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A novel route to synthesize lavendamycin analogues through an A^3 coupling reaction

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ABSTRACT

A convergent synthesis of lavendamycin analogues has been accomplished by using A^3 coupling reaction between carboline aldehydes, anilines, and phenylacetylenes. Our approach features the use of the ionic liquids as an environmentally benign solvent medium and synthesis of lavendamycin analogues with diverse substitution pattern. Additionally, the formation of α-dihydropyrido-β-carboline was observed during the reaction of α-formyl-β-carboline, aniline, and ethylpropiolate.

1. Introduction

Quinoline and tetrahydroquinoline moieties are important class of *N*-containing heterocycles due to the prevalence of these structural motif in many natural products and synthetic compounds with wide spectrum of biological activities.[1] Multicomponent reactions have received a vast amount of attention, because of their simple and convergent paths to synthesize structurally complex products from simple starting materials in a one-pot fashion.[2] The three component reactions between amines, aldehydes, and terminal acetylenes (A^3 coupling) have been continuously witnessed as a versatile method to construct quinoline ring systems.[1i,3] β-Carboline alkaloids are elegant targets in organic synthesis because of their wide range of biological activities.[4] Lavendamycin, a α-heteroaryl-β-carboline alkaloid (Fig. 1) was isolated from the fermentation broth of *Streptomyces lavendulae*, strain C22030 as a dark red solid in 1982 by Doyle and co-workers from Bristol laboratories.[5] Shortly after the isolation, Balitz and co-workers reported the intriguing structure of lavendamycin by means of analytical and spectroscopic studies.[5] Subsequently, in 1984, Kende's group succeeded in the first total synthesis of lavendamycin methyl ester based on Bischler–Napieralski reaction as the key step.[6]

This β-carboline alkaloid is a naturally occurring antitumor antibiotic, which attracted many research groups and hence it has been the subject of many synthesis.[7] However, despite being an antibiotic, they showed toxicity on human cells and hence the pre clinical use of this alkaloid has been precluded. It has been partly believed that the presence of quinolone present in the lavendamycin structure could perhaps cause for this toxicity.[8] Lavendamycin analogues are associated with remarkable attributes, such as inhibition of HIV reverse transcriptase,[9a,b] MKN45 gastric carcinoma, and WiDr colon carcinoma cells[9c] as well as antiproliferative[9c] and cytotoxicitic[9d] activities. Lavendamycin exhibits antitumor activity against topoisomerase I cell with Minimum Inhibitory Concentration (MIC) of 0.1 μg/mL.[9e] The important biological profile of these compounds and the broad scope of the A^3

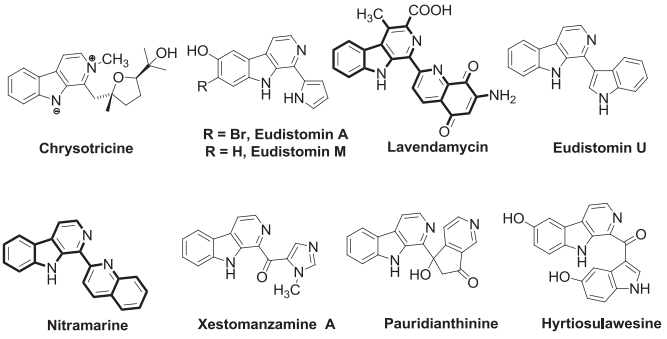

Fig. 1. Some of the representative α-heteroaryl-β-carboline alkaloids.

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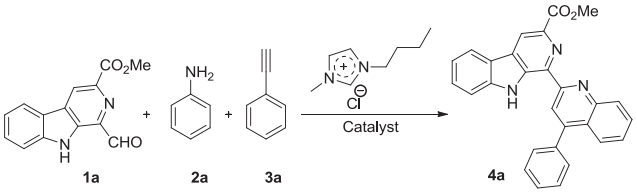
coupling reactions promoted us to synthesize a new variety of lavendamycin analogues with diverse substitution pattern. In continuation of our work on A^3 coupling reactions,[3e] we wish to report here a methodology for the synthesize of lavendamycin analogues. Considering the growing environmental awareness and the negative environmental impacts of organic volatile solvents, we decided to optimize the reaction condition with environmentally more benign and alternatives to the traditional organic volatile solvents, i.e., ionic liquids (so called green solvent) as a solvent medium.[10] Some of the physical properties, such as (i) nonvolatility, (ii) greater effective surface area, (iii) potential activity of a liquid phase and the catalytic nature make them an interesting solvent for a synthesis.[10,11]

2. Results and discussion

In the first attempt, the reaction between aldehyde (**1a**)[12] aniline (**2a**), and phenylacetylene (**3a**) in [Bmim][Cl] at room temperature without catalyst was failed to give the desired product **4a** (Table 1, entry 1). However, heating the reaction around 95–100 °C provided the compound (**4a**) in poor yield (Table 1, entry 2). Further investigation with various ionic liquids (Table 1, entry 3–8) like [Bmim][Br], [Bmim][Tfa], [Emim][Tfa], [Bmim][Tsa], [Bmim][PF_6], and [Bmim][BF_4] revealed that [Bmim][BF_4] was superior to other ionic liquids and provided **4a** in 34% yield (Table 1, entry 8). We envisaged that addition of Lewis acids along with ionic liquid could further enhance the reaction yield (Table 1, entry 9–15). To our delight, addition of La(OTf)$_3$ (10 mol %) to the reaction mixture significantly increased the yield of the product **4a** (Table 1, entry 14). Lowering the catalytic loading to 5 mol % resulted in the incomplete conversion of **4a** (Table 1, entry 15). On the other hand, the yield remained unaffected on addition of 20 mol % of La(OTf)$_3$ (Table 1, entry 16).

Table 1
Optimization for the reaction conditions



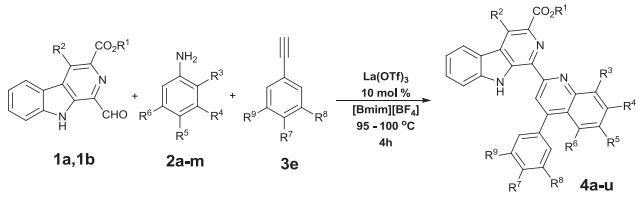
Entry	IL/catalyst	Yield[a] (%)	Time (h)
1	[Bmim][Cl]	—	48
2	[Bmim][Cl]	14	24
3	[Bmim][Br]	Trace	24
4	[Bmim][Tfa]	20	24
5	[Emim][Tfa]	22	24
6	[Bmim][Tsa]	Trace	48
7	[Bmim][PF_6]	15	24
8	[Bmim][BF_4]	34	24
9	[Bmim][BF_4]/I_2 (10 mol %)	47	12
10	[Bmim][BF_4]/Zn(OTf)$_2$ (10 mol %)	Trace	10
11	[Bmim][BF_4]/CuI (10 mol %)	—	20
12	[Bmim][BF_4]/Pd(OAc)$_2$ (10 mol %)	—	20
13	[Bmim][BF_4]/Cu(OTf)$_2$(10 mol %)	56	8
14	**[Bmim][BF_4]/La(OTf)$_3$ (10 mol %)**	**78**	**4**
15	[Bmim][BF_4]/Yb(OTf)$_3$ (10 mol %)	70	3
16	[Bmim][BF_4]/La(OTf)$_3$ (5 mol %)	72	4
17	[Bmim][BF_4]/La(OTf)$_3$ (20 mol %)	76	4

General conditions. Aldehyde (**1a**) 0.3 mmol, aniline (**2a**) 0.3 mmol, and phenylacetylene (**3a**) 0.35 mmol. Optimized reaction condition are in bold.

[a] Yield refers to column purified product. For entry 1, room temperature was maintained. For entry 2–17, 95–100 °C temperature were maintained. Tfa=CF_3COO, Tsa=*p*-toluenesulphonic acid. Emim=1-ethyl-3-methylimidazole, Bmim=1-butyl-3-methylimidazole.

With these optimized condition in hand, next we examined the scope of the reaction with variety of amines (**2a**–**m**), acetylenes (**3a**–**e**), and aldehydes (**1a**,**b**) to generate the lavendamycin analogues (**4a**–**u**).

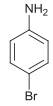
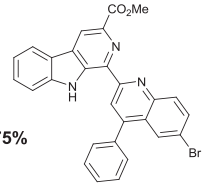
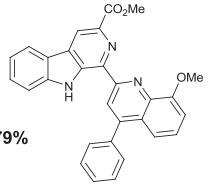
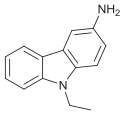
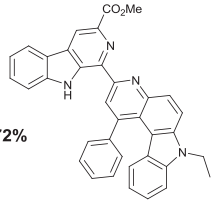
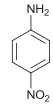
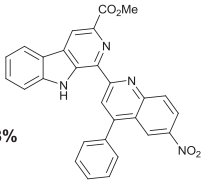
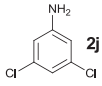
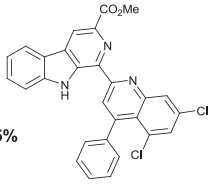
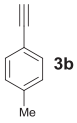
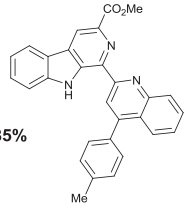
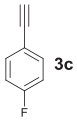
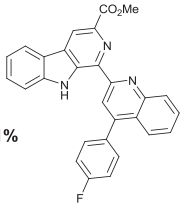
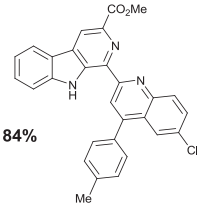
As indicated in Scheme 1, anilines with electron donating substituents (–Me, –OMe) (entries 2, 3, 7, 16, 18, and 19) and with electron withdrawing substituents (–F, –Cl, –Br, –NO_2) (entries 4–6, 9, 10, 13, 14, 20, and 21) in *ortho*-, *para*-, and *meta*-positions well tolerated the reaction with good yields. Carbazole nucleus, an important heterocyclic scaffold found in many natural products, which possess interesting biological properties.[13] In the view of introducing a carbazole unit in the β-carboline core, we tested the reactivity of 3-amino-9-ethylcarbazole (**2h**) as an amine precursor in this reaction (entry 8). As anticipated, the reaction afforded the pyridocarbazole derivative (**4h**) in good yield. The reaction with substituted phenylacetylenes (**3b**–**e**) was also efficiently proceeded to afford the desired lavendamycin analogues (entries 11, 12, 15, and



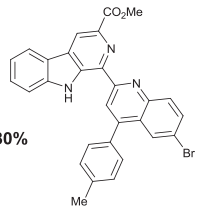
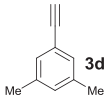
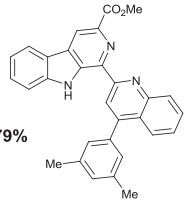
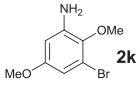
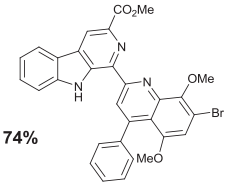
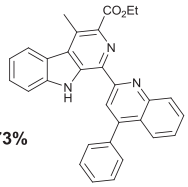
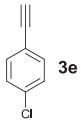
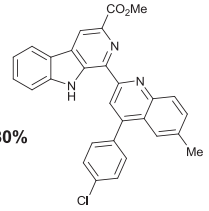
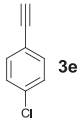
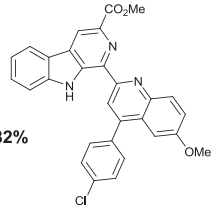
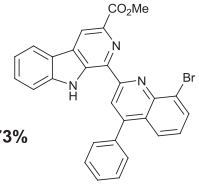
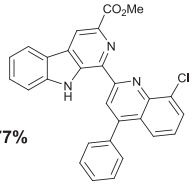
Scheme 1. Synthesis of lavendamycin analogues (**4a**–**u**).

Entry	Aniline	Phenylacetylene	Lavendamycin analogues
1	**2a**	**3a**	**4a, 78%**
2	**2b**	**3a**	**4b, 85%**
3	**2c**	**3a**	**4c, 83%**
4	**2d**	**3a**	**4d, 77%**
5	**2e**	**3a**	**4e, 80%**

(*continued*)

Entry	Aniline	Phenylacetylene	Lavendamycin analogues
6	 **2f**	**3a**	 **4f, 75%**
7	 **2g**	**3a**	 **4g, 79%**
8	 **2h**	**3a**	 **4h, 72%**
9	 **2i**	**3a**	 **4i, 68%**
10	 **2j**	**3a**	 **4j, 75%**
11	**2a**	 **3b**	 **4k, 85%**
12	**2a**	 **3c**	 **4l, 81%**
13	**2e**	**3b**	 **4m, 84%**

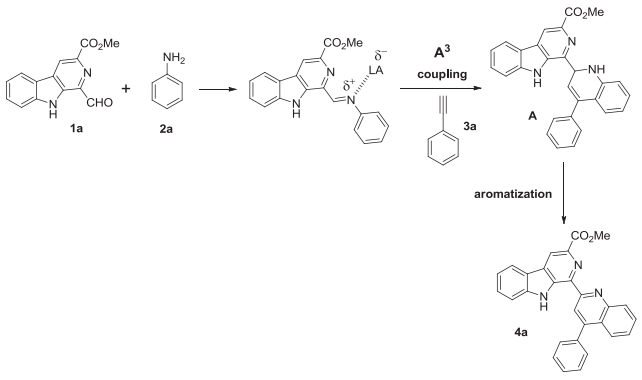
(*continued*)

Entry	Aniline	Phenylacetylene	Lavendamycin analogues
14	**2f**	**3b**	 **4n, 80%**
15	**2a**	 **3d**	 **4o, 79%**
16	 **2k**	**3a**	 **4p, 74%**
17	**2a**	**3a**	 **4q, 73%**
18	**2b**	 **3e**	 **4r, 80%**
19	**2c**	 **3e**	 **4s, 82%**
20	 **2l**	**3a**	 **4t, 73%**
21	 **2m**	**3a**	 **4u, 77%**

18) in good yields. The structure of compound **4g** is confirmed by X-ray diffraction analysis (Fig. 2).[14]

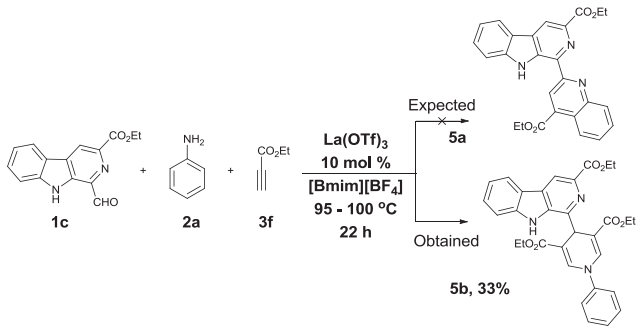
Fig. 2. The ORTEP of compound **4g**.

According to the literature,[3] the proposed mechanism is shown in Scheme 2. Aldehyde (**1a**) and aniline (**2a**) are forming aldimine, followed by Lewis acid catalyzed coupling reaction with phenylacetylene (**3a**) to give **A**. Subsequent aromatization of **A** affords **4a**.



Scheme 2. Proposed mechanism for the formation of **4a**.

After the successful synthesis of analogues **4a**–**u**, this sequence was extended from phenylacetylene (**3a**–**e**) to ethylpropiolate (**3f**) but, to our surprise the reaction (Scheme 3) failed to provide the expected α-quinolo-β-carboline (**5a**). However, according to literature reports[15] and with the help of NMR spectroscopy, the structure of the obtained compound **5b** was confirmed as a α-dihydropyrido-β-carboline. It is noteworthy that α-pyrido-β-carboline and their derivatives (Fig. 3) also have drawn attention from synthetic chemists due to their antitumor properties and hence, a few syntheses of these analogues have been reported.[16] The compound **5b** was incorporated with two units of ethylpropiolate



Scheme 3. A^3 coupling reaction between aldehyde (**1c**), aniline (**2a**), and ethylpropiolate (**3f**).

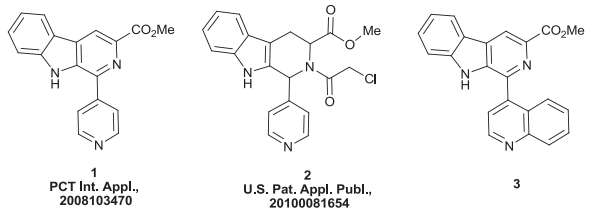
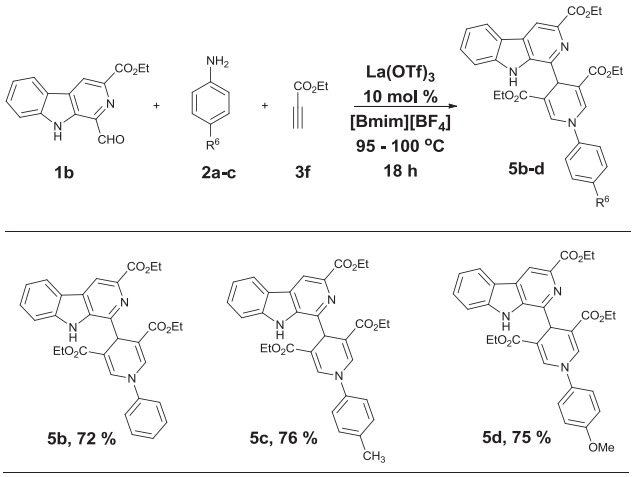
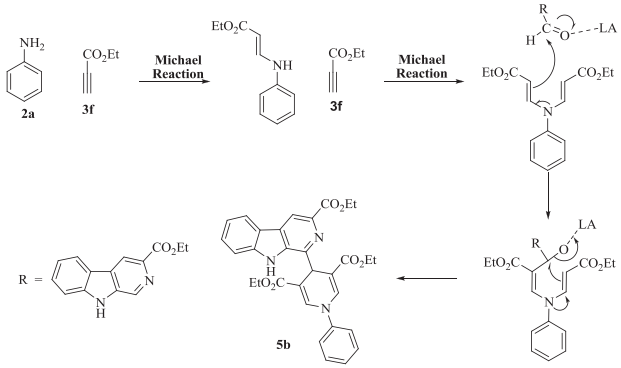


Fig. 3. Some of the representative α-pyrido-β-carboline compounds.

and hence increasing the equivalents of **3f** could perhaps enhance the yield of the product. As expected, when we used 3 equiv of **3f** along with 1 equiv of each aldehyde (**1b**) and anilines (**2a**–**c**), the α-dihydropyrido-β-carbolines (**5b**–**d**) were obtained in good yields (Scheme 4). The observed different reactivity between phenylacetylene (**3a**) and ethylpropiolate (**3f**) is explained in the proposed mechanism (Scheme 5). First, aniline **2a** undergoes Michael reaction with ethylpropiolate instead of forming imine with aldehyde **1b** as in the case of Scheme 2, followed by second Michael reaction and reaction with aldehyde afford dihydropyrido compound **5b**.



Scheme 4. Synthesis of α-dihydropyrido-β-carbolines (**5b**–**d**).



Scheme 5. Proposed mechanism for the formation of **5b**.

3. Conclusions

In summary, we have demonstrated a simple, novel, and efficient method to generate a range of lavendamycin analogues (**4a**–**u**) via an A^3 coupling protocol in good yields. This methodology can be exploited to construct new analogues of lavendamycin,

which are of great interest in the synthetic community due to their remarkable pharmaceutical and biological properties. Moreover, we delineated here the importance of ionic liquids and their applications. New analogues of 1,4-dihydro-3,5-pyridinedicarboxylate also have been efficiently synthesized.

4. Experimental section

4.1. 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 parts per million 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), and IR spectra were recorded on a JASCO FT/IR-5300 instrument. HRMS (ESI) was carried out in a Bruker Maxis instrument in the School of Chemistry, University of Hyderabad. TOF and quadrupole mass analyzer types are used for the HRMS measurements. IR spectra were recorded on a FT-IR spectrometer using KBr pellets. 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). 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.

4.2. A typical procedure for the preparation of methyl 1-(4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4a)

In a round bottom flask equipped with a magnetic stirring bar, 0.3 mmol of α-formyl-β-carboline (**1a**) and 0.3 mmol of aniline (**2a**) in 4 mL of [Bmim][BF_4] was stirred for 12 min. Into this reaction mixture were added 0.35 mmol of phenylacetylene (**3a**) and 10 mol % of La(OTf)$_3$ and then heated around 95–100 °C. After completion of the reaction, as indicated by the TLC, water was added and extracted with ethylacetate. The organic layer was dried over anhydrous Na_2SO_4. The solvent was concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: Hexanes/ethyl acetate) to afford **4a** as a colorless solid (100 mg, 78%). R_f=0.56 (20% EtOAc/Hexanes), mp: 298–300 °C; IR (KBr): 3383, 2924, 1732, 1589, 1215, 1032, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 12.01 (1H, s), 8.98 (1H, s), 8.95 (1H, s), 8.36 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=8.0 Hz), 7.99 (1H, d, J=8.4 Hz). 7.83 (1H, t, J=7.2 Hz), 7.76 (1H, d, J=8.4 Hz), 7.65–7.69 (3H, m), 7.56–7.62 (4H, m), 7.41 (1H, t, J=7.4 Hz), 4.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.7, 156.9, 149.5, 147.7, 140.9, 138.2, 137.6, 136.9, 136.8, 130.7, 129.7, 129.68, 129.5, 129.1, 128.5, 128.4, 127.1, 126.8, 126.2, 121.9, 121.6, 120.9, 119.6, 118.7, 112.4 (aromatic C), 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{19}N_3O_2$; 452.1375 (M+Na), found: 452.1375. Anal. Calcd for: C, 78.31; H, 4.46; N, 9.78%; found: C, 78.45; H, 4.41; N, 9.68%.

4.3. Methyl 1-(6-methyl-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4b)

Colorless solid, 113 mg, 85%, R_f=0.52 (20% EtOAc/Hexanes), mp: 277–279 °C; IR (KBr): 3348, 2965, 1458, 1244, 1039, 758, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.98 (1H, s), 8.95 (1H, s), 8.88 (1H, s), 8.23 (2H, t, J=8.0 Hz), 7.71–7.75 (2H, m), 7.55–7.68 (7H, m), 7.39 (1H, t, J=7.2 Hz), 4.08 (3H, s), 2.53 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.8, 156.0, 148.7, 146.2, 140.9, 138.4, 137.7, 137.2, 136.8, 136.7, 131.8, 130.6, 129.7, 129.2, 128.9, 128.5, 128.3, 126.7, 124.9, 121.9, 121.6, 120.9, 119.7, 118.5, 112.4 (aromatic C), 52.6, 21.9 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{21}N_3O_2$; 466.1532 (M+Na), found: 466.1532. Anal. Calcd for: C, 78.54; H, 4.77; N, 9.47%; found: C, 78.47; H, 4.71; N, 9.36%.

4.4. Methyl 1-(6-methoxy-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4c)

Colorless solid, 114 mg, 83%, R_f=0.60 (20% EtOAc/Hexanes), mp: 319–321 °C; IR (KBr): 3354, 2945, 1457, 1028, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.94 (1H, s), 8.95 (1H, s), 8.88 (1H, s), 8.23–8.26 (2H, m), 7.73–7.75 (1H, m), 7.66–7.69 (3H, m), 7.53–7.62 (3H, m), 7.47 (1H, dd, $J1$=2.8 Hz & $J2$=9.2 Hz), 7.40 (1H, t, J=7.6 Hz), 7.25 (1H, d, J=2.4 Hz), 4.08 (3H, s), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.8, 158.4, 154.7, 148.1, 143.7, 140.9, 138.5, 137.9, 136.8, 136.6, 130.9, 130.5, 129.5, 128.9, 128.6, 128.4, 127.8, 122.0, 121.9, 121.6, 120.9, 119.9, 118.3, 112.3, 104.2 (aromatic C), 55.5, 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{21}N_3O_3$; 482.1481 (M+Na), found: 482.1481. Anal. Calcd for: C, 75.80; H, 4.61; N, 9.14%; found: C, 75.91; H, 4.55; N, 9.21%.

4.5. Methyl 1-(6-fluoro-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4d)

Colorless solid, 103 mg, 77%, R_f=0.52 (20% EtOAc/Hexanes), mp: 255–257 °C; IR (KBr): 3353, 2969, 2843, 1720, 1342, 1019, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.79 (1H, s), 8.93 (2H, s), 8.29–8.33 (1H, m), 8.23 (1H, d, J=7.8 Hz), 7.70–7.72 (1H, m), 7.65–7.67 (1H, m), 7.54–7.63 (7H, m), 7.39 (1H, t, J=7.4 Hz), 4.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.7, 156.5, 149.0, 144.8, 140.9, 137.7, 137.4, 136.9, 136.7, 131.9, 131.8, 130.8, 129.5, 129.1, 128.8, 127.7, 122.0, 121.6, 121.0, 120.2, 119.9, 119.7, 118.7, 112.4, 109.9, 109.7 (aromatic C), 52.7 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{18}FN_3O_2$ (M+Na); 470.1281, found: 470.1281. Anal. Calcd for: C, 75.16; H, 4.05; N, 9.39%; found: C, 75.26; H, 4.15; N, 9.28%.

4.6. Methyl 1-(6-chloro-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4e)

Colorless solid, 111 mg, 80%, R_f=0.65 (20% EtOAc/Hexanes), mp: 241–243 °C; IR (KBr): 3354, 2965, 1547, 1046, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.78 (1H, s), 8.93 (2H, s), 8.24 (2H, d, J=8.4 Hz), 7.92 (1H, d, J=2.4 Hz), 7.71–7.75 (2H, m), 7.60 (1H, t, J=7.6 Hz), 7.58–7.62 (5H, m), 7.41 (1H, t, J=7.2 Hz), 4.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.6, 157.1, 148.6, 146.1, 140.9, 137.5, 137.1, 136.9, 136.7, 132.9, 130.9, 130.8, 130.5, 129.6, 129.1, 128.8, 127.4, 125.1, 121.9, 121.5, 121.0, 120.4, 118.8, 112.3 (aromatic C), 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{18}ClN_3O_2$; 486.0986 (M+Na), found: 486.0986. Anal. Calcd for: C, 72.49; H, 3.91; N, 9.06%; found: C, 72.29; H, 3.86; N, 9.15%.

4.7. Methyl 1-(6-bromo-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4f)

Colorless solid, 114 mg, 75%, R_f=0.62 (20% EtOAc/Hexanes), mp: 314–316 °C; IR (KBr): 3424, 1736, 1649, 1424, 1019, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.81 (1H, s), 8.95 (1H, s), 8.93 (1H, s), 8.25 (1H, d, J=7.9 Hz), 8.19 (1H, d, J=8.9 Hz), 8.09 (1H, s), 8.97 (1H, d, J=8.7 Hz), 7.73 (1H, d, J=8.2 Hz), 7.67 (1H, t, J=7.3 Hz), 7.57–7.61 (5H, m), 7.40 (1H, t, J=7.4 Hz), 4.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6, TMS) δ: 166.6, 157.2, 148.6, 146.3,

140.9, 137.4, 137.1, 136.9, 136.7, 133.1, 131.2, 130.8, 129.6, 129.2, 128.8, 128.3, 127.9, 121.9, 121.4, 121.2, 121.1, 120.4, 118.8, 112.5 (aromatic C), 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{18}BrN_4O_2$; 532.0460 (M+Na), found: 532.0460. Anal. Calcd for: C, 66.15; H, 3.57; N, 8.27%; found: C, 66.25; H, 3.65; N, 8.19%.

4.8. Methyl 1-(8-methoxy-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4g)

Slight yellowish color solid, 109 mg, 79%, R_f=0.56 (20% EtOAc/Hexanes), mp: 269–271 °C; IR (KBr): 3354, 1736, 1432, 1087, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 12.69 (1H, s), 8.99 (1H, s), 8.88 (1H, s), 8.27 (1H, d, J=7.6 Hz), 7.64–7.72 (4H, m), 7.53–7.59 (4H, m), 7.48 (1H, t, J=8.0 Hz), 7.39 (1H, t, J=6.8 Hz), 7.17 (1H, d, J=7.2 Hz), 4.29 (3H, s), 4.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.9, 155.4, 155.0, 149.3, 141.4, 139.4, 138.5, 138.1, 137.1, 136.6, 130.6, 129.7, 128.8, 128.5, 128.4, 127.6, 127.0, 122.0, 121.1, 120.7, 119.5, 118.7, 117.9, 112.4, 107.7 (aromatic C), 56.4, 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{21}N_3O_3$; 482.1481, found: 482.1494. Anal. Calcd for: C, 75.80; H, 4.61; N, 9.14%; found: C, 75.86; H, 4.56; N, 9.21%.

4.9. Methyl 1-(7-ethyl-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole-3-yl)-9*H*-β-carboline-3-carboxylate (4h)

Slight yellowish solid, 118 mg, 72%, R_f=0.35 (20% EtOAc/Hexanes), mp: 264–266 °C; IR (KBr): 3354, 3021, 2835, 1544, 1428, 1378, 1054, 700, 656 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, TMS) δ: 12.39 (1H, s), 9.06 (1H, s), 8.99 (1H, d, J=9.1 Hz), 8.81 (1H, s), 8.49 (1H, d, J=7.9 Hz), 8.44 (1H, d, J=9.0 Hz), 8.12 (1H, d, J=7.9 Hz), 7.59–7.71 (7H, m), 7.39 (1H, t, J=6.6 Hz), 7.28 (1H, t, J=7.3 Hz), 6.62 (1H, t, J=7.4 Hz), 5.98 (1H, d, J=7.9 Hz), 4.69 (2H, q, J=6.1 Hz), 3.97 (3H, s), 1.42 (3H, t, J=6.6 Hz); Due to limited solubility of compound **4h** in both $CDCl_3$ as well as in DMSO-d_6, we were unable to record the ^{13}C NMR spectra; HRMS (ESI-MS) calcd for $C_{36}H_{26}N_4O_2$; 547.2134 (M+Na), found: 547.2134. Anal. Calcd for: C, 79.10; H, 4.79; N, 10.25%; found: C, 79.25; H, 4.71; N, 1018%.

4.10. Methyl 1-(6-nitro-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4i)

Yellowish solid, 96 mg, 68%, R_f=0.40 (20% EtOAc/Hexanes), mp: 283–285 °C; IR (KBr): 3364, 3071, 1544, 1467, 1027, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.76 (1H, s), 9.12 (1H, s), 9.03 (1H, s), 8.93 (1H, d, J=2.3 Hz), 8.58–8.61 (1H, m), 8.48–8.50 (1H, m), 8.29 (1H, d, J=7.9 Hz), 7.79 (1H, d, J=8.0 Hz), 7.62–7.75 (6H, m), 7.44 (1H, t, J=7.6 Hz), 4.09 (3H, s); Due to limited solubility of compound **4i** in $CDCl_3$ as well as in DMSO-d_6, we were unable to record the ^{13}C NMR spectra; LCMS calcd for $C_{28}H_{18}N_4O_4$; 474.13 (m/z), found: 475.25 (M+1) (positive mode). Anal. Calcd for: C, 70.88; H, 3.82; N, 11.81%; found: C, 70.72; H, 3.93; N, 11.68%.

4.11. Methyl 1-(5,7-dichloro-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4j)

Colorless solid, 112 mg, 75%, R_f=0.54 (20% EtOAc/Hexanes), mp: 255–257 °C; IR (KBr): 3369, 1738, 1054, 709, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.64 (1H, s), 8.98 (1H, s), 8.84 (1H, s), 8.26–8.29 (2H, m), 7.78–7.80 (1H, m), 7.71 (1H, t, J=8.0 Hz), 7.61 (1H, d, J=2.0 Hz), 7.42–7.49 (6H, m), 4.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.5, 157.5, 149.4, 149.3, 140.9, 140.3, 137.1, 136.9, 136.3, 134.7, 132.5, 131.1, 130.3, 129.4, 129.1, 128.1, 128.0, 127.8, 123.2, 123.0, 122.1, 121.5, 121.3, 119.1, 112.4 (aromatic C), 52.7 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{17}Cl_2N_3O_2$; 520.0596 (M+Na), found: 520.0596. Anal. Calcd for: C, 67.48; H, 3.44; N, 8.43%; found: C, 67.38; H, 4.41; N, 8.56%.

4.12. Methyl 1-[4-(4-methylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (4k)

Colorless solid, 113 mg, 85%, R_f=0.59 (20% EtOAc/Hexanes), mp: 248–250 °C; IR (KBr): 3352, 3055, 2943, 1720, 1589, 1003, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 12.04 (1H, s), 8.99 (1H, s), 8.94 (1H, s), 8.37 (1H, d, J=8.3 Hz), 8.27 (1H, d, J=7.8 Hz), 8.01 (1H, d, J=8.4 Hz), 7.82 (1H, t, J=7.8 Hz), 7.75–7.77 (1H, m), 7.68 (1H, t, J=7.4 Hz), 7.54–7.58 (3H, m), 7.39–7.42 (3H, m), 4.08 (3H, s), 2.50 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.8, 156.9, 149.6, 147.8, 141.0, 138.4, 137.7, 136.9, 135.2, 130.7, 129.7, 129.5, 129.3, 129.1, 127.0, 126.9, 126.3, 122.0, 121.6, 120.9, 119.6, 118.7, 112.4 (aromatic C), 52.7, 21.4 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{21}N_3O_2$; 466.1532 (M+Na), found: 466.1532. Anal. Calcd for: C, 78.54; H, 4.77; N, 9.47%; found: C, 78.42; H, 4.71; N, 9.36%.

4.13. Methyl 1-[4-(4-fluorophenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (4l)

Colorless solid, 108 mg, 81%, R_f=0.50 (20% EtOAc/Hexanes), mp: 247–248 °C; IR (KBr): 3362, 2951, 1498, 1157, 1024, 767, 603 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 12.01 (1H, s), 9.00 (1H, s), 8.93 (1H, s), 8.39 (1H, d, J=8.3 Hz), 8.28 (1H, d, J=7.8 Hz), 7.95 (1H, d, J=8.3 Hz), 7.86 (1H, t, J=7.4 Hz), 7.77–7.89 (1H, m), 7.69 (1H, t, J=7.4 Hz), 7.58–7.65 (3H, m), 7.43 (1H, t, J=7.4 Hz), 7.29–7.31 (2H, m), 4.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 166.7, 164.0, 161.9, 156.9, 148.4, 147.8, 141.0, 136.8, 131.5, 131.4, 130.8, 129.8, 129.6, 129.1, 127.2, 125.9, 122.0, 121.6, 121.0, 119.7, 118.8, 115.7, 115.5, 112.4 (aromatic C), 52.8 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{18}FN_3O_2$; 448.1461 (M+Na), found: 448.1461. Anal. Calcd for: C, 75.16; H, 4.05; N, 9.39%; found: C, 74.98; H, 4.12; N, 9.26%.

4.14. Methyl 1-[6-chloro-4-(4-methylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (4m)

Colorless solid, 120 mg, 84%, R_f=0.62 (20% EtOAc/Hexanes), mp: 297–299 °C; IR (KBr): 3362, 2932, 1493, 1020, 744, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.83 (1H, s), 8.97 (1H, s), 8.95 (1H, s), 8.25–8.28 (2H, m), 7.97 (1H, d, J=2.0 Hz), 7.73–7.75 (2H, m), 7.68 (1H, t, J=7.4 Hz), 7.52–7.54 (2H, m), 7.41–7.43 (3H, m), 4.08 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.7, 157.2, 148.8, 146.1, 140.9, 138.7, 137.2, 136.9, 136.7, 134.6, 132.9, 130.9, 130.8, 130.5, 129.5, 129.4, 129.1, 127.6, 125.2, 121.9, 121.0, 120.4, 118.7, 112.3 (aromatic C), 52.6, 21.4 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{20}ClN_3O_2$; 500.1142 (M+Na), found: 500.1142. Anal. Calcd for: C, 72.88; H, 4.22; N, 8.79%; found: C, 72.96; H, 4.32; N, 8.61%.

4.15. Methyl 1-[6-bromo-4-(4-methylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (4n)

Colorless solid, 125 mg, 80%, R_f=0.55 (20% EtOAc/Hexanes), mp: 319–321 °C; IR (KBr): 3350, 3055, 1732, 1215, 1145, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 11.81 (1H, s), 8.96 (1H, s), 8.93 (1H, s), 8.25 (1H, d, J=7.8 Hz), 8.18 (1H, d, J=8.9 Hz), 8.13 (1H, s), 8.86 (1H, d, J=8.4 Hz), 7.72–7.74 (1H, m), 7.67 (1H, t, J=7.1 Hz), 7.51–7.53 (2H, m), 7.39–7.43 (3H, m), 4.08 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.6, 157.3, 148.7, 146.3, 140.9, 138.7, 137.1, 136.9, 136.7, 134.5, 133.1, 131.1, 130.8, 129.5, 129.4, 129.1, 128.4, 128.1, 121.9, 121.5, 121.1, 121.0, 120.4, 118.8, 112.3 (aromatic C), 52.6, 21.4 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{20}BrN_3O_2$; 544.0637 (M+Na), found: 544.0637. Anal. Calcd for: C, 66.68; H, 3.86; N, 8.04%; found: C, 66.52; H, 3.75; N, 8.16%.

4.16. Methyl 1-[4-(3,5-dimethylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (4o)

Colorless solid, 108 mg, 79%, R_f=0.55 (20% EtOAc/Hexanes), mp: 309–311 °C; IR (KBr): 3369, 1724, 1358, 1107, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 12.06 (1H, s), 8.99 (1H, s), 8.93 (1H, s), 8.36 (1H, d, *J*=8.3 Hz), 8.28 (1H, d, *J*=7.5 Hz), 8.00 (1H, d, *J*=8.0 Hz), 7.83 (1H, t, *J*=7.3 Hz), 7.76–7.78 (1H, m), 7.68 (1H, t, *J*=7.6 Hz), 7.57 (1H, t, *J*=7.7 Hz), 7.41 (1H, t, *J*=7.4 Hz), 7.26–7.27 (2H, m), 7.18 (1H, s), 4.08 (3H, s), 2.46 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.8, 156.9, 149.9, 147.7, 141.0, 138.1, 137.7, 136.9, 130.7, 130.0, 129.6, 129.4, 129.1, 127.5, 126.9, 126.5, 122.0, 121.6, 120.9, 119.5, 118.7, 112.4 (aromatic C), 52.6, 21.4 (aliphatic C); HRMS (ESI-MS) calcd for $C_{30}H_{23}N_3O_2$; 480.1688 (M+Na), found: 480.1688. Anal. Calcd for: C, 78.75; H, 5.07; N, 9.18%; found: C, 78.62; H, 5.15; N, 9.07%.

4.17. Methyl 1-(7-bromo-5,8-dimethoxy-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4p)

Colorless solid, 126 mg, 74%, R_f=0.52 (20% EtOAc/Hexanes), mp: 277–279 °C; IR (KBr): 3356, 2939, 2841, 1259, 1107, 744, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 12.51 (1H, s), 9.01 (1H, s), 8.77 (1H, s), 8.28 (1H, d, *J*=7.7 Hz), 7.76–7.78 (1H, m), 7.69 (1H, t, *J*=7.4 Hz), 7.40–7.45 (6H, m), 6.99 (1H, s), 4.31 (3H, s), 4.08 (3H, s), 3.56 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.7, 156.3, 153.2, 149.7, 147.2, 143.3, 141.9, 141.3, 137.3, 137.2, 136.9, 130.8, 129.2, 128.3, 127.2, 127.1, 122.1, 121.6, 121.3, 120.9, 119.0, 118.9, 116.7, 112.3, 110.3 (aromatic C), 61.6, 55.7, 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{30}H_{22}BrN_3O_4$; 590.0692 (M+Na), found: 590.0692. Anal. Calcd for: C, 63.39; H, 3.90; N, 7.39%; found: C, 63.25; H, 3.98; N, 7.21%.

4.18. Ethyl 4-methyl-1-(4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4q)

Colorless solid, 100 mg, 73%, R_f=0.45 (20% EtOAc/Hexanes), mp: 238–240 °C; IR (KBr): 3350, 2962, 1728, 1493, 1261, 700, 403 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 12.08 (1H, s), 8.89 (1H, s), 8.36–8.40 (2H, m), 7.98 (1H, d, *J*=8.3 Hz), 7.77–7.84 (2H, m), 7.63–7.68 (3H, m), 7.53–7.59 (4H, m), 7.40 (1H, t, *J*=7.6 Hz), 4.53 (2H, q, *J*=7.1 Hz), 3.20 (3H, s), 1.49 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 167.8, 157.2, 149.2, 147.8, 140.8, 138.3, 135.7, 135.1, 131.4, 129.9, 129.7, 129.6, 129.5, 128.5, 128.4, 128.1, 126.8, 126.6, 126.2, 124.0, 122.3, 120.7, 119.6, 112.3 (aromatic C), 61.4, 16.8, 14.5 (aliphatic C); HRMS (ESI-MS) calcd for $C_{30}H_{23}N_3O_2$; 480.1688 (M+Na), found: 480.1688. Anal. Calcd for: C, 78.75; H, 5.07; N, 9.18%; found: C, 78.62; H, 5.13; N, 9.25%.

4.19. Methyl 1-[4-(4-chlorophenyl)-6-methyl-2-quinolyl]-9*H*-β-carboline-3-carboxylate (4r)

Colorless solid, 115 mg, 80%, R_f=0.64 (20% EtOAc/Hexanes), mp: 288–290 °C; IR (KBr): 3337, 2945, 1562, 1265, 1003, 605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 11.97 (1H, s), 8.98 (1H, s), 8.86 (1H, s), 8.26 (2H, t, *J*=8.3 Hz), 7.75–7.77 (1H, m), 7.66–7.70 (3H, m), 7.57–7.59 (4H, m), 7.42 (1H, t, *J*=7.2 Hz), 4.09 (3H, s), 2.54 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 166.7, 156.1, 147.4, 146.3, 141.0, 137.6, 137.5, 136.9, 136.8, 136.7, 134.6, 132.0, 131.0, 130.7, 129.4, 129.0, 128.8, 126.5, 124.7, 121.9, 121.6, 120.9, 119.6, 118.6, 112.4 (aromatic C), 52.6, 21.9 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{20}ClN_3O_2$; 500.1142, found: 500.1142. Anal. Calcd for: C, 72.88; H, 4.22; N, 8.79%; found: C, 72.96; H, 4.12; N, 8.91%.

4.20. Methyl 1-[4-(4-chlorophenyl)-6-methoxy-2-quinolyl]-9*H*-β-carboline-3-carboxylate (4s)

Colorless solid, 122 mg, 82%, R_f=0.52 (20% EtOAc/Hexanes), mp: 265–267 °C; IR (KBr): 3402, 2924, 1728, 1358, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 11.88 (1H, s), 8.94 (1H, s), 8.80 (1H, s), 8.21–8.26 (2H, m), 7.73–7.74 (1H, m), 7.67 (1H, t, *J*=7.4 Hz), 7.56–7.61 (4H, m), 7.47 (1H, dd, *J*1=2.2 Hz & *J*2=9.1 Hz), 7.41 (1H, t, *J*=7.4 Hz), 7.16 (1H, d, *J*=2.4 Hz), 4.08 (3H, s), 3.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 166.7, 158.6, 154.6, 146.7, 143.7, 140.9, 137.7, 136.9, 136.8, 136.5, 134.6, 131.1, 130.8, 130.5, 128.98, 128.9, 127.5, 122.2, 121.9, 121.6, 120.9, 119.9, 118.4, 112.3, 103.8 (aromatic C), 55.6, 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{29}H_{20}ClN_3O_3$; 516.1091, found: 516.1091. Anal. Calcd for: C, 70.52; H, 4.08; N, 8.51%; found: C, 70.65; H, 4.12; N, 8.71%.

4.21. Methyl 1-(8-bromo-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4t)

Colorless solid, 111 mg, 73%, R_f=0.52 (20% EtOAc/Hexanes), mp: 245–247 °C; IR (KBr): 3354, 2781, 1547, 1327, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 12.57 (1H, s), 9.01 (1H, s), 9.00 (1H, s), 8.27 (1H, d, *J*=7.9 Hz), 8.16 (1H, dd, *J*1=0.9 Hz & *J*2=7.5 Hz), 7.96 (1H, dd, *J*1=0.8 Hz & *J*2=8.3 Hz), 7.74–7.76 (1H, m), 7.56–7.69 (6H, m), 7.39–7.44 (2H, m), 4.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 166.7, 157.1, 150.2, 144.6, 141.5, 137.8, 137.0, 136.8, 136.7, 133.1, 130.9, 129.7, 129.1, 128.7, 128.6, 128.3, 127.2, 126.2, 125.3, 121.9, 121.5, 120.9, 120.2, 119.1, 112.4 (aromatic C), 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{18}BrN_3O_2$; 532.0460 (M+Na), found: 532.0480. Anal. Calcd for: C, 66.15; H, 3.57; N, 8.27%; found: C, 66.38; H, 3.51; N, 8.35%.

4.22. Methyl 1-(8-chloro-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (4u)

Colorless solid, 107 mg, 77%, R_f=0.52 (20% EtOAc/Hexanes), mp: 267–269 °C; IR (KBr): 3329, 2922, 1711, 1356, 1016, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 12.49 (1H, s), 9.00 (1H, s), 8.99 (1H, s), 8.27 (1H, d, *J*=7.8 Hz), 7.96 (1H, d, *J*=7.4 Hz), 7.91 (1H, dd, *J*1=0.7 Hz & *J*2=8.3 Hz), 7.74–7.75 (1H, m), 7.56–7.69 (6H, m), 7.48 (1H, t, *J*=8.1 Hz), 7.41 (1H, t, *J*=7.3 Hz), 4.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 166.7, 156.8, 150.1, 143.8, 141.4, 137.8, 137.1, 136.9, 136.8, 133.5, 130.9, 129.7, 129.5, 129.1, 128.7, 128.6, 128.1, 126.6, 125.4, 121.9, 121.5, 120.9, 120.1, 119.0, 112.5 (aromatic C), 52.6 (aliphatic C); HRMS (ESI-MS) calcd for $C_{28}H_{18}ClN_3O_2$; 486.0986 (M+Na), found: 486.0986. Anal. Calcd for: C, 72.49; H, 3.91; N, 9.06%; found: C, 72.31; H, 3.85; N, 9.18%.

4.23. Diethyl 4-(3-ethyloxycarbonyl-9*H*-β-carbolin-1-yl)-1-phenyl-1,4-dihydro-3,5-pyridinedicarboxylate (5b)

Colorless solid, 116 mg, 72%, R_f=0.32 (20% EtOAc/Hexanes), mp: 166–168 °C; IR (KBr): 3344, 2955, 1597, 1211, 1012, 896, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 9.84 (1H, s), 8.72 (1H, s), 8.14 (1H, d, *J*=7.4 Hz), 7.81 (2H, s), 7.59–7.62 (1H, m), 7.53–7.57 (1H, m), 7.46–7.52 (4H, m), 7.27–7.34 (2H, m), 5.58 (1H, s), 4.40 (2H, q, *J*=6.9 Hz), 3.99–4.13 (4H, m), 1.38 (3H, q, *J*=7.0 Hz), 1.11 (6H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 167.3, 166.5, 146.9, 143.5, 141.1, 138.1, 137.9, 134.9, 129.8, 128.0, 128.3, 126.8, 122.3, 121.9, 121.7, 120.4, 116.7, 112.4, 107.8 (aromatic C), 60.9, 60.4, 35.1, 14.4, 14.2 (aliphatic C); LCMS calcd for $C_{31}H_{29}N_3O_6$; 540.21 (M+1), found: 540.15. Anal. Calcd for: C, 69.00; H, 5.42; N, 7.79%; found: C, 69.21; H, 5.53; N, 7.65%.

4.24. Diethyl 4-(3-ethyloxycarbonyl-9*H*-β-carbolin-1-yl)-1-(4-methylphenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (5c)

Colorless solid, 126 mg, 76%, R_f=0.35 (20% EtOAc/Hexanes), mp: 175–177 °C; IR (KBr): 3365, 2903, 1398, 1025, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 9.88 (1H, s), 8.73 (1H, s), 8.14 (1H, d, J=7.8 Hz), 7.78 (2H, s), 7.58–7.61 (1H, m), 7.54–7.57 (1H, m), 7.38–7.39 (2H, m), 7.29–7.32 (3H, m), 5.59 (1H, s), 4.43 (2H, q, J=7.2 Hz), 4.08–4.15 (2H, m), 3.99–4.06 (2H, m), 2.43 (3H, s), 1.41 (3H, t, J=7.1 Hz), 1.12 (6H, t, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 167.4, 166.5, 147.1, 141.2, 141.1, 138.2, 138.1, 136.7, 134.9, 130.3, 128.9, 128.3, 122.3, 122.1, 121.6, 120.4, 116.6, 112.3, 107.4 (aromatic C), 60.8, 60.4, 35.1, 20.9, 14.4, 14.2 (aliphatic C); HRMS (ESI-MS) calcd for $C_{32}H_{31}N_3O_6$; 576.2111 (M+Na), found: 576.2111. Anal. Calcd for: C, 69.43; H, 5.64; N, 7.59%; found: C, 69.28; H, 5.58; N, 7.71%.

4.25. Diethyl 4-(3-ethyloxycarbonyl-9*H*-β-carbolin-1-yl)-1-(4-methoxyphenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (5d)

Colorless solid, 128 mg, 75%, R_f=0.30 (20% EtOAc/Hexanes), mp: 165–167 °C; IR (KBr): 3387, 2980, 1672, 1197, 798 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 9.86 (1H, s), 8.71 (1H, s), 8.13 (1H, d, J=7.6 Hz), 7.69 (2H, s), 7.52–7.59 (2H, m), 7.43 (2H, d, J=8.3 Hz), 7.27–7.31 (1H, m), 6.99–7.01 (2H, m), 5.57 (1H, s), 4.42 (2H, q, J=7.1 Hz), 3.99–4.12 (4H, m), 3.86 (3H, s), 1.42 (3H, t, J=6.9 Hz), 1.10 (6H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 167.4, 166.5, 158.6, 147.1, 141.1, 138.6, 138.1, 137.0, 134.9, 128.9, 128.3, 124.2, 122.3, 121.6, 120.4, 116.6, 114.9, 112.3, 107.1 (aromatic C), 60.8, 60.3, 55.6, 34.9, 14.5, 14.2 (aliphatic C); HRMS (ESI-MS) calcd for $C_{32}H_{31}N_3O_7$; 592.2060 (M+Na), found: 592.2060 (M+Na). Anal. Calcd for: C, 67.48; H, 5.49; N, 7.38%; found: C, 67.59; H, 5.42; N, 7.51%.

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Supplementary data

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14. The CCDC deposition number for compound **4g** is 903601. Formula: $C_{29}H_{21}N_3O_3$. Unit cell parameters: a=11.7620(15), b=10.3613(13), c=18.295(2). β=100.041(3), space group $P21/c$.
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