Advanced Synthesis & Catalysis

ADVANCED SYNTHESIS & CATALYSIS
advsynthcatal.com

RESEARCH ARTICLE OPEN ACCESS

A New Synthetic Approach to the Preparation of Indolo[3,2-*c*]quinolines From Sulfonylalkyl Indoles

Francesca Cecchini | Muhammad Ehtisham Ibraheem Khan | Alessandro Palmieri | Marino Petrini

School of Science and Technology, Chemistry Division, University of Camerino, ChIP, Camerino, Italy

Correspondence: Alessandro Palmieri (alessandro.palmieri@unicam.it) | Marino Petrini (marino.petrini@unicam.it)

Received: 13 October 2025 | **Revised:** 23 April 2026 | **Accepted:** 27 April 2026

Keywords: aza-Michael reaction | cascade processes | indoloquinolines | nitro reduction | sulfonyl indoles

ABSTRACT

The reductive cyclization of sulfonylalkyl indoles obtained from 2-(*o*-nitroaryl)indoles, provides an efficient preparation of functionalized indolo[3,2-*c*]quinolines. This cascade process promoted by zinc powder in acetic acid at reflux, involves a sequential nitro group reduction, a vinylogous aza-Michael reaction, and a final aromatization.

1 | Introduction

The indoloquinoline scaffold is formally the result of a condensation between an indole and a quinoline moiety which leads to the formation of four different regioisomeric entities (Figure 1) [1, 2]. Their structural features are strictly related to those of carbolines since indoloquinolines can be considered as the corresponding benzocondensated analogs [3]. Indoloquinolines of synthetic origin are featured by notable pharmacological profiles which include antimalarial [4], antiproliferative [5, 6], and antitubercolosis activities (Figure 2) [7]. Several members of the indoloquinoline family are natural occurring compounds such as isocryptolepine, isolated from the roots of *Cryptolepis sanguinolenta*, used in folk medicine by the native people in West Africa as antimalarial agent [8]. However, most of these plant metabolites show a significant cellular toxicity which often prevents their use in preclinical treatments. This drawback has spurred the search for structural analogs of these compounds retaining the main backbone of the indoloquinoline unit but embedding diversified functional groups. This goal requires increasing efforts to elaborate new synthetic protocols for the assembling of the indoloquinoline core bearing suitable substituents at the desired positions. The main synthetic strategies currently available for the preparation of indolo[3,2-*c*]quinolines may involve the de novo build up of the indole ring on a preexisting quinoline unit or the implementation of the indole nucleus introducing the quinoline system [1].

Particularly, the utilization of *o*-substituted 2-phenylindoles represents a viable strategy to access a wide range of functionalized indolo[3,2-*c*]quinolines as reported in Scheme 1.

The reactivity of the carbon—bromine bond in 2-(*o*-bromoaryl) indoles has been exploited for the copper-catalyzed amination enabling the intermediate aniline to react with an aldehyde leading to the target indoloquinoline via the corresponding imine (Scheme 1a) [9]. The Pictet–Spengler process is effective only using arylaldehydes and the one-pot procedure require further heating at high temperature to ensure the final aromatization step. The manganese-promoted addition of boronic acids to 2-(*o*-isocyanidoaryl)indoles represents a straightforward method to prepare indolo[3,2-*c*]quinolines (Scheme 1b) [10]. Arylboronic acids are effective reactants, but the alkyl analogs only give moderate yields of products. Furthermore, being the isocyanide group introduced from the corresponding aniline by a couple of additional steps, the whole transformation seems rather redundant. In this context, the direct utilization of 2-(*o*-aminoaryl)indoles in ring closures with aldehydes appears more favorable. However, it should be observed that the traditional acid catalyzed Pictet–Spengler reaction is effective only with arylaldehydes and with moderate results [11]. The utilization of formaldehyde [12], or in situ generated 2-oxo-2-arylacetaldehydes usually provides better results (Scheme 1c) [13]. The utilization of 2-(*o*-nitroaryl) indoles as immediate precursors of the corresponding amino

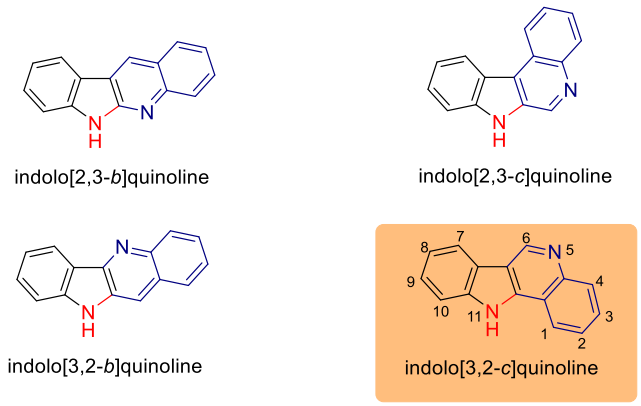


FIGURE 1 | Regioisomeric indoloquinoline skeletons.

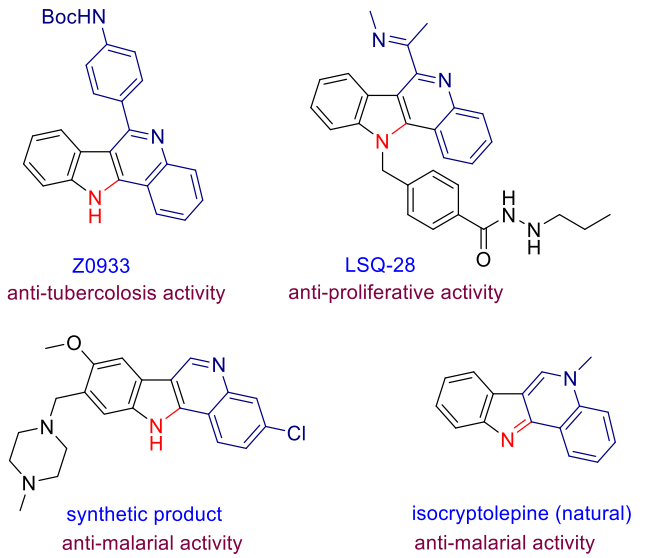
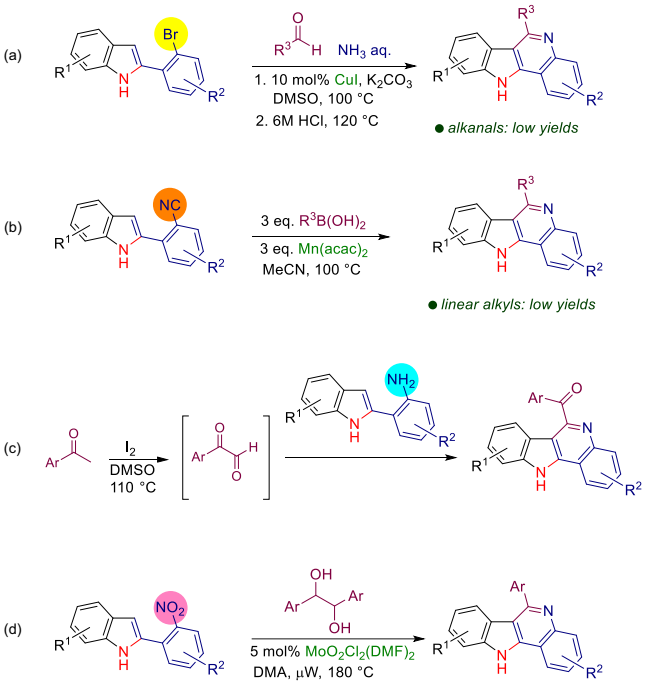


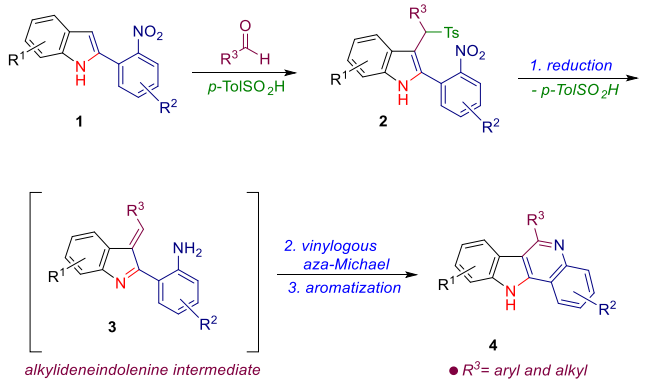
FIGURE 2 | Indoloquinolines featured by pharmacological activity.

derivatives has been poorly exploited for this purpose. The only notable example refers to the molybdenum(VI)-catalyzed reaction of 2-(*o*-nitroaryl)indoles with 1,2-diols which are preliminarily oxidatively cleaved to two molecules of aldehydes (Scheme 1d) [14]. The reduction of the nitro group is brought by the formed molybdenum(IV) species thus regenerating the active oxidizing catalyst. In order to circumvent the limited reactivity observed in the direct use of aldehydes, we sought to somewhat exploit the chemistry of sulfonylalkyl indoles as known precursors of alkylideneindolenine intermediates [15–17]. To this scope, 2-(*o*-nitroaryl)indoles **1** have been converted into sulfonylalkyl indoles **2** by a three-component Friedel–Crafts reaction with aldehydes and *p*-toluenesulfinic acid (Scheme 2) [18].

Under reductive conditions, the sulfonylalkyl indole **2** would undergo a series of transformations including reduction of the nitro group and elimination of *p*-toluenesulfinic acid leading to the alkylideneindolenine intermediate **3**. As previously demonstrated, this intermediate acts as an effective vinylogous imine which can react with the primary amino group leading to a dihydroindoloquinoline that by final aromatization, affords the target indolo[3,2-*c*]quinoline **4**. The devised strategy provides a complementary approach to the more common indoloquinoline



SCHEME 1 | Synthetic strategies for the preparation of indolo[3,2-*c*]quinolines.



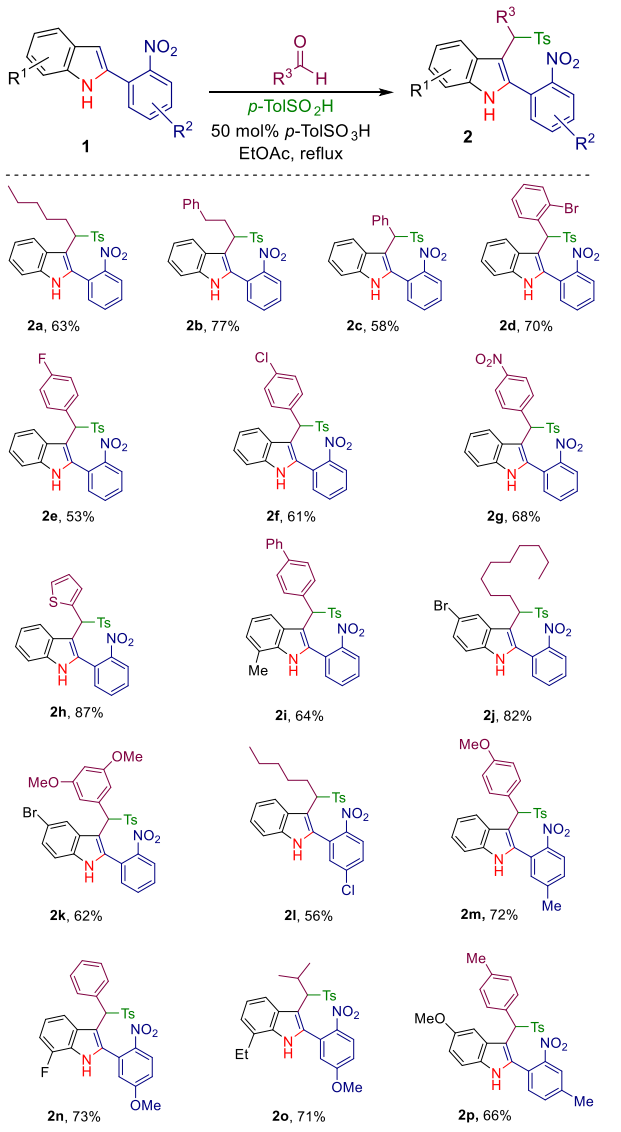
SCHEME 2 | Our approach to the synthesis of indolo[3,2-*c*]quinolines.

syntheses based on the formation of aldehyde imines to be involved in intramolecular Friedel–Crafts reaction with the indole ring.

2 | Results and Discussion

The preparation of sulfonylalkyl indoles **2** has been carried out using our improved protocol involving a three-component reaction of indoles **1** with aldehydes and *p*-toluenesulfinic acid (Table 1) [18]. The acidity level of the *p*-toluenesulfinic acid is not enough to effectively promote the preliminary Friedel–Crafts addition of the aldehyde to the indole and thus *p*-toluenesulfonic acid is required to enhance the reactivity of the aldehyde. Alkanals and arylaldehydes are reactive under the devised reaction conditions leading to the corresponding sulfonylalkyl indoles in satisfactory yields.

TABLE 1 | Synthesis of sullfonylalkyl indoles **2** from 2-(*o*-nitroaryl) indoles **1**.[a]



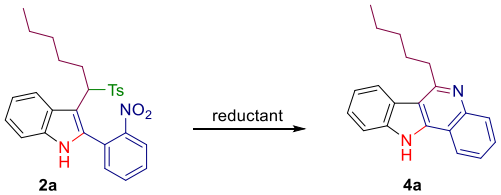
[a]Reaction conditions: indole **1** (2.0 mmol), aldehyde (2.0 mmol), *p*-TolSO$_2$H (2.4 mmol), *p*-TolSO$_3$H (1.0 mmol), in EtOAc (8 mL) at reflux for 3 h. Yields are for pure isolated products.

A somewhat limitation has been found in the availability of 2-(o-nitroaryl)indoles **1** whose preparation, for particular functionalized compounds, has been proved rather troublesome. On several occasions, procedures from literature based on the classical Fischer indole synthesis have shown poor reliability. The conversion of nitroarenes into the corresponding anilines has been largely studied and several reducing agents as well as reductant/catalyst combinations are available for this purpose [19–22]. However, the simultaneous presence of another reductable function like the *p*-toluenesulfonyl group, introduces some chemoselectivity constraints in the choice of a suitable reducing agent for the nitro group.

Since the synthetic strategy portrayed in Scheme 2 entails the generation of an alkylideneindolenine intermediate **2** by elimination of the arylsulfinic acid, a competitive reductive desulfonylation should be definitely prevented. As a matter of fact, the substitution of the arylsulfonyl group with a hydrogen atom would rule out from any possible ring closure by the generated amino group [23]. Based on this assumption, reductive methodologies focused on the utilization of nucleophilic hydride donors have been disregarded in advance since intermediates of type **3** are promptly reduced by these reagents [24]. Selecting the more appealing protocols available for the desired transformation, we were mainly concerned by sustainability and practicality issues avoiding the use of expensive, toxic, or elaborate reducing systems. Therefore, we turned our attention to the reductive properties of metals working under acidic conditions and thus we preliminarily tested iron powder in ethanol/hydrochloric acid at reflux for the conversion of sulfonylalkyl indole **2a** into indoloquinoline **4a** (Table 2, entry 1) [25]. Under these reaction conditions, the indoloquinoline **4a** is obtained but in rather poor yield. Encouraged by this result, a different method using iron powder and calcium chloride thus avoiding strongly acidic conditions was attempted (Table 2, entry 2) [26]. A slight increase in the yield of the desired product was recorded with this method which however was still unsatisfactory for synthetic purposes. The reducing properties of zinc metal under acidic conditions have been exploited for a wide number of synthetic transformations [27].

The reduction of **2a** to indoloquinoline **4a** was initially carried out using zinc powder in methanol in the presence of an excess of acetic acid (10 eq.) following a procedure devised for preparation of a related indole alkaloid (Table 2, entry 3) [28]. However, the result was not satisfactory and thus the same process has been realized in acetic acid as solvent under reflux (Table 2, entry 4). The indoloquinoline **4a** has been obtained in satisfactory yield applying these modified conditions. Despite the interesting result obtained with the latter method, we were interested in evaluating the behavior of sulfonylalkyl indoles under catalytic hydrogenation conditions. To this scope,

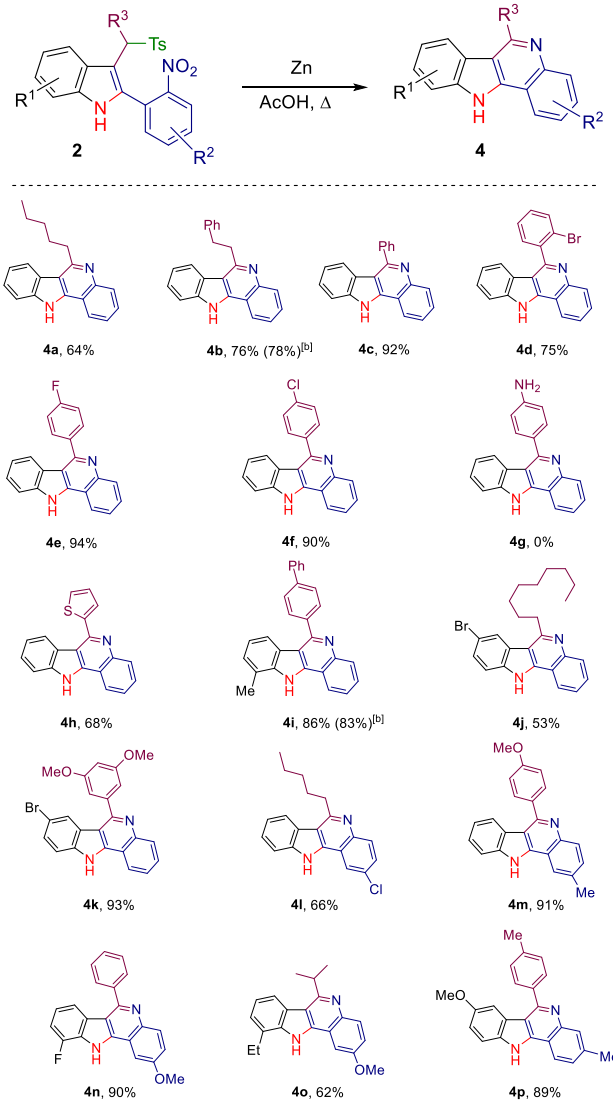
TABLE 2 | Optimization studies for the reductive cyclization of sulfonylalkyl indoles **2** to indolo[3,2-*c*]quinolines **4**.



Entry	Promoter	Solvent, T (°C)	Yield, %[a]
1	Fe powder	EtOH-HCl, Δ	28
2	Fe, $CaCl_2$	EtOH-H_2O, 60	39
3	Zn powder	AcOH, MeOH, 60	25
4	Zn powder	AcOH, reflux	64
5[b]	H_2, Raney Ni	MeOH, 80	–[c]
6[b]	H_2, 10% Pd/C	MeOH, 80	–[c]
7	Et_3SiH, $PdCl_2$	EtOH, Δ	22

[a]Yield of pure isolated products.
[b]Reaction performed under flow chemical conditions using an H-Cube Mini Plus, instrument (catalyst cartridge 30 × 4 mm; pressure: 25 bar; flow rate: 0.3 mL/min).
[c]Complex mixture of products is formed.

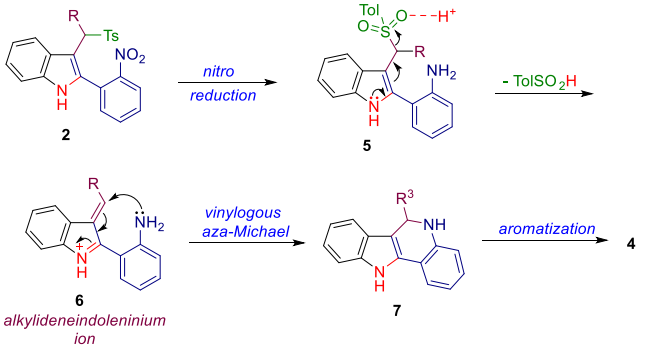
TABLE 3 | Synthesis of indolo[3,2-*c*]quinolines **4** by reductive ring closure of sulfonylalkyl indoles **2**.[a]



[a]Reaction conditions: sulfonylalkyl indole **2** (1.0 mmol), zinc powder (10 mmol), in AcOH (5 mL) at reflux for 3 h. Yields are for pure isolated products.
[b]Reaction carried out on 5.0 mmol substrate.

2a was hydrogenated under flow chemical conditions using both Raney-nickel and 10% palladium on carbon but only a complex mixture of products was evidenced for these processes (Table 2, entries 5,6).

Finally, the reductive properties of triethylsilane in palladium catalyzed reactions have been tested in this process, evidencing a positive outcome albeit with rather poor efficiency (Table 2, entry 7) [29]. The zinc/acetic acid protocol for the reductive cyclization of sulfonylalkyl indoles **2** to indoloquinolines **4** has been employed on a series of substrates leading to the target products from satisfactory to good yields (Table 3). As a preliminary observation, 6-aryl-substuted indoloquinolines are obtained in higher yields over the 6-alkyl analogs. This is presumably due to the easier elimination of the *p*-toluenesulfinic group leading to the fully



SCHEME 3 | Plausible mechanism for the cascade process.

conjugated system in the arylideneindolenine intermediate **3**. The adopted reaction conditions are compatible with the presence of halogen-containing aryl and heteroaromatic groups. However, the presence of an additional *para* nitro group in the aryl(tosyl)methyl framework of sulfonyl indole **2g** did not allow the preparation of the corresponding indoloquinoline **4g**. The utilization of zinc metal as a cheap, nontoxic reducing agent coupled with acetic acid makes this procedure quite competitive over related methods featured by limited sustainability features. The scaled-up reactions reported in Table 3 for a couple of indoloquinolines show comparable yields confirming the reliability of the synthetic protocol. Considering the acidic environment brought by the adopted reductive conditions, a plausible mechanism for the cascade process is depicted in Scheme 3. After the reduction of the nitro group, the amino derivative **5** undergoes an acid-promoted elimination to the corresponding iminium ion **6** [30, 31]. The subsequent intramolecular vinylogous aza-Mannich reaction of **6** affords the dihydropyridine intermediate **7** which upon dehydrogenation finally leads to the target compound **4**. Obviously, the possibility that the elimination of *p*-toluenesulfinic acid precedes the nitro reduction cannot be ruled out since we were unable to evidence any trace of the intermediate **5** in the reaction mixture.

3 | Conclusion

In conclusion, an improved synthesis of indolo[3,2-*c*]quinolines has been devised by a two-step protocol starting from 2-(*o*-nitroaryl)indoles. In order to circumvent the sluggish reactivity of aldehydes in Pictet–Spengler reactions with 2-(*o*-aminoaryl) indoles, the aldehyde has been trapped in the formation of sulfonylalkyl indoles by a three-component process with 2-(*o*-nitroaryl)indoles, and *p*-toluenesulfinc acid. The obtained sulfonylalkyl indoles have been subsequently converted into indolo[3,2-*c*]quinolines using zinc powder in acetic acid at reflux. The latter transformation is the result of a cascade process involving the nitro reduction, the *p*-toluenesulfinic acid elimination leading to an indoleninium ion intermediate followed by a ring closure and final aromatization. In view of the practical importance of indolo[3,2-*c*]quinolines as bioactive compounds, our disclosed procedure offers a new and improved alternative for the preparation of these polyheterocyclic derivatives.

4 | Experimental Section

4.1 | General Procedure for the Preparation of Sulfonylalkyl Indoles 2

To a stirred solution of indole **1** (2 mmol), *p*-toluenesulfinic acid (2.4 mmol) and *p*-toluenesulfonic acid monohydrate (1 mmol) in EtOAc (8 mL) were added the aldehyde (2 mmol). The resulting reaction mixture was stirred at reflux for 3 h, and after cooling at room temperature was treated with saturated $NaHCO_3$ (7 mL). The aqueous layer was extracted with EtOAc (3×20 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated at reduced pressure. The crude reaction product **2** was purified by flash chromatography (hexane:EtOAc = 70:30) to afford a yellow or orange solid.

4.2 | General Procedure for the Preparation of Indolo[3,2-c]quinolines 4

A round bottom flask equipped with a magnetic stiring bar, containing sulfonylalkyl indole **2** (1 mmol), was purged by nitrogen flow. Zinc powder (10 mmol) was then added followed by glacial acetic acid (5 mL) and the reaction mixture heated under reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (5 mL) and neutralized with 2 M aqueous solution of Na_2CO_3 until pH = 7. The resulting solution was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracted were dried on Na_2SO_4. After removal of the solvent at reduced pressure, the crude indoloquinoline **4** was purified by flash chromatography (toluene:EtOAc = 70:30) to afford a white solid.

Acknowledgments

The authors gratefully acknowledge the financial support from the University of Camerino and MUR (PON Ricerca e Innovazione 2014–2020). The research network CINMPIS-Bari is also gratefully acknowledged.

Funding

This study was supported by Università degli Studi di Camerino and Ministero dell'Università e della Ricerca.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

References

1. C. Thongsornkleeb, J. Tummatorn, and S. Ruchirawat, "A Compilation of Synthetic Strategies to Access the Most Utilized Indoloquinoline Motifs," *Chemistry – An Asian Journal* 17 (2022): e202200040.

2. K. S. Håheim and M. O. Sydnes, "Regiodivergent Syntheses and Biological Activities of Indoloquinoline Based Compounds," *Chemical Record* 24 (2024): e202300362.

3. H. Zhang, R.-H. Zhang, L.-X. Wang, Y.-J. Li, S.-G. Liao, and M. Zhou, "Synthesis Strategies for α-, β-, γ- and δ-Carbolines," *Asian Journal of Organic Chemistry* 10 (2021): 429–452.

4. P. T. Parvatkar, K. Diagne, Y. Zhao, and R. Manetsch, "Indoloquinoline Alkaloids as Antimalarials: Advances, Challenges, and Opportunities," *ChemMedChem* 19 (2024): e202400254.

5. E. Mendes, B. Bahls, I. M. Aljnadi, and A. Paulo, "Indoloquinolines as Scaffolds for the Design of Potent G-Quadruplex Ligands," *Bioorganic & Medicinal Chemistry Letters* 72 (2022): 128862.

6. S. Li, Z. Hu, W. Pan, et al., "Discovery of Highly Potent and Orally Bioavailable Histone Deacetylase 3 Inhibitors as Immunomodulators and Enhancers of DNA-Damage Response in Cancer Therapy," *Journal of Medicinal Chemistry* 68 (2025): 3212–3237.

7. G. G. Makafe, M. Hussain, G. Surineni, et al., "Quinoline Derivatives Kill Mycobacterium Tuberculosis by Activating Glutamate Kinase," *Cell Chemical Biology* 26 (2019): 1187–1194.e5.

8. J.-L. Pousset, M.-T. Martin, A. Jossang, and B. Bodo, "Isocryptolepine from Cryptolepis Sanguinolenta," *Phytochemistry* 39 (1995): 735–736.

9. S. Guo, L. Tao, W. Zhang, X. Zhang, and X. Fan, "Regioselective Synthesis of Indolo[1,2-*c*]quinazolines and 11 *H* -Indolo[3,2-*c*]quinolines via Copper-Catalyzed Cascade Reactions of 2-(2-Bromoaryl)-1 *H* -Indoles with Aldehydes and Aqueous Ammonia," *The Journal of Organic Chemistry* 80, no. 21 (2015): 10955–10964.

10. F. Teng, W. Hu, H. Hu, S. Luo, and Q. Zhu, "Selective C−H or N−H Imidoylative Annulation of 2-(2-Isocyanophenyl)-1 *H* -indoles Leading to Diverse Indole-fused Scaffolds," *Advanced Synthesis & Catalysis* 361 (2019): 1414–1418.

11. X. Peng, Z. Yu, G. Surineni, et al., "RETRACTED ARTICLE: Discovery of Novel Benzohydroxamate-Based Histone Deacetylase 6 (HDAC6) Inhibitors with the Ability to Potentiate Anti-PD-L1 Immunotherapy in Melanoma," *Journal of Enzyme Inhibition and Medicinal Chemistry* 38 (2023): 2201408.

12. P. K. Agarwal, D. Sawant, S. Sharma, and B. Kundu, "New Route to the Synthesis of the Isocryptolepine Alkaloid and Its Related Skeletons Using a Modified Pictet–Spengler Reaction," *European Journal of Organic Chemistry* 2009 (2009): 292–303.

13. M. Arockiaraj and V. Rajeshkumar, "I_2 -Promoted Sp^3 C−H Oxidation/Annulation Sequences for the Synthesis of Indoloquinolines from 2-(1 *H* -indol-2-yl)anilines and Aryl Methyl Ketones," *Advanced Synthesis & Catalysis* 366 (2024): 2557–2564.

14. R. Hernández-Ruiz, R. Rubio-Presa, S. Suárez-Pantiga, et al., "Mo–Catalyzed One-Pot Synthesis of *N* -Polyheterocycles from Nitroarenes and Glycols with Recycling of the Waste Reduction Byproduct. Substituent-Tuned Photophysical Properties," *Chemistry – A European Journal* 27 (2021): 13613–13623.

15. B. P. Kaur, J. Kaur, and S. S. Chimni, "Arenesulfonyl Indole: New Precursor for Diversification of C-3 Functionalized Indoles," *Rsc Advances* 11 (2021): 2126–2140.

16. A. Palmieri and M. Petrini, "Sulfonyl Azoles in the Synthesis of 3-Functionalized Azole Derivatives," *Chemical Record* 16 (2016): 1353–1379.

17. A. Palmieri, M. Petrini, and R. R. Shaikh, "Synthesis of 3-Substituted Indoles via Reactive Alkylideneindolenine Intermediates," *Organic & Biomolecular Chemistry* 8 (2010): 1259–1270.

18. A. Palmieri and M. Petrini, "Simplified Synthesis of 3-(1-Arylsulfonylalkyl) Indoles and Their Reaction with Reformatsky Reagents," *The Journal of Organic Chemistry* 72 (2007): 1863–1866.

19. J. Wu and C. Darcel, "Recent Developments in Manganese, Iron and Cobalt Homogeneous Catalyzed Synthesis of Primary Amines via Reduction of Nitroarenes, Nitriles and Carboxamides," *Advanced Synthesis & Catalysis* 365 (2023): 948–964.

20. A. H. Romero, "Reduction of Nitroarenes via Catalytic Transfer Hydrogenation Using Formic Acid as Hydrogen Source: A Comprehensive Review," *ChemistrySelect* 5 (2020): 13054–13075.

21. D. Formenti, F. Ferretti, F. K. Scharnagl, and M. Beller, "Reduction of Nitro Compounds Using 3d-Non-Noble Metal Catalysts," *Chemical Reviews* 119 (2019): 2611–2680.

22. M. Orlandi, D. Brenna, R. Harms, S. Jost, and M. Benaglia, "Recent Developments in the Reduction of Aromatic and Aliphatic Nitro Compounds to Amines," *Organic Process Research & Development* 22 (2018): 430–445.

23. D. A. Alonso and C. Nájera, *Organic Reactions*. 72, ed.: S. E. Denmark (Wiley & Sons, 2008), 367–656.

24. R. Ballini, A. Palmieri, M. Petrini, and E. Torregiani, "Solventless Clay-Promoted Friedel–Crafts Reaction of Indoles with α-Amido Sulfones: Unexpected Synthesis of 3-(1-Arylsulfonylalkyl) Indoles," *Organic Letters* 8 (2006): 4093–4096.

25. Y. Liu, Y. Lu, M. Prashad, O. Repič, and T. J. Blacklock, "A Practical and Chemoselective Reduction of Nitroarenes to Anilines Using Activated Iron," *Advanced Synthesis & Catalysis* 347 (2005): 217–219.

26. S. Chandrappa, K. Vinaya, T. Ramakrishnappa, and K. S. Rangappa, "An Efficient Method for Aryl Nitro Reduction and Cleavage of Azo Compounds Using Iron Powder/Calcium Chloride," *Synlett : Accounts and Rapid Communications in Synthetic Organic Chemistry* 2010 (2010): 3019–3022.

27. Y. Li and W.-D. Z. Li, "Reductive Transformations Mediated by Zinc Dust in Acetic Acid," *Tetrahedron* 152 (2024): 133817.

28. S. E. Lee, S. J. Lee, and C.-H. Cheon, "Concise Total Syntheses of Paullone and Kenpaullone via Cyanide-Catalyzed Intramolecular Imino-Stetter Reaction," *Synthesis* 49 (2017): 4247–4253.

29. M. Mirza-Aghayan, R. Boukherroub, M. Rahimifard, and M. Bolourtchian, "Palladium-catalyzed Reduction of Nitroaromatic Compounds to the Corresponding Anilines," *Applied Organometallic Chemistry* 24 (2010): 477–480.

30. L. Marsili, A. Palmieri, and M. Petrini, "Reaction of Carbon Nucleophiles with Alkylideneindazolium and Alkylideneindolium Ions Generated from Their 3-(1-Arylsulfonylalkyl) Indazole and Indole Precursors," *Organic & Biomolecular Chemistry* 8 (2010): 706–712.

31. J. Barman, S. Ananda, and S. C. Pan, "Stereoselective (3 + 3)-Cycloannulation of Carbonyl Ylides and (*Z*)-3-Benzylidene-3 *H* -Indoles Enabled by Cooperative Rh/Chiral Phosphoric Acid Catalysis," *Organic Letters* 27 (2025): 1929–1934.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.