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Total Synthesis of Calothrixin B via Sequential Sonogashira Coupling/Copper-Catalyzed Oxidative Cyclization

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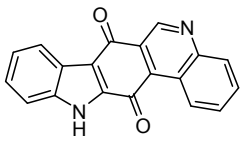
A total synthesis of antimalarial indolo[3,2-*j*]phenanthridine alkaloid, Calothrixin B is reported. The key intermediate, ketoester **11** was assembled using sequential Sonogashira coupling and intra/intermolecular fashioned copper-catalyzed oxidative cyclization reactions.

Introduction

Calothrixin B **1** is a pentacyclic quinone that possesses a indolo[3,2-*j*]phenanthridine or quinolino[4,3-*b*]carbazole skeleton and is unique among other naturally occurring alkaloids (Fig. 1). Since its first isolation from *Calothrix* cyanobacteria in 1999[1], several research groups have reported the synthesis and biological studies of Calothrixin B, principally because of its potent biological activities, such as anti-malarial and anti-cancer activities.[2, 3] Various synthetic methods have been reported for the production of Calothrixin B, including a metallation strategy,[4] Pd-catalyzed coupling,[5] electrocyclization,[6] hetero Diels-Alder reaction,[7] Friedel-Crafts acylation/alkylation[8] and a radical reaction.[9] In addition, two biomimetic approaches for Calothrixin B synthesis have also been reported.[10]



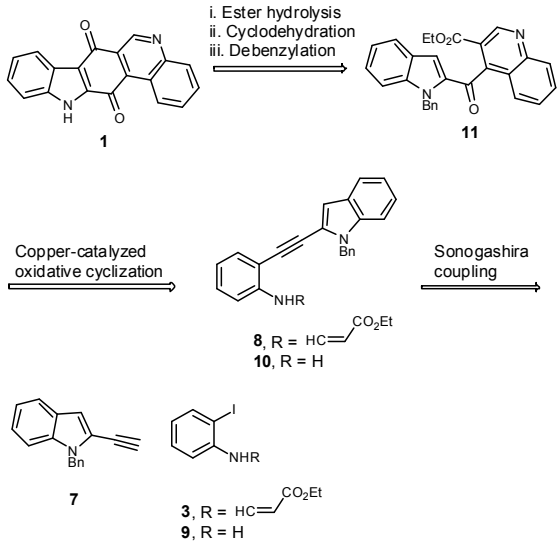
Calothrixin B 1

Figure 1. Structure of Calothrixin B

The Sonogashira coupling reaction is widely used in the synthesis of 1,n-enyne system, which is an important unit in biologically active natural compounds.[11] Copper-catalyzed oxidative cyclization of 1,n-enynes is an elegant tool for the synthesis of 4-carbonyl quinoline system that is found in many natural compounds.[12] Herein, we report a novel total synthetic route for Calothrixin B involving sequential Sonogashira coupling and copper-catalyzed oxidative cyclization reactions.

Results and discussion

The retrosynthetic disconnection pathway for the synthesis of Calothrixin B **1** is shown in Scheme 1. We envisaged that **1** could be derived from ketoester **11** through subsequent ester hydrolysis, cyclodehydration and debenzylation. The key intermediate **11** could be accessed from compounds **8** and **10** using intra/intermolecular copper-catalyzed oxidative cyclization. In turn, the compounds **8** and **10** could be obtained from the Sonogashira coupling of **7** with **3** and **9** respectively.



Scheme 1. Retrosynthetic approach to Calothrixin B (**1**)

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Electronic Supplementary Information (ESI) available: Copies of ^{1}H, ^{13}C and Mass spectra for all the compounds. See DOI: 10.1039/x0xx00000x

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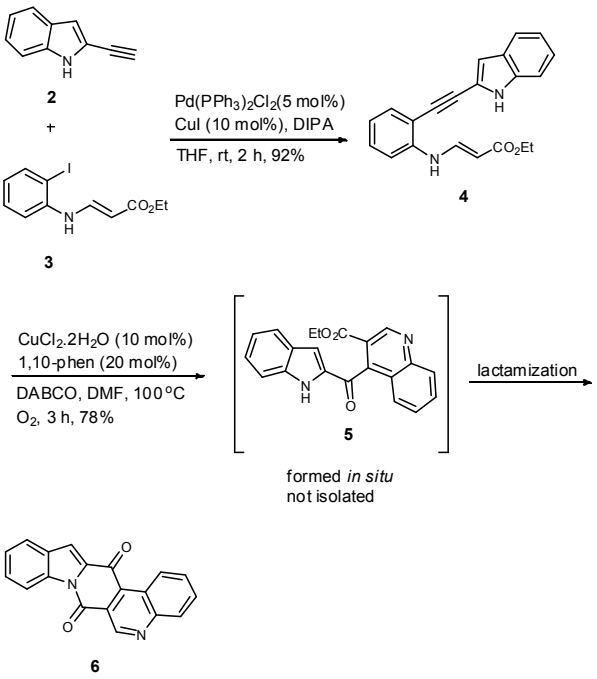
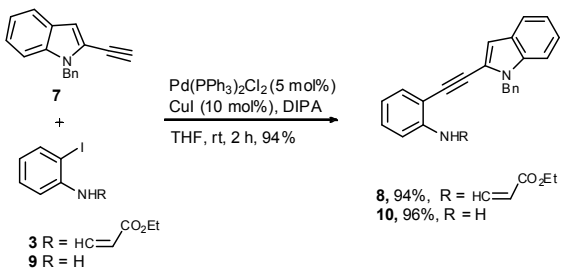
We embarked on the proposed synthetic route by conducting a Sonogashira coupling reaction of 2-ethynyl-1*H*-indole **2** and (*E*)-ethyl 3-((2-iodophenyl)aminowhich)acrylate **3** produced a coupled product **4** in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%) and diisopropylamine (DIPA) (2 equiv.) in THF with 92% yield (Scheme 2). Our next step was to focus on copper-catalyzed oxidative cyclization reaction of enyne **4**. Most surprisingly, on carrying out this reaction using $CuCl_2.2H_2O$ (10 mol%), Phen (20 mol%) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (2 equiv.) in DMF at 100 °C under oxygen atmosphere (using balloon), we isolated benzo[*f*]indolo[1,2-*b*][2,7]naphthyridine-7,14-dione **6** in 78% yield instead of the expected ketoester **5**. From this result, we concluded that ketoester **5** was formed *in situ* and readily lactamized to a compound **6** due to the presence of free indole *N*H in the enyne **4**. The isolated compound **6** has been previously reported in literature.[13] Data from spectroscopic analysis of the compound **6** matched literature report in all aspects (see Supporting information).



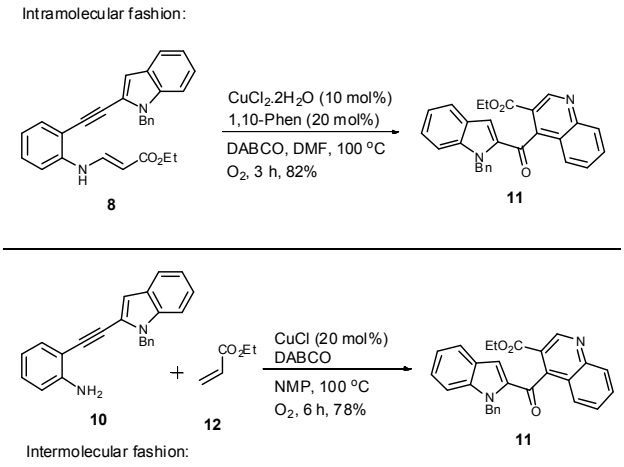
Scheme 2. Synthesis of benzo[*f*]indolo[1,2-*b*][2,7]naphthyridine-7,14-dione (**6**)

In order to achieve the desired outcome, we protected the free N*H* in indole with a benzyl group **7**. After this modification, 1-benzyl-2-ethynyl-1*H*-indole **7** was subjected to Sonogashira coupling reactions with (*E*)-ethyl 3-((2-iodophenyl)amino)acrylate **3** and 2-iodoaniline **9** by employing $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%) and diisopropylamine (DIPA) (2 equiv.) in THF at room temperature. These reactions afforded **8** and **10** in 94% and 96% yield respectively (Scheme 3).



Scheme 3. Sonogashira coupling reaction of 1-benzyl-2-ethynyl-1*H*-indole (**7**)

With the coupled products **8** and **10** in hand, we were able to obtain the key intermediate **11** in two ways; intramolecular and intermolecular copper-catalyzed oxidative cyclization reactions (Scheme 4). Firstly, we carried out intramolecular copper-catalyzed oxidative cyclization of enyne **8**. After several screening conditions, we found that the conversion of **8** to **11** proceeded smoothly in the presence of $CuCl_2.2H_2O$ (10 mol%), Phen (20 mol%) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (2 equiv.) in DMF at 100 °C under oxygen atmosphere with 82% yield in 3 h. This reaction proceeded through a sequence of intramolecular carbocupration of the alkyne **8** followed by isomerization, elimination and further oxidation gave the desired product **11**.[12e] Next, we carried out intermolecular copper-catalyzed oxidative cyclization reaction of **10** with ethyl acrylate **12**. The conversion of **10** to **11** was effected using 20 mol% CuCl and 1,4-diazabicyclo[2.2.2]octane (DABCO) (2 equiv.) in NMP at 100 °C under oxygen atmosphere for 6 h.



Scheme 4. Copper-catalyzed oxidative cyclization

At this juncture, having the key intermediate **11** in hand, we performed further functional group manipulations, consisting of ester hydrolysis, cyclodehydration and debenzylation (Scheme 5). The ketoester **11** was hydrolyzed using NaOH/EtOH to generate ketoacid **13**, which was in turn

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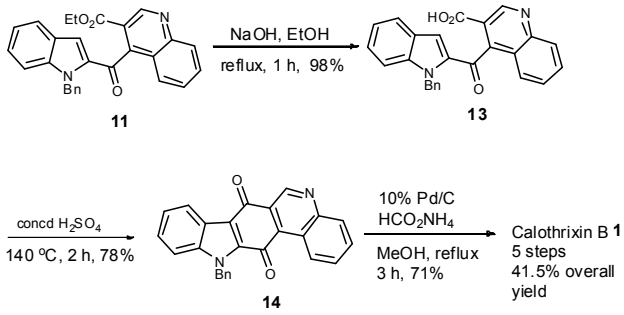
converted into a known *N*-benzyl calothrixin **14** by treatment with concd H_2SO_4 at 140 °C. The *N*-benzylated calothrixin **14** was readily deprotected by treatment with 10% Pd/C and $HCOONH_4$ in MeOH at reflux to finally obtain the target compound **1** in 71% yield. Spectroscopic data of **1** and **14** are fully consistent with those previously reported in literatures.[1, 7]



Scheme 5. Reactions to complete synthesis of Calothrixin B (**1**)

Conclusions

In summary, the total synthesis of Calothrixin B **1** has been accomplished using a novel route comprising of sequential Sonogashira coupling and copper-catalyzed oxidative cyclization reactions with an overall yield of 40.6% to 41.8% over 5 steps. This synthetic strategy provides a promising platform to synthesize novel indolonaphthyridine ring systems with ease.

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), *N*,*N*-dimethylformamide (DMF), methanol, ethyl acetate 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.

Preparation of (*E*)-ethyl 3-((2-iodophenyl)amino)acrylate (3)

Bis-dichloro(acetonitrile)palladium(II) (24 mg, 0.1 mmol), *p*-benzoquinone (98 mg, 1 mmol), lithium chloride (390 mg, 10 mmol) and ethyl acrylate **12** (100 mg, 1 mmol) were mixed in THF (5 mL) at room temperature. After stirring for 15 min, 2-iodoaniline **9** (210 mg, 1 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 12 h at room temperature and the solvent was removed under a reduced pressure. The residue was dissolved in ethyl acetate (75 mL) and repeatedly washed with 1 M NaOH solution and water. The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was removed to give the crude product which was purified by silica gel column chromatography using petroleum ether.

R_f = 0.60 (petroleum ether: EtOAc, 95:5); colourless oil (240 mg, 80%); IR (neat): 3380, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 10.16 (s, br, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.25-7.20 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 4.97 (d, *J* = 8.4 Hz, 1H), 4.28 (q, *J* = 6.8 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 141.8, 141.6, 139.9, 129.4, 123.6, 113.6, 89.7, 87.3, 59.6, 14.5; HRMS (ESI): $[M+H]^+$ calcd for $C_{11}H_{12}INO_2$ 317.9991, found 317.9987.

Preparation of 1-benzyl-2-ethynyl-1*H*-indole (7)

To a solution of 1-benzyl-2-ethynyl-1*H*-indole **2** (150 mg, 1 mmol) in DMF (10 mL), K_2CO_3 (293 mg, 2 mmol) was added and stirred for 30 min at room temperature. Benzyl bromide (0.25 mL, 2 mmol) was added and the mixture was stirred for 12 h under nitrogen atmosphere at room temperature. After completion of reaction (TLC), the reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (75 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed to give the crude product which was purified by silica gel column chromatography using petroleum ether.

R_f = 0.64 (petroleum ether:EtOAc, 95:5); light yellow solid (235 mg, 96%); mp 112-114 °C; IR (KBr): 3320, 3095, 2260, 1445, 890 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 7.6 Hz, 1H), 7.33-7.14 (m, 8H), 6.94 (s, 1H), 5.49 (s, 2H), 3.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.5, 136.6, 128.6 (2C), 127.4, 127.2, 126.7 (2C), 123.5, 121.2, 120.8, 120.4, 110.2, 109.0, 83.6, 75.6, 47.9; HRMS (ESI): $[M+H]^+$ calcd for $C_{17}H_{13}N$ 232.1126, found 232.1119.

General procedure for Sonogashira coupling reaction:

A mixture of (*E*)-ethyl 3-((2-iodophenyl)amino)acrylate **3** (150 mg, 1 mmol) or 2-iodoaniline **9** (150 mg, 1 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol) and CuI (0.1 mmol) were dissolved in THF (5 mL). Then DIPA (2 mmol) was added when the solution became clear. After stirring the mixture for 15 min at room temperature, corresponding indole **2** or **7** (1 mmol) was added. The reaction mixture was further allowed to stir for 2 h at room temperature. After completion of the reaction (TLC), the solvent was evaporated. The crude mixture was purified by silica gel column chromatography using petroleum ether/ethyl actate.

(*E*)-Ethyl 3-((2-((1*H*-indol-2-yl)ethynyl)phenyl)amino)acrylate (4)

R_f = 0.44 (petroleum ether:EtOAc, 95:5); white solid (144 mg, 92%); mp 128-130 °C; IR (KBr): 3380, 3345, 2985, 1750, 1585, 1335, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 11.04 (d, *J* = 12.4 Hz, 1H), 10.57 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.46-7.41 (m, 1H), 7.33-7.23 (m, 3H), 7.16-7.12 (m, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 0.8 Hz, 1H), 5.03 (d, *J* =

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8.0 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.49 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 141.8, 141.3, 136.7, 130.9, 129.5, 127.8, 123.3, 121.7, 121.0, 120.1, 118.8, 110.9, 110.8, 110.6, 107.5, 90.5, 88.3, 87.8, 59.9, 14.5; HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{18}N_2O_2$ 331.1446, found 331.1441.

(*E*)-Ethyl 3-((2-((1-benzyl-1*H*-indol-2-yl)ethynyl)phenyl)amino)acrylate (8)

R_f = 0.48 (petroleum ether:EtOAc, 95:5); yellow solid (186 mg, 94%); mp 146-148 ^{o}C; IR (neat): 3350, 2985, 2310, 1755, 1430, 1235, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.70 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.35-7.20 (m, 10H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 5.62 (s, 2H), 4.97 (d, *J* = 8.4 Hz, 1H), 4.22 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 141.7, 141.2, 137.8, 132.5, 129.8, 128.7, 128.6 (2C), 127.8, 127.3, 126.9 (2C), 123.2, 121.7, 121.5, 121.1, 120.2, 112.0, 110.8, 110.1, 109.3, 90.8, 89.4, 88.0, 59.4, 48.2, 14.5; HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{24}N_2O_2$ 443.1736, found 443.1730.

2-((1-Benzyl-1*H*-indol-2-yl)ethynyl)aniline (10)

R_f = 0.36 (petroleum ether:EtOAc, 90:10); yellow solid (212 mg, 96%); mp 108-110 ^{o}C; IR (KBr): 3440, 3360, 3080, 2956, 1467, 1332, 1280, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (d, *J* = 9.5 Hz, 1H), 7.33-7.28 (m, 3H), 7.26-7.21 (m, 3H), 7.16 (t, *J* = 7.0 Hz, 4H), 7.13 (s, 1H), 6.93-6.68 (m, 2H), 5.54 (s, 2H), 4.03 (s, br, 2H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 147.9, 137.7, 136.9, 132.1, 130.1, 128.7 (2C), 127.5, 127.4, 126.4 (2C), 123.2, 121.9, 121.0, 120.3, 117.9, 114.3, 109.9, 107.9, 107.1, 92.0, 86.1, 47.8; HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{18}N_2$ 323.1548, found 323.1540.

General procedure for intramolecular copper-catalyzed oxidative cyclization reaction:

To a solution of appropriate enyne **4** or **8** (100 mg, 1 mmol) in DMF (2 mL) was added $CuCl_2.2H_2O$ (0.1 mmol), DABCO (2 mmol) and 1,10-Phen (0.2 mmol). The reaction mixture was then stirred for 3 h at 100 ^{o}C under O_2 atmosphere. The resulting mixture was quenched with water and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography using petroleum ether/ethyl acetate.

Benzo[*f*]indolo[1,2-*b*][2,7]naphthyridine-7,14-dione (6)[13]

R_f = 0.57 (petroleum ether:EtOAc, 80:20); yellow solid (70 mg, 78%); mp 244-246 ^{o}C (lit.[13] mp 249 ^{o}C); IR (KBr): 1690, 1660, 1573, 1415, 1384, 1245, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.95 (s, 1H), 9.74 (dd, *J* = 1.0, 8.5 Hz, 1H), 8.60 (dd, *J* = 1.0, 8.5 Hz, 1H), 8.26 (dd, *J* = 1.0, 8.5 Hz, 1H), 7.94 (td, *J* = 1.5, 8.5 Hz, 1H), 7.85 (td, *J* = 1.0, 8.5 Hz, 1H), 7.77 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.72 (d, *J* = 0.5 Hz, 1H), 7.63 (td, *J* = 1.0, 8.5 Hz, 1H), 7.41 (td, *J* = 1.0, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.7, 158.3, 151.7, 149.5, 136.7, 134.0, 133.8, 132.4, 130.7, 130.5, 130.3, 128.7, 127.8, 125.7, 123.9, 123.3, 122.7, 117.9, 117.1; HRMS (ESI): $[M+H]^+$ calcd for $C_{19}H_{10}N_2O_2$ 299.0820, found 299.0820.

Ethyl 4-(1-benzyl-1*H*-indole-2-carbonyl)quinoline-3-carboxylate (11)

R_f = 0.42 (petroleum ether:EtOAc, 80:20); yellow solid (84 mg, 82%); mp 148-150 ^{o}C; IR (KBr): 3120, 2850, 1765, 1650; 1430, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.55 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.39-7.22 (m, 9H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.95 (d, *J* = 16.0 Hz, 1H), 4.32 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.3, 164.6, 150.2, 149.7, 149.2, 138.8, 137.9, 131.8, 129.6, 128.7 (2C), 128.2, 127.9, 127.5, 126.9 (2C), 125.6, 125.0, 124.4, 121.8, 120.9, 119.9, 116.5, 111.1, 61.8, 49.2, 13.9; HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{22}N_2O_3$ 457.1528, found 457.1520.

Procedure for intermolecular copper-catalyzed oxidative cyclization reaction:

To a solution of 2-((1-benzyl-1*H*-indol-2-yl)ethynyl)aniline **10** (100 mg, 1 mmol) and ethyl acrylate **12** (50 µL, 1.5 mmol) in NMP (2 mL), CuCl (0.2 mmol) and DABCO (2 mmol) were added. The reaction mixture was then stirred for 6 h at 100 ºC under O_2 atmosphere. The resulting mixture was quenched with water and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography using petroleum ether/ethyl acetate (80:20) afforded **11** as yellow solid (105 mg, 78%).

Synthesis of 4-(1-benzyl-1*H*-indole-2-carbonyl)quinoline-3-carboxylic acid (13)

To a solution of ethyl 4-(1-benzyl-1*H*-indole-2-carbonyl)quinoline-3-carboxylate **11** (75 mg, 1 mmol) in ethanol (3 mL), NaOH (21 mg, 3 mmol) was added and refluxed for 1 h. After completion of the reaction (TLC), crushed ice was added to the mixture and neutralized with 10% dil HCl to pH 7. The solid formed was filtered off, washed with water and dried. The crude product was used in the next step without further purification.

Note: This compound **13** exists as 'rotamers'

R_f = 0.38 (DCM:MeOH, 90:10); yellow solid (84 mg, 98%); mp 218-220 ^{o}C; IR (neat): 3110, 2930, 1740, 1690, 1455, 1375, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.05 (s, br, 2H), 9.70 (s, 1H), 9.69 (s, 1H), 8.22 (t, *J* = 7.6 Hz, 2H), 7.72-7.65 (m, 2H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.48-7.25 (m, 18H), 7.19 (t, *J* = 7.2 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.17 (d, *J* = 16.0 Hz, 2H), 5.97 (d, *J* = 16.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.0, 186.0, 167.2, 167.0, 150.6, 150.1 (2C), 149.8, 148.2, 140.6, 138.8, 138.1, 137.8 (2C), 134.7, 132.4, 129.7, 128.69 (4C), 128.62 (2C), 128.3, 128.28, 128.23, 127.4, 127.3, 127.0, 126.9 (6C), 126.2, 125.8, 125.1, 125.0, 124.8, 123.4, 121.8, 121.3, 120.9 (2C), 120.8, 116.4, 116.0, 111.1 (2C), 49.2, 48.6; HRMS (ESI): $[M+H]^+$ calcd for $C_{26}H_{18}N_2O_3$ 407.1395, found 407.1387.

Synthesis of 12-benzyl-7*H*-indolo[3,2-*j*]phenanthridine-7,13(12*H*)-dione (14)

4-(1-Benzyl-1*H*-indole-2-carbonyl)quinoline-3-carboxylic acid **13** (70 mg) was added to concd H_2SO_4 (2 mL) and heated to 140 ^{o}C for 2 h. After completion of the reaction (TLC), the

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reaction mixture was poured into ice cold water (50 mL) and extracted with ethyl acetate (70 mL). The organic layer was separated, washed with 10% aq NaOH and dried over anhydrous Na_2SO_4. The solvent was removed to give the crude residue which was purified by silica gel column chromatography using petroleum ether/ethyl acetate.

R_f = 0.30 (petroleum ether:EtOAc, 80:20); red solid (84 mg, 78%); mp 258-260 °C (lit[7]. mp 264 °C); IR (KBr): 3050, 1650, 1530, 1430, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.80 (s, 1H), 9.55 (d, *J* = 8.8 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 7.2 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 3H), 7.35-7.29 (m, 3H), 7.23 (d, *J* = 7.2 Hz, 2H), 6.01 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.0, 181.0, 152.1, 147.8, 140.1, 136.2, 135.1, 133.2, 131.3, 130.3, 130.1, 128.9 (2C), 128.0, 127.8, 127.7, 126.6 (2C), 125.1, 124.4, 123.9, 123.3, 123.1, 117.7, 111.5, 48.5; HRMS (ESI): $[M+H]^+$ calcd for $C_{26}H_{16}N_2O_2$ 389.1290, found 389.1282.

Synthesis of 7*H*-indolo[3,2-*j*]phenanthridine-7,13(12*H*)-dione (1) (Calothrixin B)

To a solution of 12-benzyl-7*H*-indolo[3,2-*j*]phenanthridine-7,13(12*H*)-dione **14** (50 mg, 0.13 mmol) in MeOH (5 mL), 10% Pd/C (14 mg, 0.13 mmol) and ammonium formate (162 mg, 2.5 mmol) were added and refluxed for 3 h under nitrogen atmosphere. After completion of the reaction using TLC, the reaction mixture was filtered through celite pad and washed with ethyl acetate (50 mL). The solvent was evaporated to give crude oil which was purified by silica gel column chromatography gave the titled product.

R_f = 0.30 (petroleum ether:EtOAc, 80:20); red solid (27 mg, 71%); mp 296-298 °C (lit.[1] mp ≥ 300 °C); IR (neat): 3420, 1650 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 13.11 (s, br, 1H), 9.56 (s, 1H), 9.52 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.91 (t, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 181.2, 180.7, 151.6, 147.9, 138.8, 138.4, 132.9, 132.0, 130.6, 130.28, 130.21, 127.6, 125.2, 124.7, 123.7, 123.0, 122.7, 115.9, 114.3; HRMS (ESI): $[M+H]^+$ calcd for $C_{19}H_{10}N_2O_2$ 299.0820, found 299.0822.

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