

Facile synthesis of Dihydroquinoline-fused-Canthines via intramolecular Aza-Diels-Alder reaction[§]

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The synthesis of dihydroquinoline-fused-canthines via intramolecular aza-Diels-Alder reaction between N-prenylated-1-formyl-9H- β -carbolines and substituted anilines in the presence of Lewis acid followed by oxidation is described. Additionally it has been found that the N-protected aldehyde in the presence of suitable catalyst (ZnBr₂ or Yb(OTf)₃) undergoes intramolecular carbonyl-ene reaction in diastereoselective fashion to afford syn- or anti-isomer of a new canthine derivative.

Keywords: Canthine / Carbonyl-ene / Aza-Diels-Alder / Yb(OTf)₃ / Lewis acid

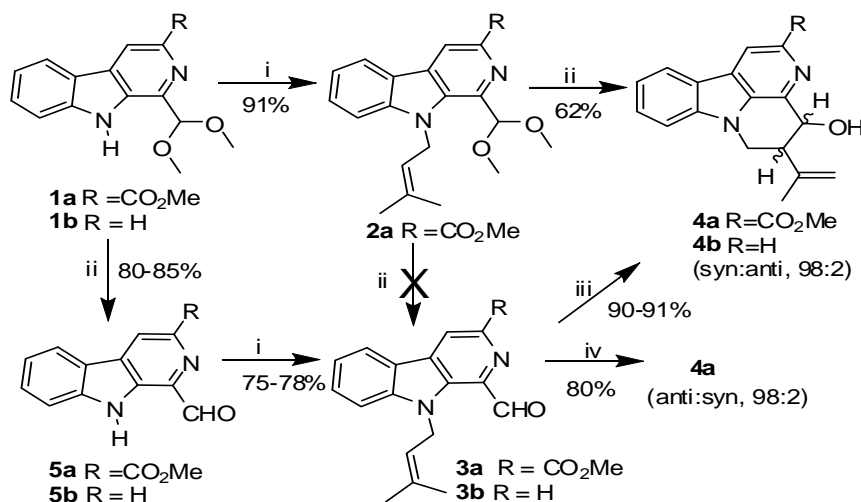
Introduction

Recently we have reported the synthesis of a variety of D-ring fused- β -carbolines from 1-formyl-9H- β -carboline following the intramolecular 1,3-dipolar cycloaddition chemistry.^[1] Aiming to diversify the range of D-ring fused- β -carbolines using cycloaddition reaction as a key step we now report the synthesis of dihydroquinoline-fused-canthines via aza-Diels-Alder reaction between the N-prenylated-1-formyl-9H- β -carbolines and anilines in the presence of Lewis acid followed by oxidation with DDQ. Such dihydroquinoline-fused-canthines are analogous to Lavendamycin-based compounds which elicit potent cytotoxic activity.^[2]

The intramolecular aza-Diels-Alder reaction is considered to be a robust synthetic option available for the construction of complex polycyclic and polyheterocyclic skeletons in efficient, economical and stereo controlled manner as compared to the sequential chemical transformations.^[3] Amongst aza-Diels-Alder, the Lewis acid-catalysed inverse-electron-demand Diels-Alder where the N-aryl imines are employed as dienes has been extensively studied.^[4] Based on the literature, we anticipated that intramolecular aza-Diels-Alder reaction of N-aryl imine generated on the formyl group at C-1 with the prenyl group present at the indole-nitrogen of N-substituted-1-formyl- β -carboline will be an attractive alternative for the construction of new β -carboline-based canthine system.

Results and Discussion

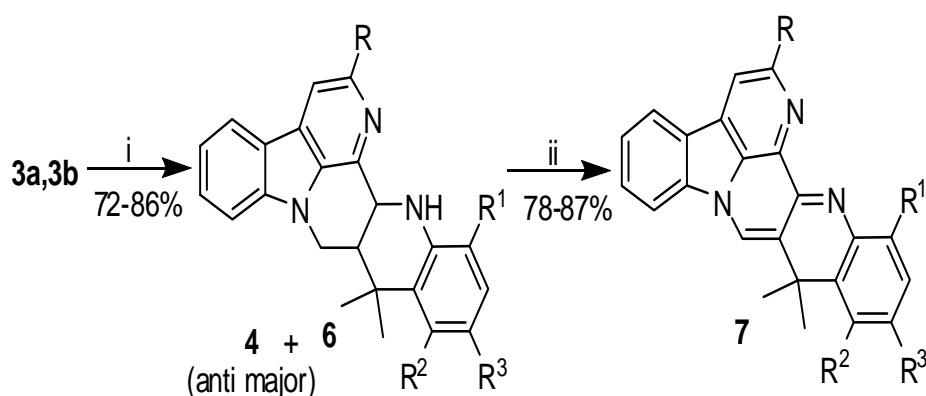
In order to achieve the synthesis of the required starting material for the study, initially **1a**^[5] was treated with prenyl bromide in the presence of Cs₂CO₃ to smoothly afford the N-prenylated acetal **2a** in 91% yields (scheme 1). Unexpectedly, however, aq. AcOH or aq.



Scheme 1. Reagents and conditions. (i) Prenyl bromide, Cs₂CO₃, dry DMF, r.t., 45 min. (ii) AcOH/H₂O (2:3), 100 °C, 45 min. (iii) ZnBr₂, dry Benzene, reflux, 12h. (iv) Yb(OTf)₃, dry MeCN, reflux, 3h.

TFA-promoted deprotection of **2a** instead of producing the aldehyde **3a** resulted in isolation of a new canthine **4a**, a product of intramolecular carbonyl-ene reaction, in 62% yield (scheme 1). To explain the formation of **4a**, it was reasoned that under the influence of acid, **2a** would have furnished the aldehyde **3a** which would have initiated an intramolecular carbonyl-ene reaction with the prenyl chain.^[6] Interestingly, the ¹H-NMR spectrum of crude **4a** indicated the reaction to be diastereoselective in favour of syn-isomer. This inference was based on the coupling constant of the *CHOH* proton which was observed to be 1.8 Hz for the syn-isomer and 8.0 Hz for the anti-isomer (vide-infra). Aiming to synthesize **3a**, aldehyde **5a** was then directly reacted with prenyl bromide in the presence of Cs₂CO₃ in dry DMF at room temperature to successfully afford the required product **3a** in 78% yield. Mechanistic considerations however, evoked us to seek chemical support for the transformation of **3a** into **4a**. The ability of Bronsted and Lewis acid for inducing intramolecular carbonyl-ene reaction is widely reported.^[6a,d] ZnBr₂ is reported to promote diastereoselective ene-cyclisation of citronellal to afford the anti- isopulegol at low temperature.^[7] Influenced by this report, **3a** was subjected to reaction with ZnBr₂ at low temperature but the reaction failed. Nevertheless heating **3a** with ZnBr₂ in dry benzene at reflux smoothly afforded **4a** in 91% yield in 12 h. But unlike earlier report, this reaction was observed to be diastereoselective in favour of syn-isomer (98:2). To assess the generality of this outcome, another prenylated aldehyde **3b** that was prepared from **5b**, was subjected to heating with ZnBr₂ in dry benzene to afford **4b** in 90% yield with syn-stereochemistry. The unusual result with ZnBr₂ prompted us to examine another Lewis acid for transformation of **3** to **4**. Hence, we considered investigating Yb(OTf)₃ for the desired transformation.^[8] Reaction of **3a** with Yb(OTf)₃ in dry MeCN under heating at reflux was observed to be complete in 3 h to furnish **4a** in 80% yield. Interestingly, as evident from the ¹H NMR spectrum of **4a** the reaction was found to be diastereoselective in favour of anti (anti:syn, 98:2). Previously, it has been reported that Lewis acid promoted ene-reaction under conditions of elevated temperature proceeds via concerted cyclization mechanism to afford the thermodynamically more stable anti-product.^[9] We presume that the formation anti-**4a** may have resulted following a similar path. Though it is difficult to account for syn-selectivity of product with ZnBr₂, based on the results it was assumed that perhaps during the reaction of ZnBr₂ with **3a**, a small amount of HBr may have liberated which could act as the Bronsted acid to afford the syn-product.

With methyl-N-prenyl-1-formyl-9*H*-β-carboline-3-carboxylate (**3a**) in hand, we next investigated the desired intramolecular aza-Diels-Alder reaction. In order to seek an optimal condition for the reaction, **3a** was treated with 4-chloroaniline under different conditions with respect to catalyst, solvent and temperature. Initially the reaction was performed with InCl₃ in MeCN, dioxane, toluene, THF or water at room temperature or under heating at reflux. Compared to reactions at room temperature, the reactions under heating were fast and gave the product **6a** as diastereomeric mixture in better yield. Further MeCN was found to be the solvent of choice for this reaction. A careful column chromatography over silica gel resulted in isolation of both the isomers. The coupling constant of the ring-junction NH*CHC*-proton of the less polar isomer was observed to be 11.0 Hz where as that of the polar isomer was 2.6 Hz. Based on this data the polar isomer was established to be the syn-isomer while the less polar product was assigned to be the anti-isomer. Additional proof for the stereochemical assignment was obtained by performing NOESY experiment with the syn-isomer wherein correlation was observed between the NH*CHC*-proton and (CH₃)₂C*CH*CH₂ protons. Subsequently other catalysts including Yb(OTf)₃, Sc(OTf)₃, La(OTf)₃, BiCl₃, CAN, BF₃·OEt₂ and *p*-TSA were also investigated. Although all catalysts successfully furnished **6a**, the best yield of **6a** (86%) was obtained when the reaction was performed in the presence of Yb(OTf)₃ in MeCN under heating at reflux for 3 h. During investigations, we isolated an additional red coloured compound in minor quantities that was identified as **7a**, the oxidized product of **6a**. The yield of **7a** was significant when the reaction was performed in the presence of CAN at higher temperature in dioxane. Moreover the formation of **4a** as a side product in minor yields was observed in all reactions where Lewis acid was employed as catalyst. Similar to the carbonyl-ene reaction of **3a** with Yb(OTf)₃, under these reaction conditions formation of **4a** was observed to be diastereoselective in favour of anti-isomer as inferred from the coupling constant of *CHOH* proton (8.0 Hz).



Scheme 2. Reagents and conditions: (i) substituted aniline, Yb(OTf)₃, dry MeCN, reflux, 3 h (ii) DDQ, dry MeCN, r.t., 30 min (for key to R, R¹, R² and R³ refer to Table 1)

Table 1. Isolated yields of **6** and **4**, and **7**

Compd. no	R	R ¹	R ²	R ³	Yield (%) 6 a)	Yield (%) 4	Yield (%) 7
a	CO ₂ Me	H	H	Cl	86	Trace	83
b	H	H	H	Cl	82	Trace	84
c	CO ₂ Me	H	H	OCH ₃	75	Trace	86
d	H	H	H	OCH ₃	79	Trace	80
e	CO ₂ Me	H	H	CH ₃	76	Trace	84
f	H	H	H	CH ₃	81	Trace	79
g	CO ₂ Me	H	H	H	82	Trace	79
h	CO ₂ Me	H	H	Br	73	Trace	78
i	CO ₂ Me	H	H	F	78	Trace	83
j	CO ₂ Me	H	H	2-Napthyl	80	Trace	87
k	CO ₂ Me	H	H	CH(CH ₃) ₂	77	Trace	85
l	CO ₂ Me	H	H	(OCH ₃) ₃	74	Trace	84
m	CO ₂ Me	H	H	C(CH ₃) ₃	72	Trace	78
n ^{b)}	CO ₂ Me	Cl	H	CH ₃	-	55	25
o ^{b)}	CO ₂ Me	CH ₃	Cl	H	-	67	14
p	CO ₂ Me	OCH ₃	H	OCH ₃	0	81	-

[a] Isolated as diastereomeric mixture. [b] **6** was not isolated, yield of **7** after one-pot reaction

Isolation of the oxidized product **7** during the Aza-Diels Alder reaction, provided impetus to examine oxidation of **6** as a mixture of isomers. It was anticipated that successful formation of **7** from **6** will obviate the need for chromatographic separation of the two isomers of **6**. Hence oxidation of **6a** as mixture of isomers was investigated and it was discovered that DDQ in MeCN within 30 min afforded **7a** as fluorescent red coloured compound in 83% yield. Next we set out to try if the two reactions i.e. aza-Diels-Alder and oxidation could be accomplished in one-pot since they utilized the same solvent. As a consequence, **3a** was treated initially with 4-chloroaniline in the presence of Yb(OTf)₃ in MeCN at reflux temperature for 3 h followed by addition of DDQ. Within 5 min the oxidation was complete to afford the final product **7a** in 70% yield. But as R_f of **7a** and **4a** was observed to be too close, the column chromatography to separate them was tedious. Hence it was considered to be appropriate to first isolate **6** as a mixture of isomers and then subject it to oxidation in the presence of DDQ.

Having successfully optimized the reaction conditions, the scope of the protocol was investigated by treating several anilines with prenylated aldehydes **3a** and **3b** in the presence of Yb(OTf)₃. As delineated in Table 2, all the para-substituted anilines irrespective of the nature of the substituents reacted with **3a** or **3b** to afford the corresponding tetrahydroquinolines **6b-m** as mixture of diastereomers in 78-87% yields. Treating **6b-m** as diastereomeric mixtures with DDQ in MeCN at room temperature for 30 min afforded the respective dihydroquinolines **7b-m** as highly fluorescent red coloured products in 73-80% yield. Although dihydroquinolines were characterized on the basis of ¹H-NMR and HRMS spectra, ¹³C-NMR of all compounds could not be recorded due to their poor solubility even in [D₆] DMSO.

In contrast, the reaction of **3a** with 2-chloro-4-methylaniline or 5-chloro-2-methylaniline resulted in the formation carbonyl-ene product **4a** (anti-isomer), as the major product whereas the required tetrahydroquinolines **6n** and **6o** were formed in minor amounts only. Therefore in both cases, DDQ was added in the reaction mixture leading to the formation of oxidized product **7n** and **7o** in 25 and 14% yields whereas **4a** (anti-isomer) was isolated in 55 and 67% yields, respectively. Notably, however, reaction of **3a** with 2,5-dimethoxyaniline resulted in formation of the carbonyl-ene product **4a** as anti-isomer exclusively.

In an attempt to expedite the reaction **3a** was treated with aniline **a,c** and **h** under microwave irradiation. It is significant to note that the reaction under microwave irradiation at 140 °C was complete within 10 min. In all cases, however, compounds **4a**, **6** and **7** were formed and the yields of the required tetrahydroquinolines were low as compared to conventional heating (Table 2).

Table 2. Isolated yields of products **6**, **4a** and **7** from the reaction of **3a** with substituted anilines under microwave irradiation^{a)}

Compd	R ¹	R ²	Yield (%) 6	Yield (%) 4a	Yield (%) 7
a	H	Cl	64	5	9
c	H	OCH ₃	61	7	8
h	H	H	59	8	6

[a] 140 °C for 10 min.

Conclusions

In conclusion, we have successfully demonstrated the synthesis of dihydroquinoline-fused-canthine skeleton via intramolecular aza Diels-Alder reaction followed by oxidation. Further we have discovered that new unnatural canthines having desired stereochemistry can be distereoselectively synthesized from N-prenylated aldehyde by an intramolecular carbonyl-ene reaction using suitable reagents. Work is underway to further investigate the utility of this aldehyde for the synthesis of β -carboline-based natural products.

Experimental Section

General- Melting points were recorded in a melting point apparatus containing silicon oil and are uncorrected. The IR spectra were recorded on FTIR spectrophotometer. The ^1H - and ^{13}C -NMR spectra were recorded on 200MHz or 300MHz spectrometer using TMS as internal standard. The mass spectra were recorded as LCMS having ES probe. The chemical analyses were carried out on a chemical analyzer. The HRMS were recorded as HREIMS or DART-HRMS. All the solvents and chemicals were used as procured from the suppliers. HPLC was performed on Agilent 1100 having a DA detector ($\lambda_{\text{max}} = 220$ and 254 nm) using a gradient run of 10-100% MeCN containing 0.01% TFA in water over a period of 30 min in a RP-18e column (250 mm x 4.6 mm) with particle size of 5 μm . The stereochemistry drawn in the structures herein is relative and not absolute. The diastereoisomeric mixture of compounds **6c-d**, **6f-m** were not separated and therefore no spectroscopic data was recorded for them.

General procedure for the preparation of compounds **2a**, **3a-b** as exemplified for **2a**.

To a stirred solution of compound **1a** (3.0 g, 9.99 mmol) in dry DMF (20 mL), Cs_2CO_3 (4.56 g, 13.99 mmol) was added at room temperature. After 15 min, prenyl bromide (1.40 mL, 11.99 mmol) in 2 mL dry DMF was added drop wise and the reaction was continued for additional 1 h at room temperature. On completion of the reaction as monitored by TLC, the contents were poured into water (200 mL) under stirring with glass rod. The resulting mixture was extracted with EtOAc (2×80 mL). The organic layers were combined, washed with water (100 mL) and subsequently with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated to yield a residue which on triturating with hexane [$R_f = 0.48$ (hexane/EtOAc, 75:25)] furnished 3.35 g (91%) of **2a** as a white solid; mp 133-134 $^\circ\text{C}$.

Methyl 1-(dimethoxymethyl)-9-(3-methylbut-2-enyl)-9H-pyrido[3,4-b]indole-3-carboxylate (2a). IR (KBr): $\nu_{\text{max}} = 1712$ (CO_2CH_3), 3067 ($=\text{CH}$) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): $\delta = 1.73$ (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 3.52 (s, 6 H, $2 \times \text{OCH}_3$), 4.04 (s, 3 H, CO_2CH_3), 5.23 (d, $J = 5.6$ Hz, 1 H, $=\text{CH}$), 5.46 (d, $J = 5.4$ Hz, 2 H, NCH_2), 5.78 (s, 1 H, CHOCH_3), 7.35 (t, $J = 7.5$ Hz, 1 H, ArH), 7.45 (d, $J = 8.3$ Hz, 1 H, ArH), 7.61 (t, $J = 7.7$ Hz, 1 H, ArH), 8.19 (d, $J = 7.8$ Hz, 1 H, ArH), 8.89 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, CDCl_3): $\delta = 18.4, 25.7, 45.1, 52.7, 55.6, 109.6, 111.3, 118.4, 120.8, 121.3, 121.6, 121.8, 128.9, 131.1, 133.5, 135.2, 135.6, 140.9, 142.6, 166.7$ ppm. MS (ES+): m/z (%) = 369.2 (100) [$\text{M} + 1$] $^+$. Anal. calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$ (368.1736): C 68.46, H 6.57, N 7.60; found C 68.24, H 6.89, N 7.45.

Methyl 1-formyl-9-(3-methylbut-2-enyl)-9H-pyrido[3,4-b]indole-3-carboxylate (3a). The title compound was prepared from **5a** following the above described general procedure and after purification by triturating [hexane/EtOAc, 95:03; $R_f = 0.57$ (hexane/EtOAc, 75:25)] obtained as a light yellow solid (2.97 g from 3.0 g), yield: 78%; mp 135-136 $^\circ\text{C}$; IR (KBr): $\nu_{\text{max}} = 1701$ (CHO and CO_2CH_3), 3066 ($=\text{CH}$) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): $\delta = 1.67$ (s, 3 H, CH_3), 1.86 (s, 3 H, CH_3), 4.10 (s, 3 H, CO_2CH_3), 5.10 (s, 1 H, $=\text{CH}$), 5.52 (s, 2 H, CH_2), 7.44 (d, $J = 6.9$ Hz, 1 H, ArH), 7.56 (d, $J = 8.2$ Hz, 1 H, ArH), 7.68 (d, $J = 7.7$ Hz, 1 H, ArH), 8.23 (d, $J = 7.3$ Hz, 1 H, ArH), 9.04 (s, 1 H, ArH), 10.38 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 18.5, 25.7, 45.8, 53.0, 111.4, 119.9, 120.7, 121.5, 121.7, 121.8, 129.9, 133.3, 135.8, 136.2, 137.0, 137.3, 143.2, 165.8, 193.2$ ppm. MS (ES+): m/z (%) = 323.2 (100) [$\text{M} + 1$] $^+$, 355.1 (33) [$\text{M} + 23$] $^+$. Anal. calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ (322.1317): C 70.79, H 5.63, N 8.69; found C 70.42, H 5.54, N 9.03.

9-(3-Methylbut-2-enyl)-9H-pyrido[3,4-b]indole-1-carbaldehyde (3b). The title compound was prepared from **5b** following the above described general procedure and after purification by triturating [hexane/EtOAc, 97:03; $R_f = 0.59$ (hexane/EtOAc, 75:25)] obtained as a white solid (2.02 g from 2.0 g), yield: 75%; mp 117-118 $^\circ\text{C}$; IR (KBr): $\nu_{\text{max}} = 1702$ (CHO), 3044 ($=\text{CH}$) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): $\delta = 1.68$ (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3), 5.13 (s, 1 H, $=\text{CH}$), 5.51 (d, $J = 5.6$ Hz, 2 H, CH_2), 7.38 (t, $J = 7.4$ Hz, 1 H, ArH), 7.53 (d, $J = 8.3$ Hz, 1 H, ArH), 7.67 (t, $J = 7.4$ Hz, 1 H, ArH), 8.19 (t, $J = 6.5$ Hz, 2 H, ArH), 8.66 (d, $J = 4.8$ Hz, 1 H, ArH), 10.34 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 18.5, 25.7, 45.5, 111.1, 118.7, 120.4, 120.9, 121.3, 121.5, 129.4, 132.9, 135.2, 135.5, 138.0, 138.6, 142.8, 193.8$ ppm. MS (ES+): m/z (%) = 265.2 (100) [$\text{M} + 1$] $^+$, 297.1 (30) [$\text{M} + 23$] $^+$. Anal. calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$ (264.1263): C 77.25, H 6.10, N 10.60; found C 77.03, H 5.87, N 10.62.

Typical procedure for the preparation of compound **4a** using AcOH.

A mixture of **2a** (1.20 g, 3.3 mmol), glacial acetic acid (15 mL) and water (25 mL), was heated for 45 min at 100 $^\circ\text{C}$. After completion of the reaction as monitored by TLC, the excess acetic acid was neutralized by saturated aq. NaHCO_3 . The resulting mixture was extracted with EtOAc (2×20 mL) and the organic layers were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated to yield a residue. Purification of this residue via short silica gel (60-120 mesh) column chromatography [$\text{CHCl}_3/\text{MeOH}$, 99:01; $R_f = 0.54$ ($\text{CHCl}_3/\text{MeOH}$, 90:10)] afforded **4a** as a white solid (0.74 g from 1.20 g); yield: 62%; mp 181-182 $^\circ\text{C}$.

syn- Methyl 4-hydroxy-5-(prop-1-en-2-yl)-5,6-dihydro-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (4a). The title compound was prepared from **2a** following the above described general procedure, IR (KBr): $\nu_{\text{max}} = 1714$ (CO_2CH_3), 3384 (OH) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): $\delta = 2.03$ (s, 3 H, CH_3), 2.80 (s, 1 H, CHOH ; exchangeable with D_2O), 3.00 (t, $J = 6.3$ Hz, 1 H, CH), 4.02 (s, 3 H, CO_2CH_3), 4.43 (d, $J = 3.9$ Hz, 1 H, NCHH), 4.45 (s, 1 H, NCHH), 5.08 (s, 1 H, $=\text{CHH}$), 5.21 (s, 1 H, $=\text{CHH}$), 5.41 (d, $J = 1.8$ Hz, 1 H, CHOH), 7.38 (t, $J = 7.1$ Hz, 1 H, ArH), 7.56 (t, $J = 7.5$ Hz, 1 H, ArH), 7.67 (t, $J = 7.2$ Hz, 1 H, ArH), 8.21 (d, $J = 7.8$ Hz, 1 H, ArH), 8.85 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 23.1, 40.0, 46.0, 52.6, 67.0, 110.1, 113.2, 118.6, 120.8, 121.8, 122.8, 126.4, 128.9, 134.4, 136.8, 141.3, 142.2, 142.7, 166.7$ ppm. MS (ES+): m/z (%) = 323.2 (100) [$\text{M} + 1$] $^+$. DART-HRMS calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_3$: 323.1396; found 323.1356.

anti- Methyl 4-hydroxy-5-(prop-1-en-2-yl)-5,6-dihydro-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (4a). The title compound was obtained from **3a** when (YbOTf)₃ was used as a catalyst and after purification by column chromatography [MeOH/CHCl₃, 99:1; R_f = 0.54 (MeOH/CHCl₃, 10:90)] was obtained as a white solid, mp 184-185 °C; IR (KBr): ν_{max} = 1722 (CO₂CH₃), 3244 (OH) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.96 (s, 3 H, CH₃), 3.11 (td, J₁ = 3.4 Hz, J₂ = 8.2 Hz, 1 H, CH), 3.98 (s, 1 H CHO*H*; exchangeable with D₂O), 4.03 (s, 3 H, CO₂CH₃), 4.29 (dd, J₁ = 8.8 Hz, J₂ = 12.4 Hz, 1 H, NCH*H*), 4.45 (dd, J₁ = 4.8 Hz, J₂ = 12.4 Hz, 1 H, NCH*H*), 4.87 (s, 1 H, =CH*H*), 5.03 (s, 1 H, =CH*H*), 5.29 (d, J = 8.0 Hz, 1 H, CHO*H*), 7.38 (t, J = 7.2 Hz, 1 H, Ar*H*), 7.53 (d, J = 8.3 Hz, 1 H, Ar*H*), 7.66 (t, J = 7.2 Hz, 1 H, Ar*H*), 8.21 (d, J = 7.9 Hz, 1 H, Ar*H*), 8.81 (s, 1 H, Ar*H*) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 21.5, 43.0, 47.8, 52.5, 68.5, 110.0, 114.3, 118.0, 120.8, 122.0, 122.8, 125.7, 128.8, 134.0, 137.0, 141.0, 142.4, 143.3, 166.6 ppm. MS (ES⁺): m/z (%) = 323.2 (100) [M + 1]⁺. Anal. calcd. for C₁₉H₁₈N₂O₃ (322.1317): C 70.79, H 5.63, N 8.69; found: C 71.05, H 5.43, N 8.85.

General procedure for the preparation of compounds 4a-b using ZnBr₂ as catalyst as exemplified for 4a.

A mixture of **3a** (0.30 g, 0.93 mmol), ZnBr₂ (0.21 g, 0.93 mmol) and dry benzene (20 mL), was heated for 3 h at reflux temperature. On completion, water (30 mL) and EtOAc (50 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 20 mL). The organic layers were combined and washed with brine (50 mL), dried (Na₂SO₄) and concentrated under vacuo to yield the crude product. Then crude product was purified via silica gel (60-120 mesh) column chromatography [CHCl₃/MeOH, 99:01; R_f = 0.54 (CHCl₃/MeOH, 90:10)] to obtain **4a** as a white solid (0.27 g from 0.30 g); yield: 91%.

syn- 5-(Prop-1-en-2-yl)-5,6-dihydro-4H-indolo[3,2,1-de][1,5]naphthyridin-4-ol (4b). The title compound was prepared following above described general procedure and after purification by column chromatography [MeOH/CHCl₃, 01:99; R_f = 0.66 (MeOH/CHCl₃, 10:90)] **4b** was obtained as a white solid (0.045 g from 0.05 g). Yield: 90%, mp 168-169 °C; IR (KBr): ν_{max} = 3331 (OH) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 2.04 (s, 3 H, CH₃), 2.33 (brs, 1 H, CHO*H*; exchangeable with D₂O), 3.04 (s, 1 H, CH), 4.36-4.45 (m, 2 H, CH₂), 5.09 (s, 1 H, CHO*H*), 5.20 (s, 1 H, =CH*H*), 5.38 (s, 1 H, =CH*H*), 7.31 (t, J = 7.4 Hz, 1 H, Ar*H*), 7.54 (d, J = 8.2 Hz, 1 H, Ar*H*), 7.63 (t, J = 7.2 Hz, 1 H, Ar*H*), 7.89 (d, J = 4.9 Hz, 1 H, Ar*H*), 8.16 (d, J = 7.9 Hz, 1 H, Ar*H*), 8.32 (d, J = 5.0 Hz, 1 H, Ar*H*) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 23.2, 40.2, 46.4, 66.1, 109.7, 113.0, 119.9, 121.5, 122.8, 127.2, 128.6, 132.9, 137.4, 141.2, 142.9, 143.7 ppm. MS (ES⁺): m/z (%) = 265.2 (100) [M + 1]⁺. Anal. calcd. for C₁₇H₁₆N₂O (264.1263): C 77.25, H 6.10, N 10.60; found: C 76.98, H 6.22, N 10.52.

General procedure for the preparation of compounds 6a-o as exemplified for 6a.

A mixture of **3a** (0.40 g, 1.24 mmol), 4-chloroaniline (0.16 g, 1.24 mmol), Yb(OTf)₃ (0.078 g, 0.12 mmol) and dry MeCN (20 mL), was heated for 3 h at reflux temperature. After completion of the reaction as monitored by TLC, MeCN was removed under vacuum. The residue was diluted with EtOAc (75 mL) and water (50 mL) and the resulting mixture was partitioned in separating funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined and washed with brine (50 mL), dried (Na₂SO₄) and evaporated under vacuo to yield the crude product. Then crude product was purified via silica gel (60-120 mesh) column chromatography [hexane/EtOAc, 86:14; R_f = 0.62 (hexane/EtOAc, 7:3)] to afford *syn*-**6a** and *anti*-**6a** as a white solid (0.46 g from 0.40 g); yield: 86%.

anti- Methyl 12-chloro-10,10-dimethyl-9a,10,15,15a-tetrahydro-9H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (6a). R_f = 23.37, R_f = 0.62 (hexane/EtOAc, 70:30), mp 217-218 °C; IR (KBr): ν_{max} = 1716 (CO₂CH₃), 3364 (NH) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.44 (s, 3 H, CH₃), 1.61 (s, 3 H, CH₃), 2.47 (td, J₁ = 3.8 Hz, J₂ = 10.8 Hz, 1 H, CH₂CH), 4.01-4.15 (m, 4 H, NCH*H* and CO₂CH₃), 4.71 (dd, J₁ = 4.2 Hz, J₂ = 12.1 Hz, NCH*H*), 4.78 (d, J = 11.0 Hz, 1 H, CHNH), 5.28 (brs, 1 H, NH; exchangeable with D₂O), 6.72 (d, J = 8.6 Hz, 1 H, Ar*H*), 6.72 (dd, J₁ = 2.2 Hz, J₂ = 8.6 Hz, 1 H, Ar*H*), 7.37-7.44 (m, 2 H, Ar*H*), 7.58 (d, J = 8.2 Hz, 1 H, Ar*H*), 7.68 (t, J = 7.0 Hz, 1 H, Ar*H*), 8.21 (d, J = 8.0 Hz, 1 H, Ar*H*), 8.80 (s, 1 H, Ar*H*) ppm. MS (ES⁺): m/z (%) = 432.2 (100) [M + 1]⁺. Anal. calcd. for C₂₅H₂₂ClN₃O₂ (431.1401): C 69.52, H 5.13, N, 9.73; found C 69.25, H 4.85, N, 9.89.

syn- Methyl 12-chloro-10,10-dimethyl-9a,10,15,15a-tetrahydro-9H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (6a). R_f = 20.52, R_f = 0.53 (hexane/EtOAc, 70:30), mp 214-215 °C; IR (KBr): ν_{max} = 1717 (CO₂CH₃), 3371 (NH) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.52 (s, 3 H, CH₃), 1.61 (s, 3 H, CH₃), 2.47 (d, J = 9.8 Hz, 1 H, CH₂CH), 3.81 (t, J = 11.9 Hz, 1 H, NCH*H*), 4.08 (s, 3 H, CO₂CH₃), 4.35 (brs, 1 H, NH; exchangeable with D₂O), 4.46 (dd, J₁ = 5.1 Hz, J₂ = 12.0 Hz, 1 H, NCH*H*), 5.21 (d, J = 2.6 Hz, 1 H, CHNH), 6.35 (d, J = 8.5 Hz, 1 H, Ar*H*), 6.95 (dd, J₁ = 2.3 Hz, J₂ = 8.6 Hz, 1 H, Ar*H*), 7.21 (d, J = 2.2 Hz, 1 H, Ar*H*), 7.34-7.39 (m, 1 H, Ar*H*), 7.47-7.50 (m, 1 H, Ar*H*), 7.61-7.66 (m, 1 H, Ar*H*), 8.20 (d, J = 8.0 Hz, 1 H, Ar*H*), 8.89 (s, 1 H, Ar*H*) ppm. MS (ES⁺): m/z (%) = 432.2 (100) [M + 1]⁺. Anal. calcd. for C₂₅H₂₂ClN₃O₂ (431.1401): C 69.52, H 5.13, N, 9.73; found C 69.46, H 4.97, N, 9.86.

anti- 12-Chloro-10,10-dimethyl-9a,10,15,15a-tetrahydro-9H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine (6b). The title compound was prepared from **3b** following the above described general procedure and after purification by column chromatography [hexane/EtOAc, 89:11; R_f = 0.68 (hexane/EtOAc, 70:30)] *syn*-**6b** and *anti*-**6b** were obtained as a white solid (0.29 g from 0.25 g). Yield: 82%, mp 186-187 °C; IR (KBr): ν_{max} = 3415 (NH), 3022 (=CH) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.44 (s, 3 H, CH₃), 1.61 (s, 3 H, CH₃), 2.45 (td, J₁ = 4.2 Hz, J₂ = 11.1 Hz, 1 H, CH₂CH), 4.07 (t, J = 12.0 Hz, 1 H, NCH*H*), 4.66 (dd, J₁ = 4.4 Hz, J₂ = 12.0 Hz, 1 H, NCH*H*), 4.79 (d, J = 10.7 Hz, 1 H, CHNH), 5.70 (brs, 1 H, NH; exchangeable with D₂O), 6.68 (d, J = 8.5 Hz, 1 H, Ar*H*), 7.01 (dd, J₁ = 2.1 Hz, J₂ = 8.4 Hz, 1 H, Ar*H*), 7.26-7.34 (m, 2 H, Ar*H*), 7.53 (d, J = 8.3 Hz, 1 H, Ar*H*), 7.63 (t, J = 7.3 Hz, 1 H, Ar*H*), 7.85 (d, J = 5.4 Hz, 1 H, Ar*H*), 8.16 (d, J = 7.7 Hz, 1 H, Ar*H*), 8.40 (d, J = 5.4 Hz, 1 H, Ar*H*) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 27.6, 27.7, 35.7, 40.5, 44.8, 49.6, 109.5, 114.1, 116.1, 119.9, 121.7, 122.1, 122.8, 125.8, 126.4, 127.3, 128.3, 131.2, 132.1, 138.4, 140.7, 141.3, 141.9 ppm. MS (ES⁺): m/z (%) = 374.3 (100) [M + 1]⁺. Anal. calcd. for C₂₃H₂₀ClN₃ (373.1346): C 73.89, H 5.39, N 11.24; found: C 74.04, H 5.69, N 10.95.

syn- 12-Chloro-10,10-dimethyl-9a,10,15,15a-tetrahydro-9H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine (6b). R_f = 0.59 (hexane/EtOAc, 70:30), mp 185-186 °C; IR (KBr): ν_{max} = 3393 (NH) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.54 (s, 3 H, CH₃), 1.62 (s, 3 H, CH₃), 2.47 (d, J = 9.6 Hz, 1 H, CH₂CH), 3.72 (t, J = 11.8 Hz, 1 H, NCH*H*), 4.34 (s, 1 H, CHNH; exchangeable with D₂O), 4.47 (dd, J₁ = 5.1 Hz, J₂ = 11.4 Hz, 1 H, NCH*H*), 5.15 (d, J = 2.6 Hz, 1 H, CHNH), 6.36 (d, J = 8.5 Hz, 1 H, Ar*H*), 6.95 (dd, J₁ = 2.2 Hz, J₂ = 8.5 Hz, 1 H, Ar*H*), 7.20-7.33 (m, 2 H, Ar*H*), 7.46 (d, J = 8.2 Hz, 1 H, Ar*H*), 7.60 (t, J =

7.7 Hz, 1 H, ArH), 7.93 (d, $J = 5.5$ Hz, 1 H, ArH), 8.16 (d, $J = 8.0$ Hz, 1 H, ArH), 8.38 (d, $J = 5.5$ Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, CDCl_3): $\delta = 26.2, 34.5, 35.2, 39.6, 43.0, 49.0, 109.7, 115.2, 115.4, 120.0, 121.6, 122.2, 122.7, 126.0, 126.7, 127.5, 128.6, 128.7, 138.1, 139.6, 141.0, 141.9$ ppm. MS (ES+): m/z (%) = 374.3 (100) $[\text{M} + 1]^+$. Anal. calcd. for $\text{C}_{23}\text{H}_{20}\text{ClN}_3$ (373.1346): C 73.89, H 5.39, N 11.24; found: C 74.21, H 5.32, N 10.92.

anti- Methyl 12-methyl-10,10-dimethyl-9a,10,15,15a-tetrahydro-9H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (6e). The title compound was prepared from **3a** following the above described general procedure, after purification by column chromatography [hexane/EtOAc, 87:12; $R_f = 0.66$ (hexane/EtOAc, 70:30)] *syn*-**6e** and *anti*-**6e** were obtained as a white solid (0.34 g from 0.35 g). Yield: 76%, mp 187-188 °C; IR (KBr): $\nu_{\text{max}} = 1712$ (CO_2CH_3), 3389 (NH) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): $\delta = 1.46$ (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.54 (td, $J_1 = 4.4$ Hz, $J_2 = 11.6$ Hz, 1 H, CH_2CH), 4.05-4.16 (m, 4 H, NCHH and CO_2CH_3), 4.71 (dd, $J_1 = 4.4$ Hz, $J_2 = 12.2$ Hz, 1 H, NCHH), 4.78 (d, $J = 10.8$ Hz, 1 H, CHNH), 5.62 (brs, 1 H, NH; exchangeable with D_2O), 6.74 (d, $J = 8.3$ Hz, 1 H, ArH), 6.90 (d, $J = 8.4$ Hz, 1 H, ArH), 7.14 (s, 1 H, ArH), 7.39 (t, $J = 7.1$ Hz, 1 H, ArH), 7.59 (d, $J = 8.1$ Hz, 1 H, ArH), 7.67 (t, $J = 7.2$ Hz, 1 H, ArH), 8.19-8.23 (m, 1 H, ArH), 8.82 (s, 1 H, ArH) ppm. MS (ES+): m/z (%) = 412.2 (100) $[\text{M} + 1]^+$. HRMS (+ESI) calcd. $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_2$: 411.1947; found 411.1918.

syn- Methyl 12-methyl-10,10-dimethyl-9a,10,15,15a-tetrahydro-9H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (6e). $R_f = 0.58$ (hexane/EtOAc, 70:30), mp 184-185 °C; IR (KBr): $\nu_{\text{max}} = 1706$ (CO_2CH_3), 3489 (NH) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): $\delta = 1.53$ (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 2.27 (s, 3 H, Ar CH_3), 2.44-2.46 (m, 1 H, CH_2CH), 3.91 (t, $J = 11.9$ Hz, 1 H, NCHH), 4.09 (s, 3 H, CO_2CH_3), 4.20 (s, 1 H, NH; exchangeable with D_2O), 4.47 (dd, $J_1 = 5.1$ Hz, $J_2 = 11.9$ Hz, 1 H, NCHH), 5.21 (d, $J = 2.1$ Hz, 1 H, CHNH), 6.36 (d, $J = 7.8$ Hz, 1 H, ArH), 6.83 (d, $J = 6.8$ Hz, 1 H, ArH), 7.07 (s, 1 H, ArH), 7.36 (t, $J = 7.1$ Hz, 1 H, ArH), 7.48 (d, $J = 8.2$ Hz, 1 H, ArH), 7.62 (t, $J = 7.3$ Hz, 1 H, ArH), 8.21 (d, $J = 8.0$ Hz, 1 H, ArH), 8.90 (s, 1 H, ArH) ppm. MS (ES+): m/z (%) = 412.2 (100) $[\text{M} + 1]^+$. DART-HRMS calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2$: 412.2025; found 412.2009.

General procedure for the preparation of compounds 7a-o as exemplified for 7a.

To a stirred solution of diastereomeric mixture of **6a** (0.20 g, 0.46 mmol) in dry MeCN (30 mL), DDQ (0.32 g, 1.34 mmol) was added and the reaction was continued for 25 min. at room temperature. On completion, excess solvent was removed under reduced pressure and then CHCl_3 (50 mL) and water (20 mL) were added. After separation of organic layer, the aqueous layer was further extracted with CHCl_3 (2×20 mL). The organic layers were combined and washed with water (50 mL), subsequently with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude product and after purification via silica gel (60-120 mesh) column chromatography [$\text{CHCl}_3/\text{MeOH}$, 98:02; $R_f = 0.50$ ($\text{CHCl}_3/\text{MeOH}$, 93:07)] **7a** was obtained as a red solid (0.16 g from 0.20 g); yield: 83%; mp > 250 °C.

Methyl 12-chloro-10,10-dimethyl-10H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (7a). IR (KBr): $\nu_{\text{max}} = 1718$ (CO_2CH_3) cm^{-1} . ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.65$ (s, 6 H, 2 x CH_3), 4.00 (s, 3 H, CO_2CH_3), 7.32 (dd, $J_1 = 2.2$ Hz, $J_2 = 8.3$ Hz, 1 H, ArH), 7.45-7.53 (m, 2 H, ArH), 7.58 (d, $J = 2.1$ Hz, 1 H, ArH), 7.79 (t, $J = 7.5$ Hz, 1 H, ArH), 8.30 (d, $J = 8.3$ Hz, 1 H, ArH), 8.48 (d, $J = 7.4$ Hz, 1 H, ArH), 8.56 (s, 1 H, ArH), 9.00 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 32.5, 36.4, 53.0, 110.6, 118.7, 122.0, 123.5, 123.8, 124.1, 124.6, 127.2, 127.7, 130.6, 131.6, 132.7, 133.9, 136.1, 137.9, 138.9, 141.3, 144.6, 150.4, 166.3$ ppm. MS (ES+): m/z (%) = 428.2 (100) $[\text{M} + 1]^+$. DART-HRMS calcd. for $\text{C}_{25}\text{H}_{19}\text{ClN}_3\text{O}_2$: 428.1166; found 428.1155.

12-Chloro-10,10-dimethyl-10H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine (7b). The title compound was prepared from **6b** following the above described general procedure and after purification by column chromatography [$\text{CHCl}_3/\text{MeOH}$, 98:02; $R_f = 0.61$ ($\text{CHCl}_3/\text{MeOH}$, 93:07)] was obtained as a red solid (0.10 g from 0.12 g). Yield: 84%, mp 185-186 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 1.67$ (s, 6 H, 2 x CH_3), 7.37 (s, 1 H, ArH), 7.44 (t, $J = 6.9$ Hz, 1 H, ArH), 7.65-7.77 (m, 4 H, ArH), 7.87 (s, 1 H, ArH), 7.97 (d, $J = 4.6$ Hz, 1 H, ArH), 8.13 (d, $J = 7.8$ Hz, 1 H, ArH), 8.96 (d, $J = 4.6$ Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 33.6, 36.3, 112.6, 118.3, 123.4, 124.2, 124.3, 125.6, 125.8, 126.5, 127.7, 128.6, 130.8, 131.4, 132.4, 137.0, 138.9, 147.1, 151.3$ ppm. MS (ES+): m/z (%) = 370.2 (100) $[\text{M} + 1]^+$. Anal. calcd. for $\text{C}_{23}\text{H}_{16}\text{ClN}_3$ (369.1033): C 74.69, H 4.36, N 11.36; found: C 74.44, H 4.49, N 11.27.

Methyl 12-methoxy-10,10-dimethyl-10H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (7c). The title compound was prepared from **6c** following the above described general procedure and after purification by column chromatography [$\text{CHCl}_3/\text{MeOH}$, 98:02; $R_f = 0.32$ ($\text{CHCl}_3/\text{MeOH}$, 93:07)] was obtained as a red solid (0.12 g from 0.14 g). Yield: 86%, mp 146-147 °C; IR (KBr): $\nu_{\text{max}} = 1722$ (CO_2CH_3) cm^{-1} . ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.72$ (s, 6 H, 2 x CH_3), 3.83 (s, 3 H, OCH_3), 4.02 (s, 3 H, CO_2CH_3), 6.94 (t, $J = 7.7$ Hz, 1 H, ArH), 7.16 (s, 1 H, ArH), 7.58 (t, $J = 6.6$ Hz, 2 H, ArH), 7.81 (d, $J = 6.4$ Hz, 1 H, ArH), 8.39 (d, $J = 7.3$ Hz, 1 H, ArH), 8.50 (d, $J = 7.6$ Hz, 1 H, ArH), 8.91 (s, 1 H, ArH), 9.07 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 33.3, 36.1, 52.8, 55.4, 111.8, 112.5, 112.9, 120.1, 123.0, 124.4, 125.2, 125.6, 129.0, 131.1, 131.5, 132.4, 132.7, 134.3, 135.7, 139.1, 145.2, 147.6, 158.8, 165.1$ ppm. MS (ES+): m/z (%) = 424.3 (100) $[\text{M} + 1]^+$. DART-HRMS calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_3$: 424.1661; found 424.1666.

12-Methoxy-10,10-dimethyl-10H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine (7d). The title compound was prepared from **6d** following the above described general procedure and after purification by column chromatography [$\text{CHCl}_3/\text{MeOH}$, 98:02; $R_f = 0.49$ ($\text{CHCl}_3/\text{MeOH}$, 93:07)] was obtained as a red solid (0.095 g from 0.12 g). Yield: 80%, mp 175-176 °C. ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.66$ (s, 6 H, 2 x CH_3), 3.81 (s, 3 H, OCH_3), 6.87 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.5$ Hz, 1 H, ArH), 7.09 (d, $J = 2.6$ Hz, 1 H, ArH), 7.37 (d, $J = 8.5$ Hz, 1 H, ArH), 7.48 (t, $J = 7.6$ Hz, 1 H, ArH), 7.76 (t, $J = 7.6$ Hz, 1 H, ArH), 8.26-8.34 (m, 3 H, ArH), 8.58 (s, 1 H, ArH), 8.83 (d, $J = 4.8$ Hz, 1 H, ArH) ppm. MS (ES+): m/z (%) = 366.3 (100) $[\text{M} + 1]^+$. Anal. calcd. for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}$ (365.1528): C 78.88, H 5.24, N 11.50; Found: C 79.02, H 5.54, N 12.01.

Methyl 12-methyl-10,10-dimethyl-10H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (7e). The title compound was prepared from **6e** following the above described general procedure and after purification by column chromatography [$\text{CHCl}_3/\text{MeOH}$, 98:02; $R_f = 0.36$ ($\text{CHCl}_3/\text{MeOH}$, 93:07)] was obtained as a red solid (0.13 g from 0.16 g). Yield: 84%, mp 177-178 °C; IR (KBr): $\nu_{\text{max}} = 1720$ (CO_2CH_3) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): $\delta = 1.68$ (s, 6 H, 2 x CH_3), 2.39 (s, 3 H, Ar CH_3), 4.10 (s, 3 H, CO_2CH_3), 7.10 (d, $J = 6.8$ Hz, 1 H, ArH), 7.22-7.26 (m, 1 H, ArH), 7.47 (t, $J = 7.3$ Hz, 1 H, ArH), 7.60 (d, $J = 7.1$ Hz, 1 H, ArH), 7.72-7.97 (m, 3 H, ArH), 8.17 (d, $J = 7.0$ Hz, 1 H, ArH), 8.84 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): δ

= 21.6, 33.2, 36.1, 52.9, 60.2, 112.4, 119.2, 122.8, 123.9, 124.2, 124.3, 126.0, 127.2, 128.1, 128.3, 130.7, 131.1, 133.6, 136.9, 138.2, 139.1, 140.6, 143.8, 149.9, 166.1 ppm. MS (ES⁺): *m/z* (%) = 408.3 (100) [*M* + 1]⁺. Anal. calcd. for C₂₆H₂₁N₃O₂ (407.1634): C 76.64, H 5.19, N 10.31; found C 76.42, H 5.07, N 10.72.

10,10,12-Trimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine (7f). The title compound was prepared from **6f** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.44 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.09 g from 0.12 g). Yield: 79%, mp 177-179 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.66 (s, 6 H, 2 x CH₃), 2.39 (s, 3 H, CH₃), 7.10 (d, *J* = 7.4 Hz, 1 H, ArH), 7.22 (s, 1 H, ArH), 7.41 (t, *J* = 7.3 Hz, 1 H, ArH), 7.64-7.75 (m, 4 H, ArH), 7.93 (d, *J* = 4.9 Hz, 1 H, ArH), 8.12 (d, *J* = 7.8 Hz, 1 H, ArH), 8.91 (d, *J* = 4.9 Hz, 1 H, ArH) ppm. MS (ES⁺): *m/z* (%) = 350.3 (100) [*M* + 1]⁺. Anal. calcd. for C₂₄H₁₉N₃ (349.1579): C 82.49, H 5.48, N 12.03; found: C 82.17, H 6.35, N 11.31.

Methyl 10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (7g). The title compound was prepared from **6g** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.40 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.15 g from 0.19 g). Yield: 79%, mp 147-149 °C; IR (KBr): *v*_{max} = 1719 (CO₂CH₃) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO + TFA): δ = 1.82 (s, 6 H, 2 x CH₃), 4.04 (s, 3 H, CO₂CH₃), 7.32 (t, *J* = 5.2 Hz, 2 H, ArH), 7.59-7.67 (m, 2 H, ArH), 7.84 (t, *J* = 7.2 Hz, 2 H, ArH), 8.49 (d, *J* = 7.7 Hz, 1 H, ArH), 8.54 (d, *J* = 8.2 Hz, 1 H, ArH), 9.22 (s, 1 H, ArH), 9.67 (s, 1 H, ArH) ppm. MS (ES⁺): *m/z* (%) = 394.3 (100) [*M* + 1]⁺. DART-HRMS calcd. for C₂₅H₁₉N₃O₂: 394.1555; found 394.1550.

Methyl 12-bromo-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (7h). The title compound was prepared from **6h** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.48 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.12 g from 0.15 g). Yield: 78%, mp >250 °C; IR (KBr): *v*_{max} = 1722 (CO₂CH₃) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.64 (s, 6 H, 2 x CH₃), 4.00 (s, 3 H, CO₂CH₃), 7.36-7.52 (m, 3 H, ArH), 7.69 (d, *J* = 1.9 Hz, 1 H, ArH), 7.77 (t, *J* = 8.3 Hz, 1 H, ArH), 8.27-8.31 (m, 1 H, ArH), 8.46 (t, *J* = 4.4 Hz, 1 H, ArH), 8.55 (s, 1 H, ArH), 8.98 (s, 1 H, ArH) ppm. ¹³C NMR (75 MHz, [D₆]DMSO): δ = 33.2, 36.3, 53.0, 112.5, 119.5, 119.8, 123.0, 124.2, 124.4, 125.2, 126.4, 128.4, 130.0, 130.7, 130.9, 131.5, 133.6, 137.7, 137.8, 139.2, 142.3, 144.2, 151.3, 166.0 ppm. MS (ES⁺): *m/z* (%) = 472.2 (100) [*M* + 1]⁺, 474.2 (100) [*M* + 3]⁺. Anal. calcd. for C₂₅H₁₈BrN₃O₂ (471.0582): C 63.57, H 3.84, N 8.90; found C 63.32, H 4.26, N 9.21.

Methyl 12-fluoro-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (7i). The title compound was prepared from **6i** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.49 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.16 g from 0.16 g). Yield: 83%, mp >250 °C; IR (KBr): *v*_{max} = 1715 (CO₂CH₃) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.65 (s, 6 H, 2 x CH₃), 4.00 (s, 3 H, CO₂CH₃), 7.11 (td, *J*₁ = 2.6 Hz, *J*₂ = 8.3 Hz, 1 H, ArH), 7.41 (dd, *J*₁ = 2.9 Hz, *J*₂ = 10.6 Hz, 1 H, ArH), 7.50 (t, *J* = 6.4 Hz, 2 H, ArH), 7.78 (t, *J* = 8.2 Hz, 1 H, ArH), 8.30 (d, *J* = 7.5 Hz, 1 H, ArH), 8.47 (d, *J* = 7.6 Hz, 1 H, ArH), 8.53 (s, 1 H, ArH), 8.98 (s, 1 H, ArH) ppm. MS (ES⁺): *m/z* (%) = 412.3 (100) [*M* + 1]⁺. HRMS (+ESI) calcd. C₂₅H₁₈FN₃O₂: 411.1509; found 412.1490.

Methyl 10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]benzo[*g*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (7j). The title compound was prepared from **6j** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.38 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.25 g from 0.30 g). Yield: 87%, mp 245-246 °C; IR (KBr): *v*_{max} = 1706 (CO₂CH₃) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO): δ = 2.20 (s, 6 H, 2 x CH₃), 4.02 (s, 3 H, CO₂CH₃), 7.40 (t, *J* = 6.8 Hz, 1 H, ArH), 7.48-7.55 (m, 2 H, ArH), 7.60 (d, *J* = 8.5 Hz, 1 H, ArH), 7.79-7.87 (m, 2 H, ArH), 8.31 (s, 1 H, ArH), 8.37 (d, *J* = 7.8 Hz, 1 H, ArH), 8.50 (d, *J* = 7.9 Hz, 1 H, ArH), 8.62 (d, *J* = 9.1 Hz, 1 H, ArH), 8.69 (s, 1 H, ArH), 9.01 (s, 1 H, ArH) ppm. MS (ES⁺): *m/z* (%) = 444.3 (100) [*M* + 1]⁺. Anal. calcd. for C₂₉H₂₁N₃O₂ (443.1634): C 78.54, H 4.77, N 9.47; found C 78.40, H 4.68, N 9.59.

Methyl 12-isopropyl-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (7k). The title compound was prepared from **6k** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.35 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.16 g from 0.20 g). Yield: 85%, mp 160-162 °C; IR (KBr): *v*_{max} = 1718 (CO₂CH₃), 3022 (=CH) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.24 (s, 3 H, CH₃), 1.26 (s, 3 H, CH₃), 1.65 (s, 6 H, 2 x CH₃), 2.89-2.98 (m, 1 H, CHCH₃), 4.00 (s, 3 H, CO₂CH₃), 7.17 (d, *J* = 8.3 Hz, 1 H, ArH), 7.40 (t, *J* = 2.9 Hz, 2 H, ArH), 7.49 (t, *J* = 7.5 Hz, 1 H, ArH), 7.78 (t, *J* = 7.2 Hz, 1 H, ArH), 8.31 (t, *J* = 5.8 Hz, 1 H, ArH), 8.48 (d, *J* = 11.2 Hz, 2 H, ArH), 8.98 (s, 1 H, ArH) ppm. MS (ES⁺): *m/z* (%) = 436.3 (100) [*M* + 1]⁺. Anal. calcd. for C₂₈H₂₅N₃O₂ (435.5170): C 77.22, H 5.79, N 9.65; found C 77.49, H 6.07, N 9.63.

Methyl 11,12,13-trimethoxy-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (7l). The title compound was prepared from **6l** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.38 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.21 g from 0.25 g). Yield: 84%, mp 178-179 °C; IR (KBr): *v*_{max} = 1715 (CO₂CH₃) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.75 (s, 6 H, 2 x CH₃), 3.79 (s, 3 H, OCH₃), 3.88 (s, 3 H, OCH₃), 3.94 (s, 3 H, OCH₃), 4.00 (s, 3 H, CO₂CH₃), 6.97 (s, 1 H, ArH), 7.51 (t, *J* = 7.5 Hz, 1 H, ArH), 7.79 (t, *J* = 7.6 Hz, 1 H, ArH), 8.32 (t, *J* = 4.6 Hz, 1 H, ArH), 8.48 (d, *J* = 8.0 Hz, 1 H, ArH), 8.57 (s, 1 H, ArH), 8.99 (s, 1 H, ArH) ppm. MS (ES⁺): *m/z* (%) = 484.3 (100) [*M* + 1]⁺. Anal. calcd. for C₂₈H₂₅N₃O₅ (483.1794): C 69.55, H 5.21, N 8.69; found C 69.89, H 4.86, N 9.03.

Methyl 12-tert-butyl-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (7m). The title compound was prepared from **6m** following the above described general procedure and after purification by column chromatography [CHCl₃/MeOH, 98:02; *R_f* = 0.39 (CHCl₃/MeOH, 93:07)] was obtained as a red solid (0.08 g from 0.10 g). Yield: 78%, mp 162-163 °C; IR (KBr): *v*_{max} = 1720 (CO₂CH₃) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.35 (s, 9 H, 3 x CH₃), 1.84 (s, 6 H, 2 x CH₃), 4.07 (s, 3 H, CO₂CH₃), 7.40 (d, *J* = 7.2 Hz, 1 H, ArH), 7.68 (d, *J* = 7.2 Hz, 2 H, ArH), 7.74 (d, *J* = 8.5 Hz, 1 H, ArH), 7.91 (t, *J* = 8.2 Hz, 1 H, ArH), 8.53 (d, *J* = 8.1 Hz, 1 H, ArH), 8.58 (d, *J* = 7.7 Hz, 1 H, ArH), 9.25 (s, 1 H, ArH), 9.44 (s, 1 H, ArH) ppm. ¹³C NMR (75 MHz, [D₆]DMSO): δ = 31.5, 34.9, 35.2, 36.5, 53.6, 114.4, 120.6, 122.3, 123.9, 124.3, 125.2, 125.4, 125.6, 127.4, 130.7, 131.2,

132.5, 132.7 132.8, 135.1, 135.7, 140.3, 148.0, 148.6, 150.9, 165.1 ppm. MS (ES+): m/z (%) = 450.3 (100) $[M + 1]^+$. DART-HRMS calcd. for $C_{29}H_{28}N_3O_2$: 450.2182; found 450.2179.

Methyl 14-chloro-10,10,12-trimethyl-10H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (7n). The title compound was prepared from **3a** through the Aza Diels-Alder product (**6n**) following the above described general procedure and after purification by column chromatography [$CHCl_3/MeOH$, 98:02; R_f = 0.38 ($CHCl_3/MeOH$, 93:07)] was obtained as a red solid (0.12 g from 0.35 g). Yield: 25%, mp >250 °C; IR (KBr): ν_{max} = 1719 (CO_2CH_3) cm^{-1} . 1H NMR (300 MHz, $[D_6]DMSO$): δ = 1.64 (s, 6 H, 2 x CH_3), 2.34 (s, 3 H, $ArCH_3$), 4.00 (s, 3 H, CO_2CH_3), 7.25 (s, 1 H, ArH), 7.34 (s, 1 H, ArH), 7.52 (t, J = 6.4 Hz, 1 H, ArH), 7.80 (t, J = 7.5 Hz, 1 H, ArH), 8.33 (d, J = 10.6 Hz, 1 H, ArH), 8.50 (d, J = 7.6 Hz, 1 H, ArH), 8.58 (s, 1 H, ArH), 9.03 (s, 1 H, ArH) ppm. MS (ES+): m/z (%) = 442.3(100) $[M + 1]^+$. Anal. calcd. for $C_{26}H_{20}ClN_3O_2$ (441.1244): C 70.67, H 4.56, N 9.51; found C 70.49, H 4.20, N 9.68.

Methyl 11-chloro-10,10,14-trimethyl-10H-indolo[3,2,1-ij]quinolino[3,2-c][1,5]naphthyridine-2-carboxylate (7o). The title compound was prepared from **3a** through the Aza Diels-Alder product (**6o**) following the above described general procedure and after purification by column chromatography [$CHCl_3/MeOH$, 98:02; R_f = 0.38 ($CHCl_3/MeOH$, 93:07)] was obtained as a red solid (0.07 g from 0.35 g). Yield: 14%, mp >250 °C; IR (KBr): ν_{max} = 1716 (CO_2CH_3) cm^{-1} . 1H NMR (300 MHz, $CDCl_3$): δ = 1.93 (s, 6 H, 2 x CH_3), 2.75 (s, 3 H, $ArCH_3$), 4.10 (s, 3 H, CO_2CH_3), 7.14 (s, 2 H, ArH), 7.50 (t, J = 4.2 Hz, 1 H, ArH), 7.76 (s, 3 H, ArH), 8.20 (d, J = 7.9 Hz, 1 H, ArH), 8.89 (s, 1 H, ArH) ppm. MS (ES+): m/z (%) = 442.3 (100) $[M + 1]^+$. Anal. calcd. for $C_{26}H_{20}ClN_3O_2$ (441.1244): C 70.67, H 4.56, N 9.51; found C 70.42, H 4.92, N 9.21.

Supporting Information Copies of NMR spectra for all compounds are provided.

Acknowledgments

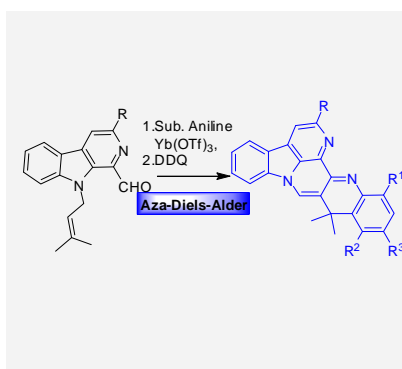
Two of the authors (SH and VS) gratefully acknowledge the financial support in the form of fellowship from Council of Scientific and Industrial Research, New Delhi. Authors acknowledge the SAIF department of CDRI for providing the spectroscopic and analytical data. SB acknowledges Department of Science and Technology, New Delhi for generously supporting his research work.

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Layout 1:

Canthines

Synthesis of new canthines either via Aza-Diels-Alder or Carbonyl-ene reaction from N-prenylated-1-formyl-9H- β -carbolines has been accomplished.



Samiran Hutait, Virender Singh, Sanjay Batra* Page No. – Page No.

Facile synthesis of Dihydroquinoline-fused-Canthines via intramolecular Aza-Diels-Alder reaction

Keywords: Canthine / Carbonyl-ene / Aza-Diels Alder / Yb(OTf)₃ / Lewis acid