

# Advancing the Morita-Baylis-Hillman chemistry of 1-formyl- $\beta$ -carbolines for the synthesis of indolizinoindole derivatives<sup>S</sup>

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*Dedicated to Dr. Vijay Nair*

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The chemistry of the Morita-Baylis-Hillman adducts of 1-formyl- $\beta$ -carbolines has been extended for obtaining indolizinoindole derivatives which mimic the harmicine and homofascaplysin frameworks. Adduct of N-substituted methyl 1-formyl-9H- $\beta$ -carboline-3-carboxylate upon bromination followed by aqueous work up results in formation of indolizinoindole derivative. On the other hand N-substituted 1-formyl-9H- $\beta$ -carboline yielded similar product in one-pot via DABCO-promoted reaction of activated alkene. Alternatively the DMAP-mediated Morita-Baylis-Hillman

reaction of N-substituted methyl 1-formyl-9H- $\beta$ -carboline-3-carboxylate with cycloalkenones yielded adducts, which cyclizes intramolecularly in the presence of  $PBr_3$  to yield compounds with homofascaplysin framework. In contrast DMAP-mediated reaction of N-substituted 1-formyl- $\beta$ -carboline with cyclohexenone directly gave product with similar framework in a single step.

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## Introduction

We have recently reported the Morita-Baylis-Hillman (MBH) reactions of 1-formyl-9H- $\beta$ -carbolines with alkyl acrylates which resulted in one-pot synthesis of unusual canthin-6-ones.<sup>[1]</sup> Moreover adducts derived from acrylonitrile were readily transformed into canthine derivatives via base-promoted intramolecular cyclization. Furthermore, installing an alkene or alkyne chain on the indole NH and generating dipolarophile in the form of nitrile oxide, azide or azomethine ylide from the formyl group allowed us to construct a variety of fused- $\beta$ -carboline-based compounds via cycloaddition reactions.<sup>[2]</sup> In our efforts to expand the repertoire of fused- $\beta$ -carbolines which could be synthesized from substituted 1-formyl- $\beta$ -carbolines, we became interested in investigating the reactivity of substrates substituted at nitrogen by allyl and alkyne groups for 3+2 cycloaddition reaction. In principle, the allyl bromide afforded from the BH reaction of such N-substituted aldehydes via bromination will lead to allyl bromide that under the influence of  $PPh_3$  or  $PBu_3$  may furnish a dipolarophile. This dipolarophile can initiate an intramolecular 3+2 cycloaddition reaction with alkene or alkyne chain on the nitrogen leading to annulated  $\beta$ -carboline (path 1, Fig. 1).<sup>[3]</sup> Alternatively, nucleophilicity of nitrogen of the C-ring of  $\beta$ -carboline may initiate an intramolecular cyclization resulting in indolizinoindole system (path 2, Fig. 1). Indeed, the formation of indolizine from 2-pyridinecarboxaldehyde have been reported to take place following the latter path.<sup>[4]</sup> More importantly for our study, either pathway would afford new annulated  $\beta$ -carboline system. Investigating this approach, we have discovered that the allyl bromide which is generated via bromination of the BH adduct of N-substituted 1-

formyl  $\beta$ -carboline immediately initiate nucleophilic attack by the nitrogen of the C-ring to furnish indolizinoindole system which represent aromatized derivative of alkaloid harmicine (Fig. 2).<sup>[5]</sup> Similar reactions with cycloalkenone lead to the synthesis of homofascaplysin type of ring framework.<sup>[6]</sup> We provide an update on the results of our study in this direction.

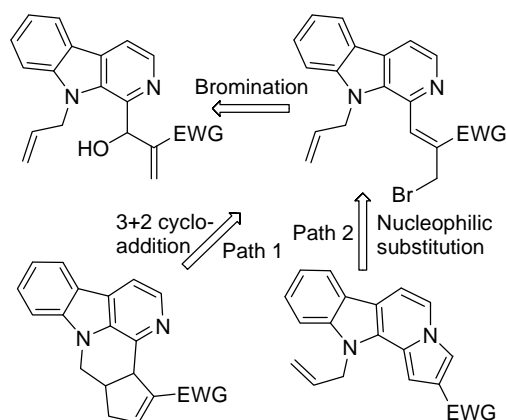


Figure 1. Retrosynthetic pathway

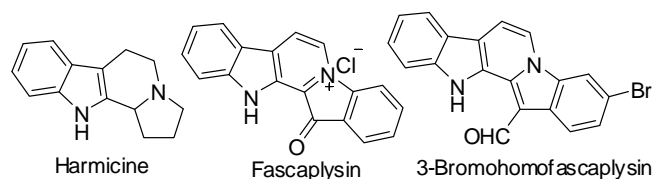
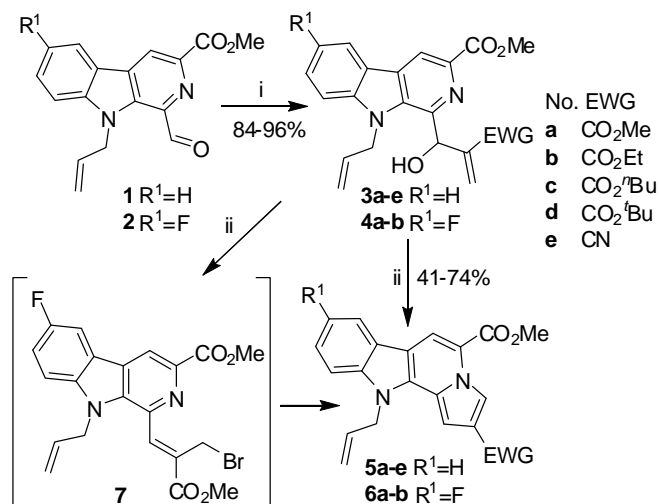


Figure 2. Core structure of alkaloids Harmicine and Fascaplysin

## Results and Discussion

This work commenced with the synthesis of aldehydes **1** and **2** following the reported procedure.<sup>[1-2]</sup> Optimization studies were initiated by reacting substrate **1** with methyl acrylate in the presence of DABCO under neat condition (scheme 1). This reaction smoothly affords the product **3a** in good yields. In order to generate the allyl bromide, **3a** was treated with PBr<sub>3</sub> in dichloromethane at 0 °C. Though the reaction was complete in 30 min, the TLC analysis revealed presence of three spots out of which the most non-polar spot displayed highly fluorescent green colour under UV light (254 nm). Quenching the reaction mixture with water followed by extraction furnished a residue which displayed two spots on TLC instead of initial three indicating either loss or transformation of one of the products into other during aqueous work up. However purification of the residue via column chromatography resulted in a single product as solid which corresponded to the fluorescent spot of TLC. On the basis of this result we presumed that either the polar fraction present in the product could not be eluted or else it too got transformed on silica-gel during chromatographic purification. The <sup>1</sup>H- and <sup>13</sup>C NMR analysis of the isolated product revealed the presence of one CH<sub>2</sub> signal instead of the expected two (one for the allyl chain and other for the allyl bromide) and two extra CH signals in the aromatic region. A HMBC spectrum coupled with HRMS data led us to establish the structure of the product as **5a** instead of the anticipated allyl bromide. Perhaps the reaction of PBr<sub>3</sub> may have proceeded with initial formation of allyl bromide which could have undergone a nucleophilic attack by the nitrogen of C-ring to form a salt which hydrates and rearranges in the presence of water to afford the isolated product (Fig. 3). This plausible mechanism inspired us to perform a few more optimization studies. In one of the experiments, the reaction after quenching with water on completion was allowed to stir for 24 h. Fortunately the mixture upon TLC analysis revealed the presence of a single spot which corresponded to the product **5a**.



Scheme 1. Reagents and conditions: i) DABCO, r.t., 3 h-15 d. ii) PBr<sub>3</sub>, 0°C, 30 min-2 h then left in water for 16-24 h.

With a view to understand the generality of this sequence we generated substrates **3b-e**, **4a-b** by reacting **1** and **2** with different activated alkenes. Treating **3b-e**, **4a-b** with PBr<sub>3</sub> for 1-2 h followed by aqueous work up for 24 h resulted in the desired products **5b-e**, **6a-b**. In support of the fact that the intramolecular cyclization

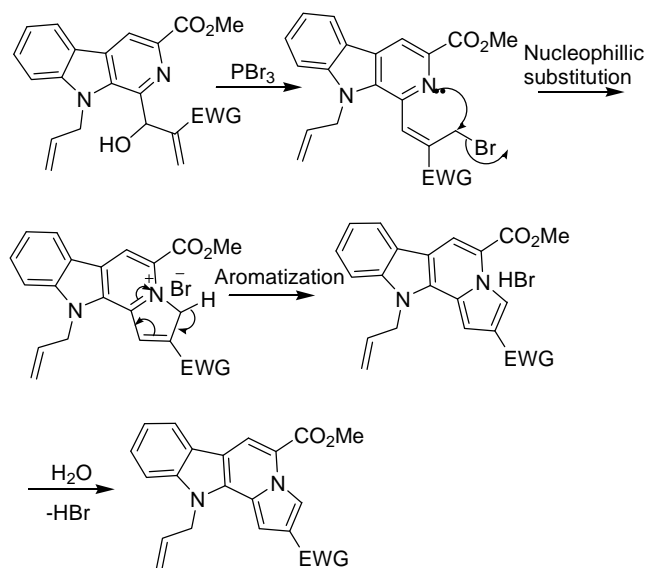
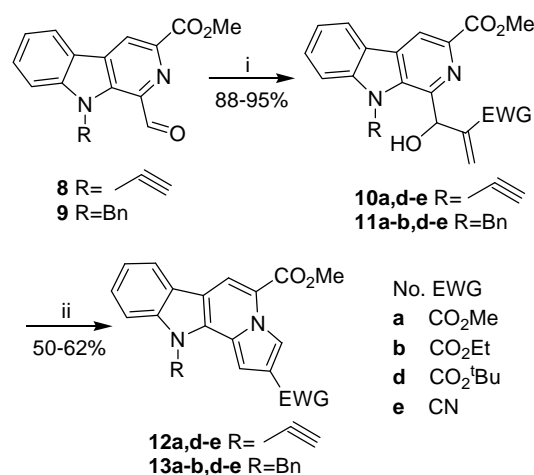


Figure 3. Plausible mechanism for the formation of indolizinoindole via allyl bromide

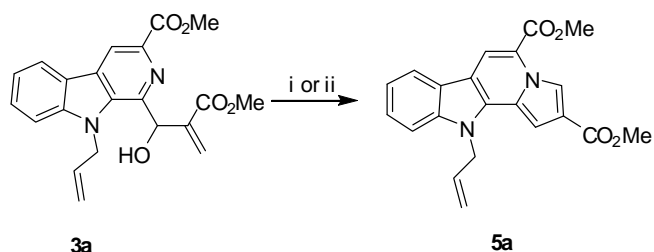
reaction is preceded by the formation of allyl bromide, during reaction of **4a** with PBr<sub>3</sub> crude **7** was separated and subjected to <sup>1</sup>H NMR and HRMS (scheme 1). Both data confirmed the presence of allyl bromide. Alternating the allyl chain on the nitrogen of indole with propargyl and benzyl groups furnish aldehydes **8** and **9**, respectively which were then examined for similar reactions. Gratifyingly these substrates too undergo the BH reaction to afford **10a, d-e** and **11a-b, d-e** which after bromination yielded the desired products **12a, d-e** and **13a-b, d-e** respectively (scheme 2). These results implied that the intramolecular cyclization is not influenced by the substitution on the nitrogen of the indole sub-unit.



Scheme 2. Reagents and conditions i) DABCO, r.t., 4 h-12 d. ii) PBr<sub>3</sub>, 0°C, 30 min-2 h. then kept in water for 16-24 h.

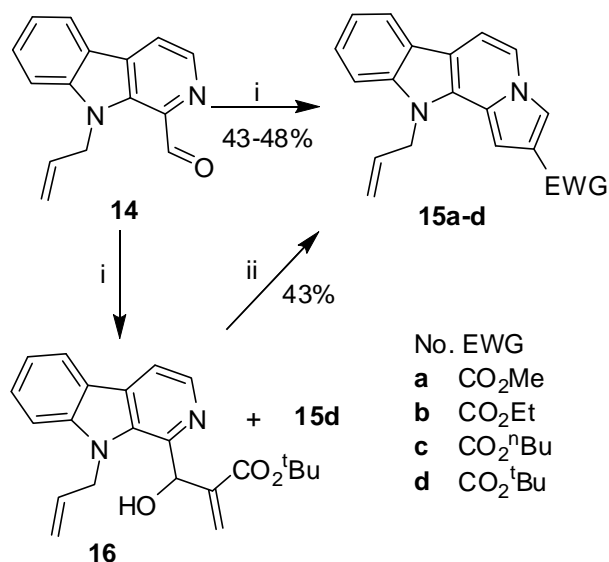
In previous study with 2-pyridinecarboxaldehyde it has been shown that acetylating the BH adduct with acetic anhydride lead to formation of indolizine derivative.<sup>[7]</sup> Therefore we decided to probe the effectiveness of acetylation for intramolecular cyclization in compound **3**. Accordingly in a pilot study **3a** was treated with acetyl chloride in the presence of pyridine in MeCN. After screening for optimum conditions, it was observed that reaction of

**3a** with 5 eq. of acetyl chloride in the presence of 2 eq. of pyridine in dry MeCN at 90 °C in 15 h yielded **5a** in 54% yield (scheme 3). On the other hand heating **3a** with 5 eq. of acetic anhydride in the presence of 2 eq. of pyridine at 80 °C for 16 h afforded the compound **5a** in 46% yield.



Scheme 3. Reagents and conditions i) AcCl, Py, dry MeCN, 80 °C, 15 h. ii) Ac<sub>2</sub>O, Py, dry MeCN, 80 °C, 16 h.

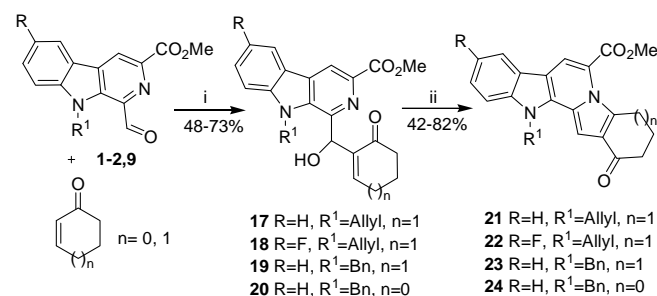
Encouraged by results of the study, we next directed our attention towards analogous N-substituted aldehyde originating from tryptamine. Accordingly, **14** was prepared and subjected to BH reaction with different acrylates at room temperature under neat conditions. As compared to reactions of aldehydes originating from tryptophan ester, reactions of **14** were found to be sluggish. But it was pleasing to note that except for the reaction of tert-butyl acrylate, in all cases the isolated products were established to be the indolizinoindoles **15a-c** (scheme 4). For the reaction of **14** with tert-butyl acrylate we could isolate adduct **16** in 86% yields beside the indolizinoindole **15d** (5%) as the minor product. Nevertheless **16** upon treatment with PBr<sub>3</sub> furnished the required product **15d** in 43% yield.



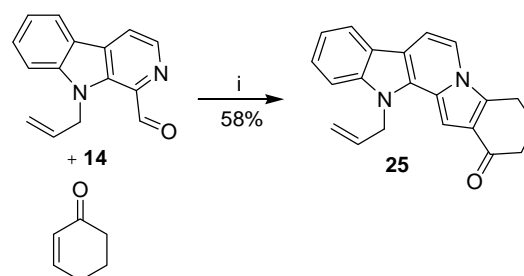
Scheme 4. Reagents and conditions i) Alkyl acrylate, DABCO, r.t., 3 d-15 d. ii) PBr<sub>3</sub>, 0 °C, 1 h. then kept in water for 16 h.

The success of the strategy invoked us to investigate similar reaction employing alkenones as the participating activated alkene. We anticipated that a successful BH reaction of cycloalkenone with different β-carboline-based aldehydes would lead to adducts which would react with PBr<sub>3</sub> to yield the allyl bromide. The bromide

would instantaneously undergo an intramolecular cyclization to afford a product having similar framework as that of alkaloid homofascaplysin. Accordingly, we examined the reaction of **1-2**, and **9** with cyclohexenone and cyclopentenone under the influence of DMAP in aqueous THF for 36 to 48 h. Gratifyingly for all reactions the corresponding products were furnished in 48-73% yields (scheme 5). However **17** could not be isolated in pure form



Scheme 5. Reagents and conditions i) DMAP, THF:H<sub>2</sub>O (1:1), r t, 36-48 h. ii) PBr<sub>3</sub>, 0 °C, 1 h., 30 min-1 h. then kept in water for 16 h.



Scheme 6. Reagents and conditions i) DMAP, THF:H<sub>2</sub>O (1:1), r. t., 4 d.

as it undergoes cyclization to afford **21** during purification via silica gel chromatography. Treating **17-20** with PBr<sub>3</sub> expectedly furnished the desired products **21-24**. Encouraged by these results, we then subjected **14** to reaction with cyclohexenone in the presence of DMAP under aqueous condition for 4 d to provide **25** in one pot in 58% yield (scheme 6).

## Conclusions

In summary we have demonstrated new application of the MBH chemistry with N-substituted β-carboline based electrophiles to generate novel indolizinoindole derivatives which are the mimics of the alkaloids harmicine and homofascaplysin. It was found that the presence of an electron-withdrawing substituent on the pyridine ring of 1-formyl-β-carboline originating from tryptophan weakens the nucleophilicity of the pyridine nitrogen. As a consequence cyclization occurs only after treatment of the MBH adduct with PBr<sub>3</sub> or acetyl chloride (acetic anhydride), so forming a more reactive allylic electrophile. On the other hand the 1-formyl-β-carboline originating from tryptamine did not require any activation and the cyclized derivatives were furnished during the MBH reaction. The strategy described herein highlight the usefulness of the MBH adduct as valuable source for important structural motifs.

## Experimental Section

Melting points are uncorrected and were determined in capillary tubes on a Precision melting point apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer's RX I FTIR spectrophotometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in  $\delta$ ). The ESMS were recorded on MICROMASS Quadro-II LCMS system. The HRMS spectra were recorded as EI-HRMS on a JEOL system or as DART-HRMS (recorded as ES+) on a JEOL-AccuTOF JMS-T100LC Mass spectrometer having DART (Direct Analysis in Real Time) source. Elemental analyses were performed on a Carlo Erba's 108 or an Elementar's Vario EL III microanalyzer. The room temperature varied between 20°C and 35°C. The  $^{13}\text{C}$  NMR spectra of fluoro-substituted derivatives display extra peaks due to the C–F couplings.

### General procedure for the synthesis of compounds 3b-e, 4a-b, 10a, d-e, 11 a-b, d-e, 15a-c and 16 as exemplified for compound 3a.

To a mixture of **1** (0.43 g, 1.69 mmol) and DABCO (0.19 g, 1.69 mmol), methyl acrylate (1.53 mL, 16.93 mmol) was added and was allowed to stir the reaction at room temperature for 3 d. After completion of the reaction as monitored by TLC, the content was poured into water (50 mL) and EtOAc (50 mL) was added. The organic layer was partitioned and the aqueous layer was further extracted with EtOAc (3 x 25 mL). The pooled organic layer was washed with brine (40 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to yield a solid residue which was further purified by triturating with (hexane/EtOAc, 95:05,  $R_f = 0.50$  (hexane/EtOAc, 60:40)) to obtain **3a** as a white solid (0.534 g from 0.43 g, 96%). For analytical grade was purified via silica gel (60-120 mesh) column chromatography by hexane/EtOAc (30:70, v/v) to afford **3a**, mp 151-153 °C.

**Methyl 9-allyl-1-[1-hydroxy-2-(methoxycarbonyl)allyl]-9H- $\beta$ -carboline-3-carboxylate (3a):** IR (KBr):  $\nu_{\text{max}}$  1722 ( $\text{CO}_2\text{CH}_3$ ), 3422 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta = 3.90$  (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.02 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.80 (d,  $J = 17.2$  Hz, 1 H, =CHH<sub>allyl</sub>), 5.03 (td,  $J_1 = 2.2$  Hz,  $J_2 = 18.3$  Hz, 1 H, CHHN), 5.18 (d,  $J = 8.6$  Hz, 1 H, =CHH<sub>allyl</sub>), 5.25 (td,  $J_1 = 2.2$  Hz,  $J_2 = 18.3$  Hz, 1 H, CHHN), 5.26 (s, 1 H, CHOH), 5.46 (d,  $J = 8.6$  Hz, 1 H, =CHH<sub>adduct</sub>), 6.00-6.12 (m, 1 H, =CH), 6.21 (d,  $J = 8.6$  Hz, 1 H, =CHH<sub>adduct</sub>), 6.24 (s, 1 H, CHOH), 7.40 (t,  $J = 7.5$  Hz, 1 H, ArH), 7.48 (d,  $J = 8.4$  Hz, 1 H, ArH), 7.62-7.67 (m, 1 H, ArH), 8.23 (d,  $J = 7.9$  Hz, 1 H, ArH), 8.88 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 47.2$ , 52.4, 52.6, 69.6, 110.5, 116.9, 117.6, 121.3, 121.6, 121.8, 126.6, 129.3, 130.4, 132.8, 135.3, 135.7, 142.1, 142.2, 166.2, 167.6 ppm. MS (ES):  $m/z$  (%) = 381.2 (100%) [ $\text{M}+1$ ]<sup>+</sup>, 403.2 (33%) [ $\text{M}+23$ ]<sup>+</sup>.  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_5$  (380.1372): calcd. C 66.31, H 5.30, N 7.36; found C 66.25, H 5.46, N 7.54.

**Methyl 11-allyl-11H-indolizino[8,7-b]indole-2-carboxylate (15a):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 15:85, v/v,  $R_f = 0.50$  (EtOAc/Hexane, 20:80, v/v)) was obtained as a white solid (0.203 g from 0.25 g). Yield: 63%. mp 126-128 °C. IR (KBr)  $\nu_{\text{max}} = 1712$  ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta = 3.91$  (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.98 (d,  $J = 17.2$  Hz, 1 H, =CHH), 5.19 (t,  $J = 4.7$  Hz, 3 H,  $\text{CH}_2\text{N}$  and =CHH), 6.09-6.21 (m, 1 H, =CH), 7.11 (s, 1 H, ArH), 7.26 (q,  $J = 5.4$  Hz, 2 H, ArH), 7.34-7.44 (m, 2 H, ArH), 7.73 (d,  $J = 7.1$  Hz, 1 H, ArH), 7.91 (d,  $J = 7.8$  Hz, 1 H, ArH), 7.95 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 46.8$ , 51.6, 98.6, 107.1, 109.6, 117.0, 118.2, 118.7, 119.0, 119.1, 120.5, 123.4, 123.8, 124.1, 130.5, 132.6, 138.8, 165.6 ppm. MS (ES):  $m/z$  (%) = 305.2 (100) [ $\text{M}+1$ ]<sup>+</sup>.  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_2$  (304.1212): calcd. C 74.98, H 5.30, N 9.20; found C 74.67, H 5.54, N 9.44

**Butyl 11-allyl-11H-indolizino[8,7-b]indole-2-carboxylate (15c):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 08:92,

v/v,  $R_f = 0.75$  (EtOAc/Hexane, 20:80, v/v)) was obtained as a yellow oil (0.126 g from 0.20 g). Yield: 43%. IR (Neat):  $\nu_{\text{max}} = 1705$  ( $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta = 1.00$  (t,  $J = 7.3$  Hz, 3 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.44-1.54 (m, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.72-1.82 (m, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 4.33 (t,  $J = 6.7$  Hz, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 4.98 (d,  $J = 16.4$  Hz, 1 H, =CHH), 5.18-5.22 (m, 3 H, =CHH and  $\text{CH}_2\text{N}$ ), 6.09-6.21 (m, 1 H, =CH), 7.11 (s, 1 H, ArH), 7.22-7.30 (m, 2 H, ArH), 7.34-7.40 (m, 1 H, ArH), 7.42 (d,  $J = 8.0$  Hz, 1 H, ArH), 7.73 (d,  $J = 6.7$  Hz, 1 H, ArH), 7.90 (d,  $J = 7.7$  Hz, 1 H, ArH), 7.94 (d,  $J = 1.4$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 14.0$ , 19.4, 29.8, 31.0, 46.9, 64.3, 98.7, 107.1, 109.6, 109.8, 117.0, 118.1, 119.0, 119.1, 120.5, 123.3, 123.8, 124.1, 130.6, 132.6, 138.7, 165.3 ppm. MS (ES):  $m/z$  (%) = 347.2 (100) [ $\text{M}+1$ ]<sup>+</sup>.  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$  (346.1681): calcd. C 76.28, H 6.40, N 8.09; found: C 76.45, H 6.38, N 7.98

### General procedure for the synthesis of compounds 5b-e, 6a-b, 12a, d-e, 13 a-b, d-e, 15d and 21-24 as exemplified for compound 5a

To a solution of **3a** (0.13 g, 0.34 mmol) in dry dichloromethane (6 mL),  $\text{PBr}_3$  (0.07 mL, 0.68 mmol) was added and the reaction was stirred at 0 °C for 30 min. After completion, the content was poured into crushed ice and left for 16 h. Thereafter, the mixture was neutralized with  $\text{NaHCO}_3$ . The organic layer was separated and the aqueous layer was further extracted with  $\text{CHCl}_3$  (3 x 25 mL). The organic layers were combined and washed with brine (50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated to yield a crude product which was further purified via silica gel (60-120 mesh) column chromatography by (hexane/EtOAc, 90:10,  $R_f = 0.60$  (hexane/EtOAc, 80:20, v/v)) to yield **5a** as a yellow solid (with green tinge) (0.092 g from 0.13 g). Yield: 74%; mp 146-148 °C.

**Dimethyl 11-allyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (5a):** IR (KBr):  $\nu_{\text{max}} = 1704$  ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta = 3.90$  (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 3.96 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.92 (d,  $J = 17.2$  Hz, 1 H, =CHH), 5.00 (t,  $J = 2.9$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 5.18 (d,  $J = 10.4$  Hz, 1 H, =CHH), 6.01-6.13 (m, 1 H, =CH), 7.17 (d,  $J = 1.4$  Hz, 1 H, ArH<sub>pyrrole</sub>), 7.25-7.41 (m, 3 H, ArH), 7.87 (d,  $J = 7.7$  Hz, 1 H, ArH), 8.21 (s, 1 H, ArH), 9.31 (d,  $J = 1.4$  Hz, 1 H, ArH<sub>pyrrole</sub>) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 46.8$ , 51.6, 52.3, 100.7, 109.0, 109.8, 116.4, 117.4, 117.8, 119.0, 119.2, 121.5, 123.6, 124.0, 124.6, 131.9, 133.7, 139.5, 163.1, 165.5 ppm. MS (ES):  $m/z$  (%) = 363.2 (100%) [ $\text{M}+1$ ]<sup>+</sup>. DART-HRMS (ES+): calcd  $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_4$  363.1345; found 363.1331.

**2-Ethyl 5-methyl 11-allyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (5b):** The title compound was prepared following the above described general procedure and after purification by triturating (EtOAc/Hexane, 05:95,  $R_f = 0.62$  (EtOAc/Hexane, 20:80, v/v)) was obtained as yellow solid with green tinge (0.094 g from 0.21 g). Yield: 45%. mp = 160-161°C. IR (KBr):  $\nu_{\text{max}} = 1704$  ( $\text{CO}_2\text{CH}_3$  and  $\text{CO}_2\text{CH}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta = 1.42$  (t,  $J = 7.1$  Hz, 3 H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 4.03 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.40 (q,  $J = 7.1$  Hz, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 4.99 (d,  $J = 17.2$  Hz, 1 H, =CHH), 5.19-5.25 (s, 3 H,  $\text{CH}_2\text{N}$  and =CHH), 6.09-6.21 (m, 1 H, =CH), 7.31-7.36 (m, 2 H, ArH), 7.43 (t,  $J = 2.6$  Hz, 2 H, ArH), 7.96 (d,  $J = 7.7$  Hz, 1 H, ArH), 8.40 (s, 1 H, ArH), 9.41 (d,  $J = 1.2$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 14.6$ , 46.8, 52.2, 60.4, 100.7, 108.9, 109.8, 116.3, 117.4, 117.8, 119.1, 119.4, 121.4, 123.5, 124.0, 124.6, 131.9, 133.7, 139.5, 163.2, 165.1 ppm. MS (ES):  $m/z$  (%) = 377.2 (100%) [ $\text{M}+1$ ]<sup>+</sup>.  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4$  (376.1423): calcd. C 78.15, H 6.89, N 4.56; found C 78.10, H 6.81, N 4.46.

**2-Butyl 5-methyl 11-allyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (5c):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 10:90,  $R_f = 0.55$  (EtOAc/Hexane, 10:90, v/v)) was obtained as light yellow solid with green tinge (0.35 g from 0.50 g). Yield: 73%; mp 161-163 °C. IR (KBr):  $\nu_{\text{max}} = 1707$  ( $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta = 1.00$  (t,  $J = 7.3$  Hz, 3 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.53 (q,  $J = 7.4$  Hz, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.77

(q,  $J = 6.8$  Hz, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 4.03 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.35 (t,  $J = 6.7$  Hz, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 4.99 (d,  $J = 17.2$  Hz, 1 H, =CHH), 5.19 (s, 2 H,  $\text{CH}_2\text{N}$ ), 5.22 (d,  $J = 17.2$  Hz, 1 H, =CHH), 6.08–6.20 (m, 1 H, =CH), 7.31–7.36 (m, 2 H, ArH), 7.43 (d,  $J = 2.4$  Hz, 2 H, ArH), 7.96 (d,  $J = 7.7$  Hz, 1 H, ArH), 8.40 (s, 1 H, ArH), 9.40 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 14.0, 19.5, 31.1, 46.9, 52.3, 64.4, 100.8, 109.0, 109.8, 116.4, 117.4, 117.9, 119.2, 119.5, 121.4, 121.5, 123.6, 124.0, 124.6, 131.9, 133.8, 139.6, 163.2, 165.2$  ppm. MS (ES):  $m/z$  (%) = 405.2 (100%)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd  $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_4$ : 405.1814; found 405.1804.

**2-(tert-butyl) 5-methyl 11-allyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (5d)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 10:90,  $R_f = 0.58$  (EtOAc/Hexane, 10:90, v/v)) was obtained as yellow solid (0.11 g from 0.20 g). Yield: 58%. mp 98–100 °C. IR (KBr):  $\nu_{\text{max}} = 1708$  ( $\text{CO}_2\text{C}_4\text{H}_9$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta = 1.63$  (s, 9 H,  $\text{CO}_2\text{C}_4\text{H}_9$ ), 4.03 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.00 (d,  $J = 17.2$  Hz, 1 H, =CHH), 5.18–5.25 (m, 3 H,  $\text{CH}_2\text{N}$  and =CHH), 6.08–6.20 (m, 1 H, =CH), 7.29 (d,  $J = 1.4$  Hz, 1 H, ArH), 7.30–7.35 (m, 1 H, ArH), 7.43 (d,  $J = 7.7$  Hz, 2 H, ArH), 7.96 (d,  $J = 7.7$  Hz, 1 H, ArH), 8.40 (s, 1 H, ArH), 9.35 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 28.6, 46.9, 52.3, 80.6, 100.9, 108.9, 109.8, 116.4, 117.5, 117.9, 119.2, 121.2, 121.4, 123.7, 123.9, 124.6, 134.0, 133.9, 139.5, 163.3, 164.7$  ppm. MS (ES):  $m/z$  (%) = 405.1 (100%)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd  $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_4$ : 405.1794; found 405.1814.

**Methyl 11-allyl-2-cyano-11H-indolizino[8,7-b]indole-5-carboxylate (5e)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 10:90,  $R_f = 0.55$  (EtOAc/Hexane, 10:90, v/v)) was obtained as light yellow solid with green tinge (0.183 g from 0.44 g). Yield: 44%. mp 183–185 °C. IR (KBr):  $\nu_{\text{max}} = 1697$  ( $\text{CO}_2\text{CH}_3$ ), 2223 (CN)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta = 4.03$  (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.97 (d,  $J = 17.2$  Hz, 1 H, =CHH), 5.14 (t,  $J = 1.4$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 5.26 (d,  $J = 10.5$  Hz, 1 H, =CHH), 6.06–6.19 (m, 1 H, =CH), 7.10 (d,  $J = 1.4$  Hz, 1 H, ArH), 7.34–7.39 (m, 1 H, ArH), 7.47 (d,  $J = 3.7$  Hz, 2 H, ArH), 7.99 (d,  $J = 7.8$  Hz, 1 H, ArH), 8.45 (s, 1 H, ArH), 9.36 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 46.9, 52.5, 96.9, 102.2, 109.8, 109.9, 116.5, 116.7, 117.7, 119.4, 121.8, 123.2, 123.3, 124.0, 125.3, 131.5, 132.8, 133.5, 139.6, 162.9$  ppm. MS (ES):  $m/z$  (%) = 330.1 (100%)  $[\text{M}+1]^+$ .  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_2$  (329.1164): calcd. C 72.94, H 4.59, N 12.76; found C 73.09, H 4.73, N 12.54.

**Dimethyl 11-allyl-8-fluoro-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (6a)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 20:80, v/v,  $R_f = 0.60$  (EtOAc/Hexane, 30:70, v/v)) was obtained as a yellow solid (0.421 g from 0.70 g). Yield: 63%. mp 195–197 °C. IR (KBr)  $\nu_{\text{max}} = 1713$  ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.93$  (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.03 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.94 (d,  $J = 17.0$  Hz, 1 H, =CHH), 5.15–5.18 (s, 2 H,  $\text{CH}_2\text{N}$ ), 5.24 (d,  $J = 10.3$  Hz, 1 H, =CHH), 6.08–6.20 (m, 1 H, =CH), 7.11–7.18 (m, 1 H, ArH), 7.30 (d,  $J = 1.4$  Hz, 1 H, ArH), 7.33–7.37 (m, 1 H, ArH), 7.61 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 8.8$  Hz, 1 H, ArH), 8.33 (s, 1 H, ArH), 9.42 (d,  $J = 1.4$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 47.1, 51.6, 52.4, 101.1, 104.6, 105.0, 108.6, 108.7, 110.5, 110.7, 112.4, 112.7, 116.2, 117.6, 118.0, 119.2, 121.8, 123.8, 124.1, 124.2, 131.7, 134.7, 135.9, 157.3, 160.5, 163.0, 165.4$  ppm. MS (ES):  $m/z$  (%) = 381.1 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{21}\text{H}_{18}\text{FN}_2\text{O}_4$  381.1251; found 381.1232.

**3-Ethyl 5-methyl 11-allyl-8-fluoro-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (6b)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 20:80, v/v,  $R_f = 0.65$  (EtOAc/Hexane, 30:70, v/v)) was obtained as a yellow solid with green tinge (0.20 g from 0.50 g); yield: 41%; mp 168–170 °C. IR (KBr)  $\nu_{\text{max}} = 1709$  ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.42$  (t,  $J = 7.1$  Hz, 3 H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 4.02 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.40 (q,  $J = 7.1$  Hz, 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 4.97 (d,  $J = 17.1$  Hz, 1 H, =CHH), 5.16 (d,  $J = 2.0$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 5.24 (d,  $J = 10.4$  Hz, 1 H, =CHH), 6.08–6.17 (m, 1 H, =CH), 7.11–7.17 (m, 1 H, ArH), 7.30–7.36 (m, 2 H, ArH), 7.59 (dd,  $J_1 = 2.1$  Hz,  $J_2 = 8.8$  Hz, 1 H, ArH), 8.30 (s, 1 H, ArH), 9.40 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 14.6, 47.1, 52.3, 60.5, 101.1, 104.6, 104.9, 108.6, 108.7, 110.5, 110.7, 112.3, 112.7, 116.1, 117.6, 118.0, 119.6, 121.7, 123.8, 124.1, 124.3, 131.7, 134.7, 135.9, 157.3, 160.5, 163.1, 165.0$  ppm. MS (ES):  $m/z$  (%) = 395.2 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd  $\text{C}_{22}\text{H}_{20}\text{FN}_2\text{O}_4$ : 395.1381; found 395.1377.

**Dimethyl 11-prop-2-ynyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (12a)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 15:85, v/v,  $R_f = 0.40$  (EtOAc/Hexane, 30:70, v/v)) was obtained as a yellow solid with green tinge (0.134 g from 0.30 g); yield: 47%; mp 242–244 °C. IR (KBr)  $\nu_{\text{max}} = 1712$  ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.39$  (d,  $J = 2.6$  Hz, 1 H, CCH), 3.94 (d,  $J = 3.4$  Hz, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.03 (d,  $J = 3.4$  Hz, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.31 (d,  $J = 2.8$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 7.33–7.39 (m, 1 H, ArH), 7.44–7.57 (m, 3 H, ArH), 7.96 (q,  $J = 3.8$  Hz, 1 H, ArH), 8.38 (d,  $J = 3.5$  Hz, 1 H, ArH), 9.43 (dd,  $J_1 = 1.3$  Hz,  $J_2 = 3.4$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 39.3, 56.7, 57.6, 81.3, 84.4, 106.2, 114.1, 115.6, 121.6, 122.9, 123.8, 124.9, 125.6, 126.9, 128.1, 128.8, 130.1, 137.8, 144.0, 167.9, 169.5$  ppm. MS (ES):  $m/z$  (%) = 361.2 (100)  $[\text{M}+1]^+$ .  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_4$  (360.1110): calcd. C 69.99, H 4.48, N 7.77; found C 70.30, H 4.54, N 7.56.

**2-tert-Butyl 5-methyl 11-(prop-2-ynyl)-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (12d)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 15:85, v/v,  $R_f = 0.50$  (EtOAc/Hexane, 20:80, v/v)) was obtained as a yellowish solid with green tinge (0.143 g from 0.30 g); yield: 50%; mp 201–203 °C. IR (KBr)  $\nu_{\text{max}} = 1708$  ( $\text{CO}_2\text{CC}_3\text{H}_9$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.64$  (s, 9 H,  $\text{CO}_2\text{CC}_3\text{H}_9$ ), 2.39 (t,  $J = 2.4$  Hz, 1 H, CCH), 4.02 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.29 (d,  $J = 2.5$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 7.32–7.37 (m, 1 H, ArH), 7.43–7.48 (m, 2 H, ArH), 7.54 (d,  $J = 8.2$  Hz, 1 H, ArH), 7.94 (d,  $J = 7.7$  Hz, 1 H, ArH), 8.35 (s, 1 H, ArH), 9.33 (d,  $J = 1.4$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 28.6, 34.2, 52.3, 74.1, 80.6, 100.9, 109.1, 109.5, 115.9, 118.1, 119.2, 121.2, 121.4, 123.6, 123.7, 124.7, 133.3, 138.8, 163.1, 164.5$  ppm. MS (ES):  $m/z$  (%) = 403.1 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_4$  403.1658; found 403.1644.

**Methyl 2-cyano-11-prop-2-ynyl-11H-indolizino[8,7-b]indole-5-carboxylate (12e)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 25:75, v/v,  $R_f = 0.42$  (EtOAc/Hexane, 20:80, v/v)) was obtained as a white solid (0.144 g from 0.30 g); yield: 51%; mp 212–214 °C. IR (KBr)  $\nu_{\text{max}} = 1724$  ( $\text{CO}_2\text{CH}_3$ ), 2224 (CN)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.44$  (t,  $J = 2.4$  Hz, 1 H, CCH), 4.04 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.25 (d,  $J = 2.5$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 7.34 (s, 1 H, ArH), 7.36–7.42 (m, 1 H, ArH), 7.49–7.58 (m, 2 H, ArH), 7.98 (d,  $J = 7.8$  Hz, 1 H, ArH), 8.43 (s, 1 H, ArH), 9.39 (d,  $J = 1.4$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 29.4, 53.0, 76.6, 79.0, 96.5, 103.6, 110.0, 111.0, 117.2, 118.0, 119.6, 120.3, 122.3, 123.1, 123.9, 125.6, 132.2, 134.8, 139.2, 162.8$  ppm. MS (ES):  $m/z$  (%) = 328.1 (100)  $[\text{M}+1]^+$ .  $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}_2$  (327.1008): calcd. C 73.38, H 4.00, N 12.84; found C 73.44, H 4.23, N 12.78.

**Dimethyl 11-benzyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (13a)**: The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 15:85, v/v,  $R_f = 0.50$  (EtOAc/Hexane, 25:75, v/v)) was obtained as a yellow solid (0.23 g from 0.40 g). Yield: 59%. mp 209–211 °C. IR (KBr)  $\nu_{\text{max}} = 1713$  ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.88$  (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.04 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.81 (s, 2 H,  $\text{CH}_2\text{N}$ ), 7.15 (t,  $J =$

6.3 Hz, 2 H, ArH), 7.22–7.32 (m, 1 H, ArH), 7.33–7.36 (m, 3 H, ArH), 7.36–7.40 (m, 3 H, ArH), 7.99 (d,  $J = 6.7$  Hz, 1 H, ArH), 8.45 (s, 1 H, ArH), 9.41 (d,  $J = 1.3$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 29.8, 48.4, 51.6, 52.4, 100.7, 109.3, 110.2, 116.5, 118.2, 119.2, 119.3, 121.6, 121.7, 123.8, 124.2, 124.8, 126.3, 127.9, 129.2, 134.1, 136.2, 139.9, 163.2, 165.5$  ppm. MS (ES):  $m/z$  (%) = 413.2 (100)  $[\text{M}+1]^+$ .  $\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}_4$  (412.1423): calcd. C 72.80, H 4.89, N 6.79; found C 72.96, H 4.78, N 6.83.

**2-Ethyl 5-methyl 11-benzyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (13b):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 15:85, v/v,  $R_f = 0.52$  (EtOAC/Hexane, 20:80, v/v)) was obtained as a yellow solid with green tinge (0.346 g from 0.80 g); Yield: 45%; mp 185–187 °C. IR (KBr)  $\nu_{\text{max}} = 1710$  ( $\text{CO}_2\text{CH}_2\text{CH}_3$  and  $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.36$  (t,  $J = 7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 4.06 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.34 (q,  $J = 7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.82 (s, 2 H,  $\text{CH}_2$ ), 7.14 (d,  $J = 6.3$  Hz, 2 H, ArH), 7.23–7.33 (m, 4 H, ArH), 7.35–7.42 (m, 3 H, ArH), 7.99 (d,  $J = 6.7$  Hz, 1 H, ArH), 8.44 (s, 1 H, ArH), 9.40 (d,  $J = 1.4$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 14.6, 48.3, 52.3, 60.4, 109.2, 110.1, 116.4, 118.1, 119.2, 119.6, 121.5, 121.7, 123.8, 124.1, 124.8, 126.3, 127.9, 129.2, 134.1, 136.2, 139.9, 163.2, 165.0$  ppm. MS (ES):  $m/z$  (%) = 427.2 (100)  $[\text{M}+1]^+$ .  $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_4$  (426.1580): calcd. C 73.23, H 5.20, N 6.57; found C 73.47, H 5.04, N 6.69.

**2-(tert-Butyl) 5-methyl 11-benzyl-11H-indolizino[8,7-b]indole-2,5-dicarboxylate (13d):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 15:85, v/v,  $R_f = 0.80$  (EtOAC/Hexane, 20:80, v/v)) was obtained as a yellow solid with green tinge (0.452 g from 1.00 g); yield: 47%; mp 179–181 °C. IR (KBr)  $\nu_{\text{max}} = 1707$  ( $\text{CO}_2\text{CC}_3\text{H}_9$  and  $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.59$  (s, 9 H,  $\text{CO}_2\text{CC}_3\text{H}_9$ ), 4.03 (d,  $J = 1.9$  Hz, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.81 (s, 2 H,  $\text{CH}_2\text{N}$ ), 7.16 (t,  $J = 8.4$  Hz, 3 H, ArH), 7.26–7.33 (m, 3 H, ArH), 7.34–7.40 (m, 3 H, ArH), 7.99 (d,  $J = 6.7$  Hz, 1 H, ArH), 8.43 (t,  $J = 6.7$  Hz, 1 H, ArH), 9.30 (d,  $J = 0.9$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 28.6, 48.3, 52.3, 80.5, 100.9, 109.1, 110.1, 116.3, 118.0, 119.2, 121.2, 123.7, 123.9, 124.7, 126.2, 127.8, 129.1, 134.1, 136.2, 139.9, 163.3, 164.5$  ppm. MS (ES):  $m/z$  (%) = 455.1 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_4$  454.1971; found 454.1959.

**Methyl 11-benzyl-2-cyano-11H-indolizino[8,7-b]indole-5-carboxylate (13e):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 10:90, v/v,  $R_f = 0.60$  (EtOAC/Hexane, 10:90, v/v)) was obtained as a white solid with green tinge (0.071 g from 0.17 g); Yield: 43%; mp 227–229 °C. IR (KBr)  $\nu_{\text{max}} = 1707$  ( $\text{CO}_2\text{CH}_3$ ), 2231 (CN)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.04$  (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.76 (s, 2 H,  $\text{CH}_2\text{N}$ ), 6.94 (d,  $J = 0.8$  Hz, 1 H, ArH), 7.08–7.11 (m, 2 H, ArH), 7.26–7.33 (m, 3 H, ArH), 7.36–7.41 (m, 1 H, ArH), 7.45 (t,  $J = 2.5$  Hz, 2 H, ArH), 8.02 (d,  $J = 7.5$  Hz, 1 H, ArH), 8.48 (s, 1 H, ArH), 9.33 (d,  $J = 1.4$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 29.8, 48.3, 52.6, 97.0, 102.3, 110.0, 110.1, 116.7, 117.9, 119.5, 122.0, 123.4, 124.0, 125.5, 125.9, 128.1, 129.4, 135.8, 140.1, 162.9$  ppm. MS (ES):  $m/z$  (%) = 455.1 (100)  $[\text{M}+1]^+$ .  $\text{C}_{24}\text{H}_{17}\text{N}_3\text{O}_2$  (379.1321): calcd. C 75.97, H 4.52, N 11.08; found C 75.88, H 4.64, N 10.94.

**tert-Butyl 11-allyl-11H-indolizino[8,7-b]indole-2-carboxylate (15d):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 10:90, v/v,  $R_f = 0.60$  (EtOAC/Hexane, 10:90, v/v)) was obtained as a yellow oil (0.128 g from 0.30 g). Yield: 45%. IR (Neat)  $\nu_{\text{max}} = 1701$  ( $\text{CO}_2\text{CC}_3\text{H}_9$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.62$  (s, 9 H,  $\text{CO}_2\text{CC}_3\text{H}_9$ ), 4.99 (d,  $J = 17.5$  Hz, 1 H, =CHH), 5.19 (t,  $J = 7.4$  Hz, 3 H,  $\text{CH}_2\text{N}$  and =CHH), 6.07–6.19 (m, 1 H, =CH), 7.06 (s, 1 H, ArH), 7.19–7.28 (m, 2 H, ArH), 7.33–7.43 (m, 2 H, ArH), 7.70 (d,  $J = 7.1$  Hz, 1 H, ArH),

7.86 (d,  $J = 1.3$  Hz, 1 H, ArH), 7.89 (d,  $J = 7.8$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 28.5, 46.8, 80.4, 98.7, 106.9, 109.5, 109.7, 117.0, 118.0, 119.0, 119.1, 120.4, 120.8, 123.4, 123.7, 123.9, 130.6, 132.7, 138.7, 164.6$  ppm. MS (ES):  $m/z$  (%) = 347.1 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_2$  347.1760; found 347.1744

**Methyl 12-allyl-1-oxo-2,3,4,12-tetrahydro-1H-benzo[2,3]indolizino[8,7-b]indole-6-carboxylate (21):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 20:80, v/v,  $R_f = 0.40$  (EtOAC/Hexane, 50:50, v/v)) was obtained as a white solid (0.576 g from 0.70 g); yield: 65%; mp 228–230 °C. IR (KBr)  $\nu_{\text{max}} = 1670$  (CO), 1718 ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.20$  (q,  $J = 6.3$  Hz, 2 H,  $\text{CH}_2$ ), 2.65 (t,  $J = 5.8$  Hz, 2 H,  $\text{CH}_2$ ), 2.86 (t,  $J = 6.0$  Hz, 2 H,  $\text{CH}_2$ ), 4.04 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.95 (d, 17.0 Hz, 1 H, =CHH), 5.21 (t,  $J = 5.0$  Hz, 3 H, =CHH and  $\text{CH}_2\text{N}$ ), 6.08–6.20 (m, 1 H, =CH), 7.30–7.35 (m, 2 H, ArH), 7.39–7.46 (m, 2 H, ArH), 7.94 (d,  $J = 7.7$  Hz, 1 H, ArH), 8.10 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 25.0, 26.6, 38.4, 46.9, 52.6, 97.0, 108.8, 109.9, 117.0, 117.3, 119.2, 119.8, 121.4, 123.6, 123.7, 124.6, 124.8, 131.9, 133.7, 138.4, 139.5, 163.5, 196.4$  ppm. MS (ES):  $m/z$  (%) = 373.2 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_3$  373.1552; found 373.1534.

**Methyl 9-fluoro-12-allyl-1-oxo-2,3,4,12-tetrahydro-1H-benzo[2,3]indolizino[8,7-b]indole-6-carboxylate (22):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 30:70, v/v,  $R_f = 0.38$  (EtOAC/Hexane, 50:50, v/v)) was obtained as a white solid (0.06 g from 0.15 g); yield: 42%; mp >250 °C. IR (KBr)  $\nu_{\text{max}} = 1655$  (CO), 1713 ( $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.18$  (t,  $J = 6.2$  Hz, 2 H,  $\text{CH}_2$ ), 2.68 (t,  $J = 6.3$  Hz, 2 H,  $\text{CH}_2$ ), 2.87 (t,  $J = 6.1$  Hz, 2 H,  $\text{CH}_2$ ), 4.03 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.92 (d,  $J = 17.1$  Hz, 1 H, =CHH), 5.15–5.23 (m, 3 H, =CHH and  $\text{CH}_2\text{N}$ ), 6.05–6.17 (m, 1 H, =CH), 7.10–7.16 (m, 1 H, ArH), 7.31–7.39 (m, 2 H, ArH), 7.56 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 8.8$  Hz, 1 H, ArH), 8.00 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 24.9, 26.2, 33.6, 47.0, 53.1, 97.7, 105.4, 105.8, 108.1, 108.4, 111.7, 112.2, 116.9, 120.5, 124.3, 133.6, 136.3, 138.6, 170.8, 174.7, 195.9$  ppm. MS (ES):  $m/z$  (%) = 391.2 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{23}\text{H}_{20}\text{FN}_2\text{O}_3$  391.1458; found 391.1454.

**Methyl 12-benzyl-1-oxo-2,3,4,12-tetrahydro-1H-benzo[2,3]indolizino[8,7-b]indole-6-carboxylate (23):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 20:80, v/v,  $R_f = 0.50$  (EtOAC/Hexane, 40:60, v/v)) was obtained as a yellow solid with green tinge (0.277 g from 0.35 g); yield: 82%; mp 198–200 °C. IR (KBr)  $\nu_{\text{max}} = 1717$  (CO and  $\text{CO}_2\text{CH}_3$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.17$  (t,  $J = 5.8$  Hz, 2 H,  $\text{CH}_2$ ), 2.65 (t,  $J = 5.8$  Hz, 2 H,  $\text{CH}_2$ ), 2.86 (t,  $J = 5.6$  Hz, 2 H,  $\text{CH}_2$ ), 4.05 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.82 (s, 2 H,  $\text{CH}_2\text{N}$ ), 7.11 (d,  $J = 7.0$  Hz, 2 H, ArH), 7.23–7.30 (m, 4 H, ArH), 7.33–7.40 (m, 3 H, ArH), 7.97 (d,  $J = 6.8$  Hz, 1 H, ArH), 8.13 (d,  $J = 1.5$  Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 25.0, 26.6, 38.4, 48.4, 52.6, 97.0, 109.0, 110.2, 117.0, 119.2, 120.0, 121.6, 123.7, 123.8, 124.7, 124.9, 126.2, 127.8, 129.1, 133.9, 136.1, 138.4, 139.8, 163.5, 196.2$  ppm. MS (ES):  $m/z$  (%) = 423.3 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_3$  423.1709; found 423.1689.

**Methyl 12-benzyl-1-oxo-2,3,4,12-tetrahydro-1H-benzo[2,3]indolizino[8,7-b]indole-6-carboxylate (24):** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAC/Hexane, 25:75, v/v,  $R_f = 0.60$  (EtOAC/Hexane, 50:50, v/v)) was obtained as a yellow solid (0.098 g from 0.20 g); yield: 51%; mp >250 °C. IR (KBr)  $\nu_{\text{max}} = 1703$  ( $\text{CO}_2\text{CH}_3$ ), 1711 (CO)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.95$ –2.99 (m, 2 H,  $\text{CH}_2$ ), 3.34–3.37 (m, 2 H,  $\text{CH}_2$ ), 4.03 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.79 (s, 2 H,  $\text{CH}_2\text{N}$ ), 6.90 (s, 1 H, ArH), 7.09 (t,  $J = 3.4$  Hz, 2 H, ArH), 7.24–7.28 (m, 4 H, ArH), 7.34–7.42 (m, 2 H, ArH), 7.99 (d,  $J = 7.0$  Hz, 1 H, ArH), 8.22 (s, 1

H, ArH) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 25.7, 41.4, 48.2, 52.6, 93.1, 109.3, 110.1, 116.2, 119.3, 119.8, 121.8, 123.5, 125.0, 125.9, 127.9, 129.2, 130.6, 130.9, 134.0, 136.0, 140.0, 153.0, 162.7 ppm. MS (ES):  $m/z$  (%) = 409.3 (100)  $[\text{M}+1]^+$ .  $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_3$  (408.1474): calcd. C 76.45, H 4.94, N 6.86; found C 76.81, H 5.06, N 6.73

#### General procedure for the synthesis of compounds 17-18, 20, 25 as exemplified for compound 19.

To a solution of **9** (0.50 g, 1.45 mmol), DMAP (0.071 g, 0.58 mmol) and cyclohexenone (2.66 mL, 29.5 mmol) in a THF/water mixture (10 mL, 1:1, v/v) was added and stirred the reaction at room temperature for 48 h. After completion of the reaction as monitored by TLC, the content was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (70 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to yield a solid residue which was further purified via silica gel column chromatography using (hexane/EtOAc, 40:60,  $R_f$  = 0.50 (hexane/EtOAc, 50:50)) to obtain **19** as a yellow solid (0.344 g from 0.50 g); yield: 54%; mp 185–187 °C.

**Methyl 1-[hydroxy(6-oxocyclohex-1-en-1-yl)methyl] -9-benzyl - $\beta$ -carboline-3-carboxylate (19):** IR (KBr):  $\nu_{\text{max}}$  = 1665 (CO), 1701 ( $\text{CO}_2\text{CH}_3$ ), 3448 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 1.57–1.63 (m, 1 H, CHH), 1.85–1.96 (m, 2 H,  $\text{CH}_2$ ), 2.04–2.14 (m, 2 H,  $\text{CH}_2$ ), 2.44–2.50 (m, 1 H, CHH), 4.03 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 5.64 (d,  $J$  = 18.0 Hz, 2 H, =CH and CHOH), 5.87 (d,  $J$  = 18.0 Hz, 1 H, CHOH), 6.27 (t,  $J$  = 4.2 Hz, 2 H,  $\text{CH}_2\text{Ph}$ ), 6.79 (t,  $J$  = 4.2 Hz, 2 H, ArH), 7.20–7.24 (m, 3 H, ArH), 7.33 (d,  $J$  = 8.3 Hz, 1 H, ArH), 7.40 (t,  $J$  = 7.4 Hz, 1 H, ArH), 7.54–7.60 (m, 1 H, ArH), 8.26 (d,  $J$  = 7.8 Hz, 1 H, ArH), 8.91 (s, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 22.1, 25.8, 38.1, 48.3, 52.6, 67.5, 111.1, 117.5, 121.5, 121.7, 121.8, 125.6, 127.6, 129.0, 129.4, 130.5, 135.3, 135.6, 136.9, 140.7, 142.4, 143.1, 148.3, 166.3 ppm. MS (ES):  $m/z$  (%) = 441.2 (100%)  $[\text{M}+1]^+$ , 464.2 (60%)  $[\text{M}+23]^+$ .  $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_4$  (440.1736): calcd. C 73.62, H 5.49, N 6.36; found C 73.59, H 5.67, N 6.57.

**12-Allyl-1,2,3,4,12-tetrahydro-1H-benzo[2,3]indolizino[8,7-b]indol-1-one (25)** The title compound was prepared following the above described general procedure and after purification by column chromatography (EtOAc/Hexane, 15:85, v/v,  $R_f$  = 0.40 (EtOAc/Hexane, 30:70, v/v)) was obtained as a white solid (0.241 g from 0.31 g). yield: 58%; mp 135–137 °C. IR (KBr)  $\nu_{\text{max}}$  = 1660 (CO)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.31–2.39 (m, 2 H,  $\text{CH}_2$ ), 2.66 (t,  $J$  = 5.8 Hz, 2 H,  $\text{CH}_2$ ), 3.04 (t,  $J$  = 6.2 Hz, 2 H,  $\text{CH}_2$ ), 4.93 (d,  $J$  = 16.5 Hz, 1 H, =CHH), 5.16–5.18 (m, 3 H, =CHH and  $\text{CH}_2\text{N}$ ), 6.06–6.18 (m, 1 H, =CH), 7.06 (s, 1 H, ArH), 7.26–7.30 (m, 2 H, ArH), 7.34–7.44 (m, 2 H, ArH), 7.51 (d,  $J$  = 7.2 Hz, 1 H, ArH), 7.91 (d,  $J$  = 7.7 Hz, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.7, 23.6, 38.5, 46.8, 93.6, 107.2, 109.6, 109.8, 115.7, 116.9, 119.0, 120.5, 122.6, 123.4, 123.9, 124.4, 130.8, 132.6, 134.4, 138.8, 195.9 ppm. MS (ES):  $m/z$  (%) = 315.3 (100)  $[\text{M}+1]^+$ . DART-HRMS (ES+): calcd.  $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}$  315.1485; found 315.1497.

**Supporting Information** Experimental details, spectroscopic data for remaining compounds and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds are provided.

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