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An efficient new route towards biologically active isocryptolepine and γ-carboline derivatives using an intramolecular thermal electrocyclization strategy

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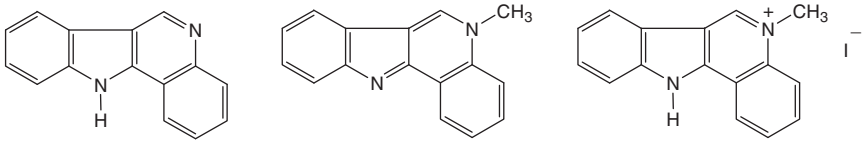
ABSTRACT

An efficient and short route is established for biologically active 11*H*-indolo[3,2-*c*]quinoline **1**, naturally occurring antiplasmodial isocryptolepine **2** and 5-methyl-11*H*-indolo[3,2-*c*]quinoline-5-inium iodide **3** using intramolecular thermal electrocyclization strategy.

Recent years have witnessed an increased interest in the total synthesis of various types of heteroaromatic alkaloids, mainly due to their potential in medical treatment. Many naturally occurring alkaloids having indole skeleton are of great importance since they possess interesting biological activities. The roots of the west African plant *Cryptolepis sanguinolenta* has been traditionally used to treat a variety of health disorders, including malaria, rheumatism, urinary tract infections and other diseases.[1,2] The linear indoloquinoline alkaloid isocryptolepine (also called as cryptosanguinolentine) was isolated[3] from this plant in 1996.

Isocryptolepine has remained an interesting synthetic target owing to its various biological activities including antimalarial, intestinal disorder, rheuma, antiplasmodial activity and cytotoxic activity. Isocryptolepine **2** and γ-carboline derivatives **1** and **3** are potential anticancer agents and show DNA binding and cytostatic activity (Fig. 1).

The synthesis of compound **2** has been carried out using various methods starting from *N*-tosylaniline,[4] palladium(0)-catalysed couplings of 2-tributylstannyl *N*-protected indoles,[5] from 2-chloroquinoline,[6] using a Fischer indole cyclization,[7] from 1-benzenesulfonylindole-2,3-dicarboxylic anhydride,[8] using a modified Pictet–Spengler reaction,[9] by an intramolecular Wittig reaction[10] etc. However, most of the existing protocols involve use of costly starting materials or reagents, multiple synthetic steps, longer reaction time and harsh reaction conditions with a moderate yield of the product. Present work demonstrates the use of intramolecular



11*H*-Indolo[3,2-c] quinoline (**1**) Isocryptolepine (**2**) 5-methyl- 11*H*-indolo[3,2-c] quinolin-5-inium iodide (**3**)

Figure 1. Biologically active γ-carboline derivatives.

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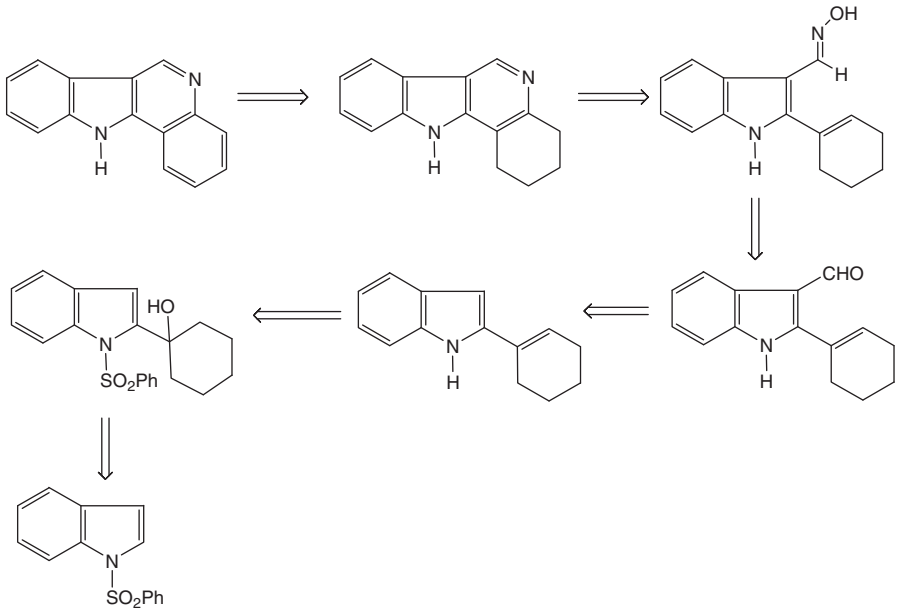
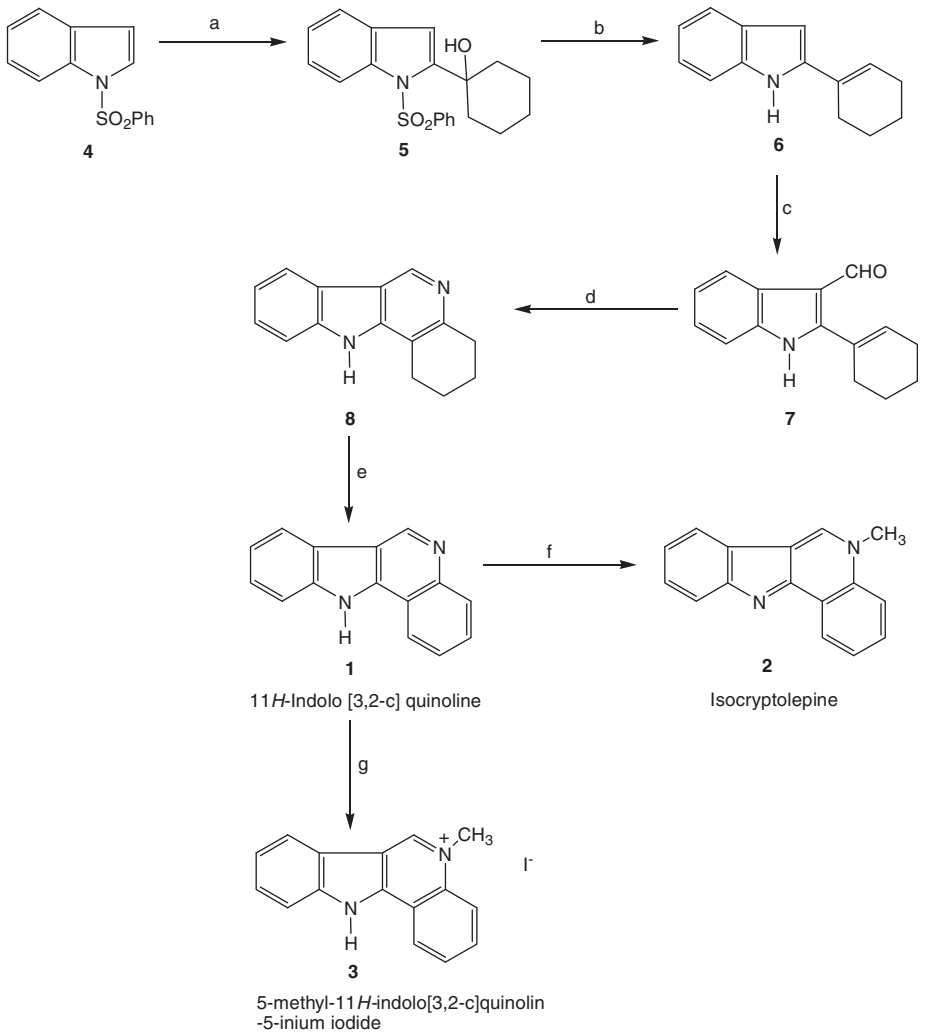


Scheme 1. Retro synthetic approach.



Scheme 2. Reagent and conditions: (a) LDA, THF, −78 °C, cyclohexanone, 4 h, 86%; (b) TBAF, THF, reflux, 2 h, 84%; (c) DMF/ $POCl_3$, rt, 1 h, 88%; (d) NH_2OH/HCl, sodium acetate, dioxane, reflux, 24 h, 78%; (e) Pd/C, *o*-dichlorobenzene, reflux, 20 h, 88%; (f) CH_3I, DMF, 80 °C, 1 h, Na_2CO_3, 85%; (g) CH_3I, acetonitrile, rt, 24 h, 92%.

thermal electrocyclization reaction for the synthesis of 11*H*-indolo[3,2-*c*]quinoline **1**, isocryptolepine **2** and 5-methyl-11*H*-indolo[3,2-*c*]quinolin-5-inium iodide **3**.The retro synthetic analysis is shown in Scheme 1.

Thus, 1-phenylsulfonylindole **4** (Scheme 2) on treatment with LDA and reaction with cyclohexanone furnished alcohol **5**. Further deprotection and dehydration was carried out using sodium methoxide which gave a very poor yield of product **6**. Tetrabutylammonium fluoride (TBAF) being a good reagent for similar deprotection[11] reactions, it was thought to carry out first deprotection using TBAF and then dehydration. Thus, compound **5** was treated with TBAF, in THF under reflux for 2 h to get a solid product in 84% yield. It showed the absence of –OH in IR and ^{1}H NMR and the presence of one olefinic triplet at 6.04 in ^{1}H NMR.

However, the spectral data were not consistent with the expected deprotected product, indicating structure **6** might be resulting from the tandem deprotection and dehydration reactions during the treatment with TBAF. Similar one step deprotection and dehydration is not reported earlier using TBAF. The yield in this reaction was very high (84%) as compared to the yield using sodium methoxide[12] (48%, 14 h reflux). Thus TBAF was shown to be a good reagent for this one-pot reaction. Vilsmeyer Haack formylation of compound **6** produced 2-(l-cyclohexenyl)-3-formylindole **7** in 88% yield.[13]

Further, oximination of **7** with hydroxylamine hydrochloride and refluxing in dioxane furnished an unreported product **8** which showed the absence of aldehydic proton and a downfield singlet at 11.50 in ^{1}H NMR. Four alicyclic methylene carbons were identified in ^{13}C NMR spectrum and confirmed by DEPT experiment.[14] Formation of **8** can be explained by initial formation of oxime and subsequent thermal intramolecular electrocyclisation. Further dehydrogenation of **8** using Pd/C in *o*-dichlorobenzene afforded compound **1** in good yield.[15] Naturally occurring isocryptolepine **2** was resulted in the overall yield of 37% by treatment of **1** with methyl iodide and sodium carbonate.[6] Compound **3** was obtained by treatment of **1** with methyl iodide in acetonitrile for 24 h stirring.[16] Spectral data[17,18] were consistent with those of the reported compounds **2** and **3**.

In summary, a new method having a key step of thermal intramolecular electrocyclisation was established for the synthesis of 11*H*-indolo[3,2-*c*]quinoline **1,** isocryptolepine **2** and its biologically active derivative, 5-methyl-11*H*-indolo[3,2-*c*]quinolin-5-inium iodide **3**.

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13. *Compound* **7**: White crystals; yield, 88%; mp 210–212 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 1.7 (m, 5H), 2.25 (m, 3H), 6.18 (br s, 1H), 7.15 (m, 2H), 7.35 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 7.2 Hz, 1H), 9.91 (s, 1H), 11.66 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 19.90, 20.65, 24.04, 26.34, 109.98, 111.92, 119.49, 120.35, 121.59, 124.18, 126.26, 133.00, 133.96, 150.60, 183.80.; GC–MS (DIP): 225(M^+); calcd for $C_{15}H_{15}NO$: C, 80.0, H, 6.66, N, 6.22; Found: C, 80.10, H, 6.72, N, 6.44.
14. *Experimental procedure for the preparation of compound* ***8:*** A mixture of 2-(1-cyclohexenyl)-3-formylindole **7** (0.225 g, 1 mmol), hydroxylamine hydrochloride (0.139 g, 2 mmol), and sodium acetate (0.164 g, 2 mmol) in 10 mL dioxane was refluxed under stirring for 24 h and the reaction was quenched by the 20 mL of water. The product was extracted with ethyl acetate (20 mL × 3) and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography($CHCl_3$/MeOH 9.8:0.2), gave compound **8** as a yellow solid, Yield, 78%; mp 280–282 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.88 (m, 4H), 2.92 (m, 4H), 7.21 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 8.14(d, J = 7.6 Hz, 1H), 9.04 (s, 1H), 11.50 (s, 1H, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.90, 22.90, 23.49, 32.02, 111.34, 114.08, 119.74, 120.24, 121.28, 125.75, 139.46, 139.72, 143.24, 151.08.; GC–MS (DIP) 222(M^+); calcd for $C_{15}H_{14}N_2$ C, 81.08, H, 6.30, N, 12.62; Found C, 81.10, H, 6.42, N, 12.50.
15. *Compound* ***1***: 11*H*-Indolo [3,2-*c*] quinoline; yield, 88%; mp 280 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.36 (t, J = 8 Hz, 1H), 7.50 (m, 1H), 7.74 (m, 3H), 8.12 (d, J = 8.2 Hz, 1H), 8.32(d, J = . 7.6 Hz, 1H), 8.52(d, J = 8.2 Hz,1H), 9.6 (s, 1H), 12.75(s, 1H); IR (Nujol): ν 1427, 3422 cm^{-1}; GC–MS (DIP) = 218(M^+); calcd for $C_{15}H_{10}N_{2:}$ C, 82.56, H, 4.58, N, 12.84; Found C, 82.14, H, 4.72, N, 12.76.
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17. *Compound* ***2***: Isocryptolepine (5-methyl-5*H*-indolo[3,2-*c*] quinoline); yellow solid; yield, 85%; mp 192–193 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.22 (s, 3H), 7.24 (t, J = 7.1 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H), 7.77–7.82 (m, 2H), 8.02 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 7.4 Hz, 1H), 8.76 (d, J = 7.6 Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 42.70, 116.16, 118.0, 118.18, 120.0, 120.52, 120.69, 124.36, 125.38, 125.92, 126.09, 130.04, 135.78, 139.04, 152.14, 153.20; IR (Nujol): ν 2940, 3047, 1616, 1636, 1596 cm^{-1}; GC–MS (DIP) = 232(M^+); calcd for $C_{16}H_{12}N_{2:}$ C, 82.73, H, 5.21, N, 12.06; Found C, 82.83, H, 5.34, N, 12.16.
18. *Compound* ***3***: 5-methyl-11*H*-indolo[3,2-*c*]quinolin-5-inium iodide; cream colour solid; yield, 92%; mp 298–299 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.58 (s, 3H), 7.58 (t, J = 7.8 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 8.09 (t, J = 7.8 Hz, 1H), 8.19 (t, J = 8.5 Hz, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.49(d, J = 8.5 Hz, 1H), 8.84(d, J = 7.8 Hz, 1H), 10.24 (s, 1H), 14.08 (br s, 1H); IR (Nujol): ν 3450 cm^{-1}; calcd for $C_{16}H_{13}IN_{2:}$ C, 53.35, H, 3.64, N, 7.78; Found C, 53.62, H, 3.52, N, 7.90.