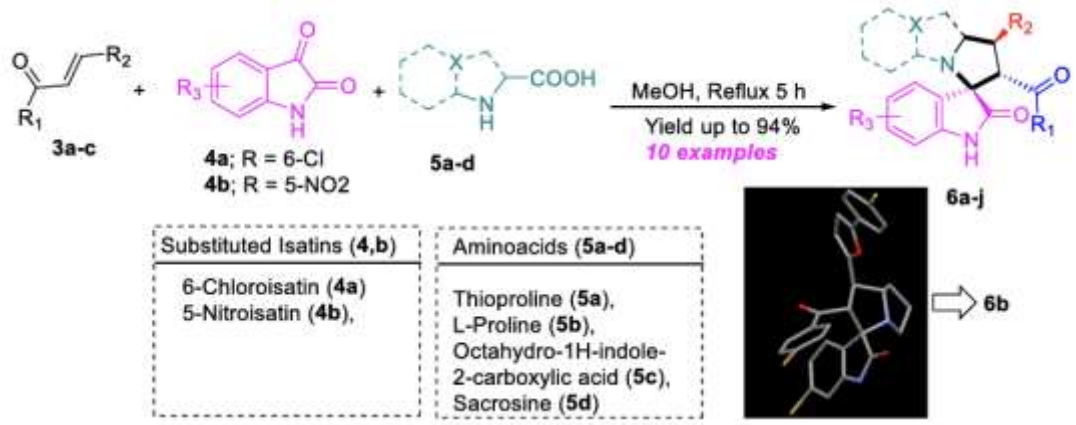
	R^1		R^1
4a	H	4e	CH_3
4b	Cl	4f	OCH_3
4c	F	4g	COOH
4d	Br		

a) HCl / reflux / 2-3 h;
b) Thiophene-2-carbaldehyde / Sodium acetate / acetic acid glacial / reflux;
c) Furan-2-carbaldehyde / Sodium acetate / acetic acid glacial / reflux;
d) Chloroacetamide / K_2CO_3 / acetone / reflux

Scheme 9. Synthetic route for the preparation of the target compounds 4a–g and 5a–g.

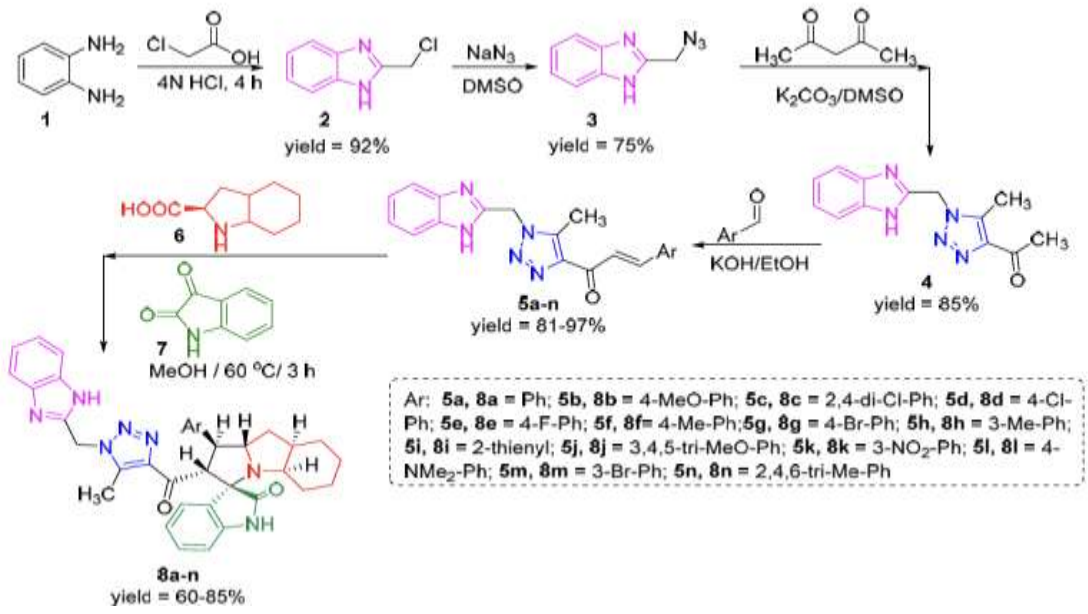
Altowyan *et al.* reported the synthesis, characterization, and cytotoxicity of new spirooxindoles engrafted furan structural motif as a potential anticancer agent. The ethylene derivatives 3a−c, having the aryl-furan scaffold was mandatory as a dipolarphile for the[3+2]cycloaddition reaction approach and were prepared from the acetophenones with the aryl-furan carbaldehydes in basic conditions to afford the corresponding chalcones in precipitated form in a high chemical yield. The ethylene derivative 3a was

successfully obtained in a single crystalline form by slow diffusion/ evaporation in DCM/EtOH, and the crystal was suitable for X-ray diffraction analysis. The required materials for the [3+2] cycloaddition reaction were ethylene derivatives having an aryl furan motif 3a-c, four amino acids 5a-d, and two substituted isatins 4a-b, which achieved the desired spirooxindoles 6a−j (**Scheme 10**).[10]



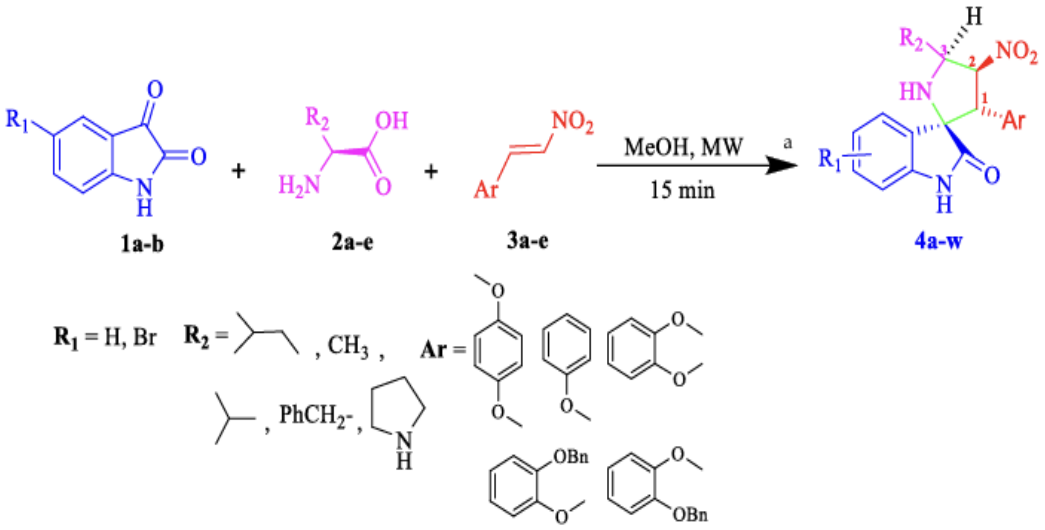
Scheme 10. A plausible mechanism for the 32 CA reaction of azomethine ylide to ethylene derivative 3a−c to afford the spirooxindole analogues 6a−j.

Alshahrani *et al.* reported the synthesis and characterization of new spirooxindoles including triazole and benzimidazole pharmacophores via [3+2] cycloaddition reaction: An MEDT study of the mechanism and selectivity. Spiro compounds (8a-n) were synthesized via a three-component reaction in which the 32CA reaction between 1,2,3 triazolyl chalcones (5a-n) and the azomethine ylide (AY), generated by the interaction between isatin and octahydroindole-2-carboxylic acid, was a key reaction step. All three-component reactions were carried out by heating an equimolar mixture of the chalcones (5a-n), isatin (7), and octahydroindole-2-carboxylic acid (6) in MeOH under reflux conditions for 3–6 h. After the completion of the reaction (which was checked using TLC), the solvent was evaporated, and the cyclized spiro compounds were purified via column chromatography to afford target spiro compounds in a pure form and in a good to excellent yield (60–85%) (**Scheme 11**).[11]



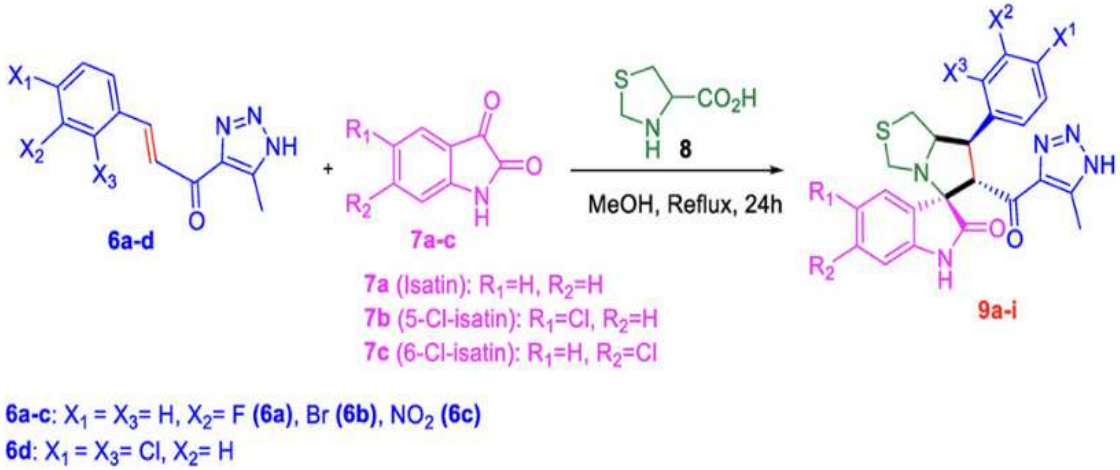
Scheme 11. Synthesis of chalcones (5a-n) and spiro compounds (8a-n).

Sharma *et al.* reported the chemo-/regio-selective synthesis of novel functionalized spiro[pyrrolidine-2,3-oxindoles] under microwave irradiation and their anticancer activity. Reaction Conditions: Substituted isatins 1a–b (0.5 mmol), various amino acids (0.5 mmol and nitrostyrenes 3a–e dissolved in methanol as solvent at 60 °C for 15 min under microwave irradiation (**Scheme 12**).[12]



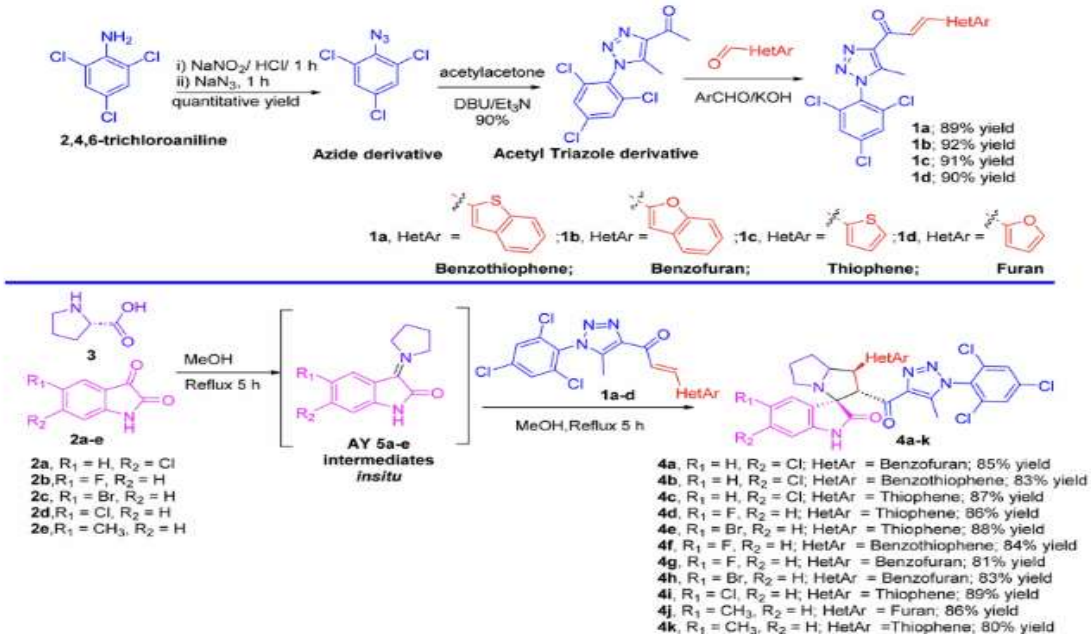
Scheme 12. Synthesis of nitrostyrene–based spirooxindole derivatives 4a–w.

Shawish *et al.* reported the synthesis of novel spirooxindole-triazole derivatives: unveiling [3+2] cycloaddition reactivity through molecular electron density theory and investigating their potential cytotoxicity against HepG2 and MDA-MB-231 cell lines. They have reported a general procedure for the synthesis of 1,2,3 triazolyl-spirooxindole derivatives, 9a-i. (s)-Thiazolidine-4-carboxylic acid (8) (1 equivalent) was added to a solution of isatin (7a) or monochloroisatin (7b or 7c) (1 equivalent) in methanol, and the mixture was stirred at rt for 15 min. Thereafter, chalcone (6a-d) was added, and the reaction was refluxed for 12 h in an oil bath. Upon completion of the reaction as indicated by TLC analysis (ethyl acetate/n-hexane 6:4), the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate-petroleum ether 4:6) to afford the spirooxindole derivatives (9a-i) as an off-white solid with a yield of (75%–90%). In some cases, the product was initially oily after solvent evaporation and required dissolution in diethyl ether, followed by the addition of a small amount of n-hexane to yield the target spirooxindole derivative as an off-white precipitate (**Scheme 13**).[13]



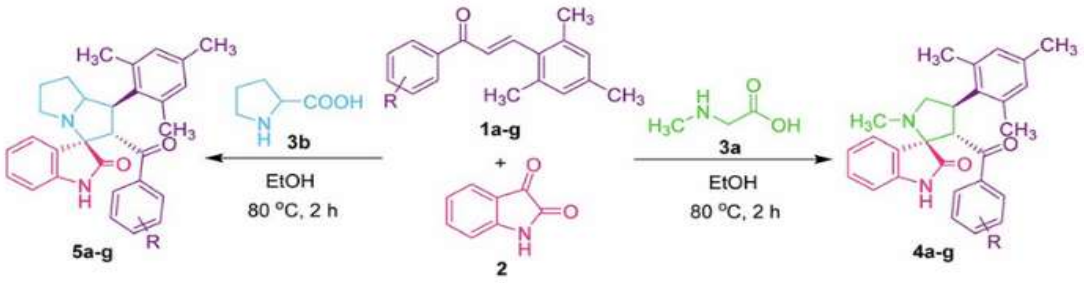
Scheme 13. Synthetic approach of spirooxindole derivatives (9a-i).

Nafie *et al.* reported potent EGFR/PARP-1 inhibition by spirooxindole triazole hybrids for targeted liver cancer therapy. They have reported the general method for the synthesis of spirooxindoles triazole hybrids 4a–k (GP2) A mixture of the chalcones 1a–d (0.5 mmol), isatin derivatives (0.5 mmol) and L-proline (57.5 mg, 0.5 mmol) in methanol (10 mL) was refluxed on oil bath for appropriate time 5–8h. After completion of the reaction, as evident from TLC, the reaction was kept at room temperature overnight, and the solid precipitated upon slow evaporation was filtered off without any further purification (**Scheme 14**).[14]



Scheme 14. Synthesis of the spirooxindoles 4a–k.

Nivetha *et al.* reported the synthesis of new spirooxindole pyrrolidine/pyrrolizidine analogs for evaluation as an anticancer agent. General procedure for the synthesis of spirooxindoles 4/5(a g). Dipolarophiles 1(a–g), isatin 2, and sarcosine 3a or L-proline 3b in an equimolar ratio in 5mL of methanol were heated under reflux for 2 h. After the reaction was completed (monitored by TLC), the reaction mixture was discharged into 50 mL of ice-cold water. The obtained crude product was purified by column chromatography using hexane: ethyl acetate (80:20 v/v) to afford the spirooxindole pyrrolidines 4(a–g)/pyrrolizidines 5(a–g) in good yields (**Scheme 15**).[15]



Entry	R	Product (4)	Yield[a] (%)	Product (5)	Yield[a] (%)
1	H	4a	73	5a	80
2	4-F	4b	88	5b	90
3	4-Cl	4c	85	5c	87
4	4-Br	4d	80	5d	83
5	4-CH_3	4e	78	5e	80
6	3-Cl	4f	80	5f	85
7	3-CH_3	4g	69	5g	70

[a] Isolated yield.

Scheme 15. Synthesis of spirooxindole derivatives 4(a–g) and 5(a–g).

CONCLUSION

Spirooxindoles have emerged as a promising class of anticancer agents due to their unique three-dimensional framework and strong interactions with key biological targets involved in tumor progression, such as MDM2–p53, tubulin, and kinases. Numerous derivatives have demonstrated potent cytotoxicity across a range of cancer cell lines, with some advancing to preclinical evaluation. This review has outlined the significant progress made in the synthesis of spirooxindole scaffolds using diverse strategies, including multicomponent reactions, asymmetric catalysis, transition metal-mediated cyclizations, and green chemistry approaches. Recent developments in synthetic methodologies continue to enhance the structural diversity and drug-like properties of spirooxindole compounds, enabling rapid construction of complex molecules with improved selectivity and pharmacokinetics. Looking forward, the integration of sustainable synthetic techniques with computer-aided drug design and biological screening is expected to accelerate the discovery of clinically viable spirooxindole-based anticancer agents. The ongoing advancements reinforce the role of spirooxindoles as a crucial platform for next-generation anticancer drug development. Overall, the insights consolidated in this review highlight the pivotal role of spirooxindoles in anticancer drug discovery and strongly advocate for continued research and innovation within this dynamic area of heterocyclic medicinal chemistry.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

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