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Facile convergent route to indoloquinolines

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ABSTRACT

A convergent route to indoloquinolines is developed through aldol condensation. This two-step method utilizes commercially available 2-oxindole and *o*-nitrobenzaldehyde as starting materials. Chromatography-free method is accomplished for preparing several derivatives of indoloquinolines with desirable aromatic substitutions on indole as well as quinoline ring.

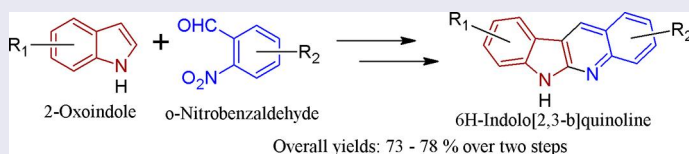
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KEYWORDS

Aldol reaction; indoloquinoline; natural product; oxindole; synthesis

GRAPHICAL ABSTRACT



Introduction

Nitrogen-containing heterocyclic compounds are a noble class of chemical entities incorporated in medicinal studies. The diverse biological responses of such compounds in antiviral, anticancer, antibacterial, and other studies make them a challenging target of synthetic development for organic chemists.^[1] Indoloquinoline alkaloids belong to one such class. 6*H*-Indolo[2,3-*b*]quinolone **1**, a natural product isolated from the leaves of *Justicia betonica*, (Fig. 1) exhibits promising biological properties.^[2] 4-Methyl-6*H*-indolo[2,3-*b*]quinoline (**I**) exhibited excellent antiproliferative activity against human hepatocellular carcinoma HepG2 and human breast carcinoma MCF-7 cells.^[3a] Neocryptopeine (**II**) or 5-methyl-5*H*-indolo[2,3-*b*]quinoline is a natural product isolated from roots of the West African plant *Cryptolepis sanguinolenta* and exhibits antiplasmodial, antitumor activity, and DNA binding properties.^[3b] *N,N*-Diethyl-*N*-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-8-yl)pentane-1,4-diamine (**III**), 1-(3-(2-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-ylamino)-propyl)-3-phenylurea (**IV**), and 1-(3-(2-methoxy-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-ylamino)propyl)-3-phenylurea (**V**) showed excellent antimalarial activity.^[4]

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📎 Supplemental data (full experimental details) can be accessed on the [publisher's website](#).

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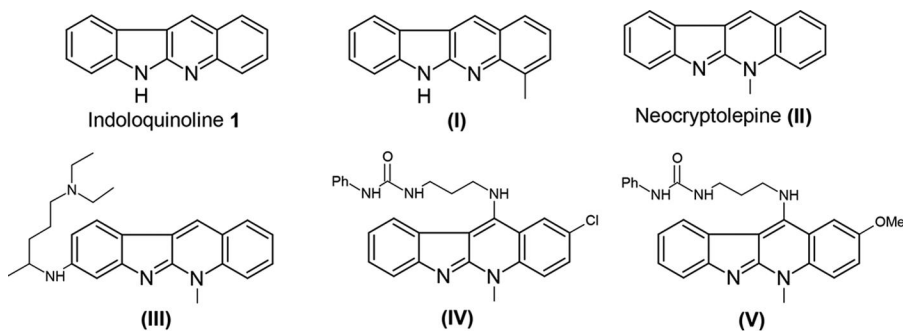


Figure 1. Indoloquinoline 1 and similar medicinally important entities.

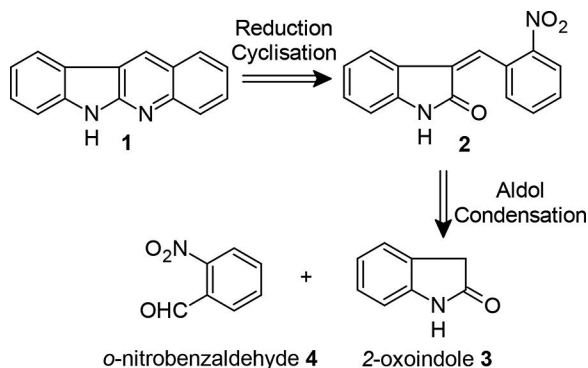
The useful biological properties and potential medicinal use of these indoloquinolines have resulted in several synthetic methods being developed and reviews in the literature.^[3–7] In this article, we report a two-step method using commercially available 2-oxoindole and *o*-nitrobenzaldehyde as starting materials for the synthesis of indoloquinolines through aldol condensation.

Results and discussion

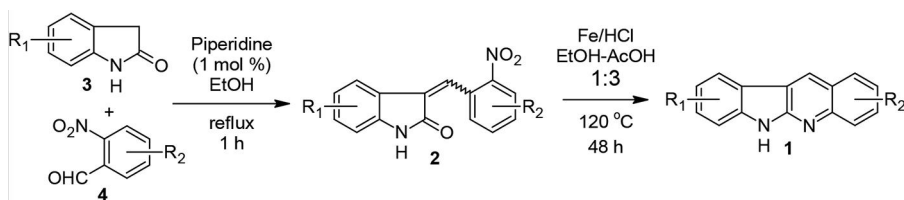
At the onset, we contemplated that 2-oxoindole **3** and *o*-nitrobenzaldehyde **4** can give us olefinic-condensed product as described in Scheme 1 through aldol reaction, which can further be converted to indoloquinolines through method involving reduction^[6] and cyclization.

In view of this, 2-oxoindole **3** and *o*-nitrobenzaldehyde **4** were reacted in aldol reaction conditions using piperidine as base to give required condensed olefinic aldol product **2** as geometrical isomeric mixture^[8] in moderate yield. This reaction was further optimized to provide maximum yield by precisely tuning the reaction condition and time. We were successful in avoiding the uneconomic, environmentally harmful, and time consuming column chromatography to obtain the required product from this step.

The aldol reaction used here provided us a convenient and efficient alternative to other costly, tedious, and laborious processes by avoiding preparation of any unstable precursors, use of toxic reagents and metals, and ultimately giving condensed olefinic compounds.



Scheme 1. Retrosynthetic analysis of Indoloquinoline 1 through aldol condensation.



Scheme 2. Two-step route to indoloquinolines.

Further the aldol product **2** was subjected to nitroreduction^[6] and cyclisation, which was further optimized with EtOH–AcOH (1:3) at 120 °C for 48 h to give indoloquinoline in good yield. The overall yield in this two-step method as described in **Scheme 2** was far more comparable with the one-step or one-pot methods available in the literature.^[5–8]

Having established a short two-step chromatography-free route from easily available starting materials, we further extended it to prepare derivatives of indoloquinolines with desirable aromatic substitutions on indole as well as quinoline ring. Dimethoxy-indoloquinoline, methylenedioxy-indoloquinoline, and chloro-indoloquinoline derivatives were obtained in around 73–78% overall yields in two steps as described in **Table 1**.

Experimental

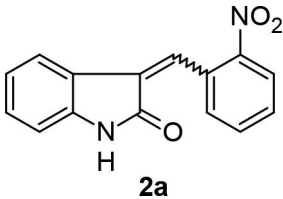
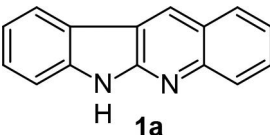
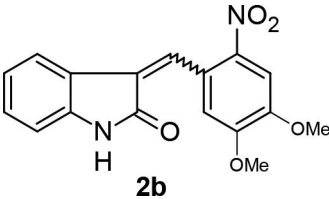
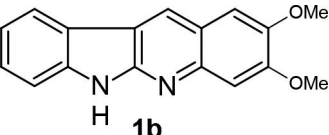
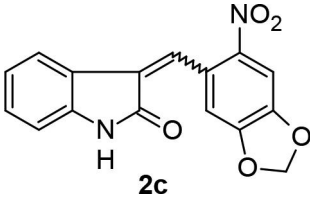
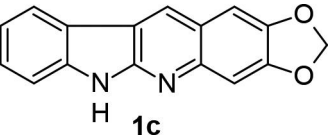
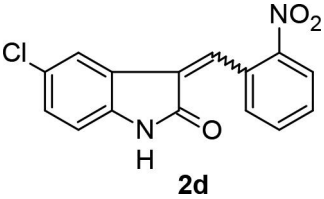
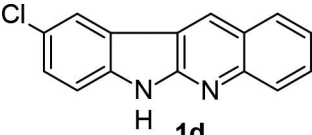
General procedure for aldol product **2a–d**: in a dry 100-mL round-bottom flask, 2-oxindole **3a–b** (1 mmol), *o*-nitrobenzaldehydes **4a–c** (1.2 mmol), and EtOH (25 mL) were mixed with stirring, and piperidine (0.85 mg, 0.01 mmol) in EtOH (2 mL) was added dropwise while stirring at RT. Mixture was then refluxed with stirring for 1 h. On completion of the reaction (monitored by thin layer chromatography (TLC)), solvent was removed under vacuum and Et₂O was added, insoluble solid aldol product **2a–d** was separated out and was isolated by filtration.

3-(2-Nitrobenzylidene)indolin-2-one (geometrical isomeric mixture)^[6]; **2a**; orange solid; mp 224–226 °C. IR (KBr): 1201, 1342, 1470, 1624, 1686, 1732, 3254, 3332 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 6.14 (d, *J* = 6.8 Hz, 1H), 6.59 (s, 1H), 6.64 (t, *J* = 8.0 Hz, 1H), 6.77 (m, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.47 (m, 1H), 10.35 (s, 1H) ppm. LC-MS: *m/z* [M+H]⁺: 267.1.

General procedure for indoloquinolines **1a–d**: in a dry 100-mL round-bottom flask, aldol product **2a–d** (0.8 mmol), Fe powder (0.280 g, 5 mmol), EtOH (5 mL), AcOH (15 mL), and conc. HCl (2 mL) were mixed. Mixture was then stirred at 120 °C for 48 h. On completion of the reaction (monitored by TLC), mixture was filtered and washed with CHCl₃. Solvent was removed under vacuum. NaOH (4N) (100 mL) was added and product was extracted in CHCl₃ (50 mL × 3). Extract was dried with anhydrous sodium sulfate, filtered, and solvent was removed under vacuum to give indoloquinoline product **1a–d**.

6H-Indolo[2,3-*b*]quinoline^[5,6]; **1a**; brown solid. Mp >300 °C. ¹H NMR (DMSO-*d*₆): δ 7.27 (t, *J* = 6.8 Hz, 1H), 7.52 (m, 3H), 7.72 (t, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 9.06 (s, 1H), 11.71 (s, 1H) ppm. ¹³C NMR (DMSO-*d*₆): δ 110.9 (CH), 117.8 (Cq), 119.6 (CH), 120.2 (Cq), 121.8 (CH), 122.7 (CH), 123.6 (Cq), 126.9 (CH), 127.5 (CH), 128.2 (CH), 128.62 (CH), 128.65 (CH), 141.4 (Cq), 146.3 (Cq), 152.8 (Cq) ppm.

Table 1. Derivatives of indoloquinolines prepared using Scheme 2.

Entry	Aldol products 2 (geometrical isomeric mixture)	Isolated yield (%)	Indoloquinolines 1	Isolated yield (%)	Overall yield over 2 steps (%)
1		91		86	78.3
2		89		82	73.0
3		88		84	73.9
4		90		84	75.6

Conclusion

In conclusion, a two-step efficient method is developed for the synthesis of indoloquinolines through aldol reaction using commercially available starting materials. The method is optimized to achieve affordable overall yields and avoiding chromatography purification. The general utility of this method is demonstrated by preparing several derivatives of indoloquinolines with desirable aromatic substitutions on indole as well as quinoline ring.

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References

- [1] (a) Majumdar, P.; Pati, A.; Patra, M.; Behera, R. K.; Behera, A. K. *Chem. Rev.* **2014**, *114*, 2942–2977; (b) Singh, I. P.; Bodiwala, H. S. *Nat. Prod. Rep.* **2010**, *27*, 1781–1800; (c) Dumitrascu, F.; Popa, M. M. *Arkivoc* **2014**, *i*, 428–452; (d) Bracca, A. B. J.; Heredia, D. A.;

- Larghi, E. L.; Kaufman, T. S. *Eur. J. Org. Chem.* **2014**, 36, 7979–8003; (e) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, 18, 6620–6662; (f) Volla, C. M. R.; Atodiressei, I.; Rueping, M. *Chem. Rev.* **2014**, 114, 2390–2431; (g) Gawande, M. B.; Bonifacio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, 42, 5522–5551.
- [2] Subbaraju, G. V.; Kavitha, J.; Rajasekhar, D.; Jimenez, J. I. *J. Nat. Prod.* **2004**, 67, 461–462.
- [3] (a) Parvatkar, P. T.; Ajay, A. K.; Bhat, M. K.; Parameswaran, P. S.; Tilve, S. G. *Med. Chem. Res.* **2013**, 22, 88–93; (b) Li, M. Y.; Xu, H. W.; Fan, W.; Ye, Q.; Wang, X.; Jiang, B.; Wang, S. L.; Tu, S. J. *Tetrahedron* **2014**, 70, 1004–1010.
- [4] (a) Mei, Z. W.; Wang, L.; Lu, W. J.; Pang, C. Q.; Maeda, T.; Peng, W.; Kaiser, M.; Sayed, I. E.; Inokuchi, T. *J. Med. Chem.* **2013**, 56, 1431–1442; (b) Sayed, I. E.; Veken, P. V.; Steert, K.; Dhooche, L.; Hostyn, S.; Baelen, G. V.; Lemiere, G.; Maes, B. U. W.; Cos, P.; Maes, L.; Joossens, J.; Haemers, A.; Pieters, L.; Augustyns, K. *J. Med. Chem.* **2009**, 52, 2979–2988.
- [5] (a) Kadam, H. K.; Parvatkar, P. T.; Tilve, S. G. *Synthesis* **2012**, 44, 1339–1342; (b) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Curr. Org. Chem.* **2011**, 15, 1036–1057; (c) Volvoikar, P. S.; Parvatkar, P. T.; Tilve, S. G. *Eur. J. Org. Chem.* **2013**, 2013, 2172–2178; (d) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, 74, 8369–8372; (e) Pitchai, P.; Sathiyaseelan, M.; Nepalraj, A.; Gengan, R. M. *Indian J. Chem.* **2015**, 54B, 1290–1292; (f) Volvoikar, P. S.; Tilve, S. G. *Org. Lett.* **2016**, 18, 892–895; (g) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2014**, 16, 3138–3141; (h) Ghosh, P.; Purkayastha, P. *RSC Adv.* **2014**, 4, 22442–22448; (i) Parvatkar, P. T.; Majik, M. S. *RSC Adv.* **2014**, 4, 22481–22486; (j) Patteux, C.; Levacher, V.; Dupas, G. *Org. Lett.* **2003**, 5, 3061–3063.
- [6] (a) Parvatkar, P. T.; Tilve, S. G. *Tetrahedron Lett.* **2011**, 52, 6594–6596; (b) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Tetrahedron Lett.* **2007**, 48, 7870–7872.
- [7] (a) Luque, P. V.; Alajarín, R.; Builla, J. A.; Vaquero, J. J. *Org. Lett.* **2006**, 8, 415–418 (b) Engqvist, R.; Bergman, J. *Org. Prep. Proc. Int.* **2004**, 36, 386–390; (c) Vaghei, R. G.; Malaekhepoor, S. M. *Tetrahedron Lett.* **2012**, 53, 4751–4753; (d) Borsche, W.; Wagner-Roemmich, M.; Barthenheier, J. *Justus Liebigs Annalen der Chemie* **1942**, 550, 160–174.
- [8] (a) Kadam, H. K.; Tilve, S. G. *J. Heterocyclic Chem.* **2016**, 53, 2066–2069; (b) Parvatkar, P. T.; Majik, M. S. *RSC Adv.* **2014**, 4, 22481–22486; (c) Hu, Y.; Kang, H.; Zeng, B. W.; Wei, P.; Huang, H. *J. Chem. Res.* **2008**, 11, 642–643; (d) Suthar, S. K.; Bansal, S.; Alam, M. M.; Jaiswal, V.; Tiwari, A.; Chaudhary, A.; Alex, A. T.; Joseph, A. *Bioorg. Med. Chem. Lett.* **2015**, 25, 5281–5285; (e) Ankati, H.; Akubathini, S. K.; Kamila, S.; Mukherjee, C.; D’Mello, S. R.; Biehl, E. R. *Open Org. Chem. J.* **2009**, 3, 1–10; (f) Wang, G.; Liu, X.; Huang, T.; Kuang, Y.; Lin, L.; Feng, X. *Org. Lett.* **2013**, 15, 76–79.