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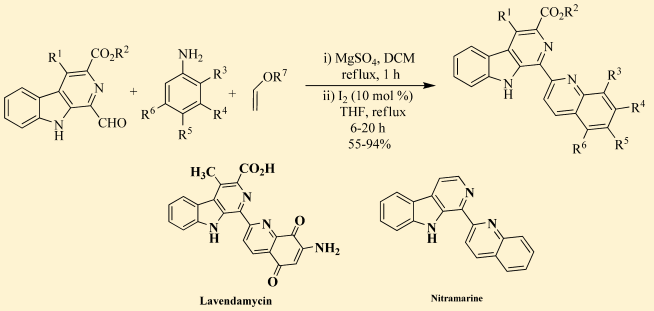
A Formal Synthesis of Lavendamycin Methyl Ester, Nitramarine, and Their Analogues: A Povarov Approach

Subburethinam Ramesh and Rajagopal Nagarajan*

School of Chemistry, University of Hyderabad, Hyderabad-500046, India

Supporting Information

ABSTRACT: A convergent formal synthesis of lavendamycin methyl ester and synthesis of its analogues have been delineated through the Povarov approach. This protocol is also applied to the formal synthesis of nitramarine (**3**) in good yield.



INTRODUCTION

For the past several years, Povarov reaction (imino Diels–Alder reaction) has played a central and crucial role to produce quinoline and tetrahydroquinoline molecules.[1−3] These nitrogen containing heterocycles have significantly attracted the synthetic community because of their prevalence in many natural products[3] and synthetic compounds with a wide spectrum of biological activities.[4] In 1981, Doyle and co-workers from Bristol Laboratories reported the isolation of naturally occurring antitumor/antibiotic lavendamycin (**1**, Figure 1) from the fermentation broth of *Streptomyces lavendulae* strain C22030 as a dark red solid.[5] Subsequently, its structure was elucidated as a pentacyclic quinone by Balitz and co-workers by means of analytical and spectroscopic studies.[5] In 1984, first total synthesis of lavendamycin was achieved by Kende et al, via Bischler–Napieralski reaction.[6] Structurally and biosynthetically, lavendamycin is related to well-known antitumor antibiotic streptonigrin alkaloid (**2**) (Figure 1).[7] Lavendamycin and its analogues exhibit promising biological properties such as inhibition of HIV reverse transcriptase,[8a,b] MKN45 gastric carcinoma and WiDr colon carcinoma cells[8c] as well as antiproliferative[8c] and cytotoxic[9a] activities. Lavendamycin exhibits antitumor activity against topoisomerase I cell with a minimum inhibitory concentration (MIC) of 0.1 μg/mL.[9b,c] Produced in a challenging atmosphere and importantly for its biological significance, lavendamycin and its analogues have stimulated the interest of synthetic community. They have been the target of various groups with extensive synthetic efforts.[6,10]

Some of the other basic methods for the synthesis of lavendamycin methyl ester include Bischler–Napieralski reaction,[6,10a] Pictet–Spengler cyclization,[10b−e] Friedlander condensation,[10f] aza-Wittig/electrocyclic ring closure,[10g] modified Knoevenagel–Stobbe condensation[10h] and transition metal catalyzed cross-coupling.[10i−l] The most recent synthetic study by Nissen et al.[11] is ruthenium-catalyzed [2 + 2 + 2] cycloaddition of an electron-deficient nitrile to an alkynylynamide. Continuing with our ongoing interest in Povarov reactions,[12] we have chosen this strategy as a novel and flexible synthetic route to generate lavendamycin and its analogues with diverse substitution patterns.

RESULTS AND DISCUSSION

Our prime target molecule would be a substituted α-quinolinyl-β-carboline **4** as mentioned in Scheme 1, because compound **4** had already been converted into lavendamycin methyl ester.[10a] We envisioned that the compound **4** would derive from α-formyl-β-carboline **5** (CDE ring) and aniline **6** (A ring) via Povarov reaction with *n*-butylvinyl ether (**7**) to construct ring B.

The compound **5** and **13** (CDE ring) were prepared from *rac-threo*-β-methyltryptophan esters (**8** and **8a**) (Scheme 2) that, in turn, is known to be derived from indole in a three steps sequence.[13] Pictet–Spengler cyclization of tryptophan esters **8** and **8a** with dimethoxy acetaledehyde in DCM/TFA (rt, 5 h) led to the desired diasteromeric mixtures **9** and **10**. Without further purification, when the diastereomeric mixtures were subjected to $KMnO_4$ oxidation (DMF, rt), α-dimethoxymethyl-β-carbolines (**11** and **12**) were obtained in good yields and then deprotection of **11** and **12** afforded α-formyl-β-carbolines (**5** and **13**) in excellent yields. The requisite aniline **6** was prepared in a four steps sequence, which commenced with commercially available 4-methoxyphenol (**14**) (Scheme 3).

We started the preliminary investigation using α-formyl-β-carboline (**18**),[14] anline (**19**) and *n*-butylvinyl ether (**7**) so as to test the feasibility of this approach (Table 1). The first experiment was performed in refluxing ethanol and in presence

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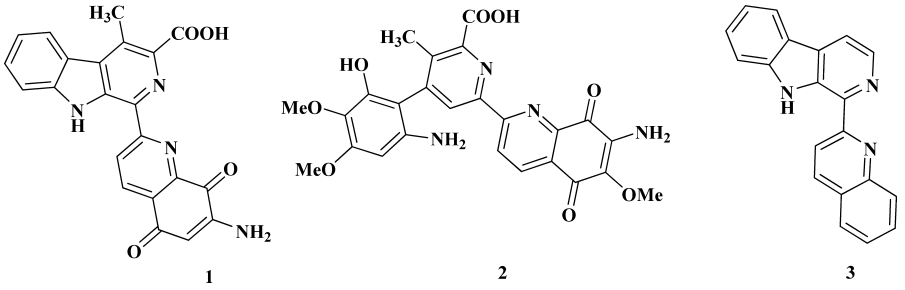
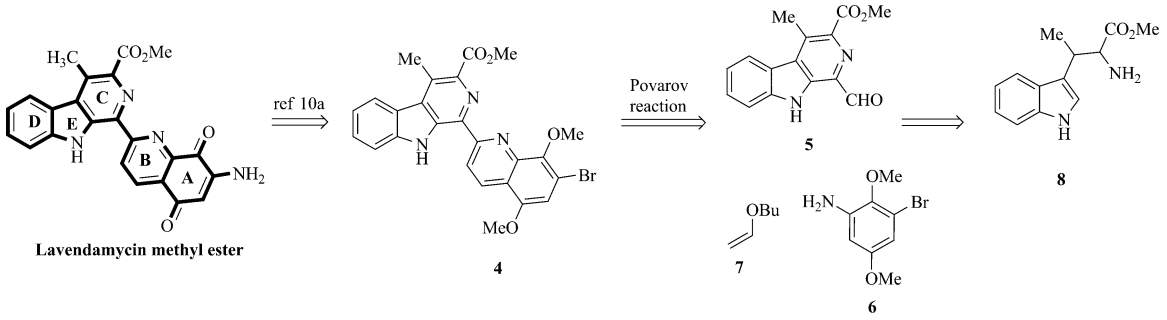
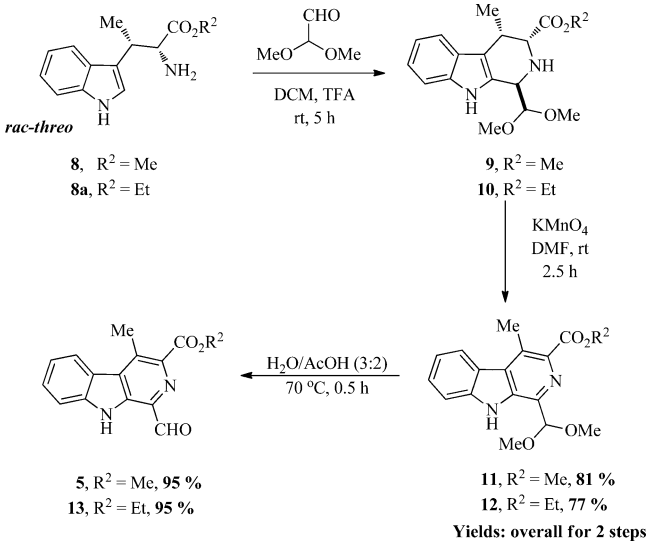


Figure 1. Lavendamycin (**1**), streptonigrin (**2**) and nitramarine (**3**).

Scheme 1. Retrosynthetic Analysis for Lavendamycin Methyl Ester



Scheme 2. Synthesis of Compound 5 and 13



Scheme 3. Synthesis of 3-Bromo-2,5-dimethoxyaniline (6)

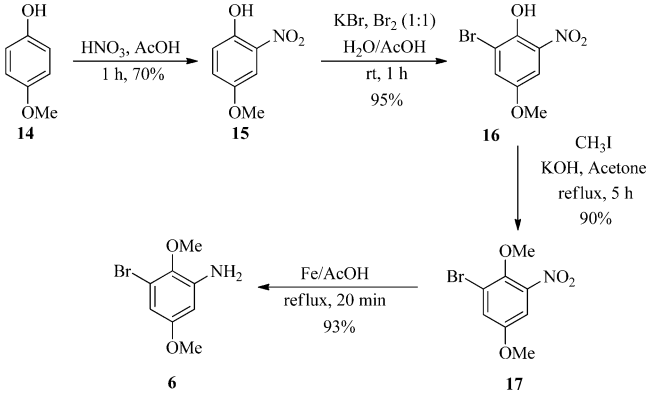
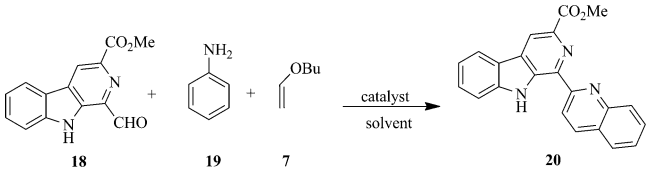


Table 1. Optimization of Reaction Conditions[a]



entry	condition	time (h)	yield (%)[b]
1	$BF_3{\cdot}OEt_2$ (10 mol %)/ethanol	24	trace
2	$BF_3{\cdot}OEt_2$ (10 mol %) /ethanol	24	28
3	$Cu(OTf)_2$ (10 mol %)/CH_3CN	24	22
4	Ag(OTf) (10 mol %)/CH_3CN	24	12
5	$La(OTf)_3$ (10 mol %)/CH_3CN	20	72
6	$La(OTf)_3$ (10 mol %)/dioxane	20	65
7	$La(OTf)_3$ (10 mol %)/toluene	32	68
8	$Sc(OTf)_3$ (10 mol %)/CH_3CN	20	55
9	$Yb(OTf)_3$ (10 mol %)/CH_3CN	18	51
10	I_2 (10 mol %)/CH_3CN	12	75
11	I_2 (10 mol %)/CH_3OH	15	61
12	I_2 (10 mol %)/toluene	20	45
13	**I_2 (10 mol %)/THF**	**8**	**89**
14	I_2 (20 mol %)/THF	24	89
15	I_2 (5 mol %)/THF	24	82

[a]General conditions. Aldehyde (**18**) 0.25 mmol, aniline (**19**) 0.25 mmol, and vinyl ether (**7**) 0.30 mmol. [b]Yield refers to column purified product. For entry 1, the Povarov reaction between aldehyde (**18**), aniline (**19**) and vinyl ether (**7**) was performed. For entries 2−15, the Povarov reaction between isolated aldimine and vinyl ether (**7**) was performed. The aldimine was prepared by refluxing the aniline and aldehyde in DCM solvent in the presence of $MgSO_4$ for 1 h. For all entries, reflux temperature of corresponding solvents was maintained.

of $BF_3{\cdot}OEt_2$ affording the desired product **20** in trace amount (Table 1, entry 1). We suspected that the formation of water during shiff base formation would be deleterious to the reaction. As anticipated, the reaction between isolated aldimine and *n*-butylvinyl ether (**7**) in the same above-mentioned

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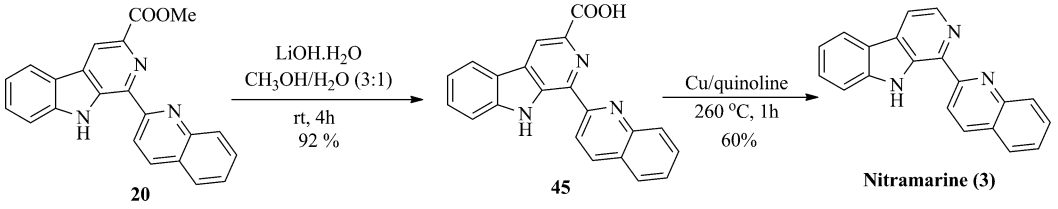
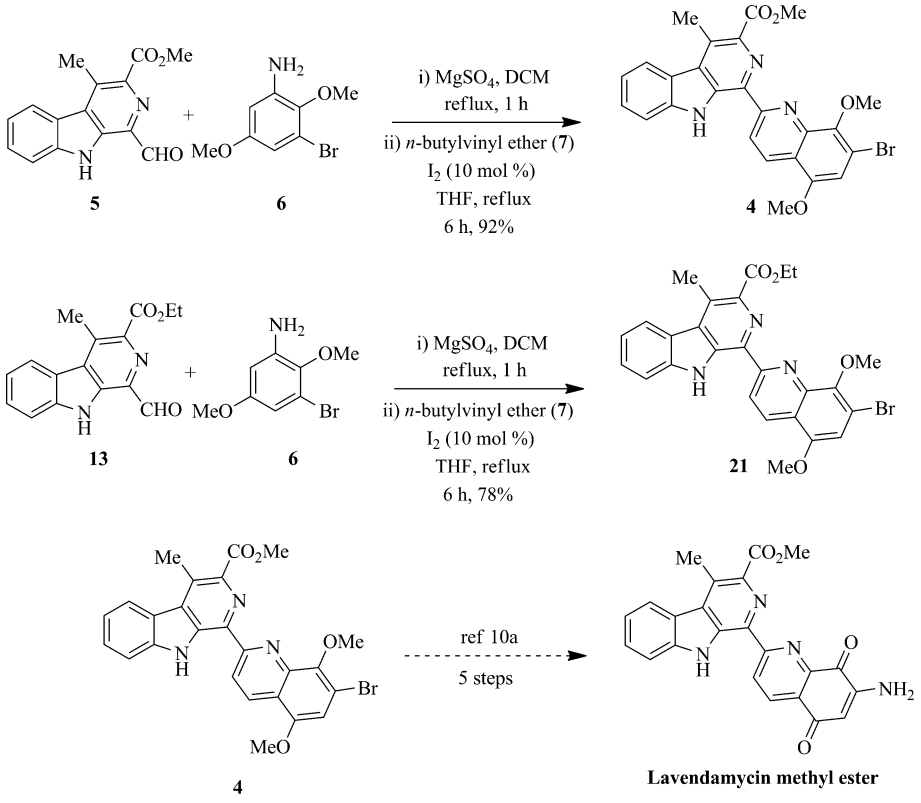
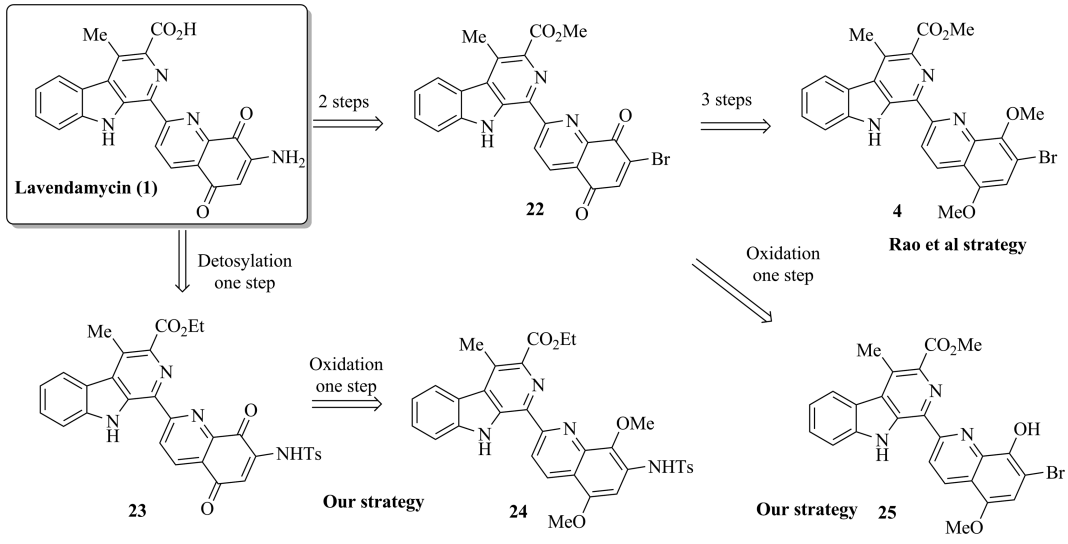
Scheme 4. Synthesis of Nitramarine Alkaloid (3)



Scheme 5. Synthesis of Compounds 4 and 21: Formal Synthesis of Lavendmycin Methyl Ester



Scheme 6. Synthetic Plan to Reduce the Steps Reported in the Literature[10a]



conditions (Table 1, entry 2), afforded the desired product in better yield. Consequently, we decided to optimize the reaction conditions only with aldimine and vinyl ether. Soft metal triflates such as $Cu(OTf)_2$ and Ag(OTf) triggered the reaction with poor yields (Table 1, entries 3 and 4). In addition, lanthanide triflates such as $La(OTf)_3$, $Sc(OTf)_3$ and $Yb(OTf)_3$

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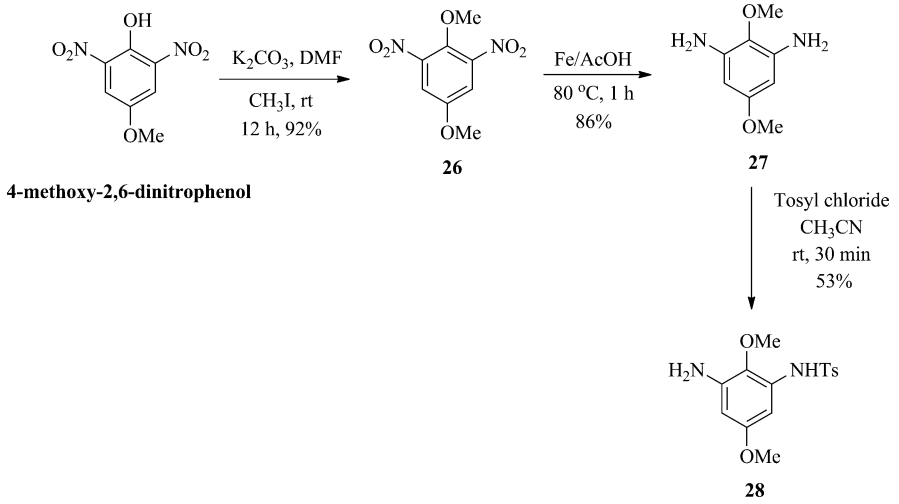
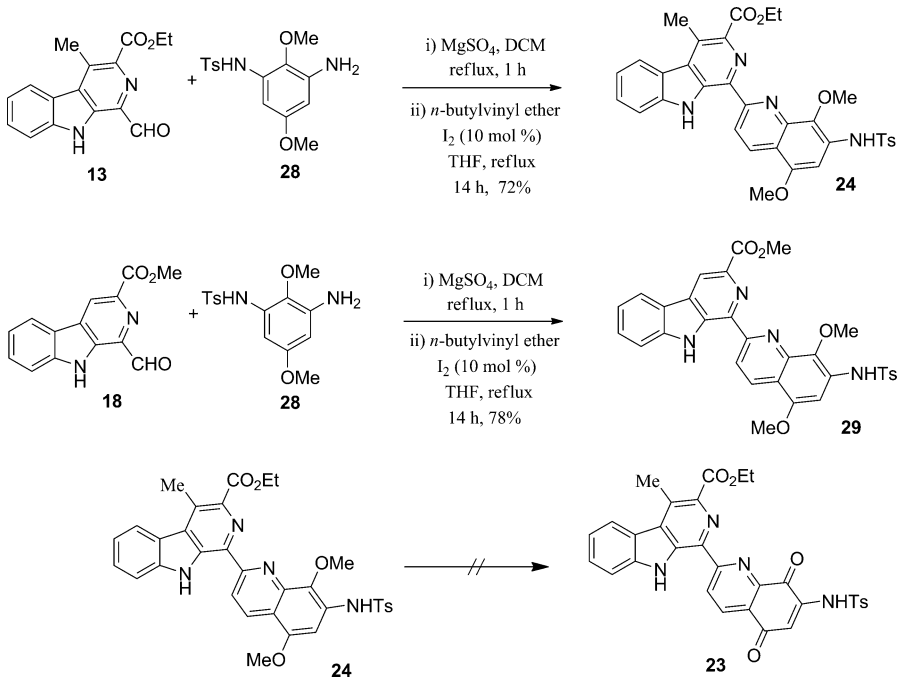
Scheme 7. Synthesis of 3-Amino-2,5-dimethoxy-1-(4-methylphenylsulfonamido)benzene (28)



Scheme 8. Synthesis of Compounds 24 and 29 and Oxidation of 24



also catalyzed the reaction with moderate yields (Table 1, entries 5−9). A satisfactory result was obtained with 10 mol % of I_2 in refluxing CH_3CN (Table 1, entry 10). With molecular iodine as a good catalyst, we next proceeded with solvents screening and catalytic loading (Table 1, entries 11−15). As shown in the Table 1, the best result was obtained using THF as a solvent and 10 mol % of I_2 as a catalyst (Table 1, entry 13).

Nitramarine (**3**) (Figure 1) is a α-quinolinyl-β-carboline alkaloid, which was isolated from *Nitraria komarovii* plant by Tulyaganov et al. in 1984.[15] It exhibits sleeping time pronging effect,[16a] hypotensive and spasmolytic activities.[16b] However, only few literature reports were available.[16a,17a−c] The compound **20** was de-esterified using LiOH in $MeOH/H_2O$ (3:1) at room temperature to furnish a 92% yield of compound **45**, which was decarboxylated using the reported procedure[17b] in moderate yield (Scheme 4). The spectroscopic data of synthetic **3** (^1H and ^{13}C NMR, LC−MS, CHN analysis) were in full accordance with those reported.[17c]

With the optimized conditions in hand, α-formyl-β-carbolines **5** and **13** and *n*-butylvinyl ether (**7**) were subjected to the Povarov reaction with aniline **6** to give the corresponding compounds **4** and **21** in excellent yields (Scheme 5). The compound **4** is identical to the Rao's intermediate, which would be converted into lavendamycin methyl ester from their literature report.[10a]

However, the conversion of the compound **4** to lavendamycin methyl ester was tedious and not in good yields. At this juncture, our endeavor was to modify the synthetic route attempted in the literature[10a] (Scheme 6). We envisioned that replacing the Br group at C-7 position of compound **4** with amino group (Scheme 6) could perhaps favor the oxidation step. Such a strategy, if successful, would be able to provide an intermediate **23**, which in turn, could easily be converted into

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lavendamycin ester (**1**), thereby reducing the 3 steps[10a] (Scheme 6).

Intermediate **24** was envisaged to be derived from α-formyl-β-carboline (**5** or **13**) and 3-amino-2,5-dimethoxy-1-(4-methylphenylsulfonamido)benzene (**28**). To examine this hypothesis, attempts were initiated to synthesize the aniline **28**, which was constructed via a three steps sequence starting with 4-methoxy-2,6-dinitrophenol (Scheme 7).

With the requisite aniline **28** in hand, we next attempted the Povarov reactions with α-formyl-β-carboline aldehyde **13** and **18** to afford compounds **24** and **29** in good yields (Scheme 8). Our attempts to oxidize the compound **24** under the conditions (Table 2) failed to deliver the desired compound **23**; however,

Table 2. Conditions Attempted for the Oxidation Step

entry	conditions
1	CAN (2.5 equiv)/CH_3CN–H_2O (1:1)/0 °C to rt, 24 h
2	AcOH/$K_2Cr_2O_7$/DCM–H_2O/rt, 1 h
3	CAN (2.5 equiv)/CH_3CN–H_2O (1:1)/80 °C, 1 h
4	H_2SO_4/70% aq. HNO_3 (3:1)/0 °C to rt, 1 h
5	CAN (2.5 equiv)/THF–H_2O (1:1)/0 °C to rt, 24 h
6	CAN (2.5 equiv)/DCM–H_2O (1:1)/0 °C to rt, 24 h
7	CAN (2.5 equiv)/DCM–H_2O (1:1)/0 °C to rt, 24 h
8	DDQ (1.2 equiv)/DCM–H_2O (1:0.5)/0 °C to rt, 24 h
9	IBX (4 equiv)/CH_3CN–H_2O (1:1)/rt, 24 h
10	DIB (4 equiv)/CH_3CN–H_2O–CH_3OH (1:1:0.1)/rt, 24 h

the compound **24** remained unaffected in some of conditions (Table 2, entries 1, 5–10) and recovered from the reaction mixture. Oxidation conditions such as a higher equivalent of CAN (more than 5 equiv), higher temperature (entry 3) and the presence of acid (entries 2 and 4) led to an unidentified complex reaction mixture. On the other hand, the Povarov reaction of aldehyde **5** and aniline **30** did not yield the expected intermediate **25** (Scheme 9).

Next, we directed a revised retrosynthetic analysis, as delineated in Scheme 10 according to the literature report.[9a] We endeavored to attain the intermediate **33** for two reasons: (i) the Povarov reaction is not working without protection of aminophenol (Scheme 9) and (ii) the quinolyl carboline, particularly protected with PMB ether (**33**), could be easily deprotected as well as oxidized by CAN in a single step to generate compound **31**.

The route to synthesize the compound **33** commenced with the preparation of *p*-methoxybenzyl (PMB)-protected aniline **34**, which in turn could be accessed from 2-nitrophenol (**35**) in a short sequence (Scheme 11). With the aniline **34** in hand, we explored the Povarov reaction of aldehydes **13** and **18** with aniline **34**, giving rise to the compounds **33** and **38**, respectively (Scheme 12). But unfortunately, all our efforts to oxidize the compound **33** were abortive under various conditions with CAN and DDQ (Table 2, entry 1, 3, 5–8). Under these conditions, the PMB-protected compound **33** was stable and could be recovered from the reaction mixture.

We failed to obtain the quinolinedione **31**, despite our extensive efforts in troubleshooting the oxidation process. Hence, we resolved to synthesize an acylated quinolyl carboline, which had been accounted by Nissen et al. in their recent total synthesis of lavendamycin methyl ester.[11]

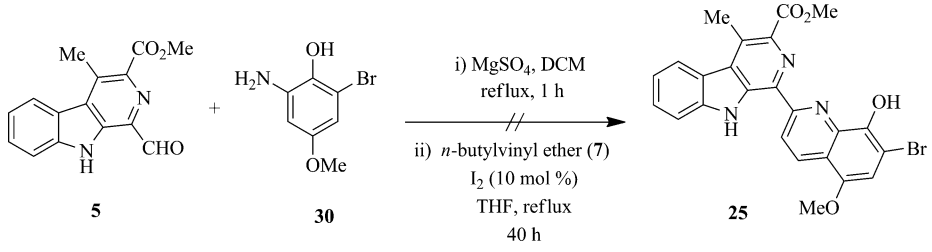
As indicated in the revised retrosynthetic analysis (Scheme 13), for the construction of the intermediate **39**, *N*1-(3-amino-2,5-dimethoxyphenyl)acetamide (**40**) had to be prepared. Upon preparation of the requisite aniline **40** (Scheme 14), we proceeded next to the Povarov reaction between aldehydes (**5** and **18**) and the aniline **40** (Scheme 15), which afforded the expected β-carbolines (**39** and **43**) in good yields, thereby completing the formal synthesis of lavendamycin methyl ester, as the compound **39** could easily be converted into lavendamycin methyl ester in a two-step sequence with excellent yields. The overall yield for our synthetic sequence toward the compound **39** is 60.02% with respect to methyltryptophan ester **8**. Upon completion of the two reported steps, our synthetic strategy would be able to provide lavendamycin methyl ester at 51.2% overall yield.

Considering the biological importance of lavendamycin analogues and scope of this methodology, we extended this reaction to different anilines (**19**, **19a–h**) and alkylvinyl ethers (**7** and **7a**), resulting in high yields of corresponding lavendamycin methyl ester derivatives (**20**, **20a–h**) (Table 3). Aromatic amines contain both electron-donating (Table 3, entries 5–7, 9) as well as electron-withdrawing (Table 3, entries 2–4, 8) groups, which tolerated the reaction in excellent yields. The compound **20** was also synthesized in good yield (83%, Table 3, entry 10) using this synthetic approach via ethylvinyl ether (**7a**) instead of *n*-butylvinyl ether (**7**). The structure of compound **20c** (Figure 2) was unambiguously confirmed by X-ray single crystal analysis.[18] The proposed reaction mechanism is shown in Scheme 16.

■ CONCLUSIONS

It is noteworthy that all the synthetic steps of this sequence involved readily available inexpensive materials to start with and gave good to excellent yields. The formal synthesis of lavendamycin methyl ester was accomplished using a Povarov approach that featured inexpensive catalyst with an overall yield of 51.2% to produce the lavendamycin methyl ester. We have also demonstrated the versatility of this approach toward the synthesis of lavendamycin analogues (**20**, **20a–h**). The synthesized lavendamycin analogue (**20**) was transformed into **45**, thereby completing the formal synthesis of nitramarine (**3**).

Scheme 9. Povarov Reaction of Aldehyde 5 and Aniline 30



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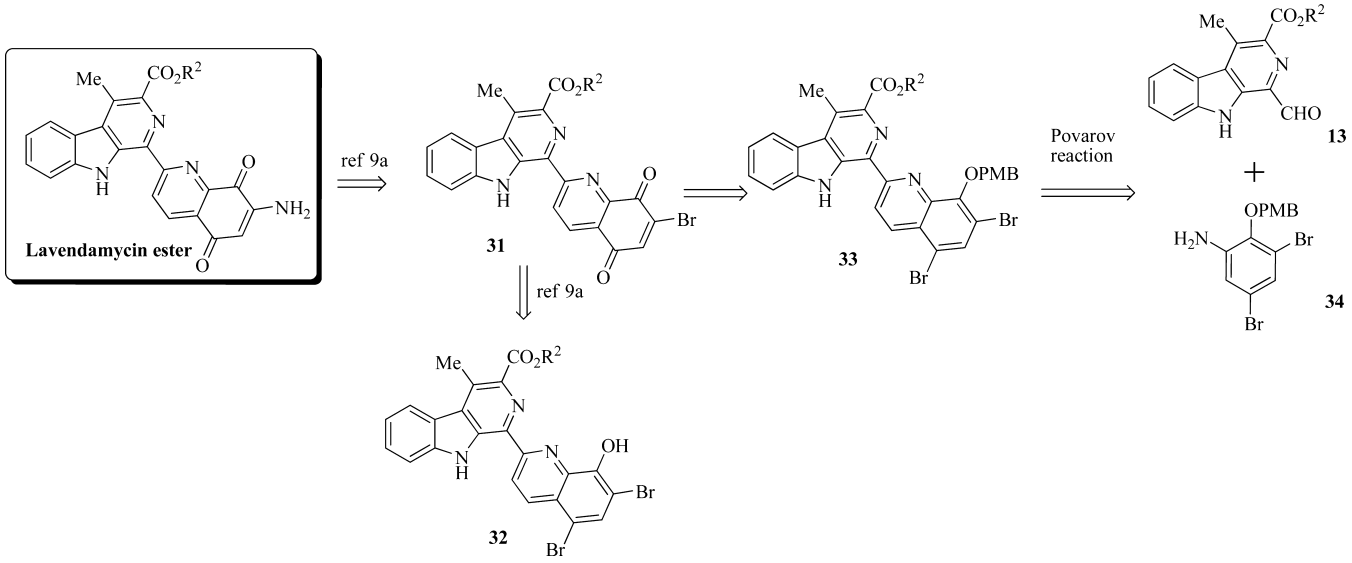
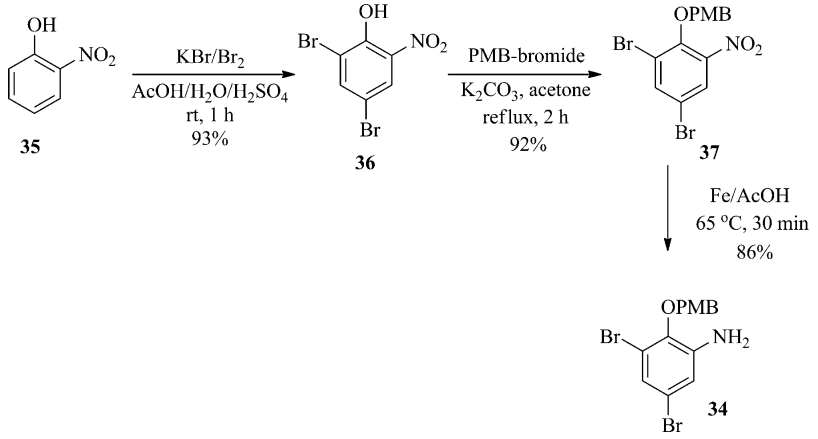
Scheme 10. Revised Strategy for Lavendamycin Ester



Scheme 11. Synthesis of PMB–Aniline 34



EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, or at 500 and 125 MHz, respectively. Chemical shifts were calculated in ppm downfield from TMS (δ = 0) for ^{1}H NMR, and relative to the central $CDCl_3$ resonance (δ = 77.0) and DMSO-d_6 (δ = 39.51) for ^{13}C NMR. Data presented in the experimental section are as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet doublet), coupling constant in Hertz (Hz). X-ray diffraction measurements were carried out at 298 K on an automated diffractometer using graphite-monochromated Mo Kα (l = 0.71073 Å) radiation with CAD4 software, or the X-ray intensity data were measured at 298 K on an instrument equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (l = 0.71073 Å). TOF and quadrupole mass analyzer types are used for the HRMS measurements. Mass spectral data was obtained from LC–MS (ESI). IR spectra were recorded on a FT-IR spectrometer using KBr pellets. Elemental analysis was carried out in CHN analyzer. Melting points were measured in open capillary tubes and are uncorrected. All the obtained products were purified by column chromatography using silica gel (100–200 mesh). All reaction solvents used were of GR grade and used without drying unless mentioned. All other commercial reagents were used as received.

Methyl 1-dimethoxymethyl-4-methyl-9*H*-β-carboline-3-carboxylates (11). To a solution of β-methyltryptophan ester (**8**) (500 mg, 2.15 mmol) in dichloromethane (25 mL) were added 60% wt. solution in water of dimethoxyacetaldehyde (3 mmol) and 98% of TFA (3 mmol). The reaction mixture was allowed to stir at room temperature for a period of 5 h. The reaction mixture was concentrated in a vacuum and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated in a vacuum and carried forward to the next step without further purification. To the crude diastereomeric mixture (**9**, 685 mg, 2.1 mmol) in DMF (20 mL) was added $KMnO_4$ (3.1 mmol). The reaction mixture was stirred over a period of 2.5 h at room temperature. The reaction mixture was filtered using Celite-545 bed. The filtrate was concentrated and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum. The residue was purified by column chromotography (silica gel: hexanes/ethyl acetate = 10:4) to give the desired product **11** as a viscous liquid in 81% yield (overall two steps) (548 mg): IR (KBr) 3366, 3059, 1716, 1215, 798, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 9.50 (1H, s), 8.26 (1H, d, J = 8.0 Hz), 7.52 (2H, d, J = 3.2 Hz), 7.28–7.33 (1H, m), 5.71 (1H, s), 3.99 (3H, s), 3.48 (6H, s), 3.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 167.7, 140.4, 137.7, 136.5, 133.8, 131.5, 129.5, 128.1, 123.8, 121.9, 120.5, 111.9, 106.8 (aromatic C), 54.7, 52.5, 16.6 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{17}H_{18}N_2O_4$; 315.1345 (M + H), found 315.1349; LC–MS m/z = 315.20 (M + H), positive mode. Anal. Calcd. for: C, 64.96; H, 5.77; N, 8.91%. Found: C, 64.79; H, 5.85; N, 8.96%.

Ethyl 1-dimethoxymethyl-4-methyl-9*H*-β-carboline-3-carboxylate (12). To a solution of β-methyltryptophan ester (**8a**) (500 mg, 2.0 mmol) in dichloromethane (25 mL) were added 60% wt.

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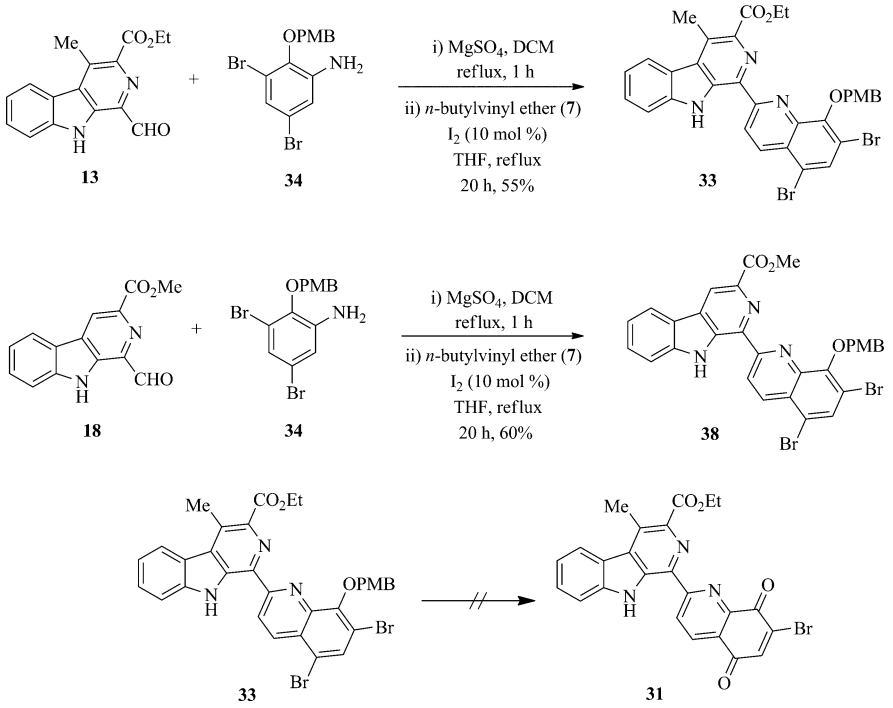
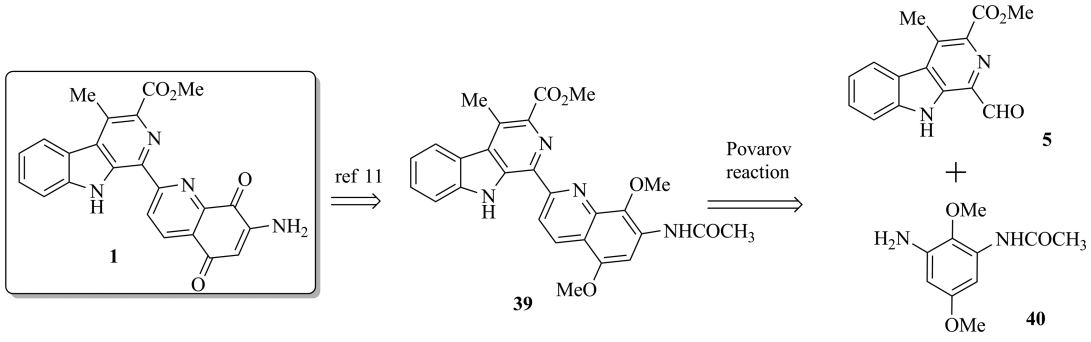
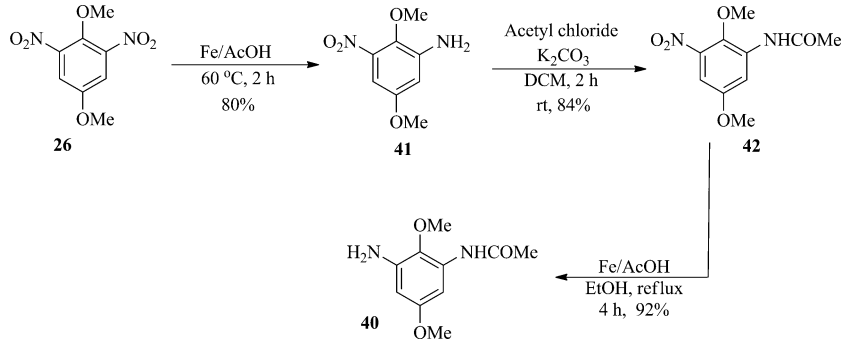
Scheme 12. Synthesis of Compounds 33, 38 and 31



Scheme 13. Revised Strategy for the Lavendamycin Metyl Ester



Scheme 14. Synthesis of Monoacylated Aniline 40



solution in water of dimethoxyacetaldehyde (3 mmol) and 98% of TFA (3 mmol). The reaction mixture was allowed to stir at room temperature for a period of 5 h. The reaction mixture was concentrated in a vacuum and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated in a vacuum and carried forward to the next step without further purification. To the crude diastereomeric mixture (**10**, 607 mg 1.83 mmol) in DMF (20 mL) was added $KMnO_4$ (3.0 mmol). The reaction mixture was stirred over a period of 2.5 h at room temperature. The reaction mixture was filtered using Celite-545 bed. The filtrate was concentrated and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum. The residue was purified by column chromotography (silica gel: hexanes/ethyl acetate = 10:4) to give the desired product **12** as a viscous liquid in 77% yield (overall two steps) (513 mg): IR (KBr) 3360, 2935, 1712, 1213, 1070, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 9.81 (1H, s), 8.16 (1H, d, J = 8.0 Hz), 7.37−7.51 (2H, m), 7.21 (1H, t, J = 6.8 Hz), 5.62 (1H, s), 4.44 (2H, q, J = 6.8 Hz), 3.37 (6H, s), 3.06 (3H, s), 1.35 (3H, t, J = 7.2

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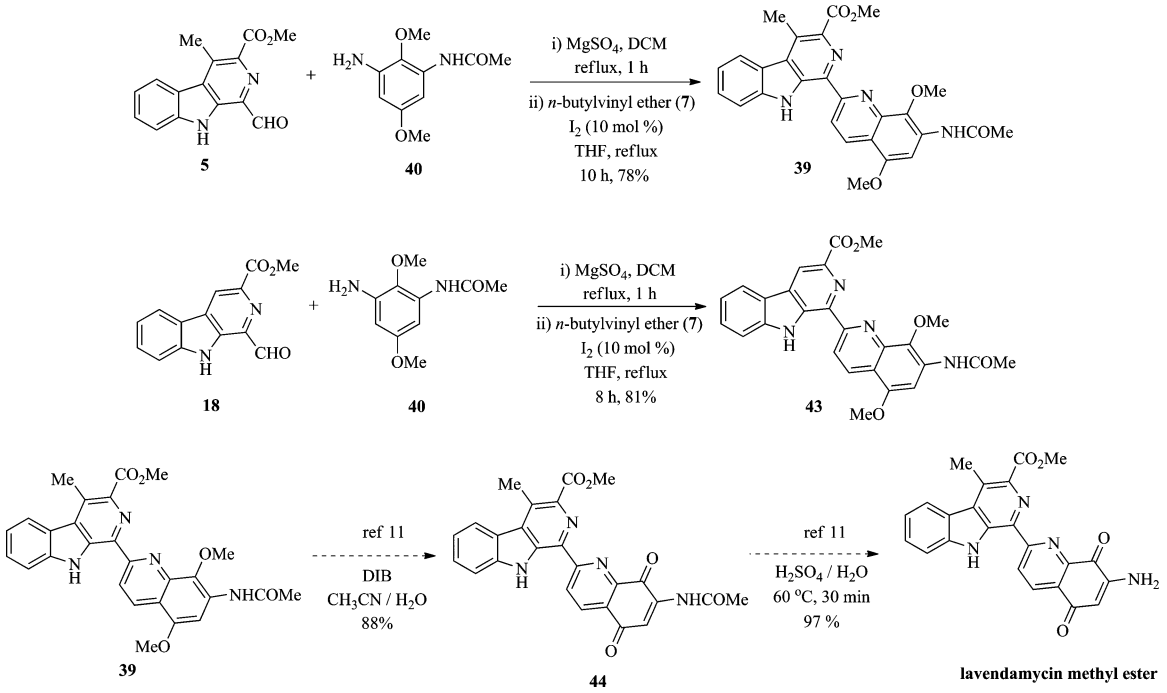
Scheme 15. Synthesis of Intermediate 39: Formal Synthesis of Lavendamycin Methyl Ester



Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 167.5, 140.5, 137.8, 137.1, 133.6, 130.6, 129.3, 127.9, 123.5, 121.8, 120.3, 112.0, 106.8 (aromatic C), 61.3, 54.7, 16.6, 14.3 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{18}H_{20}N_2O_4$; 329.1501 (M + H), found 329.1501; LC−MS m/z = 329.35 (M + H), positive mode. Anal. Calcd. for: C, 65.84; H, 6.14; N, 8.53%. Found: C, 65.73; H, 6.19 ; N, 8.45%.

Methyl 1-formyl-4-methyl-9*H*-β-carboline-3-carboxylate (5). In a 150 mL round-bottom flask equipped with a magnetic bar, compound **11** (400 mg, 1.2 mmol) was dissolved in H_2O/AcOH (40 mL/32 mL) solvent mixture, and then the solution was heated at 70 °C over a period of 30 min. The hot solution was cooled down to room temperature and concentrated under reduced pressure. The residue was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated in a vacuum. The title compound **5** was isolated as a pale yellow solid, which was carried forward to further reactions without further purifications: (324 mg, 95%) mp 160 °C; IR (KBr) 3364, 2920, 1720, 1441, 1073, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 10.34 (1H, s), 10.32 (1H, s), 8.29 (1H, d, J = 8.0 Hz), 7.63−7.64 (2H, m), 7.38−7.42 (1H, m), 4.07 (3H, s), 3.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 194.9, 166.9, 141.3, 138.5, 136.2, 135.2, 132.9, 131.1, 129.2, 124.1, 121.8, 121.4, 112.4 (aromatic C), 52.9, 17.2 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{15}H_{12}N_2O_3$; 269.0926 (M + H), found 269.0927; LC−MS m/z = 269.15 (M + H), positive mode. Anal. Calcd. for: C, 67.16; H, 4.51; N, 10.44%. Found: C, 67.25; H, 4.61; N, 10.31%.

Ethyl 1-formyl-4-methyl-9*H*-β-carboline-3-carboxylate (13). In a 150 mL round-bottom flask equipped with a magnetic bar, compound **12** (400 mg, 1.2 mmol) was dissolved in H_2O/AcOH (40 mL/32 mL) solvent mixture, and then the solution was heated at 70 °C over a period of 30 min. The hot solution was cooled down to room temperature and concentrated under reduced pressure. The residue was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated in a vacuum. The title compound **13** was isolated as a pale yellow solid, which was carried forward to further reactions without further purifications: (326 mg, 95%) mp 148 °C; IR (KBr) 3360, 2986, 1707, 1331, 1280, 927, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 10.34 (1H, s), 10.30 (1H, s), 8.30 (1H, d, J = 8.0 Hz), 7.64−7.65 (2H, m), 7.39−7.43 (1H, m), 4.56 (2H, q, J = 7.2 Hz), 3.16 (3H, s), 1.51 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 195.2, 166.7, 141.3, 139.3, 135.6, 135.2, 133.0, 131.0, 129.2, 124.1, 121.8, 121.5, 112.4 (aromatic C), 61.9, 17.3, 14.4 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{16}H_{14}N_2O_3$; 283.1082 (M + H), found 283.1084; LC−MS m/z = 283.10 (M + H), positive mode. Anal. Calcd. for: C, 68.07; H, 5.00; N, 9.92%. Found: C, 68.15; H, 5.12; N, 9.85%.

Procedure for the Synthesis of 4-Methoxy-2-nitrophenol (15). A round-bottom flask equipped with magnetic stir bar was charged with 4-methoxy-nitrophenol (**14**) (500 mg, 4 mmol) and glacial AcOH (25 mL), and then 67% nitric acid was added dropwise, and the internal temperature of the flask was maintained below 20 °C. Upon completion of acid addition, the reaction mixture was stirred at room temperature for a period of 1 h. The reaction mixture was quenched by saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The title compound (**15**) was purified by column chromotography (silica gel: hexanes/EtOAc = 10:0.5) (476 mg, yield 70%). The spectroscopic data of the compound **15** were in full accordance with those reported:[19a,b] mp 80 °C; IR (KBr) 3321, 2831, 1675, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 10.31 (1H, s), 7.48 (1H, d, J = 3.2 Hz), 7.20 (1H, dd, J = 3.2 and 9.2 Hz), 7.07 (1H, d, J = 9.2 Hz), 3.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 152.6, 150.0, 132.9, 127.3, 120.9, 105.6 (aromatic C), 55.9 (aliphatic C); LC−MS found for $C_7H_7NO_4$: m/z = 170 (M + H), positive mode. Anal. Calcd. for: C, 49.71; H, 4.17; N, 8.28%. Found: C, 49.65; H, 4.06; N, 8.35%.

Procedure for the Synthesis of 2-Bromo-4-methoxy-6-nitrophenol (16). To a solution of 4-methoxy-2-nitrophenol (**15**) (400 mg, 2.3 mmol), KBr (1 equiv) in H_2O (5 mL) and AcOH (15 mL), was added bromine (1 equiv) in dropwise. After completion of the addition, the reaction mixture was agitated at room temperature for a period of 1 h. Then, the reaction was quenched with saturated solution of $Na_2S_2O_3{\cdot}5H_2O$ and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under a vacuum. The residue was obtained (557 mg, 95%) as a yellow solid and carried forward to the next step without purification. The spectroscopic data of the compound **16** were in full accordance with those reported:[20a,b] mp 116 °C; IR (KBr) 3244, 3101, 2845, 1711, 1244, 1138, 858, 677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 10.79 (1H, s), 7.50−7.53 (2H, m), 3.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 152.2, 147.1, 133.6, 129.8, 113.8, 106.3 (aromatic C), 56.2 (aliphatic C); LC−MS found for $C_7H_6BrNO_4$: m/z = 246 (M − H), negative mode. Anal. Calcd. for: C, 33.90; H, 2.44; N, 5.65%. Found: C, 33.85; H, 2.39; N, 5.57%.

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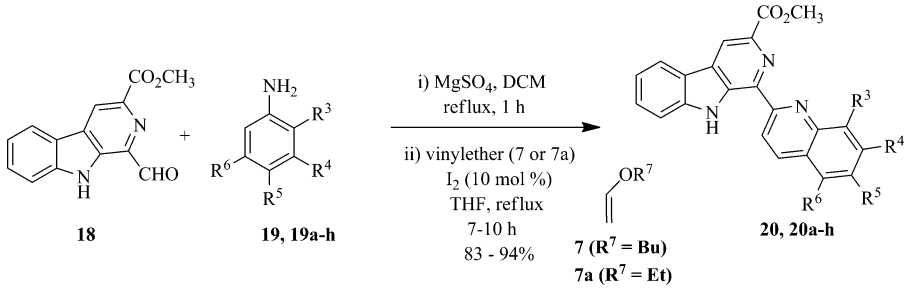
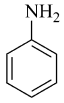
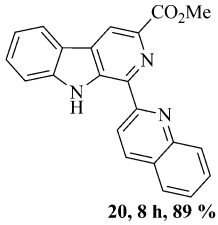
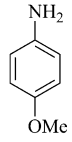
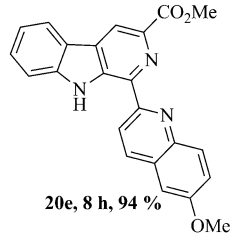
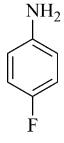
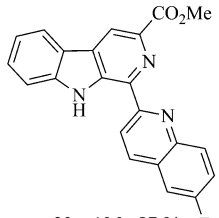
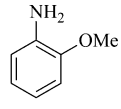
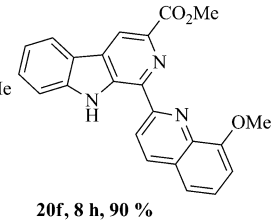
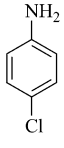
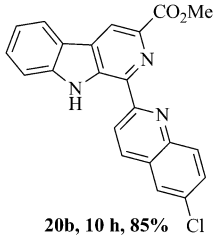
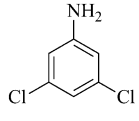
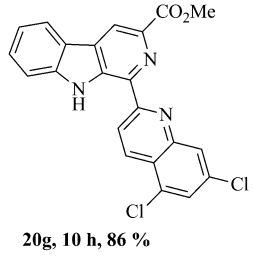
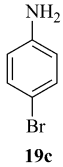
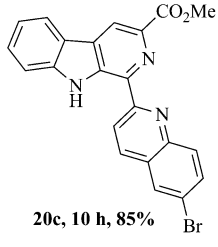
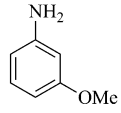
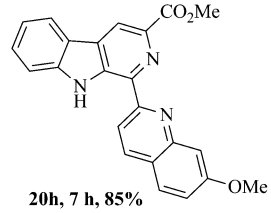
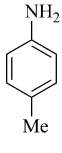
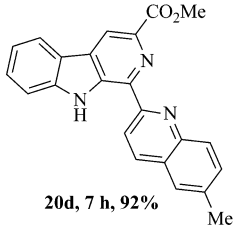
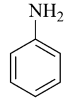
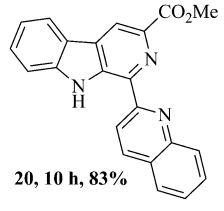
Table 3. Synthesis of Lavendamycin Analogues (20, 20a–h)



Entry	Aniline	Product Time/Yield[a]	Entry	Aniline	Product Time/Yield[a]
1	 **19**	 **20, 8 h, 89 %**	6	 **19e**	 **20e, 8 h, 94 %**
2	 **19a**	 **20a, 10 h, 87 %**	7	 **19f**	 **20f, 8 h, 90 %**
3	 **19b**	 **20b, 10 h, 85%**	8	 **19g**	 **20g, 10 h, 86 %**
4	 **19c**	 **20c, 10 h, 85%**	9	 **19h**	 **20h, 7 h, 85%**
5	 **19d**	 **20d, 7 h, 92%**	10[b]	 **19**	 **20, 10 h, 83%**

[a]Yield refers to column purified product. For entries 1–9, *n*-butylvinyl ether (**7**) was used. [b]For entry 10, ethylvinyl ether (**7a**) was used.

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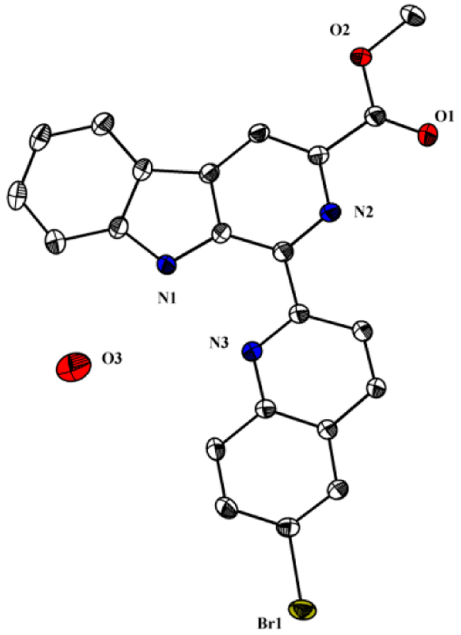


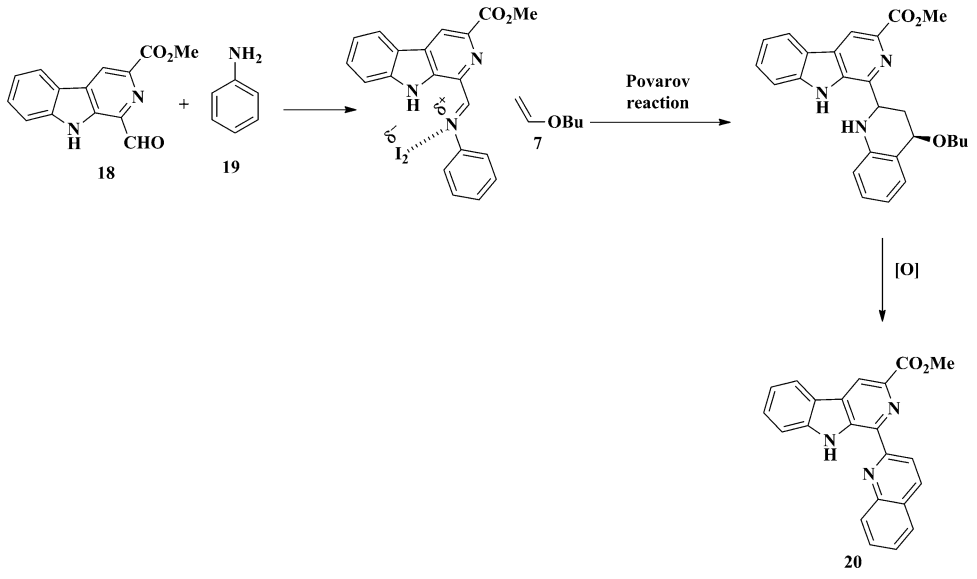
Figure 2. ORTEP of compound **20c**.[18]

Procedure for the Synthesis of 1-Bromo-2,5-dimethoxy-3-nitrobenzene (17). To the solution of compound **16** (500 mg, 2 mmol), KOH (3 equiv) in acetone (20 mL) was added CH_3I (1.5 equiv) dropwise. The reaction mixture was heated at reflux temperature of acetone. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. The reaction mass was concentrated under a vacuum and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum. The compound **17** (475 mg, 90%) was isolated as a yellow solid and carried forward to the next step without purification. The spectroscopic data of the compound **17** were in full accordance with those reported:[20b,21] mp 106 °C; IR (KBr) 2854, 1544, 1012, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.35 (1H, d, J = 3.0 Hz), 7.29 (1H, d, J = 3.0 Hz), 3.97 (3H, s), 3.84 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 155.5, 145.0, 144.5, 123.9, 120.2, 109.2 (aromatic C), 62.7, 56.3 (aliphatic C); LC−MS found for $C_8H_8BrNO_4$: m/z = 261 (M^+), 262 (M + H), 263 (M + 2), positive mode. Anal. Calcd. for: C, 36.67; H, 3.08; N, 5.34%. Found: C, 36.51; H, 3.13; N, 5.28%.

Procedure for the Synthesis of 3-Bromo-2,5-dimethoxyaniline (6). To compound **17** (400 mg, 1.5 mmol) in AcOH (20 mL) was added Fe-powder (3 equiv). The reaction mixture was heated at 80 °C for a period of 20 min and then cooled to room temperature. The mixture was filtered to remove iron powder using Celite-545 bed. The filtrate was concentrated and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum. The compound 3-bromo-2,5-dimethoxyaniline (**6**) was obtained as a brown viscous oil in 93% yield and used for further reactions without any purification. The spectroscopic data of the compound **6** were in full accordance with those reported:[20b,21,22a,b] IR (KBr) 3463, 3369, 2832, 1616, 1227, 997, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 6.31 (1H, d, J = 2.4 Hz), 6.08 (1H, d, J = 2.8 Hz), 3.88 (2H, s), 3.63 (3H, s), 3.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 156.8, 141.5, 138.6, 116.9, 106.9, 101.2 (aromatic C), 59.8, 55.6 (aliphatic C); LC−MS found for $C_8H_{10}BrNO_2$: m/z = 231 (M^+), 232 (M + H), 233 (M + 2), positive mode. Anal. Calcd. for: C, 41.40; H, 4.34; N, 6.04%. Found: C, 41.52; H, 4.31; N, 6.15%.

Typical Procedure for the Preparation of Methyl 1-(quinolin-2-yl)-9*H*-β-carboline-3-carboxylate 20. In a round-bottom flask equipped with a magnetic stirring bar, mixture of 0.3 mmol of α-formyl-β-carboline (**18**), 0.3 mmol of aniline (**19**) and 0.5 mmol of anhydrous $MgSO_4$ in 10 mL of dichloromethane was refluxed for 1 h under stirring. The yellow solution was filtered and the filtrate was concentrated under a vacuum. Without purification, to the isolated imine in 10 mL of THF solvent were added 0.32 mmol of *n*-butylvinyl ether and 10 mol % of I_2. The mixture was refluxed for 8 h. After completion of the reaction, as indicated by the TLC, the reaction mixture was quenched by saturated solution of $Na_2S_2O_3{\cdot}5H_2O$, extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was concentrated under the reduced pressure. Product was purified by column chromatography (silica gel: hexanes/ethyl acetate = 10:2) to afford **20** (yield 89%): mp 202−204 °C; IR (KBr) 3364, 3061, 2854, 1712, 1564, 1259, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 11.96 (1H, s), 9.04 (1H, d, J = 8.8 Hz), 8.98 (1H, s), 8.38 (1H, d, J = 8.8 Hz), 8.31 (1H, d, J = 8.4 Hz), 8.26 (1H, d, J = 8.0 Hz), 7.92 (1H, d, J = 8.0 Hz), 7.83 (1H, t, J = 8.0 Hz), 7.75 (1H, d, J = 8.4 Hz), 7.63−7.69 (2H, m), 7.40 (1H, t, J = 7.6 Hz), 4.13 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.8, 157.5, 147.2, 141.0, 137.5, 136.9, 136.7, 130.7, 129.8, 129.2, 129.1, 128.1, 128.0, 127.1, 122.0, 121.6, 121.0, 119.7, 118.7, 112.4 (aromatic C), 52.7 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{22}H_{15}N_3O_2$; 354.1242 (M + H), found 354.1242; LC−MS m/z = 354.15 (M + H), positive mode. Anal.

Scheme 16. Proposed Mechanism for the Synthesis of 20



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Calcd. for: C, 74.78; H, 4.28; N, 11.89%. Found: C, 74.65; H, 4.21; N, 12.07%.

Methyl-1-(7-bromo-5,8-dimethoxy-2-quinolyl)-4-methyl-9*H*-β-carboline-3-carboxylate (4). Data: mp 284−286 °C; IR (KBr) 3346, 1714, 1456, 1082, 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 12.42 (1H, s), 8.90 (1H, d, *J* = 9.0 Hz), 8.67 (1H, d, *J* = 9.0 Hz), 8.40 (1H, d, *J* = 8.0 Hz), 7.74 (1H, d, *J* = 8.5 Hz), 7.66 (1H, dt, *J* = 0.5 and 7.5 Hz), 7.41 (1H, dt, *J* = 0.5 and 8.0 Hz), 7.01 (1H, s), 4.27 (3H, s), 4.11 (3H, s), 4.05 (3H, s), 3.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 167.9, 157.8, 151.8, 146.7, 142.0, 141.0, 137.0, 135.9, 134.8, 132.6, 132.1, 130.1, 128.2, 124.1, 122.3, 120.7, 120.5, 118.7, 116.6, 112.2, 108.7 (aromatic C), 61.5, 56.1, 52.5, 16.9 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{25}H_{20}BrN_3O_4$; 506.0715 (M + H), found 506.0716; LC−MS *m*/*z* = 507.90 (M + 2), positive mode. Anal. Calcd. for: C, 59.30; H, 3.98; N, 8.30%. Found: C, 59.42; H, 3.93; N, 8.45%.

Ethyl-1-(7-bromo-5,8-dimethoxy-2-quinolyl)-4-methyl-9*H*-β-carboline-3-carboxylate (21). Data: mp 276−278 °C; IR (KBr) 3342, 2843, 1764, 1034, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 12.34 (1H, s), 8.86 (1H, d, *J* = 8.8 Hz), 8.63 (1H, d, *J* = 8.8 Hz), 8.36 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.63 (1H, t, *J* = 7.2 Hz), 7.38 (1H, t, *J* = 7.2 Hz), 6.97 (1H, s), 4.57 (2H, q, *J* = 7.2 Hz), 4.25 (3H, s), 4.02 (3H, s), 3.20 (3H, s), 1.56 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 167.6, 157.8, 151.8, 146.6, 141.9, 141.0, 137.6, 135.8, 134.7, 132.0, 130.0, 128.2, 124.0, 122.3, 120.6, 120.5, 118.6, 116.6, 112.2, 108.6 (aromatic C), 61.5, 61.4, 56.1, 16.9, 14.5 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{26}H_{22}BrN_3O_4$; 520.0872 (M + H), found 520.0870; LC−MS *m*/*z* = 520.00 (M + H), positive mode. Anal. Calcd. for: C, 60.01; H, 4.26; N, 8.07%. Found: C, 60.15; H, 4.21; N, 7.96%.

Procedure for the Synthesis of 1,4-Dimethoxy-3,5-dinitrobenzene (26). To a solution of 4-methoxy-2,6-dinitrophenol[23] (1.00 g, 4.6 mmol) in DMF (20 mL) were added methyliodide (0.99 g, 6.99 mmol) and K_2CO_3 (1.49 g, 14.03 mmol). The resultant mixture was stirred at room temperature for 12 h. The reaction mixture was poured into ice-cooled water. The solid precipitate was filtered off and dissolved in EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The compound **26** was obtained as a colorless solid in 92% yield (0.965 g) and used for further reactions without any purification. The spectroscopic data of the compound **26** were in full accordance with those reported:[23,11] mp 111−112 °C; IR (KBr) 3094, 1416, 1037, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.57 (2H, s), 4.02 (3H, s), 3.92 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 154.7, 145.7, 141.0, 114.7 (aromatic C), 65.0, 56.7 (aliphatic C); HRMS (ESI-MS) calcd. for $C_8H_8N_2O_6$; 251.0280 (M + Na), found 251.0280; LC−MS *m*/*z* = 229.15 (M + H), positive mode. Anal. Calcd. for: C, 42.11; H, 3.53; N, 12.28%. Found: C, 41.25; H, 3.43; N, 12.15%.

Procedure for the Synthesis of 2,5-Dimethoxy-1,3-benzenediamine (27). The dimethoxynitro compound **26** (0.5 g, 2.19 mmol) was dissolved in AcOH (15 mL) and heated to 80 °C. After 10 min stirring, Fe powder (0.611 g, 10.95 mmol) was added in the reaction mixture. The reaction mixture was then allowed to reach 80 °C over 1 h with stirring. After disappearance of starting material as monitored by TLC, the residue was filtered off and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 100:30) to give the desired product **27** as a viscous liquid in 86% yield (0.965 g). The spectroscopic data of the compound **27** were in full accordance with those reported:[24] IR (KBr) 3345, 2876, 1675, 1544, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 5.77 (2H, s), 3.73 (3H, s), 3.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 157.0, 140.4, 129.1, 92.1 (aromatic C), 58.8, 55.2 (aliphatic C); LC−MS found for $C_8H_{12}N_2O_2$: *m*/*z* = 169.10 (M + H), positive mode. Anal. Calcd. for: C, 57.13; H, 7.19; N, 16.66%. Found: C, 57.26; H, 7.23; N, 16.43%.

Procedure for the Synthesis of 3-Amino-2,5-dimethoxy-1-(4-methylphenylsulfonamido)benzene (28). To a solution of compound **27** (0.2 g, 1.19 mmol) in CH_3CN was added tosyl chloride (0.181 g, 0.951 mmol). The reaction mixture was stirred at room temperature for 30 min and then quenched with water. The aqueous layer was extracted with EtOAc and dried over Na_2SO_4. The organic layer was concentrated in vacuo and was purified by column chromatography (silica gel, hexanes/EtOAc = 10:3) to give the desired compound **28** (0.203 g, 53%) as a viscous liquid: IR (KBr) 3211, 2425, 1433, 1221, 1024, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.74 (2H, d, *J* = 7.5 Hz), 7.21 (2H, d, *J* = 7.3 Hz), 6.56 (1H, s), 5.98 (1H, s), 3.76 (2H, s), 3.69 (3H, s), 3.42 (3H, s), 2.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 156.8, 143.9, 140.3, 136.4, 130.9, 130.8, 129.6, 127.2, 97.6, 94.7 (aromatic C), 59.7, 55.4, 21.5 (aliphatic C); LC−MS found for $C_{15}H_{18}N_2O_4S$: *m*/*z* = 323.20 (M + H), positive mode. Anal. Calcd. for: C, 55.88; H, 5.63; N, 8.69%. Found: C, 55.68; H, 5.59; N, 8.81%.

Ethyl 1-[5,8-dimethoxy-7-(4-methylphenylsulfonamido)-2-quinolyl]-4-methyl-9*H*-β-carboline-3-carboxylate (24). Data: mp 267−269 °C; IR (KBr) 3423, 3034, 2834, 2234, 1897, 1327, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 12.08 (1H, s), 8.76 (1H, d, *J* = 8.8 Hz), 8.59 (1H, d, *J* = 8.8 Hz), 8.34 (1H, d, *J* = 7.9 Hz), 7.80 (2H, d, *J* = 8.1 Hz), 7.62−7.64 (2H, m), 7.52 (1H, s), 7.34−7.39 (2H, m), 7.24−7.27 (1H, m), 4.56 (2H, q, *J* = 7.0 Hz), 4.05 (3H, s), 3.86 (3H, s), 3.17 (3H, s), 2.30 (3H, s), 1.55 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 167.6, 157.7, 152.1, 144.4, 141.1, 140.8, 137.7, 136.9, 136.2, 135.6, 134.7, 131.9, 131.8, 130.3, 129.97, 129.9, 128.1, 127.2, 124.0, 122.3, 120.7, 118.1, 117.6, 111.9, 98.1 (aromatic C), 61.9, 61.4, 56.1, 21.5, 16.8, 14.5 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{33}H_{30}N_4O_6S$; 633.1784 (M + Na), found 633.1786. Anal. Calcd. for: C, 64.90; H, 4.95; N, 9.17%. Found: C, 64.71; H, 4.86; N, 9.25%.

Ethyl 1-[5,8-dimethoxy-7-(4-methylphenylsulfonamido)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (29). Data: mp 284−286 °C; IR (KBr) 3423, 2639, 1123, 1102, 732 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, TMS) δ 12.11 (1H, s), 10.29 (1H, s), 9.06 (1H, s), 8.65 (2H, s), 8.50 (1H, d, *J* = 7.7 Hz), 7.80−7.82 (3H, m), 7.69 (1H, t, *J* = 7.5 Hz), 7.36−7.42 (3H, m), 7.21 (1H, s), 3.97 (3H, s), 3.94 (3H, s), 3.86 (3H, s), 2.29 (3H, s); Due to limited solubitity of the compound **29** both in $CDCl_3$ as well as in DMSO-d_6, we were unable to record ^{13}C NMR spectrum. HRMS (ESI-MS) calcd. for $C_{31}H_{26}N_4O_6S$; 583.1651 (M + H), found 583.1656. Anal. Calcd. for: C, 63.91; H, 4.50; N, 9.62%. Found: C, 63.85; H, 4.45; N, 9.56%.

Procedure for the Synthesis of 2,4-Dibromo-6-nitrophenol (36). A mixture of *o*-nitrophenol (**35**) (1.0 g, 7.18 mmol), KBr (0.846 g, 7.18 mmol) in acetic acid/water (10 mL/5 mL) was stirred for 10 min and cooled on ice. Then, 1 mL of conc. H_2SO_4 was added dropwise over a period of 10 min. Into the ice cooled solution was added bromine (1.133 g, 7.18 mmol) dropwise. After the addition, the reaction was left stirring at room temperature for a further 1 h. After completion of the reaction as indicated by TLC, the reaction was then quenched with saturated solution of $Na_2S_2O_3{\cdot}5H_2O$ and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to yield the desired compound **36** (1.97 g, 93%) as a bright yellow solid. The spectroscopic data of the compound **36** were in full accordance with those reported:[25a,b] mp 108−110 °C; IR (KBr) 3387, 3088, 1704, 1453, 1022, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 11.05 (1H, s), 8.25 (1H, d, *J* = 2.2 Hz), 7.99 (1H, d, *J* = 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 151.4, 142.9, 134.4, 126.8, 114.5, 111.5 (aromatic C); LC−MS found for $C_6H_3Br_2NO_3$: 296.05 (M + 2), positive mode. Anal. Calcd. for: C, 24.27; H, 1.02; N, 4.72%. Found: C, 24.36; H, 1.12; N, 4.85%.

Procedure for the Synthesis of 1,5-Dibromo-2-(4-methoxybenzyloxy)-3-nitrobenzene (37). A solution of compound **36** (1.0 g, 3.39 mmol) and K_2CO_3 (1.41 g, 10.17 mmol) in 20 mL of acetone was vigorously stirred while adding *p*-methoxybenzyl bromide (0.812 g, 4.06 mmol). The reaction mixture was heated at reflux temperature of acetone. Upon completion (disappearance of starting materials as indicated by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/ethylacetate = 10:1) to give the desired product **37** as a colorless solid (1.48 g, 92%): mp 105−107 °C; IR (KBr) 3299, 3099, 1654, 1455, 1287, 876, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.90−7.96 (2H, m), 7.45 (2H, d, *J* = 7.9 Hz), 6.93 (2H, d, *J* =

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7.9 Hz), 5.11 (2H, s), 3.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 160.2, 148.5, 145.9, 140.1, 130.8, 127.4, 127.1, 121.3, 116.9, 114.0 (aromatic C), 76.7, 55.3 (aliphatic C); LC−MS found for $C_{14}H_{11}Br_2NO_4$: 415.25 (M + 1), positive mode. Anal. Calcd. for: C, 40.32; H, 2.66; N, 3.36%. Found: C, 40.38; H, 2.62; N, 3.31%.

Procedure for the Synthesis of 3,5-Dibromo-2-(4-methoxybenzyloxy)aniline (34). Into a solution of compound **37** (1.0 g, 2.41 mmol) in 20 mL of acetic acid was added Fe powder (0.672 g, 12.05 mmol), and the mixture was heated around 65−70 °C. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered off. The filtrate was quenched with water and extracted with EtOAc. The combined organic layer was concentrated under reduced pressure and purified using column chromatography (silica gel: hexanes/EtOAc = 10:3) as a colorless solid **34** (0.798 g, 86%): mp 88−90 °C; IR (KBr) 3455, 2976, 1527, 1235, 987 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42 (2H, d, J = 8.6 Hz), 7.06 (1H, d, J = 2.2 Hz), 6.93 (2H, d, J = 8.6 Hz), 6.79 (1H, d, J = 2.2 Hz), 4.89 (2H, s), 3.83−3.85 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 159.9, 142.8, 142.3, 130.2, 128.8, 124.3, 118.0, 117.6, 114.1 (aromatic C), 74.1, 55.3 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{14}H_{13}Br_2NO_2$; 385.9391 (M + H), found 385.9393; LC−MS m/z = 385.35 (M^+), positive mode. Anal. Calcd. for: C, 43.44; H, 3.39; N, 3.62%. Found: C, 43.52; H, 3.32; N, 3.51%.

Methyl 1-[5,7-dibromo-8(4-methoxybenzyloxy)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (38). Data: mp 320−322 °C; IR (KBr) 3432, 3133, 2298, 1723, 1673, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 11.64 (1H, s), 8.96 (1H, d, J = 8.5 Hz), 8.89 (1H, s), 8.54 (1H, d, J = 8.5 Hz), 8.14 (1H, d, J = 7.3 Hz), 8.00 (1H, s), 7.49 (2H, d, J = 7.6 Hz), 7.40 (1H, t, J = 6.96 Hz), 7.29−7.31 (1H, m), 6.86 (2H, d, J = 7.8 Hz), 6.55 (1H, d, J = 7.8 Hz), 5.20 (2H, s), 4.11 (3H, s), 3.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.5, 159.9, 157.9, 151.8, 142.8, 140.9, 136.8, 136.5, 136.4, 133.7, 130.9, 129.8, 128.7, 128.6, 127.5, 121.5, 121.2, 120.9, 119.0, 117.3, 114.2, 113.1 (aromatic C), 75.9, 55.4, 52.7 (aliphatic C); LC−MS found for $C_{30}H_{21}Br_2N_3O_4$: m/z = 647.30 (M + 2), positive mode. Anal. Calcd. for: C, 55.66; H, 3.27; N, 6.49%. Found: C, 55.76; H, 3.21; N, 6.43%.

Ethyl 1-[5,7-dibromo-8(4-methoxybenzyloxy)-2-quinolyl]-4-methyl-9*H*-β-carboline-3-carboxylate (33). Data: mp 298−300 °C; IR (KBr) 3011, 2109, 1543, 1109, 621 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 11.75 (1H, s), 8.97 (1H, d, J = 8.9 Hz), 8.59 (1H, d, J = 8.9 Hz), 8.30 (1H, d, J = 7.9 Hz), 8.03 (1H, s), 7.52 (2H, d, J = 8.7 Hz), 7.40 (1H, dt, $J1$ = 1.0 and $J2$ = 7.2 Hz), 7.32 (1H, dt, J_1 = 1.0 and J_2 = 7.2 Hz), 6.86−6.89 (2H, m), 6.62 (1H, d, J = 8.2 Hz), 5.24 (2H, s), 4.59 (2H, q, J = 7.1 Hz), 3.83 (3H, s), 3.20 (3H, s), 1.58 (3H, t, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 167.5, 159.9, 158.2, 151.8, 142.9, 140.7, 137.7, 136.4, 135.6, 133.9, 133.5, 132.3, 130.2, 129.9, 128.7, 127.7, 127.5, 123.6, 122.0, 120.9, 120.6, 117.3, 117.2, 114.2, 112.9 (aromatic C), 75.9, 61.4, 55.4, 16.9, 14.5 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{32}H_{25}Br_2N_3O_4$; 674.0290 (M + H), found 674.0290. Anal. Calcd. for: C,56.91; H, 3.73; N, 6.22%. Found: C, 56.85; H, 3.68; N, 6.15%.

Procedure for the Synthesis of 2,5-Dimethoxy-3-nitroaniline (41). To a solution of dinitro compound **26** (0.5 g, 2.19 mmol) in AcOH (20 mL) was added Fe powder (0.367 g, 6.58 mmol). After stirring for 2 h at 60 °C, water was added and the reaction mixture was filtered off. The residue was extracted with EtOAc. The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified using column chromatography (silica gel: hexanes/EtOAc = 10:2) to give compound **41** as a red color solid (80%, 0.347 g). The spectroscopic data of the compound **41** were in full accordance with those reported:[11] mp 85−87 °C; IR (KBr) 3456, 2876, 1498, 1231, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.71 (1H, d, J = 3.2 Hz), 6.49 (1H, d, J = 3.2 Hz), 4.13 (2H, s), 3.84 (3H, s), 3.76 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 155.7, 143.9, 142.9, 134.9, 106.1, 98.3 (aromatic C), 61.2, 55.7 (aliphatic C); LC−MS found for $C_8H_{10}N_2O_4$: m/z = 199.10 (M + H), positive mode. Anal. Calcd. for: C,48.48; H, 5.09; N, 14.14%. Found: C, 48.37; H, 5.15; N, 14.06%.

Procedure for the Synthesis of *N*1-(2,5-Dimethoxy-3-nitrophenyl)acetamide (42). The mixture of mononitro compound **41** (0.3 g, 1.51 mmol), acetylchloride (0.177 g, 2.27 mmol) and K_2CO_3 (0.631 g, 4.54 mmol) was stirred in CH_2Cl_2 at room temperature for 2 h. The mixture was directly concentrated under reduced pressure and the residue was purified by column chromatography (silica gel: hexanes/EtOAc = 10:2) to afford the compound **42** as a light brownish color solid (0.304 g, 84%). The spectroscopic data of the compound **42** were in full accordance with those reported:[24] mp 140−142 °C; IR (KBr) 3321, 2987, 1548, 1290, 1092, 947 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.29 (1H, d, J = 2.8 Hz), 7.85 (1H, s), 7.09 (1H, d, J = 3.2 Hz), 3.87 (3H, s), 2.99 (3H, s), 2.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 168.7, 155.6, 134.2, 111.3, 104.3 (aromatic C), 62.6, 56.0, 25.0 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{10}H_{12}N_2O_5$; 241.0824 (M + H), found 241.0825; LC−MS m/z = 241.30 (M + H), positive mode. Anal. Calcd. for: C, 50.00; H, 5.04; N, 11.66%. Found: C, 50.12; H, 5.12; N, 11.43%.

Procedure for the Synthesis of *N*1-(3-Amino-2,5-dimethoxyphenyl)acetamide (40). To a solution of **42** (0.250 g, 1.04 mmol) in AcOH (5 mL)/ethanol (10 mL) mixture was added Fe powder (0.174 g, 3.12 mmol). The reaction mixture was heated to 85 °C. After completion of the reaction as indicated by TLC (disappearance of starting material), water was added and extracted with EtOAc. The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: hexanes/EtOAc = 10:3) to afford the compound **40** as a viscous liquid (92%, 0.201 g). The spectroscopic data of the compound **40** were in full accordance with those reported:[23,24] IR (KBr) 3321, 2987, 1548, 1290, 1092, 947 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.75 (1H, s), 7.34 (1H, d, J = 2.6 Hz), 6.02 (1H, d, J = 2.8 Hz), 3.88 (2H, s), 3.67 (3H, s), 3.66 (3H, s), 2.16 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 168.5, 156.6, 139.8, 131.9, 130.3, 97.5, 95.8 (aromatic C), 59.7, 55.4, 24.9 (aliphatic C); LC−MS found for $C_{10}H_{14}N_2O_3$: m/z = 211.15 (M + H), positive mode. Anal. Calcd. for: C, 57.13; H, 6.71; N, 13.33%. Found: C, 57.23; H, 6.75; N, 13.43%.

Methyl 1-(5,8-dimethoxy-7-methylcarboxamido-2-quinolyl)-9*H*-β-carboline-3-carboxylate (43). Data: mp 323−325 °C; IR (KBr) 3438, 3056, 2987, 1223, 1098, 864 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 12.25 (1H, s), 8.95 (1H, s), 8.83 (1H, d, J = 8.8 Hz), 8.64 (1H, d, J = 8.8 Hz), 8.24 (1H, d, J = 8.0 Hz), 8.16 (1H, s), 8.13 (1H, s), 7.63−7.68 (2H, m), 7.37−7.41 (1H, m), 4.22 (3H, s), 4.12 (3H, s), 4.04 (3H, s), 2.36 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 168.8, 166.8, 157.2, 151.9, 141.1, 140.8, 137.6, 136.8, 135.4, 132.1, 132.0, 130.6, 129.0, 122.1, 121.6, 120.9, 118.7, 117.7, 117.3, 112.0, 99.0 (aromatic C), 61.7, 56.0, 52.7, 25.3 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{26}H_{22}N_4O_5$; 471.1668 (M + H), found 471.1668. Anal. Calcd. for: C, 66.37; H, 4.71; N, 11.91%. Found: C, 66.25; H, 4.65; N, 11.85%.

Methyl 1-(5,8-dimethoxy-7-methylcarboxamido-2-quinolyl)-4-methyl-9*H*-β-carboline-3-carboxylate (39). Data: mp 336−338 °C; IR (KBr) 3432, 3083, 2234, 1876, 1276, 865 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 12.24 (1H, s), 8.72 (1H, d, J = 8.5 Hz), 8.57 (1H, d, J = 8.5 Hz), 8.35 (1H, d, J = 8.0 Hz), 8.15 (1H, s), 8.11 (1H, s), 7.63−7.65 (2H, m), 7.39 (1H, t, J = 7.0 Hz), 4.20 (3H, s), 4.11 (3H, s), 4.03 (3H, s), 3.19 (3H, s), 2.37 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 168.8, 168.0, 157.3, 151.8, 140.8, 140.7, 137.0, 135.7, 135.5, 135.0, 132.2, 131.8, 130.0, 128.0, 124.0, 122.3, 120.6, 117.4, 117.0, 112.0, 99.0 (aromatic C), 61.6, 56.0, 52.4, 25.2, 16.8 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{27}H_{24}N_4O_5$; 485.1825 (M + H), found 485.1825. Anal. Calcd. for: C, 66.93; H, 4.99; N, 11.56%. Found: C, 67.06; H, 4.89; N, 11.43%.

Methyl-1-(6-fluoro-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20a). Data: mp 204−206 °C; IR (KBr) 3386, 3046, 1742, 1254, 1227, 734, 586 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 11.59 (1H, s), 8.93 (1H, d, J = 8.4 Hz), 8.84 (1H, s), 8.16−8.20 (3H, m), 7.60−7.63 (2H, m), 7.52 (1H, t, J = 6.0 Hz), 7.44 (1H, d, J = 8.4 Hz), 7.36 (1H, t, J = 6.0 Hz), 4.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.6, 161.9, 159.5, 156.9, 144.1, 140.8, 137.0, 136.8, 136.3, 136.0, 131.5, 131.4, 130.6, 128.9, 128.7, 128.6, 121.9, 121.5, 120.9, 120.3, 119.9, 119.7, 118.5, 112.3, 111.2, 110.9 (aromatic C), 52.6 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{22}H_{14}FN_3O_2$; 372.1147 (M + H),

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found 372.1148; LC−MS m/z = 370.15 (M − H), negative mode. Anal. Calcd. for: C, 71.15; H, 3.80; N, 11.32%. Found: C, 71.28; H, 3.73; N, 11.22%.

Methyl-1-(6-chloro-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20b). Data: mp 230−232 °C; IR (KBr) 3348, 2922, 1749, 1431, 889, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 11.70 (1H, s), 9.02 (1H, d, J = 8.5 Hz), 8.94 (1H, s), 8.24 (2H, d, J = 8.0 Hz), 8.19 (1H, d, J = 9.0 Hz), 7.86 (1H, d, J = 2.0 Hz), 7.71−7.74 (2H, m), 7.67 (1H, t, J = 7.5 Hz), 7.41 (1H, t, J = 7.0 Hz), 4.13 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 166.6, 157.7, 145.5, 140.9, 136.9, 136.8, 136.5, 135.8, 132.7, 130.8, 130.7, 130.6, 129.1, 128.6, 126.7, 121.9, 121.5, 121.1, 120.5, 118.7, 112.3 (aromatic C), 52.7 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{22}H_{14}ClN_3O_2$; 388.0853 (M + H), found 388.0853; LC−MS m/z = 387.30 (M^+), positive mode. Anal. Calcd. for: C, 68.13; H, 3.64; N, 10.83%. Found: C, 68.06; H, 3.75; N, 10.75%.

Methyl-1-(6-bromo-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20c). Data: mp 270−271 °C; IR (KBr) 3465, 2976, 1765, 1288, 1043, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 11.72 (1H, s), 9.01 (1H, d, J = 8.8 Hz), 8.96 (1H, s), 8.24 (2H, d, J = 8.4 Hz), 8.14 (1H, d, J = 8.8 Hz), 8.05 (1H, s), 7.85−7.88 (1H, m), 7.71−7.73 (1H, m), 7.67 (1H, t, J = 7.2 Hz), 7.41 (1H, t, J = 7.2 Hz), 4.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.6, 157.9, 145.8, 140.9, 136.9, 136.6, 135.8, 133.2, 130.8, 130.7, 130.1, 129.2, 129.1, 122.0, 121.5, 121.1, 120.9, 120.6, 118.8, 112.3 (aromatic C), 52.7 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{22}H_{14}BrN_3O_2$; 432.0347 (M + H), found 432.0349; LC−MS m/z = 432 (M + H), 433.15 (M + 2), positive mode. Anal. Calcd. for: C, 61.13; H, 3.26; N, 9.72%. Found: C, 61.05; H, 3.21; N, 9.85%.

Methyl-1-(6-methyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20d). Data: mp 218−220 °C; IR (KBr) 3358, 2854, 1709, 1103, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 11.89 (1H, s), 8.96 (1H, d, J = 8.8 Hz), 8.93 (1H, s), 8.22−8.25 (2H, m), 8.14 (1H, d, J = 8.4 Hz), 7.69−7.71 (1H, m), 7.60−7.66 (3H, m), 7.38 (1H, t, J = 7.6 Hz), 4.11 (3H, s), 2.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.8, 156.6, 145.7, 140.9, 137.7, 137.1, 136.8, 136.6, 136.1, 132.0, 130.5, 128.9, 128.8, 128.1, 126.9, 121.9, 121.6, 120.9, 119.6, 118.4, 112.3 (aromatic C), 52.6, 21.7 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{23}H_{17}N_3O_2$; 368.1399 (M + H), found 368.1399; LC−MS m/z = 368.10 (M + H), positive mode. Anal. Calcd. for: C, 75.19; H, 4.66; N, 11.44%. Found: C, 75.36; H, 4.61; N, 11.32%.

Methyl-1-(6-methoxy-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20e). Data: mp 195−197 °C; IR (KBr) 3366, 2854, 1707, 1500, 1261, 746, 597 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 11.79 (1H, s), 8.93 (1H, d, J = 9.0 Hz), 8.89 (1H, s), 8.19−8.22 (2H, m), 8.12 (1H, d, J = 9.0 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.64 (1H, t, J = 7.5 Hz), 7.42 (1H, dd, J = 2.0 and 9.0 Hz), 7.38 (1H, t, J = 7.5 Hz), 7.12 (1H, d, J = 2.5 Hz), 4.12 (3H, s), 3.98 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 166.8, 158.2, 155.1, 143.1, 140.9, 137.7, 136.7, 136.3, 135.5, 130.5, 130.4, 129.1, 128.9, 122.5, 121.9, 121.6, 120.8, 119.9, 118.2, 112.3, 105.4 (aromatic C), 55.6, 52.6 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{23}H_{17}N_3O_3$; 384.1348 (M + H), found 384.1348; LC−MS m/z = 384.00 (M + H), positive mode. Anal. Calcd. for: C, 72.05; H, 4.47; N, 10.96%. Found: C, 72.15; H, 4.41; N, 10.86%.

Methyl-1-(8-methoxy-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20f). Data: mp 206−208 °C; IR (KBr) 3456, 2962, 1711, 1504, 1018, 798 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 12.49 (1H, s), 8.92−8.94 (2H, m), 8.30 (1H, d, J = 8.5 Hz), 8.23 (1H, d, J = 7.5 Hz), 7.64 (2H, d, J = 3.5 Hz), 7.51 (1H, t, J = 8.0 Hz), 7.45 (1H, d, J = 8.0 Hz), 7.35−7.40 (1H, m), 7.11 (1H, d, J = 7.0 Hz), 4.24 (3H, s), 4.14 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 166.8, 155.5, 155.1, 141.3, 138.7, 137.8, 136.8, 136.5, 136.4, 130.4, 128.8, 128.7, 127.2, 121.9, 121.6, 120.7, 119.5, 119.4, 118.6, 112.4, 107.7 (aromatic C), 56.2, 52.6 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{23}H_{17}N_3O_3$; 384.1348 (M + H), found 384.1356; LC−MS m/z = 384.05 (M + H), positive mode. Anal. Calcd. for: C, 72.05; H, 4.47; N, 10.96%. Found: C, 72.15; H, 4.41; N, 10.85%.

Methyl-1-(5,7-dichloro-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20g). Data: mp 254 °C; IR (KBr) 3365, 2928, 1593, 1259, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 11.56 (1H, s), 9.09 (1H, d, J = 9.0 Hz), 8.96 (1H, s), 8.67 (1H, d, J = 9.0 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.19 (1H, d, J = 1.0 Hz), 7.75−7.76 (1H, m), 7.69−7.71 (1H, m), 7.67 (1H, d, J = 1.0 Hz), 7.43 (1H, t, J = 7.5 Hz), 4.14 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 166.5, 159.1, 147.9, 140.9, 137.1, 136.6, 136.3, 135.0, 133.5, 132.7, 131.1, 129.3, 127.6, 127.2, 124.6, 122.0, 121.4, 121.2, 120.7, 119.0, 112.4 (aromatic C), 52.7 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{22}H_{13}Cl_2N_3O_2$; 422.0463 (M + H), found 422.0463; LC−MS m/z = 419.25 (M − 2), negative mode. Anal. Calcd. for: C, 62.58; H, 3.10; N, 9.95%. Found: C, 62.45; H, 3.17; N, 9.88%.

Methyl-1-(7-methoxy-2-quinolyl)-9*H*-β-carboline-3-carboxylate (20h). Data: mp 178 °C; IR (KBr) 3433, 2920, 1726, 1585, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 11.72 (1H, s), 8.86 (1H, s), 8.80 (1H, d, J = 8.5 Hz), 8.17−8.19 (2H, m), 7.68−7.70 (2H, m), 7.62 (1H, t, J = 7.5 Hz), 7.42 (1H, s), 7.37 (1H, t, J = 6.0 Hz), 7.21 (1H, dd, $J1$ = 2.0, $J2$ = 8.5 Hz), 4.11 (3H, s), 4.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 166.7, 160.9, 157.6, 148.8, 140.9, 137.5, 136.8, 136.5, 136.3, 130.5, 128.83, 128.82, 123.3, 121.9, 121.5, 120.8, 119.8, 118.3, 117.5, 112.3, 107.3 (aromatic C), 55.7, 52.6 (aliphatic C); HRMS (ESI-MS) calcd. for $C_{23}H_{17}N_3O_3$; 384.1348 (M + H), found 384.1344; LC−MS m/z = 384.00 (M + H), positive mode. Anal. Calcd. for: C, 72.05; H, 4.47; N, 10.96%. Found: C, 71.89; H, 4.56; N, 10.86%.

1-(2-Quinolyl)-9*H*-β-carboline-3-carboxylic acid (45). Data: mp 276 °C; IR (KBr) 3478, 3054, 2876, 1785, 1022, 739, 643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 12.89 (1H, br), 12.37 (1H, s), 9.08 (1H, s), 9.04 (1H, d, J = 8.8 Hz), 8.77 (1H, d, J = 8.4 Hz), 8.60 (1H, d, J = 8.8 Hz), 8.48 (1H, d, J = 7.6 Hz), 8.05−8.08 (2H, m), 7.91 (1H, t, J = 7.6 Hz), 7.67−7.71 (2H, m), 7.37 (1H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 167.1, 157.0, 147.6, 142.0, 137.5, 137.1, 135.8, 131.1, 130.3, 130.2, 129.5, 128.3, 128.1, 127.8, 122.6, 121.3, 121.2, 119.8, 118.7, 114.0 (aromatic C); HRMS (ESI-MS) calcd. for $C_{21}H_{13}N_3O_2$; 362.0906 (M + Na), found 362.0906; LC−MS m/z = 340 (M + H), positive mode. Anal. Calcd. for: C, 74.33; H, 3.86; N, 12.38%. Found: C, 74.26; H, 3.94; N, 12.25%.

1-(2-Quinolyl)-9*H*-β-carboline (3). Data: mp 176 °C; IR (KBr) 3360, 3049, 2851, 1626, 1502, 1284, 1151, 682, 474 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 11.72 (1H, s), 8.93 (1H, d, J = 8.5 Hz), 8.64 (1H, d, J = 5.0 Hz), 8.37 (1H, d, J = 8.5 Hz), 8.33 (1H, d, J = 8.5 Hz), 8.23 (1H, d, J = 8.0 Hz), 8.10 (1H, d, J = 5.0 Hz), 7.92 (1H, dd, J = 1.0 and 8.0 Hz), 7.82−7.85 (1H, m), 7.72−7.74 (1H, m), 7.61−7.66 (2H, m), 7.34−7.37 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 158.3, 147.4, 140.7, 138.3, 138.0, 136.7, 135.3, 130.6, 129.7, 129.2, 128.6, 127.9, 127.8, 126.8, 121.8, 121.3, 120.0, 119.3, 115.9, 112.0 (aromatic C); HRMS (ESI-MS) calcd. for $C_{20}H_{13}N_3$; 296.1187 (M + H), found 296.1188; LC−MS m/z = 296.15 (M + H), positive mode. Anal. Calcd. for: C, 81.34; H, 4.44; N, 14.23%. Found: C, 81.25; H, 4.51; N, 14.12%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H, ^{13}C spectra, mass and elemental analysis reports of compounds (**3**−**6**, **11**−**13**, **15**−**17**, **20**, **20a**−**h**, **21**, **24**, **26**−**29**, **33**, **34**, **36**−**43**, **45**) and crystal data (CIF). 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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DEDICATION

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