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Facile Synthesis of Dihydroquinoline-Fused Canthines by Intramolecular Aza-Diels–Alder Reaction[‡]

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The synthesis of dihydroquinoline-fused canthines by intramolecular aza-Diels–Alder reaction between *N*-prenylated 1-formyl-9*H*-β-carbolines and substituted anilines in the presence of a Lewis acid, followed by oxidation, is described. Additionally, it has been found that the *N*-protected aldehyde in the presence of a suitable catalyst [$ZnBr_2$ or $Yb(OTf)_3$] undergoes intramolecular carbonyl–ene reaction in a diastereoselective fashion to afford the *syn* or *anti* isomer of a new canthine derivative.

Introduction

Recently, we reported on the synthesis of a variety of D-ring-fused β-carbolines from 1-formyl-9*H*-β-carboline by using intramolecular 1,3-dipolar cycloaddition chemistry.[1] Aiming to diversify the range of D-ring-fused β-carbolines using cycloaddition reactions as a key step, we now report the synthesis of dihydroquinoline-fused canthines through aza-Diels–Alder reactions between *N*-prenylated 1-formyl-9*H*-β-carbolines and anilines in the presence of a Lewis acid, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (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 that is available for the construction of complex polycyclic and polyheterocyclic skeletons in an efficient, economical, and stereocontrolled manner as compared to sequential chemical transformations.[3] Among the aza-Diels–Alder reactions available, the Lewis-acid-catalysed inverse-electron-demand Diels–Alder reaction, whereby arylimines are employed as dienes, has been extensively studied.[4] Based on the literature, we anticipated that intramolecular aza-Diels–Alder reaction of arylimines generated from the formyl group at C-1 with the prenyl group present at the indole nitrogen atom of *N*-substituted 1-formyl-β-carboline, should be an attractive alternative for the construction of new β-carboline-based canthine systems.

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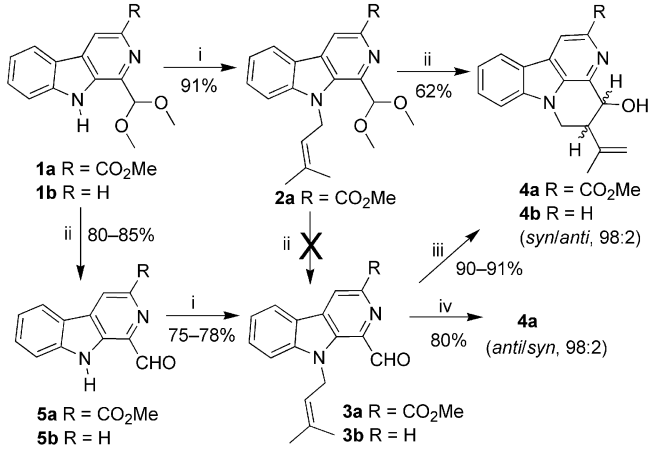
Results and Discussion

To achieve the synthesis of the required starting material for the study, initially **1a**[5] was treated with prenyl bromide in the presence of Cs_2CO_3 to smoothly afford the *N*-prenylated acetal **2a** in 91% yield (Scheme 1).

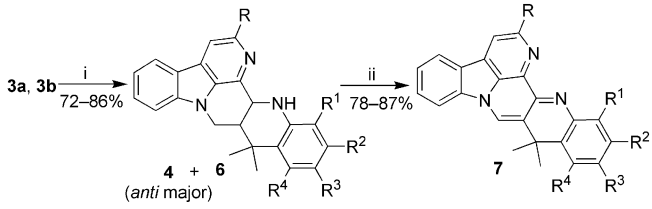


Scheme 1. Reagents and conditions: (i) prenyl bromide, Cs_2CO_3, anhydrous DMF, room temp., 45 min; (ii) AcOH/H_2O (2:3), 100 °C, 45 min; (iii) $ZnBr_2$, anhydrous benzene, reflux, 12 h; (iv) $Yb(OTf)_3$, anhydrous MeCN, reflux, 3 h.

Unexpectedly, however, use of aqueous acetic acid or aqueous trifluoroacetic acid (TFA) promoted the deprotection of **2a** instead of producing the aldehyde **3a** and led to the isolation of a new canthine **4a**, which formed as a product of an 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 furnish the aldehyde **3a**, which would initiate an intramolecular carbonyl–ene reaction with the prenyl chain.[6] Interestingly, the ^1H NMR spectrum of crude **4a** indicated that the reaction was diastereoselective and favoured the formation of

the *syn* isomer. This conclusion was based on the coupling constant associated with the C*H*OH proton, which was observed to be 1.8 Hz for the *syn* isomer and 8.0 Hz for the *anti* isomer (see below). With the aim of synthesising **3a**, aldehyde **5a** was then directly treated with prenyl bromide in the presence of Cs_2CO_3 in anhydrous *N*,*N*-dimethylformamide (DMF) at room temperature to successfully afford the required product **3a** in 78% yield. Mechanistic considerations, however, prompted us to seek chemical support for the transformation of **3a** into **4a**. The ability of Brønsted and Lewis acids to induce intramolecular carbonyl–ene reactions has been widely reported.[6a,6d] Zinc(II) bromide ($ZnBr_2$) is reported to promote the diastereoselective ene cyclisation of citronellal to afford *anti*-isopulegol at low temperatures.[7] Influenced by this report, **3a** was subjected to a reaction with $ZnBr_2$ at low temperatures, but the reaction failed. Nevertheless, heating of **3a** with $ZnBr_2$ in anhydrous benzene to reflux temperature smoothly afforded **4a** in 91% yield in 12 h. However, unlike the earlier report, this reaction was observed to be diastereoselective in favour of the *syn* isomer (98:2). To assess the generality of this outcome, another prenylated aldehyde **3b**, which was prepared from **5b**, was subjected to heating with $ZnBr_2$ in anhydrous benzene to afford **4b** in 90% yield with *syn* stereoselectivity. The unusual result with $ZnBr_2$ prompted us to apply another Lewis acid to the transformation of **3** into **4**. Hence, we investigated the use of $Yb(OTf)_3$ in the desired transformation.[8] Reaction of **3a** with $Yb(OTf)_3$ in anhydrous acetonitrile under heating at reflux furnished **4a** in 80% yield; the reaction was observed to be complete in 3 h. Interestingly, as evident from the ^{1}H NMR spectrum of **4a**, the reaction was found to be diastereoselective in favour of the *anti* isomer (*anti*/*syn*, 98:2). It has been reported that Lewis acids promote ene reactions at elevated temperatures and that the reaction proceeds through a concerted cyclisation mechanism to afford the thermodynamically more stable *anti* product.[9] We presume that *anti*-**4a** may have formed through a similar path. Although it is difficult to account for the *syn* selectivity of the product formed with $ZnBr_2$, based on the results, it was assumed that perhaps during the reaction of $ZnBr_2$ with **3a**, a small amount of HBr may have been liberated, which could act as a Brønsted 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. To establish optimal conditions for the reaction, **3a** was treated with 4-chloroaniline under a range of conditions with respect to catalyst, solvent and temperature. Initially, the reaction was performed with $InCl_3$ in acetonitrile, dioxane, toluene, tetrahydrofuran (THF) or water, either at room temperature or under heating at reflux. Compared to reactions conducted at room temperature, the reactions conducted under heating were fast and gave the product **6a** as a diastereomeric mixture in better yield. Acetonitrile was found to be the solvent of choice for this reaction. Careful column chromatography on silica gel resulted in the isolation of both isomers. The coupling constant of the ring-junction NHC*H*C proton of the less polar isomer was observed to be 11.0 Hz, whereas that of the polar isomer was 2.6 Hz. Based on this data, the polar species was established to be the *syn* isomer, whereas the less polar product was assigned as the *anti* isomer. Additional proof of the stereochemical assignment was obtained by performing NOESY experiments with the *syn* isomer, whereby correlation was observed between the NHC*H*C proton and the $(CH_3)_2CC\mathit{H}CH_2$ protons. Subsequently, other catalysts, including $Yb(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$, $BiCl_3$, cerium(IV) ammonium nitrate (CAN), $BF_3{\cdot}OEt_2$ and *p*-TSA, were also investigated. Although all catalysts successfully furnished **6a**, the best yield (86%) was obtained when the reaction was performed in the presence of $Yb(OTf)_3$ in acetonitrile under heating at reflux for 3 h. During the investigations, we isolated minor amounts of an additional red compound, which was identified as **7a**, the oxidised product of **6a**. The amount of **7a** formed was significant when the reaction was performed in the presence of CAN at higher temperatures in dioxane. Moreover, the formation of **4a** as a side-product in minor amounts was observed in all reactions where a 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 the *anti* isomer, as inferred from the coupling constant of the C*H*OH proton (J = 8.0 Hz) (Scheme 2 and Table 1).



Scheme 2. Reagents and conditions: (i) substituted aniline, $Yb(OTf)_3$, anhydrous MeCN, reflux, 3 h; (ii) DDQ, anhydrous MeCN, room temp., 30 min (R, R^1, R^2, R^3 and R^4: see Table 1).

Isolation of the oxidised product **7** during the aza-Diels–Alder reaction prompted us to examine the oxidation of **6** as a mixture of isomers. It was anticipated that successful formation of **7** from **6** would obviate the need for chromatographic separation of the two isomers of **6**. Hence, oxidation of **6a** as a mixture of isomers was investigated, and it was discovered that treatment with DDQ in acetonitrile afforded **7a** as a fluorescent red compound in 83% yield within 30 min. We then investigated whether the two reactions, i.e., aza-Diels–Alder and oxidation, could be accomplished in one pot, considering that they could both be run in the same solvent. Thus, **3a** was treated initially with 4-chloroaniline in the presence of $Yb(OTf)_3$ in acetonitrile at reflux temperature for 3 h followed by addition of DDQ. It was found that the oxidation was complete within 5 min to afford the final product **7a** in 70% yield. However, because the R_f values for **7a** and **4a** are very similar, column chromatographic separation was tedious. Hence, it was more convenient to first isolate **6** as a mixture of isomers and then subject it to oxidation in the presence of DDQ.

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

Compound	R	R^1	R^2	R^3	R^4	Yield of **6** [%][a]	Yield of **4** [%]	Yield of **7** [%]
a	CO_2Me	H	H	Cl	H	86	trace	83
b	H	H	H	Cl	H	82	trace	84
c	CO_2Me	H	H	OMe	H	75	trace	86
d	H	H	H	OMe	H	79	trace	80
e	CO_2Me	H	H	Me	H	76	trace	84
f	H	H	H	Me	H	81	trace	79
g	CO_2Me	H	H	H	H	82	trace	79
h	CO_2Me	H	H	Br	H	73	trace	78
i	CO_2Me	H	H	F	H	78	trace	83
j	CO_2Me	H	H	2-naphthyl	H	80	trace	87
k	CO_2Me	H	H	$CHMe_2$	H	77	trace	85
l	CO_2Me	H	OMe	OMe	OMe	74	trace	84
m	CO_2Me	H	H	CMe_3	H	72	trace	78
n[b]	CO_2Me	Cl	H	Me	H	–	55	25
o[b]	CO_2Me	Me	H	H	Cl	–	67	14
p	CO_2Me	OMe	H	H	OMe	0	81	–

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

Having successfully optimised 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 mixtures of diastereomers in 78–87% yields. Treatment of **6b**–**m** as diastereomeric mixtures with DDQ in acetonitrile at room temperature for 30 min afforded the respective dihydroquinolines **7b**–**m** as highly fluorescent red products in 73–80% yield. Although the dihydroquinolines were characterised on the basis of their ^{1}H NMR and HRMS spectra, ^{13}C NMR spectra of some compounds could not be recorded due to their poor solubility even in [D_6]DMSO.

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

Compound	R^1	R^3	Yield of **6** [%]	Yield of **4a** [%]	Yield of **7** [%]
a	H	Cl	64	5	9
c	H	OMe	61	7	8
h	H	Br	59	8	6

[a] 140 °C for 10 min.

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

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

Conclusions

We have successfully demonstrated the synthesis of the dihydroquinoline-fused canthine skeleton through intramolecular aza-Diels–Alder reaction followed by oxidation. Furthermore, we have discovered that new, unnatural canthines having the desired stereochemistry can be distereoselectively synthesised from *N*-prenylated aldehydes by an intramolecular carbonyl–ene reaction by 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 are uncorrected and were determined in capillary tubes with a Precision melting point apparatus containing silicon oil. IR spectra were recorded with a Perkin–Elmer RX I FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded either with a Bruker DPX-200 FT or a Bruker Avance DRX-300 spectrometer by using TMS as an internal standard (chemical shifts in δ). The ESMS data were recorded with MICROMASS Quadro-II LCMS system. The HRMS data were recorded as EI-HRMS with a JEOL system or as DART-HRMS (recorded as ES+) with a JEOL-AccuTOF JMS-T100LC Mass spectrometer having DART (Direct Analysis in Real Time) source. All solvents and chemicals were used as received from the suppliers. HPLC was performed with an Agilent 1100 instrument equipped with a DA detector (λ_{max} = 220 and 254 nm) by using a gradient run of 10–100% MeCN containing 0.01% TFA in water over a period of 30 min using an RP18e column (250 mm × 4.6 mm) with particle size 5 μm. The stereochemistry drawn in the structures herein are rela-

tive and not absolute. The diastereoisomeric mixtures of compounds **6c**, **6d** and **6f**–**m** were not separated, and therefore no spectroscopic data were recorded for them.

Preparation of Compounds 2a, 3a and 3b. Typical Procedure for 2a: To a stirred solution of **1a** (3.0 g, 9.99 mmol) in anhydrous DMF (20 mL), Cs_2CO_3 (4.56 g, 13.99 mmol) was added at room temp. After 15 min, prenyl bromide (1.40 mL, 11.99 mmol) in anhydrous DMF (2 mL) was added dropwise, and the reaction was continued at room temp. for an additional 1 h. On completion of the reaction (indicated by TLC), the contents were poured into water (200 mL) whilst stirring with a glass rod. The resulting mixture was extracted with EtOAc (2× 80 mL), and the organic layers were combined, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated to yield a residue, which, on triturating with hexane [R_f = 0.48 (hexane/EtOAc, 75:25)] furnished **2a** (3.35 g, 91%) as a white solid; m.p. 133–134 °C.

Methyl 1-(Dimethoxymethyl)-9-(3-methylbut-2-enyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2a): IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3), 3067 (=CH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 3.52 (s, 6 H, 2 OCH_3), 4.04 (s, 3 H, CO_2CH_3), 5.23 (d, J = 5.6 Hz, 1 H, =CH), 5.46 (d, J = 5.4 Hz, 2 H, NCH_2), 5.78 (s, 1 H, C*H*OCH_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, $CDCl_3$): δ = 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) [M + 1]$^+$. $C_{21}H_{24}N_2O_4$ (368.1736): calcd. 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)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (3a): Prepared from **5a** according to the above procedure after purification by trituration [hexane/EtOAc, 95:03; R_f = 0.57 (hexane/EtOAc, 75:25)]. Yield: 2.97 g (78%); light-yellow solid; m.p. 135–136 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1701 (CHO and CO_2CH_3), 3066 (=CH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 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, =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, $CDCl_3$): δ = 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) [M + 1]$^+$, 355.1 (33) [M + 23]$^+$. $C_{19}H_{18}N_2O_3$ (322.1317): calcd. C 70.79, H 5.63, N 8.69; found C 70.42, H 5.54, N 9.03.

9-(3-Methylbut-2-enyl)-9*H*-pyrido[3,4-*b*]indole-1-carbaldehyde (3b): Prepared from **5b** according to the above procedure after purification by trituration [hexane/EtOAc, 97:03; R_f = 0.59 (hexane/EtOAc, 75:25)]. Yield: 2.02 g (75%); white solid; m.p. 117–118 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1702 (CHO), 3044 (=CH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.68 (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3), 5.13 (s, 1 H, =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, $CDCl_3$): δ = 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) [M + 1]$^+$, 297.1 (30) [M + Na]$^+$. $C_{17}H_{16}N_2O$ (264.1263): calcd. C 77.25, H 6.10, N 10.60; found C 77.03, H 5.87, N 10.62.

Preparation of 4a by Using AcOH. Typical Procedure: A mixture of **2a** (1.20 g, 3.3 mmol), glacial acetic acid (15 mL) and water (25 mL), was heated at 100 °C for 45 min. After completion of the reaction (monitored by TLC), the excess acetic acid was neutralized with satd. 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 give a residue, which was purified by short silica gel (60–120 mesh) column chromatography [$CHCl_3$/MeOH, 99:01; R_f = 0.54 ($CHCl_3$/MeOH, 90:10)] to afford **4a** (0.74 g, 62%) as a white solid; m.p. 181–182 °C.

Methyl *syn*-4-Hydroxy-5-(prop-1-en-2-yl)-5,6-dihydro-4*H*-indolo-[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (4a): Prepared from **2a** according to the above procedure. IR (KBr): $\tilde{\nu}_{max}$ = 1714 (CO_2CH_3), 3384 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H, CH_3), 2.80 (s, 1 H, CHO*H*; 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, NC*H*H), 4.45 (s, 1 H, NCH*H*), 5.08 (s, 1 H, =C*H*H), 5.21 (s, 1 H, =CH*H*), 5.41 (d, J = 1.8 Hz, 1 H, C*H*OH), 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, $CDCl_3$): δ = 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) [M + 1]$^+$. DART-HRMS: calcd. for $C_{19}H_{19}N_2O_3$: 323.1396; found 323.1356.

Methyl *anti*-4-Hydroxy-5-(prop-1-en-2-yl)-5,6-dihydro-4*H*-indolo-[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (4a): Obtained from **3a** when $(YbOTf)_3$ was used as a catalyst, after purification by column chromatography [MeOH/$CHCl_3$, 99:1; R_f = 0.54 (MeOH/$CHCl_3$, 10:90)]. White solid; m.p. 184–185 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1722 (CO_2CH_3), 3244 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3 H, CH_3), 3.11 (td, J = 3.4, 8.2 Hz, 1 H, CH), 3.98 (s, 1 H, CHO*H*; exchangeable with D_2O), 4.03 (s, 3 H, CO_2CH_3), 4.29 (dd, J = 8.8, 12.4 Hz, 1 H, NC*H*H), 4.45 (dd, J = 4.8, 12.4 Hz, 1 H, NCH*H*), 4.87 (s, 1 H, =C*H*H), 5.03 (s, 1 H, =CH*H*), 5.29 (d, J = 8.0 Hz, 1 H, C*H*OH), 7.38 (t, J = 7.2 Hz, 1 H, ArH), 7.53 (d, J = 8.3 Hz, 1 H, ArH), 7.66 (t, J = 7.2 Hz, 1 H, ArH), 8.21 (d, J = 7.9 Hz, 1 H, ArH), 8.81 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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]$^+$. $C_{19}H_{18}N_2O_3$ (322.1317): calcd. C 70.79, H 5.63, N 8.69; found C 71.05, H 5.43, N 8.85.

Preparation of Compounds 4a and 4b by Using $ZnBr_2$ as Catalyst. Typical Procedure for 4a: A mixture of **3a** (0.30 g, 0.93 mmol), $ZnBr_2$ (0.21 g, 0.93 mmol) and anhydrous benzene (20 mL), was heated at reflux temperature for 12 h. 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 (Na_2SO_4) and concentrated under vacuum to give the crude product, which was purified by silica gel (60–120 mesh) column chromatography [$CHCl_3$/MeOH, 99:01; R_f = 0.54 ($CHCl_3$/MeOH, 90:10)] to obtain **4a** (0.27 g, 91%) as a white solid.

***syn*-5-(Prop-1-en-2-yl)-5,6-dihydro-4*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-ol (4b):** Prepared according to the above procedure, after purification by column chromatography [MeOH/$CHCl_3$, 01:99; R_f = 0.66 (MeOH/$CHCl_3$, 10:90)]. Yield: 0.045 g (90%); white solid; m.p. 168–169 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3331 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, CH_3), 2.33 (br. s, 1 H, CHO*H*; exchangeable with D_2O), 3.04 (s, 1 H, CH), 4.36–4.45 (m, 2 H, CH_2), 5.09 (s, 1 H, C*H*OH), 5.20 (s, 1 H, =C*H*H), 5.38 (s, 1 H,

=CH*H*), 7.31 (t, *J* = 7.4 Hz, 1 H, ArH), 7.54 (d, *J* = 8.2 Hz, 1 H, ArH), 7.63 (t, *J* = 7.2 Hz, 1 H, ArH), 7.89 (d, *J* = 4.9 Hz, 1 H, ArH), 8.16 (d, *J* = 7.9 Hz, 1 H, ArH), 8.32 (d, *J* = 5.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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) $[M + 1]^+$. $C_{17}H_{16}N_2O$ (264.1263): calcd. C 77.25, H 6.10, N 10.60; found C 76.98, H 6.22, N 10.52.

Preparation of Compounds 6a–o. Typical Procedure 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 anhydrous MeCN (20 mL), was heated at reflux temperature for 3 h. After completion of the reaction (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 a 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 (Na_2SO_4) and concentrated under vacuum to give the crude product, which was purified by 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, 86%).

Methyl *anti*-12-Chloro-10,10-dimethyl-9a,10,15,15a-tetrahydro-9*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (6a): R_t = 23.37; R_f = 0.62 (hexane/EtOAc, 70:30); m.p. 217–218 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1716 (CO_2CH_3), 3364 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 2.47 (td, *J* = 3.8, 10.8 Hz, 1 H, CH_2CH), 4.01–4.15 (m, 4 H, NC*H*H and CO_2CH_3), 4.71 (dd, *J* = 4.2, 12.1 Hz, 1 H, NCH*H*), 4.78 (d, *J* = 11.0 Hz, 1 H, C*H*NH), 5.28 (br. s, 1 H, NH; exchangeable with D_2O), 6.72 (d, *J* = 8.6 Hz, 1 H, ArH), 6.72 (dd, *J* = 2.2, 8.6 Hz, 1 H, ArH), 7.37–7.44 (m, 2 H, ArH), 7.58 (d, *J* = 8.2 Hz, 1 H, ArH), 7.68 (t, *J* = 7.0 Hz, 1 H, ArH), 8.21 (d, *J* = 8.0 Hz, 1 H, ArH), 8.80 (s, 1 H, ArH) ppm. MS (ES^+): *m*/*z* (%) = 432.2 (100) $[M + 1]^+$. $C_{25}H_{22}ClN_3O_2$ (431.1401): calcd. C 69.52, H 5.13, N 9.73; found C 69.25, H 4.85, N 9.89.

Methyl *syn*-12-Chloro-10,10-dimethyl-9a,10,15,15a-tetrahydro-9*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (6a): R_t = 20.52; R_f = 0.53 (hexane/EtOAc, 70:30); m.p. 214–215 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1717 (CO_2CH_3), 3371 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 2.47 (d, *J* = 9.8 Hz, 1 H, CH_2CH), 3.81 (t, *J* = 11.9 Hz, 1 H, NC*H*H), 4.08 (s, 3 H, CO_2CH_3), 4.35 (br. s, 1 H, NH; exchangeable with D_2O), 4.46 (dd, *J* = 5.1, 12.0 Hz, 1 H, NCH*H*), 5.21 (d, *J* = 2.6 Hz, 1 H, C*H*NH), 6.35 (d, *J* = 8.5 Hz, 1 H, ArH), 6.95 (dd, *J* = 2.3, 8.6 Hz, 1 H, ArH), 7.21 (d, *J* = 2.2 Hz, 1 H, ArH), 7.34–7.39 (m, 1 H, ArH), 7.47–7.50 (m, 1 H, ArH), 7.61–7.66 (m, 1 H, ArH), 8.20 (d, *J* = 8.0 Hz, 1 H, ArH), 8.89 (s, 1 H, ArH) ppm. MS (ES^+): *m*/*z* (%) = 432.2 (100) $[M + 1]^+$. $C_{25}H_{22}ClN_3O_2$ (431.1401): calcd. 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-9*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine (6b):** Prepared from **3b** according to the above procedure, after purification by column chromatography [hexane/EtOAc, 89:11; R_f = 0.68 (hexane/EtOAc, 70:30)] to give *syn*-**6b** and *anti*-**6b** as a white solid (0.29 g, 82%); m.p. 186–187 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3415 (NH), 3022 (=CH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 2.45 (td, *J* = 4.2, 11.1 Hz, 1 H, CH_2CH), 4.07 (t, *J* = 12.0 Hz, 1 H, NC*H*H), 4.66 (dd, *J* = 4.4, 12.0 Hz, 1 H, NCH*H*), 4.79 (d, *J* = 10.7 Hz, 1 H, C*H*NH), 5.70 (br. s, 1 H, NH; exchangeable with D_2O), 6.68 (d, *J* = 8.5 Hz, 1 H, ArH), 7.01 (dd, *J* = 2.1, 8.4 Hz, 1 H, ArH), 7.26–7.34 (m, 2 H, ArH), 7.53 (d, *J* = 8.3 Hz, 1 H, ArH), 7.63 (t, *J* = 7.3 Hz, 1 H, ArH), 7.85 (d, *J* = 5.4 Hz, 1 H, ArH), 8.16 (d, *J* = 7.7 Hz, 1 H, ArH), 8.40 (d, *J* = 5.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): 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) $[M + 1]^+$. $C_{23}H_{20}ClN_3$ (373.1346): calcd. 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-9*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine (6b):** R_f = 0.59 (hexane/EtOAc, 70:30); m.p. 185–186 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3393 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 2.47 (d, *J* = 9.6 Hz, 1 H, CH_2CH), 3.72 (t, *J* = 11.8 Hz, 1 H, NC*H*H), 4.34 (s, 1 H, CHN*H*; exchangeable with D_2O), 4.47 (dd, *J* = 5.1, 11.4 Hz, 1 H, NCH*H*), 5.15 (d, *J* = 2.6 Hz, 1 H, C*H*NH), 6.36 (d, *J* = 8.5 Hz, 1 H, ArH), 6.95 (dd, *J* = 2.2, 8.5 Hz, 1 H, ArH), 7.20–7.33 (m, 2 H, ArH), 7.46 (d, *J* = 8.2 Hz, 1 H, ArH), 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, $CDCl_3$): δ = 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) $[M + 1]^+$. $C_{23}H_{20}ClN_3$ (373.1346): calcd. C 73.89, H 5.39, N 11.24; found C 74.21, H 5.32, N 10.92.

Methyl *anti*-10,10,12-Trimethyl-9a,10,15,15a-tetrahydro-9*H*-indolo-[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (6e): Prepared from **3a** according to the above procedure, after purification by column chromatography [hexane/EtOAc, 87:12; R_f = 0.66 (hexane/EtOAc, 70:30)] to give *syn*-**6e** and *anti*-**6e** as a white solid (0.34 g, 76%); m.p. 187–188 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1712 (CO_2CH_3), 3389 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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* = 4.4, 11.6 Hz, 1 H, CH_2CH), 4.05–4.16 (m, 4 H, NC*H*H and CO_2CH_3), 4.71 (dd, *J* = 4.4, 12.2 Hz, 1 H, NCH*H*), 4.78 (d, *J* = 10.8 Hz, 1 H, C*H*NH), 5.62 (br. s, 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) $[M + 1]^+$. HRMS (+ESI): calcd. for $C_{26}H_{25}N_3O_2$ 411.1947; found 411.1918.

Methyl *syn*-10,10,12-Trimethyl-9a,10,15,15a-tetrahydro-9*H*-indolo-[3,2,1-*ij*]quinolino[3,2-*c*][1,5]naphthyridine-2-carboxylate (6e): R_f = 0.58 (hexane/EtOAc, 70:30); m.p. 184–185 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1706 (CO_2CH_3), 3489 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 2.27 (s, 3 H, $ArCH_3$), 2.44–2.46 (m, 1 H, CH_2CH), 3.91 (t, *J* = 11.9 Hz, 1 H, NC*H*H), 4.09 (s, 3 H, CO_2CH_3), 4.20 (s, 1 H, NH; exchangeable with D_2O), 4.47 (dd, *J* = 5.1, 11.9 Hz, 1 H, NCH*H*), 5.21 (d, *J* = 2.1 Hz, 1 H, C*H*NH), 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) $[M + 1]^+$. DART-HRMS: calcd. for $C_{26}H_{26}N_3O_2$ 412.2025; found 412.2009.

Preparation of Compounds 7a–o. Typical Procedure for 7a: To a stirred solution of a diastereomeric mixture of **6a** (0.20 g, 0.46 mmol) in anhydrous MeCN (30 mL), DDQ (0.32 g, 1.34 mmol) was added and the reaction was continued at room temp. for 30 min. On completion, excess solvent was removed under reduced pressure, and then $CHCl_3$ (50 mL) and water (20 mL) were added. After separation of the 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) and brine (50 mL),

dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product. After purification by silica gel (60–120 mesh) column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.50 ($CHCl_3$/MeOH, 93:07)], **7a** was obtained as a red solid (0.16 g, 83%); m.p. >250 °C.

Methyl 12-Chloro-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino-[3,2-*c*][1,5]naphthyridine-2-carboxylate (7a): IR (KBr): $\tilde{\nu}_{max}$ = 1718 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.65 (s, 6 H, 2 CH_3), 4.00 (s, 3 H, CO_2CH_3), 7.32 (dd, J = 2.2, 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, $CDCl_3$): δ = 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) $[M + 1]^+$. DART-HRMS: calcd. for $C_{25}H_{19}ClN_3O_2$: 428.1166; found 428.1155.

12-Chloro-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]-naphthyridine (7b): Prepared from **6b** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.61 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.10 g (84%); red solid; m.p. 185–186 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67 (s, 6 H, 2 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, $CDCl_3$): δ = 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) $[M + 1]^+$. $C_{23}H_{16}ClN_3$ (369.1033): calcd. 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-10*H*-indolo[3,2,1-*ij*]quinolino-[3,2-*c*][1,5]naphthyridine-2-carboxylate (7c): Prepared from **6c** according to the above general procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.32 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.12 g (86%); red solid; m.p. 146–147 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1722 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.72 (s, 6 H, 2 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, [D_6]DMSO): δ = 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) $[M + 1]^+$. DART-HRMS: calcd. for $C_{26}H_{22}N_3O_3$: 424.1661; found 424.1666.

12-Methoxy-10,10-dimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]-naphthyridine (7d): Prepared from **6d** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.49 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.095 g (80%); red solid; m.p. 175–176 °C. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 1.66 (s, 6 H, 2 CH_3), 3.81 (s, 3 H, OCH_3), 6.87 (dd, J = 2.6, 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) $[M + 1]^+$. $C_{24}H_{19}N_3O$ (365.1528): calcd. C 78.88, H 5.24, N 11.50; found C 79.02, H 5.54, N 12.01.

Methyl 10,10,12-Trimethyl-10*H*-indolo[3,2,1-*ij*]quinolino[3,2-*c*][1,5]-naphthyridine-2-carboxylate (7e): Prepared from **6e** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.36 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.13 g (84%); red solid; m.p. 177–178 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1720 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.68 (s, 6 H, 2 CH_3), 2.39 (s, 3 H, $ArCH_3$), 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, [D_6]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) $[M + 1]^+$. $C_{26}H_{21}N_3O_2$ (407.1634): calcd. 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]naphth-yridine (7f): Prepared from **6f** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.44 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.09 g (79%); red solid; m.p. 177–179 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.66 (s, 6 H, 2 CH_3), 2.39 (s, 3 H, CH_3), 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) $[M + 1]^+$. $C_{24}H_{19}N_3$ (349.1579): calcd. 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): Prepared from **6g** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.40 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.15 g (79%); red solid; m.p. 147–149 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1719 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, TFA): δ = 1.82 (s, 6 H, 2 CH_3), 4.04 (s, 3 H, CO_2CH_3), 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 $C_{25}H_{19}N_3O_2$ 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): Prepared from **6h** following the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.48 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.12 g (78%); red solid; m.p. >250 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1722 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.64 (s, 6 H, 2 CH_3), 4.00 (s, 3 H, CO_2CH_3), 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. ^{13}C NMR (75 MHz, [D_6]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) $[M + 3]^+$. $C_{25}H_{18}BrN_3O_2$ (471.0582): calcd. 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): Prepared from **6i** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.49 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.16 g (83%); red solid; m.p. >250 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1715 (CO_2CH_3) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.65 (s, 6 H, 2 CH_3), 4.00 (s, 3 H, CO_2CH_3), 7.11 (td, J = 2.6, 8.3 Hz, 1 H, ArH), 7.41 (dd, J = 2.9, 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. for $C_{25}H_{18}FN_3O_2$ 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): Prepared from **6j** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.38 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.25 g (87%); red solid; m.p. 245–246 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1706 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.20 (s, 6 H, 2 CH_3), 4.02 (s, 3 H, CO_2CH_3), 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]$^+$. $C_{29}H_{21}N_3O_2$ (443.1634): calcd. 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): Prepared from **6k** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.35 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.16 g (85%); red solid; m.p. 160–162 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1718 (CO_2CH_3), 3022 (=CH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.24 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.65 (s, 6 H, 2 CH_3), 2.89–2.98 (m, 1 H, C*H*CH_3), 4.00 (s, 3 H, CO_2CH_3), 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]$^+$. $C_{28}H_{25}N_3O_2$ (435.5170): calcd. 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): Prepared from **6l** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.38 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.21 g (84%); red solid; m.p. 178–179 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1715 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.75 (s, 6 H, 2 CH_3), 3.79 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.00 (s, 3 H, CO_2CH_3), 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]$^+$. $C_{28}H_{25}N_3O_5$ (483.1794): calcd. 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): Prepared from **6m** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.39 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.08 g (78%); red solid; m.p. 162–163 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1720 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.35 (s, 9 H, 3 CH_3), 1.84 (s, 6 H, 2 CH_3), 4.07 (s, 3 H, CO_2CH_3), 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. ^{13}C NMR (75 MHz, [D$_6$]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-10*H*-indolo[3,2,1-*ij*]quinolino-[3,2-*c*][1,5]naphthyridine-2-carboxylate (7n): Prepared from **3a** via the aza-Diels–Alder product **6n** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.38 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.12 g (25%); red solid; m.p. >250 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1719 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.64 (s, 6 H, 2 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]$^+$. $C_{26}H_{20}ClN_3O_2$ (441.1244): calcd. 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-10*H*-indolo[3,2,1-*ij*]quinolino-[3,2-*c*][1,5]naphthyridine-2-carboxylate (7o): Prepared from **3a** via the aza-Diels–Alder product **6o** according to the above procedure, after purification by column chromatography [$CHCl_3$/MeOH, 98:02; R_f = 0.38 ($CHCl_3$/MeOH, 93:07)]. Yield: 0.07 g (14%); red solid; m.p. >250 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1716 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93 (s, 6 H, 2 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]$^+$. $C_{26}H_{20}ClN_3O_2$ (441.1244): calcd. C 70.67, H 4.56, N 9.51; found C 70.42, H 4.92, N 9.21.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra for all compounds.

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A minor change has been made in Table 2 after publication in Early View.

