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ARTICLE TYPE

Palladium Mediated Intramolecular Multiple C-X/C-H Cross Coupling & C-H Activation: Synthesis of Carbazole Alkaloids Calothrixin B & Murrayaquinone A

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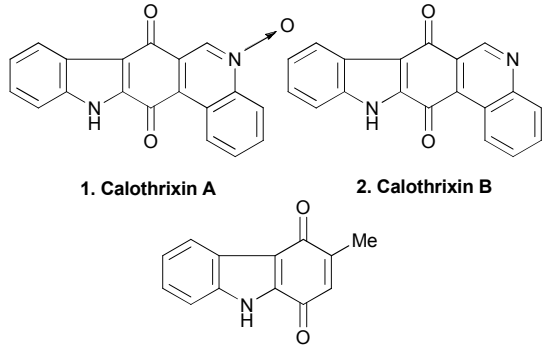
Abstract: A straightforward palladium mediated synthesis of calothrixin B and murrayaquinone A are described. Regioselective palladium mediated intramolecular multiple C-X/C-H cross coupling reaction on *N*-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-*N*-(2-iodophenyl)acetamide followed by CAN oxidation afforded calothrixin B in excellent yield in two steps. A linear synthesis has also been developed for calothrixin B. Utilizing C-H functionalization as well as palladium mediated intramolecular C-X/C-H cross coupling reaction, murrayaquinone A synthesis was achieved. Overall, these synthetic methodologies provide an expedient entry to the biologically active alkaloids in short reaction sequence

INTRODUCTION

The pentacyclic carbazole alkaloids calothrixin A (**1**) and B (**2**) were isolated by Rickards *et al.* from *Calothrix cyanobacteria* in 1999.[1] Calothrixins possess unprecedented indolo[3,2-*j*]phenanthiridine framework with a striking assemblage of quinoline, quinone and indole pharmacophores. Calothrixin A (**1**) and B (**2**) exhibited antimalarial activity as well as inhibitory effects on chloroquine resistant strain of the malarial parasite *Plasmodium falciparum*.[2] Both **1** and **2** inhibit the growth of human HeLa cancer cell lines and act as inhibitors of bacterial-RNA polymerase.[3] Kelly *et al.*[4] reported the first total synthesis of calothrixins in 2000 utilizing *ortho*-lithiation strategy. Further



1. Calothrixin A **2. Calothrixin B**

3. Murrayaquinone A

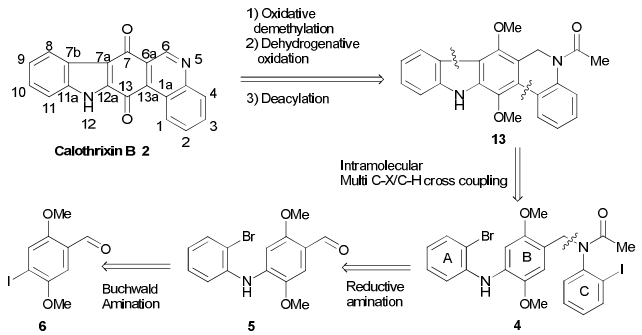
Fig. 1 Carbazole alkaloids

several elegant total syntheses of **1** and **2** were illustrated in literature utilizing hetero Diels-Alder protocol,[5] Friedel Crafts reaction,[6] palladium mediated tandem cyclization-cross coupling reaction[7] C-H activation,[8] $FeCl_3$ mediated domino reaction[9] and radical assisted cyclization[10] as well as biomimetic approach.[11]

Murrayaquinone A (**3**) is an indole alkaloid isolated by Furukawa *et al.* from *Murraya euchrestifolia*.[12] The plant genus *Murraya* has been used as a folk medicine for analgesia and local anesthesia and also for the treatment of eczema, rheumatism and dropsy (Fig 1).

RESULTS & DISCUSSION

Multiple Heck reaction of polyhaloarenes provides the opportunity for building several C-C bonds in a single synthetic operation,[13] however multiple intramolecular C-X/C-H cross coupling reactions are rarely explored.[14] Herein we report the total synthesis of calothrixin B (**2**) *via* multiple as well as stepwise palladium mediated intramolecular multiple C-X/C-H cross coupling reactions and murrayaquinone A (**3**) synthesis by C-H activation and also by C-X/C-H cross coupling reaction from its basic starting materials.



Scheme 1 Reterosynthetic analogy for Calothrixin B

The disconnection strategy for the synthesis of calothrixin B (**2**) is depicted in Scheme 1. Calothrixin B (**2**) could be obtained by the oxidative demethylation, dehydrogenative oxidation and

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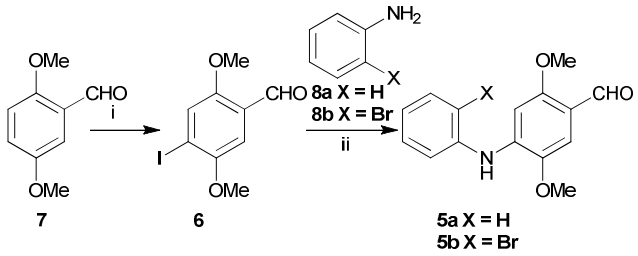
deacylation of **13**. The most salient features of our strategy are the creation of C7a-C7b and C13a-C1a bonds under palladium mediated intramolecular multiple C-X/C-H cross coupling reaction in a single synthetic operation from **4**. The substitution pattern on A and C rings of **4** would allow the regioselective C-X/C-H cross couplings. The dihaloarene **4** could be accessed *via* the reductive amination of biarylaminoaldehyde **5** with aniline **10**. The iodoaldehyde **6** could be used as a synthetic precursor for palladium mediated Buchwald aryl amination reaction with **8** to access the biarylaminoaldehyde **5.**

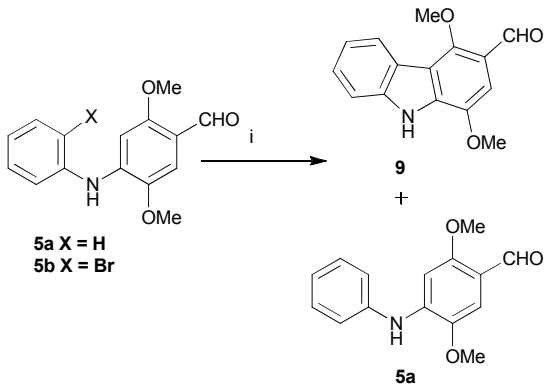


Scheme 2 Buchwald-Hartwig amination. Reagents and conditions: (i) I_2, $AgNO_3$, MeOH, r.t., 12 h, 95%; (ii) $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, (±)-BINAP, Cs_2CO_3, **8a** or **8b**, MeCN, 70 °C, 12 h, (X = Br, 85%; X = H, 90%);

The synthesis of key intermediates, 2,5-dimethoxy-4-(phenylamino)benzaldehyde **5a** and 2,5-dimethoxy-4-(2-bromophenylamino)benzaldehyde **5b** required for the preparation of calothrixin B (**2**) is outlined in Scheme 2**.** The synthesis of **5a** and **5b** were initiated with commercially accessible aldehyde **7**. The iodination of aldehyde **7** with stochiometric amount of iodine in presence of silver nitrate afforded the iodo aldehyde **6** in 95% yield.[15] The Buchwald–Hartwig coupling reaction of amine **8b** with iodoaldehyde **6** was carried out with $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, *rac*-BINAP and Cs_2CO_3 combination in acetonitrile at 60-70 °C for 10-12 hours, and produced **5b** in excellent yield. Though the Buchwald aryl amination on **6** with aryl halo amines are not well exemplified in the literature,[16] our attempted aryl amination reaction went very well, notably with less background reaction. Other phosphine ligands such as PPFA, PPFE, DPPP, DPPE, PPh_3 and P(*o*-tolyl)$_3$ have been employed in Buchwald amination, and gave either low conversion or poor product/reduced substrate ratios. To check the possibility of carbazole synthesis *via* C-H functionalization, **5a** was synthesized by Buchwald–aryl amination protocol. Owing to the moderate conditions employed in the synthesis of **5b** *via* Buchwald amination reaction, no C-C bond formation and dehalogenation were observed.

Initially the synthesis of carbazole **9** was attempted under intramolecular C-X/C-H cross coupling reaction conditions from **5b** (Scheme 3). To identify the appropriate conditions for palladium mediated intramolecular C-X/C-H cross coupling reaction, $Pd(OAc)_2$ have been chosen as the catalyst and the reaction was attempted with various solvent/base combinations in the presence of phosphine ligands. The results of these studies are summarized in Table 1.

1,4-dimethoxy-9*H*-carbazole-3-carbaldehyde (**9**) was obtained in good yield when the reaction was carried out with 5 mol% of $Pd(OAc)_2$, 20 mol% PCy_3 and 10 mol% JohnPhos in the presence of K_2CO_3 base in acetonitrile. The reaction was complete after 12 hours at 100 °C (entry 6) and afforded 9*H*-carbazole-3-carbaldehyde **9** in 90% yield along with a small percentage (7%) of **5a**.



Scheme 3 Synthesis of carbazole derivatives. Reagents and conditions: (i) X = H, $Pd(OAc)_2$ (2 equiv.), AcOH, 130 °C, 6 h, 91%; X = Br, $Pd(OAc)_2$, K_2CO_3, 10 mol% JohnPhos, 20 mol% PCy_3, MeCN, 100 °C, 12 h, 90%;

Table 1 Synthesis of carbazole 9 from 5b by C-X/C-H cross coupling reaction

Entry	Catalyst	Solvent	Ligand	X	Time h	Yield (%) 5a	Yield (%) 9
1	5 mol% $Pd(OAc)_2$	Toluene	20 mol% PPh_3	Br	12	0	0
2	5 mol% $Pd(OAc)_2$	DMF	20 mol% PPh_3	Br	14	5	30
3	10 mol% $PdCl_2$	DMF	20 mol% PPh_3	Br	14	0	30
4	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PPh_3	Br	16	0	20
5	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PCy_3	Br	12	30	60
6	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PCy_3 & 10 mol% JohnPhos	Br	12	7	90

We also extensively studied the C-H activation methodology for the construction of **9** (Table 2) from **5a** (Scheme 3)**.** More importantly, the synthesis of carbazole by C-H activation was carried out in the absence of an oxidizing agent.

Table 2 Synthesis of carbazole 9 from 5a by C-H activation reaction

entry	Catalyst	Solvent	Ligand	Time h	X	Yield (%) 9
1	5 mol% $Pd(OAc)_2$	Toluene	20 mol% PPh_3	24	H	0
2	5 mol% $Pd(OAc)_2$	DMF	20 mol% PPh_3	24	H	0
3	10 mol% $PdCl_2$	DMF	20 mol% PPh_3	24	H	0
4	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PPh_3	24	H	0
5	5 mol% $Pd(OAc)_2$	AcOH	---	24	H	0[a]
6	0.5equiv $Pd(OAc)_2$	AcOH	---	24	H	30[a]
7	1 equiv. $Pd(OAc)_2$	AcOH	---	10	H	75[a]
8	2 equiv. $Pd(OAc)_2$	AcOH	---	6	H	91[a]

[a] *Reaction was conducted in absence of ligand and oxidizing agent*

Unreacted starting material **5a** was significantly decreased

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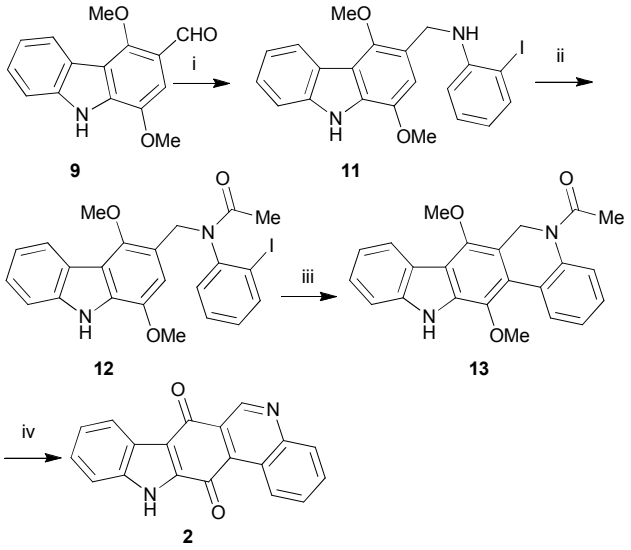
when the C-H activation reactions were performed with stoichiometric amount or excess of palladium acetate. Using 2 equiv. of $Pd(OAc)_2$, the complete consumption of **5a**, along with substantially higher yields of the desired product **9** (more than 90%) was obtained within 6 hour when the C-H activation reaction was conducted in acetic acid as solvent.

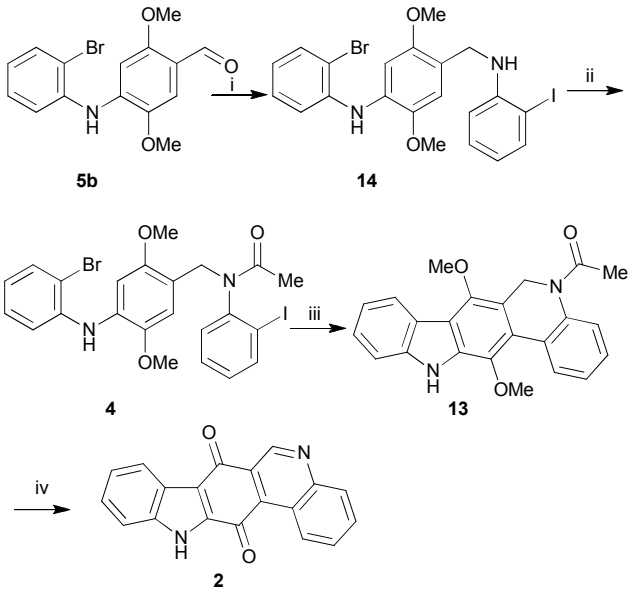
The direct reductive amination on **9** with 2-iodoaniline (**10**) was then carried out with sodium triacetoxyborohydride in the presence of TFA in isopropyl acetate solvent[17] and afforded **11** in 95% yield (Scheme 4).



Scheme 4 Iterative synthesis of calothrixin B (**2**). Reagents and conditions: (i) 2-iodoaniline (**10**), TFA, $NaBH(OAc)_3$, *i*-PrOAc, rt., 10 min, 95%; (ii) NEt_3, AcCl, CH_2Cl_2, 5 °C to rt., 2 h, 94%; (iii) $Pd(OAc)_2$, K_2CO_3, 20 mol% PCy_3, DMF, 110 °C, 10 h, 90%; (iv) CAN, MeCN/Water, rt., 2 h, 85%;

The palladium mediated intramolecular C-X/C-H cross coupling reaction on **11** under various conditions failed to yield to the calothrixin framework probably due to the electronic effect. To reduce the electron density and to afford effective coordination with Pd(II), *N*-acylation on **11** was carried out with acetyl chloride in the presence of triethylamine in dichloromethane to afford **12**. Subsequently **12** was subjected to the intramolecular reaction using 5 mol% of $Pd(OAc)_2$, 20 mol% PCy_3 and powdered K_2CO_3 in DMF. The C-X/C-H cross coupling reaction proceeded as expected and **13** was isolated in 90% yield after purifications.[18] The CAN was found to be a very effective reagent for the oxidation of phenanthiridine **13** to afford the corresponding quinone. However, during the oxidative demethylation of **13**, concomitant aromatization as well deacylation was observed and the natural alkaloid, calothrixin B (**2**) was obtained in 85% yield.

After the successful completion of the calothrxins B (**2**) synthesis *via* iterative process, we focussed our attention towards the synthesis of **2** under double intramolecular C-X/C-H cross coupling reaction conditions (Scheme 5). Though, the use of C-H activation methodology was initially planned for the construction of C7a–C7b bond, owing to the high Pd(II) loading required for the reactions, instead of C-H activation methodology, intramolecular multiple C-X/C-H cross coupling reaction was utilized for the synthesis of **2**.



Scheme 5 Synthesis of Calothrixin B (2) by intramolecular multiple C-X/C-H cross coupling reaction. Reagents and conditions: (i) 2-iodoaniline (**10**), TFA, $NaBH(OAc)_3$, *i*-PrOAc, rt., 10 min, 95%; (ii) NEt_3, AcCl, CH_2Cl_2, 5 °C to rt., 2 h, 94%; (iii) $Pd(OAc)_2$, K_2CO_3, 10 mol% JohnPhos, 30 mol% PCy_3, DMF, 110 °C, 10 h, 88%; (iv) CAN, MeCN/Water, rt., 2 h, 85%;

The reductive amination of 4-((2-bromophenyl)amino)-2,5-dimethoxy benzaldehyde (**5b**) with 2-iodoaniline (**10**) was then carried out with sodium triacetoxyborohydride in the presence of TFA in isopropyl acetate solvent afforded **14** in 95% yield. The intermediate **14** has all the structural requisite for carrying out the multifold C-X/C-H cross coupling reaction to construct the alkaloid **2** framework. The acylation of **14** with acetyl chloride in the presence of triethylamine exclusively afforded **4** and no trace of diacetyl product were observed in this reaction. The double intramolecular C-X/C-H cross coupling reaction was then attempted on **4** under several conditions and the best yield was obtained when the reaction was carried out with 5 mol% of $Pd(OAc)_2$ in the presence of 30 mol% of PCy_3 and 10 mol% of JohnPhos. The reaction went smoothly when performed with 4 equiv. of powdered K_2CO_3 in DMF at 110 °C. The progress of the reaction was monitored by LCMS method, which clearly confirmed the early formation C13a-C1a bond leading to the phenathridine framework, followed by the C7a-C7b bond construction. This probably due to the lower activation energy required for the insertion of transition metal at C13 position, because of the presence of adjacent *N*-acetyl group. The oxidative demethylation, deacylation and further aromatization on **13** were carried out with CAN in a single pot reaction and produced the natural alkaloid **2** in good yield.

As a part of these studies, we also synthesized the Murrayaquinone A (**3**) (Scheme 6). The carbazole-3-carbaldehyde **9** obtained by C-H activation of **5a** was subjected to reduction with TMSCl/TES to yield 3-methyl-9*H*- carbazole **15**. Owing to the decomposition of **15** under CAN oxidation conditions,[19] the demethylative oxidation of **15** was attempted with boron tribromide under aerial oxidation conditions as reported by Moody *et al.*[20] and the alkaloid **3** was isolated in 74% yield.

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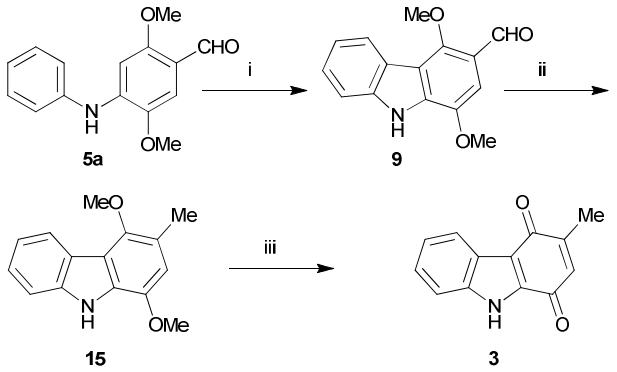
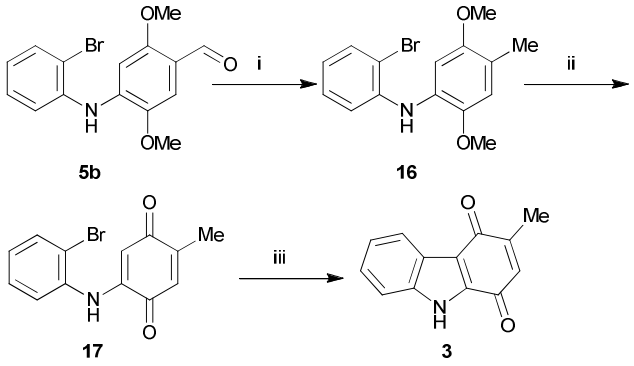


Scheme 6 Synthesis of Murrayaquinone-A (3) by C-H activation. Reagents and conditions: (i) $Pd(OAc)_2$, AcOH, 130 °C, 6 h, 91%; (ii) TMSCl, TES, MeCN, rt., 4 h, 83%; (iii) BBr_3, CH_2Cl_2, -78 °C, 22 h, 74%;

In an alternate attempt for the synthesis of murayaquinone **3** (Scheme 7), 4-((2-bromophenyl) amino)-2,5-dimethoxybenzaldehyde (**5b**) was reduced with TES/TMSCl conditions to afford **16**.



Scheme 7 Synthesis of Murrayaquinone-A (3) *via* intramolecular C-X/C-H cross coupling reaction. Reagents and conditions: (i) TMSCl, TES, MeCN, rt., 6 h, 80%; (ii) CAN, MeCN/Water, rt., 2 h, 88%; (iii) $Pd(OAc)_2$, K_2CO_3, 10 mol% JohnPhos, 20 mol% PCy_3, MeCN, 110 °C, 9 h, 88%;;

The CAN oxidation on **16** followed by intramolecular C-X/C-H reaction using $Pd(OAc)_2$, PCy_3, JohnPhos and powdered K_2CO_3, afforded the natural alkaloid murrayaquinone A (**3**) in 88% yield

Conclusion:

In conclusion, two efficient protocols for the synthesis of calothrixin B (**2**) have been developed in overall excellent yields. These syntheses were achieved through the development of efficient mono and double C-X/C-H cross coupling reactions through the exploration of various palladium catalysts and ligands. Utilizing C-H activation as well as intramolecular C-X/C-H reaction protocols, murrayaquinone A (**3**) has also been synthesized. Studies are underway to expand the scope of these methodologies for the synthesis of more complex bisindole alkaloids.

EXPERIMENTAL SECTION

General. All reactions were carried out in the oven dried glassware under an atmosphere of N_2, with magnetic stirring and the reactions were monitored by TLC, using *Merck* aluminum-backed plates pre-coated with silica (0.25 mm, 60, F254). The TLC plates were visualized under UV light (254 nm) or developed using a sol. of $KMnO_4$. Purifications were performed by column chromatography (CC) with silica gel (60-120 mesh) purchased from *SRL* and eluted with hexanes/EtOAc.

Mp. were determined on E*lectrothermal* melting point apparatus and are uncorrected. Infrared spectra were recorded on a *Perkin-Elmer 1650 Fourier Transform* spectrometer. NMR spectra were measured in $CDCl_3$, CD_3OD or DMSO-D_6 (all with TMS as an internal standard) on *Varian Gemini 400 MHz FT* magnetic resonance spectrometers. Chemical shifts are reported in ppm, and coupling constants (*J*) are in Hz. The following abbreviations were used to explain the multiplicities: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet. Mass spectra were recorded on an *HP-5989A quadrupole* mass spectrometer

Procedure for 4-iodo-2,5-dimethoxybenzaldehyde (6)

A mixture of 2,5-dimethoxybenzaldehyde **7** (10.2 g, 61.4 mmol), silver nitrate (10.4 g, 61.4 mmol), and iodine (16.2 g, 64 mmol) in 250 mL of methanol was stirred under nitrogen for overnight. The yellow precipitate was filtered and washed with methanol. The remaining iodine was reduced with saturated sodium bisulfite solution and the solvent was removed on a rotary evaporator and recrystallized from 95% ethanol to yield off white coloured title compound **6** (17.08 g, 95%).

mp: 139-141°C[15]. IR (ν_{max}/cm^{-1}) 3410, 2942, 1676, 1595, 1386, 1216, 1035 and 770. δ_H ($CDCl_3$, 400 MHz) 3.87 (s, 3H), 3.89 (s, 3H), 7.22 (s, 1H), 7.47 (s, 1H) and 10.40 (s, 1H). δ_C ($CDCl_3$, 100 MHz) 56.6, 56.7, 97.0, 107.5, 124.0, 124.3, 152.2, 155.7 and 188.4. LRMS (ESI) m/z: = 293 $(M+H)^+$. HRMS (ESI) calcd for $C_9H_{10}IO_3$ $(M+H)^+$: 292.9675, Found: 292.9674.

Procedure for the Preparation of 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (5b)

A mixture of 4-iodo-2,5-dimethoxybenzaldehyde (**6**) (10 g, 34 mmol), 2-bromoaniline **8b** (5.9 g, 34 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.40 g, 1.7 mmol), (±)-2,2-bis(diphenylphosphino)- 1,1 '-binaphinyl [(±)-BINAP] (1.06 g, 1.7 mmol) and cesium carbonate (22 g, 68 mmol) in acetonitrile (150 ml) was stirred at 60-70 ^{0}C under N_2 for 12 hours (The reaction was monitored by TLC). The reaction mixture was filtered over celite bed and washed with EtOAc. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 1:10) which gave the title compound **5b** as a Pale yellow colored solid (9.8 g, 85%).

mp: 124-126 °C. IR (ν_{max}/cm^{-1}) 3398, 3019, 2400, 1657, 1584, 1525, 1215. δ_H ($CDCl_3$, 400 MHz) 3.79 (s, 3H), 3.95 (s, 3H), 6.72 (s, 1H), 6.93-7.01 (m, 2H), 7.26-7.35 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H) and 10.26 (s, 1H). δ_C ($CDCl_3$, 100 MHz) 56.1, 56.2, 95.6, 108.2, 116.3, 116.8, 121.2, 124.6, 128.2, 133.6, 138.2, 140.3, 141.9, 158.9 and 187.4. LRMS (ESI): m/z = 336, 338 $(M+H)^+$. HRMS (ESI) calcd for $C_{15}H_{15}BrNO_3$ $(M+H)^+$: 336.0235, Found: 336.0231.

Procedure for the Preparation 2,5-dimethoxy-4-(phenylamino)benzaldehyde (5a)

The compound **5a** was prepared as shown in the general experimental procedure of **5b** and isolated as an off white colored solid (7.9 g, 90%).

mp: 122-124 °C. IR (ν_{max}/cm^{-1}) 3778, 3411, 3019, 2905, 2834, 1656, 1497, 1275, 1216. δ_H (DMSO-d_6, 400 MHz) 3.74 (s, 3H), 3.86 (s, 3H), 6.75 (s, 1H), 7.08 (td, J = 2.9, 5.4 Hz, 1H), 7.17 (s,

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1H), 7.34-7.39 (m, 4H), 8.27 (s, 1H) and 10.09 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 55.8, 55.8, 94.8, 107.9, 114.3, 121.5 (2C), 123.1, 129.2 (2C), 140.2, 141.6, 141.8, 158.6 and 185.4. LRMS (ESI): m/z = 258 $(M+H)^+$. HRMS (ESI) calcd for $C_{15}H_{16}NO_3$ $(M+H)^+$: 258.1130, Found: 258.1139.

Procedure for the Preparation of 1,4-dimethoxy-9*H*-carbazole-3-carbaldehyde (9)

From 2, 5-dimethoxy-4-(phenylamino)benzaldehyde (5a)

A mixture of 2,5-dimethoxy-4-(phenylamino)benzaldehyde (**5a**) (0.5 g, 1.9 mmol), palladium (II) acetate (0.873 g, 3.9 mmol) in glacial acetic acid (10 mL) was heated to 130°C for 6 hours with gentle stirring under argon atmosphere. After the completion of the reaction, the mixture was cooled to room temperature and poured into aqueous sodium hydrogen carbonate solution (25 mL). Solid sodium hydrogen carbonate was added to the reaction mixture till it is neutral. The reaction mixture was extracted with EtOAc (3*30 mL) and the layer was separated. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 1:5) which gave the title compound **9** as a Pale yellow colored solid (0.449 g, 91%).

From 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (5b)

A mixture of 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) (1 g, 2.9 mmol), powdered K_2CO_3 (0.823 g, 5.9 mmol), palladium (II) acetate (0.033 g, 0.1 mmol), tricyclohexylphosphine (0.167 g, 0.6 mmol) and 10 mol% of (2-Biphenyl)di-tert-butylphosphine (JohnPhos) (0.089 g, 0.3 mmol) in acetonitrile (20 mL) was heated 100 °C for 12 hours with gentle stirring under argon atmosphere. After completion of the reaction, the mixture was filtered over celite bed and washed with EtOAc. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 1:5) which gave the title compound **9** as a pale yellow colored solid (0.679 g, 90%).

mp: 173-175 °C. IR (ν_{max}/cm^{-1}) 3349, 2851, 1657, 1622, 1586, 1340. δ_H (DMSO-d_6, 400 MHz) 4.02 (s, 3H), 4.09 (s, 3H), 7.24 (s, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 10.36 (s, 1H) and 12.09 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 55.8, 63.7, 102.4, 112.1, 115.8, 119.8, 120.5, 120.9, 122.1, 126.0, 135.8, 139.7, 142.7, 155.4 and 187.8. LRMS (ESI): m/z = 256 $(M+H)^+$. HRMS (ESI) calcd for $C_{15}H_{14}NO_3$ $(M+H)^+$: 256.0974, Found: 256.0973.

Procedure for *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-2-iodoaniline (11).

To a round bottom flask charged 2-iodoaniline (**10**) (0.24 g, 1.1 mmol) and 1,4-dimethoxy-9*H*-carbazole-3-carbaldehyde (**9**) (0.28 g, 1.1 mmol) followed by *i*-PrOAc (6 mL) and trifluoroacetic acid (0.250 g, 2.2 mmol). Sodium triacetoxyborohydride (0.465 g, 2.2 mmol) was added as a solid over 2 min (an exothermicity was observed up to ~ 40 °C). After 10 min agitation TLC showed the completion of the reaction. The reaction mixture was diluted with EtOAc (20 mL). A solution of 2 wt% of aqueous NaOH was added into the reaction mixture until pH 8-9. The layer was separated and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 2:5) which gave the title compound **11** as a pale brown colour gummy liquid (0.477 g, 95%).

IR (ν_{max}/cm^{-1}) 3584, 3392, 2921, 1589, 1449, 1219. δ_H (DMSO-d_6, 400 MHz) 3.90 (s, 3H), 3.95 (s, 3H), 4.52 (d, *J* = 5.4 Hz, 2H), 5.23 (t, *J* = 5.9 Hz, 1H), 6.38 (t, *J* = 6.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.99 (s, 1H), 7.12-7.21 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H) and 11.41 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 55.7, 59.7, 61.0, 85.1, 106.9, 111.1, 111.3, 116.1, 118.3, 119.0, 120.5, 120.7, 121.9, 125.2, 129.7, 130.2, 138.6, 139.6, 142.1, 146.8 and 147.4. LRMS (ESI): m/z = 457 $(M-H)^+$. 240 (M–iodoanline). HRMS (ESI) calcd for $C_{21}H_{18}IN_2O_2$ $(M-H)^+$: 457.0413, Found: 457.0417.

Procedure for *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-*N*-(2-iodophenyl)acetamide (12).

To a round bottom flask charged *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-2-iodoaniline (**11**) (0.41 g, 0.89 mmol) and triethylamine (0.135 g, 1.33 mmol) in dichloromethan (5 mL) and cooled to less than 5°C. Freshly distilled acetyl chloride was slowly added (0.084 g, 1.07 mmol). The reaction was stirred at room temperature for 2 hours. After completion of the reaction, ice cold water was added into the reaction mixture and extracted with 3*20 mL of dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0.5:10) gave the title compound **12** as a Pale yellow gummy liquid (0.423 g, 94%).

IR (ν_{max}/cm^{-1}) 3778, 3584, 3469, 2401, 1648, 1470, 1305, 1215. δ_H ($CDCl_3$, 400 MHz) 1.87 (s, 3H), 3.54 (s, 3H), 3.94 (s, 3H), 4.52 (d, *J* = 14.2 Hz, 1H), 5.71 (d, *J* = 14.2 Hz, 1H), 6.69 (dd, *J* = 7.8 Hz, 1H), 6.92 (s, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.37-7.45 (m, 2H), 7.91 (dd, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H) and 8.32 (s, 1H). δ_C ($CDCl_3$ 100 MHz) 23.0, 44.7, 54.9, 56.0, 100.4, 108.3, 110.8, 119.5, 119.8, 121.9, 122.6 (2C), 125.4 (2C), 129.2, 130.7 (2C), 138.9, 140.0, 144.4, 147.1, 154.3 and 170.4. LRMS (ESI): m/z = 501 $(M+H)^+$. HRMS (ESI) calcd for $C_{23}H_{22}IN_2O_3$ $(M+H)^+$: 501.0675, Found: 501.0696.

Preparation of *N*-(2-bromophenyl)-4-(((2-iodophenyl) amino)methyl)-2,5-dimethoxyaniline (14)

To a round bottom flask charged 2-iodoaniline (**10**) (0.358 g, 1.5 mmol) and 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) (0.5 g, 1.5 mmol) followed by *i*-PrOAc (10 mL) and trifluoroacetic acid (0.339 g, 3 mmol). Sodium triacetoxyborohydride (0.630 g, 3 mmol) was added as a solid over 2 min (exothermicity was observed up to ~ 40 °C). After 10 min agitation TLC showed the completion of the reaction. The reaction mixture was diluted with ethyl acetate (30 mL). A solution of 2 wt% of aqueous NaOH was added into the reaction mixture until pH 8-9. The layer was separated and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 2:5) gave the title compound **14** as a dark brown coloured gummy liquid (0.764 g, 95%).

IR (ν_{max}/cm^{-1}) 3584, 3393, 3019, 2918, 1588, 1456, 1217. δ_H (DMSO-d_6, 400 MHz) 3.69 (s, 3H), 3.77 (s, 3H), 4.31 (d, *J* = 5.9 Hz, 2H), 5.20 (t, *J* = 5.9 Hz, 1H), 6.39 (t, *J* = 7.8 Hz, 1H), 6.63 (t,

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J = 7.8 Hz, 1H), 6.69 (s, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.86 (s, 1H), 7.02 (s, 1H), 7.10-7.17 (m, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H) and 7.63 (d, *J* = 7.9Hz, 1H). δ_C (DMSO-d_6, 100 MHz) 42.3, 55.9, 56.2, 85.2, 103.3, 111.2, 112.3, 112.9, 116.9, 118.3, 120.1, 121.3, 128.5, 129.3, 130.0, 132.7, 138.7, 140.9, 143.8, 147.3 and 151.1. LRMS (ESI): m/z = 537, 538, 539, 540, 541 $(M+H)^+$. HRMS (ESI) calcd for $C_{21}H_{21}BrIN_2O_2$ $(M+H)^+$: 538.9831, Found: 538.9850.

Preparation of *N*-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-*N*-(2-iodophenyl)acetamide (4)

To a round bottom flask charged *N*-(2-bromophenyl)-4-(((2-iodophenyl) amino)methyl)-2,5-dimethoxyaniline (**14**) (0.5 g, 0.92 mmol) and triethylamine (0.141 g, 0.14 mmol) in dichloromethane (20 mL) and cooled to less than 5°C. Freshly distilled acetyl chloride was slowly added (0.088 g, 1.1 mmol). The reaction was stirred at room temperature for 2 hours. After the completion of the reaction, ice cold water was added into the reaction mixture and extracted with 3*30 mL of dichloromethane and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0.5:10) gave the title compound **4** as a brown coloured gummy liquid (0.505 g, 94%).

IR (ν_{max}/cm^{-1}) 3778, 3399, 3019, 2400, 1648, 1524, 1215. δ_H (DMSO-d_6, 400 MHz) 1.71 (s, 3H), 3.40 (s, 3H), 3.71 (s, 3H), 4.29 (d, *J* = 14.2 Hz, 1H), 5.13 (d, *J* = 14.2 Hz, 1H), 6.54 (s, 1H), 6.68 (s, 1H), 6.73-6.79 (m, 1H), 6.81 (s, 1H), 7.02 (d, *J* = 6.4 Hz, 1H), 7.05-7.11 (m, 2H), 7.23 (t, *J* = 8.3 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H) and 7.96 (d, *J* = 7.8Hz, 1H). δ_C (DMSO-d_6, 100 MHz) 22.7, 44.8, 55.7, 56.2, 101.2, 102.9, 112.6, 114.3, 117.2, 117.5, 121.5, 128.4, 129.2, 129.8, 130.6, 130.7, 132.8, 139.4, 140.8, 143.5, 144.2, 151.5 and 168.8. LRMS (ESI): m/z = 579.9, 580.9, 582.99, 583.99 $(M+H)^+$. HRMS (ESI) calcd for $C_{23}H_{23}N_2O_3BrI$ $(M+H)^+$: 580.9937, Found: 580.9914

Preparation of 1-(7,13-dimethoxy-6,12-dihydro-5*H*-indolo[3,2-*j*]phenanthridin-5-yl)ethanone (13)

From N-((1,4-dimethoxy-9H-carbazol-3-yl)methyl)-N-(2-iodophenyl)acetamide (12).

To a solution of *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-*N*-(2-iodophenyl)acetamide (**12**) (0.2 g, 0.4 mmol) in degassed dry DMF (6 mL), PCy_3 (0.025 g, 0.08 mmol), anhydrous powdered K_2CO_3 (0.110 g, 0.8 mol) and $Pd(OAc)_2$ (0.005 g, 0.02 mmol) were added. The reaction mixture was stirred at 110 °C under argon atmosphere for 10 hours (The reaction was monitored by TLC). The reaction mixture was cooled to room temperature and filtered over celite bed and washed with EtOAc (10 ml). The combined organic layer was concentrated under reduced pressure to yield the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 2.5:5) which gave the desired compound as a brown solid **13** (1.034 g, 90%).

From N-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-N-(2-iodophenyl)acetamide (4)

To a solution of *N*-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-*N*-(2-iodophenyl)acetamide (**4**) (0.5 g, 0.86 mmol) in degassed dry DMF (6 mL), PCy_3 (0.072 g, 0.25), JohnPhos (0.025 g, 0.08 mmol), anhydrous powdered K_2CO_3 (0.475 g, 3.5 mmmol) and $Pd(OAc)_2$ (0.010 g, 0.04 mmol) were added. The reaction mixture was stirred at 110°C under argon atmosphere for 10 hours (The reaction was monitored by TLC). The reaction mixture was cooled to room temperature and filtered over celite bed and washed with EtOAc (10 ml). The combined organic layer was concentrated under reduced pressure to yield the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 2.5:5) which gave the desired compound as a brown solid **13** (0.280 g, 88%).

mp: 239-241 °C. IR (ν_{max}/cm^{-1}) 3231, 2837, 1734, 1638, 1624, 1396. δ_H (DMSO-d_6, 400 MHz) 2.11 (s, 3H), 3.82 (s, 3H), 3.98 (s, 3H), 4.5-5.2 (b, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.41-7.46 (m, 3H), 7.55 (d, *J* = 8.0 Hz, 2H), 8.11 (d, *J* = 7.7 Hz, 1H), 8.46 (m, 1H) and 11.59 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 22.0, 60.3, 61.0, 111.3 (2C), 116.3, 119.4 (2C), 120.7 (2C), 122.0 (2C), 125.0 (2C), 125.9, 127.7, 134.0, 138.5, 139.4, 140.2, 146.4 and 168.2. LRMS (ESI): m/z = 373 $(M+H)^+$. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_3$ $(M+H)^+$: 373.1552, Found: 373.1548

Preparation of Calothrixin B (2)

To a stirred solution of compound **13** (0.2 g, 0.54 mmol) in acetonitrile (5 mL) and water (5 mL), ceric ammonium nitrate (CAN) (0.740 g, 1.35 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, water (20 mL) was added into the reaction mixture and extracted with EtOAc (3*20 mL). The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0.4:10) which afforded red colored Calothrixin **B** (**2**) (0.137 g, 85%).

mp: >300 °C[4]. IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H (DMSO-d_6, 400 MHz) 7.40 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.89 (t, *J* = 8.3 Hz, 1H), 7.95 (t, *J* = 8.3 Hz, 1H), 8.16-8.19 (m, 2H), 9.58 (d, *J* = 8.3 Hz, 1H), 9.63 (s, 1H) and 13.17 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 113.9, 115.5, 122.3, 122.6, 123.3, 124.4, 124.9, 127.2 (2C), 129.8, 130.3, 131.6, 132.7, 138.0, 138.4, 147.5, 151.2, 180.4 and 180.9. LRMS (ESI): m/z = 299 $(M+H)^+$. HRMS (ESI) calcd for $C_{19}H_{11}N_2O_2$ $(M+H)^+$: 299.0821, Found: 299.0811.

Preparation of 1,4-dimethoxy-3-methyl-9*H*-carbazole (15)

In a round bottom flask under nitrogen atmosphere triethylsilane (0.683 g, 5.8 mmol) and trimethylsilyl chloride (0.532 g, 4.9 mmol) were charged. Then the solution of 1,4-dimethoxy-9*H*-carbazole-3-carbaldehyde (**9**) (0.5 g, 1.9 mmol) in acetonitrile (5 mL) was added slowly at room temperature and stirred for 4 hours. After completion of the reaction, water (10 mL) was added and volatile was removed under vacuum. The reaction mixture was extracted with 3*20 mL of EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0.5:5) which gave the title compound **15** as an orange coloured solid (0.393 g, 83%).

mp: 99-101 °C[19] (reported 98-100 °C). IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H ($CDCl_3$, 400 MHz) 2.37 (s, 3H), 3.88 (s, 6H), 6.61 (s, 1H), 7.15 (ddd, *J* = 6.9 and 2.0 Hz, 1H), 7.31 (m, 2H) and 8.14 (d, *J* = 7.8 Hz, 2H). δ_C ($CDCl_3$, 100 MHz) 15.4, 55.8, 60.2, 108.8, 110.6, 117.3, 119.5, 120.1,

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122.0, 122.6, 125.3, 129.3, 139.1, 141.7 and 147.1. LRMS (ESI): m/z = 242 $(M+H)^+$. HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $(M+H)^+$: 242.1181, Found: 242.1175.

Preparation of *N*-(2-bromophenyl)-2,5-dimethoxy-4-methylaniline (16)

In a round bottom flask under nitrogen atmosphere triethylsilane (1.01 g, 8.7 mmol) and trimethylsilyl chloride (0.793 g, 7.3 mmol) were charged. Then the solution of 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) (1 g, 2.9 mmol) in acetonitrile (10 mL) was added slowly at room temperature and stirred for 6 hours. After completion of the reaction, water (10 mL) was added and volatile was removed under vacuum. The mixture was extracted with 3*20 mL of EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 1:10) which gave the title compound **16** as a light brown coloured gummy liquid (0.770 g, 80%).

IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H (DMSO-d_6, 400 MHz) 2.09 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 6.59 (s, 1H), 6.74 (t, J = 7.8 Hz, 1H), 6.81 (s, 1H), 6.91 (s, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.20 (t, J = 8.3 Hz, 1H) and 7.54 (d, J = 7.8 Hz, 1H). δ_C ($CDCl_3$, 100 MHz) 15.9, 56.2, 56.5, 103.3, 112.6 and 114.5, 115.5, 120.1, 120.6, 128.0, 128.9, 133.0, 141.6, 144.1, 151.5. LRMS (ESI): m/z = 322, 324 $(M+H)^+$. HRMS (ESI) calcd for $C_{15}H_{17}BrNO_2$ $(M+H)^+$: 322.0443, Found: 322.0435.

Preparation of 2-((2-bromophenyl) amino)-5-methylcyclohexa-2,5-diene-1,4-dione (17)

To a stirred solution of *N*-(2-bromophenyl)-2,5-dimethoxy-4-methylaniline (**16**) (0.7 g, 2.2 mol) in acetonitrile (15 mL) and water (15 mL), CAN (3 g, 5.4 mol) was added. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, water (40 mL) was added into the reaction mixture and extracted with EtOAc (3*30 mL). The organic layer was concentrated under reduced pressure to give the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0.2:10) which afforded red colored title compound (0.559 g, 88%).

mp. 231-233 °C. IR (ν_{max}/cm^{-1}) 3434, 3306, 2954, 2919, 2346, 1735, 1670, 1530, 1223. δ_H (DMSO-d_6, 400 MHz) 1.97 (s, 3H), 5.24 (s, 1H), 6.72 (s, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H) and 8.71 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 16.3, 101.8, 117.4, 122.7, 126.2, 128.3, 129.5, 133.5, 135.8, 142.3, 149.3, 183.3 and 186.8. LRMS (ESI): m/z = 291.9, 293.9 $(M+H)^+$. HRMS (ESI) calcd for $C_{13}H_{11}BrNO_2$ $(M+H)^+$: 291.9973, Found: 291.9968.

Preparation of Murrayaquinone A (3)

From 1,4-dimethoxy-3-methyl-9H-carbazole (15)

To a solution of 1,4-dimethoxy-3-methyl-9*H*-carbazole (**15**) (0.3 g, 1.2 mmol) in dichloromethane (5 ml) was cooled to -78 °C. Boron tribromide in dichloromethane (1 M; 2.5 ml, 2.4 mmol) was added at -78 °C and the mixture was stirred for 22 hours at room temperature under air. The reaction mixture was then poured into ice water (10 ml) and the product was extracted into EtOAc (3*20 ml). The organic layer was separated and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 1:5) which afforded red colored title compound (0.194 g, 74%).

From 2-((2-bromophenyl) amino)-5-methylcyclohexa-2,5-diene-1,4-dione (17)

A mixture of 2-((2-bromophenyl) amino)-5-methylcyclohexa-2,5-diene-1,4-dione (**17**) (0.1 g, 0.34 mmol), anhydrous powdered K_2CO_3 (0.094g, 0.68 mmol), palladium (II) acetate (0.038 g, 0.02 mmol), tricyclohexylphosphine (0.019 g, 0.07 mmol) and 10 mol% of JohnPhos (0.010 g, 0.03mol) in acetonitrile (5 mL) was heated to 110 °C under argon atmosphere for 9 hours. The reaction mixture was filtered over celite bed and washed with EtOAc. The combined organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 1:5) which gave red colored title compound **3** (0.064 g, 88 % yield).

mp: 240-242 °C[12] (reported 246-247 °C) . IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H ($CDCl_3$, 400 MHz) 2.18 (d, J = 1.5 Hz, 3H), 6.52 (s, 1H), 7.33-7.45 (m, 2H), 7.48 (d, J = 8.3 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H) and 9.18 (br s, 1H). δ_C ($CDCl_3$+DMSO-d_6 100 MHz) 20.9, 118.8, 120.7, 126.7, 128.6, 128.8, 131.0, 136.6, 141.0, 142.7, 153.0, 185.1 and 188.1. LRMS (ESI): m/z = 212 $(M+H)^+$.

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Notes and references

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