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Versatility of Substituted 1-Formyl-9*H*-β-carbolines for the Synthesis of New Fused β-Carbolines via Intramolecular 1,3-Dipolar Cycloaddition[‡]

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Dedicated to Professor Mitchell A. Avery

Keywords: Nitrogen heterocycles / β-Carbolines / Cycloaddition / Alkylation / Microwave chemistry

Substituted 1-formyl-9*H*-β-carbolines are demonstrated to be viable precursors for the synthesis of a library of new β-carboline-based polycyclic systems via 1,3-dipolar cycloaddition strategy.

Introduction

Alkaloids comprising of the β-carboline core are ubiquitously present in Nature including plants, marine organisms, insects, mammalian as well as human tissues (Figure 1).[1] Such alkaloids are constitutionally a large group of indole alkaloids with different scale of aromaticity. Recently an array of pharmacological applications of alkaloids belonging to the β-carboline class were reviewed by Cao et al.[2] Especially they have been demonstrated to intercalate with DNA and display activities against CNS and infectious disorders. We have recently reported the synthesis of unnatural canthin-6-ones and canthines via Baylis–Hillman reaction of substituted 1-formyl-9*H*-β-carbolines.[3] During the course of this study we engineered a facile route to generate these aldehydes in good yields using readily available reagents. It occurred to us that these aldehydes may serve as viable precursors to a library of β-carboline-based compounds containing a D-ring utilizing intramolecular 1,3-cycloaddition as the key step.[4] The presence of free NH group of the indole subunit and the formyl group at 1-position in close proximity provides opportunity to place the dipole and the alkene or alkyne dipolariphile within the same molecule. The resulting species can be further manipulated using established strategies leading to a variety of bicyclic or polycyclic products. These considerations guided us to explore the utility of these aldehydes to obtain new β-carboline derivatives. This paper incorporates the results of our endeavour in this direction.

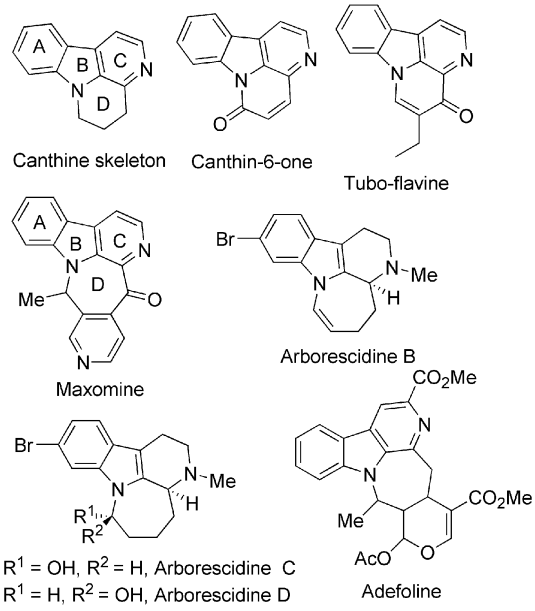

Figure 1. A few examples of β-carboline alkaloids containing D-ring.

Results and Discussion

For initiating study, in the first instance masked substituted β-carboline aldehydes **7**–**9** were synthesized in high yields following the recently reported procedure (Scheme 1).[3]

In their efforts to develop new route to canthines, Condie and Bergman have earlier reported the alkylation of methyl 1-formyl-9*H*-β-carboline carboxylate via allyl bromide in the presence of NaH in DMSO in high yields.[5] However in our hands the experiment did not work well and the desired compound was obtained in minor yields only. Consequently we decided to first install the allyl chain on NH of the β-

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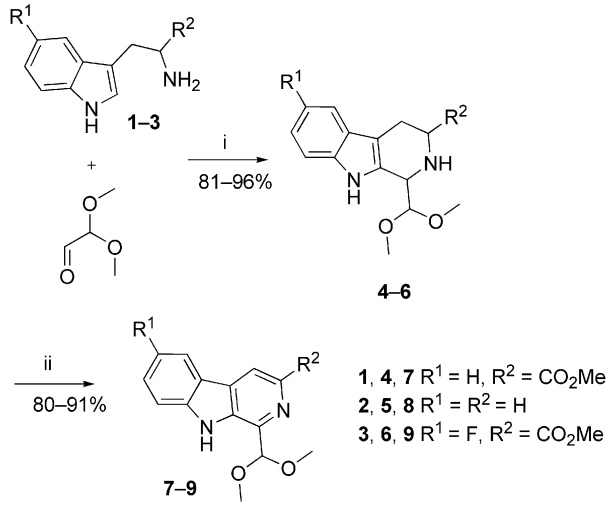
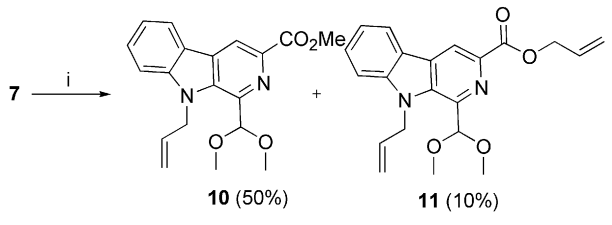


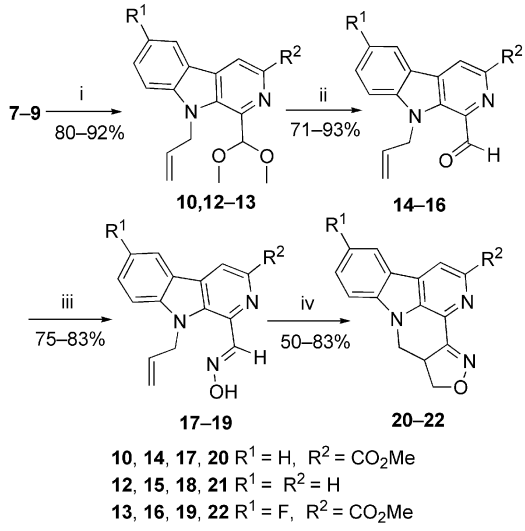
Scheme 1. Reagents and conditions: i) 2–5% TFA in CH_2Cl_2, 4 h–3 d. ii) $KMnO_4$, dry THF, room temp., 6 h–5 d.

carboline in **7**–**9** through allyl bromide and then deprotect the acetal functionality. Following, the nitrile oxide could be generated from the formyl group which should participate in intramolecular 1,3-dipolar cycloaddition to afford new β-carbolines. With the aim to optimize the reaction, studies were initiated with **7** by alkylating it with allyl bromide in the presence of NaH in dry DMF at room temperature. The reaction of **7** with 1.2 equiv. of allyl bromide resulted in only 70% conversion (TLC analysis) in 2 h to yield **10**. Increasing the amount of allyl bromide to 1.5 equiv. was also found to be insufficient to take the reaction to completion. Subsequently, reaction was investigated with 2.0 equiv. of allyl bromide. Fortunately this ratio of bromide resulted in completion of reaction but a mixture of two products was formed which could be separated only after a careful chromatography (Scheme 2). On the basis of spectroscopic data, the structure of the less polar product that was isolated in minor quantity (10%) was established as **11** whereas the major product (50%) was the required product **10**. The formation of **11** is attributed to hydrolysis of the methyl ester followed by substitution with allyl bromide in the presence of base in **7**. To avoid the tedious separation of **10** and **11**, we continued seeking a reaction condition wherein only the required product **10** is formed.



Scheme 2. Reagents and conditions: i) allyl bromide, NaH, dry DMF, 0 °C–room temp., 2 h.

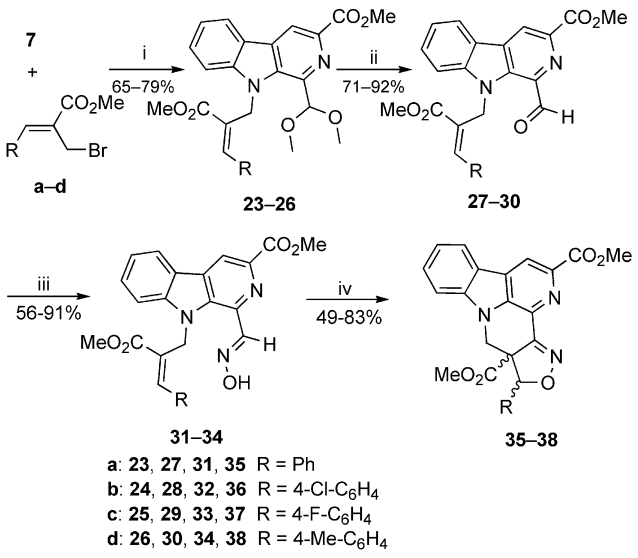
It was pleasing to discover that the reaction with Cs_2CO_3 as base in dry DMF in 2 h furnished **10** as the sole product in 92% yields (Scheme 3). Additionally this procedure did not require chromatographic purification as **10** was obtained in sufficiently pure form. It is significant to note that the reaction was unsuccessful when K_2CO_3 was used as a base in dry DMF at room temperature or under heating at 100 °C. Like **7**, substrates **8** and **9** reacted with allyl bromide to furnish the corresponding products **12** and **13**. In the next step the acetal group in **10**,**12**–**13** was deprotected by heating in the presence of AcOH/water (2:3, v/v) at 120 °C to afford respective aldehydes **14**–**16**. More importantly this route works well to afford higher amount (ca. 5.0 g) of *N*-alkylated aldehyde. Aldehydes **14**–**16** reacted with $NH_2OH{\cdot}HCl$ in the presence of NaOAc to furnish the substituted oximes **17**–**19**, respectively in good yields. Treatment of **17**–**19** with NaOCl in the presence of Et_3N at room temperature for three days resulted in the formation of the desired 9a,10-dihydro-9*H*-indolo[3,2,1-*ij*]isoxazolo[4,3-*c*]-[1,5]naphthyridines **20**–**22**.



Scheme 3. Reagents and conditions: i) allyl bromide, Cs_2CO_3, dry DMF, room temp., 2–3 h. ii) AcOH/H_2O (2:3, v/v), reflux, 45 min. iii) $NH_2OH{\cdot}HCl$, AcONa, MeOH, reflux, 1 h. iv) NaOCl, Et_3N, CH_2Cl_2, room temp., 3 d.

In our attempt to increase the diversity of products which could be generated via this strategy, the substituted allyl bromides prepared from the Baylis–Hillman chemistry using known protocol were utilized to alkylate the NH to produce highly substituted alkenes. Accordingly the reaction of **7** with several substituted allyl bromides (labelled **a**–**d**) in the presence of Cs_2CO_3 in dry DMF were performed to smoothly afford the required products **23**–**26** in 2–3 h (Scheme 4). The spectroscopic analysis of these products revealed them to be the *E*-isomer exclusively. Deprotection of the acetal group in **23**–**26** was carried out as described earlier to obtain the aldehydes **27**–**30** in high yields and good purity. Reaction of aldehydes **27**–**30** with $NH_2OH{\cdot}HCl$ resulted in the corresponding oximes **31**–**34** which upon treatment with NaOCl in the presence of Et_3N afforded the substituted isoxazoline derivatives **35**–**38**, respectively. Although these products were obtained as a mixture of diastereomers, based on the literature precedence of the chemical shift of the CH proton it was found that the diastereomers where the phenyl and the ester groups were

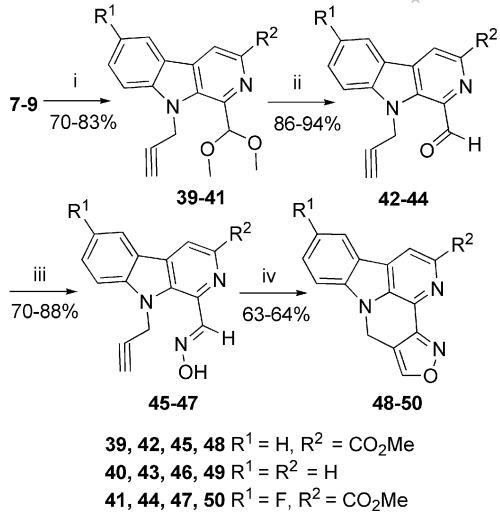
placed syn to each other were formed in major quantity.[6] Unfortunately these diastereomers could not be separated via column chromatography.



Scheme 4. Reagents and conditions: i) methyl 2-bromomethyl-3-phenylacrylate, methyl 2-bromomethyl-3-(4-chlorophenyl)acrylate, methyl 2-bromomethyl-3-(4-fluorophenyl)acrylate, methyl 2-bromomethyl-3-*p*Tol-acrylate, Cs_2CO_3, dry DMF, room temp., 3 h. ii) AcOH/H_2O (2:3, v/v), reflux, 45 min. iii) $NH_2OH{\cdot}HCl$, AcONa, MeOH, reflux, 1 h. iv) NaOCl, Et_3N, CH_2Cl_2, room temp., 3 d.

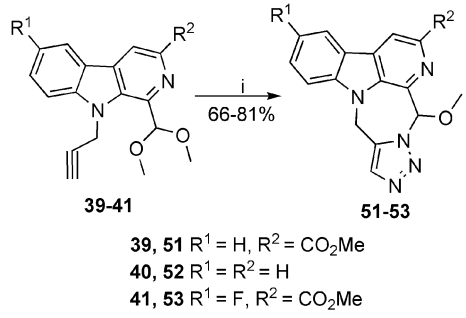
Having established the protocol with allyl bromides, we next shifted our investigations to substrates afforded from the reaction of **7**–**9** with propargyl bromide. For this purpose, initially substrates **7**–**9** were treated with propargyl bromide in dry DMF using Cs_2CO_3 as the base to smoothly furnish the desired product **39**–**41**, respectively in good yields (Scheme 5). Deprotection of the acetal moiety in the presence of AcOH/H_2O resulted in the formation of aldehydes **42**–**44**. Transformation of **42**–**44** to oximes **45**–**47** was achieved by their reaction with $NH_2OH{\cdot}HCl$. Treating oximes **45**–**47** with NaOCl produced the required isoxazole derivatives **48**–**50**.

Recently Taguchi and co-workers reported an $In(OTf)_3$-catalysed efficient azidation reaction of ω,ω-dialkoxy alkyne with $TMSN_3$ and its further application in 1,3-dipolar cycloaddition reaction to yield the annulated six and five membered ring system under heating condition.[7] Inspired by their results, we envisaged that the ε,ε-dimethoxy alkyne derivatives **39**–**41** generated during the present study may undergo similar reaction to afford β-carboline-based system containing seven-member D-ring found in natural compounds such as maxomine, arborescidine-B, C and D. With the aim to optimize the conditions, in the first instance acetal **39** was treated with $TMSN_3$ in the presence of $In(OTf)_3$ in dry DCE under heating at 50 °C. The reaction was observed to be sluggish and took 3 d to go to completion to yield the desired product in 67% yield. However, when the same conditions were applied to reaction of acetal **40**, even after 5 d only 30% (HPLC analysis) conversion was observed. To facilitate the reaction it was decided to



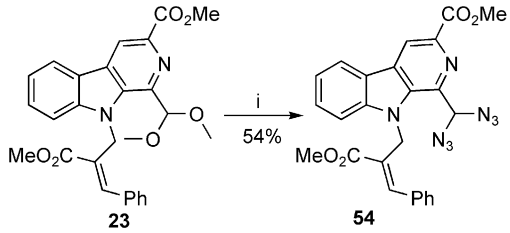
Scheme 5. Reagents and conditions: i) propargyl bromide, Cs_2CO_3, dry DMF, room temp., 2–3 h. ii) AcOH/H_2O (2:3, v/v), reflux, 45 min. iii) $NH_2OH{\cdot}HCl$, AcONa, MeOH, reflux, 1–1.5 h. iv) NaOCl, Et_3N, CH_2Cl_2, room temp., 3 d.

evaluate this reaction under microwave heating. It was pleasing to note that the reaction of **40** in the presence of $In(OTf)_3$ in DCE at 150 °C was completed in 15 min to afford the desired product **52** in 83% yield (Scheme 6). Encouraged by these results we repeated the reaction with substrate **39** and **41** under microwave heating and in both cases the reaction was complete in 10 min to yield the β-carboline-containing triazoles **51** and **53** in 72% and 55% yield, respectively. Similar reaction with the alkene **23** under microwave heating, however, yielded the diazido derivative **54** in 54% yield (Scheme 7). An analogous derivative was obtained as side product also by Taguchi et al.



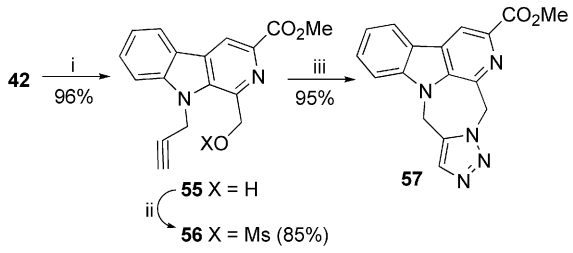
Scheme 6. Reagents and conditions: i) $TMSN_3$, DCE, MW, 150 °C, 10–15 min.

The triazoles **51**–**53** generated via the above-reported sequence invariably carried the methoxy group originating from the acetal moiety of the precursor. Hence it was decided to formulate another simple route for generating such triazole derivative devoid of the methoxy substitution. Consequently, in a model study **42** was subjected to reduction with $NaBH_4$ to yield the alcohol **55** as a solid in 96% yield (Scheme 8). Reacting **55** with mesyl chloride in the presence of Et_3N in dichloromethane led to the mesyl derivative **56** (85%). Treatment of **56** with NaN_3 in DMF under heating



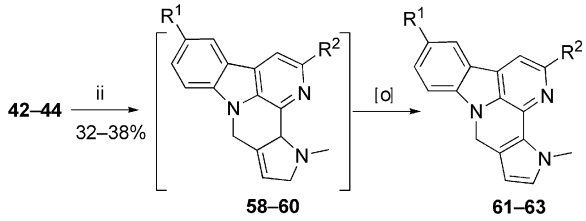
Scheme 7. i) $TMSN_3$, DCE, MW, 150 °C, 15 min.

for 3 h gave the product in 95% yield which was spectroscopically analysed to be the desired compound **57**. Fortunately in this sequence of reactions at no stage purification protocols were required.



Scheme 8. Reagents and conditions: i) $NaBH_4$, MeOH, room temp., 20 min. ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min. iii) NaN_3, DMF, 90 °C, 3 h.

In order to further diversify the range of the products which could be generated by applying intramolecular 1,3-dipolar cycloaddition reaction, we decided to generate unstable azomethane ylide which may have the potential to react with alkyne. Towards this objective aldehyde **42** was treated with sarcosine in dry toluene under refluxing condition. This reaction resulted in compound **61** (Scheme 9). Repeating the reaction with **43** and **44** with sarcosine yielded the β-carboline-fused pyrroles **62**–**63**, albeit in low yield. The final product may have formed via oxidation of the intermediate **58**–**60**.



Scheme 9. Reagents and conditions: 1) Sarcosine, dry PhMe, reflux, 24–36 h.

Conclusions

In summary, we have disclosed the potential of substituted 1-formyl-9*H*-β-carbolines for achieving the synthesis of a library of β-carboline fused systems containing D-ring via intramolecular 1,3-dipolar cycloaddition reactions. This approach is attractive because all reagents utilized in the study are cheap and readily available and reaction conditions are simple. Although we have showcased 1,3-dipolar cycloaddition only for building up new β-carbolines, we envisage that this aldehyde could provide intermediates for RCM, Diels–Alder and other established reactions for constructing a large library of β-carboline-based derivatives. Work toward these objectives is underway in our laboratory.

Experimental Section

General: 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. ^1H NMR and ^{13}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 are given as δ values). 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. Microwave-mediated reactions were performed in Biotage initiator 2.5 microwave system. The room temperature varied between 21 °C and 35 °C. ^{13}C NMR could not be recorded for a few derivatives (fluoro-analogs) due to poor solubility even in [D_6]DMSO.

General Procedure for the Synthesis of Compounds 10, 12–13, 23–26, 39–41, as Exemplified for Compound 10: To a stirred solution of **7** (6.0 g, 20.0 mmol) in dry DMF (30 mL), Cs_2CO_3 (9.8 g, 30.0 mmol) was added and stirred the reaction at room temperature for 30 min. Thereafter allyl bromide (2.6 mL, 30.0 mmol) in 5 mL dry DMF was added drop wise and the reaction was stirred for additional 1.5 h at room temperature. On completion of the reaction as monitored by TLC, the contents were poured into water (150 mL) whilst stirring with a glass rod. Thereafter the aqueous layer was extracted with EtOAc (4 × 60 mL). The organic layers were combined and washed with water (40 mL), subsequently with brine (80 mL), dried with anhydrous Na_2SO_4 and concentrated to yield the product (6.25 g from 6.00 g, 92%) which was utilized for the next step without any purification. For analytical grade, purification via short silica gel (60–120 mesh) column chromatography [EtOAc/hexane, 30:70, R_f = 0.50 (EtOAc/hexane, 20:80, v/v)] afforded **10** as a white solid.

Methyl 9-Allyl-1-(dimethoxymethyl)-9*H*-β-carboline-3-carboxylate (10): M.p. 106–108 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1721 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.51 (s, 6 H, 2 × OCH_3), 4.05 (s, 3 H, CO_2CH_3), 4.97 (dd, J_1 = 1.2, J_2 = 10.4 Hz, 1 H, =C*H*H), 5.15 (dd, J_1 = 1.2, J_2 = 10.4 Hz, 1 H, =CH*H*), 4.49 (q, J = 1.7 Hz, 2 H, CH_2N), 5.76 (s, 1 H, C*H*OCH_3), 5.96–6.07 (m, 1 H, =CH), 7.36 (t, J = 7.4 Hz, 1 H, ArH), 7.51 (d, J = 8.3 Hz, 1 H, ArH), 7.59–7.65 (m, 1 H, ArH), 8.20 (d, J = 7.8 Hz, 1 H, ArH), 8.90 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 48.9, 52.8, 55.8, 109.7, 111.5, 116.0, 118.4, 120.9, 121.3, 121.7, 128.9, 131.2, 134.1, 135.5, 135.7, 141.0, 142.6, 166.6 ppm. MS (ES): *m*/*z* (%) = 341.0 (100) [M + 1]$^+$, 363.2 (30) [M + 23]$^+$. $C_{19}H_{20}N_2O_4$ (340.1423): calcd. C 67.05, H 5.92, N 8.23; found C 67.23, H 6.05, N 8.02.

(9-Allyl-9*H*-β-carbolin-1-yl)(methoxy)methyl Methyl Ether (12): 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 = 0.60 (EtOAC/hexane, 80:20, v/v)] was obtained as yellow oil (3.00 g from 3.20 g); yield 80%. IR (neat): $\tilde{\nu}_{max}$ = 3020 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.48 (s, 6 H, 2×OCH_3), 4.89 (d, J = 17.3 Hz, 1 H, =C*H*H), 5.12 (d, J = 17.3 Hz, 1 H, =CH*H*), 5.41 (t, J = 2.2 Hz, 2 H, CH_2N), 5.78 (s, 1 H, C*H*OCH_3), 6.01–6.10 (m, 1 H, =CH), 7.30 (t, J = 7.5 Hz, 1 H, ArH), 7.45 (d, J = 8.3 Hz, 1 H, ArH), 7.59 (t, J = 7.7 Hz, 1 H, ArH), 8.02 (d, J = 5.1 Hz, 1 H, ArH), 8.15 (d, J = 7.8 Hz, 1 H, ArH), 8.43 (d, J = 5.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.2, 54.7, 107.1, 110.7, 115.3, 115.7, 120.0, 121.2, 121.3, 128.6, 131.0, 134.2, 134.3, 137.2, 140.4, 142.2 ppm. MS (ES): m/z (%) = 283.0 (100) $[M + 1]^+$. $C_{17}H_{18}N_2O_2$ (282.1368): calcd. C 72.32, H 6.43, N 9.92; found C 72.57, H 6.56, N 9.85.

Methyl 9-Allyl-1-(dimethoxymethyl)-6-fluoro-9*H*-β-carboline-3-carboxylate (13): The title compound was prepared following the above described general procedure and after purification by triturating with hexane [R_f = 0.55 (EtOAC/hexane, 30:70, v/v)] was obtained as white solid (0.766 g from 0.800 g); yield 85%; m.p. 114–116 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.52 (s, 6 H, 2×OCH_3), 4.05 (s, 3 H, CO_2CH_3), 4.97 (dd, J_1 = 1.1, J_2 = 17.3 Hz, 1 H, =C*H*H), 5.15 (dd, J_1 = 1.1, J_2 = 10.4 Hz, 1 H, =CH*H*), 4.48 (q, J = 1.7 Hz, 2 H, CH_2N), 5.75 (s, 1 H, C*H*OCH_3), 5.95–6.07 (m, 1 H, =CH), 7.32–7.39 (s, 1 H, ArH), 7.45 (q, J = 4.2 Hz, 1 H, ArH), 7.84 (dd, J_1 = 2.4, J_2 = 8.3 Hz, 1 H, ArH), 8.84 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 49.2, 52.8, 55.8, 106.5, 106.9, 109.9, 112.5, 112.7, 116.2, 117.0, 117.5, 118.6, 122.1, 122.3, 130.5, 130.6, 134.0, 135.3, 136.4, 138.9, 141.4, 155.7, 160.5, 166.4 ppm. MS (ES): m/z (%) = 359.0 (100) $[M + 1]^+$. $C_{19}H_{19}FN_2O_4$ (358.1329): calcd. C 63.68, H 5.34, N 7.82; found C 63.83, H 5.53, N 7.91.

(*E*)-Methyl 1-(Dimethoxymethyl)-9-[2-(methoxycarbonyl)-3-phenylallyl]-9*H*-pyrido[3,4-*b*]indole-3-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 = 0.45 (EtOAC/hexane, 30:70, v/v)] was obtained as a white solid (1.80 g from 1.50 g); yield 76%; m.p. 159–161 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1716 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.46 (s, 3 H, =CO_2CH_3), 3.55 (s, 6 H, 2×OCH_3), 4.05 (s, 3 H, ArCO_2CH_3), 5.87 (d, J = 3.2 Hz, 1 H, C*H*OCH_3), 6.02 (s, 2 H, CH_2N), 7.05–7.10 (m, 6 H, ArH), 7.24 (t, J = 7.7 Hz, 1 H, ArH), 7.45 (t, J = 7.7 Hz, 1 H, ArH), 7.80 (s, 1 H, ArCH), 8.00 (d, J = 7.7 Hz, 1 H, ArH), 8.74 (d, J = 3.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.6, 52.0, 52.7, 55.6, 109.4, 111.5, 118.1, 120.7, 121.1, 121.7, 127.8, 128.2, 128.3, 128.5, 128.8, 131.0, 134.1, 135.3, 137.0, 140.8, 141.1, 142.0, 166.6, 167.3 ppm. MS (ES): m/z (%) = 475.1 (100) $[M + 1]^+$. $C_{27}H_{26}N_2O_6$ (474.1791): calcd. C 68.34, H 5.52, N 5.90; found C 68.44, H 5.46, N 6.13.

(*E*)-Methyl 9-[3-(4-Chlorophenyl)-2-(methoxycarbonyl)allyl]-1-(dimethoxymethyl)-9*H*-pyrido[3,4-*b*]indole-3-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 = 0.40 (EtOAC/hexane, 30:70, v/v)] was obtained as colorless oil (1.10 g from 1.00 g); yield 65%. IR (neat): $\tilde{\nu}_{max}$ = 1718 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.54 (s, 6 H, 2×OCH_3), 3.62 (d, J = 2.7 Hz, 3 H, =CO_2CH_3), 4.11 (d, J = 2.7 Hz, 3 H, ArCO_2CH_3), 5.81 (d, J = 2.7 Hz, 1 H, C*H*OCH_3), 5.99 (s, 2 H, CH_2N), 6.77 (t, J = 8.0 Hz, 3 H, ArH), 7.62 (dd, J_1 = 2.4, J_2 = 8.3 Hz, 1 H, ArH), 7.23–7.27 (m, 2 H, ArH), 7.45–7.50 (m, 1 H, ArH), 7.70 (s, 1 H, ArH), 7.99 (d, J = 7.8 Hz, 1 H, ArH), 8.72 (d, J = 2.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.9, 52.3, 52.8, 55.9, 109.9, 111.4, 118.1, 120.3, 120.8, 121.1, 127.5, 128.6, 128.9, 129.0, 129.5, 131.1, 132.1, 139.6, 140.9, 166.5, 167.3 ppm. MS (ES): m/z (%) = 509.1 (100) $[M + 1]^+$. $C_{27}H_{25}ClN_2O_6$ (508.1461): calcd. C 63.72, H 4.95, N 5.50; found C 63.68, H 5.08, N 5.59.

(E)-Methyl 1-(Dimethoxymethyl)-9-[3-(4-fluorophenyl)-2-(methoxycarbonyl)allyl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (25): 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 = 0.38 (EtOAC/hexane, 30:70, v/v)] was obtained as white solid (1.13 g from 1.00 g); yield 69%; m.p. 203–205 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1718 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.55 (s, 6 H, 2×OCH_3), 3.57 (s, 3 H, =CO_2CH_3), 4.06 (d, J = 2.7 Hz, 3 H, CO_2CH_3), 5.84 (d, J = 5.0 Hz, 1 H, C*H*OCH_3), 6.00 (s, 2 H, CH_2N), 6.55 (t, J = 8.5 Hz, 2 H, ArH), 6.88 (t, J = 6.6 Hz, 2 H, ArH), 7.11 (d, J = 8.3 Hz, 1 H, ArH), 7.24 (q, J = 6.2 Hz, 1 H, ArH), 7.46 (t, J = 7.7 Hz, 1 H, ArH), 7.73 (s, 1 H, ArCH), 7.99 (d, J = 7.7 Hz, 1 H, ArH), 8.74 (d, J = 4.9 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.8, 52.2, 52.8, 55.8, 109.8, 111.4, 114.3, 114.7, 118.1, 120.8, 121.1, 121.7, 128.6, 128.8, 129.7, 129.8, 129.9, 131.0, 135.4, 136.8, 139.9, 140.8, 141.9, 166.5, 167.4 ppm. MS (ES): m/z (%) = 493.1 (M^+ + 1, 30%), 515.2 (100) $[M + 23]^+$. $C_{27}H_{25}FN_2O_6$ (492.1697): calcd. C 65.85, H 5.12, N 5.69; found C 65.97, H 5.34, N 5.77.

(E)-Methyl 1-(Dimethoxymethyl)-9-[2-(methoxycarbonyl)-3-*p*-tolylallyl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (26): 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 = 0.52 (EtOAC/hexane, 30:70, v/v)] was obtained as a white solid (1.93 g from 1.50 g); yield 79%; m.p. 162–164 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1720 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, $ArCH_3$), 3.39 (s, 3 H, =CO_2CH_3), 3.54 (s, 6 H, 2×OCH_3), 4.06 (s, 3 H, ArCO_2CH_3), 5.89 (s, 1 H, C*H*OCH_3), 6.02 (d, J = 8.0 Hz, 2 H, CH_2N), 6.94 (t, J = 8.0 Hz, 2 H, ArH), 7.03–7.08 (m, 3 H, ArH), 7.22–7.27 (m, 1 H, ArH), 7.41–7.46 (m, 1 H, ArH), 7.78 (s, 1 H, ArCH), 8.03 (d, J = 7.7 Hz, 1 H, ArH), 8.77 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 44.4, 51.9, 52.7, 55.5, 109.0, 111.6, 118.1, 120.7, 121.1, 121.8, 128.2, 128.5, 128.8, 131.0, 131.3, 135.3, 137.2, 138.7, 140.8, 141.5, 142.0, 166.7, 167.4 ppm. MS (ES): m/z (%) = 489.1 (100) $[M + 1]^+$. $C_{28}H_{28}N_2O_6$ (488.1947): calcd. C 68.84, H 5.78, N 5.73; found C 68.99, H 5.65, N 5.86.

Methyl 1-(Dimethoxymethyl)-9-prop-2-ynyl-9*H*-β-carboline-3-carboxylate (39): The title compound was prepared following the above described general procedure and purified crystallization by triturating with EtOAC/hexane, 05:95, v/v, (R_f = 0.48) (EtOAC/hexane, 30:70, v/v) was obtained as a white solid (1.87 g from 2.00 g); yield 83%; m.p. 114–118 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2106 (CCH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27 (t, J = 2.9 Hz, 1 H, CCH), 3.56 (s, 6 H, 2×OCH_3), 4.04 (s, 3 H, CO_2CH_3), 5.64 (d, J = 2.3 Hz, 2 H, CH_2N), 5.77 (s, 1 H, C*H*OCH_3), 7.35–7.40 (m, 1 H, ArH), 7.66–7.69 (m, 2 H, ArH), 8.17 (d, J = 7.9 Hz, 1 H, ArH), 8.88 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 36.5, 52.8, 56.0, 71.9, 79.1, 109.8, 111.1, 118.5, 121.4, 121.5, 121.8, 129.3, 131.5, 135.0, 135.9, 141.1, 142.1, 166.4 ppm. MS (ES): m/z (%) = 338.1 (100) $[M + 1]^+$. EI-HRMS: calcd. for $C_{19}H_{18}N_2O_4$ 338.1267; found 338.1394.

Methoxy(9-prop-2-ynyl-9*H*-β-carbolin-1-yl)methyl Methyl Ether (40): 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, 20:80, v/v) was obtained as a white solid (0.74 g from 0.87 g); yield 73%; m.p. 115–117 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2106 (CCH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 1 H, CCH), 3.54 (s, 6 H, 2 × OCH_3), 5.58 (d, J = 2.4 Hz, 2 H, CH_2N), 5.76 (s, 1 H, C*H*OCH_3), 7.31–7.36 (m, 1 H, ArH), 7.64 (t, J = 2.1 Hz, 2 H, ArH), 8.00 (t, J = 2.6 Hz, 1 H, ArH), 8.13 (d, J = 7.9 Hz, 1 H, ArH), 8.41 (d, J = 2.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.0, 55.4, 71.8, 79.6, 108.9, 110.6, 115.4, 120.5, 121.3, 121.6, 128.8, 131.4, 133.6, 137.6, 140.9, 141.8 ppm. MS (ES): m/z (%) = 281.0 (100) $[M + 1]^+$. $C_{17}H_{16}N_2O_2$ (280.1212): calcd. C 72.84, H 5.75, N 9.99; found C 73.02, H 5.83, N 10.06.

Methyl 1-(Dimethoxymethyl)-6-fluoro-9-prop-2-ynyl-9*H*-β-carboline-3-carboxylate (41): The title compound was prepared following the above described general procedure and after purification by triturating with hexane (R_f = 0.46, EtOAC/hexane, 30:70, v/v) was obtained as white solid (1.33 g from 1.70 g); yield 70%; m.p. 163–165 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1720 (CO_2CH_3), 2108 (CCH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.21 (s, 1 H, CCH), 3.50 (d, J = 1.0 Hz, 6 H, 2 × OCH_3), 3.94 (s, 3 H, CO_2CH_3), 5.66 (d, J = 1.1 Hz, 2 H, CH_2N), 5.69 (s, 1 H, C*H*OCH_3), 7.62 (d, J = 9.2 Hz, 1 H, ArH), 7.82 (dd, J_1 = 4.1, J_2 = 8.9 Hz, 1 H, ArH), 8.40 (d, J = 8.9 Hz, 1 H, ArH), 9.06 (d, J = 1.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 36.1, 52.2, 55.7, 74.6, 79.3, 107.5, 107.8, 109.2, 113.0, 113.1, 117.2, 117.6, 118.9, 121.7, 121.9, 130.2, 130.3, 135.0, 135.2, 137.9, 141.1, 156.1, 159.3, 165.4 ppm. MS (ES): m/z (%) = 357.1 (100) $[M + 1]^+$, 379.2 (30) $[M + 23]^+$. $C_{19}H_{17}FN_2O_4$ (356.1172): calcd. C 64.04, H 4.81, N 7.86; found C 64.32, H 4.61, N 7.93.

General Procedure for the Synthesis of Compounds 20, 21–22, 35–38, 48–50 as Exemplified for Compound 20: To a solution/suspension of **17** (0.5 g, 1.29 mmol) in CH_2Cl_2 (10 mL), NaOCl (10 mL, 4% aq. sol. in water) was added drop wise and stirred the reaction at room temperature for 3 d. After completion of the reaction as monitored by TLC, the content was extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined and washed with brine (40 mL), dried with anhydrous Na_2SO_4 and concentrated to yield the yellow solid (0.324 g from 0.423 g, 81%) which was purified via short silica gel (60–120 mesh) column chromatography [$CHCl_3$/MeOH, 99.5:0.5, R_f = 0.50 ($CHCl_3$/MeOH, 95:05, v/v)] to obtained **20** as a yellow solid.

Methyl 9a,10-Dihydro-9*H*-indolo[3,2,1-*ij*]isoxazolo[4,3-*c*][1,5]naphthyridine-2-carboxylate (20): M.p. 243–245 °C. IR (neat): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3), 2110 (CNOH), 3353 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.94 (s, 3 H, CO_2CH_3), 3.94–4.25 (m, 2 H, CH_2N), 4.48–4.62 (m, 1 H, CH), 4.93 (t, J = 9.1 Hz, 1 H, OC*H*H), 5.13 (q, J = 5.1 Hz, 1 H, OCH*H*), 7.42 (t, J = 7.1 Hz, 1 H, ArH), 7.70–7.80 (m, 2 H, ArH), 8.48 (t, J = 7.9 Hz, 1 H, ArH), 8.98 (s, 1 H, ArH) ppm. ^{13}C NMR: *not recorded due to poor solubility.* MS (ES): m/z (%) = 308.2 (100) $[M + 1]^+$. $C_{17}H_{13}N_3O_3$ (307.0957): calcd. C 66.44, H 4.26, N 13.67; found C 66.62, H 4.34, N 13.81.

9a,10-Dihydro-9*H*-indolo[3,2,1-*ij*]isoxazolo[4,3-*c*][1,5]naphthyridine (21): The title compound was prepared following the above described general procedure and after purification by triturating [EtOAc/hexane, 10:90, R_f = 0.50 ($CHCl_3$/MeOH, 95:05, v/v)] was obtained as a light brown solid (0.124 g from 0.15 g); yield 83%; m.p. 218–220 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3), 2110 (CNOH), 3353 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 4.06–4.20 (m, 2 H, CH_2), 4.45–4.59 (m, 1 H, CH), 4.90 (dd, J_1 = 2.1, J_2 = 8.1 Hz, 1 H, OC*H*H), 5.08 (q, J = 6.9 Hz, 1 H, OCH*H*), 7.32–7.37 (m, 1 H, ArH), 7.68 (q, J = 7.6 Hz, 2 H, ArH), 8.17 (d, J = 5.2 Hz, 1 H, ArH), 8.31 (d, J = 7.9 Hz, 1 H, ArH), 8.44 (d, J = 5.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 44.0, 46.7, 72.1, 110.4, 116.6, 120.2, 121.1, 122.8, 126.7, 128.9, 130.2, 136.1, 139.7, 140.4, 152.8 ppm. MS (ES): m/z (%) = 250.1 (100) $[M + 1]^+$. $C_{15}H_{11}N_3O$ (249.0902): calcd. C 72.28, H 4.45, N 16.86; found C 72.22, H 4.63, N 16.97.

Methyl 5-Fluoro-9a,10-dihydro-9*H*-indolo[3,2,1-*ij*]isoxazolo[4,3-*c*]-[1,5]naphthyridine-2-carboxylate (22): The title compound was prepared following the above described general procedure and after purification by triturating [EtOAc/hexane, 10:90, R_f = 0.35 ($CHCl_3$/MeOH, 95:05, v/v)] was obtained as yellow solid (0.10 g from 0.20 g); yield 50%; m.p. 211–213 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1718 (CO_2CH_3), 2229 (CNOH), 3450 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.10 (s, 3 H, CO_2CH_3), 5.00 (d, J = 10.2 Hz, 1 H, C*H*H), 5.29 (d, J = 10.2 Hz, 1 H, CH*H*), 5.44–5.47 (m, 2 H, CH and C*H*H), 6.07–6.17 (m, 1 H, CH*H*), 7.53 (t, J = 5.0 Hz, 2 H, ArH), 7.92 (d, J = 7.6 Hz, 1 H, ArH), 9.00 (s, 1 H, ArH) ppm. ^{13}C NMR: *not recorded due to poor solubility.* MS (ES): m/z (%) = 326.1 (100) $[M + 1]^+$. $C_{17}H_{12}FN_3O_3$ (325.0863): calcd. C 62.77, H 3.72, N 12.92; found C 62.83, H 3.90, N 12.87.

Dimethyl 10-Phenyl-9a,10-dihydro-9*H*-indolo[3,2,1-*ij*]isoxazolo-[4,3-*c*][1,5]naphthyridine-2,9a-dicarboxylate (35): The title compound was prepared following the above described general procedure and after purification by column chromatography [$CHCl_3$/MeOH, 95:05, R_f = 0.50 ($CHCl_3$/MeOH, 99:01, v/v)] was obtained as a light yellow solid (0.113 g from 018 g); yield 63%; m.p. 137–139 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1720 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.31 (d, J = 12.1 Hz, 2 H, 2 × C*H*HN), 3.54 (s, 3 H, CO_2CH_3), 3.65 (s, 3 H, CO_2CH_3), 4.08 (s, 6 H, 2 × Ar-CO_2CH_3), 4.84 (d, J = 12.1 Hz, 2 H, 2 × CH*H*N), 6.00 (s, 1 H, ArCH), 6.15 (s, 1 H, ArCH), 7.35–7.42 (m, 14 H, 2 × ArH), 7.61 (t, J = 7.8 Hz, 2 H, 2 × ArH), 8.10 (d, J = 7.9 Hz, 1 H, ArH), 8.16 (d, J = 7.9 Hz, 1 H, ArH), 8.90 (s, 1 H, ArH), 8.94 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.8, 45.7, 53.0, 54.2, 64.8, 88.9, 110.5, 119.3, 121.9, 122.6, 123.1, 125.8, 128.2, 129.0, 129.4, 129.5, 129.8, 135.1, 136.5, 139.7, 141.4, 148.6, 166.5, 171.3 ppm. MS (ES): m/z (%) = 442.2 (100) $[M + 1]^+$. DART-HRMS [ES+]: calcd. for $C_{25}H_{20}N_3O_5$ 442.1403; found 442.1391.

Dimethyl 10-(4-Chlorophenyl)-9a,10-dihydro-9*H*-indolo[3,2,1-*ij*]-isoxazolo[4,3-*c*][1,5]naphthyridine-2,9a-dicarboxylate (36): The title compound was prepared following the above described general procedure and after purification by column chromatography [$CHCl_3$/hexane, 70:30, R_f = 0.48 ($CHCl_3$/MeOH, 99:01, v/v)] was obtained as pale yellow solid (0.073 g from 0.15 g); yield 49%; m.p. 154–156 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1723 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.32 (d, J = 12.0 Hz, 2 H, 2 × C*H*HN), 3.56 (s, 3 H, CO_2CH_3), 3.65 (s, 3 H, CO_2CH_3), 4.08 (s, 6 H, 2 × Ar-CO_2CH_3), 4.84 (d, J = 12.0 Hz, 2 H, 2 × CH*H*N), 5.95 (s, 1 H, ArCH), 6.12 (s, 1 H, ArCH), 7.25 (d, J = 5.8 Hz, 2 H, 2 × ArH), 7.35 (t, J = 6.1 Hz, 4 H, 2 × ArH), 7.41 (d, J = 7.7 Hz, 6 H, 2 × ArH), 7.63 (t, J = 7.9 Hz, 2 H, 2 × ArH), 8.16 (t, J = 7.9 Hz, 2 H, 2 × ArH), 8.90 (s, 1 H, ArH), 8.93 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 45.8, 53.0, 54.2, 64.8, 88.2, 110.5, 119.4, 122.0, 122.6, 123.1, 127.2, 128.4, 129.2, 129.7, 129.9, 130.1, 130.4, 133.6, 135.6, 136.5, 139.8, 141.4, 148.7, 166.5, 171.1 ppm. MS (ES): m/z (%) = 476.1 (100) $[M + 1]^+$. $C_{25}H_{18}ClN_3O_5$ (475.0935): calcd. C 63.10, H 3.81, N 8.83; found C 63.17, H 3.97, N 8.99.

Dimethyl 10-(4-Fluorophenyl)-9a,10-dihydro-9*H*-indolo[3,2,1-*ij*]isoxazolo[4,3-*c*][1,5]naphthyridine-2,9a-dicarboxylate (37): The title compound was prepared following the above described general procedure and after purification by triturating [EtOAc/hexane, 20:80,

R_f = 0.50 ($CHCl_3$/MeOH, 98:02, v/v)] was obtained as a white solid (0.102 g from 0.16 g); yield 64%; m.p. 156–158 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1723 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.32 (d, J = 12.1 Hz, 2 H, 2 × C*H*HN), 3.64 (s, 6 H, 2 × CO_2CH_3), 4.08 (s, 6 H, 2 × $ArCO_2CH_3$), 4.83 (d, J = 12.0 Hz, 2 H, 2 × CH*H*N), 6.13 (s, 2 H, 2 × ArCH), 7.12 (t, J = 7.7 Hz, 4 H, 2 × ArH), 7.39 (s, 8 H, 2 × ArH), 7.61 (d, J = 7.5 Hz, 2 H, 2 × ArH), 8.17 (d, J = 7.1 Hz, 2 H, 2 × ArH), 8.90 (s, 2 H, 2 × ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 45.8, 53.0, 54.2, 64.8, 88.3, 110.5, 116.4, 116.8, 119.4, 122.0, 122.6, 123.2, 127.7, 127.9, 128.4, 129.8, 130.9, 131.0, 136.5, 139.9, 141.5, 148.7, 160.8, 165.8, 166.5, 171.2 ppm. MS (ES): *m*/*z* (%) = 460.1 (100) $[M + 1]^+$. $C_{25}H_{18}FN_3O_5$ (459.1230): calcd. C 65.36, H 3.95, N 9.15; found C 65.43, H 4.13, N 8.99.

Dimethyl 10-*p*-Tolyl-9a,10-dihydro-9*H*-indolo[3,2,1-*ij*]isoxazolo-[4,3-*c*][1,5]naphthyridine-2,9a-dicarboxylate (38): The title compound was prepared following the above described general procedure and after purification by triturating [EtOAc/hexane, 10:90, R_f = 0.50 ($CHCl_3$/MeOH, 99:01, v/v)] was obtained as yellow solid (0.44 g from 0.53 g); yield 83%; m.p. 148–150 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1724 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, $ArCH_3$), 2.40 (s, 3 H, $ArCH_3$), 3.32 (d, J = 12.0 Hz, 2 H, 2 × C*H*HN), 3.56 (s, 3 H, CO_2CH_3), 3.65 (s, 3 H, CO_2CH_3), 4.08 (s, 6 H, 2 × $ArCO_2CH_3$), 4.84 (d, J = 12.0 Hz, 2 H, 2 × CH*H*N), 6.01 (s, 1 H, ArCH), 6.12 (s, 1 H, ArCH), 7.16–7.26 (m, 8 H, 2 × ArH), 7.34–7.42 (t, 4 H, 2 × ArH), 7.61 (t, J = 7.4 Hz, 2 H, 2 × ArH), 8.02 (t, J = 7.9 Hz, 1 H, ArH), 8.16 (t, J = 7.9 Hz, 1 H, ArH), 8.89 (s, 1 H, ArH), 8.95 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 45.7, 52.9, 54.1, 64.7, 89.0, 110.5, 119.3, 121.8, 122.6, 123.1, 125.7, 128.2, 129.7, 129.9, 130.1, 132.1, 136.5, 139.5, 139.7, 141.5, 148.6, 166.6, 171.3 ppm. MS (ES): *m*/*z* (%) = 456.1 (100) $[M + 1]^+$. DART-HRMS [ES+]: calcd. for $C_{25}H_{20}N_3O_5$ 455.1481; found 455.1493.

Methyl 9*H*-Indolo[3,2,1-*ij*]isoxazolo[4,3-*c*][1,5]naphthyridine-2-carboxylate (48): The title compound was prepared following the above described general procedure and after purification by triturating with [EtOAC/hexane, 20:80, v/v, R_f = 0.25 (EtOAC/hexane, 40:60, v/v)] was obtained as a light yellow solid (0.127 g from 0.20 g); yield 64%; m.p. >250 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1716 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.96 (s, 3 H, CO_2CH_3), 5.65 (s, 2 H, CH_2N), 7.42–7.48 (m, 1 H, ArH), 7.75 (d, J = 3.8 Hz, 2 H, ArH), 8.49 (d, J = 7.8 Hz, 1 H, ArH), 8.97 (s, 1 H, ArH), 9.17 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 53.0, 56.5, 111.8, 113.8, 120.3, 121.6, 122.2, 122.3, 123.9, 126.9, 130.1, 137.0, 138.2, 141.5, 156.9, 166.5 ppm. MS (ES): *m*/*z* (%) = 306.1 (100) [M + 1]$^+$. $C_{17}H_{11}N_3O_3$ (305.0800): calcd. C 66.88, H 3.63, N 13.76; found C 66.72, H 3.75, N 13.97.

9*H*-Indolo[3,2,1-*ij*]isoxazolo[4,3-*c*][1,5]naphthyridine (49): The title compound was prepared following the above described general procedure and after purification by column chromatography [$CHCl_3$/MeOH, 95:05, R_f = 0.50 ($CHCl_3$/MeOH, 95:05, v/v)] was obtained as a brown solid (0.124 g from 0.20 g); yield 63%; m.p. 246–248 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1716 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 5.59 (d, J = 1.0 Hz, 2 H, CH_2N), 7.36–7.41 (m, 1 H, ArH), 7.69 (d, J = 3.7 Hz, 2 H, ArH), 8.16 (d, J = 5.3 Hz, 1 H, ArH), 8.32 (d, J = 7.9 Hz, 1 H, ArH), 8.42 (d, J = 5.3 Hz, 1 H, ArH), 9.11 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 38.7, 110.5, 112.7, 116.8, 120.4, 121.2, 122.7, 126.2, 128.8, 129.7, 134.9, 139.3, 140.3, 154.1, 155.6 ppm. MS (ES): *m*/*z* (%) = 248.1 (100) $[M + 1]^+$. $C_{15}H_9N_3O$ (247.0746): calcd. C 72.87, H 3.67, N 16.99; found C 72.96, H 3.87, N 17.02.

Methyl 5-Fluoro-9*H*-indolo[3,2,1-*ij*]isoxazolo[4,3-*c*][1,5]naphthyridine-2-carboxylate (50): The title compound was prepared following the above described general procedure and after purification by triturating with [EtOAC/hexane, 20:80, v/v, R_f = 0.25 (EtOAC/hexane, 50:50, v/v)] was obtained as a light yellow solid (0.127 g from 0.20 g); yield 63%; m.p. >250 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1708 (CO_2CH_3) cm^{-1}. ^1H NMR (600 MHz, [D_6]DMSO): δ = 3.93 (s, 3 H, CO_2CH_3), 5.63 (s, 2 H, CH_2N), 7.60–7.63 (m, 1 H, ArH), 7.73 (d, J = 4.5 Hz, 1 H, ArH), 8.36 (d, J = 9.7 Hz, 1 H, ArH), 8.99 (s, 1 H, ArH), 9.15 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]-DMSO): *not recorded due to poor solubility*. MS (ES): *m*/*z* (%) = 324.1 (100) $[M + 1]^+$. $C_{17}H_{10}FN_3O_3$ (323.0706): calcd. C 63.16, H 3.12, N 13.00; found C 63.34, H 3.04, N 13.29.

General Procedure for the Synthesis of Compounds 51–53 as Exemplified for Compound 51: To a solution of **39** (0.162 g, 0.48 mmol) in dichloroethane (5 mL) in a vial (10–20 mL size), $TMSN_3$ (0.075 mL, 0.57 mmol) and $In(OTf)_3$ (0.028 g, 0.05 mmol) were added and irradiated with microwave under low absorption at 150 °C for 15 min. with pre-stirring of 30 sec. After completion of the reaction as monitored by TLC, the content was poured into 10% aqueous $NaHCO_3$ (25 mL) solution and extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined and washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated to yield the off white solid which was further purified via short silica gel (60–120 mesh) column chromatography [EtOAC/hexane, 90:10, v/v, R_f = 0.50 ($CHCl_3$/MeOH, 90:10, v/v)] to obtained (0.162 g from 0.22 g, 72%) **51** as a white solid.

Methyl 5-Methoxy-1*H*,5*H*-3,4,4a,6,12b-pentaazaazuleno[5,6,7-*jk*]-fluorene-7-carboxylate (51): M.p. 243–245 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.55 (s, 3 H, OCH_3), 4.09 (s, 3 H, CO_2CH_3), 5.62 (d, J = 14.9 Hz, 1 H, C*H*HN), 5.80 (d, J = 14.9 Hz, 1 H, CH*H*N), 7.23 (s, 1 H, C*H*OCH_3), 7.43 (t, J = 7.2 Hz, 1 H, ArH), 7.62 (d, J = 8.4 Hz, 1 H, ArH), 7.71–7.76 (m, 1 H, ArH), 7.82 (s, 1 H, $ArH_{triazole}$), 8.22 (d, J = 7.9 Hz, 1 H, ArH), 8.93 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 36.3, 52.3, 56.3, 91.8, 110.8, 119.0, 120.1, 121.3, 122.5, 129.6, 130.4, 130.7, 133.9, 134.0, 136.3, 136.6, 140.7, 165.2 ppm. MS (ES): *m*/*z* (%) = 350.1 (100) $[M + 1]^+$. $C_{18}H_{15}N_5O_3$ (349.1175): calcd. C 61.89, H 4.33, N 20.05; found C 62.04, H 4.20, N 20.33.

1*H*,5*H*-3,4,4a,6,12b-Pentaazaazuleno[5,6,7-*jk*]fluoren-5-yl Methyl Ether (52): The title compound was prepared following the above-described general procedure and after purification by column chromatography [EtOAC/hexane, 70:30, v/v, R_f = 0.50 ($CHCl_3$/MeOH, 95:05, v/v)] was obtained as a white solid (0.65 g from 0.75 g); yield 81%; m.p. 173–175 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1074, 1448, 1621, 2829, 2928, 3423 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (s, 3 H, OCH_3), 5.56 (d, J = 14.8 Hz, 1 H, C*H*HN), 5.76 (d, J = 14.8 Hz, 1 H, CH*H*N), 7.07 (s, 1 H, C*H*OCH_3), 7.36 (t, J = 7.8 Hz, 1 H, ArH), 7.58 (d, J = 8.3 Hz, 1 H, ArH), 7.66–7.72 (m, 1 H, ArH), 7.81 (m, 1 H, ArH), 8.03 (d, J = 5.2 Hz, 1 H, ArH), 8.16 (d, J = 7.8 Hz, 1 H, ArH), 8.49 (d, J = 5.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 36.8, 57.1, 93.4, 109.1, 116.3, 120.7, 120.8, 122.1, 129.3, 130.2, 131.0, 133.3, 133.6, 137.2, 138.8, 140.4 ppm. MS (ES): *m*/*z* (%) = 292.1 (100) $[M + 1]^+$. DART-HRMS [ES+]: calcd. for $C_{16}H_{14}N_5O$ 292.1198; found 292.1181.

Methyl 5-Fluoro-12-methoxy-8*H*,12*H*-1,7b,10,11,11a-pentaaza-azuleno[5,6,7-*jk*]fluorene-2-carboxylate (53): The title compound was prepared following the above described general procedure and after purification by column chromatography [EtOAC/hexane, 90:10, v/v, R_f = 0.50 ($CHCl_3$/MeOH, 90:10, v/v)] was obtained as a white solid (0.189 g from 0.28 g); yield 66%; m.p. >245 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1709 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]-

DMSO): δ = 3.46 (s, 3 H, OCH_3), 3.95 (s, 3 H, CO_2CH_3), 5.50 (d, J = 15.2 Hz, 1 H, C*H*HN), 6.40 (d, J = 15.2 Hz, 1 H, CH*H*N), 7.05 (s, 1 H, C*H*OCH_3), 7.64–7.71 (m, 1 H, ArH), 8.00 (s, 1 H, $ArH_{triazole}$), 8.04 (q, J = 4.5 Hz, 1 H, ArH), 8.41 (dd, J_1 = 2.5, J_2 = 8.9 Hz, 1 H, ArH), 9.12 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 36.6, 52.3, 56.3, 91.7, 107.9, 108.2, 112.3, 112.4, 117.6, 117.9, 119.5, 120.7, 120.8, 129.8, 129.9, 130.6, 134.1, 134.7, 136.1, 137.0, 137.2, 155.9, 159.0, 165.2 ppm. MS (ES): m/z (%) = 368.1 (100) $[M + 1]^+$. $C_{18}H_{14}FN_5O_3$ (367.1081): calcd. C 58.85, H 3.84, N 19.07; found C 58.76, H 3.96, N 19.23.

Typical Procedure for the Synthesis of Compound 55: To a stirred suspension of **42** (1.50 g, 5.12 mmol) in dry methanol (60 mL), $NaBH_4$ (0.28 g, 7.68 mmol) was added in small portions at 0 °C. After the addition was complete, the reaction was continued for 20 min at room temperature. On completion of the reaction as monitored by TLC, the precipitated solid was filtered and dried in air. The filtrate was evaporated in vacuo and the residue was dissolved in EtOAc (50 mL). Thereafter water (50 mL) was added and the organic layer partitioned in a separating funnel. The aqueous layer was further extracted with EtOAc (2 × 30 mL). The organic layers were combined and washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated to yield a yellowish product which was pooled with the solid isolated earlier. The crude product was further purified by triturating with EtOAC/hexane, 05:95, v/v, [R_f = 0.50 (EtOAC/hexane, 40:60, v/v)] to afford **55** as a yellowish brown solid (1.45 g from 1.50 g, 96%).

Methyl 1-(Hydroxymethyl)-9-prop-2-ynyl-9*H*-β-carboline-3-carboxylate (55): M.p. 215–217 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (d, J = 2.2 Hz, 1 H, CCH), 4.05 (s, 3 H, CO_2CH_3), 5.34 (d, J = 2.2 Hz, 2 H, CH_2N), 5.43 (s, 2 H, CH_2O), 7.42 (t, J = 7.5 Hz, 1 H, ArH), 7.60 (d, J = 8.6 Hz, 1 H, ArH), 7.70 (t, J = 7.7 Hz, 1 H, ArH), 8.22 (d, J = 7.8 Hz, 1 H, ArH), 8.84 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 33.7, 52.0, 64.1, 75.6, 79.7, 110.8, 117.4, 121.1, 121.2, 122.0, 129.1, 129.6, 135.7, 136.0, 141.1, 143.6, 165.6 ppm. MS (ES): m/z (%) = 295.1 (100) $[M + 1]^+$. $C_{17}H_{14}N_2O_3$ (294.1004): calcd. C 69.38, H 4.79, N 9.52; found C 69.51, H 4.93, N 9.69.

Typical Procedure for the Synthesis of Compounds 56: To a suspension of **55** (0.70 g, 2.37 mmol) in dry dichloromethane (30 mL), Et_3N (0.49 mL, 3.56 mmol) was added and stirred at 0 °C for 10 min. Thereafter MsCl (0.23 mL, 2.85 mmol) in dichloromethane (5 mL) was added drop wise at 0 °C and continued stirring for additional 45 min. After completion of the reaction as monitored by TLC, the content was poured into water and extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined and washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated to yield the crude product which was further purified by triturating with EtOAc/hexane, 05:95, v/v, R_f = 0.60 (EtOAC/hexane, 40:60, v/v) to obtain **56** as a brown solid (0.75 g from 0.70 g, 85%); m.p. 188–190 °C.

Methyl 1-[(Methylsulfonyloxy)methyl]-9-(prop-2-ynyl)-9*H*-pyrido-[3,4-*b*]indole-3-carboxylate (56): M.p. 188–190 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (t, J = 2.4 Hz, 1 H, CCH), 3.15 (s, 3 H, SO_2CH_3), 4.06 (s, 3 H, CO_2CH_3), 5.36 (d, J = 2.4 Hz, 2 H, CH_2N), 6.01 (s, 2 H, CH_2O), 7.45 (t, J = 7.5 Hz, 1 H, ArH), 7.62 (d, J = 8.3 Hz, 1 H, ArH), 7.74 (t, J = 7.3 Hz, 1 H, ArH), 8.22 (d, J = 7.9 Hz, 1 H, ArH), 8.93 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 34.8, 52.3, 72.6, 76.9, 78.9, 110.9, 117.8, 120.6, 120.7, 121.6, 122.2, 129.6, 130.2, 133.8, 135.8, 137.6, 141.4, 165.2 ppm. MS (ES): m/z (%) = 373.1 (100) $[M + 1]^+$. $C_{18}H_{16}N_2O_5S$ (372.0780): calcd. C 58.05, H 4.33, N 7.52; found C 58.21, H 4.46, N 7.50.

Typical Procedure for the Synthesis of Compounds 57: To a solution of **56** (0.40 g, 1.08 mmol) in dry DMF (8 mL), NaN_3 (0.14 g, 2.16 mmol) was added and heated at 90 °C for 3 h. After completion of the reaction as monitored by TLC, the content was poured into water (100 mL) and extracted with EtOAc (3 × 30 mL). The organic layers were combined and washed with water (50 mL) and brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated to yield the crude product which was further purified by triturating with EtOAC/hexane, 05:95, v/v, (R_f = 0.35) ($CHCl_3$/MeOH, 95:05, v/v) to yield **57** as a white solid (0.33 g from 0.40 g, 95%).

Methyl 1*H*,5*H*-3,4,4a,6,12b-Pentaazaazuleno[5,6,7-*jk*]fluorene-7-carboxylate (57): M.p. >250 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (s, 3 H, CO_2CH_3), 5.71 (s, 2 H, CH_2), 6.37 (s, 2 H, CH_2), 7.42 (t, J = 7.5 Hz, 1 H, ArH), 7.61 (d, J = 8.4 Hz, 1 H, ArH), 7.74 (t, J = 7.5 Hz, 1 H, ArH), 7.82 (s, 1 H, $ArH_{triazole}$), 8.21 (d, J = 7.9 Hz, 1 H, ArH), 8.86 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 36.3, 52.2, 53.3, 110.6, 118.0, 120.1, 122.5, 128.9, 129.3, 132.7, 133.1, 135.4, 136.2, 137.3, 140.5, 165.5 ppm. MS (ES): m/z (%) = 320.1 (100) $[M + 1]^+$. $C_{17}H_{13}N_5O_2$ (319.1069): calcd. C 63.94, H 4.10, N 21.93; found C 64.12, H 4.11, N 22.04.

General Procedure for the Synthesis of Compounds 61–63 as Exemplified for Compound 61: To a suspension of **42** (0.12 g, 0.41 mmol) in dry toluene (8 mL), sarcosine (0.30 g, 3.37 mmol) was added and heated at reflux for 24 h. After completion of the reaction as monitored by TLC, the content was poured into 10% aqueous $NaHCO_3$ (25 mL) solution and extracted with EtOAc (3 × 30 mL). The organic layers were combined and washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated to yield the crude product which was further purified via short silica gel (60–120 mesh) column chromatography [EtOAc/hexane, 20:80, R_f = 0.50 (EtOAc/hexane, 20:80, v:v)] to obtained (0.046 g from 0.12 g, 35%) **61** as a white solid.

Methyl 12-Methyl-9,12-dihydroindolo[3,2,1-*ij*]pyrrolo[3,2-*c*][1,5]-naphthyridine-2-carboxylate (61): M.p. 153–155 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1724 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.01 (s, 3 H, CO_2CH_3), 4.34 (s, 3 H, NCH_3), 5.57 (s, 2 H, CH_2N), 6.15 (d, J = 2.6 Hz, 1 H, $ArH_{pyrrole}$), 6.81 (d, J = 2.6 Hz, 1 H, $ArH_{pyrrole}$), 7.36 (d, J = 7.9 Hz, 1 H, ArH), 7.44 (d, J = 8.2 Hz, 1 H, ArH), 7.57–7.62 (m, 1 H, ArH), 8.12 (d, J = 7.9 Hz, 1 H, ArH), 8.52 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.5, 43.4, 52.4, 106.0, 109.8, 116.1, 119.4, 120.7, 122.2, 122.7, 123.2, 127.4, 127.6, 134.2, 136.0, 136.3, 140.5, 167.2 ppm. MS (ES): m/z (%) = 318.1 (100) $[M + 1]^+$. $C_{19}H_{15}N_3O_2$ (317.1164): calcd. C 71.91, H 4.76, N 13.24; found C 72.26, H 4.96, N 13.43.

12-Methyl-9,12-dihydroindolo[3,2,1-*ij*]pyrrolo[3,2-*c*][1,5]naphthyridine (62): The title compound was prepared following the above described general procedure and after purification by short silica gel (60–120) column chromatography [EtOAC/hexane, 10:90, v/v, R_f = 0.60 (EtOAC/hexane, 10:90, v/v)] was obtained as white solid (0.08 g from 0.20 g); yield 38%; m.p. 145–147 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1216, 2145, 2928, 3021, 3451 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.27 (s, 3 H, NCH_3), 5.58 (s, 2 H, CH_2N), 6.15 (s, 1 H, $ArH_{pyrrole}$), 6.78 (s, 1 H, $ArH_{pyrrole}$), 7.26–7.33 (m, 1 H, ArH), 7.42 (d, J = 7.8 Hz, 1 H, ArH), 7.57 (t, J = 5.8 Hz, 2 H, ArH), 8.09 (d, J = 7.8 Hz, 1 H, ArH), 8.16 (dt, J = 5.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.7, 43.2, 105.8, 109.4, 112.1, 118.9, 119.7, 122.1, 122.5, 123.8, 124.0, 126.7, 127.1, 136.7, 137.7, 140.2 ppm. MS (ES): m/z (%) = 260.1 (100) $[M + 1]^+$. DART-HRMS calcd. For $C_{17}H_{14}N_3$ (260.1188); found (260.1183).

Methyl 5-Fluoro-12-methyl-9,12-dihydroindolo[3,2,1-*ij*]pyrrolo[3,2-*c*]-[1,5]naphthyridine-2-carboxylate (63): The title compound was pre-

pared following the above described general procedure and after purification by column chromatography [EtOAC/hexane, 20:80, v/v, R_f = 0.50 (EtOAC/hexane, 20:80, v/v)] was obtained as white solid (0.07 g from 0.20 g); yield 32%; m.p. 159–161 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1719 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.00 (s, 3 H, CO_2CH_3), 4.31 (s, 3 H, NCH_3), 5.51 (s, 2 H, CH_2N), 6.13 (d, J = 2.6 Hz, 1 H, $ArH_{pyrrole}$), 6.79 (d, J = 2.6 Hz, 1 H, $ArH_{pyrrole}$), 7.31–7.34 (m, 2 H, ArH), 7.73 (t, J = 8.1 Hz, 1 H, ArH), 8.41 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ or [D_6]-DMSO): *not recorded due to poor solubility.* MS (ES): *m*/*z* (%) = 336.1 (100) $[M + 1]^+$. $C_{19}H_{14}FN_3O_2$ (335.1070): calcd. C 68.05, H 4.21, N 12.53; found C 67.83, H 4.35, N 12.78.

Supporting Information (see also the footnote on the first page of this article): Experimental details, spectroscopic data for remaining compounds and copies of ^1H and ^{13}C NMR spectra for all compounds are provided.

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