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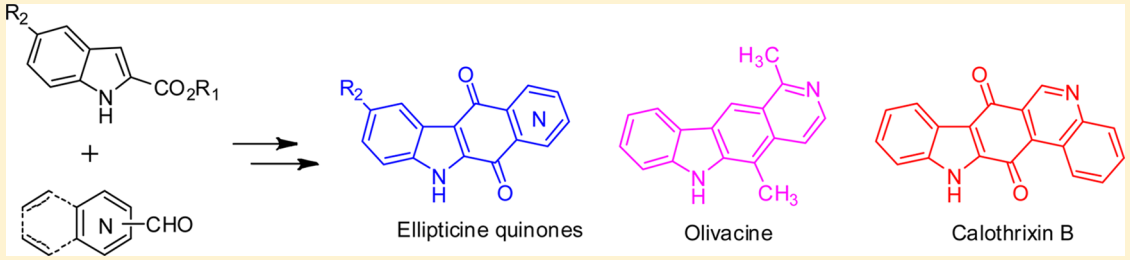
Total Synthesis of Ellipticine Quinones, Olivacine, and Calothrixin B

Nagarajan Ramkumar and Rajagopal Nagarajan*

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

Supporting Information



ABSTRACT: A direct route to the synthesis of biologically active ellipticine quinones, olivacine, and calothrixin B is described. The prominent key steps involved are Friedel–Crafts hydroxyalkylation followed by oxidation and directed *ortho*-lithiation reactions of readily available indole-2-carboxylate esters with appropriately substituted pyridine and quinoline carboxaldehydes.

INTRODUCTION

Several natural and synthetic heterocyclic quinones have important biological activities such as antitumoral, antiprotozoan, and antibiotic activities.[1] Many of these molecules possess antineoplastic chemotherapeutic properties.[2] Quinones are a class of compounds found in many drugs that are used in the clinical therapy of solid tumors.[3] Among them, carbazolequinone alkaloids (Figure 1) display notable biological properties such as cardiotonic, antituberclosis, and neutronal cell-protecting activities.[4] Pyrido and quinolinocarbazole alkaloids (Figure 1) are well-known for their wide range of potent biological activities.[5] Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole)[6] **3** and 9-methoxyellipticine **4** were isolated from the leaves of *Ochrosia elliptica* Labill by Goodwin et al. in 1959. The biological activity of ellipticine was considered to be based mainly on DNA intercalation and topoisomerase II inhibition.[7] The first clinical success of celiptium **7** led to extensive studies into the synthesis of ellipticinium derivatives, and several of these progressed to clinical trials.[8] Since the commercialization of some ellipticine derivatives and their successful clinical uses prompted tremendous development in the chemistry and biology of pyridocarbazole alkaloids.[7,8] Olivacine **8** was isolated from different members of the Apocynaceae family,[9] and limited reports are available for its synthesis.[10] The synthesis and biological activity of ellipticine and its congeners have been covered by several comprehensive reviews.[11]

Ellipticine quinone[12] **15** is a pivotal synthetic intermediate in the early Gribble syntheses of ellipticines that shows activity against antitumors.[13] The only known quinolino[4,3-*b*]-carbazole alkaloid, calothrixin B **10** (7*H*-indolo[3,2-*j*]-phenanthridine-7,13(12*H*)-dione), was first obtained from a blue-green algae *Calothrix* cyanobacteria by Rickards group in 1999.[14] It is a pentacyclic quinone that exhibits antimalarial activity as well as activity against human HeLa cancer cells and inhibition of RNA polymerase.[15] Several recent publications have highlighted the synthesis and biological activities of calothrixin B.[16]

Friedel–Crafts hydroxyalkylation reaction of aromatic compounds with carbonyl compounds is one of the best methods for the synthesis of pyridyl aryl/heteroaryl carbinols and their derivatives.[17] Directed *ortho*-metalation (DoM) reaction is widely used in modern organic synthesis of natural products.[18] In this paper, we explored the utility of these reactions in synthesizing biologically important heterocyclic quinones such as ellipticine quinones, calothrixin B, and further few steps to olivacine.

RESULTS AND DISCUSSION

The synthesis of ellipticine quinone **15** is summarized in Scheme 1. After several screening conditions, we treated commercially available ethyl 1*H*-indole-2-carboxylate **11** with pyridine-3-carboxaldehyde **12** in presence of 1.1 equiv of $AlCl_3$ at 0 °C to room temperature followed by oxidation using 1.2 equiv of IBX in DMSO, giving ketone **14** in 94% yield. The carbinol formed **13** was not isolated from the reaction mixture, and subsequently we carried out oxidation after the reaction work up. The ketone **14** was then subjected to directed *o*-lithiation reaction using 5 equiv of LiTMP (lithium tetramethylpiperidide) as a base to afford a single regioisomer **15** in 72% yield. Thus, ellipticine quinone **15** was obtained in 3 steps and 67.6% overall yield.

Also, we tested the stability of ester groups present in the indole moiety by introducing methyl and *t*-butyl groups in Scheme 2. Because of the high mobility of *t*-butyl group, we obtained **20** as acid under Friedel–Crafts hydroxyalkylation reaction. The acid **20** was directly converted into **15** by LiTMP in 43% yield. Thus, we synthesized 9-methoxy ellipticine

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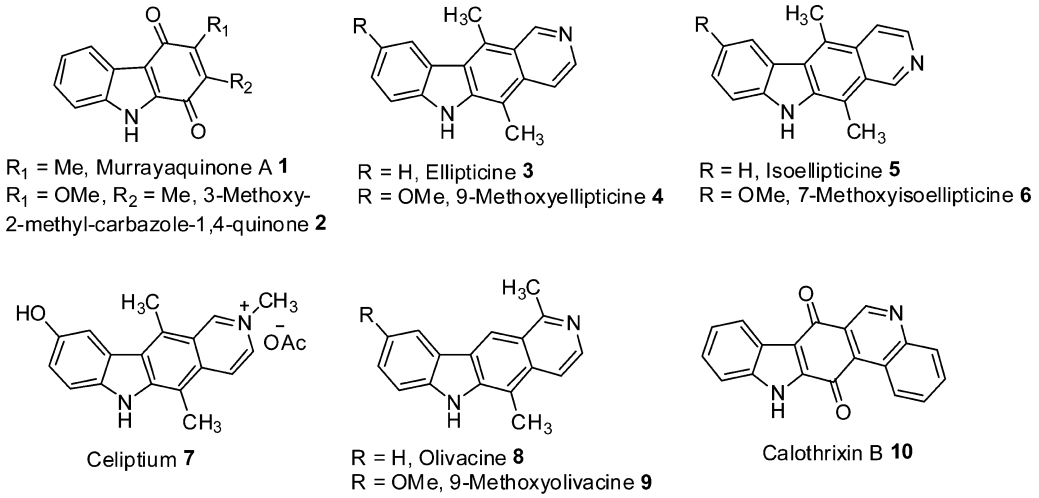
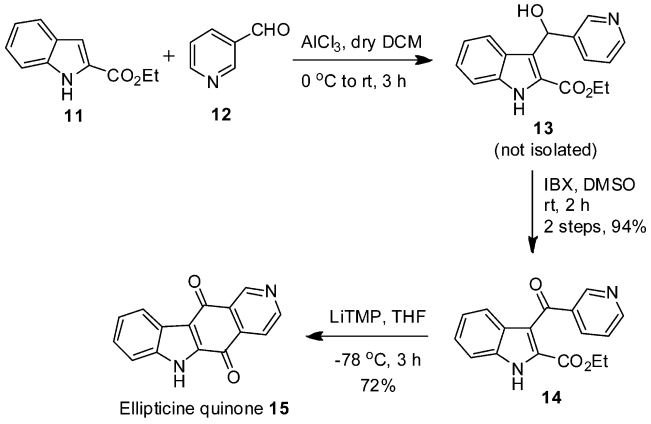


Figure 1. Examples of carbazolequinone, pyrido, and quinolinocarbazole alkaloids.

Scheme 1. Synthesis of Ellipticine Quinone (15)



quinone **22**, which can be considered as a key intermediate in synthesizing 9-methoxyellipticine **4**.

By employing our route, isoellipticines **5** and **6** can also be prepared, which are the known isomeric structures of ellipticines. Hence, isoellipticine quinones **26** and **27** can be obtained by varying pyridine part **23** as shown in Scheme 3. Also the other isomer of ellipticine quinone **30** was synthesized by using pyridine-2-carboxaldehyde **28**. The ketones obtained **19**, **25**, and **29** were confirmed by a single crystal XRD (see Supporting Information).

We have successfully applied our synthetic route to the synthesis of olivacine **8** and calothrixin B **10**. In both cases, we surprisingly observed the formation of bisindolylmethane derivatives under Lewis acid conditions, and one of the derivative **32** (confirmed by a single crystal XRD, see Supporting Information) was isolated as indicated in Scheme 4.

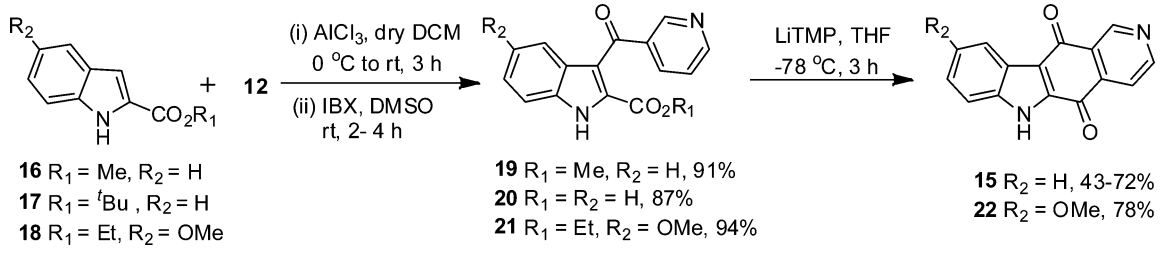
Therefore, we switched to base-mediated reaction to form indolyl/pyridyl or quinolyl methanols.[18] Treatment of **11** with 2-methylnicotinaldehyde **31** in the presence of 1.5 equiv of 1,1,3,3,-tetramethylguanidine (TMG) in MeOH at room temperature for 8 h followed by oxidation using IBX afforded the ketone **33** in 84% yield. Wolff–Kishner reduction of the ketone **33** gave reduced compound **34**. The cyclized compound **35** was obtained by treating **34** with LDA/HMPA at −78 °C for 3 h. Finally, the addition of MeMgI into **35** followed by treatment upon $NaBH_4/AlCl_3$ (3:1) in dry THF at room temperature for 3 h produced **8** in 58% yield. Thus, olivacine **8** was obtained in 6 steps and 15.6% overall yield as shown in Scheme 4.

The synthesis of calothrixin B **10** is outlined in Scheme 5. The reaction of **11** with quinoline-3-carboxaldehyde **36** in the presence of 1.5 equiv of TMG in MeOH followed by oxidation with 1.5 equiv of Dess–Martin periodinane (DMP) in DCM/AcOH (9:1) at room temperature for 6 h gave the ketone **37** in 80% yield. Then intramolecular directed *o*-lithiation reaction of **37** in the presence of LiTMP afforded **10** in 48% yield. Thus, calothrixin B **10** was obtained in three steps and 38.4% overall yield.

■ CONCLUSIONS

In summary, we demonstrated a novel and concise total synthesis of biologically important ellipticine quinone and calothrixin B in three-step sequences of 67 and 38% good overall yields, respectively. Also, we have extended this route to the synthesis of olivacine in 16% overall yield over 6 steps. It is

Scheme 2. Stability of Indole-2-carboxylate Esters and Synthesis of 9-Methoxyellipticine Quinone (22)



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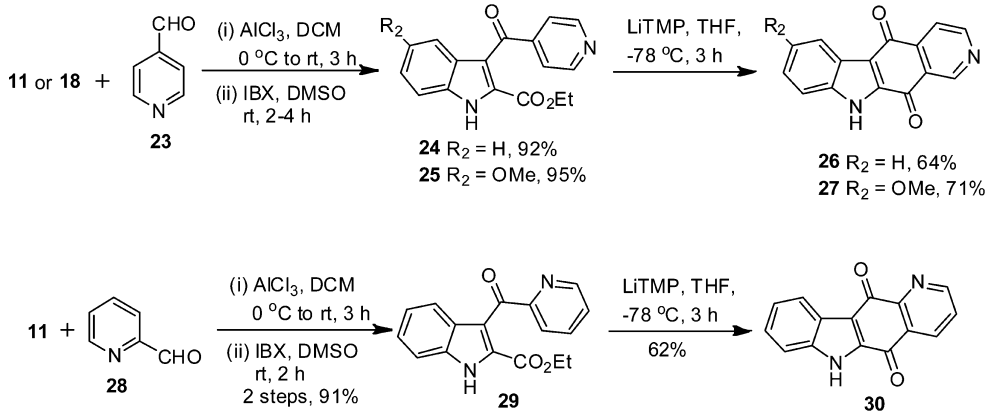
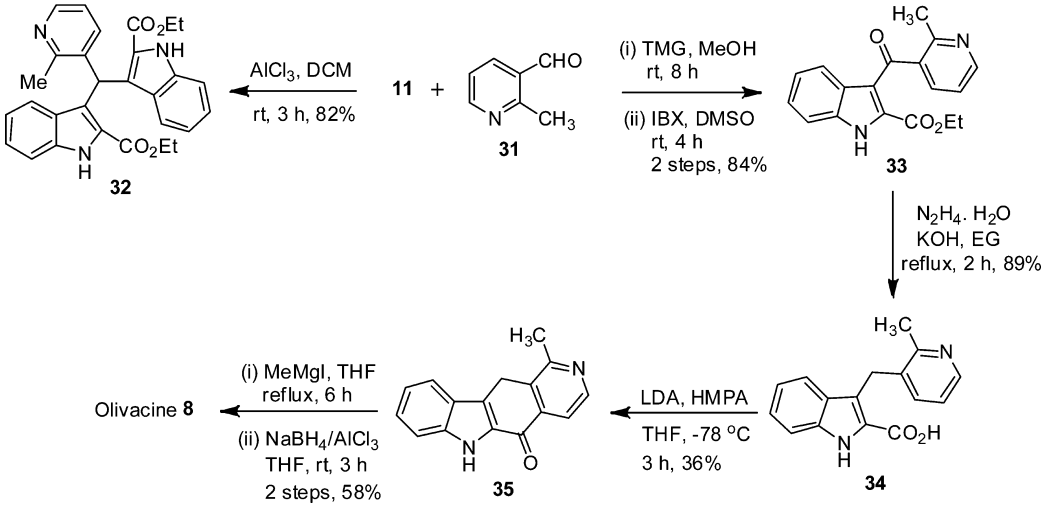
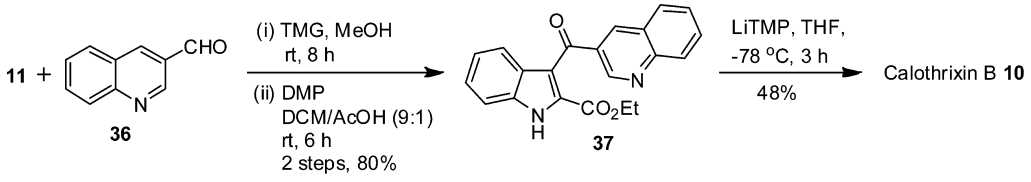
Scheme 3. Synthesis of Isomeric Ellipticine Quinones



Scheme 4. Synthesis of Olivacine 8



Scheme 5. Synthesis of Calothrixin B 10



worth mentioning that our synthetic approach for these compounds is superior to that of previously reported methods in terms of availability of starting materials, overall yields, and the number of steps used. We are screening suitable reagents to convert ellipticine quinones into ellipticines, and these results will be reported in due course.

EXPERIMENTAL SECTION

General Information and Materials. The NMR experiments were performed with 400 or 500 MHz spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Coupling constant J values are given in Hz. IR spectra were recorded by using KBr pellets or neat. ESI-TOF mass analyzer type was used for the HRMS measurements. Reactions were carried out under an inert atmosphere, referring to the use of nitrogen, and monitored by TLC. Column chromatography was performed on silica gel (100−200 mesh) in glass columns to purify the compounds. Solvents tetrahydrofuran (THF), methanol, and dichloromethane were dried by using standard distillation methods. Commercially available reagents and solvents were used without further purification and were purchased. Melting points were determined using open capillary tubes and are uncorrected.

General Procedure for the Synthesis of Ketones 14, 19−21, 24, 25, and 29. To the solution of desired indole carboxylate ester (1 mmol) in dry DCM (20 mL) was added anhydrous $AlCl_3$ (1.1 mmol), and the mixture was stirred at room temperature for 30 min under nitrogen atomsphere. Appropriate pyridine carboxaldehyde (1 mmol) was added to the mixture at 0 °C, which was brought back to room temperature and stirred for 2−4 h. The completion of the reaction was monitored by TLC. The mixture was then quenched with ice cold water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give solid material. The solid obtained was dissolved in DMSO (7 mL) followed by the addition of IBX (1.2 mmol). The reaction mixture was then stirred at room temperature for 2−4 h. After completion of reaction, ice cold water (75 mL) was added to the mixture. The aqueous layer was extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. After the removal of the solvent, the

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crude compound was purified by silica gel column chromatography using hexanes/ethyl acetate as eluent to afford the title compounds.

Ethyl 3-nicotinoyl-1*H*-indole-2-carboxylate (14). R_f = 0.41 (hexanes:EtOAc, 4:6); light yellow solid (146 mg, 94%): mp 152−154 °C; IR (KBr) 3418, 2854, 1653, 1545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, br, 1H), 9.03 (s, 1H), 8.79 (d, J = 3.2 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.46−7.38 (m, 2H), 7.27−7.23 (m, 1H), 4.07 (q, J = 7.2 Hz, 2H), 0.90 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 160.8, 152.8, 150.8, 136.4, 135.6, 135.1, 127.3, 127.0, 126.4, 123.4, 122.7, 121.9, 118.7, 112.1, 61.7, 13.5; HRMS (ESI) $[M + H]^+$ calcd for $C_{17}H_{14}N_2O_3$ 295.1083, found 295.1085.

Methyl 3-nicotinoyl-1*H*-indole-2-carboxylate (19). R_f = 0.40 (hexanes:EtOAc, 3:7); light yellow solid (145 mg, 91%): mp 156−158 °C; IR (KBr) 3426, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, br, 1H), 9.03 (s, 1H), 8.81 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.46−7.41 (m, 2H), 7.28−7.25 (m, 1H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 161.0, 152.8, 150.6, 136.3, 135.5, 134.9, 127.2, 126.8, 126.5, 123.4, 122.8, 121.9, 119.1, 112.1, 52.3; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{12}N_2O_3$ 281.0927, found 281.0929.

3-Nicotinoyl-1*H*-indole-2-carboxylic acid (20). R_f = 0.66 (hexanes:EtOAc, 5:5); yellow solid (106 mg, 87%): mp 182−184 °C; IR (KBr) 3415, 1672, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 8.98 (s, br, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.64−7.55 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.39−7.35 (m, 2H), 7.27 (m, 1H), 7.20−7.11 (m, 2H); note −COO***H*** not observed; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 190.9, 163.4, 152.7, 150.7, 137.1, 137.0, 135.8, 128.3, 127.0, 124.2, 123.1, 121.8, 119.9, 112.3, 107.6; HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{10}N_2O_3$ 267.0770, found 267.0767.

Ethyl 5-methoxy-3-nicotinoyl-1*H*-indole-2-carboxylate (21). R_f = 0.50 (hexanes:EtOAc, 4:6); bright yellow solid (139 mg, 94%): mp 188−190 °C; IR (KBr) 3382, 1678, 1338, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, br, 1H), 9.04 (d, J = 1.2 Hz, 1H), 8.80−8.79 (m, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.46−7.42 (m, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.05−7.02 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 160.8, 156.3, 152.5, 150.6, 136.4, 135.6, 131.0, 128.1, 127.9, 123.4, 118.5, 117.9, 113.2, 101.3, 61.6, 55.6, 13.4; HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{16}N_2O_4$ 325.1189, found 325.1188.

Ethyl 3-isonicotinoyl-1*H*-indole-2-carboxylate (24). R_f = 0.48 (hexanes:EtOAc, 3:7); pale yellow solid (143 mg, 92%): mp 182−184 °C; IR (KBr) 3387, 1645, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, br, 1H), 8.51 (d, J = 4.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.41−7.40 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.15−7.11 (m, 1H), 7.01−6.97 (m, 1H), 3.75 (q, J = 7.2 Hz, 2H), 0.62 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 160.8, 150.3 (2C), 146.1, 135.6, 127.5, 127.3, 126.4, 122.8, 122.3 (2C), 121.9, 118.0, 112.1, 61.7, 13.4; HRMS (ESI) $[M + H]^+$ calcd for $C_{17}H_{14}N_2O_3$ 295.1083, found 295.1082.

Ethyl 3-isonicotinoyl-5-methoxy-1*H*-indole-2-carboxylate (25). R_f = 0.50 (hexanes:EtOAc, 5:5); bright yellow solid (140 mg, 95%): mp 180−182 °C; IR (KBr) 3383, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, br, 1H), 8.82 (s, 2H), 8.04−7.97 (m, 1H), 7.70 (d, J = 4.0 Hz, 2H), 7.42 (d, J = 7.2 Hz, 1H), 7.10−7.07 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 160.7, 156.6, 149.8 (2C), 147.0, 141.5, 132.8, 130.7, 128.2, 127.9, 122.5, 118.7 (2C), 113.1, 61.8, 55.6, 13.4; HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{16}N_2O_4$ 325.1189, found 325.1188.

Ethyl 3-picolinoyl-1*H*-indole-2-carboxylate (29). R_f = 0.53 (hexanes:EtOAc, 6:4); yellow solid (141 mg, 91%): mp 160−162 °C; IR (KBr) 3378, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, br, 1H), 8.63−8.62 (m, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.95−7.89 (m, 2H), 7.47−7.41 (m, 2H), 7.35−7.31 (m, 1H), 7.23 (d, J = 8.0 Hz, 1H), 3.96 (q, J = 7.2 Hz, 2H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 161.3, 156.2, 148.6, 136.9, 135.4, 129.0, 127.6, 126.2, 125.8, 123.2, 122.6, 122.1, 117.4, 111.9, 61.4, 13.5; HRMS (ESI) $[M + H]^+$ calcd for $C_{17}H_{14}N_2O_3$ 295.1083, found 295.1085.

General Procedure for the Synthesis of Ellipticine Quinones and Its Isomers. A schlenck tube was charged with tetramethylpiperidine (5 mmol) in dry THF and sealed by rubber septum. 1.6 M *n*-BuLi in hexanes (10 mmol) was added to it under nitrogen atmosphere at −78 °C and stirred for 15 min. The respective ketone (1 mmol) in dry THF was added to the mixture at the same temperature and stirred for 2−3 h. After completion of the reaction, the mixture was poured into saturated aqueous solution of NH_4Cl (30 mL). The whole solution was then extracted with ethyl acetate (3 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude material was purified by silica gel column chromatography using ethyl acetate/hexanes as eluent.

5*H*-Pyrido[4,3-*b*]carbazole-5,11(6*H*)-dione (Ellipticine Quinone) (15). R_f = 0.53 (hexanes:EtOAc, 6:4); red solid (60 mg, 72%): mp >300 °C; IR (KBr) 3387, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 12.54 (s, br, 1H), 9.30 (s, 1H), 8.89 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 4.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 6.8 Hz, 1H), 7.29−7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 181.2, 180.4, 154.4, 148.0, 146.8, 136.4, 134.3, 131.9, 127.6, 127.4, 125.1, 124.2, 123.3, 118.1, 113.7; HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_8N_2O_2$ 249.0665, found 249.0664.

9-Methoxy-5*H*-pyrido[4,3-*b*]carbazole-5,11(6*H*)-dione (22). R_f = 0.46 (hexanes:EtOAc, 6:4); orange red solid (66 mg, 78%): mp >300 °C; IR (KBr) 3356, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 12.53 (s, br, 1H), 9.06 (s, 1H), 8.67 (d, J = 4.4 Hz, 1H), 7.60 (d, J = 4.8 Hz, 1H), 7.37 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 3.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$+DMSO-d_6) δ 187.0, 185.8, 155.2, 154.3, 149.7, 147.5, 136.3, 135.9, 130.9, 126.9, 123.1, 119.1, 117.0, 114.7, 113.9, 54.8; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{10}N_2O_3$ 279.0769, found 279.0768.

5*H*-Pyrido[3,4-*b*]carbazole-5,11(10*H*)-dione (26). R_f = 0.51 (hexanes:EtOAc, 5:5); red solid (57 mg, 64%): mp >300 °C; IR (KBr) 3396, 1665 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, br, 1H), 9.34 (s, 1H), 9.07 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 5.2 Hz, 1H), 7.65 (m, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 178.0, 176.2, 159.6, 154.4, 149.2, 137.4, 135.6, 129.6, 128.3, 126.1, 123.1, 122.9, 121.5, 118.0, 112.8; HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_8N_2O_2$ 249.0665, found 249.0658.

7-Methoxy-5*H*-pyrido[3,4-*b*]carbazole-5,11(10*H*)-dione (27). R_f = 0.44 (hexanes:EtOAc, 6:4); orange red solid (61 mg, 71%): mp >300 °C; IR (KBr) 3383, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 12.87 (s, br, 1H), 9.39 (s, 1H), 9.02 (d, J = 5.2 Hz, 1H), 7.94 (d, J = 4.8 Hz, 1H), 7.71−7.57 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 175.6, 174.3, 155.2, 152.3, 149.7, 147.5, 135.9, 130.9, 126.9, 126.5, 123.1, 119.1, 117.0, 114.7, 113.9, 55.1; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{10}N_2O_3$ 279.0769, found 279.0768.

5*H*-Pyrido[3,2-*b*]carbazole-5,11(6*H*)-dione (30). R_f = 0.48 (hexanes:EtOAc, 6:4); red solid (52 mg, 62%): mp >300 °C; IR (KBr) 3411, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 12.27 (s, br, 1H), 9.04 (d, J = 4.8 Hz, 1H), 8.75 (d, J = 6.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 4.8 Hz, 1H), 7.63−7.61 (m, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 180.0, 178.6, 157.1, 149.6, 137.8, 136.3, 129.9, 128.5, 127.1, 126.8, 124.1, 123.5, 123.0, 118.3, 112.8; HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_8N_2O_2$ 249.0665, found 249.0661.

Synthesis of Diethyl 3,3′-((2-methylpyridin-3-yl)methylene)-bis(1*H*-indole-2-carboxylate) (32). To a solution of **11** (1 mmol) in dry DCM (20 mL) was added anhydrous $AlCl_3$ (1.1 mmol), and the mixture was stirred for 30 min at room temperature under nitrogen atmosphere. 2-Methylnicotinaldehyde **31** (1 mmol) in dry DCM (10 mL) was added to the mixture and stirred for 2 h at room temperature. After completion of the reaction, ice cold water was added, extracted with ethyl acetate (3 × 50 mL), and dried over anhydrous Na_2SO_4. The solvent was removed, and crude material was purified by column

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chromatography to afford the title compound. R_f = 0.33 (hexanes:EtOAc, 5:5); pale yellow solid (208 mg, 82%): mp 192−194 °C; IR (KBr) 3349, 1567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, br, 2H), 8.43 (d, J = 4.4 Hz, 1H), 7.45 (s, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 1H), 7.26−7.24 (m, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.04−7.01 (m, 1H), 6.85 (t, J = 7.6 Hz, 1H), 6.73−6.65 (m, 1H), 6.52 (d, J = 8.4 Hz, 1H), 4.31−4.21 (m, 4H), 2.38 (s, 3H), 1.28−1.21 (m, 6H); note aliphatic methine proton (C***H***) not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.6, 157.6, 146.8 (2C), 138.0, 136.3 (2C), 135.9, 135.7, 128.0, 127.8, 125.2, 125.0, 124.8, 124.4, 123.7, 122.3, 122.2, 121.0, 120.8 (2C), 120.3, 112.1, 111.8, 60.9, 37.8, 32.3, 14.1; HRMS (ESI) $[M + H]^+$ calcd for $C_{29}H_{27}N_3O_4$ 482.2081, found 482.2079.

Synthesis of Ethyl 3-(2-methylnicotinoyl)-1*H*-indole-2-carboxylate (33). To a solution of **11** (1 mmol) and **31** (1 mmol) in MeOH (30 mL), TMG (1.5 mmol) was added, and the mixture was stirred for 8 h at room temperature. After completion of the reaction, distilled water (100 mL) was added and extracted with ethyl acetate (3 × 60 mL). After removal of the solvent, crude material obtained was dissolved in DMSO (10 mL), and IBX was added (1.5 mmol). The whole mixture was stirred at room temperature for 4 h. The reaction was monitored by TLC. Then water (75 mL) was added, extracted with ethyl acetate (3 × 40 mL), and washed with saturated aq. NH_4Cl solution. After removal of the solvent, the crude was purified by silica gel column chromatography to give the title compound. R_f = 0.58 (hexanes:EtOAc, 6:4); pale yellow solid (683 mg, 84%): mp 162−164 °C; IR (KBr) 3381, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, br, 1H), 8.85 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.50−7.48 (m, 1H), 7.45−7.42 (m, 1H), 7.37 (t, J = 7.6 Hz, 1H), 4.05 (q, J = 7.6 Hz, 2H), 2.33 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 160.8, 157.8, 154.4, 136.4, 135.1, 131.3, 127.2, 127.1, 126.2, 123.4, 122.5, 121.7, 118.5, 112.1, 61.5, 32.4, 13.4; HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{16}N_2O_3$ 309.1240, found 309.1243.

Synthesis of 3-((2-Methylpyridin-3-yl)methyl)-1*H*-indole-2-carboxylic acid (34). To a solution of **32** (1 mmol) in 25 mL of ethylene glycol (EG), KOH (2.5 mmol) and hydrazine hydrate (3 mmol) were added. The mixture was refluxed for 2 h and diluted with water (100 mL). The aqueous layer was treated with 1 N HCl and brought up to pH 1. Then, the reaction mixture was extracted with ethyl acetate (3 × 30 mL), washed with brine, and dried over anhydrous Na_2SO_4. The crude material obtained was purified by silica gel column chromatography to afford the title compound. R_f = 0.51 (hexanes:EtOAc, 3:7); pale yellow solid (384 mg, 89%): mp 174−176 °C; IR (KBr) 3364, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, br, 1H), 8.58 (d, J = 4.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.23 (t, J = 5.2 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.05−7.00 (m, 1H), 4.20 (s, 2H), 2.36 (s, 3H); note −COO***H*** not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 154.5, 150.6, 135.6, 135.2, 131.5, 127.3, 126.3, 124.2, 123.5, 122.6, 121.8, 118.6, 112.2, 35.8, 19.8; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{14}N_2O_2$ 267.1133, found 267.1113.

Synthesis of 1-Methyl-6,11-dihydro-5*H*-pyrido[4,3-*b*]-carbazol-5-one (35). A schlenck tube was charged with freshly distilled diisopropylamine (5 mmol) in dry THF (20 mL) under nitrogen atmosphere and fitted with rubber septum. 1.6 M *n*-BuLi in hexanes (7.5 mmol) was added to it at −78 °C, followed by the addition of HMPA (2.5 mmol) and stirred for 15 min. The acid **33** (1 mmol) in dry THF (5 mL) was added to the mixture via rubber septum and maintained the same temperature for 3 h. After completion, saturated aqueous NH_4Cl solution (30 mL) was added and extracted with ethyl acetate (3 × 30 mL). The solvent was removed and purified by silica gel column chromatography to give the title compound. R_f = 0.41 (hexanes:EtOAc, 5:5); pale yellow solid (100 mg, 36%): mp 242−244 °C; IR (KBr) 3421, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, br, 1H), 8.16 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.36−7.32 (m, 1H), 7.26−7.25 (m, 2H), 7.19−7.15 (m, 1H), 3.67 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 155.1, 151.7, 147.1, 142.4, 136.9, 131.9, 127.4, 127.1, 125.4, 122.6, 120.8, 111.9, 108.8, 36.8, 20.6; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{12}N_2O$ 249.1028, found 249. 1030.

Synthesis of 1,5-Dimethyl-6*H*-pyrido[4,3-*b*]carbazole (Olivacine) (8). To a freshly prepared MeMgI (about 2−3 mmol) in dry THF (10 mL), the compound **35** (1 mmol) in dry THF (5 mL) was added at 0 °C, and after 30 min at room temperature, the solution was then refluxed for 6 h. Then, saturated aqueous NH_4Cl solution (30 mL) was added and extracted with ethyl acetate (3 × 20 mL). The organic layer was concentrated and gave a brown oil, which was again dissolved in dry THF (7 mL). To this, $NaBH_4$ (3 mmol) followed by $AlCl_3$ (1 mmol) were added and stirred for 3 h at room temperature. Then, the solution was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude was purified by silica gel column chromatography afforded the title compound. R_f = 0.43 (hexanes:EtOAc, 7:3); dark yellow solid (43 mg, 58%): mp >300 °C; IR (KBr) 3362, 1345 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, br, 1H), 8.39 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 6.4 Hz, 1H), 7.82 (d, J = 6.4 Hz, 1H), 7.54−7.52 (m, 2H), 7.26 (ddd, J = 7.6, 5.2, and 1.6 Hz, 2H), 3.05 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 147.9, 143.8, 138.8, 132.9, 127.7, 126.4, 123.8, 122.8, 120.8, 119.2, 116.9, 116.3, 110.5, 110.4, 21.4, 13.2; HRMS (ESI) $[M]^+$ calcd for $C_{17}H_{14}N_2$ 246.1157, found 246.1156.

Synthesis of Ethyl 3-(quinoline-3-carbonyl)-1*H*-indole-2-carboxylate (37). We followed the same procedure used for the compound **32** except oxidation step. Instead of IBX, DMP (1.5 mmol) in DCM/AcOH (9:1) was used. R_f = 0.56 (hexanes:EtOAc, 2:8); red solid (145 mg, 80%): mp 212−214 °C; IR (KBr) 3385, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, br, 1H), 8.95 (s, 1H), 8.51 (s, 1H), 8.23 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.67 (t, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 6.8 Hz, 1H), 7.39 (d, J = 4.4 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 161.9, 150.4, 149.9, 147.5, 144.7, 143.3, 136.7, 130.2, 130.0, 129.6, 129.4, 129.3, 128.3, 126.4, 125.8, 124.4, 123.8, 121.8, 60.9, 14.2; HRMS (ESI) $[M + H]^+$ calcd for $C_{21}H_{16}N_2O_3$ 345.1234, found 345.1239.

Synthesis of 7*H*-Indolo[3,2-*j*]phenanthridine-7,13(12*H*)-dione (Calothrixin B) (10). We followed the same procedure used for the synthesis of ellipticine quinones. R_f = 0.45 (hexanes:EtOAc, 8:2); red solid (41 mg, 48%): mp >300 °C; IR (KBr) 3389, 1653 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, br, 1H), 9.63 (s, 1H), 9.47 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 6.4 Hz, 2H), 7.84 (t, J = 8.0 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.1, 180.7, 151.7, 147.9, 138.9, 138.4, 133.1, 132.1, 130.7, 130.3, 127.5, 125.3 (2C), 124.5, 123.7, 123.1, 122.8, 116.2, 114.4; HRMS (ESI) $[M + H]^+$ calcd for $C_{19}H_{10}N_2O_2$ 299.0821, found 299.0823.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data (^1H, ^{13}C NMR, mass spectra, crystallographic structures). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rnsc@uohyd.ernet.in.

Notes

The authors declare no competing financial interest.

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